

SMALL MOLECULE FSH RECEPTOR MODULATORS

FIELD

[001] The present disclosure is in the field of pharmaceutical compounds and compositions and therapeutic methods of their use. In particular, the present disclosure is in the field of follicle-stimulating hormone (FSH) receptor modulators and their use.

BACKGROUND

[002] Gonadotropins serve important functions in several physiological processes including metabolism, temperature regulation, and reproduction. Gonadotropins act on specific gonadal cell types to initiate ovarian and testicular cell differentiation and steroidogenesis. The gonadotropin FSH (follicle-stimulating hormone) is released from the anterior pituitary under the influence of gonadotropin-releasing hormone and estrogens. FSH is a heterodimeric glycoprotein hormone that shares structural similarities with luteinizing hormone (LH), human chorionic gonadotropin (hCG) and thyroid-stimulating hormone (TSH), all of which are proteins (28-38 kDa) composed of a common α -subunit non-covalently bound to a distinct β -subunit that confers receptor binding specificity. *See, e.g.*, Ulloa-Aguirre, A., et al., *Front Endocrinol (Lausanne)*, 2018, 9:707. FSH, LH, and TSH are produced in the pituitary gland, while hCG is produced primarily by the placenta. The cellular receptor for FSH (FSHR) is expressed on testicular Sertoli cells and ovarian granulosa cells. *See, e.g.*, Anderson, R.C., et al., *Endocr Rev*, 2018, 39(6):911-937.

[003] In the female, FSH plays a pivotal role in the stimulation of follicle development and maturation. Binding of FSH to FSHR initiates an increase in the level of the intracellular second messenger adenosine 3', 5'-monophosphate (cAMP), which stimulates aromatase induction that catalyzes the conversion of androstenedione to estradiol within the ovary, enabling follicle growth. *See, e.g.*, Donadeu, F.X. and M. Ascoli, *Endocrinology*, 2005, 146(9):3907-16.

[004] FSHR activation also stimulates the expression of LH receptors on granulosa cells, allowing them to respond to the preovulatory LH surge. In the male, FSH is expressed on the Sertoli cells of the testis and plays a key role in stimulating spermatogenesis. Prepubertally, FSH

is responsible for Sertoli cell proliferation and in adulthood FSH stimulates spermatogonial proliferation and can support spermatogenesis to the round spermatid stage.

[005] The FSH receptor is a class A member of the G-coupled protein (GPCR) class of receptors, belonging to the subfamily of glycoprotein hormone receptors, which also includes luteinizing hormone/ choriogonadotropin receptor (LHCGR) and thyroid stimulating hormone receptor (TSHR). *See, e.g.* Ulloa-Aguirre, *supra*. Hydropathicity plots of the amino acid sequences of these receptors reveal three general domains: a hydrophilic amino-terminal region, considered to be the amino-terminal extracellular domain; seven hydrophobic segments of membrane-spanning length, considered to be the transmembrane domain; and a carboxy-terminal region that contains potential phosphorylation sites (serine, threonine, and tyrosine residues), considered to be the carboxyterminal intracellular or cytoplasmic domain. The glycoprotein hormone receptor family is distinguished from other G protein-coupled receptors, such as the β -2-adrenergic, rhodopsin, and substance K receptors, by the large size of the hydrophilic amino-terminal domain, which is involved in hormone binding.

[006] Annually in the U.S. there are 2.4 million couples experiencing infertility that are potential candidates for treatment. FSH, either extracted from urine or produced by recombinant DNA technology, is a parenterally-administered protein product used by specialists for ovulation induction and for controlled ovarian stimulation. Whereas ovulation induction is directed at achieving a single follicle to ovulate, controlled ovarian stimulation is directed at aspirating multiple oocytes for use in various *in-vitro* assisted reproductive technologies, *e.g.*, *in-vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). *See, e.g.*, *ESHRE guideline: Ovarian Stimulation for IVF/ICSI, (October 2019)*. FSH is also used clinically to treat male hypogonadism and male infertility, *e.g.*, some types of failure of spermatogenesis. *See, e.g.*, Behre, H.M., *Front Endocrinol (Lausanne)*, 2019, 10:322.

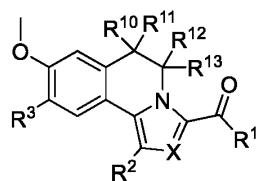
[007] FSHR is a highly specific target in the ovarian follicle growth process in the female and is almost exclusively expressed in the ovary. However, the use of FSH is limited by its high cost, lack of oral dosing, and the need for extensive monitoring by specialist physicians. Hence,

identification of a non-peptidic small molecule substitute for FSH that could potentially be developed for oral administration is desirable.

[008] FSH and small molecule FSH receptor modulators may be used to treat diseases, disorders, and conditions such as female infertility, male infertility, hypogonadism, and failure of spermatogenesis. Small molecule FSH agonists have been disclosed in, *e.g.*, WO 2002/09706, WO 2009/098283, WO 2010/136438, U.S. Patent No. 6,653,338, US Patent No. 8,431,564, WO 2011/012600, WO 2014/209978, and WO 2015/196759. One small molecule FSH receptor modulator, MK-8389, was evaluated in clinical trials, but did not reach approval. *See, e.g.*, Gerrits, M.G.F. et al., Fertility and Sterility Vol. 105, No. 4, April 2016. There remains a need for small molecule FSH receptor modulators that selectively activate FSHR.

SUMMARY

[009] In one aspect, provided herein is a compound of Formula (A)



Formula (A)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the

atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl; or

- (ii) R^f is C₁-C₆ alkyl; and R^g is C₁-C₆ alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C₁-C₆ alkyl; C₁-C₆ haloalkyl; C₁-C₆ hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C₄-C₆ cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C₄-C₆ cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

X is CR²⁰ or N;

R^{20} is selected from H, halogen, nitrile, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

- (i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C₁-C₃ alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or

partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

- (ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or R^{11} and R^{12} together form a double bond, and R^{10} and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0010] In some embodiments, R^1 is $-NR^fR^g$, wherein:

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4

group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or

- (ii) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile.

[0011] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.

[0012] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.

[0013] In some embodiments, R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the

atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

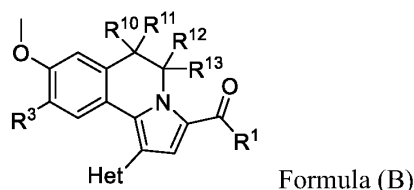
[0014] In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

[0015] In some embodiments, R¹ is -NR^fR^g, wherein R^f is C₁-C₆ alkyl; and R^g is C₁-C₆ alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile.

[0016] In some embodiments, R² is C₁-C₆ alkyl or C₁-C₆ alkenyl. In some embodiments, R² is C₁-C₆ haloalkyl. In some embodiments, R² is C₁-C₆ hydroxyalkyl. In some embodiments, R² is phenyl optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl. In some embodiments, R² is 4-fluorophenyl. In some embodiments, R² is C₄-C₆ cycloalkyl optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl. In some embodiments, R² is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl. In some embodiments, R² is 3,3-difluorocyclobutyl, 5-fluoropyridin-2-yl, 2-thiophenyl, 5-thiazolyl, or 1,3,4-thiadiazolyl.

[0017] In some embodiments, X is CR²⁰. In some embodiments, X is N.

[0018] In another aspect, provided herein is a compound of Formula (B)



Formula (B)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

Het is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

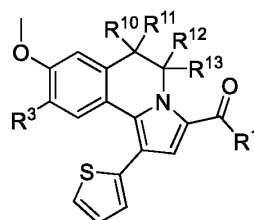
each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0019] In some embodiments, Het is a 5-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with

1 to 4 R^5 groups independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and C_1-C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1-C_3 alkyl. In some embodiments, Het is a 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R^5 groups independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and C_1-C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1-C_3 alkyl.

[0020] In another aspect, provided herein is a compound of Formula (C)



Formula (C)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1-C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3-C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1-C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl

ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

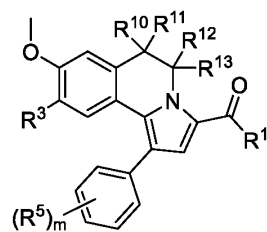
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0021] In another aspect, provided herein is a compound of Formula (D)



Formula (D)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

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

each R^5 is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

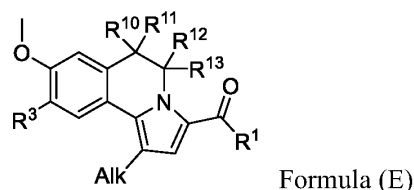
(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are

attached, form a 3- to 6-membered ring, , and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;
wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0022] In another aspect, provided herein is a compound of Formula (E)



Formula (E)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

Alk is C₁-C₆ alkyl or C₁-C₆ alkenyl;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C₁-C₃ alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

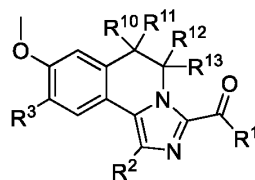
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0023] In another aspect, provided herein is a compound of Formula (F)



Formula (F)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl; or
- (i) R^f is C₁-C₆ alkyl; and R^g is C₁-C₆ alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R² is selected from C₁-C₆ alkyl; C₁-C₆ alkenyl; C₁-C₆ haloalkyl; C₁-C₆ hydroxyalkyl; -(C₁-C₃ alkyl)-SO₂CH₃; -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) optionally substituted with 1 to 13 halogens; -(C₁-C₆ alkyl)-NR^{5a}R^{5b}; phenyl; C₄-C₆ cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C₄-C₆ cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_n C(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1-C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1-C_3 alkyl;

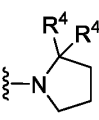
(ii) C_1-C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and hydroxy; and

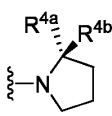
(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1-C_3 alkyl optionally substituted with 1 to

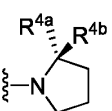
7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0024] In some embodiments, R¹ is , wherein each R⁴ is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from

C₃-C₆ cycloalkyl, hydroxy, and halogen. In some embodiments, R¹ is , wherein R^{4a} is C₁-C₆ alkyl and R^{4b} is selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen. In some

embodiments, R¹ is , wherein R^{4b} is C₁-C₆ alkyl and R^{4a} is selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

[0025] In some embodiments, R³ is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂. In some embodiments, R³ is 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heteroaryl ring contains 1

to 4 ring nitrogens, and wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂. In some embodiments, R³ is tetrazole, pyrazole, imidazole, oxazole, or pyridine, wherein R³ may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂. In some embodiments, R³ is -C(O)NHR⁶.

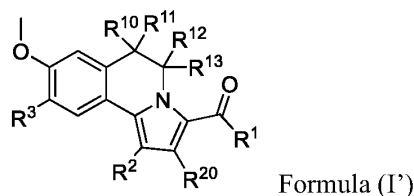
[0026] In some embodiments, R⁶ is -(CR⁷R⁸)_nC(O)NR^dR^e. In some embodiments, each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl. In some embodiments, R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen.

[0027] In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy. In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or tetrazole. In some embodiments, R⁶ is phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens. In some embodiments, R⁶ is cyclopropane optionally substituted with nitrile or is 19cyclobutene optionally substituted with nitrile.

[0028] In some embodiments, each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, any two of R¹⁰, R¹¹, R¹², and R¹³,

together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

[0029] In another aspect, provided herein is a compound of Formula (I')



or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R² is selected from C₁-C₆ alkyl; C₁-C₆ haloalkyl; C₁-C₆ hydroxyalkyl; -(C₁-C₃ alkyl)-SO₂CH₃; -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) optionally substituted with 1 to 13 halogens; -(C₁-C₆ alkyl)-NR^{5a}R^{5b}; phenyl; C₄-C₆ cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C₄-C₆ cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

R²⁰ is selected from H, halogen, nitrile, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

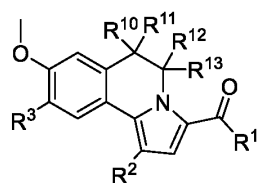
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or R^{11} and R^{12} together form a double bond, and R^{10} and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0030] In another aspect, provided herein is a compound of Formula (I)



Formula (I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 3 R^4 groups, wherein each R^4 group is independently selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 haloalkyl; phenyl; and 5- to 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy;

R^3 is selected from $-C(O)NHR^6$ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-

membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl,

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0031] In another aspect, provided herein is a compound selected from Table 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof. In another aspect, provided herein is a compound selected from Table 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0032] In another aspect, provided herein are salts, hydrates, solvates, analogs, conjugates, isomers, polymorphs, esters, prodrugs, metabolites, complexes, co-crystals, intermediates, modifications and derivatives of the compounds, stereoisomers, and tautomers described herein.

[0033] In another aspect, provided herein is a pharmaceutical composition comprising the compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein, and a pharmaceutically acceptable carrier.

[0034] In another aspect, provided herein is a method of modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, comprising administering to a subject in need thereof the compound disclosed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, or the composition disclosed herein.

[0035] In another aspect, provided herein is a method of modulating follicle-stimulating hormone receptor (FSHR) activity in a biological sample, comprising contacting the biological sample with the compound disclosed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, or the composition disclosed herein.

[0036] In another aspect, provided herein is a method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound disclosed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, or the composition disclosed herein. In some embodiments, the disease or disorder is selected from hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal

beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency.

[0037] In another aspect, provided herein is a method for treating a fertility disorder in a female or male subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, or a composition as disclosed herein. The method may be a method for stimulating follicular development, a method for ovulation induction, a method of controlled ovarian hyperstimulation, a method of controlled ovarian stimulation, a method of assisted reproductive technology (ART) (including *in vitro* fertilization), a method of treating male hypogonadism, or a method of treating male infertility, including failure of spermatogenesis.

[0038] In another aspect, provided herein is a compound as disclosed herein or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, or a composition disclosed herein, for use in modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, or for use in treating a disease or disorder in a subject in need thereof, such as a disease or disorder selected from hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency, or for use in treating a fertility disorder in a subject in need thereof, such as for stimulating follicular development, ovulation induction, controlled

ovarian hyperstimulation, controlled ovarian stimulation, assisted reproductive technology (ART) (including *in vitro* fertilization), treating male hypogonadism, or treating male infertility, including failure of spermatogenesis.

[0039] In another aspect, provided herein is the use of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, or a composition disclosed herein, in the preparation of a medicament for modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, or for treating a disease or disorder in a subject in need thereof, such as a disease or disorder selected from hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency, or for treating a fertility disorder in a subject in need thereof, such as for stimulating follicular development, ovulation induction, controlled ovarian hyperstimulation, controlled ovarian stimulation, assisted reproductive technology (ART) (including *in vitro* fertilization), treating male hypogonadism, or treating male infertility, including failure of spermatogenesis.

DETAILED DESCRIPTION

DEFINITIONS

[0040] Technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art to which the present disclosure pertains, unless otherwise defined.

[0041] As used herein, the singular forms "a," "an," and "the" and the like designate both the singular and the plural, unless expressly stated to designate the singular only.

[0042] As used herein, the term "about" means that the stated parameter is not limited to the exact number stated. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term. As used herein, ranges are to be construed as shorthand for each and every value falling within the range, and each separate value should be understood to be expressly disclosed herein.

[0043] The phrase "consisting essentially of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. When "consisting essentially of" is used to refer to compositions with only one active agent disclosed herein, the compositions cannot include any additional active agents that are not otherwise recited. When "consisting essentially of" is used to refer to combinations of active agents disclosed herein, the combinations cannot include any additional active agents that are not otherwise recited.

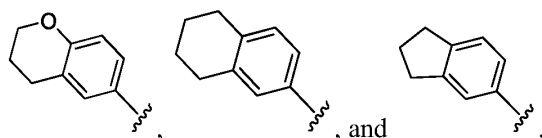
[0044] As used herein, "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to a patient to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reaction of a compound disclosed herein with an acid or base. Typically, but not necessarily unless otherwise stated, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present disclosure may comprise acid addition salts. Representative salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate,

phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium, and valerate salts. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this disclosure and these should be considered to form a further aspect of the present technology.

[0045] Where compounds disclosed herein have one or more chiral centers, they may exist as, be provided or formulated as, or be used as, a racemate or as individual enantiomers. It should be noted that all such stereoisomers and mixtures thereof are included in the scope of the present disclosure. Thus, the illustration of a chiral center without a designation of R or S signifies that the scope of the disclosure includes the R isomer, the S isomer, racemic mixtures of the isomers, and mixtures where one isomer is present in greater abundance than another.

[0046] Where processes for the preparation of compounds disclosed herein give rise to mixtures of stereoisomers, such isomers may be separated by conventional techniques such as preparative chiral chromatography. The compounds may be prepared in racemic form or individual enantiomers may be prepared by stereoselective synthesis or by resolution. The compounds may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides followed by chromatographic separation and removal of the chiral auxiliary.

[0047] As used herein, “aryl” refers to a carbocyclic (all carbon) ring that is fully aromatized. An “aryl” group can be made up of two or more fused rings (rings that share two adjacent carbon atoms). When an aryl group is a fused ring system, then the ring that is connected to the rest of the molecule is fully aromatized. The other ring(s) in the fused ring system may or may not be fully aromatized. Examples of aryl groups include, without limitation, the radicals of benzene, naphthalene and azulene. Additional non-limiting examples include:



[0048] As used herein, “heteroaryl” refers to a ring that is fully aromatized and contains one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur in the ring. In some examples, a heteroaryl ring may comprise an oxo group directly appended to a ring carbon, the oxo group forming part of the aromatized system. A “heteroaryl” group can be made up of two or more fused rings (rings that share two adjacent carbon atoms). When a heteroaryl group is a fused ring system, then the ring that is connected to the rest of the molecule is fully aromatized. The other ring(s) in the fused ring system may or may not be fully aromatized. Examples of heteroaryl rings include, without limitation, furan, thiophene, phthalazinone, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, triazole, thiadiazole, pyridine, 2-pyridonyl, pyridazine, pyrimidine, pyrazine and triazine. As described herein, in some examples, the heteroaryl group may be substituted. In other words, the heteroaryl group may comprise one or more substituents on the heteroaromatic ring. When a heteroaryl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s) provided that valencies are satisfied. In some cases, the heteroaryl group may be substituted at the heteroatom, e.g., a N-containing heteroaryl group may be an N-substituted heteroaryl group (such as a N-substituted 2-pyridonyl group).

[0049] As used herein, “alkyl” refers to a straight or branched chain fully saturated (no double or triple bonds) hydrocarbon group. An alkyl group of the presently disclosed compounds may comprise from 1 to 20 carbon atoms. An alkyl group herein may have 1 to 4 carbon atoms, 1 to 5 carbon atoms, 1 to 6 carbon atoms, 1 to 7 carbon atoms, 1 to 8 carbon atoms, 1 to 9 carbon atoms, 1 to 10 carbon atoms, 1 to 11 carbon atoms, 1 to 12 carbon atoms, 1 to 13 carbon atoms, 1 to 14 carbon atoms, or 1 to 15 carbon atoms. As used herein, a C₁-C₆ alkyl represents an alkyl group having 1 to 6 carbon atoms, a C₁-C₄ alkyl represents an alkyl group having 1 to 4 carbon atoms and a C₁-C₃ alkyl represents an alkyl group having 1 to 3 carbon atoms, etc. Examples of alkyl groups include, without limitation, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, amyl, *t*-amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl.

[0050] As used herein, “cycloalkyl” refers to a completely saturated (no double bonds) hydrocarbon ring. Cycloalkyl groups of the presently disclosed compounds may range from C₃ to C₅, C₃ to C₆, C₃ to C₇, or C₃ to C₈. As used herein, a C₃-C₅ cycloalkyl represents a cycloalkyl group containing 3 to 5 carbon atoms and a C₃-C₆ cycloalkyl represents a cycloalkyl group containing 3 to 6 carbon atoms.

[0051] As used herein, “heterocycloalkyl” refers to a ring having in the ring system one or more heteroatoms independently selected from nitrogen, oxygen and sulfur. The ring may also contain one or more double bonds provided that the ring is not fully aromatized. A “heterocycloalkyl” ring as defined herein can be a stable 3- to 18-membered ring (which includes a 3- to 5-membered or 3- to 6-membered ring) that consists of carbon atoms and from one to five ring heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur.

[0052] As used herein, “alkoxy” refers to an alkyl group, as defined above, appended to the parent molecular moiety through an oxy group, -O-. As used herein, a C₁-C₆ alkoxy represents an alkoxy group containing 1 to 6 carbon atoms and a C₁-C₃ alkoxy represents an alkoxy group containing 1 to 3 carbon atoms. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy etc.

[0053] As used herein, “haloalkyl” refers to an alkyl group, as defined above, in which one or more of the hydrogen atoms thereon has been replaced with a halogen atom (e.g. F, Cl, Br or I). As used herein, “C₁-C₆ haloalkyl” represents an alkyl group containing 1 to 6 carbon atoms, in which one or more hydrogens thereon has been replaced with a halogen atom.

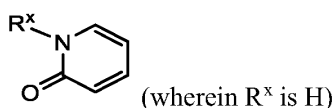
[0054] As used herein, “haloalkoxy” refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms thereon has been replaced with a halogen atom (e.g. F, Cl, Br or I). As used herein, “C₁-C₃ haloalkoxy” represents a haloalkoxy group containing 1 to 3 carbon atoms.

[0055] As used herein, unless otherwise stated, “independently selected” indicates that each one of a designated group is selected independently from a subsequent list of species.

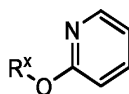
[0056] As used herein, and unless otherwise stated, where a group is described as being optionally substituted, one or more hydrogen atoms on the group may each independently be replaced with a substituent, provided valencies are satisfied.

[0057] It is to be understood that, in any compound of the presently disclosed compounds having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be R or S. In addition, it is to be understood that, in any compound of the presently disclosed compounds having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z.

[0058] It is to be understood that the disclosure of a compound herein inherently includes the disclosure of a tautomer thereof, if applicable. For instance, the disclosure of:



also includes the disclosure of:



and vice versa, even if only one of the two structures is disclosed.

[0059] Throughout the present disclosure, when a compound is illustrated or named, it is to be understood that isotopically enriched analogs of the compound are also contemplated and encompassed by the disclosure. For example, a compound may have a deuterium incorporated instead of a hydrogen, or a carbon-13 instead of carbon with natural isotopic distribution. The isotopic enrichment may be in one location on the compound, i.e., only one hydrogen is replaced by a deuterium, or in more than one location, i.e., two or more or all or a plurality less than all hydrogens are replaced by deuterium. For example, in some embodiments, 1 to 10 hydrogens are replaced by deuterium. The present disclosure also encompasses compounds where all similar atoms are replaced by a less common isotope, for example, a perdeutero compound where all hydrogen atoms are replaced by deuterium. The isotopically enriched compounds may be useful,

for example, when obtaining NMR spectra or when making use of an isotope effect in managing the kinetics of the reaction the compound is undergoing.

[0060] Throughout the present disclosure, when a compound is illustrated or named, it is to be understood that salts, hydrates, solvates, analogs, conjugates, isomers, polymorphs, esters, prodrugs, metabolites, complexes, co-crystals, intermediates, modifications, and derivatives thereof are contemplated and encompassed by the disclosure.

[0061] The term “pharmaceutical composition” refers to a mixture of one or more compounds disclosed herein with another pharmaceutically acceptable excipient, such as one or more pharmaceutically acceptable diluents or carriers or one or more other pharmaceutically acceptable excipients known in the art. Formulating a compound in a pharmaceutical composition may facilitate administration of the compound to an organism, e.g., the subject to be treated. The specific components of a pharmaceutical composition may depend on and vary with the intended route of administration.

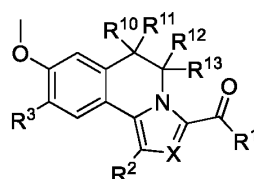
[0062] As used herein, the terms “patient” and “subject” refer to a vertebrate, such as but not limited to a mammal (including a human), bird, fish, or reptile, that has been or will be the object of treatment, observation, or experiment. “Subject” and “patient” may be used interchangeably. Mammals include, but are not limited to, humans, mice, rodents, rats, simians, farm animals, dogs, cats, sport animals, and pets. The methods described herein may be useful in human therapy and/or veterinary/animal husbandry applications. Without being limiting, the discussion that follows is written with reference to adult human patients.

[0063] As used herein, the terms “therapeutically effective amount” and “effective amount” are used interchangeably and refer to an amount that provides the specific intended pharmacological effect in a patient in need of treatment. It is emphasized that a therapeutically effective amount will not always be effective in treating the conditions described herein in a given patient, even though such amount is deemed to be a therapeutically effective amount by those of skill in the art. Exemplary therapeutically effective amounts are provided herein with reference to adult human patients. The therapeutically effective amount may vary depending upon

characteristics of the patient being treated, the condition being treated, and the severity of the condition, for example.

COMPOUNDS

[0064] In one aspect, disclosed herein is a compound of Formula (A)



Formula (A)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is $-NR^fR^g$, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or
- (ii) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen,

wherein the phenyl, C₄-C₆ cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

X is CR²⁰ or N;

R²⁰ is selected from H, halogen, nitrile, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

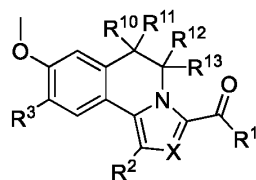
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0065] In another aspect, disclosed herein is a compound of Formula (A)



Formula (A)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from

oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or

- (ii) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

X is CR^{20} or N;

R^{20} is selected from H, halogen, nitrile, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

- (i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

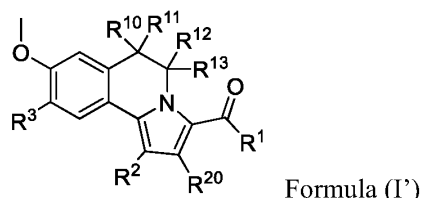
- (ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0066] In some embodiments, X is CR²⁰. In some embodiments, X is N.

[0067] In another aspect, disclosed herein is a compound of Formula (I')



or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R² is selected from C₁-C₆ alkyl; C₁-C₆ haloalkyl; C₁-C₆ hydroxyalkyl; -(C₁-C₃ alkyl)-SO₂CH₃; -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) optionally substituted with 1 to 13 halogens; -(C₁-C₆ alkyl)-NR^{5a}R^{5b}; phenyl; C₄-C₆ cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C₄-C₆ cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

R²⁰ is selected from H, halogen, nitrile, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from

oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

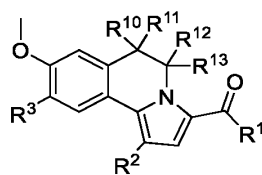
(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected

from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0068] In another aspect, disclosed herein is a compound of Formula (I)



Formula (I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R² is selected from C₁-C₆ alkyl; C₁-C₆ haloalkyl; phenyl; and 5- to 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 or 2 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy;

R³ is selected from -C(O)NHR⁶ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C_1 - C_3 alkyl optionally substituted with one or more independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0069] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4-membered heterocycloalkyl ring optionally containing 1

additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.

[0070] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.

[0071] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 3 R^4 groups, wherein each R^4 group is independently selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

[0072] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are

attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen.

[0073] In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 3 R^4 groups, wherein each R^4 group is independently selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

[0074] In some embodiments, R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1

is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-

C₃ alkyl. In some embodiments, R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; ; and each R^{4a} and R^{4b} is independently selected

from C₁-C₃ alkyl. In some embodiments, R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆

cycloalkyl, hydroxy, and halogen. In some embodiments, R¹ is , wherein R¹ is substituted with 2 to 4 R⁴ groups, wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring and each remaining R⁴ group, if present, is independently selected from halogen, hydroxy, nitrile, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

[0075] In some embodiments, R¹ is , wherein R¹ is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

[0076] In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen,

hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 2 to 4 R^4 groups, wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring and each remaining R^4 group, if present, is independently selected from halogen, hydroxy, nitrile, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen. In some embodiments, R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group

is independently selected from halogen, hydroxy, nitrile, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

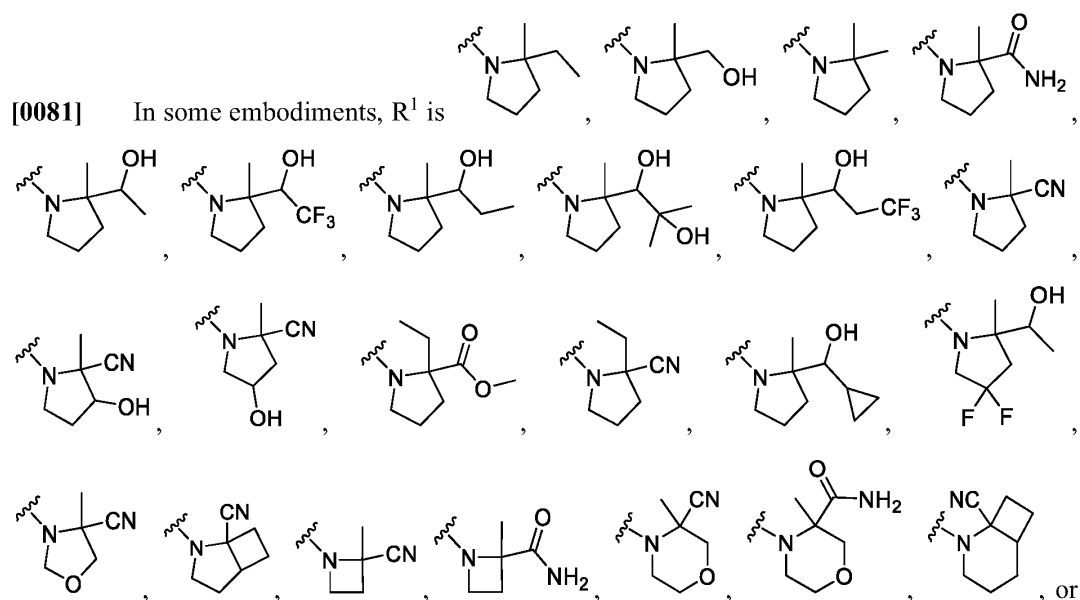
[0077] In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

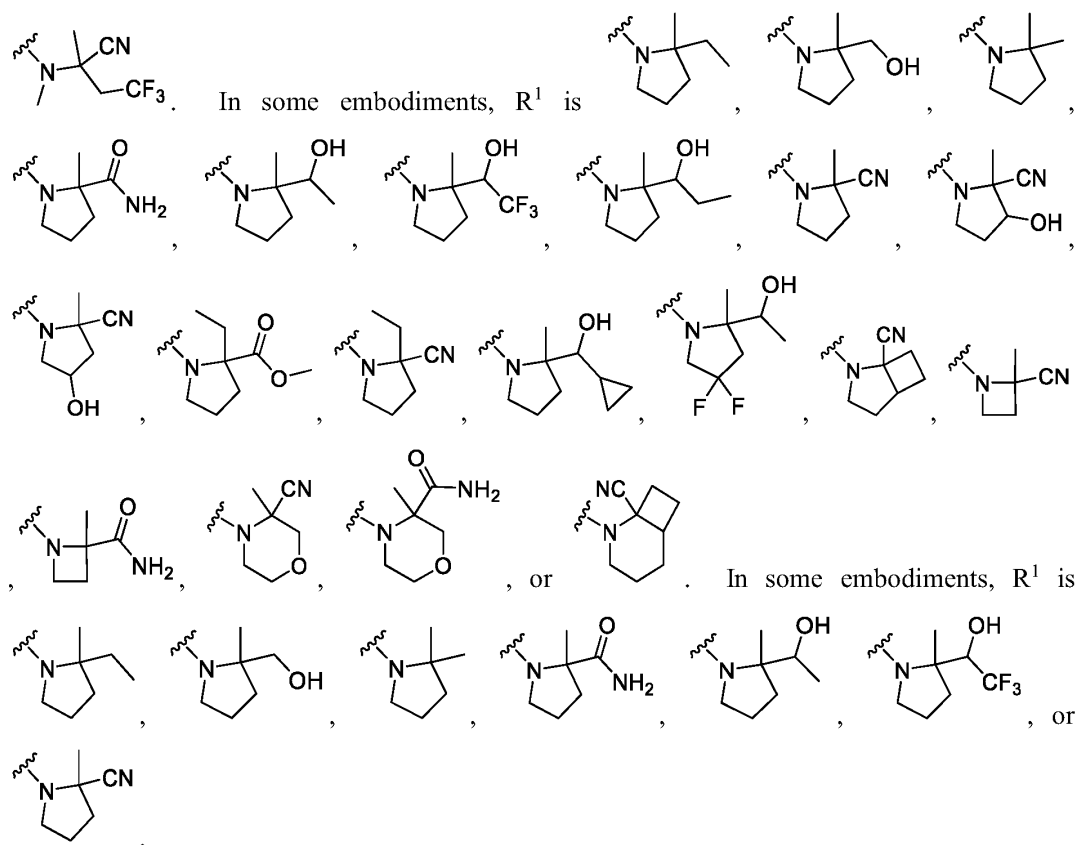
[0078] In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 7-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl. In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 7-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

[0079] In some embodiments, R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen,

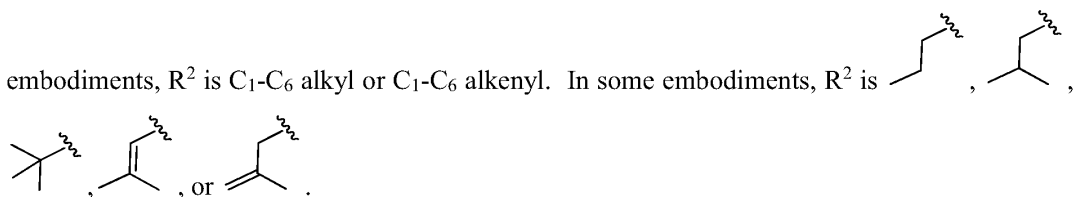
hydroxy, nitrile, $-\text{NR}^{4a}\text{R}^{4b}$, $-\text{SR}^{4a}$, $-\text{S}(\text{O})_2\text{R}^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents (e.g. 1 to 6, or 1 to 5 substituents) independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl. In some embodiments, R^1 is $-\text{NR}^f\text{R}^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-\text{NR}^{4a}\text{R}^{4b}$, $-\text{SR}^{4a}$, $-\text{S}(\text{O})_2\text{R}^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.

[0080] In some embodiments, R^1 is $-\text{NR}^f\text{R}^g$, wherein R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile.





[0082] In some embodiments, R² is C₁-C₆ alkyl. In some embodiments, R² is C₁-C₄ alkyl. In some embodiments, R² is C₁-C₃ alkyl. In some embodiments, R² is C₁-C₆ alkenyl. In some embodiments, R² is C₁-C₆ alkyl or C₁-C₆ alkenyl. In some embodiments, R² is



[0083] In some embodiments, R² is C₁-C₆ haloalkyl. In some embodiments, R² is C₁-C₄ haloalkyl. In some embodiments, R² is C₁-C₃ haloalkyl.

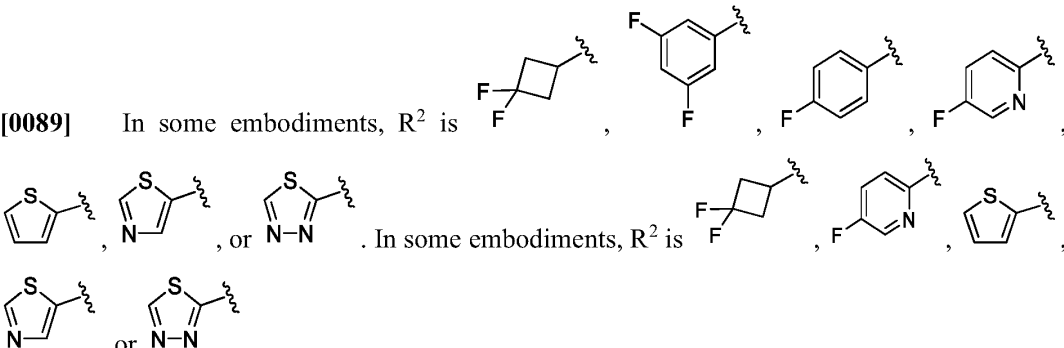
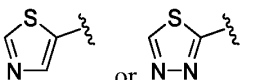
[0084] In some embodiments, R² is C₁-C₆ hydroxyalkyl. In some embodiments, R² is C₁-C₄ hydroxyalkyl. In some embodiments, R² is C₁-C₃ hydroxyalkyl.

[0085] In some embodiments, R^2 is phenyl optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl. In some embodiments, R^2 is phenyl optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy.

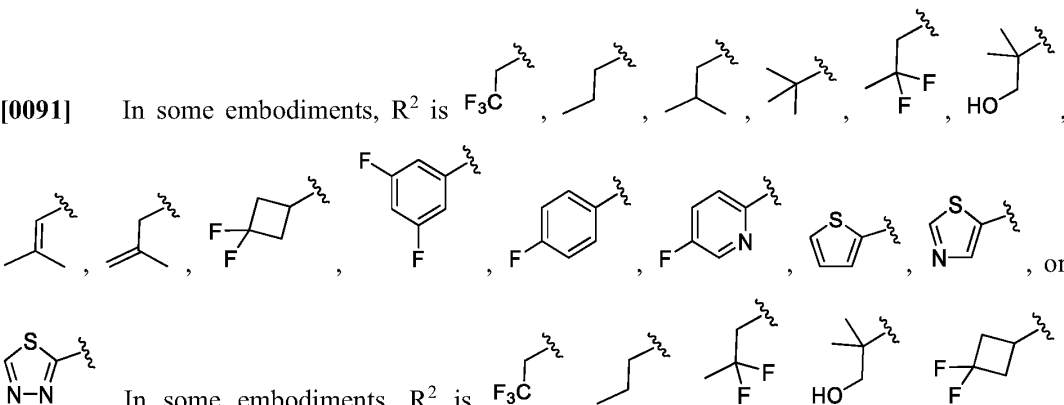
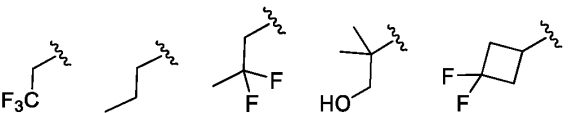
[0086] In some embodiments, R^2 is phenyl optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy. In some embodiments, R^2 is 4-fluorophenyl.

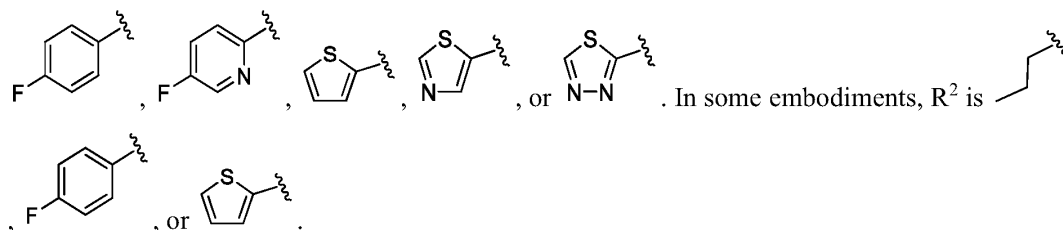
[0087] In some embodiments, R^2 is C_4 - C_6 cycloalkyl optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl. In some embodiments, R^2 is C_4 - C_6 cycloalkyl optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy.

[0088] In some embodiments, R^2 is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl. In some embodiments, R^2 is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy.

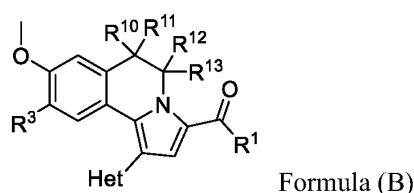
[0089] In some embodiments, R^2 is . In some embodiments, R^2 is .

[0090] In some embodiments, R^2 is a 5- to 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy. In some embodiments, R^2 is a 5-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy. In some embodiments, R^2 is a 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 or 2 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy. In some embodiments, R^2 is 2-thiophene.

[0091] In some embodiments, R^2 is . In some embodiments, R^2 is .



[0092] In another aspect, disclosed herein is a compound of Formula (B)



or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is ---N--- (cyclopentyl ring), wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $\text{---NR}^{4a}\text{R}^{4b}$, ---SR^{4a} , $\text{---S(O)}_2\text{R}^{4a}$, and $\text{C}_1\text{---C}_6$ alkyl optionally substituted with 1 to 4 substituents independently selected from $\text{C}_3\text{---C}_6$ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from $\text{C}_1\text{---C}_3$ alkyl;

Het is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R^5 groups independently selected from halogen, nitrile, $\text{---C(O)NR}^{5a}\text{R}^{5b}$, $\text{C}_1\text{---C}_3$ alkyl, $\text{C}_1\text{---C}_3$ haloalkyl, and $\text{C}_1\text{---C}_3$ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and $\text{C}_1\text{---C}_3$ alkyl;

R^3 is selected from ---C(O)NHR^6 , $\text{---SO}_2\text{---(C}_1\text{---C}_3\text{ alkyl)}$, $\text{---SO}_2\text{---(C}_3\text{---C}_6\text{ cycloalkyl)}$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the

phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

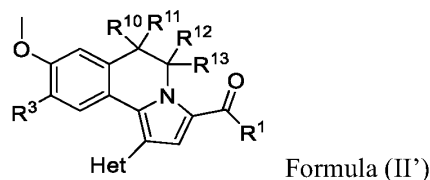
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0093] In another aspect, disclosed herein is a compound of Formula (II')



or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

Het is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

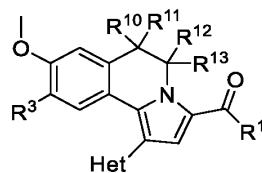
(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0094] In another aspect, disclosed herein is a compound of Formula (II)



Formula (II)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

Het is a 5- to 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 or 2 R⁵ groups independently selected from halogen, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy;

R³ is selected from -C(O)NHR⁶ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

- (ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

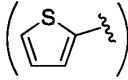
wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[0095] In some embodiments, Het is a 5-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl. In some embodiments, Het is a 5-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy.

[0096] In some embodiments, Het is a 5-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with

1 or 2 R^5 groups independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and

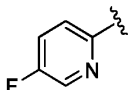
C_1 - C_3 alkoxy. In some embodiments, Het is , , or . In some

embodiments, Het is 2-thiophene () . In some embodiments, Het is . In some

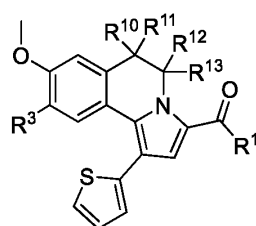
embodiments, Het is . In some embodiments, Het is  or .

[0097] In some embodiments, Het is a 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R^5 groups independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl. In some embodiments, Het is a 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R^5 groups independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy.

[0098] In some embodiments, Het is a 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 or 2 R^5 groups independently selected from halogen, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and

C_1 - C_3 alkoxy. In some embodiments, Het is .

[0099] In another aspect, disclosed herein is a compound of Formula (C)



Formula (C)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and

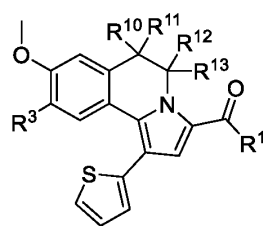
nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00100] In another aspect, disclosed herein is a compound of Formula (IIa')



Formula (IIa')

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

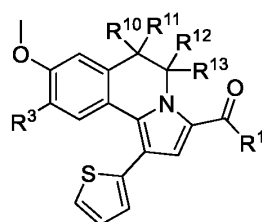
(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the

heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00101] In another aspect, disclosed herein is a compound of Formula (IIa)



Formula (IIa)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R³ is selected from -C(O)NHR⁶ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-

membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

R⁶ is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

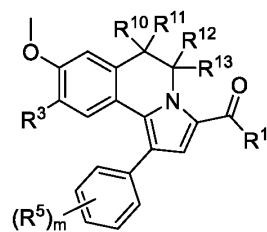
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00102] In another aspect, disclosed herein is a compound of Formula (D)



Formula (D)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

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

each R^5 is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

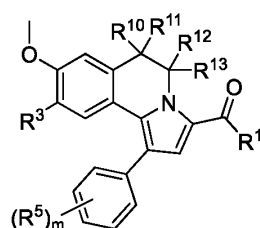
(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are

attached, form a 3- to 6-membered ring, , and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00103] In another aspect, disclosed herein is a compound of Formula (III')



Formula (III')

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

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

each R^5 is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

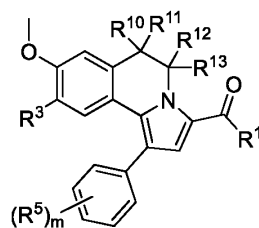
(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are

attached, form a 3- to 6-membered ring, , and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;
 wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00104] In another aspect, disclosed herein is a compound of Formula (III)



Formula (III)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R³ is selected from -C(O)NHR⁶ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

m is 0, 1, or 2;

each R⁵ is independently selected from halogen;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1-C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1-C_3 alkyl;

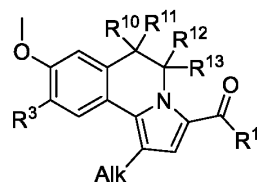
(ii) C_1-C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C_1-C_3 alkyl optionally substituted with one or more independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00105] In another aspect, disclosed herein is a compound of Formula (E)



Formula (E)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

Alk is C₁-C₆ alkyl or C₁-C₆ alkenyl;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or

partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

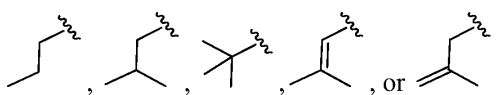
each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

- (ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

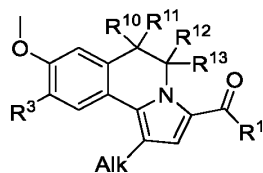
each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00106] In some embodiments, Alk is C_1 - C_6 alkyl. In some embodiments, Alk is C_1 - C_6 alkenyl.

In some embodiments, Alk is  , or .

[00107] In another aspect, disclosed herein is a compound of Formula (IV')



Formula (IV')

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

Alk is C_1 - C_6 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

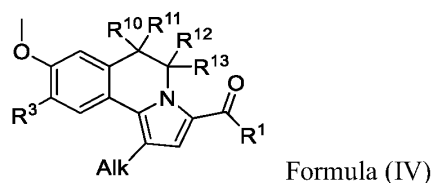
each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

- (ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00108] In another aspect, disclosed herein is a compound of Formula (IV)



or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 3 R^4 groups, wherein each R^4 group is independently selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R^3 is selected from $-C(O)NHR^6$ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C_1 - C_3 alkyl;

Alk is C_1 - C_6 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

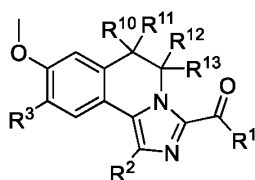
(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, and wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently

selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00109] In another aspect, disclosed herein is a compound of Formula (F)



Formula (F)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl; or
- (i) R^f is C₁-C₆ alkyl; and R^g is C₁-C₆ alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

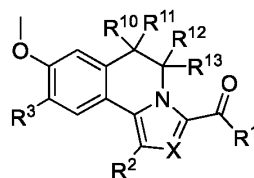
(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00110] In another aspect, disclosed herein is a compound of Formula (A)



Formula (A)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from

oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or

- (ii) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

X is CR^{20} or N;

R^{20} is selected from H, halogen, nitrile, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; and

R^3 is 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heteroaryl ring contains 1 to 4 ring nitrogens, and wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or R^{11} and R^{12} together form a double bond, and R^{10} and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

[00111] As stated above, for each of Formulas (A), (B), (C), (D), (E), and (F), R¹ is or may be

represented as , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

[00112] As stated above, for each of Formulas (I'), (II'), (IIa'), (III') and (IV'), R¹ is or may be

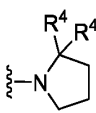
represented as , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

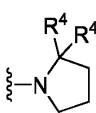
[00113] As stated above, for each of Formulas (I), (II), (IIa), (III) and (IV), R¹ is or may be

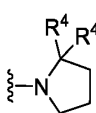
represented as , wherein R¹ is substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

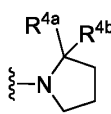
[00114] In some embodiments, R¹ may be a pyrrolidinyl ring (as shown above) that may be substituted with two R⁴ groups. By way of example, the pyrrolidinyl ring may be substituted with at least two R⁴ groups on an atom adjacent the nitrogen atom. For example, the pyrrolidinyl group may comprise two R⁴ groups in a geminal substitution pattern (e.g., each R⁴ group may be appended to the same atom on the pyrrolidinyl ring).

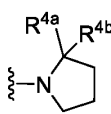
[00115] As such, in some embodiments of any of Formulas (A), (B), (C), (D), (E), and (F), R^1

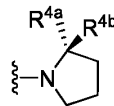
may be represented as , in which two R^4 groups are appended to a carbon atom adjacent the nitrogen atom. In some embodiments of any of Formulas (I'), (II'), (IIa'), (III'), and (IV'), R^1

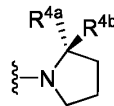
may be represented as , in which two R^4 groups are appended to a carbon atom adjacent the nitrogen atom. In some embodiments of any of Formulas (I), (II), (IIa), (III) and (IV), R^1 may

be represented as , in which two R^4 groups are appended to a carbon atom adjacent the nitrogen atom. At least one of the R^4 groups may be C_1 - C_6 alkyl. At least one of the R^4 groups may be selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen.

[00116] By way of example only, R^1 may be represented as , wherein R^{4a} is C_1 - C_6 alkyl (such as methyl); and R^{4b} is selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen. Representative examples of suitable R^{4b} groups include, but are not limited to, nitrile, methyl, ethyl, CH_2OH , $CH(OH)CH_3$, and $CH(OH)CF_3$.

[00117] By way of example only, R^1 may be represented as , wherein R^{4b} is C_1 - C_6 alkyl (such as methyl); and R^{4a} is selected from nitrile and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen. Representative examples of suitable R^{4a} groups include, but are not limited to, nitrile, methyl, ethyl, CH_2OH , $CH(OH)CH_3$, and $CH(OH)CF_3$.

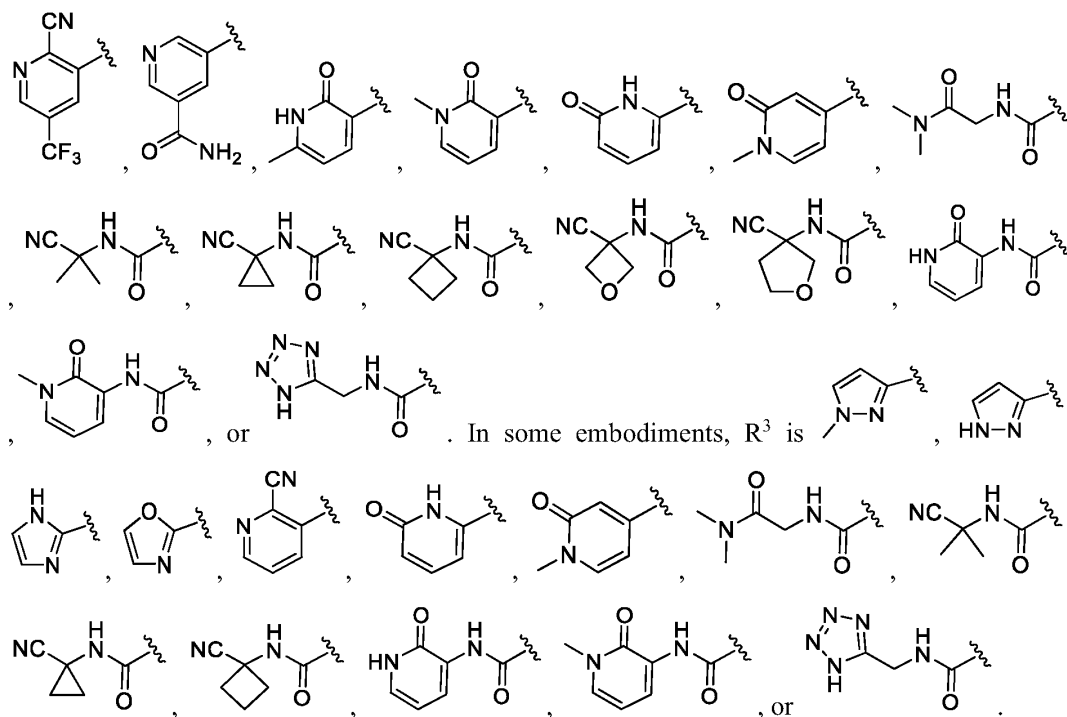


[00118] In some embodiments, R^1 may be represented as , wherein R^{4a} and R^{4b} are as defined above.

[00119] In some embodiments of any one or more of Formulas (A), (B), (C), (D), (E), (F), (I'), (II'), (IIa'), (III'), (IV'), (I), (II), (IIa), (III) and (IV), R^3 is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$. In some embodiments, R^3 is tetrazole, pyrazole, imidazole, oxazole, or pyridine, wherein R^3 may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$.

[00120] In some embodiments of any one or more of Formulas (I), (II), (IIa), (III) and (IV), R^3 is a 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C_1 - C_3 alkyl. In some embodiments, R^3 is pyrazole, imidazole, oxazole, pyridonyl (e.g., 2-pyridonyl), or pyridine, wherein R^3 may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C_1 - C_3 alkyl. Where the heteroaryl ring comprises a ring nitrogen atom, the substituent may be bonded directly to the nitrogen atom. By way of example only, R^3 may be a N-(C_1 - C_3 alkyl) pyridonyl group.

[00121] In some embodiments of any one or more of Formulas (A), (B), (C), (D), (E), (F), (I'), (II'), (IIa'), (III'), (IV'), (I), (II), (IIa), (III) and (IV), R^3 is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring nitrogens, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$. In some embodiments, R^3 is a tetrazolyl, optionally substituted with C_1 - C_3 alkyl, e.g. a methyl-substituted tetrazolyl ring.



[00128] In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy. In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy. In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile. In some embodiments, R⁶ is a 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy. In some embodiments, R⁶ is pyrazolyl, oxazolyl, imidazolyl, pyridinyl, or 2-pyridonyl, each of which may be optionally substituted with 1 to 4

substituents independently selected from halogen, C₁-C₃ alkyl, and C₁-C₃ haloalkyl. Where the heteroaryl ring comprises a ring nitrogen atom, the substituent may be bonded directly to the nitrogen atom.

[00129] In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or tetrazole. By way of example only, R⁶ may be a C₁-C₃ alkyl (such as a C₃ alkyl) optionally substituted with nitrile or tetrazole.

[00130] In some embodiments, R⁶ is phenyl, a 3- to 6-membered saturated or partially unsaturated ring, or a 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with one or more independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens. In some embodiments, R⁶ is phenyl, a 3- to 6-membered saturated or partially unsaturated ring, or a 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens. In some embodiments, R⁶ is phenyl optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens. In some embodiments, R⁶ is a 3- to 6-membered saturated or partially unsaturated ring optionally containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently

selected halogens. In some embodiments, R⁶ is cyclopropane optionally substituted with nitrile or is cyclobutane optionally substituted with nitrile. In some embodiments, R⁶ is a 5- to 6-membered heteroaryl ring, wherein the ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens. Representative examples include but are not limited to, pyridonyl (e.g., 2-pyridonyl) which may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens. In some examples, R⁶ may be 2-pyridonyl optionally substituted with a C₁-C₃ alkyl (e.g., methyl), further optionally wherein the 2-pyridonyl is substituted at the nitrogen atom with a C₁-C₃ alkyl (e.g., methyl)

[00131] In some embodiments of any one or more of Formulas (A), (B), (C), (D), (E), and (F), each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, each of R¹⁰, R¹¹, R¹², and R¹³ is hydrogen. In some embodiments, two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a cyclopropyl ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

[00132] In some embodiments of any one or more of Formulas (I'), (II'), (IIa'), (III') and (IV'), each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, each of R¹⁰, R¹¹, R¹², and R¹³ is hydrogen. In some embodiments, two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a cyclopropyl ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

[00133] In some embodiments of any one or more of Formulas (I), (II), (IIa), (III) and (IV), each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments, each of R¹⁰, R¹¹, R¹², and R¹³ is hydrogen. In some embodiments, two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

[00134] In some embodiments of Formula (A), R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl. In some embodiments of Formula (I'), R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

[00135] The presently disclosed compounds were and can be synthesized using the general synthetic procedures set forth in reaction schemes below. The carrying out of each individual illustrated step is within the skill of an ordinary artisan guided by this disclosure, who also knows how to modify the synthetic procedures of the below schemes to synthesize the full scope of the compounds disclosed herein. The synthetic procedure for individual compounds is provided in the Examples section, below.

[00136] In another aspect, disclosed herein is a compound selected from Table 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[00137] Table 1

Compd No.	Name
4-1	[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone
4-2	(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>S</i>)-2-methyl-2-((<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone

4-3	(<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
6-1	(3 <i>S</i>)-4-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-methyl-morpholine-3-carbonitrile
6-2	(2 <i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
6-3	(<i>R</i>)-1-(1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
6-4	(<i>R</i>)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
6-5	(<i>R</i>)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
6-6	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
6-7	(<i>R</i>)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
6-8	(<i>R</i>)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
7-1	(2 <i>R</i>)-1-[8-methoxy-9-oxazol-2-yl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-2	4-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-6-methyl-1 <i>H</i> -pyridin-2-one
7-3	(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-oxazol-2-yl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
7-4	3-[3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile
7-5	3-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile

7-6	[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
7-7	(2 <i>R</i>)-1-[9-(1 <i>H</i> -imidazol-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-8	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-9	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-10	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
7-11	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-12	[(5 <i>R</i>)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
7-13	[(5 <i>R</i>)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
7-14	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
7-15	(<i>R</i>)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl)-5-(trifluoromethyl)picolinonitrile
7-16	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2 <i>H</i> -tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
7-17	(8-methoxy-9-(2-methyl-2 <i>H</i> -tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>S</i>)-2-methyl-2-((<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
7-18	(<i>R</i>)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2 <i>H</i> -tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile

7-19	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
7-20	(<i>R</i>)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
7-21	(<i>R</i>)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
7-22	((<i>R</i>)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
7-23	5-((<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl)nicotinamide
7-24	3-((<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl)picolinonitrile
7-25	((<i>R</i>)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
7-26	((1 <i>aR</i> ,9 <i>bR</i>)-8-methoxy-7-(2-methyl-2H-tetrazol-5-yl)-5-(thiophen-2-yl)-1 <i>a</i> ,9 <i>b</i> -dihydro-1 <i>H</i> -cyclopropa[<i>c</i>]pyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
7-27	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)methanone
7-28	[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl)methanone
8-1	(2 <i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
8-2	(2 <i>R</i>)-1-[8-methoxy-9-(1 <i>H</i> -pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile

8-3	(2 <i>R</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
8-4	(2 <i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
8-5	4-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-1-methyl-pyridin-2-one
8-6	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1 <i>H</i> -pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
8-7	6-[8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-1 <i>H</i> -pyridin-2-one
8-8	4-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-1-methyl-pyridin-2-one
8-9	3-[3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile
8-10	[(5 <i>R</i>)-8-methoxy-5-methyl-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
8-11	(<i>R</i>)-1-(8-methoxy-9-(1-methyl-1 <i>H</i> -pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
8-12	(<i>R</i>)-1-((<i>S</i> *)-8-methoxy-6-methyl-9-(1-methyl-1 <i>H</i> -pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
8-13	((<i>R</i>)-8-methoxy-5-methyl-9-(1-methyl-1 <i>H</i> -pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
8-14	((<i>R</i>)-2-((<i>R</i>)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)((<i>S</i>)-8-methoxy-5-methyl-9-(1-methyl-1 <i>H</i> -pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)methanone
8-15	((1 <i>aR</i> ,9 <i>bR</i>)-8-methoxy-7-(1-methyl-1 <i>H</i> -pyrazol-3-yl)-5-(thiophen-2-yl)-1 <i>a</i> ,9 <i>b</i> -dihydro-1 <i>H</i> -cyclopropa[<i>c</i>]pyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone

8-16	(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
9-1	[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[9-(1H-imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]methanone
9-2	(2R)-1-[9-(1H-imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
10-1	<i>N</i> -(1-cyanocyclobutyl)-3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-2	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-3	3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy- <i>N</i> -(2-oxo-1H-pyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-4	3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-5	3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(2-oxo-1H-pyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-6	3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-7	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-8	<i>N</i> -(1-cyanocyclobutyl)-3-[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-9	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2R)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-10	<i>N</i> -[2-(dimethylamino)-2-oxo-ethyl]-3-[(2R)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-11	3-(2,2-dimethylpyrrolidine-1-carbonyl)-8-methoxy- <i>N</i> -(1H-tetrazol-5-ylmethyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide

10-12	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-13	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(2-oxo-1 <i>H</i> -pyridin-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-14	<i>N</i> -(1-cyano-1-methyl-ethyl)-8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-15	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-16	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-17	<i>N</i> -(1-cyanocyclobutyl)-1-(4-fluorophenyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-18	<i>N</i> -(1-cyano-1-methyl-ethyl)-1-(4-fluorophenyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-19	<i>N</i> -(1-cyanocyclopropyl)-8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-20	<i>N</i> -(1-cyanocyclopropyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-21	8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-22	<i>N</i> -(1-cyanocyclobutyl)-8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-23	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-24	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide

10-25	<i>N</i> -(3-cyanooxetan-3-yl)-8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-26	<i>N</i> -(3-cyanooxetan-3-yl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-27	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-28	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>R</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-29	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>S</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-30	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -(3-cyanooxetan-3-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-31	<i>N</i> -(1-cyanocyclopropyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-32	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-33	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -(3-cyanooxetan-3-yl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-34	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -(3-cyanooxetan-3-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-35	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-36	(<i>R</i>)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy- <i>N</i> -(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
10-37	(<i>R</i>)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy- <i>N</i> -(2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide

10-38	N-(1-cyanocyclobutyl)-8-methoxy-3-((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxy ethyl)pyrrolidine-1-carbonyl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-39	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-40	(S*)-N-(1-cyanocyclobutyl)-3-((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-41	(S*)-3-((R)-2-cyano-2-methylpyrrolidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-42	(R)-N-(1-cyanocyclobutyl)-3-((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-43	(R)-N-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-44	(S)-N-(1-cyanocyclobutyl)-3-((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-45	(4S)-N-(1-cyanocyclobutyl)-7-methoxy-4-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-3a,5-dihydro-4H-cyclopenta[a]naphthalene-8-carboxamide
10-46	(S)-3-((R)-2-cyano-2-methylpyrrolidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-47	(R)-N-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
10-48	(1aR,9bR)-N-(1-cyanocyclobutyl)-8-methoxy-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-5-(thiophen-2-yl)-1a,9b-dihydro-1H-cyclopropa[c]pyrrolo[2,1-a]isoquinoline-7-carboxamide

11-1	<i>N</i> -[2-(dimethylamino)-2-oxo-ethyl]-3-[(2 <i>S</i>)-2-ethyl-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
13-1	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
13-2	[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
13-3	[(2 <i>R</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
13-4	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
13-5	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone
13-6	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone
13-7	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone
13-8	[(2 <i>S</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone
13-9	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone
13-10	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-[(1 <i>S</i> *)-1-hydroxypropyl]-2-methyl-pyrrolidin-1-yl]methanone
13-11	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone
13-12	(<i>R</i> *)-2-(<i>R</i> *)-cyclopropyl(hydroxy)methyl)-2-methylpyrrolidin-1-yl)(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone

18-1	(<i>R</i>)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)- <i>N</i> -(2-cyanopropan-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-2	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-3	3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-4	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-5	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(2-oxo-1 <i>H</i> -pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-6	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>R</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
18-7	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>S</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
20-1	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i> or <i>S</i>)-4,4-difluoro-2-methyl-2-[(1 <i>R</i> or <i>S</i>)-1-hydroxyethyl]pyrrolidin-1-yl]methanone
24-1	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
24-2	<i>N</i> -(1-cyanocyclobutyl)-8-methoxy-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide
25-1	(2 <i>R</i> *)-2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]pyrrolidine-2-carbonitrile
26-1	<i>rel</i> -(2 <i>R</i> ,3 <i>S</i>)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
26-2	<i>rel</i> -(2 <i>R</i> ,3 <i>S</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile

32-1	(1 <i>S</i> *,6 <i>R</i> *)-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-azabicyclo[4.2.0]octane-1-carbonitrile
32-2	(1 <i>S</i> ,5 <i>S</i>)-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-5-methyl-2-azabicyclo[3.2.0]heptane-1-carbonitrile
33-1	(2 <i>R</i> ,4 <i>S</i>)-4-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile
34-1	(2 <i>R</i> ,4 <i>S</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-4-hydroxy-2-methyl-pyrrolidine-2-carbonitrile

[00138] In another aspect, disclosed herein is a compound selected from Table 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[00139] Table 2

Example	Name
1	(2R,4S)-4-hydroxy-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
2	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
3	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
4	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
5	(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide
6	(2R,4S)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile

7	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
8	(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
9	(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl) methanone
10	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
11	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
12	(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide

13	(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide
14	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
15	((S)-2-((R)-1,2-dihydroxy-2-methylpropyl)-2-methylpyrrolidin-1-yl)(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)methanone
16	(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
17	(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
18	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide

19	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
20	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
21	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
22	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
23	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
24	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone

25	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
26	(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
27	(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
28	(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide
29	(1-(3,5-difluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
30	{(S)-2-[(S)-3,3,3-trifluoro-1-hydroxypropyl]-2-methyl-1-pyrrolidinyl} {11-methoxy-12-(2-methyl-2H-tetraazol-5-yl)-3-(2-thienyl)-6-azatricyclo[7.4.0.0 ^{2,6}]trideca-1(13),2,4,9,11-pentaen-5-yl}methanone

31	(R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
32	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
33	(S)-3-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile
34	(S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile
35	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
36	(R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile

37	(R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
38	(S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile
39	(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
40	(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
41	(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
42	(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
43	(R)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile

44	(R)-3-(3-(2-cyano-2-methylazetidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile
45	(R)-1-(9-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
46	(R)-8-methoxy-5-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide
47	3-((R)-3-((2R,4S)-2-cyano-4-hydroxy-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-9-yl)picolinonitrile
48	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
49	(2R,4S)-4-hydroxy-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile

50	(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide
51	(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(2,2-difluoropropyl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide
52	(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide
53	(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(5-fluoropyridin-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-1,2,3-triazol-4-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide
54	((R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
55	(1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone

56	(R)-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
57	(R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile
58	(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
59	(1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone
60	(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone
61	(2R,4S)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile

62	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylallyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile
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ACTIVITY OF THE COMPOUNDS

[00140] As noted above, the compounds disclosed herein have activity as FSHR modulators. This activity may be assessed by any suitable FSHR interaction assay, such as a cAMP accumulation assay as illustrated in the examples, and the other assays outlined below and illustrated in the examples. The compounds disclosed herein may show EC₅₀ values of less than 1000 nM, less than or equal to 500 nM, less than or equal to 100 nM, less than or equal to 10 nM, or less than or equal to 1 nM, wherein the EC₅₀ is the effective concentration of a compound at which 50% of the maximum response of that that would be obtained with FSH is observed.

[00141] Glycoprotein hormone receptors, FSHR, TSHR and LHR/LHCGR predominantly activate G_{αs} class of intracellular G proteins, resulting in cAMP accumulation. The Homogeneous Time Resolved Fluorescence (HTRF) assay illustrated in the examples is based on competition between native cAMP produced by cells and cAMP labeled with the dye d2 (red acceptor) for binding to a cryptate labeled antibody (Europium donor). The specific energy transfer signal is inversely proportional to the concentration of cAMP in the standard or sample. *See, e.g.,* Nataraja, S.G., et al., *Frontiers in Endocrinology*. 2015, 6:142.

[00142] Another assay uses the immortalized rat steroidogenic granulosa cell line, GFSHR-17, which stably expresses the FSH Receptor and is responsive to FSH stimulation with human FSH. *See, e.g.,* Keren-Tal, I., et al., *Molecular and Cellular Endocrinology*, 1993, 95:R1-R10. This engineered cell line lacks the aromatase found in primary granulosa cells required for conversion of androgen precursors to estrogens. However it shows a robust progesterone response which can serve as a surrogate to verify the activity of FSHR agonists. It can be used in a cell-based assay to evaluate the ability of compounds to activate FSHR in GFSHR-17 cells by measuring progesterone released into the supernatant, such as by using a progesterone HTRF kit from Cisbio. A ratiometric

HTRF read-out has been established to assess agonist activity of compounds and is described in the examples below.

[00143] The activity of the compounds described herein as agonists of the FSHR can be investigated using a modification of the classic FSH bioassay (Steelman-Pohley) which is based on the increase in ovarian weight in immature female rats. *See* Steelman, S.L. and F.M. Pohley, *Endocrinology*, 1953, 53(6):604-16. It is well-documented that activation of the FSHR in females stimulates granulosa cells of the ovarian follicles to proliferate and induce the expression of aromatase and luteinizing hormone receptor. *See, e.g.*, Donadeu, F.X. and M. Ascoli, *Endocrinology*, 2005, 146(9):3907-16. Proper granulosa cell expansion and gene expression is essential to induce steroid synthesis and secretion to allow the follicle to respond to the preovulatory luteinizing hormone surge, which triggers ovulation of the oocytes contained within follicles into the oviduct where they can be fertilized. Therefore, it is reasonable to measure ovarian weight gain as a function of granulosa cell expansion, the number of ovulated oocytes as a function of follicle maturation, and uterine weight as a function of estradiol synthesis and secretion.

[00144] In some embodiments, a compound as disclosed herein selectively activates FSHR as compared to, for example, TSHR. This selective activity may be assessed by any suitable FSHR/TSHR assay comparing the potency in cAMP accumulation specific to the individual receptors, such as an assay illustrated in the examples (assessing selectivity based on EC₅₀ ratios).

[00145] In some embodiments, a compound as disclosed herein selectively activates FSHR as compared to, for example, luteinizing hormone receptor. This selective activity may be assessed by any suitable FSHR/LHR assay comparing the potency in cAMP accumulation specific to the individual receptors, such as an assay illustrated in the examples (assessing selectivity based on EC₅₀ ratios).

[00146] In some embodiments, a compound as disclosed herein exhibits at least 5-fold greater selectivity for FSHR than for TSHR. This includes at least 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 26-, 27-, 28-, 29-, 30-, 31-, 32-, 33-, 34-, 35-, 36-, 37-, 38-, 39-, 40-, 41-, 42-, 43-, 44-, 45-, 46-, 47-, 48-, 49-, or 50-fold, or more, greater selectivity for follicle-stimulating hormone receptor than for thyroid-stimulating hormone

receptor. A compound as disclosed herein may exhibit about 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 26-, 27-, 28-, 29-, 30-, 31-, 32-, 33-, 34-, 35-, 36-, 37-, 38-, 39-, 40-, 41-, 42-, 43-, 44-, 45-, 46-, 47-, 48-, 49-, or 50-fold greater selectivity for follicle-stimulating hormone receptor than for thyroid-stimulating hormone receptor.

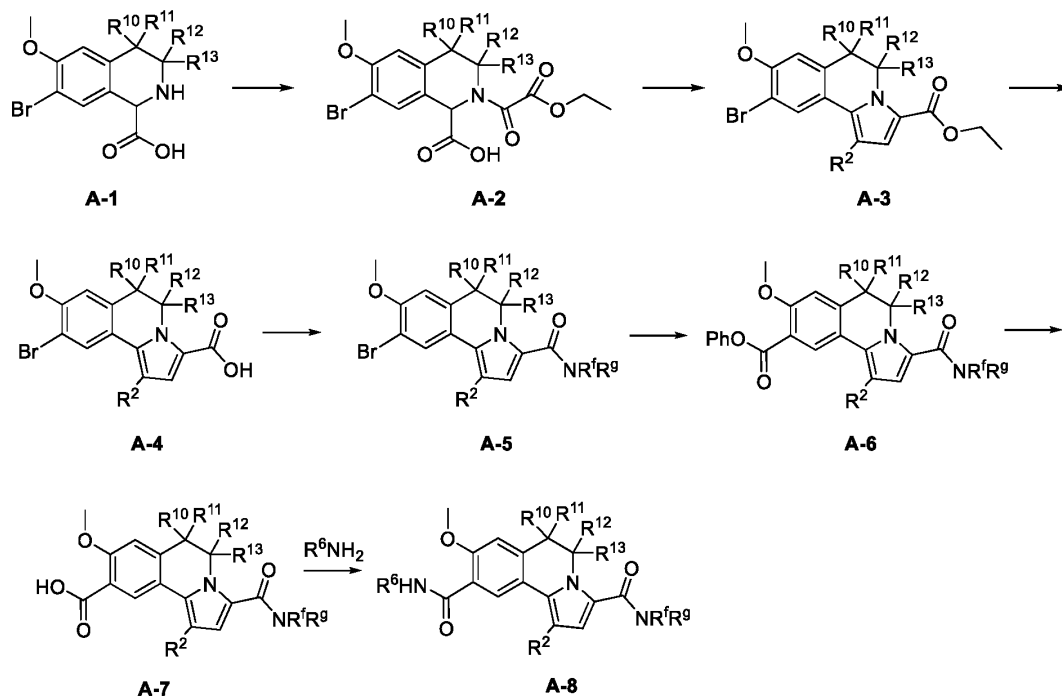
[00147] In some embodiments, a compound as disclosed herein exhibits at least 5-fold greater selectivity for FSHR than for luteinizing hormone receptor. This includes at least 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 26-, 27-, 28-, 29-, 30-, 31-, 32-, 33-, 34-, 35-, 36-, 37-, 38-, 39-, 40-, 41-, 42-, 43-, 44-, 45-, 46-, 47-, 48-, 49-, or 50-fold, or more, greater selectivity for follicle-stimulating hormone receptor than for luteinizing hormone receptor. A compound as disclosed herein may exhibit about 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 26-, 27-, 28-, 29-, 30-, 31-, 32-, 33-, 34-, 35-, 36-, 37-, 38-, 39-, 40-, 41-, 42-, 43-, 44-, 45-, 46-, 47-, 48-, 49-, or 50-fold greater selectivity for follicle-stimulating hormone receptor than for luteinizing hormone receptor.

SYNTHESIS OF THE COMPOUNDS

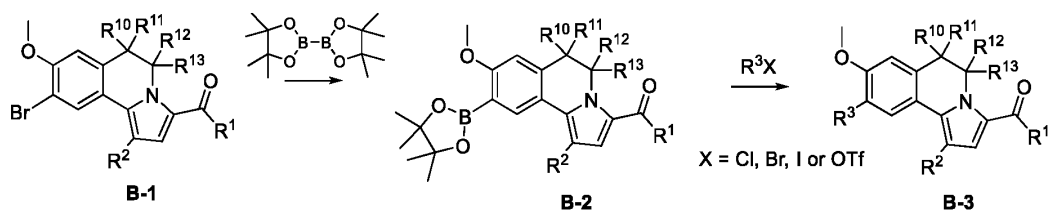
[00148] In another aspect there is provided a method of manufacture of any one of the compounds disclosed herein. The presently disclosed compounds were and can be synthesized using the general synthetic procedures set forth in Schemes A-D below. The carrying out of each individual illustrated step is within the skill of an ordinary artisan guided by this disclosure, who also knows how to modify the synthetic procedures of the below schemes to synthesize the full scope of the compounds disclosed herein. Definitions for R^1 , R^2 , R^3 , R^6 , R^{10} , R^{11} , R^{12} , R^{13} , R^f , and

R^g are as provided in the formulas described herein. The synthetic procedure for individual compounds is disclosed in the Examples section below.

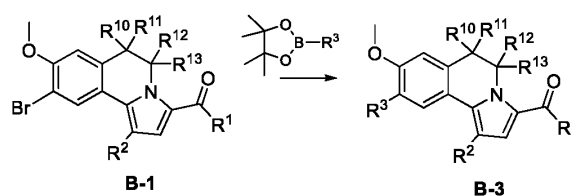
[00149] Scheme A



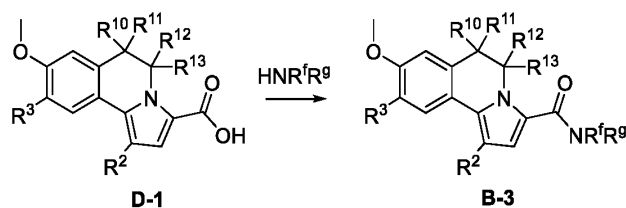
[00150] As shown in Scheme A, compound A-1 (which may be synthesized as described in Method 1 below) was converted to oxalyl amide A-2. Cyclization of intermediate compound A-2 provided intermediate compound A-3. Subsequent saponification to intermediate compound A-4 followed by coupling with amine HNR^fR^g resulted in intermediate compound A-5. Metal-mediated coupling of intermediate compound A-5 led to intermediate compound A-6, which after ester hydrolysis provided intermediate compound A-7. Coupling of compound A-7 with amine H_2NR^6 afforded compound A-8 (compounds as disclosed herein).

[00151] Scheme B

[00152] Scheme B illustrates metal-mediated conversion of compound B-1 to a boronate ester which is then reacted with R^3X ($X = Cl, Br, I$, or OTf) to compound B-3 (a compound as disclosed herein) through another metal-mediated conversion.

[00153] Scheme C

[00154] Scheme C illustrates metal-mediated conversion of compound B-1 with an R^3 -boronate ester to compound B-3 (a compound as disclosed herein).

[00155] Scheme D

[00156] Scheme D illustrates amide coupling of compound D-1 with amine HNR^fR^g to arrive at compound B-3 (a compound as disclosed herein).

PHARMACEUTICAL COMPOSITIONS

[00157] In another aspect, disclosed herein are pharmaceutical compositions comprising, consisting essentially of, or consisting of a compound as described herein, and one or more pharmaceutically acceptable excipients.

[00158] In another aspect, disclosed herein are pharmaceutical compositions comprising, consisting essentially of, or consisting of a compound of Formulas (I), (II), (IIa), (III), or (IV) as described herein, and one or more pharmaceutically acceptable excipients.

[00159] The compounds may be formulated for administration by any suitable route of administration, such as for example, oral, topical (including transdermal), rectal, vaginal, transmucosal, or intestinal administration; parenteral delivery, including by intramuscular, subcutaneous, or intravenous injection, as well as inhalation, intrathecal, direct intraperitoneal, or intranasal delivery.

[00160] Pharmaceutical compositions as disclosed herein may comprise, as one or more pharmaceutically acceptable excipients, a pharmaceutically acceptable carrier, diluent, disintegrant, sweetening agent, glidant (such as magnesium stearate), flavoring agent, emulsifying agent, suspending agent, stabilizer, isotonic agent, etc. Pharmaceutical compositions as disclosed herein may be formulated into an oral dosage form such as tablets, capsules, powders, granules, suspensions, emulsions, or syrups; or a topical (including transdermal) or transmucosal dosage form such as liquids, suspensions, emulsions, gels (ointments or the like), or a parenteral dosage form such as liquids, suspensions, emulsions, and freeze-dried powders. Said dosage forms may be formulated in various forms, e.g., a dosage form for single administration or for multiple administrations.

[00161] Exemplary excipients include, without limitation, lactose, polyethylene glycol (PEG), hydrogenated castor oil (HCO), cremophors, carbohydrates, starches (e.g., corn starch), inorganic salts, antimicrobial agents, antioxidants, binders/fillers, surfactants, lubricants (e.g., calcium or

magnesium stearate), glidants such as talc, disintegrants, diluents, buffers, acids, bases, film coats, combinations thereof, and the like.

[00162] The amount of any individual excipient in the composition will vary depending on the role of the excipient, the dosage requirements of the active agent, and particular needs of the composition. Generally, however, the excipient will be present in the composition in an amount of from about 1% to about 99% by weight, such as from about 5% to about 98% by weight, including from about 15 to about 95% by weight of the composition. In general, the amount of excipient present in a composition of the disclosure is selected from the following: about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% by weight.

[00163] A pharmaceutical composition as disclosed herein may include a compound disclosed herein as the only active agent, or may be formulated with other active agents.

[00164] Techniques for formulation and administration of the compounds disclosed herein may be found in “Remington: The Science and Practice of Pharmacy,” Academic Press, London, United Kingdom, 23rd edition, 2020.

[00165] Pharmaceutical compositions as disclosed herein may be formulated to provide a therapeutically effective amount of a compound as disclosed herein in a reasonable volume or mass of the composition, which may be administered by any effective dosing schedule, such as once a day. Although the exact dosage may be determined on a drug-by-drug (compound-by-compound) basis, for most compounds, some generalizations regarding the dosage can be made. For example, the daily dosage regimen for an adult human patient may be between 0.001 mg and 1000 mg, such as between 0.01 mg and 500 mg, for example from 1 to 200 mg of the compound or pharmaceutically acceptable salt thereof, calculated as the free base or free acid.

METHODS OF TREATMENT

[00166] In another aspect, disclosed herein are methods of modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, comprising, consisting essentially of, or consisting of administering to a subject in need thereof a compound as disclosed herein or a pharmaceutical

composition as disclosed herein. In an alternative aspect, disclosed herein are methods of modulating follicle-stimulating hormone receptor activity in a biological sample, comprising contacting the biological sample with a compound or pharmaceutical composition as disclosed herein.

[00167] In another aspect, disclosed herein are methods of treating a disease or disorder in a subject in need thereof, comprising, consisting essentially of, or consisting of administering to the subject a therapeutically effective amount of a compound as disclosed herein or a pharmaceutical composition as disclosed herein. The disease or disorder may be any for which modulation of FSHR activity is desired, such as one or more of hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency.

[00168] In another aspect, disclosed herein are methods for treating a fertility disorder in a male or female subject in need thereof, comprising, consisting essentially of, or consisting of administering to the subject a therapeutically effective amount of a compound as disclosed herein or a pharmaceutical composition as disclosed herein. Such a method may be for stimulating follicular development, ovulation induction, controlled ovarian hyperstimulation, controlled ovarian stimulation, assisted reproductive technology (ART) (including *in vitro* fertilization), treating male hypogonadism, or treating male infertility, including failure of spermatogenesis.

[00169] In another aspect, disclosed herein are compounds for use in modulating follicle-stimulating hormone receptor (FSHR) activity in a subject.

[00170] In another aspect, disclosed herein are compounds for use in treating a disease or disorder in a subject in need thereof. The disease or disorder may be any for which modulation of

FSHR activity is desired, such as one or more of hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency.

[00171] In another aspect, disclosed herein are compounds for use in treating a fertility disorder in a female or male subject in need thereof, such as for stimulating follicular development, ovulation induction, controlled ovarian hyperstimulation, controlled ovarian stimulation, assisted reproductive technology (ART) (including *in vitro* fertilization), treating male hypogonadism, or treating male infertility, including failure of spermatogenesis.

[00172] In other aspects, disclosed herein are uses of the compounds disclosed herein in the preparation of medicaments for modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, for treating a disease or disorder in a subject in need thereof, such as any one or more listed above, or for treating a fertility disorder in a female or male subject in need thereof, such as for stimulating follicular development, ovulation induction, controlled ovarian hyperstimulation, controlled ovarian stimulation, assisted reproductive technology (ART) (including *in vitro* fertilization), treating male hypogonadism, or treating male infertility, including failure of spermatogenesis.

[00173] In accordance with any of these methods or uses, the compound or composition may be administered by any suitable route of administration as discussed above, and may be administered in a therapeutically effective amount as discussed above. As also discussed above, the administration may be by any effective dosing schedule, such as once a day, 1 to 4 times per day, once a week, 1 to 4 times per week, once a month, 1 to 4 times month, etc. Although the exact dosage may be determined on a drug-by-drug (compound-by-compound) basis, the daily dosage

regimen for an adult human patient may be, for example, between 0.001 mg and 1000 mg, such as between 0.01 mg and 500 mg, for example 1 to 200 mg of the compound or pharmaceutically acceptable salt thereof, calculated as the free base or free acid.

[00174] The present technology, thus generally described, may be further understood by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present technology.

EXAMPLES

[00175] **Analytical LCMS conditions were as follows:**

[00176] **Analytical Method 1 (M1):**

[00177] Analytical HPLC-MS were performed on a Shimadzu LCMS system using a Kinetex Core shell C18 column (2.1 mm x 50 mm, 5 µm; temperature: 40 °C) and a gradient of 5-100% B (A = 0.1% formic acid in water; B = 0.1% formic acid in acetonitrile) over 1.2 min, then 100% B for 0.1 min. A second gradient of 100-5% B was then applied over 0.01 min and held for 0.39 min with an injection volume of 3 µL at a flow rate of 1.2 mL/min. UV spectra were recorded at 215 nm using a SPD-M20A PDA detector spectrum range: 200-400 nm. Mass spectra were obtained using a 2010EV detector. Data were integrated and reported using Shimadzu LCMS-Solutions and PsiPort software.

[00178] **Analytical Method 2 (M2)**

[00179] Analytical uHPLC-MS were performed on a Waters ACQUITY uPLC system using a Waters uPLC® BEH™ C18 column (2.1 mm x 50 mm, 1.7 µm; temperature 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 1.1 min, then 100% B for 0.25 min. A second gradient of 100-5% B was then applied over 0.05 min and held for 0.1 min with an injection volume of 1 µL at a flow rate of 0.9 mL/min. UV spectra were recorded at 215 nm on a Waters ACQUITY PDA with a spectrum range of 200-400 nm. Mass spectra were obtained using a Waters SQD (MSQ1) or Waters ACQUITY QDA (MSQ2, MSQ4). Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00180] Analytical Method 3 (M3):

[00181] Analytical uHPLC-MS were performed on a Waters ACQUITY uPLC system using Waters uPLC® BEH™ C18 column (2.1 mm x 30 mm, 1.7 µm; temperature 40 °C) and a gradient of 5-100% B (A = 2 mM ammonium bicarbonate, buffered to pH 10, B: acetonitrile) over 0.75 min, then 100% B for 0.1 min. A second gradient of 100-5% B was then applied over 0.05 min and held for 0.1 min with an injection volume of 1 µL at a flow rate of 1 mL/min. UV spectra were recorded 215 nm Waters ACQUITY PDA spectrum range of 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00182] Analytical Method 4 (M4):

[00183] Analytical uHPLC-MS were performed on a Waters ACQUITY uPLC system using a Phenomenex Kinetex-XB C18 column (2.1 mm x 100 mm, 1.7 µm; temperature: 40 °C) and a gradient of 5-100% B (A = 0.1% formic acid in water; B = 0.1% formic acid in acetonitrile) over 5.3 min, then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 µL at flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters ACQUITY PDA detector spectrum range: 200-400 nm, ELS data was collected using a Waters ACQUITY ELS detector (where fitted). Mass spectra were obtained using a Waters SQD (MSQ1) or Waters ACQUITY QDA (MSQ2, MSQ4). Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00184] Analytical Method 5 (M5):

[00185] Analytical uPLC-MS were performed on a Waters ACQUITY uPLC system using a Waters uPLC® BEH™ C18 column (2.1 mm x 100 mm, 1.7 µm column; temperature: 40°C) and a gradient of 5-100% B (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = acetonitrile) over 5.3 min, then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 µL and at flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters ACQUITY PDA detector Spectrum range: 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE mass detector

(MS16) or a Waters SQD2 (MSQ5). Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00186] Analytical Method 6 (M6):

[00187] Analytical uPLC-MS were performed on a Waters ACQUITY uPLC system using a Phenomenex Kinetex Core-Shell C8 column (50 x 2.1mm, 5µm column; temperature: 40°C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 1.83 min, then 100% B for 0.42 min. A second gradient of 100-5% B was then applied over 0.42 min and held for 0.54 min with an injection volume of 3 µL and at flow rate of 1.2 mL/min. UV spectra were recorded at 215 nm using a SPD-M20A PDA detector spectrum range: 200-400 nm. Mass spectra were obtained using a 2010EV detector. Data were integrated and reported using Shimadzu LCMS-Solutions and PsiPort software.

[00188] Analytical Method 7 (M7):

[00189] Analytical HPLC-MS were performed on a Waters LCMS systems using a Waters uPLC CORTEX C8 column (2.1 mm x 100 mm, 1.6 µm; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 5.3 min, then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1µL at a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters ACQUITY PDA detector spectrum range: 200-400 nm, ELS data was collected using a Waters ACQUITY ELS detector (where fitted). Mass spectra were obtained using a Waters SQD or Waters ACQUITY QDa. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00190] Analytical Method 8 (M8):

[00191] Analytical HPLC-MS were performed on a Waters LCMS systems using a Waters uPLC CORTEX C8 column (2.1 mm x 50 mm, 1.6 µm; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.01% formic acid in acetonitrile) over 1.1 min, then 100% B for 0.3 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 0.28 min with an injection volume of 1µL at a flow rate of 0.9 mL/min. UV spectra were recorded

at 215 nm using a Waters ACQUITY PDA detector spectrum range: 200-400 nm, ELS data was collected using a Waters ACQUITY ELS detector (where fitted). Mass spectra were obtained using a Waters SQD or Waters ACQUITY QDa. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00192] Analytical Method 9 (M9):

[00193] Analytical HPLC-MS were performed on a Waters LCMS systems using a Waters CSH C18 column (2.1 mm x 100 mm, 1.7 μ m; temperature: 40 °C) and a gradient of 5-100% B (A= 5 mM ammonium acetate, buffered to pH 7; B= acetonitrile) over 5.3 min, then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 μ L at a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters ACQUITY PDA detector spectrum range: 200-400 nm, ELS data was collected using a Waters ACQUITY ELS detector (where fitted). Mass spectra were obtained using a Waters SQD or Waters ACQUITY QDa. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00194] Analytical Method 10 (M10):

[00195] Analytical (M14) uHPLC-MS were performed on a Waters ACQUITY uPLC system using a Waters uPLC® BEH™ C18 column (2.1 mm x 30 mm, 1.7 μ m; temperature 40 °C) and a gradient of 1-100% B (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = acetonitrile) over 1.1 min, then 100% B for 0.25 min. A second gradient of 100-1% B was then applied over 0.05 min and held for 0.4 min with an injection volume of 1 μ L at a flow rate of 1.0 mL/min. UV spectra were recorded at 215 nm on a Waters ACQUITY PDA with a spectrum range of 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE mass detector (MS16) or a Waters SQD2 (MSQ5). Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00196] Analytical Method 11 (M11):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: Kinetex C18 2.6 μm , 2.1*30mm; Column temperature: 40°C

Mobile phase A (MPA) $\text{H}_2\text{O}+0.04\%$ (v/v) TFA

Mobile phase B (MPB) $\text{ACN}+0.02\%$ (v/v) TFA

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.01	3.00	3.50	3.51	4.30
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MPA (%)	95	5	5	95	95
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MPB (%)	5	95	95	5	5
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00197] Analytical Method 12 (M12):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: Kinetex C18 2.6 μm , 2.1*30mm; Column temperature: 40°C

Mobile phase A (MPA) $\text{H}_2\text{O}+0.04\%$ (v/v) TFA

Mobile phase B (MPB) $\text{ACN}+0.02\%$ (v/v) TFA

Flow rate: 1.5 mL/min

Gradient Ratio:

Time(min)	0.01	0.70	1.15	1.16	1.50
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MPA (%)	95	5	5	95	95
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MPB (%)	5	95	95	5	5
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00198] Analytical Method 13 (M13):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: HALO C18 5.0 μm , 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) $\text{H}_2\text{O}+0.04\%$ (v/v) TFA

Mobile phase B (MPB) $\text{ACN}+0.02\%$ (v/v) TFA

Flow rate: 1.0 mL/min (0.01-3.0 min) 1.2 mL/min (3.01-3.5 min)

Gradient Ratio: Time (min) 0.01 2.5 3.0 3.01 3.5

MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00199] Analytical Method 14 (M14):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: HALO C18 2.7 µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04% (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.5 mL/min

Gradient Ratio:

Time(min)	0.01	0.70	1.15	1.16	1.50
MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00200] Analytical Method 15 (M15):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5 µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04% (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 2.0 mL/min (0.00-0.9 min)

Gradient Ratio: Time (min) 0.00 0.50 0.90

MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00201] Analytical Method 16 (M16):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: Xbridge-C18 2.1*30mm 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10mM NH₄HCO₃

Mobile phase B (MPB) Acetonitrile

Flow rate: 1.5 mL/min

Gradient Ratio:

Time(min)	0.01	0.70	1.16	1.50
MPA (%)	95	5	5	95
MPB (%)	5	95	95	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00202] Analytical Method 17 (M17):

Instrument: Waters Arc&Qda;

Column: HALO 2.7 µm C18 90A 30×3.0mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.0 mL/min (0.01-4.00 min)

Gradient Ratio:

Time(min)	0.01	3.00	3.50	3.51	4
MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1200

[00203] Analytical Method 18 (M18):

Instrument: Shimadzu LC-30AD&MS 2020;

Column: InfinityLab Poroshell 120 SB-C18 2.7 µm 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.5 mL/min (0.01-1.50 min)

Gradient Ratio:

Time(min)	0.01	0.70	1.16	1.50
MPA (%)	95	5	5	95

MPB (%) 5 95 95 5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00204] Analytical Method 19 (M19):

Instrument: Shimadzu LC-30AD&MS 2020;

Column: InfinityLab Poroshell 120 SB-C18 2.7 µm 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.5 mL/min (0.01-1.50 min)

Gradient Ratio:

Time(min)	0.01	0.70	1.16	1.50
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MPA (%)	95	5	5	95
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MPB (%)	5	95	95	5
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00205] Analytical Method 20 (M20):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: Kinetex EVO C18 30*2.1mm, 5 µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1 mL/min (0.01-3.00 min)-1.2 mL/min (3.01-3.50 min)

Gradient Ratio:

Time(min)	0.01	2.50	3.00	3.01
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MPA (%)	95	5	5	95
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MPB (%)	5	95	95	5
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00206] Analytical Method 21 (M21):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 3.0*30mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.5 mL/min (0.00-1.30 min)

Gradient Ratio:

Time(min)	0.01	0.8	1.30
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MPA (%)	90	0	0
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MPB (%)	10	100	100
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00207] Analytical Method 22 (M22):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.50 mL/min

Gradient Ratio:

Time(min)	0	0.70	1.30
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MPA (%)	95	5	5
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MPB (%)	5	95	95
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-500

[00208] Analytical Method 23 (M23):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04% (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 2.0 mL/min (0.00-0.9 min)

Gradient Ratio:	Time (min)	0.00	0.50	0.90
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MPA (%)	90	0	0
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MPB (%)	10	100	100
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Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00209] Analytical Method 24 (M24):

Instrument: Agilent 1260 & 6125B;

Column: Xbridge C18 2.1*50mm, 5 µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10mM NH₄HCO₃

Mobile phase B (MPB) Acetonitrile

Flow rate: 0.8 mL/min

Gradient Ratio:

Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00210] Analytical Method 25 (M25):

Instrument: Shimadzu 20AB&MS 2020;

Column: Xbridge C18 2.1*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10 mMOL/L NH₄HCO₃

Mobile phase B (MPB) 100%ACN

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.01	3.00	3.50	3.51	4.30
MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00211] Analytical Method 26 (M26):

Instrument: Shimadzu LC-20AB&MS 2020;

Column: Xbridge-C18 2.1*50mm 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10 mM NH₄HCO₃

Mobile phase B (MPB) Acetonitrile

Flow rate: 1.0 mL/min (0.01-3.01 min), 1.2 mL/min (3.02-3.50 min)

Gradient Ratio:

Time(min)	0.01	2.50	3.00	3.01	3.5
MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00212] Analytical Method 27 (M27):

Instrument: Shimadzu 20AB&MS 2020;

Column: Xbridge C18 2.1*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10 mMOL/L NH₄HCO₃

Mobile phase B (MPB) 100%ACN

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.01	3.00	3.50	3.51	4.30	4.30
MPA (%)	95	5	5	95	95	95
MPB (%)	5	95	95	5	5	5

Detection: 220 nm & 254 nm; MS Mode: Negative; MS Range: 100-2000

[00213] Analytical Method 28 (M28):

Instrument: Agilent 1260 & 6125B;

Column: Luna-C18 (2) 2.0*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.0 mL/min

Gradient Ratio:

Time (min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00214] Analytical Method 29 (M29):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5 μ m, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.50 mL/min

Gradient Ratio:

Time(min)	0	0.70	1.30
MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-1500

[00215] Analytical Method 30 (M30):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5 μ m, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 2.0 mL/min (0.00-0.9 min)

Gradient Ratio:

Time(min)	0	0.5	0.90
MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00216] Analytical Method 31 (M31):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 3.0*30mm, 5 μ m; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.5 mL/min (0.00-1.30 min)

Gradient Ratio:

Time(min)	0.01	0.8	1.30
MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00217] Analytical Method 32 (M32):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 2.0 mL/min (0.00-0.9 min)

Gradient Ratio:

Time(min)	0	0.5	0.90
MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00218] Analytical Method 33 (M33):

Instrument: Shimadzu LC-20AD XR&MS 2020;

Column: HALO C18 5µm, 3.0*30mm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 2.0 mL/min (0.00-0.9 min)

Gradient Ratio:

Time(min)	0	0.5	0.90
MPA (%)	90	0	0
MPB (%)	10	100	100

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00219] Analytical Method 34 (M34):

Instrument: Agilent 1260 & 6125B;

Column: Luna-C18 (2) 2.0*50mm, 5 µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm&254nm; MS Mode: Positive; MS Range: 100-1000

[00220] Analytical Method 35 (M35):

Instrument: Agilent 1200 & 6110A;

Column: Luna-C18 (2) 2.0*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00221] Analytical Method 36 (M36):

Instrument: Agilent 1200 & 6130;

Column: Xbridge-C18 2.1*50mm 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10 mM NH₄HCO₃

Mobile phase B (MPB) Acetonitrile

Flow rate: 0.8 mL/min

Gradient Ratio:

Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00222] Analytical Method 37 (M37):

Instrument: Agilent 1200 & 6110A;

Column: Luna-C18 (2) 2.0*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+0.04 % (v/v) TFA

Mobile phase B (MPB) ACN+0.02 % (v/v) TFA

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00223] Analytical Method 38 (M38):

Instrument: Shimadzu LC-20AD&MS 2020;

Column: Gemini C18 2.0*50mm, 5 µm; Column temperature: 40°C

Mobile phase A (MPA) H₂O+10 mM NH₄HCO₃

Mobile phase B (MPB) Acetonitrile

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.01	2.50	3.00	3.01	3.50
MPA (%)	95	5	5	95	95
MPB (%)	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 50-2000

[00224] Analytical Method 39 (M39):

Instrument: Agilent 1200 HPLC MSD: 1956A single quadrupole MSD

Column: Luna C18, 2.0*50mm, 5µm; Column temperature: 40°C

Mobile phase A (MPA) 0.04%TFA in H₂O

Mobile phase B (MPB) 0.02%TFA in ACN

Flow rate: 1.0 mL/min

Gradient Ratio:

Time(min)	0.01	0.40	3.00	4.00	4.01	4.50
MPA (%)	95	95	5	5	95	95
MPB (%)	5	5	95	95	5	5

Detection: 220 nm & 254 nm; MS Mode: Positive; MS Range: 100-1000

[00225] Analytical Method 40 (M40):

[00226] All the analysis were performed using an Agilent G1956A LC/MSD quadrupole coupled to an Agilent 1100 series liquid chromatography (LC) system consisting of a binary pump with degasser, autosampler, thermostated column compartment and diode array detector. The mass spectrometer (MS) was operated with an atmospheric pressure electro-spray ionization (API-ES) source in positive ion mode. The capillary voltage was set to 3000 V, the fragmentor voltage to 70 V and the quadrupole temperature was maintained at 100°C. The drying gas flow and temperature values were 12.0 L/min and 350 °C, respectively. Nitrogen was used as the nebuliser gas, at a pressure of 35 psig. Data acquisition was performed with Agilent Chemstation software.

[00227] Analysis were carried out on a YMC pack ODS-AQ C18 column (50 mm long x 4.6 mm I.D.; 3 µm particle size) at 35 °C, with a flow rate of 2.6 mL/min. A gradient elution was performed from 95% (Water + 0.1% Formic acid)/5% Acetonitrile to 5% (Water + 0.1% Formic acid)/95% Acetonitrile in 4.8 min; the resulting composition was held for 1.0 min; from 5% (Water + 0.1% formic acid)/95% Acetonitrile to 95% (Water + 0.1% formic acid)/5% Acetonitrile in 0.2 min. The injection volume was 2 µL. Acquisition ranges were set to 190-400 nm for the UV-PDA detector and 100-1400 m/z for the MS detector.

[00228] Analytical Method 41 (M41):

[00229] All the analysis were performed using an Agilent G6224A TOF-LC/MS quadrupole coupled to an Agilent 1290 Infinity series liquid chromatography (LC) system consisting of a binary pump with degasser, autosampler, thermostated column compartment and diode array detector. The TOF-mass spectrometer (TOF-MS) was operated with an atmospheric pressure dual-electro-spray ionization (Dual-ESI) source in positive ion mode. The capillary voltage was set to 3000 V, the fragmentor voltage to 70 V and the quadrupole temperature was maintained at 100°C. The drying gas flow and temperature values were 12.0 L/min and 350 °C, respectively. Nitrogen was used as the nebuliser gas, at a pressure of 35 psig. Data acquisition was performed with MassHunter software.

[00230] Analysis were carried out on a YMC pack ODS-AQ C18 column (50 mm long x 4.6 mm I.D.; 3 µm particle size) at 35 °C, with a flow rate of 2.6 mL/min. A gradient elution was performed using ISET 2V1.0 Emulated Agilent Pump G1312A V1.0 from 94.51% (Water + 0.1% Formic acid)/5.49% Acetonitrile to 5% (Water + 0.1% Formic acid)/95% Acetonitrile in 4.8 min; the resulting composition was held for 1.0 min; from 5% (Water + 0.1% formic acid)/95% Acetonitrile to 95% (Water + 0.1% formic acid)/5% Acetonitrile in 0.2 min. The injection volume was 4 µL. Acquisition ranges were set to 190-400 nm for the UV-PDA detector and 100-1000 m/z for the TOF-MS detector.

[00231] Analytical Method 42 (M42):

[00232] Analytical HPLC-MS were performed on Agilent 1260 Infinity (Quat. Pump) DAD LC/MS G6120B system using a Thermo Scientific Accucore C18 (50 x 4.6 mm, 2.6 µm; temperature: 35 °C) and a gradient From 90% A to 10% A in 1.5 min, held for 0.9 min, to 95% A in 0.1 min (A: 0.1% HCOOH in H₂O; B: CH₃CN) with an injection volume of 3 µL at a flow rate of 3 mL/min. UV spectra were recorded at 254 nm using a 1260 Infinity II Diode Array Detector HS spectrum range: 200-400 nm. Mass spectra were obtained using a LC/MS G6120B system. Data were integrated and reported using ACD Labs software.

[00233] Analytical Method 43 (M43):

[00234] Analytical HPLC-MS were performed on Agilent 1290 Infinity II HPLC DAD LC/MSD G6125C ISET emulating Agilent G4220A system using a Phenomenex Kinetex C18 (50 x 2.1 mm, 1.7 µm; temperature: 60 °C) and a gradient of from 90% A to 10% A in 2.4 min, held for 0.4 min, to 90% A in 0.2 min (A: 0.1% HCOOH in H₂O; B: CH₃CN) with an injection volume of 3 µL at a flow rate of 0.9 mL/min. 254 nm using 1290 Infinity II Diode Array Detector spectrum range: 200-400 nm. Mass spectra were obtained using a LC/MSD G6125C detector. Data were integrated and reported using ACD Labs software.

[00235] Analytical Method 44 (M44):

[00236] Analytical HPLC-MS were performed on Agilent 1290 Infinity II HPLC DAD LC/MSD iQ G6160A using a Phenomenex Kinetex C18 (50 x 2.1 mm, 1.7 µm; Temperature: 60 °C) and a gradient from 90% A to 10% A in 1.6 min, held for 0.4 min, to 90% A in 0.2 min. (A: 0.1% HCOOH in H₂O; B: CH₃CN) over 2.2 min with an injection volume of 3 µL at a flow rate of 1.2 mL/min. UV spectra were recorded at 254 nm using 1290 Infinity II Diode Array Detector spectrum range: 200-400 nm. Mass spectra were obtained using a LC/MSD iQ G6160A detector. Data were integrated and reported using ACD Labs software.

[00237] Analytical Method a:

Instrument:	Shimadzu LC-20AD&MS 2020					
Column:	HALO C18 5.0µm,3.0*30mm					
Column temperature:	40°C					
Mobile phase A(MPA)	H ₂ O+0.04%(v/v) TFA					
Mobile phase B(MPB)	ACN+0.02 %(v/v) TFA					
Flow rate:	1.0mL/min (0.01-3.0min) 1.2mL/min (3.01-3.5min)					
Gradient Ratio:	Time(min)	0.01	2.5	3.0	3.01	3.5
	MPA(%)	95	5	5	95	95
	MPB(%)	5	95	95	5	5
Detection:	220 nm 254nm					
MS Mode:	Positive					

MS Range: 50-2000

[00238] Analytical Method b.

Instrument: Agilent 1260 & 6125B
Column: Luna-C18(2) 2.0*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA(%)	95	95	5	5	95	95
MPB(%)	5	5	95	95	5	5

Detection: 220 nm
MS Mode: Positive
MS Range: 100-1000

[00239] Analytical Method c.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Halo C18 3.0*30mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.5 mL/min (0.00-1.30min)
Gradient Ratio:

Time(min)	0.01	0.8	1.30
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00240] Analytical Method d.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Halo C18 3.0*30mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.5 mL/min (0.00-1.30min)
Gradient Ratio:

Time(min)	0.01	0.8	1.30
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive
MS Range: 50-2000

[00241] Analytical Method e.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: HALO C18 5µm, 3.0*30mm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 2.0 mL/min (0.00-0.9min)
Gradient Ratio:

Time(min)	0	0.5	0.90
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00242] Analytical Method f.

Instrument: Agilent 1260 & 6125B
Column: Xbridge C18 2.1*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 0.8 mL/min
Gradient Ratio:

Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
MPA(%)	95	95	5	5	95	95
MPB(%)	5	5	95	95	5	5

Detection: 220 nm &254 nm
MS Mode: Positive
MS Range: 100-1000

[00243] Analytical Method g.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: HALO C18 5µm, 3.0*30mm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 2.0 mL/min (0.00-0.9min)
Gradient Ratio:

Time(min)	0	0.5	0.90
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00244] Analytical Method h.

Instrument: Shimadzu LC-20AB&MS 2020
Column: Xtimate C18 2.1*50mm 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 1.0 mL/min(0.01-3.01min,1.2mL/min(3.02-3.50min)
Gradient Ratio:

Time(min)	0.01	2.50	3.00	3.01	3.5
MPA(%)	95	5	5	95	95
MPB(%)	5	95	95	5	5

Detection: 220 254nm
MS Mode: Positive
MS Range: 50-2000

[00245] Analytical Method i.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Halo C18 3.0*30mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.5 mL/min (0.00-1.30min)
Gradient Ratio:

Time(min)	0.01	0.8	1.30
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00246] Analytical Method j.

Instrument: Agilent 1260 & 6125B
Column: Luna-C18(2) 2.0*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA(%)	95	95	5	5	95	95
MPB(%)	5	5	95	95	5	5

Detection: 220 nm&254nm
MS Mode: Positive
MS Range: 100-1000

[00247] Analytical Method k.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Tiank C18 50*2.1mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 1 mL/min (0.00-4.5min)
Gradient Ratio:

Time(min)	0.01	3.5	4.5
MPA(%)	95	5	5
MPB(%)	5	95	95

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00248] Analytical Method l.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: HALO C18 5µm, 3.0*30mm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 2.0 mL/min (0.00-0.9min)
Gradient Ratio:

Time(min)	0	0.5	0.90
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive
MS Range: 50-2000

[00249] Analytical Method m.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Halo C18 3.0*30mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 2.0 mL/min (0.00-0.90min)
Gradient Ratio:

Time(min)	0.01	0.5	0.9
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive

MS Range: 50-2000

[00250] Analytical Method n.

Instrument: Shimadzu LC-20AD XR&MS 2020
Column: Titank C18, 3.0*30mm 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 1.5 mL/min (0.00-0.90min)
Gradient Ratio:

Time(min)	0.01	0.5	0.9
MPA(%)	90	0	0
MPB(%)	10	100	100

Detection: 220 nm 254nm
MS Mode: Positive&Negative
MS Range: 50-2000

[00251] Analytical Method o.

Instrument: Shimadzu LC-20ADXR&MS 2020
Column: Xtimate C18 2.1*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.01	2.50	3.00
MPA(%)	95	5	5
MPB(%)	5	95	95

Detection: 220 nm 254 nm
MS Mode: Positive

MS Range: 50-2000

[00252] Analytical Method p.

Instrument: Agilent 1260 & 6125B
Column: Luna-C18(2) 2.0*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA(%)	95	95	5	5	95	95
MPB(%)	5	5	95	95	5	5

Detection: 220 nm
MS Mode: Positive
MS Range: 100-1000

[00253] Analytical Method q.

Instrument: Agilent 1260 & 6125B
Column: Luna-C18(2) 2.0*50mm,5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA
Mobile phase B(MPB) ACN+0.02 %(v/v) TFA
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
MPA(%)	95	95	5	5	95	95
MPB(%)	5	5	95	95	5	5

Detection: 220 nm&254nm
MS Mode: Positive

MS Range: 100-1000

[00254] Analytical Method r.

Instrument: Agilent 1200 & 6120B

Column: Xbridge C18 2.1*50mm,5µm

Column temperature: 40°C

Mobile phase A(MPA) H₂O+10mM NH₄HCO₃

Mobile phase B(MPB) Acetonitrile

Flow rate: 0.8 mL/min

Gradient Ratio:	Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
	MPA(%)	95	95	5	5	95	95
	MPB(%)	5	5	95	95	5	5

Detection: 220 nm&254nm

MS Mode: Positive

MS Range: 100-1000

[00255] Analytical Method s.

Instrument: Agilent 1200 & 6130

Column: Xbridge-C18 2.1*50mm 5µm

Column temperature: 40°C

Mobile phase A(MPA) H₂O+10mM NH₄HCO₃

Mobile phase B(MPB) Acetonitrile

Flow rate: 0.8 mL/min

Gradient Ratio:	Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
	MPA(%)	95	95	5	5	95	95
	MPB(%)	5	5	95	95	5	5

Detection: 220 nm 254nm
MS Mode: Positive
MS Range: 100-1000

[00256] Analytical Method t.

Instrument: Shimadzu LC-20AD&MS 2020
Column: Xtimate C18 2.1*50mm 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+10mM NH₄HCO₃
Mobile phase B(MPB) Acetonitrile
Flow rate: 1.0 mL/min
Gradient Ratio:

Time(min)	0.01	2.50	3.00	3.01	3.5
MPA(%)	95	5	5	95	95
MPB(%)	5	95	95	5	5

Detection: ELSD 220 nm 254nm
MS Mode: Positive
MS Range: 50-2000

[00257] Analytical Method u.

Instrument: Shimadzu LC-30AD&MS 2020
Column: Halo C18 3.0*30mm, 5µm
Column temperature: 40°C
Mobile phase A(MPA) H₂O+0.04 %(v/v) TFA

Mobile phase	ACN+0.02 %(v/v) TFA					
B(MPB)						
Flow rate:	1 mL/min(0.01-3.00min),1.2mL/min(3.01-3.50min)					
Gradient Ratio:	Time(min)	0.01	2.50	3.00	3.01	3.5
	MPA(%)	95	5	5	95	95
	MPB(%)	5	95	95	5	5
Detection:	ELSD 220 nm 254nm					
MS Mode:	Positive					
MS Range:	50-2000					

[00258] Purification methods were as follows:

[00259] Purification Method 1 (P1):

[00260] Purifications LC were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm x 100 mm, 10 μ M; temperature: rt) and a gradient of 10-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 14.44 min then 95% B for 2.11 min. A second gradient of 95-10% B was then applied over 0.2 min with an injection volume of 1500 μ L at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

[00261] Purification Method 2 (P2):

[00262] Purifications LC were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm x 10 mm, 10 μ M; temperature: rt) and a gradient of 30-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 11.00 min then 95% B for 2.10 min. A second gradient of 95-30% B was then applied over 0.2 min with an injection volume of 1500 μ L at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

[00263] Purification Method 3 (P3):

[00264] Purifications LC were performed on a Gilson LC system using a Waters X-Bridge C18 column (30 mm x 100 mm, 10 μ M; temperature: rt) and a gradient of 10-95% B (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 14.44 min

then 95% B for 2.11 min. A second gradient of 95-10% B was then applied over 0.2 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

[00265] Purification Method 4 (P4):

[00266] Purifications LC were performed on a Gilson LC system using a Waters X-Bridge C18 column (30 mm x 10 mm, 10 µM; temperature: rt) and a gradient of 30-95% B (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 11.00 min then 95% B for 2.10 min. A second gradient of 95-30% B was then applied over 0.21 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

[00267] Purification Method 5 (P5):

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (0.04% HCl); B: ACN;

Column: Phenomenex Luna C18 100*30mm*3µm;

Column temperature: ambient, variable gradient;

Flow rate: 25 mL/min;

Monitor wavelength: 220 nm & 254 nm

[00268] Purification Method 6 (P6):

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: water (NH₄HCO₃); B: ACN;

Column: Phenomenex C18 80*40mm*3µm;

Column temperature: ambient, variable gradient;

Flow rate: 25 mL/min;

Monitor wavelength: 220 nm & 254 nm

[00269] Purification Method 7 (P7):

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: water (NH₄HCO₃); B: ACN;

Column: Waters Xbridge Prep OBD C18 150*40mm*10µm;

Column temperature: ambient, variable gradient;

Flow rate: 25 mL/min;

Monitor wavelength: 220 nm & 254 nm

[00270] Purification Method 8 (P8):

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: water (NH₄HCO₃); B: ACN;

Column: Waters Xbridge BEH C18 100*30mm*10μm;

Column temperature: ambient, variable gradient;

Flow rate: 25 mL/min;

Monitor wavelength: 220 nm & 254 nm

[00271] Purification Method 9 (P9):

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: water (NH₄HCO₃); B: ACN;

Column: Waters Xbridge BEH C18 250*70mm*10μm;

Column temperature: ambient, variable gradient;

Flow rate: 25 mL/min;

Monitor wavelength: 220 nm & 254 nm

[00272] Purification Method 10 (P10):

Instrument: Orienda;

Mobile phase: A: water+HCl; B: ACN

Column: 4kg Agela C18 column;

Flow rate: 500 mL/min;

[00273] Purification Method 11 (P11):

Instrument: Waters SFC350 preparative SFC;

Mobile phase: A for CO₂ and B for EtOH (0.1% NH₃H₂O); B%=55% isocratic elution mode

Column: DAICEL CHIRALPAK AD (250mm*50mm,10 μm);

Column temperature: ambient, variable gradient;

Flow rate: 200 g/min;

Monitor wavelength: 220 nm

[00274] Purification Method 12 (P12):

Instrument: Waters SFC350 preparative SFC;

Mobile phase: A for CO₂ and B for EtOH; B%=20% isocratic elution mode

Column: DAICEL CHIRALCEL OJ (250mm*50mm,10 μm);

Column temperature: ambient, variable gradient;

Flow rate: 200 g/min;

Monitor wavelength: 220 nm

[00275] Purification Method 13 (P13):

[00276] The raw material was purified by using a Jasco System consisting of a CO₂ Preparative Pump (PU-4387), a Preparative Pump for organic solvent (PU-4087 with six channel selector), Preparative SFC Autosampler (AS-4358), column oven with four valve selector (CO-4065), a PDA detector (MD-4015), a Back Pressure Regulator (BP-4340), two open-bed collectors (Gilson-223) and a Julabo recirculating cooler (FL 1201). Data acquisition was performed with ChromNAV 2.04.00 software, equipped with a Phenomenex Lux Amylose-1 column (250x30mm 5μm, 5 μM; temperature: 35 °C), with a flow rate of 30 mL/min and BPR set at 120 Bar. An isocratic mode elution was performed 60% B (A= CO₂; B= 0.1% diethylamine in 2-propanol) in 20 min on a stacked injection mode. Acquisition frequency was set to 220 nm for the PDA detector.

[00277] Purification Method 14 (P14):

[00278] The raw material was purified by using a Jasco System consisting of a CO₂ Preparative Pump (PU-4387), a Preparative Pump for organic solvent (PU-4087 with six channel selector), Preparative SFC Autosampler (AS-4358), column oven with four valve selector (CO-4065), a PDA detector (MD-4015), a Back Pressure Regulator (BP-4340), two open-bed collectors (Gilson-223) and a Julabo recirculating cooler (FL 1201). Data acquisition was performed with ChromNAV 2.03.05 software, equipped with a Phenomenex Lux Amylose-1 column (250x30mm 5μm, 5 μM; temperature: 35 °C), with a flow rate of 30 mL/min and BPR set at 120 Bar. An isocratic mode elution was performed 55% B (A= CO₂; B= 0.1% diethylamine in 2-propanol) in 20 min on a stacked injection mode. Acquisition frequency was set to 220 nm for the PDA detector.

[00279] Purification Method 15:

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (10mM NH₄HCO₃); B: ACN;

Column: Waters Xbridge Prep OBD C18 150*40mm*10μm;

Column temperature: ambient;

Gradient: 30%-60% B over 8.0 min;

Flow rate: 25mL/min;

Monitor wavelength: 220&254nm

[00280] Purification Method 16:

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (10mM NH₄HCO₃); B: ACN;

Column: Phenomenex Gemini-NX 150*30mm*5μm;

Column temperature: ambient;

Gradient: 30%-70% B over 20.0 min;

Flow rate: 25mL/min;

Monitor wavelength: 220&254nm

[00281] Purification Method 17:

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (0.2% FA)-ACN; B: ACN;

Column: Phenomenex Luna C18 100*30mm*3μm; mobile phase;

Column temperature: ambient;

Gradient: 25%-55% B over 8.0 min;

Flow rate: 25mL/min;

Monitor wavelength: 220&254nm

[00282] Purification Method 18:

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (10mM NH₄HCO₃); B: ACN;

Column: Agela DuraShell C18 250*70mm*10μm;

Column temperature: ambient;

Gradient: 80%-95% B over 20.0 min;

Flow rate: 25mL/min;

Monitor wavelength: 220&254nm

[00283] Purification Method 19:

Instrument: Gilson 281 semi-preparative HPLC system;

Mobile phase: A: H₂O (0.05% NH₃H₂O+10mM NH₄HCO₃); B: ACN;

Column: Welch Xtimate C18 250*100mm*10μm;

Column temperature: ambient;

Gradient: 40%-70% B over 24.0 min;

Flow rate: 25mL/min;

Monitor wavelength: 220&254nm

[00284] SFC Purification Method A:

Instrument: Auno-600;

Mobile phase: A for Heptane and B for EtOH (0.1% NH₃H₂O); B%=20% isocratic elution mode;

Column: DAICEL CHIRALPAK IG (250mm*50mm,10 μm) ;

Column temperature: 25 °C

Flow rate: 130mL/min

Monitor wavelength: 200nm

[00285] NMR Conditions

[00286] Unless otherwise stated, ^1H NMR spectra were recorded at 500 MHz or 400 MHz on either a Bruker Avance III HD 500 MHz or a Bruker Avance III HD 400 MHz spectrometer respectively. Chemical shifts, δ , are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used to denote the multiplicities and general assignments: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), hep (heptet), m (multiplet), pent (pentet), td (triplet of doublets), qd (quartet of doublets), app. (apparent) and br. (broad). Coupling constants, J , are quoted to the nearest 0.1 Hz.

[00287] List of Abbreviations

AIBN	α,α' -azoisobutyronitrile
Ac	acyl
AcN	acetonitrile
Ac ₂ O	acetic anhydride
Ar	aromatic
aq	aqueous
Bn	benzyl
BOC	tertbutoxy carbonyl
Cbz	carboxybenzyl group
CDI	carbonyldiimidazole
CuI	copper iodide
CV	column volumes
d	doublet
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DCE	1,2-dichloroethane
DBA	dibenzylideneacetone
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropyl ethylamine
DMA	<i>N,N</i> -dimethylacetamide
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenyl phosphoryl azide
DPPE	ethylenebis(diphenylphosphine)
dppb	1,3-bis(diphenylphosphino)propane

dppf	1,1'-bis(diphenylphosphino)ferrocene
dtbpf	1,1-bis(di-tert-butylphosphino) ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ESI+	Electrospray ionization under positive ion mode
Et ₂ O	diethyl ether
EtOAc or EA	ethyl acetate
EtOH	ethyl alcohol
EtONa	sodium ethoxide
FCC	flash column chromatography
h	hour(s)
HATU	(1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
HFIP	hexafluoroisopropanol
HOAc	acetic acid
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
i-PrOH	isopropyl alcohol
KOAc	potassium acetate
KOH	potassium hydroxide
LAH	lithium aluminum hydride
LCMS	liquid chromatography and mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
M+H	ion observed by mass spectrometry created by addition of a hydrogen cation
mCPBA	3-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol

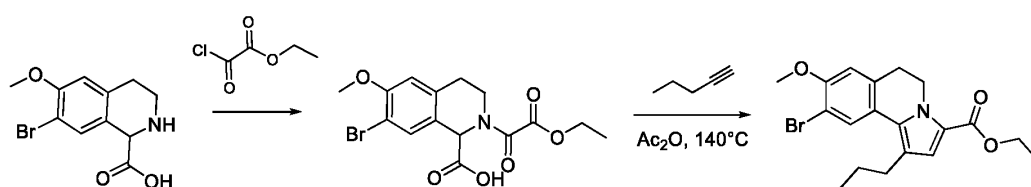
Me4tBuXphos	2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl
MTBE	methyl tert-butyl ether
m	multiplet
min	minute(s)
mL	millilitre
mol/M	mole/molar
mmol	millimole
N ₂	nitrogen
NBS	<i>N</i> -bromo succinimide
NH ₄ OAc	ammonium acetate
NMO	4-methylmorpholine <i>N</i> -oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
PE	petroleum ether
PPA	polyphosphoric acid
q	quartet
rt	room temperature
RT	retention time
s	singlet
Sat.	saturated
SFC	supercritical fluid chromatography
STAB	sodium triacetoxy borohydride
t	triplet
TBAF	tetrabutyl ammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate

TBDPS	tertbutyl diphenyl silyl
TBSCl	tert-butylchlorodimethylsilane
t-BuOH	tert-butanol
t-BuOK	potassium tert-butoxide
t-BuOLi	lithium tert-butoxide
TCFH	N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate
TEA	triethylamine
TFA	2,2,2-trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSN ₃	azidotrimethylsilane
TMSOK	potassium trimethylsilanolate
μL	microliter
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
XPhos Pd G3	(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

[00288] Compounds were named with the aid of OpenEye Scientific software (Lexichem TK).

[00289] Synthetic Method 1

[00290] Scheme for Method 1



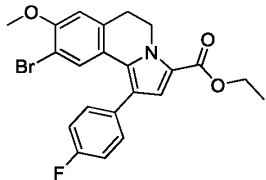
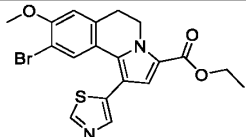
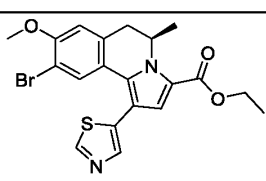
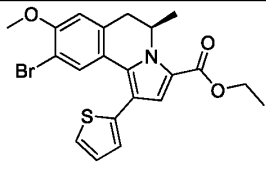
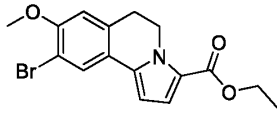
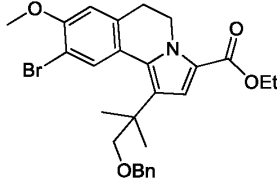
[00291] Step 1, Method 1

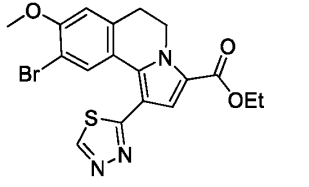
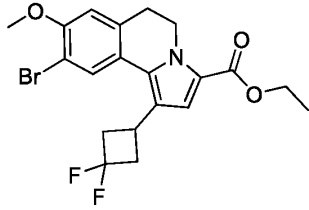
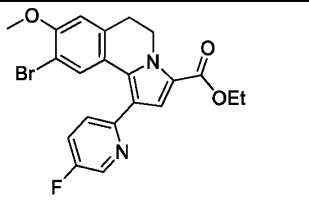
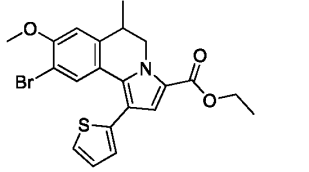
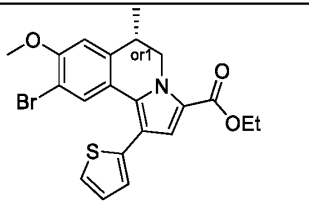
[00292] Ethyl 2-chloro-2-oxo-acetate (12.0 mL, 105.0 mmol, CAS 4755-77-5) was added to a solution of 7-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (20.00 g, 69.9 mmol) in anhydrous THF (300 mL) and the reaction mixture stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* to give 7-bromo-2-(2-ethoxy-2-oxo-acetyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylic acid as a yellow solid which was used directly in the next step assuming quantitative yield. RT (M2) = 0.75 min, [M+H]⁺ (ESI⁺) 386.1 / 388.1.

[00293] Step 2, Method 1

[00294] Pent-1-yne (8.6 mL, 87.4 mmol, CAS 627-19-0) was added to a stirred solution of 7-bromo-2-(2-ethoxy-2-oxo-acetyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylic acid (26.99 g, 69.9 mmol) in acetic anhydride (207 mL). The reaction mixture was placed into a pre-heated heating block at 140 °C and stirred for 45 min. The reaction mixture was cooled and concentrated *in vacuo*. The resulting residue was taken up in DCM (200 mL) and stirred with sat. aq. NaHCO₃ (100 mL). The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. Heptane (200 mL) and diethyl ether (50 mL) were added and the resulting mixture heated at 85 °C for 30 min. A hot filtration was carried out to afford a solid. This solid was dried and ground with a pestle and mortar to give ethyl 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (13.90 g, 48% yield) as a brown solid. The filtrate was left overnight at rt and orange crystals formed which were isolated by filtration to give more desired product (3.13 g, 11% yield) as an orange solid. RT (M2) = 1.31 min, [M+H]⁺ (ESI⁺) 392.3/394.3; ¹H NMR (500 MHz, DMSO) δ 7.68 (s, 1H), 7.16 (s, 1H), 6.78 (s, 1H), 4.48 (t, *J* = 6.6 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 2.99 (t, *J* = 6.5 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H).

[00295] The following analogs were made by analogous method:

Structure	Name	LCMS
	ethyl 9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M8) = 1.10 min, [M+H] ⁺ (ESI ⁺) 444.1/446.1
	ethyl 9-bromo-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M3) = 1.10 min, [M+H] ⁺ (ESI ⁺) 433.1/435.1
	ethyl (5 <i>R</i>)-9-bromo-8-methoxy-5-methyl-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M2) = 1.09 min, [M+H] ⁺ (ESI ⁺) 447.1/449.0
	ethyl (5 <i>R</i>)-9-bromo-8-methoxy-5-methyl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M2) = 1.32 min, [M+H] ⁺ (ESI ⁺) 446.1/448.1
	ethyl 9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M11) = 2.04 min, [M+H] ⁺ (ESI ⁺) 350.1/352.1
	ethyl 1-(1-(benzyloxy)-2-methylpropan-2-yl)-9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M13) = 2.67 min, [M+H] ⁺ (ESI ⁺) 512.3/514.1

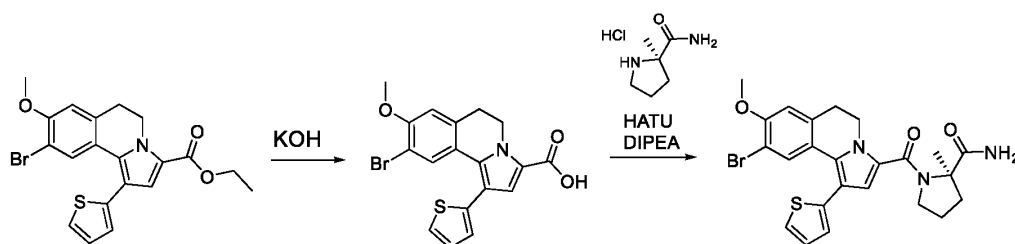
	ethyl 9-bromo-8-methoxy-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M14) = 1.13 min, [M+H] ⁺ (ESI ⁺) 434.1/436.0
	ethyl 9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M22) = 0.97 min, [M+H] ⁺ (ESI ⁺) 440.1/442.1
	ethyl 9-bromo-1-(5-fluoropyridin-2-yl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M19) = 0.89 min, [M+H] ⁺ (ESI ⁺) 445.2/447.1
	ethyl (R*)- 9-bromo-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M25) = 3.13 min, [M+H] ⁺ (ESI ⁺) RT = 0.89 min, [M+H] ⁺ (ESI ⁺) 445.2/447.1
	ethyl (R*)- 9-bromo-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	SFC Method (11) First enantiomer RT (M25) = 0.89 min, [M+H] ⁺ (ESI ⁺) 446.0/447.9 Second enantiomer RT (M25) = 1.80 min, [M+H] ⁺ (ESI ⁺) 417.9/419.9

	ethyl (R*)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	SFC Method (11) Second enantiomer RT (M15) = 1.08 min, [M+H] ⁺ (ESI ⁺) 444.8/446.1
	ethyl 9-bromo-8-methoxy-5-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M1) = 2.07 min, [M+H] ⁺ (ESI ⁺) 364.1/366.1
	ethyl (1aR,9bR)-7-bromo-8-methoxy-5-(thiophen-2-yl)-1a,9b-dihydro-1H-cyclopropa[c]pyrrolo[2,1-a]isoquinoline-3-carboxylate	RT (M22) = 1.02 min, [M+H] ⁺ (ESI ⁺) 444.1/446.1

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00296] Synthetic Method 2

[00297] Scheme for Method 2



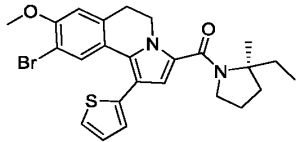
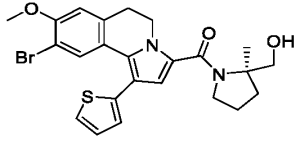
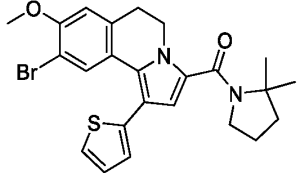
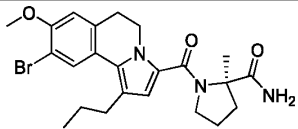
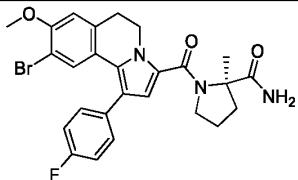
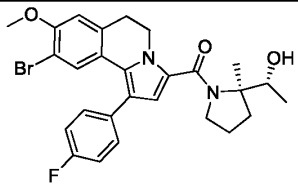
[00298] Step 1, Method 2

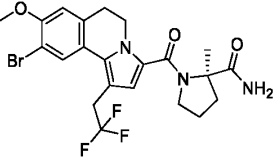
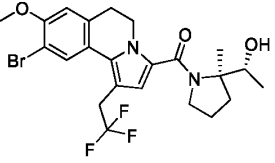
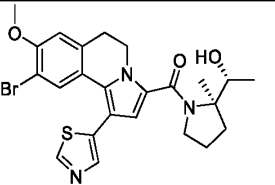
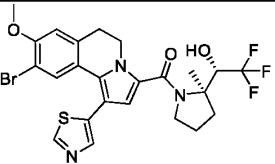
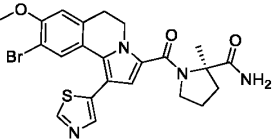
[00299] Potassium hydroxide (7.93 g, 139.0 mmol) was added to a stirred solution of ethyl 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (prepared in accordance with an analogous method to method 1 (steps 1 and 2) using 2-ethynyl-thiophene) (15.00 g, 34.7 mmol) in ethanol (300 mL) and water (100 mL) at 80 °C. After 1 h, the reaction mixture was cooled to rt and concentrated *in vacuo*. The aqueous residue was acidified to pH 1 using 1 M aq HCl, and the solid suspended in the aqueous layer was collected by filtration to give 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (83% purity, 14.70 g, 87% yield) as a pale brown solid. RT (M2) = 1.03 min, [M+H]⁺ (ESI⁺) 402.9/404.9.

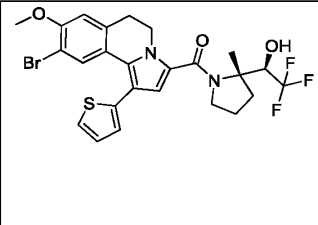
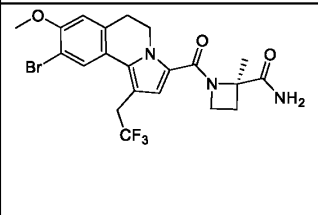
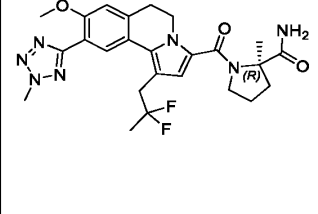
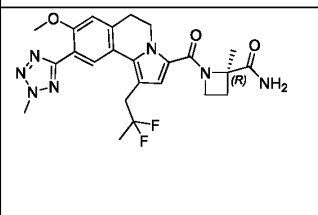
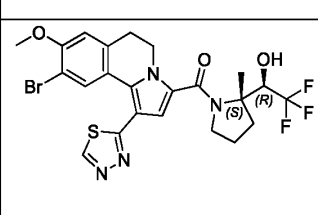
[00300] Step 2, Method 2

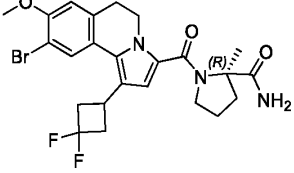
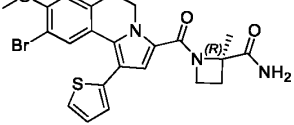
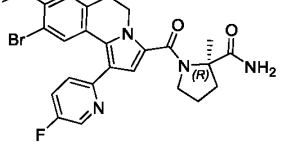
[00301] DIPEA (30 mL, 173.0 mmol, CAS 7087-68-5), HATU (14.11 g, 37.1 mmol, CAS 148893-10-1) and (2*R*)-2-methylpyrrolidine-2-carboxamide hydrochloride (4.89 g, 29.7 mmol, CAS 1262381-66-7) were added to a stirred solution of 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (10.00 g, 24.7 mmol) in DCM (400 mL) at rt. The reaction mixture was stirred overnight and then diluted with DCM and water. The layers were separated, the organic passed through a phase separator and then concentrated *in vacuo* to yield the crude product as a brown oil. The crude was purified by FCC (silica, eluting with 0-100% EtOAc in heptane, then 0-20% MeOH in EtOAc). The product containing fractions were concentrated *in vacuo* to give (2*R*)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (10.27 g, 77% yield) as a pale brown foam. RT (M2) = 1.00 min, [M+H]⁺ (ESI⁺) 514.2/516.2; ¹H NMR (400 MHz, DMSO) δ 8.16 (s, 1H), 7.57 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.45 (s, 1H), 7.18 – 7.10 (m, 2H), 7.07 (dd, *J* = 3.4, 1.2 Hz, 1H), 6.82 (s, 1H), 6.66 (s, 1H), 4.24 – 4.20 (m, 1H), 3.96 – 3.91 (m, 1H), 3.86 (s, 3H), 3.81 – 3.74 (m, 1H), 3.69 – 3.57 (m, 1H), 3.20 – 3.09 (m, 1H), 3.05 – 2.97 (m, 1H), 2.10 – 2.02 (m, 1H), 1.89 – 1.84 (m, 3H), 1.53 (s, 3H).

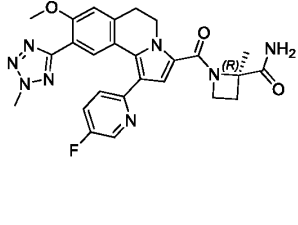
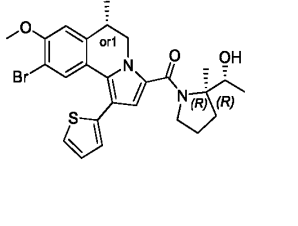
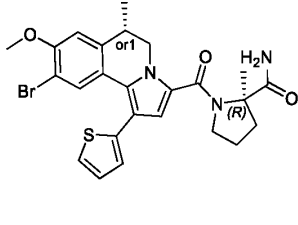
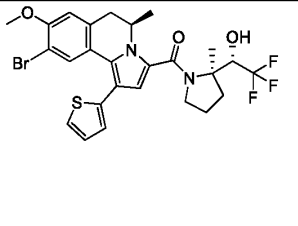
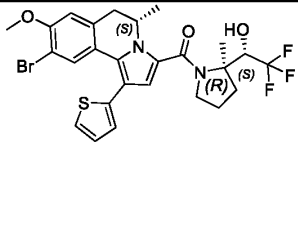
[00302] The following analogs were made by analogous method:

Structure	Name	LCMS
	[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-[(2S)-2-ethyl-2-methyl-pyrrolidin-1-yl]methanone	RT (M2) = 1.23 min, [M+H] ⁺ (ESI ⁺) 499.1/501.1
	[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-[(2R)-2-(hydroxymethyl)-2-methyl-pyrrolidin-1-yl]methanone	RT (M2) = 0.95 min, [M+H] ⁺ (ESI ⁺) 501.2 / 503.2
	[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-(2,2-dimethylpyrrolidin-1-yl)methanone	RT (M2) = 1.18 min, [M+H] ⁺ (ESI ⁺) 485.1 / 487.1
	(2R)-1-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methyl-pyrrolidine-2-carboxamide	RT (M2) = 0.96 min, [M+H] ⁺ (ESI ⁺) 474.2 / 476.2
	(2R)-1-[9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide	RT (M2) = 0.98 min, [M+H] ⁺ (ESI ⁺) 526.0/528.0
	[9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M3) = 0.99 min, [M+H] ⁺ (ESI ⁺) 527.3/529.3

	(2 <i>R</i>)-1-[9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methylpyrrolidine-2-carboxamide	RT (M3) = 0.90 min, [M+H] ⁺ (ESI ⁺) 514.1/516.1
	[9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidin-1-yl]methanone	RT (M3) = 1.09 min, [M+H] ⁺ (ESI ⁺) 515.3/517.3
	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidin-1-yl]-[8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone	RT (M2) = 0.91 min, [M+H] ⁺ (ESI ⁺) 516.1/518.1
	(9-bromo-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone	RT (M2) = 0.99 min, [M+H] ⁺ (ESI ⁺) 570.0/572.0
	(2 <i>R</i>)-1-(9-bromo-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M2) = 0.97 min, [M+H] ⁺ (ESI ⁺) 515.1/517.1

	[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-[(2S)-2-methyl-2-[(1R)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone	RT (M2) = 1.14 min, [M+H] ⁺ (ESI ⁺) 569.1/571.1
	(R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	RT (M13) = 1.74 min [M+H] ⁺ (ESI ⁺) 500.3/502.0
	(R)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M29) = 0.62 min [M+H] ⁺ (ESI ⁺) 514.1
	(R)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	RT (M13) = 1.38 min [M+H] ⁺ (ESI ⁺) 500.3
	(9-bromo-8-methoxy-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M11) = 1.13 min [M+H] ⁺ (ESI ⁺) 571.2/573.2

	(R)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M13) = 1.86 min [M-128.1] ⁺ (ESI ⁺) 394.2/396.2
	(R)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 7.58 (br, d, <i>J</i> = 5.13 Hz, 2 H), 7.41 (s, 1 H), 7.21 (br s, 1 H), 7.10 - 7.16 (m, 2 H), 7.06 (br d, <i>J</i> = 2.75 Hz, 1 H), 6.69 (br s, 1 H), 4.46 - 4.57 (m, 1 H), 4.28 - 4.45 (m, 3 H), 3.86 (s, 3 H), 3.01 (br t, <i>J</i> = 6.38 Hz, 2 H), 2.36 - 2.46 (m, 1 H), 1.97 - 2.09 (m, 1 H), 1.68 (br s, 3 H)
	(R)-1-(9-bromo-1-(5-fluoropyridin-2-yl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M13) = 1.48 min [M+H] ⁺ (ESI ⁺) 528.2/530.2

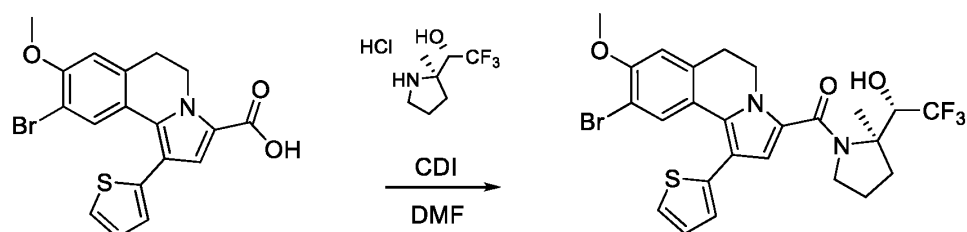
	(<i>R</i>)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	RT (M20) = 1.34 min [M+H] ⁺ (ESI ⁺) 517.2
	((<i>S</i> [*])-9-bromo-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((<i>R</i>)-2-((<i>R</i>)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)methanone	RT (M11) = 2.11 min [M+H] ⁺ (ESI ⁺) 529.2/531.2
	(<i>R</i>)-1-((<i>S</i> [*])-9-bromo-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M11) = 3.21 min [M+H] ⁺ (ESI ⁺) 528.2/530.2
	((<i>R</i>)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M11) = 2.12 min [M+H] ⁺ (ESI ⁺) 583.3/585.3
	((<i>S</i>)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M11) = 2.28 min [M+H] ⁺ (ESI ⁺) 583.2/585.3

	((R)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)methanone	RT (M11) = 2.12 min [M+H] ⁺ (ESI ⁺) 529.1/531.1
	((S)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)methanone	RT (M11) = 2.12 min [M+H] ⁺ (ESI ⁺) 529.1/531.2
	(R)-1-((S)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide	RT (M27) = 2.47 min [M+H] ⁺ (ESI ⁺) 528.4/530.0
	((R)-9-bromo-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M30) = 0.62 min [M+H] ⁺ (ESI ⁺) 583.2/585.1
	((1aR,9bR)-7-bromo-8-methoxy-5-(thiophen-2-yl)-1a,9b-dihydro-1H-cyclopropa[c]pyrrolo[2,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M11) = 0.72 min [M+H] ⁺ (ESI ⁺) 581.2/583.2

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

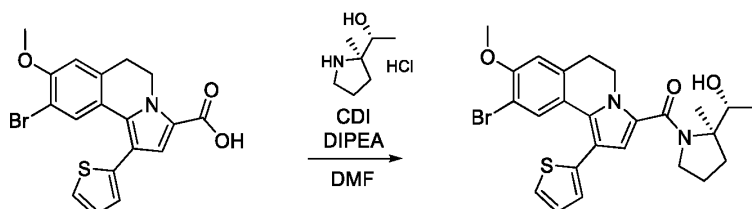
[00303] Synthetic Method 3

[00304] Scheme for Method 3



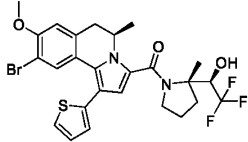
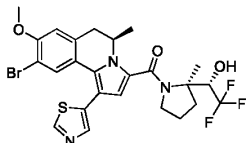
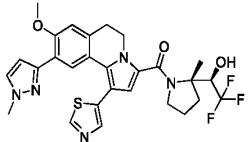
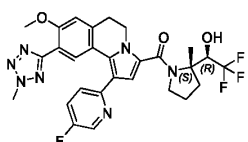
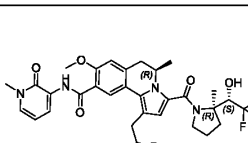
[00305] Step 1, Method 3

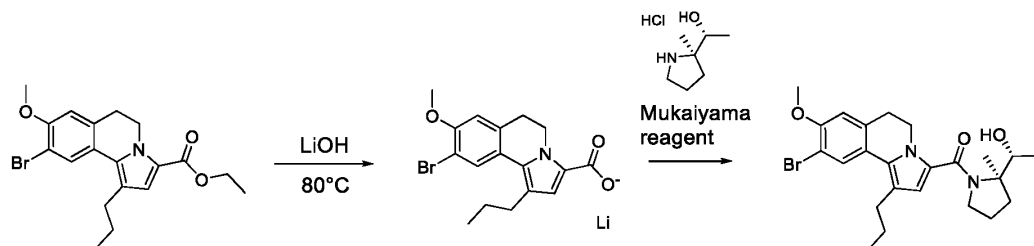
[00306] (1S)-2,2,2-trifluoro-1-[(2R)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (447 mg, 2.0 mmol, synthesized by method 16) was added to a stirred solution of di(imidazol-1-yl)methanone (412 mg, 2.5 mmol, CAS 530-62-1) and 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (690 mg, 1.7 mmol) in anhydrous DMF (10 mL) and left at rt overnight. The reaction was then heated to 50 °C and stirred for 8 h before it was retreated with (1S)-2,2,2-trifluoro-1-[(2R)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (447 mg, 2.0 mmol) and stirred at rt for a further 72 h. The reaction mixture was concentrated *in vacuo* and partitioned between DCM and water. The layers were separated, the organic passed through a phase separator and concentrated *in vacuo* to give the crude product as a yellow oil which was purified by FCC (silica, eluting 0-100% EtOAc in heptane). Product containing fractions were collected, combined and the solvent removed *in vacuo* to give [9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl]-[(2R)-2-methyl-2-[(1S)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone (80% purity, 1.05 g, 87% yield) as a beige solid. RT (M2) = 1.15 min [M+H]⁺ (ESI⁺) 569.1 / 571.1; ¹H NMR (400 MHz, DMSO) δ 7.56 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.43 (s, 1H), 7.16 – 7.09 (m, 2H), 7.06 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.50 (s, 1H), 4.99 (p, *J* = 8.4 Hz, 1H), 4.31 – 4.10 (m, 2H), 3.88-3.84 (m, 4H), 3.70 – 3.59 (m, 1H), 3.02 (t, *J* = 6.5 Hz, 2H), 2.43 – 2.28 (m, 1H), 1.85 – 1.74 (m, 2H), 1.74 – 1.63 (m, 1H), 1.60 (s, 3H).

[00307] Synthetic Method 4**[00308] Scheme for Method 4****[00309] Step 1, Method 4**

[00310] (1*R*)-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (492 mg, 3.0 mmol, synthesized by method 15) was added to a stirred solution of di(imidazol-1-yl)methanone (602 mg, 3.7 mmol, CAS 530-62-1) and 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (1.00 g, 2.5 mmol) in anhydrous DMF (14 mL) and the reaction mixture heated at 90 °C for 2.5 h. DIPEA (1.1 mL, 6.2 mmol, CAS 7087-68-5) was added and the mixture stirred at 90 °C overnight. The reaction mixture was concentrated *in vacuo* and dissolved in DCM and water. The layers were separated, the organic passed through a phase separator and concentrated *in vacuo* to give an oil that was purified by FCC (silica, eluting 0-100% EtOAc in heptane). The fractions were concentrated *in vacuo* to give [9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone (72.0% purity) (594 mg, 0.8 mmol, 34% yield) as a pale brown solid. RT (M3) = 0.99 min, (ESI+) (M+H)⁺ 515.3 / 517.3. ¹H NMR (500 MHz, DMSO) δ 7.55 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.43 (s, 1H), 7.14 – 7.10 (m, 2H), 7.06 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.53 (s, 1H), 4.96 (d, *J* = 4.9 Hz, 1H), 4.44 (p, *J* = 6.3 Hz, 1H), 4.31 (dt, *J* = 13.0, 6.5 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.85 (s, 3H), 3.81 (ddd, *J* = 10.0, 6.6, 3.5 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.01 (t, *J* = 6.5 Hz, 2H), 2.07 (ddd, *J* = 12.6, 10.2, 7.7 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.57 – 1.51 (m, 1H), 1.50 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H).

[00311] The following analogs were made by analogous method:

Structure	Name	LCMS
	[(5 <i>R</i>)-9-bromo-8-methoxy-5-methyl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M2) = 1.25 min, (ESI ⁺) (M+H) ⁺ 583.0/585.0
	[(5 <i>R</i>)-9-bromo-8-methoxy-5-methyl-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M2) = 1.25 min, (ESI ⁺) (M+H) ⁺ 583.0/585.0
 Compound 4-1	[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M4) = 3.46 min, (ESI ⁺) (M+H) ⁺ 572.2
 Compound 4-2	(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl)((<i>S</i>)-2-methyl-2-((<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M36) = 3.99 min, (ESI ⁺) (M+H) ⁺ 586.3
 Compound 4-3	(<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M34) = 2.77 min, (ESI ⁺) (M+H) ⁺ 655.3

[00312] Synthetic Method 5**[00313] Scheme for Method 5****[00314] Step 1, Method 5**

[00315] 1 M Aqueous lithium hydroxide (1.1 mL, 1.1 mmol) was added to a stirred suspension of ethyl 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (200 mg, 0.5 mmol, synthesized by method 1) in ethanol (4.7 mL) and the mixture heated at 80 °C for 3 h, forming a solution. After cooling to rt the mixture was concentrated *in vacuo* to afford the product lithium 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate hydroxide (226 mg, quantitative) as an off-white powder. RT (M2) = 1.03 min, (ESI+) (M+H)⁺ 364.1/366.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 (s, 1H), 7.06 (s, 1H), 6.30 (s, 1H), 4.62 (t, *J* = 6.3 Hz, 2H), 3.84 (s, 3H), 2.84 (t, *J* = 6.3 Hz, 2H), 2.60 – 2.53 (m, 2H), 1.59 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

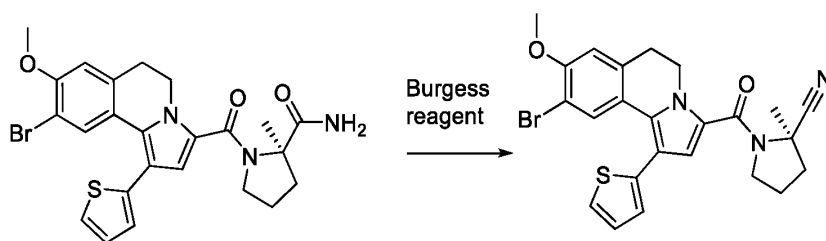
[00316] Step 2, Method 5

[00317] DIPEA (1.4 mL, 8.0 mmol, CAS 7087-68-5) was added to a stirred suspension of lithium 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate hydroxide (1.04 g, 2.6 mmol) and (1*R*)-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (580 mg, 1.3 mmol, synthesized by method 15) in DMA (25 mL) and the mixture stirred at 20 °C for 5 min, forming a hazy solution. 2-Chloro-1-methylpyridinium iodide (1.50 g, 5.9 mmol, CAS 14338-32-0) was added and the reaction mixture stirred at 20 °C for 17 h. The reaction mixture was diluted with water (150 mL), sonicated and left to stand for 10 min. The solids were collected by filtration, washing with water (3 x 30 mL). The solids were then dissolved into EtOAc (200

mL) and the organic mixture filtered through a hydrophobic filter paper. The organic filtrate was concentrated *in vacuo* to afford the crude product (913 mg) as a tan powder. The crude product was purified by FCC (silica, eluting with 10-100% EtOAc in heptane) to give (9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone (507 mg, 38% yield) as a pale tan powder. RT (M2) = 1.02 min, (ESI+) (M+H)⁺ 475.2/477.2; ¹H NMR (400 MHz, DMSO) δ 7.62 (s, 1H), 7.12 (s, 1H), 6.38 (s, 1H), 5.01 (d, *J* = 4.7 Hz, 1H), 4.47 – 4.35 (m, 1H), 4.25 (dt, *J* = 13.0, 6.5 Hz, 1H), 4.05 (dt, *J* = 12.6, 6.2 Hz, 1H), 3.86 (s, 3H), 3.77 (dt, *J* = 10.4, 5.2 Hz, 1H), 3.66 – 3.52 (m, 1H), 2.93 (t, *J* = 6.5 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.05 (dt, *J* = 12.8, 8.8 Hz, 1H), 1.86 – 1.68 (m, 2H), 1.67 – 1.44 (m, 3H), 1.49 (s, 3H), 1.02 – 0.92 (m, 6H).

[00318] Synthetic Method 6

[00319] Scheme for Method 6



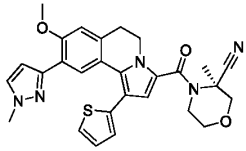
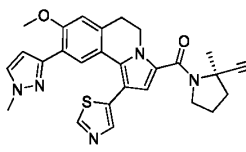
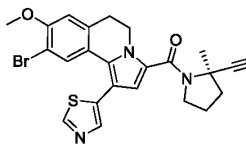
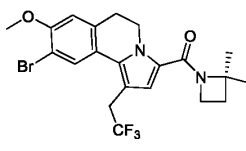
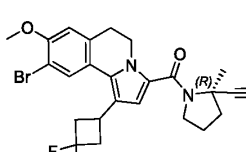
[00320] Step 1, Method 6

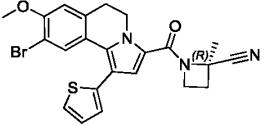
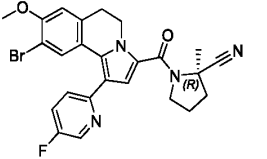
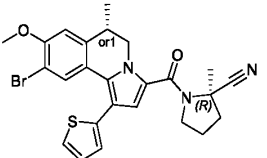
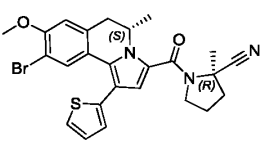
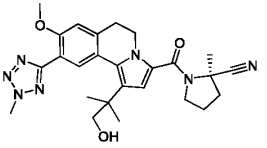
[00321] (Methyl *N*-(triethylammoniumsulfonyl)carbamate) (2.35 g, 9.9 mmol, CAS 29684-56-8) (Burgess reagent) was added to a mixture of (2*R*)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (2.54 g, 4.9 mmol, synthesized by method 2) in THF (20 mL) and DCM (20 mL) at 0 °C and the reaction mixture warmed to 20 °C and stirred for 1 h. The reaction mixture was poured into water (20 mL) and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine (saturated solution of NaCl in deionized water) (50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by FCC (silica, eluting 0-100% EtOAc in heptane) and the product containing fractions concentrated *in vacuo* to

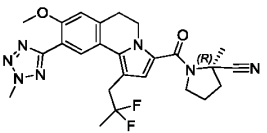
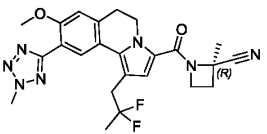
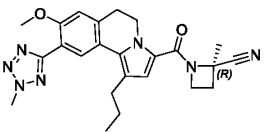
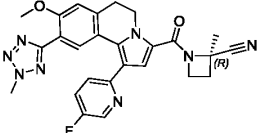
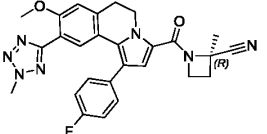
give (2*R*)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (92%) (2.10 g, 79% yield) as a pale yellow solid. RT (M2) = 1.09 min, (ESI+) (M+H)⁺ 496.0/497.9; ¹H NMR (500 MHz, DMSO) δ 7.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.43 (s, 1H), 7.16 – 7.11 (m, 2H), 7.08 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.72 (s, 1H), 4.46 – 4.37 (m, 1H), 4.33 – 4.20 (m, 1H), 3.91-3.85 (m, 4H), 3.84 – 3.77 (m, 1H), 3.05 (t, *J* = 6.5 Hz, 2H), 2.47 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.12 (ddd, *J* = 12.8, 10.1, 6.0 Hz, 1H), 2.02 – 1.99 (m, 1H), 1.95 – 1.85 (m, 1H), 1.74 (s, 3H).

[00322] The following analogs were made by analogous method:

Structure	Name	LCMS
	(2 <i>R</i>)-1-[9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M2) = 1.11 min, (ESI+) (M+H) ⁺ 508.0 / 510.0
	(2 <i>R</i>)-1-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methyl-pyrrolidine-2-carbonitrile	RT (M2) = 1.13 min, (ESI+) (M+H) ⁺ 456.2 / 458.2
	(2 <i>R</i>)-1-[9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M3) = 1.06 min, (ESI+) (M+H) ⁺ 496.2/498.2

 Compound 6-1	(3 <i>S</i>)-4-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-methyl-morpholine-3-carbonitrile	RT (M5) = 3.78 min, (ESI+) (M+H)+ 514.3
 Compound 6-2	(2 <i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.17 min, (ESI+) (M+H)+ 499.3
	(2 <i>R</i>)-1-(9-bromo-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methyl-pyrrolidine-2-carbonitrile	RT (M2) = 0.93 min, (ESI+) (M+H)+ 497.1/499.1
	(R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M11) = 1.99 min, (ESI+) (M+H)+ 482.2/484.1
	(R)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M27) = 2.61 min, (ESI+) (M+H)+ 504.0/506.0

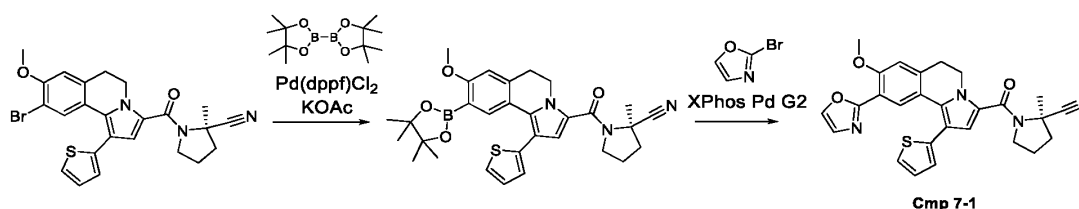
	(R)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M25) = 2.66 min, (ESI+) (M+H)+ 482.0/484.0
	(R)-1-(9-bromo-1-(5-fluoropyridin-2-yl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M13) = 1.88 min, (ESI+) (M+H)+ 509.2/511.1
	(R*)-1-((S)-9-bromo-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M11) = 2.14 min, (ESI+) (M+H)+ 510.2/512.2
	(R)-1-((S)-9-bromo-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M12) = 0.733 min, (ESI+) (M+H)+ 510.2/512.2
 Compound 6-3	(R)-1-(1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M36) = 3.08 min, (ESI+) (M-OH)+ 472.1

 Compound 6-4	(R)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M36) = 2.92 min, (ESI+) (M+H)+ 496.3
 Compound 6-5	(R)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M24)= 2.84 min, (ESI+) (M+H)+ 482.2
 Compound 6-6	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M37) = 2.67 min, (ESI+) (M+H)+ 446.2
 Compound 6-7	(R)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M24) = 2.76 min, (ESI+) (M+H)+ 499.1
 Compound 6-8	(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M24) = 3.02 min, (ESI+) (M+H)+ 498.2

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00323] Synthetic Method 7

[00324] Scheme for Method 7



[00325] Step 1, Method 7

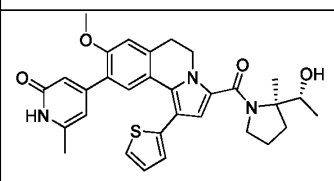
[00326] In a pressure relief vial, 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (338 mg, 1.3 mmol, CAS 73183-34-3), (2*R*)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (600 mg, 1.2 mmol, synthesized by method 6) and potassium acetate (300 mg, 3.0 mmol, CAS 127-08-2) were dissolved in anhydrous 1,4-dioxane (13 mL) and degassed with nitrogen. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (99 mg, 121 μ mol, CAS 95464-05-4) was added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was concentrated and partitioned between DCM and water. The layers were separated, the organics passed through a phase separator cartridge and concentrated *in vacuo*. The crude material was then purified by FCC (silica, eluting with 0-100% EtOAc in heptane). Product containing fractions were collected, combined and the solvent removed *in vacuo* to give (2*R*)-1-[8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (425 mg, 57% yield) as a pale brown solid. RT (M2) = 1.1 min $[M+H]^+$ (ESI⁺) 544.3; ¹H NMR (500 MHz, DMSO) δ 7.67 (s, 1H), 7.50 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.09 – 7.03 (m, 2H), 6.94 (s, 1H), 6.72 (s, 1H), 4.40 (dt, *J* = 13.3, 6.5 Hz, 1H), 4.26 (dt, *J* = 13.1, 6.2 Hz, 1H), 3.89 (td, *J* = 8.8, 7.3, 3.8 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.76 (s, 3H), 3.06 (t, *J* = 6.5 Hz, 2H), 2.48 – 2.44

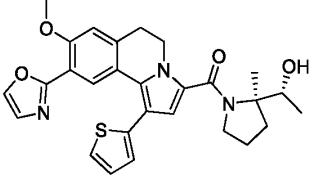
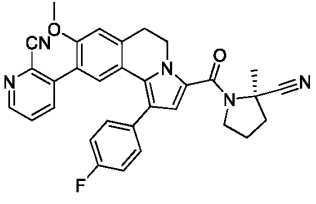
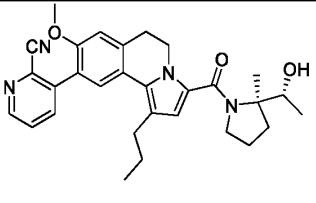
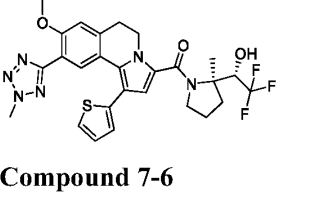
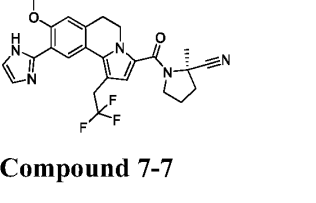
(m, 1H), 2.17 – 2.08 (m, 1H), 1.99 (s, 1H), 1.93 (dd, $J = 15.5, 6.8$ Hz, 1H), 1.74 (s, 3H), 1.17 (s, 12H)

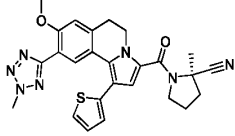
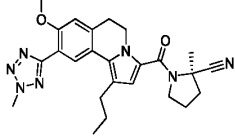
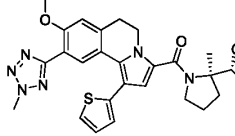
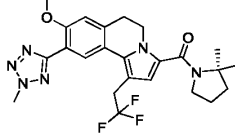
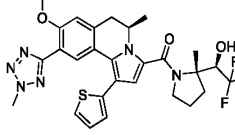
[00327] Step 2, Method 7

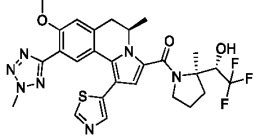
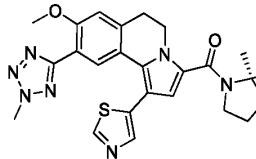
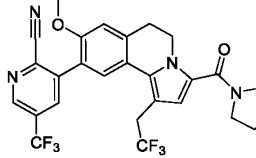
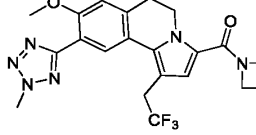
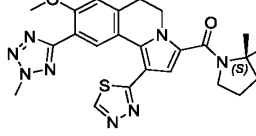
[00328] A solution of (2*R*)-1-[8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (100 mg, 184 μ mol), 2-bromo-1,3-oxazole (34 mg, 221 μ mol, CAS 125533-82-6) and dicaesium carbonate (240 mg, 736 μ mol, CAS 534-17-8) in 1,4-dioxane (2.4 mL) and water (0.6 mL) was degassed with nitrogen for 5 min. XPhos Pd G2 (29 mg, 18 μ mol, CAS 1310584-14-5) was then added and the mixture degassed with nitrogen for 5 min. The reaction mixture was stirred at 80 °C overnight. The reaction was allowed to cool to rt, treated with water (5 mL) and extracted with EtOAc (3 x 5 mL). The organic phases were combined, passed through a phase separator and concentrated *in vacuo*. The compound was purified by acidic prep HPLC (Method P2) and then basic prep HPLC (Method P4) to give a white solid. The white solid was further purified by chiral prep (Chiralpak AD-H, mobile phase ethanol at 9 mL/min) and freeze dried to give (2*R*)-1-[8-methoxy-9-oxazol-2-yl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (Compound 7-1) (24 mg, 27% yield) as a white solid. RT (M4) = 3.62 min, (ESI⁺) (M+H)⁺ 485.2; ¹H NMR (400 MHz, DMSO) δ 8.09 (s, 1H), 7.96 (s, 1H), 7.51 (dd, $J = 3.9, 2.5$ Hz, 1H), 7.28 – 7.20 (m, 2H), 7.12 – 7.05 (m, 2H), 6.73 (s, 1H), 4.50 – 4.39 (m, 1H), 4.35 – 4.23 (m, 1H), 3.93 – 3.86 (m, 4H), 3.86 – 3.77 (m, 1H), 3.13 (t, $J = 6.4$ Hz, 2H), 2.47 – 2.42 (m, 1H), 2.19 – 2.08 (m, 1H), 2.05 – 1.85 (m, 2H), 1.74 (s, 3H).

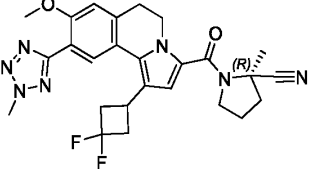
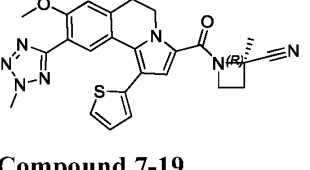
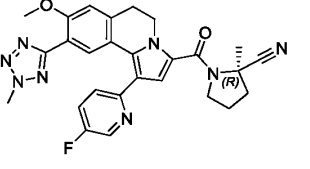
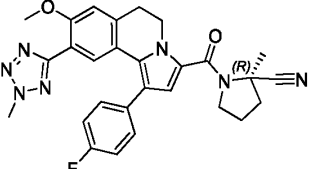
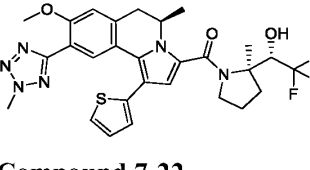
[00329] The following analogs were made by analogous method:

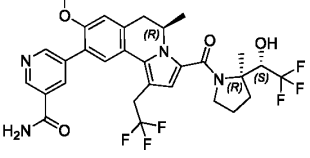
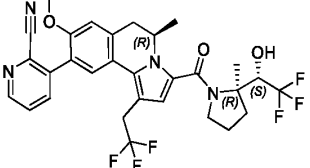
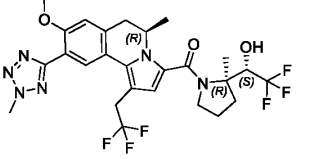
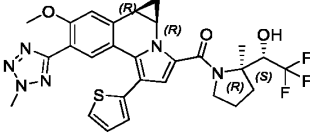
Structure	Name	LCMS
 Compound 7-2	4-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-6-methyl-1 <i>H</i> -pyridin-2-one	RT (M4) = 3.17 min [M+H] ⁺ (ESI ⁺) 544.3

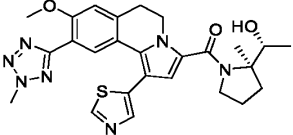
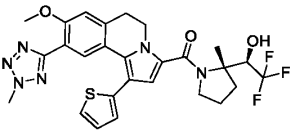
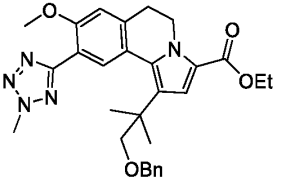
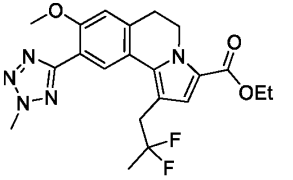
 Compound 7-3	[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-oxazol-2-yl-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 3.54 min [M+H]⁺ (ESI⁺) 504.3
 Compound 7-4	3-[3-[(2<i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile	RT (M4) = 4.02 min [M+H]⁺ (ESI⁺) 532.3
 Compound 7-5	3-[3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile	RT (M2) = 0.99 min [M+H]⁺ (ESI⁺) 499.7
 Compound 7-6	[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M4) = 3.80 min [M+H]⁺ (ESI⁺) 573.2
 Compound 7-7	(2<i>R</i>)-1-[9-(1<i>H</i>-imidazol-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 2.05 min [M+H]⁺ (ESI⁺) 484.3

 Compound 7-8	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.53 min [M+H] ⁺ (ESI ⁺) 500.2
 Compound 7-9	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.61 min [M+H] ⁺ (ESI ⁺) 460.1
 Compound 7-10	[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 3.57 min [M+H] ⁺ (ESI ⁺) 519.1
 Compound 7-11	(2 <i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.52 min [M+H] ⁺ (ESI ⁺) 500.1
 Compound 7-12	[(5 <i>R</i>)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone	RT (M4) = 4.04 min [M+H] ⁺ (ESI ⁺) 587.4

 Compound 7-13	[(5<i>R</i>)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone	RT (M5) = 3.49 min [M+H]⁺ (ESI⁺) 588.3
 Compound 7-14	(2<i>R</i>)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl]-2-methylpyrrolidine-2-carbonitrile	RT (M4) = 2.93 min [M+H]⁺ (ESI⁺) 501.2
 Compound 7-15	(<i>R</i>)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl)-5-(trifluoromethyl)picolinonitrile	RT (M36) = 3.45 min [M+H]⁺ (ESI⁺) 588.3
 Compound 7-16	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M24) = 2.89 min [M+H]⁺ (ESI⁺) 489.1
 Compound 7-17	(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl)((<i>S</i>)-2-methyl-2-((<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M36) = 2.71 min [M+H]⁺ (ESI⁺) 575.3

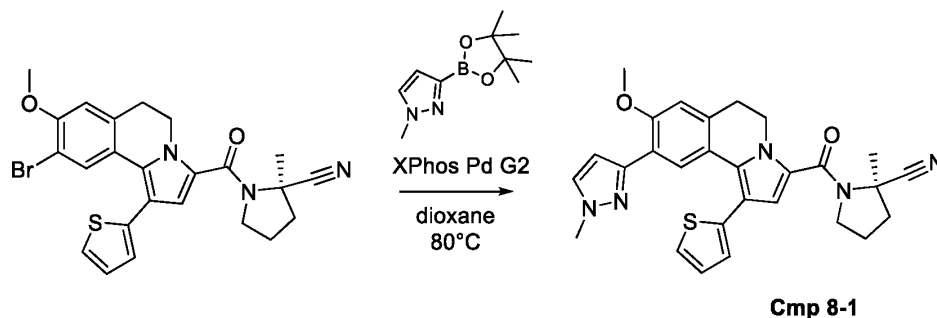
 Compound 7-18	(<i>R</i>)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M36) = 3.04 min [M+H]⁺ (ESI⁺) 508.3
 Compound 7-19	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M24) = 2.96 min [M+H]⁺ (ESI⁺) 486.1
 Compound 7-20	(<i>R</i>)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M36) = 2.82 min [M+H]⁺ (ESI⁺) 513.2
 Compound 7-21	(<i>R</i>)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M24) = 3.10 min [M+H]⁺ (ESI⁺) 512.1
 Compound 7-22	((<i>R</i>)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M35) = 3.07 min [M+H]⁺ (ESI⁺) 587.2

 Compound 7-23	5-((<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl)nicotinamide	RT (M35) = 2.91 = min [M+H]⁺ (ESI⁺) 625.0
 Compound 7-24	3-((<i>R</i>)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl)picolinonitrile	RT (M35) = 3.14 min [M+H]⁺ (ESI⁺) 607.3
 Compound 7-25	((<i>R</i>)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M25) = 2.42 min [M+H]⁺ (ESI⁺) 587.2
 Compound 7-26	((1<i>aR</i>,9<i>bR</i>)-8-methoxy-7-(2-methyl-2H-tetrazol-5-yl)-5-(thiophen-2-yl)-1<i>a</i>,9<i>b</i>-dihydro-1<i>H</i>-cyclopropa[<i>c</i>]pyrrolo[2,1-<i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M13) = 3.20 min [M+H]⁺ (ESI⁺) 585.2

 Compound 7-27	[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 2.82 min [M+H]⁺ (ESI⁺) 520.2
 Compound 7-28	[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>S</i>)-2-methyl-2-[(1<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M4) = 3.80 min [M+H]⁺ (ESI⁺) 573.2
 Compound 7-29	ethyl 1-(1-(benzyloxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carboxylate	RT (M34) = 0.65 min [M+H]⁺ (ESI⁺) 516.4
 Compound 7-30	ethyl 1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carboxylate	RT (M29) = 1.32 min [M+Et]⁺ (ESI⁺) 404.2

[00330] Synthetic Method 8

[00331] Scheme for Method 8

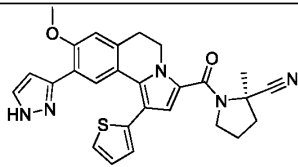
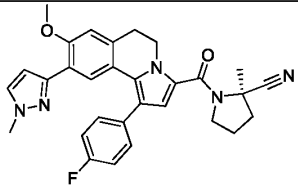
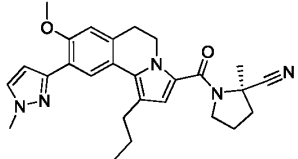
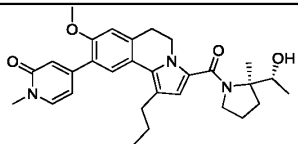


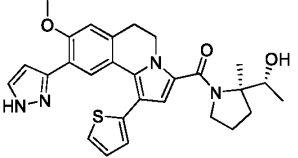
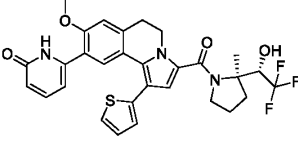
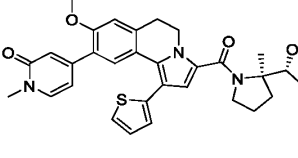
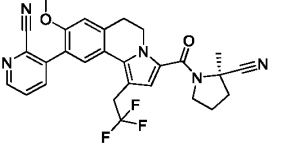
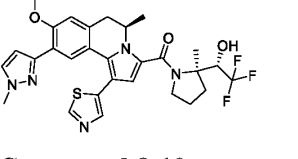
[00332] Step 1, Method 8

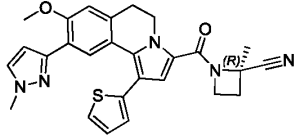
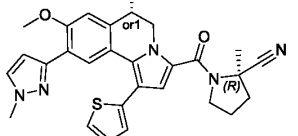
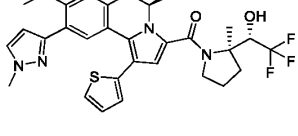
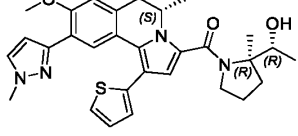
[00333] A solution of (2R)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (600 mg, 1.2 mmol, synthesized by method 6), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (334 mg, 1.6 mmol, CAS 1020174-04-2), dicaesium carbonate (1.58 g, 4.8 mmol, CAS 534-17-8) in 1,4-dioxane (15 mL) and water (6 mL) was degassed with nitrogen. XPhos Pd G2 (190 mg, 121 μ mol, CAS 1310584-14-5) was added and the reaction mixture was heated to 80 °C for 2 h. The mixture was allowed to cool to rt, poured into water (50 mL) and extracted with DCM (3 x 50 mL). The organic phases were combined, passed through a phase separator and concentrated *in vacuo*. The compound was purified by FCC (0-100% EtOAc in heptane) to give a brown solid which was further purified by reverse phase FCC (10-100% MeCN in water). Product containing fractions were concentrated *in vacuo*, freeze dried and dried in vacuum oven over the weekend to give (2R)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (Compound 8-1) (349 mg, 57% yield) as a white solid. RT (M4) = 3.82 min $[M+H]^+$ (ESI⁺) 498.3; ¹H NMR (400 MHz, DMSO) δ 8.09 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 3.8, 2.6 Hz, 1H), 7.12 – 7.09 (m, 2H), 7.06 (s, 1H), 6.72 (s, 1H), 6.52 (d, J = 2.2 Hz, 1H), 4.51 – 4.37 (m, 1H), 4.34 – 4.20 (m, 1H), 3.94 – 3.88 (m, 1H), 3.87 (s,

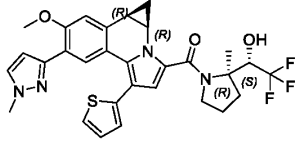
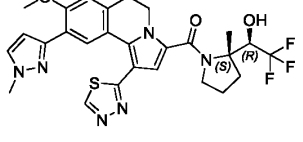
3H), 3.85 – 3.78 (m, 1H), 3.76 (s, 3H), 3.06 (t, $J = 6.4$ Hz, 2H), 2.48 – 2.42 (m, 1H), 2.20 – 2.08 (m, 1H), 2.05 – 1.87 (m, 2H), 1.74 (s, 3H).

[00334] The following analogs were made by analogous method:

Structure	Name	LCMS
 Compound 8-2	(2 <i>R</i>)-1-[8-methoxy-9-(1 <i>H</i> -pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.57 min [M+H] ⁺ (ESI ⁺) 484.2
 Compound 8-3	(2 <i>R</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.94 min [M+H] ⁺ (ESI ⁺) 510.3
 Compound 8-4	(2 <i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.95 min [M+H] ⁺ (ESI ⁺) 458.3
 Compound 8-5	4-[3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-9-yl]-1-methyl-pyridin-2-one	RT (M4) = 3.36 min [M+H] ⁺ (ESI ⁺) 504.4

 Compound 8-6	[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1<i>H</i>-pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 3.5 min [M+H]⁺ (ESI⁺) 503.3
 Compound 8-7	6-[8-methoxy-3-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl]-1<i>H</i>-pyridin-2-one	RT (M4) = 3.66 min [M+H]⁺ (ESI⁺) 584.2
 Compound 8-8	4-[3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl]-1-methyl-pyridin-2-one	RT (M4) = 3.28 min [M+H]⁺ (ESI⁺) 544.3
 Compound 8-9	3-[3-[(2<i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-9-yl]pyridine-2-carbonitrile	RT (M4) = 3.71 min [M+Na]⁺ (ESI⁺) 542.2
 Compound 8-10	[(5<i>R</i>)-8-methoxy-5-methyl-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M4) = 3.62 min [M+H]⁺ (ESI⁺) 586.2

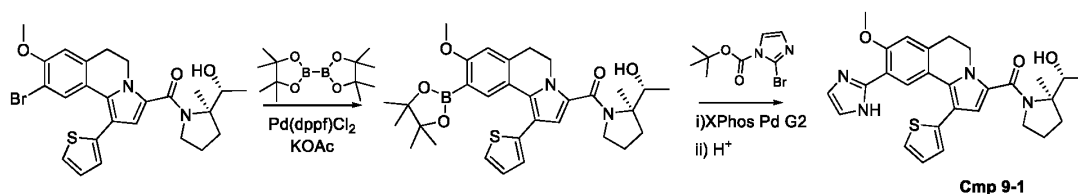
 Compound 8-11	(R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	RT (M36) = 3.10 min [M+H] ⁺ (ESI ⁺) 484.2
 Compound 8-12	(R)-1-((S*)-8-methoxy-6-methyl-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	RT (M36) = 3.24 min [M+H] ⁺ (ESI ⁺) 512.3
 Compound 8-13	((R)-8-methoxy-5-methyl-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M35) = 3.19 min [M+H] ⁺ (ESI ⁺) 585.2
 Compound 8-14	((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)((S)-8-methoxy-5-methyl-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)methanone	RT (M35) = 2.99 min [M+H] ⁺ (ESI ⁺) 531.2

 Compound 8-15	((1<i>aR</i>,9<i>bR</i>)-8-methoxy-7-(1-methyl-1H-pyrazol-3-yl)-5-(thiophen-2-yl)-1<i>a</i>,9<i>b</i>-dihydro-1H-cyclopropa[<i>c</i>]pyrrolo[2,1-<i>a</i>]isoquinolin-3-yl)((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M25) = 2.54 min [M+H]⁺ (ESI⁺) 583.2
 Compound 8-16	(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl)((<i>S</i>)-2-methyl-2-((<i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	RT (M36) = 2.84 min [M+H]⁺ (ESI⁺) 573.3/574.3

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00335] Synthetic Method 9

[00336] Scheme for Method 9



[00337] Step 1, Method 9

[00338] 4,4,5,5-Tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (234 mg, 922 μ mol, CAS 73183-34-3), [9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-

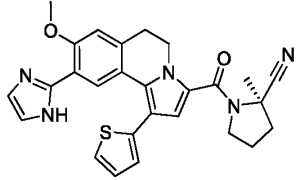
yl]methanone (540 mg, 838 μ mol, synthesized by method 4) and potassium acetate (208 mg, 2.1 mmol, CAS 127-08-2) were dissolved in anhydrous 1,4-dioxane (8 mL) and the mixture degassed with N_2 . [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (68 mg, 84 μ mol, CAS 95464-05-4) was added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was cooled, concentrated *in vacuo* and partitioned between DCM and water. The organic layer was separated, dried through a phase separator cartridge and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (silica, eluting with 0-100% EtOAc in heptane). Product containing fractions were combined and concentrated *in vacuo* to give [(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (230 mg, 44% yield) as a brown solid. RT (M5) = 1.02 min [M+H]⁺ (ESI)⁺ 563.5; ¹H NMR (500 MHz, DMSO) δ 7.67 (s, 1H), 7.49 – 7.46 (m, 1H), 7.07 – 7.01 (m, 2H), 6.91 (s, 1H), 6.52 (s, 1H), 4.98 (d, *J* = 4.8 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.34 – 4.27 (m, 1H), 4.11 – 4.04 (m, 1H), 3.85 – 3.79 (m, 1H), 3.75 (s, 3H), 3.67 – 3.60 (m, 1H), 3.02 (t, *J* = 6.5 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.80 – 1.69 (m, 2H), 1.56 – 1.51 (m, 1H), 1.51 (s, 3H), 1.17 (s, 12H), 1.00 (d, *J* = 6.4 Hz, 3H).

[00339] Step 2, Method 9

[00340] A solution of [(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (110 mg, 176 μ mol), *tert*-butyl 2-bromoimidazole-1-carboxylate (52 mg, 211 μ mol, CAS 1207457-15-5), dicaesium carbonate (229 mg, 704 μ mol, CAS 534-17-8) in 1,4-dioxane (2 mL) and water (680 μ L) was degassed with N_2 . XPhos Pd G2 (28 mg, 18 μ mol, CAS 1310584-14-5) was added, the reaction heated to 80 °C and stirred overnight. The reaction was cooled to rt and concentrated *in vacuo*. The resulting residue was diluted with water and extracted with DCM (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* and purified by acidic prep HPLC (P3). Product containing fractions were concentrated *in vacuo* and freeze dried to give [(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[9-(1*H*-imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (Compound

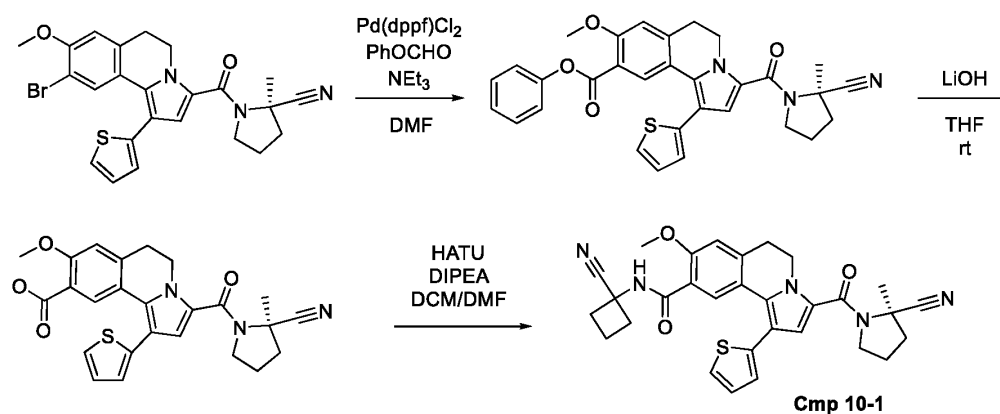
9-1) (13 mg, 14% yield) as a white solid. RT (M4) = 2.1 min $[M+H]^+$ (ESI⁺) 503.3; ¹H NMR (500 MHz, DMSO) δ 11.68 (s, 1H), 8.36 (s, 1H), 7.48 – 7.43 (m, 1H), 7.13 (s, 1H), 7.11 – 7.04 (m, 3H), 6.89 (s, 1H), 6.54 (s, 1H), 4.99 (s, 1H), 4.49 – 4.41 (m, 1H), 4.37 – 4.29 (m, 1H), 4.13 – 4.04 (m, 1H), 3.97 (s, 3H), 3.87 – 3.79 (m, 1H), 3.69 – 3.62 (m, 1H), 3.05 (t, J = 6.4 Hz, 2H), 2.12 – 2.03 (m, 1H), 1.83 – 1.70 (m, 2H), 1.58 – 1.53 (m, 1H), 1.52 (s, 3H), 1.02 (d, J = 6.3 Hz, 3H).

[00341] The following analog was made by analogous method:

Structure	Name	LCMS
 Compound 9-2	(2 <i>R</i>)-1-[9-(1 <i>H</i> -imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 2.15 min $[M+H]^+$ (ESI ⁺) 484.3

[00342] Synthetic Method 10

[00343] Scheme for Method 10



[00344] Step 1, Method 10

[00345] In a 20 mL pressure tube, a stirred solution of (2*R*)-1-[9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (300 mg, 604 μ mol, synthesized by method 6), phenyl formate (340 μ L, 3.0 mmol, CAS 1864-94-

4) and triethylamine (420 μ L, 3.0 mmol, CAS 121-44-8) in anhydrous DMF (5 mL) was degassed with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (44 mg, 60 μ mol, CAS 72287-26-4) was added, the solution degassed with nitrogen for 5 min and heated to 100 °C for 4 h. The reaction mixture was cooled to rt, the CO released slowly and then purged with nitrogen. The mixture was concentrated *in vacuo*, diluted with water (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were concentrated *in vacuo* to afford a residue that was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give phenyl 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (280 mg, 78% yield) as a brown solid. RT (M2) = 1.05 min, (ESI⁺) (M+H)⁺ 538.2; ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.99 (s, 1H), 7.54 – 7.50 (m, 1H), 7.46 – 7.41 (m, 2H), 7.30 – 7.23 (m, 2H), 7.13 – 7.03 (m, 4H), 6.75 (s, 1H), 4.50 – 4.43 (m, 1H), 4.35 – 4.28 (m, 1H), 3.92 – 3.85 (m, 4H), 3.86 – 3.77 (m, 1H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.17 – 2.09 (m, 1H), 2.03 – 1.99 (m, 1H), 1.95 – 1.85 (m, 1H), 1.75 (s, 3H), 1.67 – 1.53 (m, 1H).

[00346] Step 2, Method 10

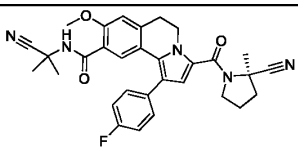
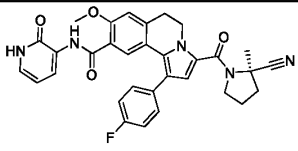
[00347] 2 M lithium hydroxide hydrate aq. (1.4 mL, 2.8 mmol) was added to a stirred solution of phenyl 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (90% purity, 280 mg, 469 μ mol) in THF (3 mL) at rt and the reaction mixture stirred overnight. The reaction mixture was concentrated *in vacuo*, acidified to pH 1 with 1 M aq HCl and extracted with EtOAc (3 x 10 mL). The organics were combined, passed through a phase separator cartridge and concentrated *in vacuo* to give 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (80% purity, 270 mg, 100% yield) as a brown solid. RT (M2) = 0.83 min, (ESI⁺) (M+H)⁺ 462.2.

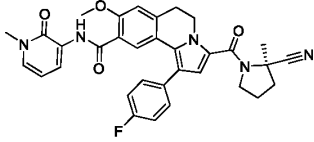
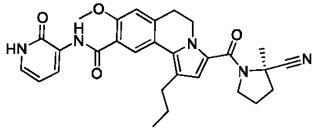
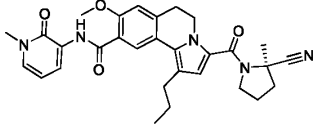
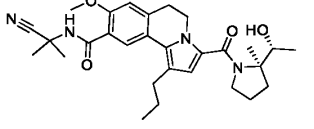
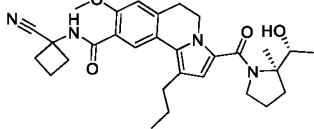
[00348] Step 3, Method 10

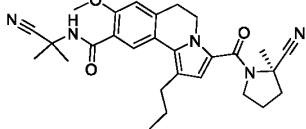
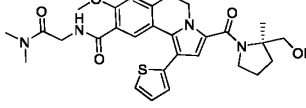
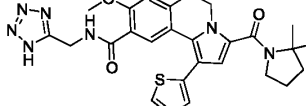
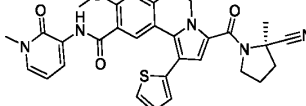
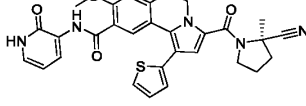
[00349] HATU (111 mg, 293 μ mol, CAS 148893-10-1) and 1-aminocyclobutanecarbonitrile hydrochloride (1:1) (31 mg, 234 μ mol, CAS 845821-84-3) were added to a stirred solution of 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (90 mg, 195 μ mol) and DIPEA (140 μ L, 780

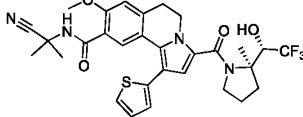
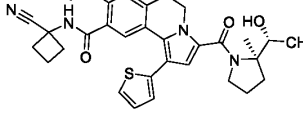
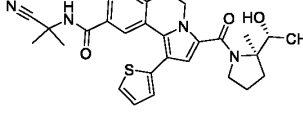
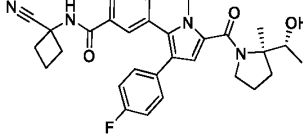
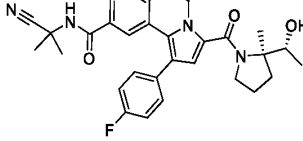
μmol , CAS 7087-68-5) in DCM (4 mL) and anhydrous DMF (400 μL) at rt and the reaction mixture stirred overnight. The reaction mixture was poured into water (3 mL) and extracted with DCM (3 x 3 mL). The organic phases were combined, passed through a phase separator and concentrated *in vacuo*. The crude was purified by acidic prep HPLC (Method P2) and the product-containing fractions freeze dried to give *N*-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide (Compound 10-1) (36 mg, 34% yield) as a white solid. RT (M4) = 3.76 min, (ESI+) (M+H)⁺ 540.3; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.73 (s, 1H), 7.79 (s, 1H), 7.53 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.19 (s, 1H), 7.13 – 7.07 (m, 2H), 6.73 (s, 1H), 4.43 (dt, *J* = 13.2, 6.6 Hz, 1H), 4.28 (dt, *J* = 12.9, 6.2 Hz, 1H), 3.92 (s, 3H), 3.91 – 3.76 (m, 2H), 3.12 (t, *J* = 6.6 Hz, 2H), 2.71 – 2.58 (m, 2H), 2.54 – 2.52 (m, 1H), 2.34 (ddd, *J* = 12.9, 9.4, 7.7 Hz, 2H), 2.14 (ddd, *J* = 12.7, 10.1, 5.9 Hz, 1H), 2.08 – 1.86 (m, 4H), 1.75 (s, 3H).

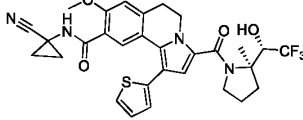
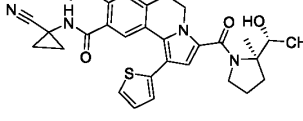
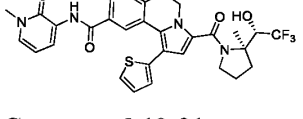
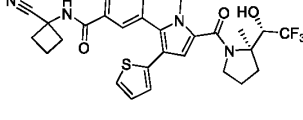
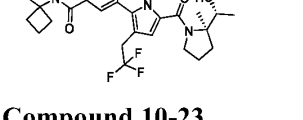
[00350] The following analogs were made by analogous method:

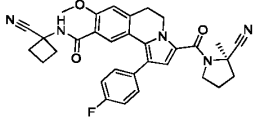
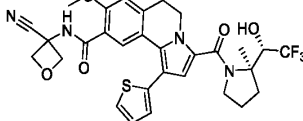
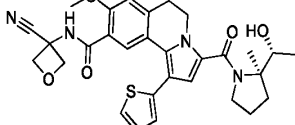
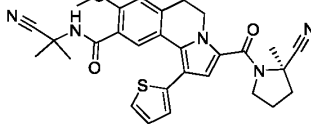
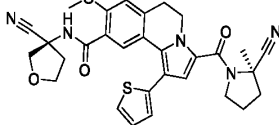
Structure	Name	LCMS
 Compound 10-2	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.81 min, (ESI+) (M+H) ⁺ 540.2
 Compound 10-3	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy- <i>N</i> -(2-oxo-1 <i>H</i> -pyridin-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.53 min, (ESI+) (M+H) ⁺ 566.2

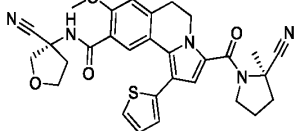
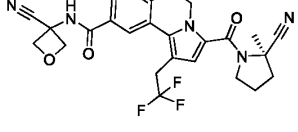
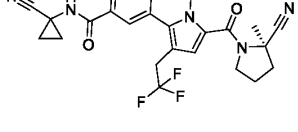
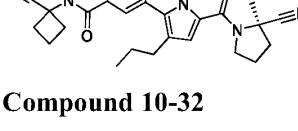
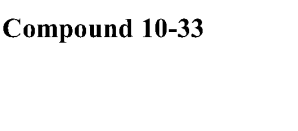
 Compound 10-4	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-<i>N</i>-(1-methyl-2-oxo-3-pyridyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.79 min, (ESI+) (M+H)⁺ 580.2
 Compound 10-5	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-8-methoxy-<i>N</i>-(2-oxo-1<i>H</i>-pyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.48 min, (ESI+) (M+H)⁺ 514.3
 Compound 10-6	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-8-methoxy-<i>N</i>-(1-methyl-2-oxo-3-pyridyl)-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.79 min, (ESI+) (M+H)⁺ 528.3
 Compound 10-7	<i>N</i>-(1-cyano-1-methyl-ethyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.89 min, (ESI+) (M+H)⁺ 507.7
 Compound 10-8	<i>N</i>-(1-cyanocyclobutyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.97 min, (ESI+) (M+H)⁺ 519.3

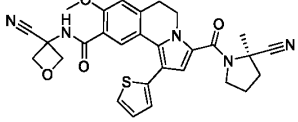
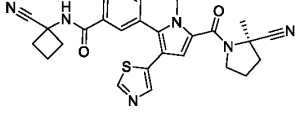
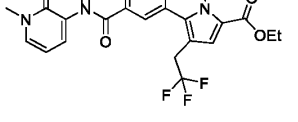
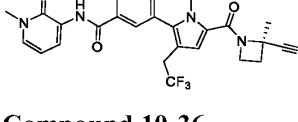
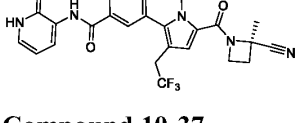
 Compound 10-9	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.80 min, (ESI+) (M+H) ⁺ 488.3
 Compound 10-10	<i>N</i> -[2-(dimethylamino)-2-oxo-ethyl]-3-[(2 <i>R</i>)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 2.97 min, (ESI+) (M+H) ⁺ 551.3
 Compound 10-11	3-(2,2-dimethylpyrrolidine-1-carbonyl)-8-methoxy- <i>N</i> -(1 <i>H</i> -tetrazol-5-ylmethyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.46 min, (ESI+) (M+H) ⁺ 532.3
 Compound 10-12	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.64 min, (ESI+) (M+H) ⁺ 568.2
 Compound 10-13	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(2-oxo-1 <i>H</i> -pyridin-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.35 min, (ESI+) (M+H) ⁺ 554.2

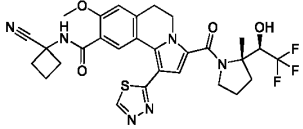
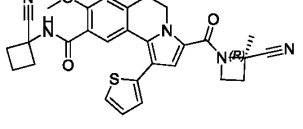
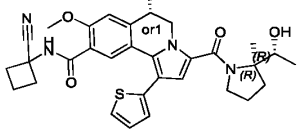
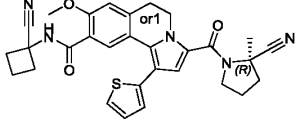
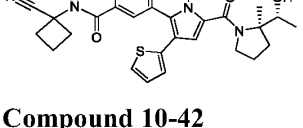
 Compound 10-14	<i>N</i>-(1-cyano-1-methyl-ethyl)-8-methoxy-3-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.91 min, (ESI+) (M+H)⁺ 601.3
 Compound 10-15	<i>N</i>-(1-cyanocyclobutyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.68 min, (ESI+) (M+H)⁺ 559.3
 Compound 10-16	<i>N</i>-(1-cyano-1-methyl-ethyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.61 min, (ESI+) (M+H)⁺ 547.3
 Compound 10-17	<i>N</i>-(1-cyanocyclobutyl)-1-(4-fluorophenyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.82 min, (ESI+) (M+H)⁺ 571.3
 Compound 10-18	<i>N</i>-(1-cyano-1-methyl-ethyl)-1-(4-fluorophenyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.74 min, (ESI+) (M+H)⁺ 559.3

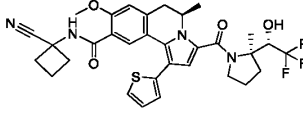
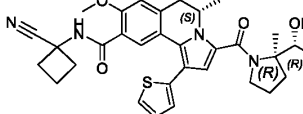
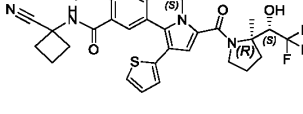
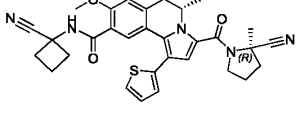
 Compound 10-19	<i>N</i>-(1-cyanocyclopropyl)-8-methoxy-3-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.78 min, (ESI⁺) (M+H)⁺ 599.2
 Compound 10-20	<i>N</i>-(1-cyanocyclopropyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.44 min, (ESI⁺) (M+H)⁺ 545.4
 Compound 10-21	8-methoxy-<i>N</i>-(1-methyl-2-oxo-3-pyridyl)-3-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.91 min, (ESI⁺) (M+H)⁺ 641.3
 Compound 10-22	<i>N</i>-(1-cyanocyclobutyl)-8-methoxy-3-[(2<i>R</i>)-2-methyl-2-[(1<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 4.02 min, (ESI⁺) (M+H)⁺ 613.3
 Compound 10-23	<i>N</i>-(1-cyanocyclobutyl)-3-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M5) = 3.61 min, (ESI⁺) (M+H)⁺ 559.4

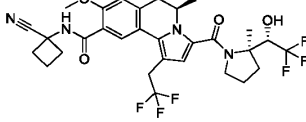
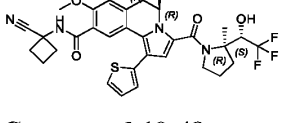
 Compound 10-24	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.88 min, (ESI ⁺) (M+H) ⁺ 552.3
 Compound 10-25	<i>N</i> -(3-cyano-2,2,2-trifluoro-1-hydroxyethyl)-3-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.87 min, (ESI ⁺) (M+H) ⁺ 615.1
 Compound 10-26	<i>N</i> -(3-cyano-2-methyl-1-hydroxyethyl)-3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M5) = 3.45 min, (ESI ⁺) (M+H) ⁺ 561.4
 Compound 10-27	<i>N</i> -(1-cyano-1-methyl-ethyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M5) = 3.66 min, (ESI ⁺) (M+H) ⁺ 528.4
 Compound 10-28	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>R</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.65 min, (ESI ⁺) (M+H) ⁺ 556.1

 Compound 10-29	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-<i>N</i>-[(3<i>S</i>*)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.64 min, (ESI⁺) (M+H)⁺ 556.1
 Compound 10-30	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-<i>N</i>-(3-cyanooxetan-3-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.39 min, (ESI⁺) (M+H)⁺ 542.2
 Compound 10-31	<i>N</i>-(1-cyanocyclopropyl)-3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M5) = 3.48 min, (ESI⁺) (M+H)⁺ 526.4
 Compound 10-32	<i>N</i>-(1-cyanocyclobutyl)-3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 4.00 min, (ESI⁺) (M+H)⁺ 500.1
 Compound 10-33	3-[(2<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl]-<i>N</i>-(3-cyanooxetan-3-yl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.71 min, (ESI⁺) (M+H)⁺ 502.1

 Compound 10-34	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -(3-cyanooxetan-3-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.63 min, (ESI ⁺) (M+H) ⁺ 542.1
 Compound 10-35	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.21 min, (ESI ⁺) (M+H) ⁺ 541.2
 Compound 10-36	ethyl (<i>R</i>)-8-methoxy-5-methyl-9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylate	RT (M30) = 0.57 min, (ESI ⁺) (M+H) ⁺ 518.3
 Compound 10-37	<i>R</i> -3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy- <i>N</i> -(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M28) = 2.60 min, (ESI ⁺) (M+H) ⁺ 554.2
 Compound 10-37	<i>R</i> -3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy- <i>N</i> -(2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M24) = 2.80 min, (ESI ⁺) (M+H) ⁺ 540.1

 Compound 10-38	N-(1-cyanocyclobutyl)-8-methoxy-3-((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-carbonyl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M36) = 2.85 min, (ESI⁺) (M+H)⁺ 615.3
 Compound 10-39	(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M24) = 3.09 min, (ESI⁺) (M+H)⁺ 526.0
 Compound 10-40	(S*)-N-(1-cyanocyclobutyl)-3-((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidin-1-carbonyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M35) = 3.02 min, (ESI⁺) (M+H)⁺ 573.3
 Compound 10-41	(S*)-3-((R)-2-cyano-2-methylpyrrolidin-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M39) = 2.12 min, (ESI⁺) (M+H)⁺ 554.1
 Compound 10-42	(R)-N-(1-cyanocyclobutyl)-3-((R)-2-((R)-1-hydroxyethyl)-2-methylpyrrolidin-1-carbonyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M35) = 3.99 min, (ESI⁺) (M+H)⁺ 573.3

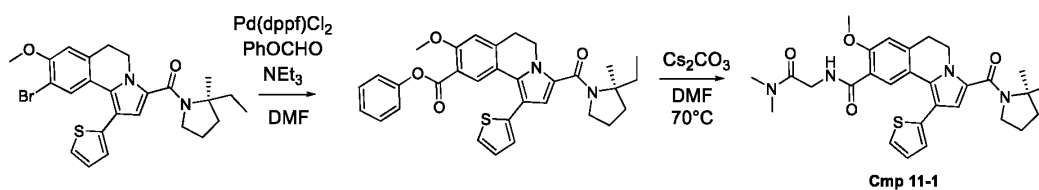
 Compound 10-43	(<i>R</i>)-N-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M36) = 3.35 min, (ESI⁺) (M+H)⁺ 627.3
 Compound 10-44	(<i>S</i>)-N-(1-cyanocyclobutyl)-3-((<i>R</i>)-2-((<i>R</i>)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M35) = 2.98 min, (ESI⁺) (M+H)⁺ 573.3
 Compound 10-45	(4<i>S</i>)-N-(1-cyanocyclobutyl)-7-methoxy-4-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-3a,5-dihydro-4H-cyclopenta[a]naphthalene-8-carboxamide	RT (M35) = 3.16 min, (ESI⁺) (M+H)⁺ 627.2
 Compound 10-46	(<i>S</i>)-3-((<i>R</i>)-2-cyano-2-methylpyrrolidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M36) = 3.25 min, (ESI⁺) (M+H)⁺ 554.3

 Compound 10-47	(<i>R</i>)-<i>N</i>-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M39) = 2.93 min, (ESI⁺) (M+H)⁺ 627.2
 Compound 10-48	(1<i>aR</i>,9<i>bR</i>)-<i>N</i>-(1-cyanocyclobutyl)-8-methoxy-3-((<i>R</i>)-2-methyl-2-((<i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-5-(thiophen-2-yl)-1<i>a</i>,9<i>b</i>-dihydro-1<i>H</i>-cyclopropa[<i>c</i>]pyrrolo[2,1-<i>a</i>]isoquinoline-7-carboxamide	RT (M36) = 3.29 min, (ESI⁺) (M+H)⁺ 625.3

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00351] Synthetic Method 11

[00352] Scheme for Method 11



[00353] Step 1, Method 11

[00354] In a 40 mL pressure tube, a solution of (2*S*)-1-[9-bromo-8-methoxy-1-(thiophen-2-yl)-5*H*,6*H*-pyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-ethyl-2-methylpyrrolidine (94% purity, 390 mg,

671 μmol , synthesized from method 2) in anhydrous DMF (5 mL) was degassed with nitrogen for 5 min. Phenyl formate (340 μL , 3.1 mmol, CAS 1864-94-4), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45 mg, 62 μmol , CAS 72287-26-4) and triethylamine (430 μL , 3.1 mmol, 121-44-8) were added and the reaction mixture was heated to 100 °C for 3 h 30 min. The reaction mixture was cooled to rt and the CO released under vacuum. The pressure tube was evacuated and refilled with N_2 3 times and the reaction mixture concentrated *in vacuo*. The resulting residue was partitioned between DCM (20 mL) and water (30 mL) and extracted with DCM (2 x 20 mL). The organics were combined and the solvent removed *in vacuo* to give the crude product as a brown oil, which was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give phenyl 3-[(2*S*)-2-ethyl-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (86% purity, 206 mg, 62% yield) as a brown oil. RT (M2) = 1.21 min, (ESI+) (M+H)⁺ 541.3; ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.99 (s, 1H), 7.50 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.29 – 7.25 (m, 1H), 7.23 (s, 1H), 7.10 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.08 – 7.04 (m, 3H), 6.56 (s, 1H), 4.40 – 4.30 (m, 1H), 4.23 – 4.11 (m, 1H), 3.89 (s, 3H), 3.80 – 3.73 (m, 1H), 3.70 – 3.59 (m, 1H), 3.13 (t, *J* = 6.5 Hz, 2H), 2.15 – 2.05 (m, 1H), 1.97 – 1.91 (m, 1H), 1.85 – 1.71 (m, 3H), 1.68 – 1.56 (m, 1H), 1.46 (s, 3H), 0.89 – 0.73 (m, 3H).

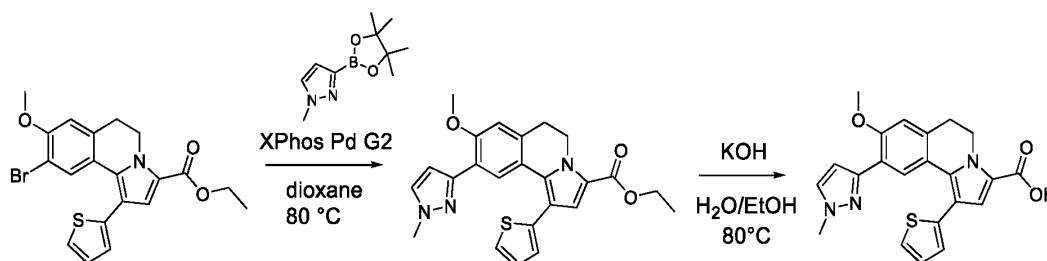
[00355] Step 2, Method 11

[00356] *N,N*-dimethylglycinamide (25 mg, 246 μmol , CAS 1857-19-8) and dicaesium carbonate (112 mg, 345 μmol , CAS 534-17-8) were added to a stirred solution of phenyl 3-[(2*S*)-2-ethyl-2-methyl-cyclopentanecarbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (86% purity, 103 mg, 164 μmol) in anhydrous DMF (2 mL) at rt. The mixture was warmed to 70 °C and stirred for 5 h 30 min before being cooled to rt and left to stir at rt over the weekend period. The reaction mixture was warmed to 70 °C and stirred for 51 h. The reaction mixture was concentrated *in vacuo*, DCM (20 mL) and water (20 mL) were added and the layers separated. The aqueous was washed with DCM (2 x 20 mL). The organics were combined, passed through a phase separator and concentrated *in vacuo* to give the crude product as a brown oil. The crude product was purified by acidic prep HPLC (Method P2) and the product

containing fractions freeze dried to give *N*-[2-(dimethylamino)-2-oxo-ethyl]-3-[(2*S*)-2-ethyl-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide (Compound 11-1) (29 mg, 32% yield) as an off-white solid. RT (M4) = 3.83 min, (ESI+) (M+H)⁺ 549.3; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.63 (t, *J* = 4.4 Hz, 1H), 8.19 (s, 1H), 7.47 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.18 (s, 1H), 7.06 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.04 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.52 (s, 1H), 4.39 – 4.28 (m, 1H), 4.18 – 4.07 (m, 3H), 3.97 (s, 3H), 3.81 – 3.73 (m, 1H), 3.71 – 3.60 (m, 1H), 3.08 (t, *J* = 6.4 Hz, 2H), 2.95 (s, 3H), 2.87 (s, 3H), 2.16 – 2.06 (m, 1H), 2.01 – 1.90 (m, 1H), 1.78 (dp, *J* = 13.6, 7.1 Hz, 3H), 1.66 – 1.59 (m, 1H), 1.46 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 3H).

[00357] Synthetic Method 12

[00358] Scheme for Method 12



[00359] Step 1, Method 12

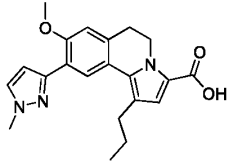
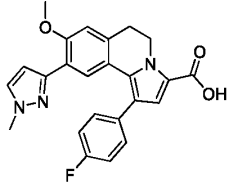
[00360] 1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.59 g, 7.6 mmol, CAS 1020174-04-2), caesium carbonate (6.63 g, 20.4 mmol CAS 534-17-8) and XPhos Pd G2 (400 mg, 509 μ mol, CAS 1310584-14-5) was added to a solution of ethyl 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (2.20 g, 5.1 mmol, synthesized by method 1) in 1,4-dioxane (60 mL) and water (30 mL). The reaction mixture was degassed with nitrogen and heated to 80 °C for 2 hours. The reaction mixture was allowed to cool to rt, poured into water (20 mL) and extracted with DCM (3 x 20 mL). The organic phases were combined, passed through a phase separator and concentrated *in vacuo*. The resulting residue was purified by FCC (silica, eluting with 0-100% EtOAc in heptane). Product containing fractions were

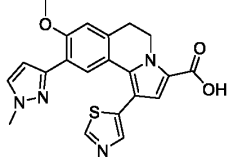
concentrated *in vacuo* to give ethyl 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (2.11 g, 94% yield) as a brown solid. RT (M2) = 1.08 [M+H]⁺ (ESI⁺) 434.3

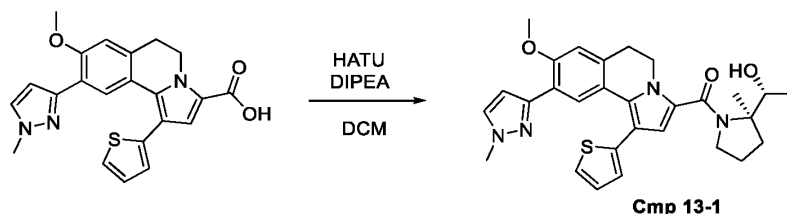
[00361] Step 2, Method 12

[00362] To a solution of potassium hydroxide (1.11 g, 19.5 mmol) in water (15 mL) was added ethyl 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (2.11 g, 4.9 mmol) in ethanol (45 mL). The resultant suspension was heated to 80 °C forming a solution and stirred overnight. The reaction mixture was cooled to rt, concentrated *in vacuo* and acidified to pH 1 with 1M aq. HCl. The acidic aqueous was extracted with DCM (3 x 20 mL). The organics were combined and passed through a phase separator cartridge. Some product precipitated on the cartridge. The filtrate was collected together with the concentrated organics to give 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (1.71 g, 82% yield) as a brown solid. RT (M2) = 0.83 [M+H]⁺ (ESI⁺) 406.2; ¹H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 8.09 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.50 (dd, *J* = 3.8, 2.6 Hz, 1H), 7.12 – 7.08 (m, 2H), 7.07 (s, 1H), 6.87 (s, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 4.55 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.08 (t, *J* = 6.5 Hz, 2H).

[00363] The following analogs were made by analogous method:

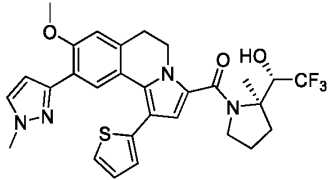
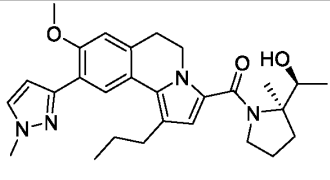
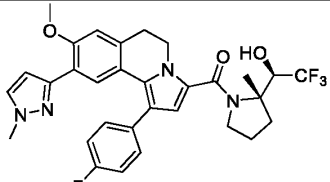
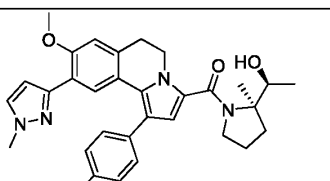
Structure	Name	LCMS
	8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-propyl-5H,6H-pyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylic acid	RT (M2) = 0.87 min, (ESI+) (M+H) ⁺ 366.2
	1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5H,6H-pyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylic acid	RT (M2) = 0.88 min, (ESI+) (M+H) ⁺ 418.3

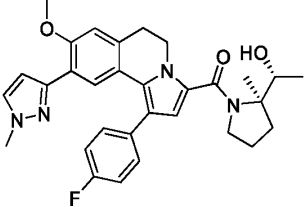
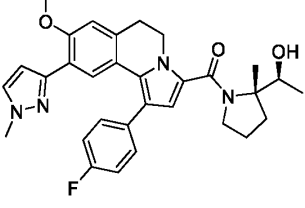
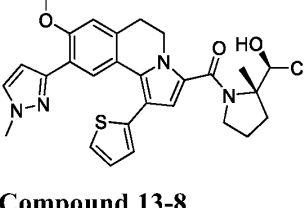
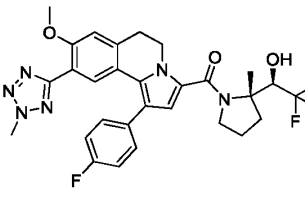
	8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylic acid	RT (M2) = 0.71 min, (ESI ⁺) (M+H) ⁺ 407.2
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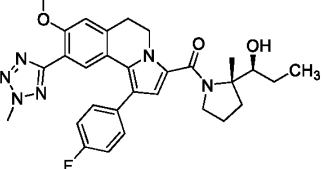
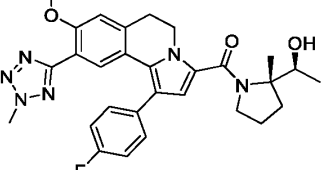
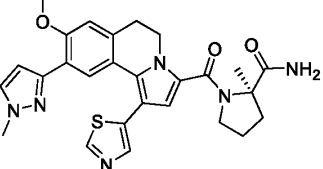
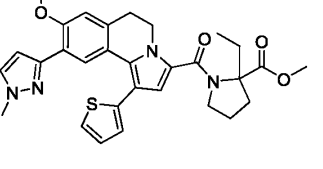
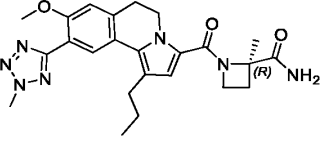
[00364] Synthetic Method 13**[00365] Scheme for Method 13****[00366] Step 1, Method 13**

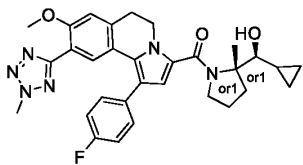
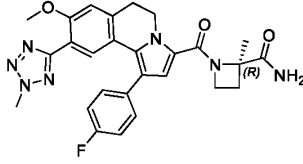
[00367] DIPEA (1.3 mL, 7.3 mmol, CAS 1205744-09-7), HATU (1.03 g, 2.7 mmol, CAS 148893-10-1) and (1*R*)-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (360 mg, 2.2 mmol, synthesized by method 15) were added to a stirred solution of 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (735 mg, 1.8 mmol, synthesized by method 12) in DCM (20 mL) at rt. After 24 h, the reaction mixture was retreated with (1*R*)-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (360 mg, 2.2 mmol) and DIPEA (1.3 mL, 7.3 mmol) and stirred for a further 2 days. The reaction mixture was diluted with DCM (20 mL) and water (20 mL), the organic phase passed through a phase separator and then concentrated *in vacuo* to yield the crude product as a brown oil. The crude was then purified by FCC (silica, eluting with 30-100% EtOAc in heptane). Product-containing fractions were collected, combined and the solvent removed *in vacuo* to yield a brown oil which was further purified by acidic prep HPLC (Method P2). Product containing fractions were collected, combined and the solvent removed *in vacuo* to give [(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (Compound 13-1) (415 mg, 44% yield) as a white solid. RT (M4) = 3.69 min [M+H]⁺ (ESI⁺) 517.3; ¹H NMR (500 MHz, DMSO) δ 8.08 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.12 – 7.06 (m, 2H), 7.03 (s, 1H), 6.53 (s, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 4.99 (d, *J* = 4.8 Hz, 1H), 4.51 – 4.40 (m, 1H), 4.38 – 4.26 (m, 1H), 4.16 – 4.03 (m, 1H), 3.93 – 3.79 (m, 4H), 3.76 (s, 3H), 3.69 – 3.59 (m, 1H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.14 – 1.99 (m, 1H), 1.87 – 1.67 (m, 2H), 1.59 – 1.45 (m, 4H), 1.01 (d, *J* = 6.3 Hz, 3H).

[00368] The following analogs were made by analogous method:

Structure	Name	LCMS
 Compound 13-2	[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-methyl-2-[(1 <i>S</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M5) = 3.97 min [M+H] ⁺ (ESI ⁺) 571.4
 Compound 13-3	[(2 <i>R</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 4.01 min [M+H] ⁺ (ESI ⁺) 477.4
 Compound 13-4	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>S</i>)-2-methyl-2-[(1 <i>R</i>)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone	RT (M4) = 4.22 min [M+H] ⁺ (ESI ⁺) 583.3
 Compound 13-5	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinolin-3-yl]-[(2 <i>R</i>)-2-[(1 <i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M4) = 3.99 min [M+H] ⁺ (ESI ⁺) 529.3

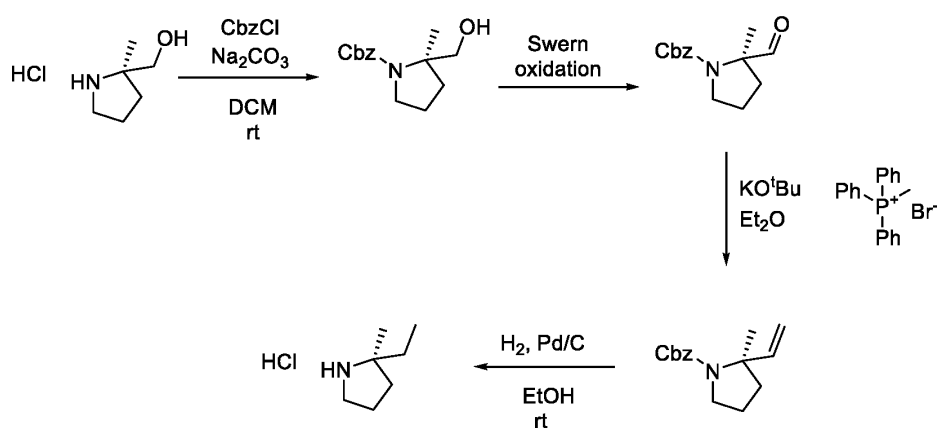
 Compound 13-6	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>R</i>)-2-[(1<i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M4) = 3.87 min [M+H]⁺ (ESI⁺) 529.3
 Compound 13-7	[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>S</i>)-2-[(1<i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M4) = 3.87 min [M+H]⁺ (ESI⁺) 529.3
 Compound 13-8	[(2<i>S</i>)-2-[(1<i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]methanone	RT (M4) = 3.77 min [M+H]⁺ (ESI⁺) 571.1
 Compound 13-9	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>S</i>)-2-methyl-2-[(1<i>R</i>)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone	RT (M4) = 3.97 min [M+H]⁺ (ESI⁺) 583.3

 Compound 13-10	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>S</i>)-2-[(1<i>S</i>*)-1-hydroxypropyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M4) = 4.04 min [M+H]⁺ (ESI⁺) 545.5
 Compound 13-11	[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinolin-3-yl]-[(2<i>S</i>)-2-[(1<i>S</i>)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone	RT (M4) = 3.60 min [M+H]⁺ (ESI⁺) 531.3
	(2<i>R</i>)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide	RT (M2) = 0.68 min [M+H]⁺ (ESI⁺) 517.2
	methyl 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl]pyrrolidine-2-carboxylate	RT (M2) = 1.03 min [M+H]⁺ (ESI⁺) 545.2
	(<i>R</i>)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl)-5,6-dihydropyrrolo[2,1-<i>a</i>]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	RT (M16) = 0.86 min [M+H]⁺ (ESI⁺) 464.3

 Compound 13-12	(<i>R</i>[*])-2-(<i>R</i>[*])-cyclopropyl(hydroxy)methyl-2-methylpyrrolidin-1-yl(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)methanone	RT (M28) = 3.17 min [M+H]⁺ (ESI⁺) 557.3
	(<i>R</i>)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide	RT (M13) = 1.53 min [M+H]⁺ (ESI⁺) 516.3

[00369] Synthetic Method 14

[00370] Scheme for Method 14



[00371] Step 1, Method 14

[00372] Cbz-Cl (3.1 mL, 21.8 mmol, CAS 501-53-1) was added dropwise to a stirring mixture of [(2*S*)-2-methylpyrrolidin-2-yl]methanol hydrochloride (3.00 g, 19.8 mmol, CAS 1408057-43-1), 2 M sodium carbonate (35.0 mL, 69.2 mmol) and DCM (45 mL) at 0 °C. The reaction was

stirred and allowed to warm to rt overnight. The reaction mixture was diluted with DCM and water, then the layers separated. The aqueous was extracted with further DCM, the combined organic passed through a phase separator and then concentrated. The material was purified by FCC (Silica, eluting 0-100% EtOAc in heptane) to give benzyl (2*S*)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate (3.82 g, 76% yield) as a colorless oil. RT (M2) = 0.80 min $[M^+H]^+$ (ESI⁺) 250.2

[00373] Step 2, Method 14

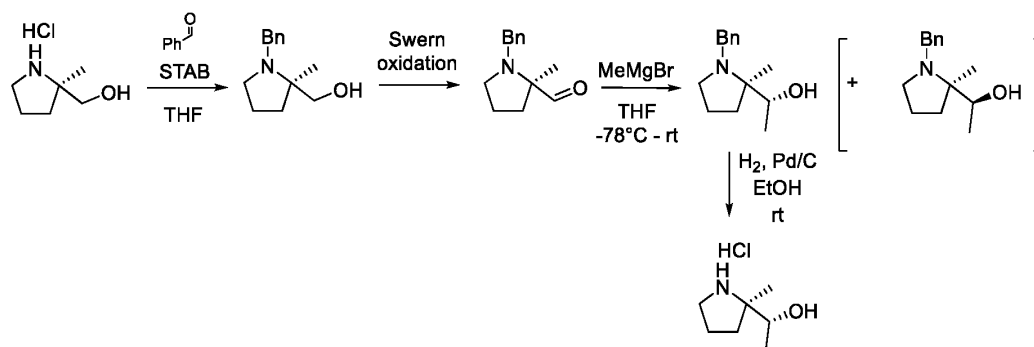
[00374] Oxalyl chloride (3.8 mL, 44.0 mmol, CAS 79-37-8) was dissolved in DCM (92 mL) and cooled to -78 °C. DMSO (6.3 mL, 88.5 mmol) was added dropwise and the reaction stirred at -78 °C for 10 min. Benzyl (2*S*)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate (3.00 g, 12.0 mmol) (as a solution in 5 mL DCM) was added, and stirred at -78 °C for 15 min. Triethylamine (21.0 mL, 0.150 mol) was added dropwise and the reaction stirred at -78 °C for 3 h. The reaction was quenched by addition of water (20 mL), warmed to rt, diluted with DCM (20 mL) and saturated aq. NaHCO₃ solution (50 mL) added. The aqueous was extracted into DCM (3 x 50 mL), dried over MgSO₄ and concentrated under reduced pressure. The resulting oil was purified by FCC (silica, eluting 0-60% EtOAc in heptane) to give benzyl (2*S*)-2-formyl-2-methyl-pyrrolidine-1-carboxylate (2.13 g, 65% yield, 91% purity) as a colorless oil. RT (M2) = 0.87 min $[M^+H]^+$ (ESI⁺) 248.1.

[00375] Step 3, Method 14

[00376] Potassium *t*-butoxide (1.82 g, 16.2 mmol) was added to a suspension of methyl(triphenyl)phosphonium bromide (5.78 g, 16.2 mmol, CAS 1779-49-3) in diethyl ether (130 mL) and the reaction was stirred at rt for 2 h under N₂. A solution of benzyl (2*S*)-2-formyl-2-methyl-pyrrolidine-1-carboxylate (2.00 g, 8.1 mmol) in diethyl ether (20 mL) was then added dropwise. The reaction was then stirred for 2 h before it was diluted with heptane (50 mL) and filtered. The filtrand was washed with diethyl ether/heptane (1:2 mixture, 150 mL) and the combined filtrate was concentrated under reduced pressure. The resulting solid was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give benzyl (2*S*)-2-methyl-2-vinyl-pyrrolidine-1-carboxylate (1.64 g, 79% yield) as a colorless oil. RT (M2) = 1.01 min $[M^+H]^+$ (ESI⁺) 246.2.

[00377] Step 4, Method 14

[00378] To a solution of benzyl (2*S*)-2-methyl-2-vinyl-pyrrolidine-1-carboxylate (1.64 g, 6.7 mmol) in ethanol (65 mL) was added palladium on carbon (10%, 683 mg, 640 μ mol) under N_{2(g)}. The mixture was stirred under an atmosphere of H_{2(g)} at rt for 4 h. The reaction mixture was filtered through Celite, washing with MeOH. To the filtrate was added 4 M HCl in dioxane (3.3 mL, 13.4 mmol), stirred at rt for 10 min and then concentrated to give a yellow semi-solid. The residue was dissolved in DCM and concentrated (x3) to give (2*S*)-2-ethyl-2-methyl-pyrrolidine hydrochloride (958 mg, 94% yield) as a white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.11 (br s, 1H), 8.94 (br s, 1H), 3.19 (s, 2H), 2.03 – 1.86 (m, 2H), 1.76 – 1.65 (m, 4H), 1.25 (br s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).

[00379] Synthetic Method 15**[00380] Scheme for Method 15****[00381] Step 1, Method 15**

[00382] Sodium triacetoxyborohydride (2.80 g, 13.2 mmol, CAS 56553-60-7) was added to a stirred solution of [(2*R*)-2-methylpyrrolidin-2-yl]methanol hydrochloride (1.25 g, 8.2 mmol, CAS 1408057-43-1) and benzaldehyde (1.0 mL, 9.9 mmol, CAS 100-52-7) in anhydrous THF (41 mL) at rt. The solution was stirred for 24 h. Sat. aq. NH₄Cl was added (50 mL) and the resulting mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with sat. aq. NH₄Cl (2 x 30 mL). The aqueous layers were combined, basified to pH 10 using sat. aq. Na₂CO₃ solution and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (30 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give [(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]methanol (1.37 g, 6.0 mmol, 73% yield) as a pale yellow oil which was used without further purification. RT (M10) = 0.77 min [M+H]⁺ (ESI⁺) 206.2; ¹H NMR (500 MHz, DMSO) δ 7.31 – 7.24 (m, 4H), 7.23 – 7.16 (m, 1H), 4.37 – 4.24 (m, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.43 (d, *J* = 13.4 Hz, 1H), 3.32 – 3.29 (m, 2H), 2.70 – 2.61 (m, 1H), 2.43 (q, *J* = 8.1 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.69 – 1.54 (m, 2H), 1.51 – 1.41 (m, 1H), 1.00 (s, 3H).

[00383] Step 2, Method 15

[00384] Oxalyl chloride (5.0 mL, 58.3 mmol, CAS 79-37-8) was dissolved in DCM (70 mL) and cooled to -78 °C. DMSO (8.5 mL, 0.120 mol) was added dropwise and the reaction mixture

stirred at -78 °C for 30 min. [(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]methanol (3.38 g, 17.0 mmol) (as a solution in 10 mL DCM) was added, and the reaction mixture stirred at -78 °C for 30 min. Triethylamine (27.0 mL, 0.194 mol, CAS 121-44-8) was added dropwise and the reaction stirred at -78 °C for 15 min before warming to rt and stirring overnight. The reaction mixture was quenched by addition of water (5 mL) and warmed to rt. DCM (10 mL) and sat. aq. NaHCO₃ (20 mL) were added, the layers separated and the aqueous extracted with DCM (3 x 20 mL). The organics were combined, dried over MgSO₄ and concentrated *in vacuo*. The resulting oil was purified by FCC (silica, eluting with 0-20% EtOAc in heptane) to give (2*R*)-1-benzyl-2-methyl-pyrrolidine-2-carbaldehyde (3.29 g, 81% Yield) as an orange oil. RT (M10) = 0.83 min [M+H]⁺ (ESI⁺) 204.4; ¹H NMR (400 MHz, DMSO) δ 9.34 (s, 1H), 7.36 – 7.27 (m, 4H), 7.23 (ddt, *J* = 7.7, 5.7, 2.4 Hz, 1H), 3.63 – 3.51 (m, 2H), 2.86 (td, *J* = 8.6, 4.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.01 (ddd, *J* = 12.5, 10.1, 6.5 Hz, 1H), 1.90 – 1.70 (m, 2H), 1.59 – 1.49 (m, 1H), 1.09 (s, 3H).

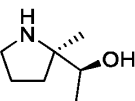
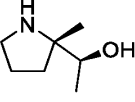
[00385] Step 3, Method 15

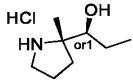
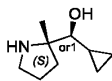
[00386] (2*R*)-1-benzyl-2-methyl-pyrrolidine-2-carbaldehyde (10.0 g, 49.2 mmol) was dissolved in anhydrous THF (106 mL) and cooled to 0 °C under N₂. 3 M bromo(methyl)magnesium in ether (25 mL, 73.8 mmol, CAS 75-16-1) was added over 10 min and the reaction mixture was stirred for 30 min before warming to rt. The reaction mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO₄) and concentrated *in vacuo*. The crude was purified by FCC (C18 silica, eluting with 0-100% EtOAc in heptane) to give (1*R*)-1-[(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]ethanol (6.9 g, 64% yield) as a colorless oil. ¹H NMR (500 MHz, DMSO) δ 7.29 (d, *J* = 4.5 Hz, 4H), 7.20 (h, *J* = 4.1 Hz, 1H), 4.38 (d, *J* = 5.3 Hz, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.63 (p, *J* = 6.2 Hz, 1H), 3.23 (d, *J* = 13.5 Hz, 1H), 2.70 (td, *J* = 8.4, 2.6 Hz, 1H), 2.35 – 2.22 (m, 1H), 1.86 (ddd, *J* = 12.8, 9.9, 5.0 Hz, 1H), 1.67 – 1.56 (m, 1H), 1.57 – 1.43 (m, 1H), 1.32 (ddd, *J* = 12.8, 9.0, 7.0 Hz, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 3H). The minor diastereoisomer (1*S*)-1-[(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]ethanol (430 mg, 4% yield) was also isolated as a colorless oil. RT (M2) = 0.39 min [M+H]⁺ (ESI⁺) 220.2

[00387] Step 4, Method 15

[00388] A solution of (1*R*)-1-[(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]ethanol (6.90 g, 31.5 mmol) and palladium on carbon (10%, 0.70 g, 658 μ mol, CAS 7440-05-3) in ethanol (200 mL) was stirred under an atmosphere of H₂ at rt. After 18 h the reaction was stopped, filtered through a pad of Celite, cooled to 0 °C and 2 M HCl in ether (15 mL, 62.9 mmol, CAS 7647-01-0) was added. The resulting solution was stirred for 10 min at 0 °C and allowed to warm to rt over 30 min. The solvent was removed *in vacuo*. The residual oil was dissolved in ethanol (200 mL), palladium on carbon (10%, 0.70 g, 658 μ mol, CAS 7440-05-3) added and the reaction stirred under a hydrogen atmosphere for a further 24 h. The mixture was filtered through a pad of celite, washed through with methanol (50 mL) and 2 M HCl in ether (15 mL, 62.9 mmol, CAS 7647-01-0) was added. The solvent was removed *in vacuo*, and DCM added to the resultant oil and the mixture was concentrated *in vacuo* to give (1*R*)-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (3.50 g, 67% yield) as a light pink solid. ¹H NMR (400 MHz, DMSO) δ 8.86 (s, 1H), 8.58 (s, 1H), 3.78 (q, *J* = 6.4 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.22 – 3.08 (m, 2H), 2.05 – 1.84 (m, 2H), 1.82 – 1.72 (m, 1H), 1.69 – 1.57 (m, 1H), 1.19 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H).

[00389] The following analogs were made by analogous method:

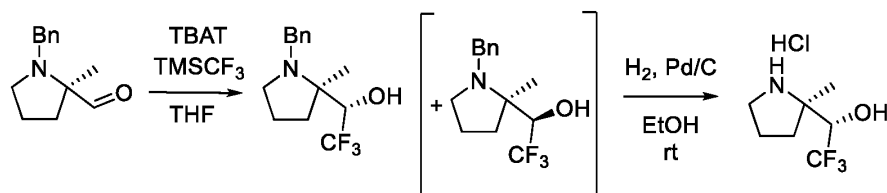
Structure	Name	NMR
HCl 	(1 <i>S</i>)-1-[(2 <i>R</i>)-2-methylpyrrolidin-2-yl]ethan-1-ol hydrochloride	¹ H NMR (500 MHz, DMSO) δ 9.02 (s, 1H), 8.45 (s, 1H), 5.52 (d, <i>J</i> = 5.0 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.25 – 3.09 (m, 2H), 2.08 – 1.80 (m, 3H), 1.63 – 1.53 (m, 1H), 1.21 (s, 3H), 1.10 (d, <i>J</i> = 6.4 Hz, 3H).
HCl 	(1 <i>S</i>)-1-[(2 <i>S</i>)-2-methylpyrrolidin-2-yl]ethan-1-ol hydrochloride	¹ H NMR (500 MHz, DMSO) δ 8.86 (s, 1H), 8.58 (s, 1H), 5.49 (s, 1H), 3.77 (q, <i>J</i> = 6.4 Hz, 1H), 3.24 – 3.11 (m, 2H), 2.06 – 1.85 (m, 2H), 1.83 – 1.73 (m, 1H), 1.70 – 1.60 (m, 1H), 1.19 (s, 3H), 1.09 (d, <i>J</i> = 6.4 Hz, 3H).

	(1 <i>S</i> [*])-1-[(2 <i>S</i>)-2-methylpyrrolidin-2-yl]propan-1-ol hydrochloride	¹ H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 8.88 (s, 1H), 5.16 (t, J = 5.9 Hz, 1H), 4.41 (s, 1H), 3.74 – 3.70 (m, 1H), 3.22 – 3.09 (m, 1H), 2.25 – 2.12 (m, 1H), 2.08 – 1.85 (m, 2H), 1.84 – 1.72 (m, 1H), 1.47 – 1.37 (m, 1H), 1.33 – 1.24 (m, 1H), 1.19 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H).
	(S [*])-cyclopropyl-[(2 <i>S</i>)-2-methylpyrrolidin-2-yl]methanol	¹ H NMR (400 MHz, CDCl ₃) δ = 4.90 (q, J = 5.9 Hz, 1H), 3.08 (td, J = 6.7, 10.9 Hz, 1H), 2.98 - 2.81 (m, 3H), 1.37 - 1.31 (m, 3H), 1.30 - 1.23 (m, 4H), 0.95 - 0.78 (m, 3H), 0.67 - 0.58 (m, 1H), 0.58 - 0.46 (m, 3H), 0.43 - 0.26 (m, 3H), 0.17 (qd, J = 4.8, 9.7 Hz, 1H)

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00390] Synthetic Method 16

[00391] Scheme for Method 16



[00392] Step 1, Method 16

[00393] Trimethyl(trifluoromethyl)silane (2.4 mL, 16.3 mmol, CAS 81290-20-2) in anhydrous THF (50 mL) was added to a flask containing (2*R*)-1-benzyl-2-methyl-pyrrolidine-2-carbaldehyde (2.21 g, 10.9 mmol, synthesized by method 15, step 2) under N₂. The reaction was cooled to 0 °C and tetrabutylammonium difluorotriphenylsilicate (60 mg, 0.11 mmol, CAS 163931-61-1) was added. The reaction was stirred at 0 °C for 1 h and then allowed to warm to rt. After stirring at rt

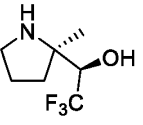
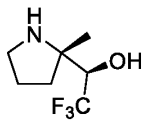
for 1 h, the reaction mixture was concentrated *in vacuo*, dissolved in DCM (3 mL) and 1M aq. HCl (8 mL), and stirred vigorously for 5 h. Sat. aq. NaHCO₃ was added until pH 10 was reached, the layers separated and the aqueous extracted with DCM (10 x 25 mL). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo* to give a brown oil which was purified by FCC (silica, eluting with 0-100% EtOAc in heptane then 0-100% MeOH in EtOAc). Product containing fractions were concentrated *in vacuo* to give (1*S*)-1-[(2*R*)-1-benzyl-2-methylpyrrolidin-2-yl]-2,2,2-trifluoro-ethanol (960 mg, 32% yield) as a yellow oil. RT (M2) = 0.44 min [M+H]⁺ (ESI⁺) 274.1; ¹H NMR (500 MHz, DMSO) δ 7.34 – 7.26 (m, 4H), 7.25 – 7.16 (m, 1H), 6.31 (s, 1H), 4.15 (d, *J* = 13.4 Hz, 1H), 3.99 (q, *J* = 8.5 Hz, 1H), 3.31 (d, *J* = 13.4 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.30 (q, *J* = 8.5 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.70 – 1.60 (m, 1H), 1.60 – 1.53 (m, 1H), 1.53 – 1.45 (m, 1H), 1.15 (s, 3H).

[00394] Mixed fractions (containing minor diastereoisomer) were concentrated to give a colorless oil (625 mg), that was purified by FCC (silica, 0-100% DCM in heptane) to give (1*R*)-1-[(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]-2,2,2-trifluoro-ethanol (287 mg, 10% yield) as a colorless oil. ¹H NMR (500 MHz, DMSO) δ 7.35 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 5.64 (s, 1H), 4.05 (q, *J* = 8.5 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.33 – 3.28 (m, 1H), 2.72 (td, *J* = 8.2, 3.9 Hz, 1H), 2.35 (q, *J* = 8.1 Hz, 1H), 2.25 – 2.13 (m, 1H), 1.73 – 1.56 (m, 2H), 1.49 – 1.38 (m, 1H), 1.12 – 1.10 (m, 3H).

[00395] Step 2, Method 16

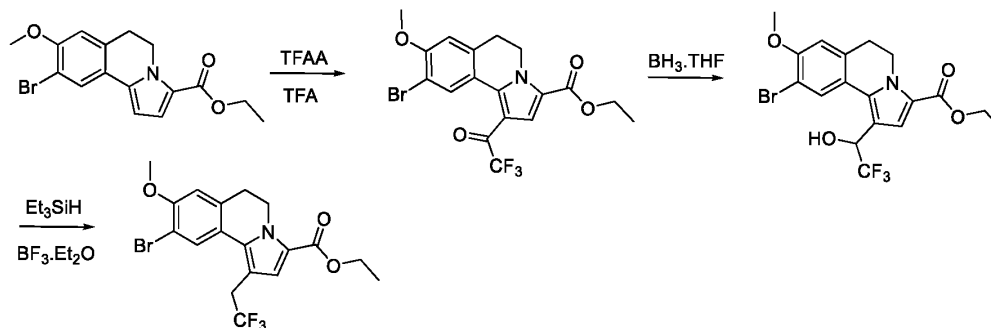
[00396] A solution of palladium on carbon (10%, 234 mg, 220 μmol, CAS 7440-05-3) and (1*S*)-1-[(2*R*)-1-benzyl-2-methyl-pyrrolidin-2-yl]-2,2,2-trifluoro-ethanol (300 mg, 1.1 mmol) in ethanol (7 mL) was stirred under an atmosphere of H₂ at rt overnight. The reaction mixture was filtered through Celite washing with DCM (100 mL) and methanol (25 mL). 2 M HCl in diethyl ether (1.0 mL, 2.0 mmol, CAS 7647-01-0) was added to the filtrate and the mixture was allowed to stand for 5 min before it was concentrated *in vacuo* to give (1*S*)-2,2,2-trifluoro-1-[(2*R*)-2-methylpyrrolidin-2-yl]ethanol hydrochloride (240 mg, 95% yield) as a pink solid. ¹H NMR (400 MHz, DMSO) δ 9.11 (s, 2H), 7.55 (d, *J* = 6.3 Hz, 1H), 4.57 – 4.34 (m, 1H), 3.28 – 3.16 (m, 2H), 2.16 – 1.93 (m, 3H), 1.93 – 1.74 (m, 1H), 1.29 (s, 3H).

[00397] The following analogs were made by analogous method:

Structure	Name	NMR
	(1 <i>R</i>)-2,2,2-trifluoro-1-[(2 <i>R</i>)-2-methylpyrrolidin-2-yl]ethan-1-ol hydrochloride	¹ H NMR (400 MHz, DMSO) δ 9.19 (s, 2H), 7.35 (d, <i>J</i> = 6.7 Hz, 1H), 4.45 (s, 1H), 3.30 – 3.21 (m, 2H), 2.14 – 1.91 (m, 3H), 1.86 – 1.71 (m, 1H), 1.32 (s, 3H)
	(1 <i>R</i>)-2,2,2-trifluoro-1-[(2 <i>S</i>)-2-methylpyrrolidin-2-yl]ethan-1-ol hydrochloride	¹ H NMR (400 MHz, DMSO) δ 9.17 (s, 2H), 7.55 (d, <i>J</i> = 6.3 Hz, 1H), 4.57 – 4.42 (m, 1H), 3.27 – 3.14 (m, 2H), 2.17 – 1.91 (m, 3H), 1.89 – 1.75 (m, 1H), 1.29 (d, <i>J</i> = 1.6 Hz, 3H).

[00398] Synthetic Method 17

[00399] Scheme for Method 17



[00400] Step 1, Method 17

[00401] To a solution of ethyl 9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (118 g, 336.94 mmol) in TFA (600 mL) was added with TFAA (353.84 g, 1.68 mol). The mixture was stirred at 80°C for 12 hr under N₂ atmosphere. The mixture was concentrated, added with H₂O (500 mL), solid Na₂CO₃ to adjust pH=8. The mixture was extracted with EtOAc

(300 mL×4). The organic layers were concentrated under reduced pressure to give a crude product, which was triturated with Petroleum ether (400 mL) at 20°C for 15 min and filtered. The solid was collected and dried under vacuum to afford ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroacetyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate_(118 g, 78%) as a brown solid. RT (M11) = 2.20 min $[M^+H]^+$ (ESI⁺) 446.1/448.2.

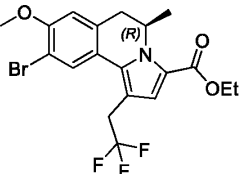
[00402] Step 2, Method 17

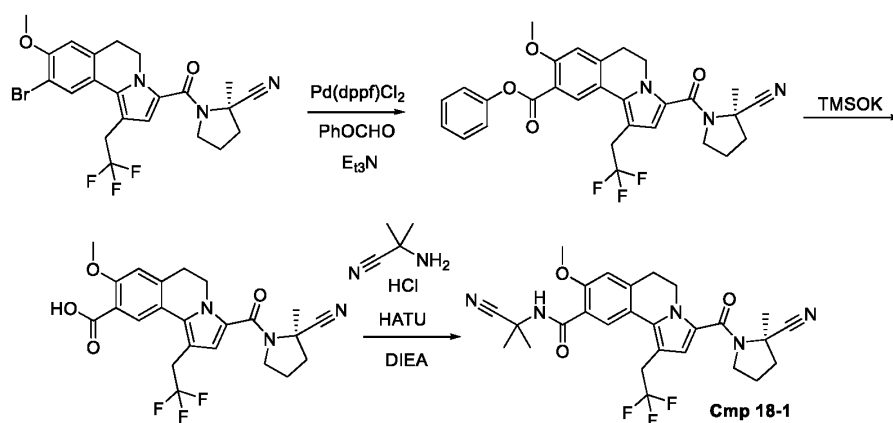
[00403] To a solution of ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroacetyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (90 g, 201.70 mmol) in THF (900 mL) was added with BH₃.THF (1 M, 221.87 mL) at 0°C. The mixture was stirred at 25°C for 2 h under N₂ atmosphere. 240 mL sat. NaHCO₃ was added with and extracted with EtOAc (150 mL×3). The combined organic phase was washed with brine (100 mL), dried by Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with petroleum ether (100 mL) at 25°C for 10 min and filtered to afford ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoro-1-hydroxyethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate_(80 g, 88%) as a brown solid. RT (M14) = 0.98 min $[M^+H]^+$ (ESI⁺) 448.0/450.0.

[00404] Step 3, Method 17

[00405] To a solution of ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoro-1-hydroxyethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (105 g, 234.25 mmol) in DCM (1200 mL) was added with BF₃.Et₂O (166.24 g, 1.17 mol, 144.55 mL) and Et₃SiH (136.19 g, 1.17 mol, 187.08 mL). The mixture was stirred at 20°C for 1 h under N₂ atmosphere. The mixture was added with H₂O (100 mL). The aqueous layer was separated and extracted with DCM (200 mL×3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =20/1 to 1/1) to afford ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate_(80 g, 79.01%) as a white solid. RT (M25) = 2.89 min $[M^+H]^+$ (ESI⁺) 432.0/434.1.

[00406] The following analog was made by analogous method:

Structure	Name	LCMS
	ethyl (<i>R</i>)-9-bromo-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo [2,1-a]isoquinoline-3-carboxylate	RT (M11) = 2.18 min [M+H] ⁺ (EST ⁺) 446.2/448.2

[00407] Synthetic Method 18**[00408] Scheme for Method 18****[00409] Step 1, Method 18**

[00410] In a 20 mL pressure tube, a stirred solution of (2*R*)-1-[9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (400 mg, 0.8 mmol, synthesized by method 6), phenyl formate (450 μ L, 4.0 mmol, CAS 1864-94-4) and triethylamine (560 μ L, 4.0 mmol, CAS 121-44-8) in anhydrous DMF (5 mL) was degassed with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (59 mg, 81 μ mol, CAS 72287-26-4) was added, the solution degassed with nitrogen for 5 min and heated to 100 °C for 4 h. The reaction mixture was cooled to rt, the pressure released and the vessel purged with nitrogen. The mixture was concentrated *in vacuo*, diluted with water (20 mL) and extracted with dichloromethane (3 x

20 mL). The combined organic extracts were concentrated *in vacuo* to afford a residue that was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give phenyl 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (290 mg, 65% yield) as a light yellow solid. RT (M2) = 1.07 min, (ESI⁺) (M+H)⁺ 538.4.

[00411] Step 2, Method 18

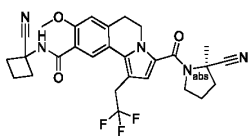
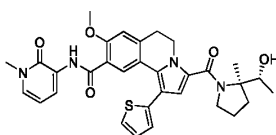
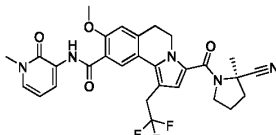
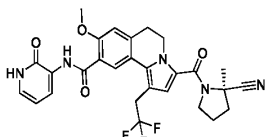
[00412] To a solution of phenyl 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (290 mg, 0.5 mmol) in THF (7 mL) was added potassium trimethylsilanolate (350 mg, 2.6 mmol, CAS 10519-96-7) and the reaction stirred at rt for 18 h. The reaction mixture was concentrated and treated with water (10 mL). The mixture was acidified to pH 1 with 1 M aq HCl and the formation of a precipitate was observed. The mixture was extracted with ethyl acetate (3 x 30 mL). The organics were combined, dried (MgSO₄), filtered and the solvent removed *in vacuo* to give 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (86% purity, 280 mg, 100% Yield) as a yellow solid. RT (M2) = 0.84 min, (ESI⁺) (M+H)⁺ 462.4.

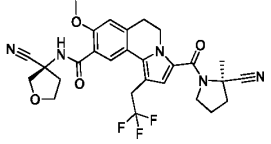
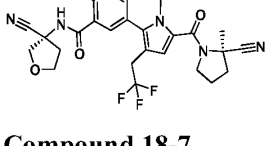
[00413] Step 3, Method 18

[00414] HATU (145 mg, 0.4 mmol, CAS 148893-10-1) and 2-amino-2-methylpropanenitrile hydrochloride (1:1) (31 mg, 0.2 mmol, CAS 50846-36-1) were added to a stirred solution of 3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (88% purity, 100 mg, 0.2 mmol) and DIPEA (130 µL, 0.8 mmol, CAS 7087-68-5) in DCM (1.5 mL) in anhydrous DMF (0.5 mL) at RT and the reaction mixture stirred overnight. The reaction mixture was poured into water (3 mL) and extracted with DCM (3 x 3 mL). The organic phases were combined, passed through a phase separator and concentrated *in vacuo*. The crude was purified by acidic prep HPLC (Method P2) and the product containing fractions freeze dried to give (*R*)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-N-(2-cyanopropan-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide (Compound 18-1) (34 mg, 33% yield) as a white solid.; ¹H NMR

(400 MHz, DMSO) δ 8.44 (s, 1H), 8.00 (s, 1H), 7.24 (s, 1H), 6.70 (s, 1H), 4.43 – 4.20 (m, 2H), 3.95 (s, 3H), 3.89 – 3.81 (m, 1H), 3.81 – 3.66 (m, 3H), 3.05 (t, J = 6.5 Hz, 2H), 2.46 (d, J = 6.0 Hz, 1H), 2.21 – 2.09 (m, 1H), 2.07 – 1.96 (m, 1H), 1.95 – 1.84 (m, 1H), 1.74 (s, 3H), 1.70 (s, 6H); RT (M4) = 3.67 min, (ESI⁺) (M+H)⁺ 528.1.

[00415] The following analogs were made by analogous method:

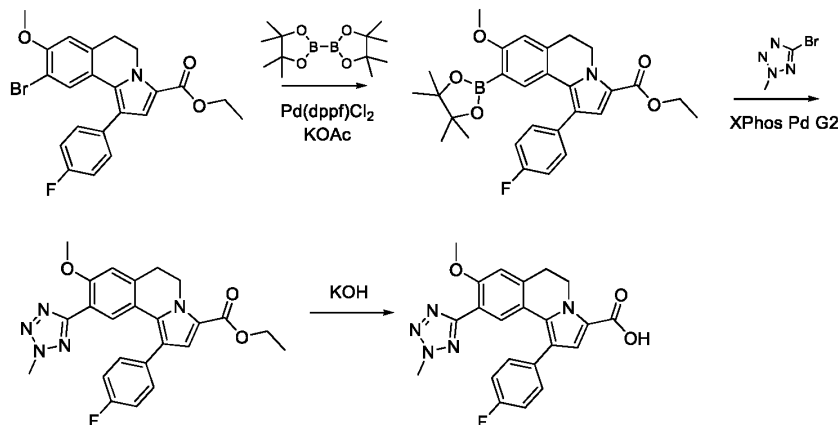
Structure	Name*	LCMS
 Compound 18-2	<i>N</i> -(1-cyanocyclobutyl)-3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.66 min, (ESI ⁺) (M+H) ⁺ 540.3
 Compound 18-3	3-[(2 <i>R</i>)-2-[(1 <i>R</i>)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M5) = 0.83 min, (ESI ⁺) (M+H) ⁺ 587.4
 Compound 18-4	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(1-methyl-2-oxo-3-pyridyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.64 min, (ESI ⁺) (M+H) ⁺ 568.1
 Compound 18-5	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy- <i>N</i> -(2-oxo-1 <i>H</i> -pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.26 min, (ESI ⁺) (M+H) ⁺ 554.2

 Compound 18-6	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>R</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.59 min, (ESI ⁺) (M+H) ⁺ 556.2
 Compound 18-7	3-[(2 <i>R</i>)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]- <i>N</i> -[(3 <i>S</i> *)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-9-carboxamide	RT (M4) = 3.58 min, (ESI ⁺) (M+H) ⁺ 556.2

*denotes unknown stereochemistry, isolated from a diastereomeric mixture using SCF chromatography

[00416] Synthetic Method 19

[00417] Scheme for Method 19



[00418] Step 1, Method 19

[00419] 4,4,5,5-Tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (19.0 g, 74.7 μ mol, CAS 73183-34-3), ethyl 9-bromo-1-(4-fluorophenyl)-8-

methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (30.2 g, 67.9 mmol) and potassium acetate (20.0 g, 203.4 mmol) were dissolved in anhydrous 1,4-dioxane (530 mL). The suspension was sparged with nitrogen for 5 minutes before the addition of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (2.8 g, 3.4 mmol, CAS 95464-05-4) and the suspension was sparged with nitrogen for 5 minutes. The mixture was stirred under nitrogen and heated at 90 °C for 16 hours. The reaction was cooled to rt and filtered, washing with DCM (2 x 100 mL). The filtrate was concentrated and purified by trituration with DCM to give ethyl 1-(4-fluorophenyl)-8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14.8 g, 26.4 mmol, 39% Yield) as an off white solid.

[00420] A second crop precipitated from the filtrate and was filtered to give ethyl 1-(4-fluorophenyl)-8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (7.9 g, 14.5 mmol, 21% yield) as an off white solid. ¹H NMR (400 MHz, DMSO) δ 7.43 – 7.32 (m, 3H), 7.27 – 7.15 (m, 2H), 6.93 (d, *J* = 17.2 Hz, 2H), 4.57 – 4.49 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 4.1 Hz, 3H), 3.10 (t, *J* = 6.7 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 8.0 Hz, 12H); RT (M2) = 1.24 min, (ESI⁺) (M+H)⁺ 492.3.

[00421] Step 2, Method 19

[00422] A solution of ethyl 1-(4-fluorophenyl)-8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14.8 g, 30.0 mmol) in 1,4-dioxane (380 mL) and water (150 mL), 5-bromo-2-methyl-tetrazole (6.4 g, 39.1 mmol, CAS 16681-80-4), dicesium carbonate (39.2 g, 120.2 mmol, CAS 534-17-8) was degassed with nitrogen and XPhos Pd G2 (4.7 g, 3.0 mmol, CAS 1310584-14-5) was added. The reaction was heated to 80 °C for 2 h. The reaction was allowed to cool to RT and the organics concentrated *in vacuo*. The residual aqueous was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The organics were dried (MgSO₄) and concentrated. The residue was triturated with DCM to give ethyl 1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12.8 g, 27.1 mmol, 90% Yield) as an off white solid. ¹H NMR (400 MHz, DMSO)

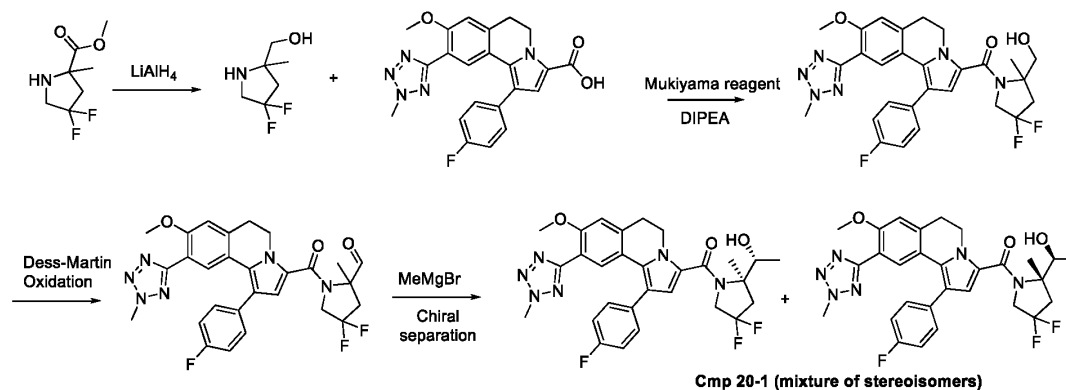
δ 7.70 (s, 1H), 7.48 – 7.38 (m, 2H), 7.26 (s, 1H), 7.24 – 7.15 (m, 2H), 6.93 (s, 1H), 4.62 – 4.54 (m, 2H), 4.33 (s, 3H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.88 (s, 3H), 3.18 (t, $J = 6.5$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); RT (M2) = 1.07 min, (ESI⁺) (M+H)⁺ 448.2.

[00423] Step 3, Method 19

[00424] To a solution of ethyl 1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12.8 g, 28.5 mmol) in ethanol (177 mL) and water (44 mL) was added potassium hydroxide (6.5 g, 114.0 mmol). The resultant suspension was heated to 80 °C and stirred for 2 h. The reaction was cooled to RT, partially concentrated (to remove any ethanol) and diluted with water (50 mL) then acidified to pH 1 with 1 M aq. HCl. The formation of a precipitate was observed. The mixture was filtered, and the grey precipitate dried under vacuum to give 1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (10.8 g, 25.7 mmol, 90% Yield) as an off white solid. ¹H NMR (400 MHz, DMSO) δ 12.46 (s, 1H), 7.69 (s, 1H), 7.47 – 7.37 (m, 2H), 7.25 (s, 1H), 7.24 – 7.14 (m, 2H), 6.89 (s, 1H), 4.62 – 4.54 (m, 2H), 4.33 (s, 3H), 3.88 (s, 3H), 3.17 (t, $J = 6.5$ Hz, 2H); RT (M2) = 0.82 min, (ESI⁺) (M+H)⁺ 420.2.

[00425] The following analogs were made by analogous method:

Structure	Name	LCMS
	8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylic acid	RT (M24) = 2.04 min, (ESI ⁺) (M+H) ⁺ 368.1
	1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carboxylic acid	RT (M13) = 1.29 min, (ESI ⁺) (M+H) ⁺ 421.2

[00426] Synthetic Method 20**[00427] Scheme for Method 20****[00428] Step 1, Method 20**

[00429] 2.4 M LiAlH₄ (1.2 mL, 2.80 mmol) was added to a stirred solution of methyl 4,4-difluoro-2-methyl-pyrrolidine-2-carboxylate hydrochloride (301 mg, 1.4 mmol, CAS 16853-85-3) in anhydrous THF (5 mL) at 0 °C, under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 60 min. The reaction mixture was quenched with water and extracted with DCM. 4 M HCl in dioxane (2 mL) was added to the combined organics and they were dried and concentrated to give (4,4-difluoro-2-methyl-pyrrolidin-2-yl)methanol hydrochloride (260 mg, 89% Yield) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.84 (s, 2H), 5.79 (s, 1H), 3.98 – 3.62 (m, 3H), 3.57 – 3.46 (m, 1H), 2.65 – 2.52 (m, 1H), 2.47 – 2.28 (m, 1H), 1.40 (s, 3H).

[00430] Step 2, Method 20

[00431] 2-Chloro-1-methylpyridinium iodide (1.6 g, 6.2 mmol) was added to a stirred suspension of 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (1.0 g, 2.5 mmol, synthesized by method 19), DIPEA (1.3 mL, 7.4 mmol, CAS 7087-68-5) and (4,4-difluoro-2-methyl-pyrrolidin-2-yl)methanol hydrochloride (694 mg, 3.7 mmol) in DMF (13 mL). The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with water and DCM the resultant precipitate isolated by filtration. The filtrate was purified by FCC (silica, eluting with 0-100% EtOAc in heptane). The

product containing fractions were concentrated *in vacuo* to give [4,4-difluoro-2-(hydroxymethyl)-2-methyl-pyrrolidin-1-yl]-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (426 mg, 28% Yield) a white solid. RT (M2) = 1.01 min, $[M+H]^+$ (ESI⁺) 553.3.

[00432] Step 3, Method 20

[00433] Dess-Martin periodinane (491 mg, 1.2 mmol) was added to a stirred a solution of [4,4-difluoro-2-(hydroxymethyl)-2-methyl-pyrrolidin-1-yl]-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (426 mg, 0.8 mmol) in DCM (50 mL). The reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with DCM and washed with water. The precipitate was filtered, and the organics were separated, dried and concentrated. The crude was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give 4,4-difluoro-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbaldehyde (321 mg, 67% Yield) as a white solid. RT (M2) = 0.98 min, $[M+H]^+$ (ESI⁺) 551.0.

[00434] Step 4, Method 20

[00435] 4,4-Difluoro-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbaldehyde (321 mg, 0.6 mmol) was dissolved in anhydrous THF (5 mL) and cooled to 0 °C under nitrogen. 3 M Bromo(methyl)magnesium (290 µL, 0.9 mmol) was added over 10 min, and the reaction mixture was stirred for 30 min then allowed to warm to RT. The reaction mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO₄) and concentrated. The compound was purified by acidic prep HPLC (Method P2) to give the crude product as a white solid.

[00436] The method was repeated on a larger scale and both batches were combined for chiral separation. Yields based on combined theoretical yield.

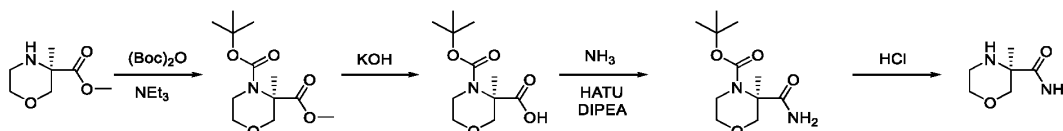
[00437] Chiral separation on Waters Thar SFC [Column: Chiralpak AD-H (4.6 x 250mm, 5µm) at 40°C; Isocratic eluent: 8 70:30 Heptane: Ethanol; Flow rate: 18mL/min; Dilution solvent:

MeOH, i-PrOH, acetonitrile; injection volume: 250 μ L] to give [1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R* or *S*)-4,4-difluoro-2-methyl-2-[(1*R* or *S*)-1-hydroxyethyl]pyrrolidin-1-yl]methanone (Compound 20-1) (26 mg 7% Yield), as a white powder. RT (M4) = 3.64 min, (ESI⁺) (M+H)⁺ 567.2; ¹H NMR (400 MHz, DMSO) δ 7.72 (s, 1H), 7.50 – 7.41 (m, 2H), 7.23 (s, 1H), 7.22 – 7.13 (m, 2H), 6.71 (s, 1H), 5.03 (d, *J* = 5.1 Hz, 1H), 4.55 – 4.48 (m, 1H), 4.48 – 4.35 (m, 2H), 4.33 (s, 3H), 4.32 – 4.21 (m, 1H), 4.17 – 4.06 (m, 1H), 3.87 (s, 3H), 3.13 (t, *J* = 6.5 Hz, 2H), 2.74 – 2.58 (m, 1H), 2.07 (t, *J* = 15.5 Hz, 1H), 1.68 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H).

[00438] [1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S* or *R*)-4,4-difluoro-2-methyl-2-[(1*S* or *R*)-1-hydroxyethyl]pyrrolidin-1-yl]methanone (Compound 20-1, isomer 2) (28 mg, 6% Yield), as a white powder. RT (M4) = 3.64 min, (ESI⁺) (M+H)⁺ 567.2; ¹H NMR (400 MHz, DMSO) δ 7.72 (s, 1H), 7.50 – 7.39 (m, 2H), 7.23 (s, 1H), 7.22 – 7.13 (m, 2H), 6.71 (s, 1H), 5.03 (d, *J* = 5.3 Hz, 1H), 4.55 – 4.48 (m, 1H), 4.48 – 4.35 (m, 2H), 4.33 (s, 3H), 4.32 – 4.21 (m, 1H), 4.17 – 4.06 (m, 1H), 3.87 (s, 3H), 3.13 (t, *J* = 6.5 Hz, 2H), 2.73 – 2.58 (m, 1H), 2.07 (t, *J* = 15.6 Hz, 1H), 1.68 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H).

[00439] Synthetic Method 21

[00440] Scheme for Method 21



[00441] Step 1, Method 21

[00442] Di-tert-butyl dicarbonate (2.2 g, 10.2 mmol, CAS 24424-99-5) was added portionwise over 5 min to a solution of methyl (3*R*)-3-methylmorpholine-3-carboxylate;hydrochloride (1.0 g, 5.1 mmol, CAS 1434126-90-5) and triethylamine (780 μ L, 5.6 mmol) in anhydrous methanol (10 mL). The reaction was stirred at RT. After 90 hours, 4-dimethylaminopyridine (31 mg, 0.3 mmol, CAS 1122-58-3) was added. After a further 24 hours, the solvent was removed *in vacuo*. The crude material was dissolved in EtOAc (10 mL) and washed with aq. NaHCO₃ (3 x 10 mL). The organic

layer was passed through a phase separator and the solvent removed *in vacuo* to give *O*4-tert-butyl *O*3-methyl (3*R*)-3-methylmorpholine-3,4-dicarboxylate (680 mg, 49% yield) as a white solid. RT (M3) = 0.67 min [M+H]⁺ (ESI⁺) 260.2; ¹H NMR (500 MHz, DMSO) δ 3.86 – 3.73 (m, 1H), 3.67 – 3.61 (m, 3H), 3.61 – 3.55 (m, 2H), 3.55 – 3.50 (m, 1H), 3.50 – 3.43 (m, 1H), 3.20 – 3.08 (m, 1H), 1.40 (s, 3H), 1.36 (s, 9H).

[00443] Step 2, Method 21

[00444] To a flask containing *O*4-tert-butyl *O*3-methyl (3*R*)-3-methylmorpholine-3,4-dicarboxylate (680 mg, 2.6 mmol) in ethanol (10 mL) and water (7 mL) was added potassium hydroxide (589 mg, 10.5 mmol, CAS 1310-58-3). The reaction mixture was stirred at rt for 6 days then heated to 80 °C. After a further 24 h the reaction mixture was concentrated *in vacuo*. The resulting brown oil treated with water (10 mL) and acidified to pH 1 with 1 M aq. HCl and extracted with DCM (3 x 10 mL). The combined organic extracts were passed through a phase separator and concentrated *in vacuo* to give (3*R*)-4-tert-butoxycarbonyl-3-methyl-morpholine-3-carboxylic acid (660 mg, 82% yield) as a brown oil. RT (M3) = 0.32 min [M+H]⁺ (ESI⁺) 246.2; ¹H NMR (500 MHz, DMSO) δ 12.58 (s, 1H), 5.75 (s, 2H), 3.73 (s, 1H), 3.67 – 3.56 (m, 2H), 3.49 – 3.39 (m, 2H), 3.20 – 3.09 (m, 1H), 1.38 (d, *J* = 3.0 Hz, 12H).

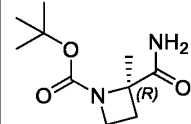
[00445] Step 3, Method 21

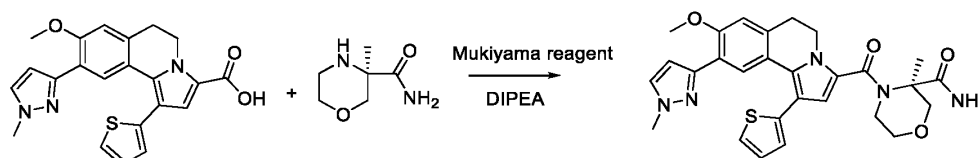
[00446] DIPEA (1.9 mL, 10.8 mmol, CAS 7087-68-5), HATU (1.5 g, 4.0 mmol, CAS 148893-10-1) and ammonia (35% in water, 180 µL, 3.2 mmol, CAS 7664-41-7) were added to a stirred solution of (3*R*)-4-tert-butoxycarbonyl-3-methyl-morpholine-3-carboxylic acid (660 mg, 2.7 mmol) in DCM (10 mL) at RT. The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with water (10 mL), extracted with DCM (3 x 10 mL) and the combined organic extracts passed through a phase separator and concentrated under vacuum to yield the crude product as a yellow oil. The crude oil was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give tert-butyl (3*R*)-3-carbamoyl-3-methyl-morpholine-4-carboxylate (440 mg, 43% yield) as a pale yellow solid. RT (M3) = 0.45 min [M+H]⁺ (ESI⁺) 245.2; ¹H NMR (500 MHz, DMSO) δ 7.13 (s, 1H), 6.91 (s, 1H), 3.82 – 3.73 (m, 1H), 3.65 – 3.57 (m, 2H), 3.51 – 3.44 (m, 1H), 3.44 – 3.38 (m, 1H), 3.16 – 3.05 (m, 1H), 1.37 (s, 9H), 1.34 (s, 3H).

[00447] Step 4, Method 21

[00448] HCl (4 M in dioxane, 2.9 mL, 11.5 mmol, CAS 7647-01-0) was added to a stirred solution of tert-butyl (3*R*)-3-carbamoyl-3-methyl-morpholine-4-carboxylate (440 mg, 1.2 mmol) in dioxane (6 mL) and the mixture stirred at rt over the weekend. The reaction mixture was concentrated *in vacuo* to give (3*R*)-3-methylmorpholine-3-carboxamide;hydrochloride (219 mg, 100% Yield) as a white solid. ¹H NMR (500 MHz, DMSO) δ 10.28 – 8.99 (m, 2H), 8.00 (s, 1H), 7.79 (s, 1H), 4.14 (d, *J* = 12.7 Hz, 1H), 3.80 – 3.71 (m, 3H), 3.20 – 3.06 (m, 2H), 1.45 (s, 3H).

[00449] The following analog was made by analogous method:

Structure	Name	LCMS
	tert-butyl (<i>R</i>)-2-carbamoyl-2-methylazetidine-1-carboxylate	RT (M13) = 0.98 min, (ESI ⁺) (M+Na) ⁺ 237.3

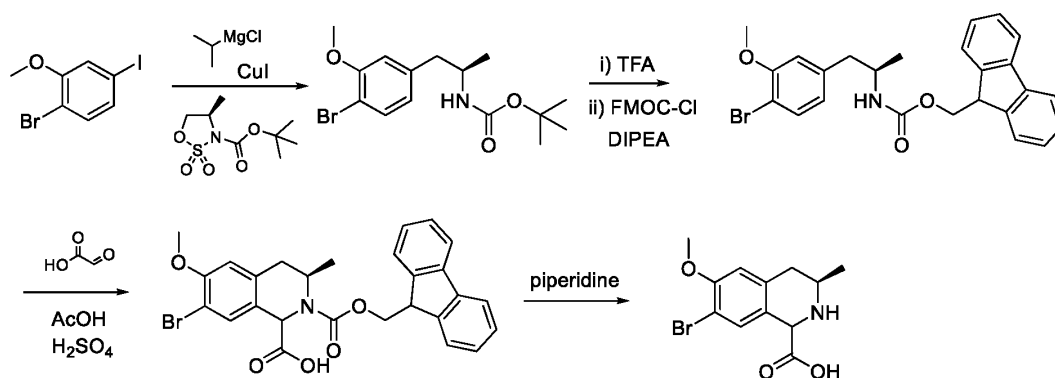
[00450] Synthetic Method 22**[00451] Scheme for Method 22****[00452] Step 1, Method 22**

[00453] 2-Chloro-1-methylpyridinium iodide (236 mg, 0.9 mmol, CAS 14338-32-0) was added to a stirred suspension of 8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (150 mg, 0.4 mmol, prepared by method 22), DIPEA (190 μ L, 1.1 mmol, CAS 7087-68-5) and (3*R*)-3-methylmorpholine-3-carboxamide;hydrochloride (100 mg, 0.6 mmol, prepared by method 22) in DMA (2 mL). The reaction mixture was stirred at RT. After 21 h the mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were passed through a phase

separator and concentrated *in vacuo*. The crude product was purified by FCC (silica, eluting with 0-100% EtOAc in heptane then 0-15% MeOH in EtOAc) to give (3*R*)-4-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-3-methyl-morpholine-3-carboxamide (100 mg, 0.1 mmol, 34% Yield) as an orange solid. RT (M2) = 0.80 min $[M+H]^+$ (ESI⁺) 532.2; ¹H NMR (500 MHz, DMSO) δ 8.08 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.48 (dd, *J* = 3.7, 2.7 Hz, 1H), 7.18 (s, 1H), 7.10 (s, 1H), 7.10 – 7.08 (m, 1H), 7.05 (s, 1H), 6.96 (s, 1H), 6.64 (s, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 4.30 – 4.21 (m, 1H), 4.14 – 4.04 (m, 1H), 3.95 – 3.89 (m, 1H), 3.86 (s, 3H), 3.83 – 3.78 (m, 3H), 3.76 (s, 3H), 3.64 – 3.55 (m, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.03 (t, *J* = 6.5 Hz, 2H), 1.48 (s, 3H).

[00454] Synthetic Method 23

[00455] Scheme for Method 23



[00456] Step 1, Method 23

[00457] Chloro(propan-2-yl)magnesium (2 M in Et₂O, 18 mL, 36.0 mmol, CAS 1068-55-9) was added dropwise to a solution of 1-bromo-4-iodo-2-methoxybenzene (11.3 g, 36.1 mmol, CAS 755027-18-0) in diethyl ether (10 mL) at -15 °C. The solution was stirred for 1h 45min at -15 °C. Copper(1+) iodide (45 mg, 0.2 mmol, CAS 7681-65-4) was then added and the suspension stirred for a further 15 min at -15 °C to give a cloudy green-brown suspension.

[00458] This suspension was then added in 5 mL portions to a suspension of tert-butyl (4*R*)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (4.5 g, 18.0 mmol, CAS 454248-53-4) in

diethyl ether (50 mL) at -15 °C, over 10 min. After 2 h stirring at -15 °C the reaction was sonicated and hand-swirled for 15 min. Citric acid (10% w/v in water, 50 mL) was added slowly at -15 °C and the reaction was then allowed to warm to rt while stirring. After stirring for 90 min the organic was collected and the aqueous extracted with ethyl acetate (50 mL). The combined organics were washed with brine (10 mL) and concentrated *in vacuo*. The residue was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give *tert*-butyl *N*-[(1*R*)-2-(4-bromo-3-methoxy-phenyl)-1-methyl-ethyl]carbamate (91% purity, 5.7 g, 15.2 mmol, 84% Yield) as a brown solid. RT (M2) = 0.98 min [M+H]⁺ (ESI⁺) 288.2/290.2; ¹H NMR (400 MHz, DMSO) δ 7.43 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.83 (s, 3H), 3.72 – 3.64 (m, 1H), 2.72 – 2.54 (m, 2H), 1.33 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H).

[00459] Step 2, Method 23

[00460] *tert*-Butyl *N*-[(1*R*)-2-(4-bromo-3-methoxy-phenyl)-1-methyl-ethyl]carbamate (5.7 g, 16.7 mmol) was dissolved in DCM (50 mL) and treated with trifluoroacetic acid (5.0 mL, 65.3 mmol, CAS 76-05-1). After stirring for 1 h the reaction was retreated with trifluoroacetic acid (5 mL, 65.3 mmol, CAS 76-05-1). After stirring for a further 1 h the volatiles were removed under reduced pressure. The residue was dissolved in DCM (50 mL) and treated with DIPEA (5.8 mL, 33.3 mmol, CAS 7087-68-5) and 9*H*-fluoren-9-ylmethyl carbonochloridate (4.8 g, 18.3 mmol, CAS 28920-43-6) (exothermic). After stirring overnight the reaction was washed with ammonium chloride (sat. in H₂O, 2 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was triturated with heptane (200 mL) and filtered to give 9*H*-fluoren-9-ylmethyl *N*-[(1*R*)-2-(4-bromo-3-methoxy-phenyl)-1-methyl-ethyl]carbamate (9.6 g, 86% Yield) as a tan solid. RT (M2) = 1.11 min [M+H]⁺ (ESI⁺) 466.2/468.2

[00461] Step 3, Method 23

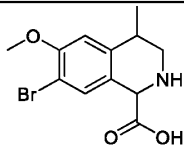
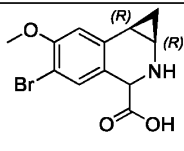
[00462] A suspension of 9*H*-fluoren-9-ylmethyl *N*-[(1*R*)-2-(4-bromo-3-methoxy-phenyl)-1-methyl-ethyl]carbamate (9.6 g, 20.6 mmol) and oxoacetic acid hydrate (1:1) (2.8 g, 30.9 mmol, CAS 563-96-2) in acetic acid (100 mL) was treated with sulphuric acid (10 mL) and stirred for 2 h. Acetic acid (50 mL) and sulphuric acid (5 mL) were added to the suspension. After stirring for 90 min the mixture was sonicated for 2 h to give a red solution. The solution was poured into water

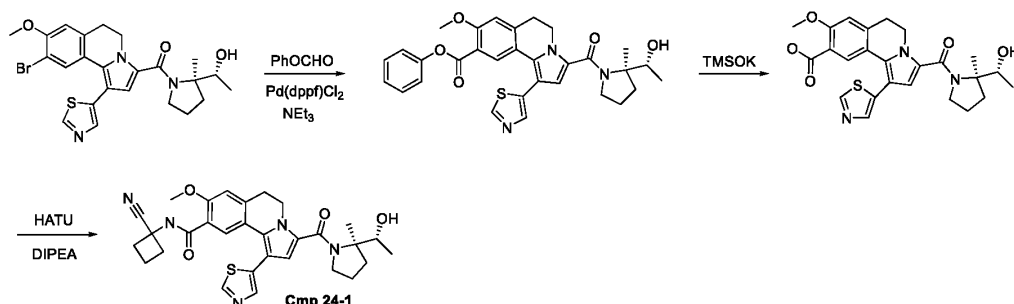
(1 L) and the precipitate was collected by filtration. The pink solid was dissolved in EtOAc (200 mL) and dried over Na₂SO₄, filtered and concentrated to give (3*R*)-7-bromo-2-(9*H*-fluoren-9-ylmethoxycarbonyl)-6-methoxy-3-methyl-3,4-dihydro-1*H*-isoquinoline-1-carboxylic acid (8.5 g, 69% Yield) as a pink solid. RT (M2) = 1.30-1.32 min [M+H]⁺ (ESI⁺) 522.0/524.0

[00463] Step 4, Method 23

[00464] To a solution of (3*R*)-7-bromo-2-(9*H*-fluoren-9-ylmethoxycarbonyl)-6-methoxy-3-methyl-3,4-dihydro-1*H*-isoquinoline-1-carboxylic acid (87% purity, 8.5 g, 14.1 mmol) in DMF (80 mL) was added piperidine (8.2 mL, 83.2 mmol, CAS 110-89-4) and the reaction was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure and the residue was dissolved in THF (100 mL) before the addition of Et₂O (100 mL). The precipitate was collected by filtration to give (3*R*)-7-bromo-6-methoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (79% purity, 2.8 g, 52% Yield) as a pink solid. RT (M2) = 0.46-0.47 min [M+H]⁺ (ESI⁺) 299.9/301.9

[00465] The following analogs were made by analogous method:

	7-bromo-6-methoxy-4-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid	RT (M12) = 0.35 min, [M+H] ⁺ (ESI ⁺) 300.1 /302.1
	(1a <i>R</i> ,7b <i>R</i>)-5-bromo-6-methoxy-1a,2,3,7b-tetrahydro-1 <i>H</i> -cyclopropa[<i>c</i>]isoquinoline-3-carboxylic acid	RT (M14) = 0.303 min, [M+H] ⁺ (ESI ⁺) 297.9/300.0

[00466] Synthetic Method 24**[00467] Scheme for Method 24****[00468] Step 1, Method 24**

[00469] In a 20 mL pressure tube, a mixture of (9-bromo-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)-[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone (250 mg, 0.5 mmol, synthesized by method 2), phenyl formate (0.3 mL, 2.7 mmol, CAS 1864-94-4) and triethylamine (0.4 mL, 2.7 mmol, CAS 121-44-8) in anhydrous DMF (4 mL) was degassed with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (36 mg, 0.05 mmol, CAS 72287-26-4) was added, the solution degassed with nitrogen for 5 mins and heated to 100 °C for 6 h.

[00470] The mixture was cooled to rt and the pressure released slowly and the vessel purged with nitrogen. The mixture was concentrated, diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* to afford a residue that was purified by FCC (silica, eluting with 0-100% EtOAc in heptane) to give phenyl 3-[(2R)-2-[(1R)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylate (150 mg, 50% Yield) as a white solid. RT (M2) = 0.91 min, (ESI⁺) (M+H)⁺ 558.2; ¹H NMR (400 MHz, DMSO-d₆) δ 9.08 (d, *J* = 0.6 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.48 – 7.39 (m, 2H), 7.31 – 7.23 (m, 2H), 7.07 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.64 (s, 1H), 4.96 (d, *J* = 4.9 Hz, 1H), 4.50 – 4.41 (m, 1H), 4.41 – 4.30 (m, 1H), 4.21 – 4.10 (m, 1H), 3.90 (s, 3H), 3.86 – 3.78 (m, 1H), 3.71 – 3.60 (m, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.14 – 2.02 (m, 1H), 1.87 – 1.69 (m, 2H), 1.60 – 1.45 (m, 4H), 1.01 (d, *J* = 6.3 Hz, 3H).

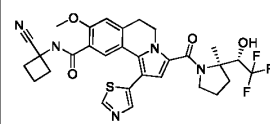
[00471] Step 2, Method 24

[00472] To a solution of phenyl 3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylate (150 mg, 0.3 mmol) in THF (10 mL) was added potassium trimethylsilanolate (182 mg, 1.3 mmol, CAS 10519-96-7). The reaction was stirred at rt for 2 h. The reaction mixture was partially concentrated and the mixture treated with water (10 mL). The mixture was acidified to pH 1 with aq. 1 M HCl and the formation of a precipitate was observed. The mixture was extracted with DCM (3x10 mL) and the combined organic passed through a phase separator and concentrated *in vacuo* to give 3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (77% purity, 160 mg, 95% Yield) as a yellow solid. RT (M2) = 0.68 min, (ESI⁺) (M+H)⁺ 482.2.

[00473] Step 3, Method 24

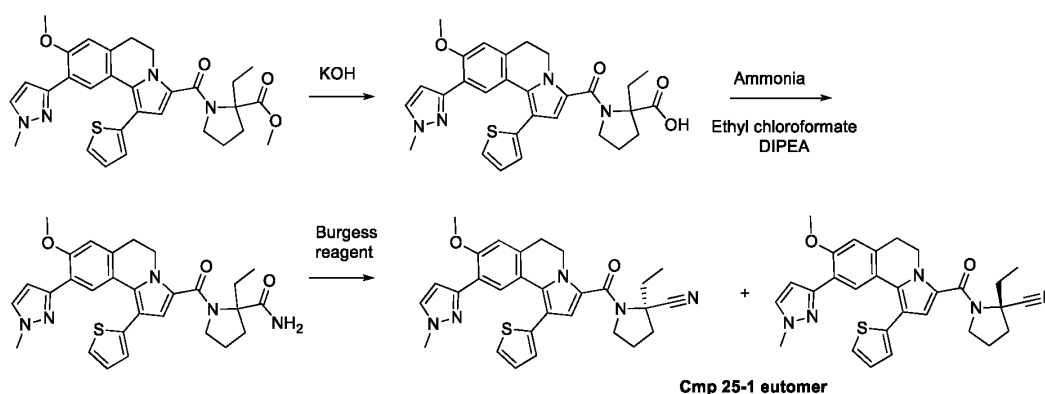
[00474] HATU (243 mg, 0.6 mmol, CAS 148893-10-1) was added to a stirred suspension of 3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxylic acid (77%, 160 mg, 0.3 mmol), DIPEA (134 µL, 0.8 mmol, CAS 7087-68-5) and 1-aminocyclobutanecarbonitrile hydrochloride (1:1) (51 mg, 0.5 mmol, CAS 845821-84-3) in DCM (2 mL) and 1,4-dioxane (5 mL). The reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo*. The mixture was diluted with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were passed through a phase separator and concentrated to give a brown oil. The brown oil was purified by acidic prep HPLC (P1) and freeze dried to give *N*-(1-cyanocyclobutyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide (compound 24-1) (56 mg, 38% Yield) as a white solid. RT (M4) = 3.09 min, (ESI⁺) (M+H)⁺ 560.2. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 8.70 (s, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.18 (s, 1H), 6.62 (s, 1H), 4.96 (d, *J* = 4.8 Hz, 1H), 4.49 – 4.40 (m, 1H), 4.38 – 4.28 (m, 1H), 4.16 – 4.06 (m, 1H), 3.92 (s, 3H), 3.85 – 3.77 (m, 1H), 3.69 – 3.59 (m, 1H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.67 – 2.58 (m, 2H), 2.39 – 2.30 (m, 2H), 2.14 – 1.91 (m, 3H), 1.85 – 1.70 (m, 2H), 1.58 – 1.52 (m, 1H), 1.51 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H).

[00475] The following analog was made by analogous method:

Structure	Name	LCMS
 Compound 24-2	N-(1-cyanocyclobutyl)-8-methoxy-3-[(2R)-2-methyl-2-[(1S)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	RT (M4) = 3.45 min, (ESI ⁺) (M+H) ⁺ 614.2

[00476] Synthetic Method 25

[00477] Scheme for Method 25



[00478] Step 1, Method 25

[00479] To a stirring solution of methyl 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]pyrrolidine-2-carboxylate (468 mg, 0.9 mmol, synthesized by method 13) in ethanol (8 mL) and water (3 mL), potassium hydroxide (193 mg, 3.4 mmol CAS 1310-58-3) was added and the reaction was stirred at 80 °C for 4 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The aqueous residue was acidified to pH 1 using 1M aq. HCl and extracted with DCM (3 x 20 mL). The organics were dried through a

phase separator and concentrated to give 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carboxylic acid (465 mg, 84% Yield) as an off white solid. RT (M2) = 0.93 min $[M+H]^+$ (ESI⁺) 531.2.

[00480] Step 2, Method 25

[00481] Ethyl carbonochloridate (110 μ L, 1.1 mmol, CAS 541-41-3) was added dropwise to a stirred solution of 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carboxylic acid (465 mg, 0.9 mmol) and *N,N*-diethylethanamine (240 μ L, 1.8 mmol, CAS 121-44-8) in anhydrous THF (6.5 mL) at -20°C under N_2 . The resulting solution was stirred at -20°C for 40 min. Ammonia (35%, 340 μ L, 7.0 mmol, CAS 1336-21-6) was added and the mixture, was allowed to warm to RT over 60 min. The solvent was evaporated *in vacuo* and the residue dissolved in EtOAc (50 mL). The organic layer was washed with sat. aq. NaHCO_3 solution (40 mL) and brine (40 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. The crude was purified by acidic prep HPLC (Method P1) to give 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carboxamide (60 mg, 12% Yield) as a white solid. RT (M2) = 0.83 min $[M^+H]^+$ (ESI⁺) 530.2.

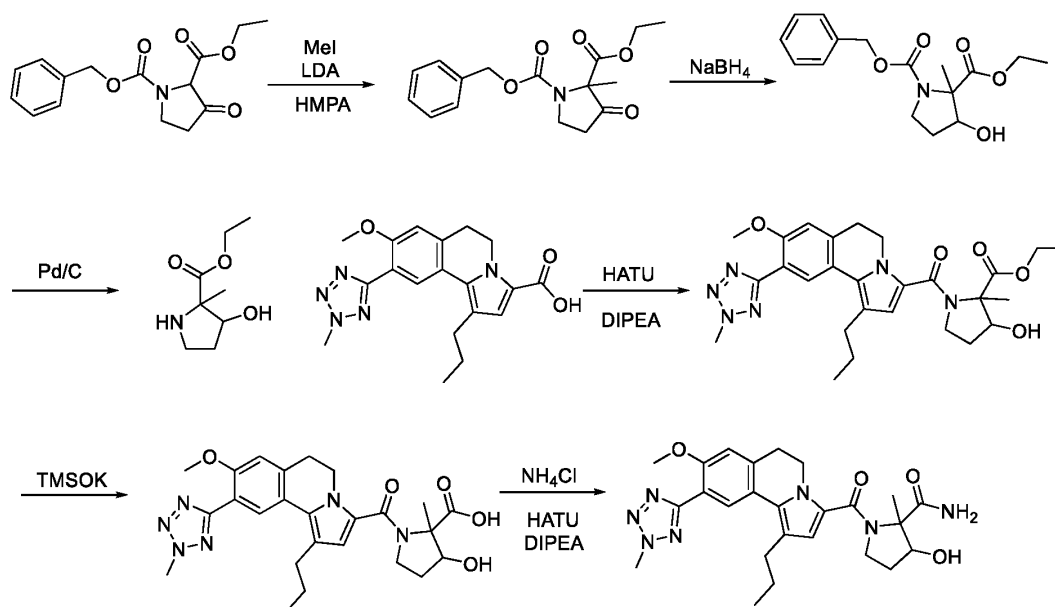
[00482] Step 3, Method 25

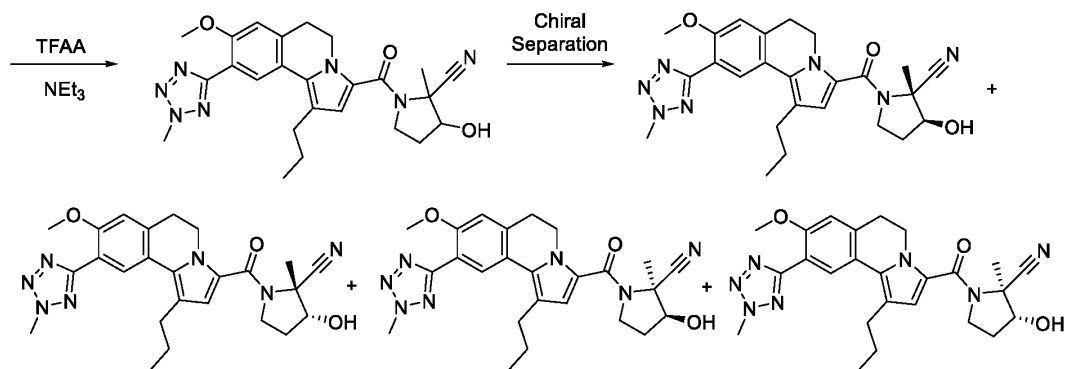
[00483] To a mixture of 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carboxamide (60 mg, 0.1 mmol) in THF (0.5 mL) and DCM (0.5 mL) was added (methoxycarbonyl)[(triethylazaniumyl)sulfonyl]azanide (37 mg, 0.157 mmol, CAS 29684-56-8) at 0°C under N_2 for 1 h. The mixture was stirred at 20°C for 1 h. The reaction mixture was poured into water (10 mL) and the aqueous phase extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude was purified by acidic prep HPLC (Method P1) to give 2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carbonitrile (40 mg, 69% Yield) as a white powder.

[00484] Chiral separation on Waters Thar SFC [Column: Chiralpak AD-H (20 x 250mm, 5 μ m) at 40°C; Isocratic eluent: 70:30 Heptane: EtOH; Flow rate: 18mL/min; Dilution solvent: MeOH, i-PrOH; injection volume: 250 μ L] to give (2*R**)-2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carbonitrile (compound 25-1) (17 mg, 29% yield) as an off white powder. RT (M4) = 3.92 min, (ESI⁺) (M+H)⁺ 512.2; ¹H NMR (500 MHz, DMSO) δ 8.09 (s, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 4.3, 2.1 Hz, 1H), 7.14 – 7.09 (m, 2H), 7.07 (s, 1H), 6.73 (s, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 4.52 – 4.43 (m, 1H), 4.27 – 4.18 (m, 1H), 3.98 – 3.91 (m, 1H), 3.87 (s, 3H), 3.81 – 3.75 (m, 4H), 3.07 (t, *J* = 6.6 Hz, 2H), 2.44 – 2.31 (m, 2H), 2.21 – 2.12 (m, 1H), 2.04 – 1.96 (m, 1H), 1.96 – 1.85 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). * Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00485] Synthetic Method 26

[00486] Scheme for Method 26





Cmp 26-1 enantiomer configuration unknown

[00487] Step 1, Method 26

[00488] Under N₂, at 0 °C, 2 M lithium dipropan-2-ylazanide in THF/heptane/ethylbenzene (13 mL, 26.8 mmol, CAS 4111-54-0) was added to a solution of *O*I-benzyl *O*2-ethyl 3-oxopyrrolidine-1,2-dicarboxylate (7.10 g, 24.4 mmol, CAS 51814-19-8) in THF (150 mL). The reaction mixture was stirred at this temperature for 1 h. A mixture of iodomethane (2.3 mL, 36.6 mmol, CAS 74-88-4) in *N,N,N',N',N'',N''*-hexamethylphosphoric triamide (5.6 mL, 32.4 mmol, CAS 680-31-9) was added to the reaction mixture, and the mixture allowed to warm to rt and stirred overnight. Another portion of iodomethane (390 µL, 6.26 mmol, CAS 74-88-4) was added and the reaction mixture stirred at RT for 1 h. At 0 °C, sat. aq. NH₄Cl (150 mL) was added and the mixture was stirred vigorously for 10 min. Water (100 mL) was added and the suspension was extracted with EtOAc (3 x 80 mL). The combined extracts were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give the crude material, which was purified by FCC (silica, eluting with 10-100% EtOAc/heptane) to give *O*I-benzyl *O*2-ethyl 2-methyl-3-oxo-pyrrolidine-1,2-dicarboxylate (2.27 g, 29% yield) as a pale yellow oil. RT (M2) = 0.86 min, (ESI⁺) (M+H)⁺ 306.1; ¹H NMR (400 MHz, DMSO) δ 7.43 – 7.21 (m, 5H), 5.21 – 5.06 (m, 2H), 4.15 – 3.94 (m, 2H), 3.77 (t, *J* = 7.8 Hz, 2H), 2.89 – 2.70 (m, 2H), 1.52 (s, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

[00489] Step 2, Method 26

[00490] Under N₂, at 0 °C, sodium tetrahydroborate (795 mg, 21.0 mmol, CAS 16940-66-2) was added to a solution of *OI*-benzyl *O2*-ethyl 2-methyl-3-oxo-pyrrolidine-1,2-dicarboxylate (3.21 g, 10.5 mmol) in MeOH (50 mL). The reaction mixture was stirred at this temperature for 2 h, and sat. aq. NH₄Cl (50 mL) was added. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give *OI*-benzyl *O2*-ethyl 3-hydroxy-2-methyl-pyrrolidine-1,2-dicarboxylate (2.93 g, 82% yield) as a colorless oil. RT (M2) = 0.76 min, (ESI⁺) (M+H)⁺ 308.3.

[00491] Step 3, Method 26

[00492] At rt, palladium on carbon (10%, 477 mg, 0.4 mmol, CAS 7440-05-3) was added to a solution of *OI*-benzyl *O2*-ethyl 3-hydroxy-2-methyl-pyrrolidine-1,2-dicarboxylate (90% purity, 2.93 g, 8.6 mmol) in EtOH (50 mL). The reaction mixture was stirred under H₂ (1 atm) overnight. The reaction mixture was filtered through Celite, washing through with MeOH (100 mL) and the filtrate was concentrated *in vacuo* to give ethyl 3-hydroxy-2-methyl-pyrrolidine-2-carboxylate (1.53 g, 98% yield) as a pale yellow solid. ¹H NMR* (400 MHz, DMSO) δ 4.89 (d, *J* = 5.4 Hz, 1H), 4.15 – 3.97 (m, 3H), 3.88 (td, *J* = 5.4, 2.5 Hz, 1H), 3.09 (dt, *J* = 10.4, 8.2 Hz, 1H), 2.75 (ddd, *J* = 10.4, 9.1, 4.3 Hz, 1H), 1.96 (dddd, *J* = 12.9, 9.0, 7.3, 5.4 Hz, 1H), 1.63 (dddd, *J* = 13.0, 8.4, 4.3, 2.6 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 3H). *NMR shifts for major diastereomers reported.

[00493] Step 4, Method 26

[00494] At rt, HATU (3.34 g, 8.8 mmol, CAS 148893-10-1) was added to a solution of ethyl 3-hydroxy-2-methyl-pyrrolidine-2-carboxylate (1.1 g, 6.1 mmol), 8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (2.15 g, 5.9 mmol, synthesized by method 19) and *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (3.1 mL, 17.6 mmol, CAS 7087-68-5) in 1,4-dioxane (15 mL) and DCM (15 mL). The reaction mixture was stirred at RT for 4 days. Water (50 mL) was added and the mixture extracted with DCM (3 x 50 mL). The combined extracts were dried over anhydrous MgSO₄, filtered and concentrated to give the crude material,

which was purified by FCC (silica, eluting with 10-100% EtOAc/heptane then 0-10% MeOH/EtOAc) to give ethyl 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxylate (2.66 g, 85% Yield) as an off white solid. RT (M2) = 0.88 min, (ESI⁺) (M+H)⁺ 523.3; ¹H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.22 (s, 1H), 6.54 – 6.46 (m, 1H), 5.69 – 5.52 (m, 1H), 4.43 (s, 4H), 4.17 – 3.98 (m, 4H), 3.89 (s, 3H), 3.86 – 3.66 (m, 2H), 3.04 (t, *J* = 6.3 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.19 – 1.78 (m, 2H), 1.69 – 1.59 (m, 2H), 1.59 – 1.41 (m, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H).

[00495] Step 5, Method 26

[00496] At rt, potassium trimethylsilanolate (90% purity, 2.93 g, 20.6 mmol, CAS 10519-96-7) was added to a solution of ethyl 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxylate (2.15 g, 4.1 mmol) in THF (40 mL). The reaction mixture was stirred at 40 °C for 3 h. Water (30 mL) was added and the mixture was concentrated *in vacuo* to remove organics. The suspension was adjusted to pH 1 with addition of 6 M aq. HCl (5 mL) and was then extracted with DCM/MeOH (4:1, 2 x 50 mL) and DCM (50 mL). The combined extracts were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxylic acid (1.89 g, 47% yield) as a pale green solid. RT (M2) = 0.78 min, (ESI⁺) (M+H)⁺ 495.3.

[00497] Step 6, Method 26

[00498] At rt, ammonium chloride (1.25 g, 23.4 mmol, CAS 12125-02-9) was added to a solution of 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxylic acid (55% purity, 2.31 g, 2.6 mmol) and *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (4.9 mL, 28.0 mmol, CAS 7087-68-5) in DCM (22 mL). The mixture was stirred for 5 min and then HATU (2.66 g, 7.0 mmol, CAS 148893-10-1) was added. The reaction mixture was stirred at room temperature for 3 days. Water (100 mL) was added and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with DCM/MeOH (4:1, 3 x 50 mL). The combined extracts were dried over anhydrous MgSO₄,

filtered and concentrated *in vacuo* to give 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (22% purity, 5.60 g, assumed quant. yield) as a pale green solid. RT (M2) = 0.68 min, (ESI⁺) (M+H)⁺ 494.3.

[00499] Step 7, Method 26

[00500] Under nitrogen, at 0 °C, trifluoroacetic anhydride (0.8 mL, 5.8 mmol, CAS 407-25-0) was added to a solution of 3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (4.80 g, 2.1 mmol) and *N,N*-diethylethanamine (1.6 mL, 11.7 mmol, CAS 121-44-8) in THF (40 mL). The reaction mixture was stirred at this temperature for 1 h and then at rt for 1 h. At 0 °C, further portions of *N,N*-diethylethanamine (1.6 mL, 11.7 mmol, CAS 121-44-8) and trifluoroacetic anhydride (0.8 mL, 5.8 mmol, CAS 407-25-0) were added. The reaction mixture was stirred at this temperature for 1 h. 1 M aqueous NaOH (20 mL) was added to the reaction mixture and stirred vigorously for 10 min. Water (50 mL) was added and the mixture was concentrated to remove THF. The suspension was extracted with EtOAc (3 x 50 mL) and the combined extracts were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give crude material, which was purified by FCC (silica, eluting with 10-100% heptane/EtOAc) and by acidic prep HPLC (Method P2) to give the pairs of enantiomers.

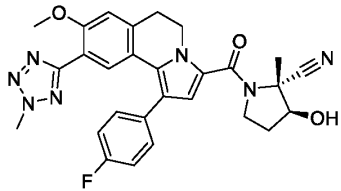
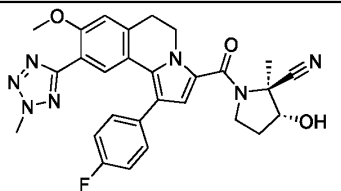
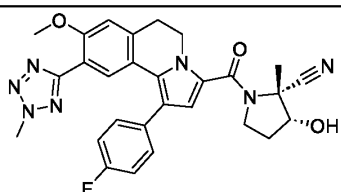
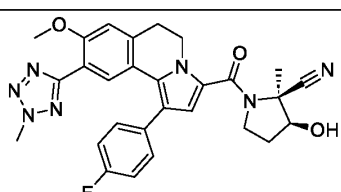
[00501] Chiral separation by chiral HPLC [Column: Chiralpak AD-H (20 x 250mm, 5µm) at 40°C; Isocratic eluent: 70:30 Heptane: i-PrOH; Flow rate: 15 mL/min; Dilution solvent: MeOH, i-PrOH, acetonitrile, formic acid] gave *rel*-(2*R*,3*S*)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (stereoisomer 26-1) (101 mg, 9% yield) as a colorless solid. RT (M4) = 3.27 min, (ESI⁺) (M+H)⁺ 476.3. ¹H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.23 (s, 1H), 6.59 (s, 1H), 6.06 (s, 1H), 4.44 – 4.34 (m, 5H), 4.28 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.88 (s, 3H), 3.84 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.70 – 2.61 (m, 2H), 2.14 – 2.03 (m, 1H), 1.96 – 1.86 (m, 1H), 1.69 – 1.58 (m, 5H), 0.96 (t, *J* = 7.3 Hz, 3H).

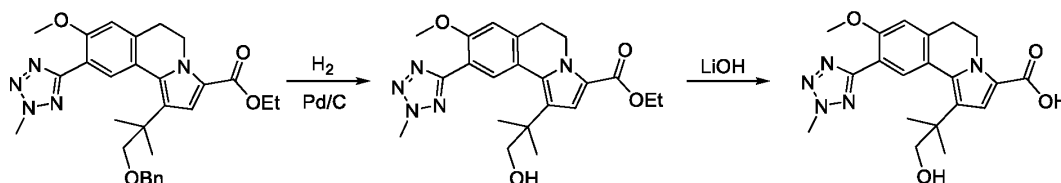
[00502] *rel*-(2*S*,3*R*)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (stereoisomer 26-1) (103 mg, 9% yield) as a colorless solid. RT (M4) = 3.26 min, (ESI⁺) (M+H)⁺ 476.3. ¹H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.23 (s, 1H), 6.59 (s, 1H), 6.06 (s, 1H), 4.44 – 4.35 (m, 5H), 4.28 (dt, *J* = 13.0, 6.3 Hz, 1H), 3.88 (s, 3H), 3.84 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.14 – 2.04 (m, 1H), 1.96 – 1.86 (m, 1H), 1.68 – 1.57 (m, 5H), 0.97 (t, *J* = 7.3 Hz, 3H).

[00503] Chiral separation by chiral SFC [Column: Chiralpak AD-H (10 x 250mm, 5μm) at 40°C; Isocratic eluent: 70:30 CO₂:MeOH; Flow rate: 15 mL/min; Dilution solvent: methanol, acetonitrile] gave *rel*-(2*R*,3*R*)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (stereoisomer 26-1) (40 mg, 4% yield) as a colorless solid. RT (M4) = 3.15 min, (ESI⁺) (M+H)⁺ 476.3. ¹H NMR (500 MHz, DMSO) δ 8.07 (s, 1H), 7.23 (s, 1H), 6.57 (s, 1H), 6.19 (s, 1H), 4.41 (s, 4H), 4.27 (dt, *J* = 13.0, 6.3 Hz, 1H), 4.08 (dd, *J* = 8.1, 5.2 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.73 (m, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.68 – 2.63 (m, 2H), 2.14 – 2.07 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 (s, 3H), 1.68 – 1.58 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

[00504] *rel*-(2*S*,3*S*)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (stereoisomer 26-1) (48 mg, 4% yield) as a colorless solid. RT (M4) = 3.15 min, (ESI⁺) (M+H)⁺ 476.3. ¹H NMR (500 MHz, DMSO) δ 8.07 (s, 1H), 7.23 (s, 1H), 6.57 (s, 1H), 6.19 (s, 1H), 4.44 – 4.35 (m, 4H), 4.31 – 4.22 (m, 1H), 4.08 (dd, *J* = 7.8, 5.3 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.72 (m, 2H), 3.05 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.16 – 2.04 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 (s, 3H), 1.67 – 1.59 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

[00505] The following analogs were made by analogous method:

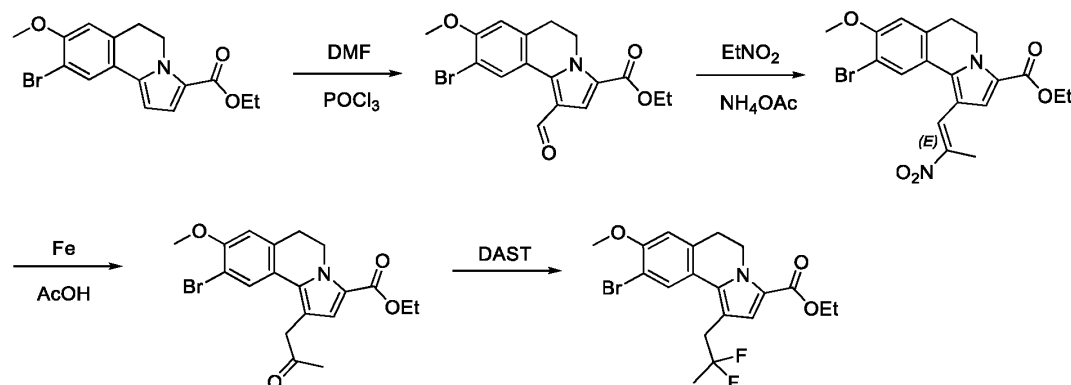
Structure	Name	LCMS
 Stereoisomer 26-2	<i>rel</i> -(2 <i>R</i> ,3 <i>S</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.43 min, [M+H] ⁺ (ESI ⁺) 528.4
 Stereoisomer 26-2	<i>rel</i> -(2 <i>S</i> ,3 <i>R</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.45 min, [M+H] ⁺ (ESI ⁺) 528.3
 Stereoisomer 26-2	<i>rel</i> -(2 <i>R</i> ,3 <i>R</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.35 min, [M+H] ⁺ (ESI ⁺) 528.3
 Stereoisomer 26-2	<i>rel</i> -(2 <i>S</i> ,3 <i>S</i>)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile	RT (M4) = 3.35 min, [M+H] ⁺ (ESI ⁺) 528.3

[00506] Synthetic Method 27**[00507] Scheme for Method 27****[00508] Step 1, Method 27**

[00509] To a solution of ethyl 1-(1-(benzyloxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (900 mg, 1.75 mmol) in THF (10 mL) was added with Pd/C (900mg, 1.75 mmol, 10% purity). The mixture was stirred at 45°C under H₂ (15 psi) for 12 hr. The mixture was filtered and concentrated under vacuum to afford ethyl 1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (650 mg, 87.52%) as a white solid. RT (M32) = 0.36 min, [M+H]⁺ (ESI⁺) 426.2.

[00510] Step 2, Method 27

[00511] To a solution of ethyl 1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (400 mg, 940.12 μmol) in THF (3 mL), H₂O (3 mL) and EtOH (3 mL) was added with KOH (131.86 mg, 2.35 mmol). The mixture was stirred at 45°C for 6 hr. The mixture was added with 1M HCl to adjust pH=5. The mixture was extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford 1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (350 mg, 93.68%) as a white solid. RT (M32) = 0.77 min, [M+H]⁺ (ESI⁺) 398.1.

[00512] Synthetic Method 28**[00513] Scheme for Method 28****[00514] Step 1, Method 28**

[00515] POCl₃ (35.03 g, 228.44 mmol) in DCE (100 mL) was dropwise added to DMF (16.70 g, 228.44 mmol) in DCE (200 mL) at 0°C and stirred at 0°C for 0.5 hr. Then the mixture of ethyl 9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (20.00 g, 57.11 mmol) in DCE (200 mL) was added to the reaction mixture under N₂. The mixture was stirred at 60°C for 2 hr. The mixture was slowly added into sat. Na₂CO₃ (500 mL) at 0°C until pH = 8 and stirred at 20°C for 1.5 hr. The aqueous phase was extracted with DCM (300 mL × 2). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give ethyl 9-bromo-1-formyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (19.00 g, 88%) as a white solid. RT (M13) = 1.93 min [M+H]⁺ (ESI⁺) 378.1/380.1.

[00516] Step 2, Method 28

[00517] To a solution of ethyl 9-bromo-1-formyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (19.00 g, 50.24 mmol) in nitroethane (99.75 g, 1.33 mol) was added with NH₄OAc (7.74 g, 100.47 mmol) at 20°C. The mixture was stirred at 120°C for 2 hr. The residue was poured into water (300 mL) at 0°C. The aqueous phase was extracted with DCM (100 mL × 3). The combined organic phase was washed with brine (60 mL × 2), dried with anhydrous

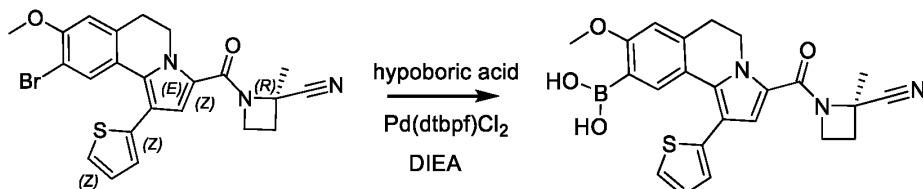
Na₂SO₄, filtered and concentrated in vacuum to give ethyl (E)-9-bromo-8-methoxy-1-(2-nitroprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (21.00 g, 96%) as a yellow solid. RT (M13) = 2.29 min [M+H]⁺ (ESI⁺) 435.2/437.2.

[00518] Step 3, Method 28

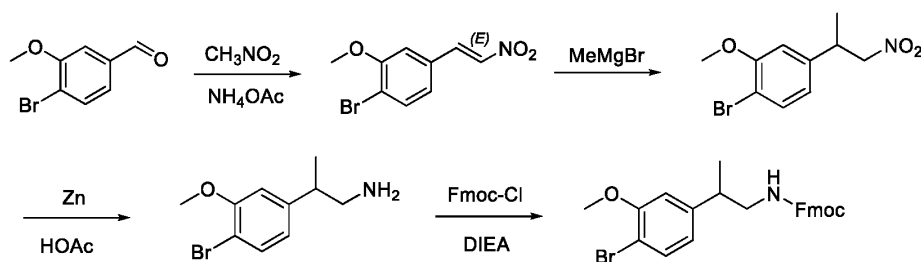
[00519] To a solution of ethyl (E)-9-bromo-8-methoxy-1-(2-nitroprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (27.00 g, 62.03 mmol) in AcOH (270 mL) was added with Fe (34.64 g, 620.31 mmol) at 90°C. The mixture was stirred at 130°C for 2 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure. DCM (200 mL) and H₂O (100 mL) was added to the reaction mixture. The aqueous phase was extracted with DCM (100 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give ethyl 9-bromo-8-methoxy-1-(2-oxopropyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (24.00 g, 84%) as a white solid. RT (M13) = 2.00 min [M+H]⁺ (ESI⁺) 406.2/408.1.

[00520] Step 4, Method 28

[00521] To a solution of ethyl 9-bromo-8-methoxy-1-(2-oxopropyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (11.00 g, 27.08 mmol) in DCM (55 mL) was added with DAST (67.10 g, 416.28 mmol) at 0°C and stirred at 80°C for 2 hr. The reaction mixture was poured into the sat. Na₂CO₃ (300 mL) at 0°C to adjust the mixture pH to 7~8. The aqueous phase was extracted with DCM (60 mL × 2). The combined organic phase was washed with brine (50 mL × 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give ethyl 9-bromo-1-(2,2-difluoropropyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (10.00 g, 86%) as a yellow solid. RT (M13) = 2.27 min [M+H]⁺ (ESI⁺) 428.2/430.2.

[00522] Synthetic Method 29**[00523] Scheme for Method 29****[00524] Step 1 Method 29**

[00525] To a solution of (*R*)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-carbonyl)-2-methylazetidine-2-carbonitrile (700 mg, 1.45 mmol) in EtOH (7 mL) was added with hypoboric acid (390.28 mg, 4.35 mmol), Pd(dtbpf)Cl₂ (9.46 mg, 14.51 μmol) and DIPEA (937.70 mg, 7.26 mmol, 1.26 mL). The mixture was stirred at 60 °C for 2 hr. The reaction mixture containing (*R*)-(3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-9-yl)boronic acid was cooled and used directly in next step. RT (M32) = 0.47 min [M+H]⁺ (ESI⁺) 448.0.

[00526] Synthetic Method 30**[00527] Scheme for Method 30****[00528] Step 1, Method 30**

[00529] To a solution of 4-bromo-3-methoxy-benzaldehyde (43 g, 0.2 mol) in AcOH (86 mL) was added with NH₄OAc (16.9 g, 0.22 mol) and CH₃NO₂ (61 g, 1 mol, 54 mL). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was cooled down to ~25°C. H₂O (430 mL) was

added to the reaction mixture and the mixture was stirred at 25 °C for 15 min, then it was filtered to afford a filter cake. The filter cake was triturated with MeCN (215 mL) at 25 °C for 15 min, filtered to afford filter cake. The filter cake was triturated with Petroleum ether (430 mL) at 25 °C for 15 min, filtered to give a cake, which was dried in vacuum to give (*E*)-1-bromo-2-methoxy-4-(2-nitrovinyl)benzene (40 g, 90.43%). ¹H NMR (400 MHz, CDCl₃) δ = 7.96 (d, *J* = 13.7 Hz, 1H), 7.67 - 7.61 (m, 1H), 7.58 (s, 1H), 7.05 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 4.03 - 3.92 (m, 3H).

[00530] Step 2, Method 30

[00531] To a solution of (*E*)-1-bromo-2-methoxy-4-(2-nitrovinyl)benzene (40 g, 155.00 mmol) in THF (800 mL) was added with MeMgBr (3 M, 55.91 mL) dropwise at -40°C under N₂. The mixture was stirred at -40°C for 2 hr. The mixture was poured into NH₄Cl (200 mL) at 0-10°C. The mixture was extracted with DCM (200 mL x 3), dried over Na₂SO₄ and organic phase was concentrated. The residue was purified by column (SiO₂, PE/EtOAc=3/1 to 1/1). 1-Bromo-2-methoxy-4-(1-nitropropan-2-yl)benzene (27 g, 64%) was obtained as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 1.4 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.5 Hz, 1H), 4.86 (s, 2H), 3.80 - 3.89 (m, 3H), 3.50 - 3.60 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H)

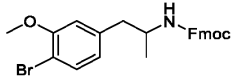
[00532] Step 3, Method 30

[00533] To a solution of 1-bromo-2-methoxy-4-(1-nitropropan-2-yl)benzene (11 g, 40.13 mmol) in EtOH (110 mL) was added Zn (39.36 g, 601.95 mmol) and HOAc (48.20 g, 802.60 mmol) at 0°C under N₂. The mixture was stirred at 20°C for 12 hours. The mixture was filtered and filtrate was adjusted pH to 13 with 2N NaOH solution. The mixture was extracted with DCM (150 mL x 3), dried over Na₂SO₄ and organic phase was concentrated. The residue was used directly next step without purification. 2-(4-Bromo-3-methoxyphenyl)propan-1-amine (15.1 g, crude) was obtained as yellow oil. RT (M11) = 0.70 min [M+H]⁺ (ESI⁺) 244.1/246.1.

[00534] Step 4, Method 30

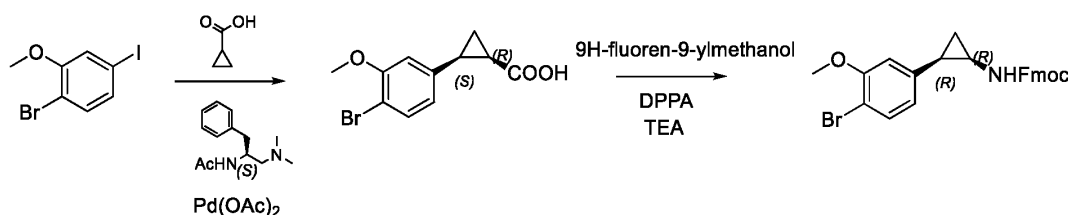
[00535] To a solution of 2-(4-bromo-3-methoxyphenyl)propan-1-amine (15 g, 61.44 mmol) in DCM (150 mL) was added with DIPEA (23.82 g, 184.33 mmol) and Fmoc-Cl (18.28 g, 70.66

mmol) at 0°C under N₂. The mixture was stirred at 15 °C for 1 hr. The mixture was poured into 1 M HCl (130 mL) and extracted with DCM (100 mL x 3). The combined organic phase was washed with 1 M HCl (80 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column (SiO₂, PE/EtOAc=3/1). (9H-Fluoren-9-yl) methyl (2-(4-bromo-3-methoxyphenyl)propyl)carbamate (28 g, 88%, 90% purity) was obtained as white solid. RT (M14) = 1.04 min) [M+Na]⁺ (ESI⁺) 488.1/490.1.

Structure	Name	LCMS
	(9H-fluoren-9-yl)methyl (1-(4-bromo-3-methoxyphenyl)propan-2-yl)carbamate	RT (M12) = 0.72 min [M+H] ⁺ (ESI ⁺) 466.2/468.2

[00536] Synthetic Method 31

[00537] Scheme for Method 31



[00538] Step 1, Method 31

[00539] To a solution of Pd(OAc)₂ (5.02 g, 22.37 mmol) and cyclopropanecarboxylic acid (28.89 g, 335.54 mmol, 26.50 mL) in HFIP (700 mL) was added (S)-N-(1-(dimethylamino)-3-phenylpropan-2-yl)acetamide (9.86 g, 44.74 mmol) and Ag₂CO₃ (92.52 g, 335.54 mmol, 15.22 mL), Na₂CO₃ (35.56 g, 335.54 mmol) and 1-bromo-4-iodo-2-methoxy-benzene (70.00 g, 223.69 mmol). The mixture was stirred at 80°C for 12 h. The solvent was adjusted to pH 2-3 with 1M HCl. The mixture was filtered and the filtrate was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with sat. NaHCO₃ (100 mL x 2), and the aqueous layer was adjusted to pH 2-3 with 1M HCl. The aqueous layer was extracted with ethyl acetate DCM (200

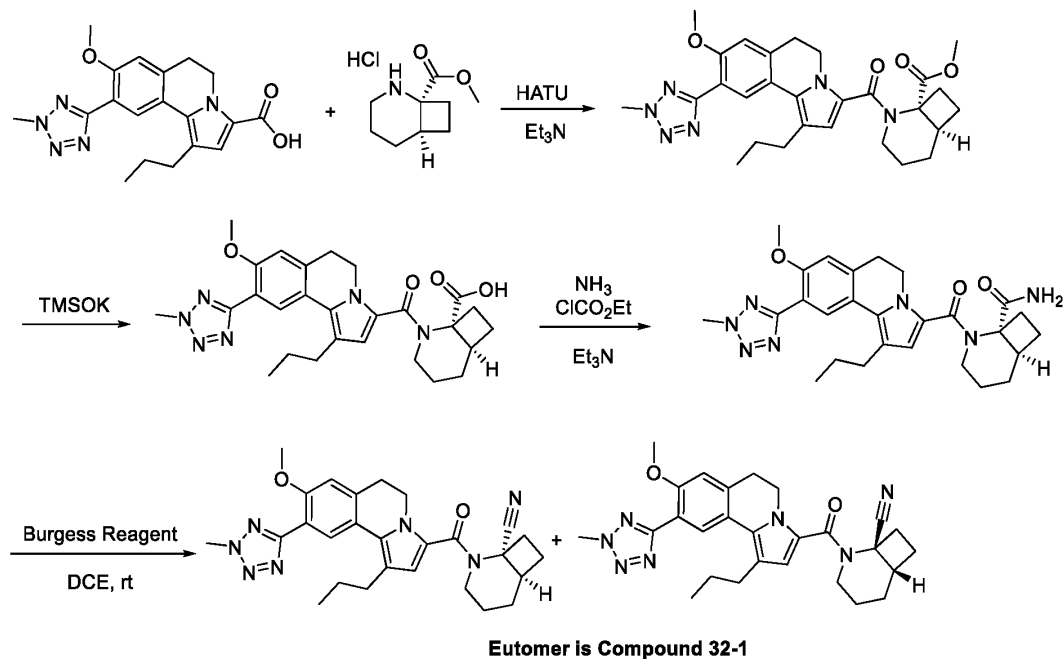
mL x 3). The combined organic phase was washed with brine (100 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC to give (1*R*,2*S*)-2-(4-bromo-3-methoxyphenyl)cyclopropane-1-carboxylic acid (31.50 g, 51.94% yield) was obtained as a brown oil. RT (M27) = 1.14 min [M+Na]⁺ (ESI⁺) 269.1/271.0.

[00540] Step 2, Method 31

[00541] To a solution of (1*R*,2*S*)-2-(4-bromo-3-methoxyphenyl)cyclopropane-1-carboxylic acid (36.00 g, 132.79 mmol) in toluene (360 mL) was added TEA (14.78 g, 146.07 mmol, 20.33 mL), DPPA (40.20 g, 146.07 mmol, 31.65 mL) and 9H-fluoren-9-ylmethanol (31.27 g, 159.35 mmol), then it was stirred at 120°C for 0.5 hr. The mixture was diluted with EtOAc (100 mL), then filtered. The filtrate was poured into H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic phase was washed with brine (100 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated with MeCN (100 mL) at 20°C for 10 min to give the (9H-fluoren-9-yl)methyl((1*R*,2*R*)-2-(4-bromo-3-methoxyphenyl)cyclopropyl) carbamate (28 g, 45.41%, yield) as a white solid. RT (M11) = 2.06 min [M+Na]⁺ (ESI⁺) 486.2/488.2.

[00542] Synthetic Method 32

[00543] Scheme for Method 32



[00544] Step 1, Method 32

[00545] HATU (698.57 mg, 1.84 mmol, 1.5 eq) was added to a solution of 8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (450 mg, 1.22 mmol), *rac*-methyl (1*R*,6*S*)-2-azabicyclo[4.2.0]octane-1-carboxylate hydrochloride, *cis* (302.31 mg, 1.47 mmol) and triethylamine (433.79 mg, 4.29 mmol, 597.50 μ L) in DMF (6 mL, 0.2 M) and the reaction was stirred at 50 °C for 16 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (5 mL) and diluted with EtOAc (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol to give *rac*-methyl (1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-

2-azabicyclo[4.2.0]octane-1-carboxylate, *cis* (619 mg, 1.04 mmol, 85% yield) as a purple solid. RT (M42) = 1.64 min, $[M+H]^+$ (ESI⁺) 519.1.

[00546] Step 2, Method 32

[00547] Potassium trimethylsilanolate (111.9 mg, 0.87 mmol, 2 eq) was added to a solution of *rac*-methyl (1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-azabicyclo[4.2.0]octane-1-carboxylate, *cis* (260 mg, 0.44 mmol, 1 eq) in dry THF (11 mL, 0.04 M) and stirred at 50 °C for 16 h. The reaction was followed by LCMS. Water was added and the pH of the mixture was adjusted to 4 by addition of HCl 1N. The crude was diluted with EtOAc (60 mL) and washed with H₂O (50 mL). The aqueous layer was extracted with CHCl₃:iPrOH (3:1). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. Crude was used in the next step without further purification. RT (M44) = 1.14 min, $[M+Na]^+$ (ESI⁺) 505.2.

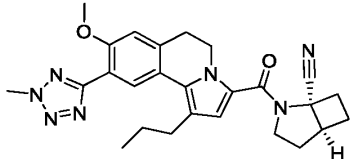
[00548] Step 3, Method 32

[00549] Under argon atmosphere triethylamine (69.89 mg, 0.69 mmol, 96.27 µL, 1 eq) was added to a solution of *rac*-(1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-azabicyclo[4.2.0]octane-1-carboxylic acid, *cis* (410 mg, 0.69 mmol, 1 eq) and ethyl chloroformate (149.91 mg, 1.38 mmol, 131.96 µL, 2 eq) in THF (17 mL, 0.04M) at -10°C. Reaction was stirred at -10°C for 30 min. Then, ammonia (g) was bubbled into the reaction for 15 min and the mixture was stirred at rt for 1 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (10 mL) and diluted with EtOAc (40 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol to give *rac*-(1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-azabicyclo[4.2.0]octane-1-carboxamide, *cis* (114 mg, 0.22 mmol, 32% yield) was isolated as a blue solid. RT (M44) = 1.07 min, $[M+H]^+$ (ESI⁺) 504.3.

[00550] Step 4, Method 32

[00551] Methyl N-(triethylammoniumsulfonyl)carbamate (Burgess reagent) (107.89 mg, 0.45 mmol, 2 eq) was added to a solution of *rac*-(1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-azabicyclo[4.2.0]octane-1-carboxamide, *cis* (114 mg, 0.23 mmol, 1 eq) in DCM (9 mL, 0.03M). The reaction is stirred at rt for 16 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (10 mL) and diluted with DCM (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol to give *rac*-(1*R*,6*S*)-2-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-azabicyclo[4.2.0]octane-1-carbonitrile (102 mg, 0.21 mmol, 94%). RT (M44) = 1.25 min, (ESI⁺) 486.1 [M+H]⁺. The racemic mixture was separated using prep method 13 (P13) to give the eutomer (compound 32-1) (1*S**,6*R**)-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-azabicyclo[4.2.0]octane-1-carbonitrile (35.1 mg, 0.07 mmol, 32%) as a white solid. RT (M41) = 3.86 min, [M+H]⁺ (Dual-ESI⁺) 486.23; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 8.02 (s, 1H), 6.44 (s, 1H), 4.4-4.3 (m, 4H), 4.2-4.0 (m, 2H), 3.83 (s, 3H), 3.02 (br t, *J* = 6.4 Hz, 4H), 2.8-2.7 (m, 1H), 2.7-2.6 (m, 2H), 2.1-2.0 (m, 2H), 2.0-1.8 (m, 3H), 1.7-1.5 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H).

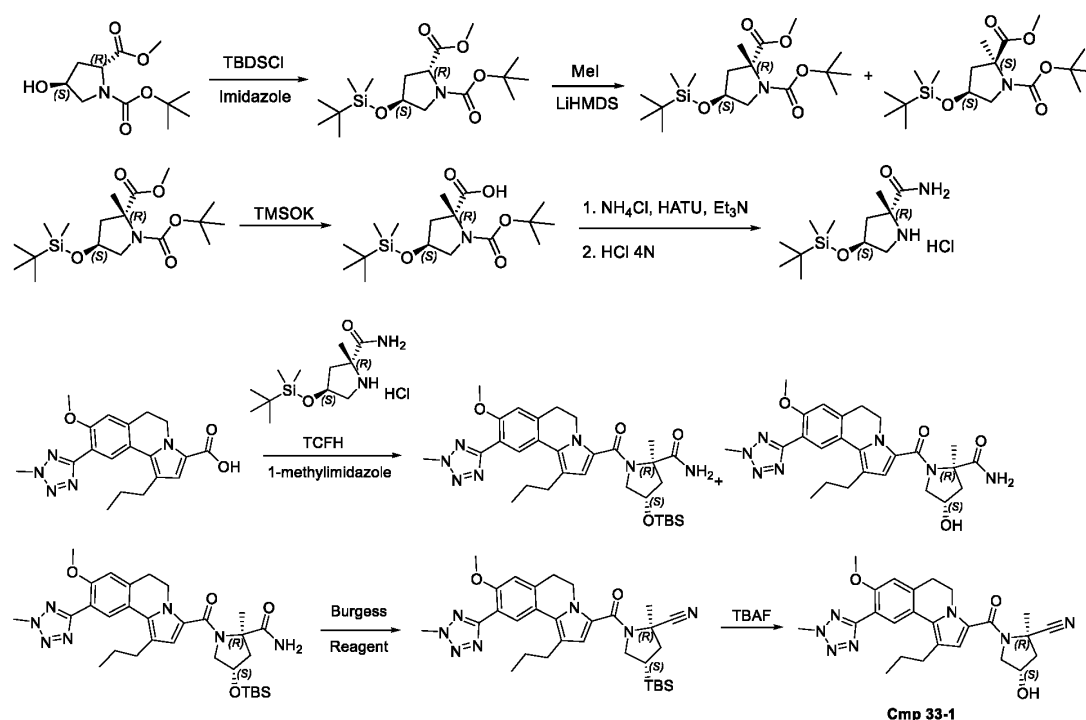
[00552] The following analog was made by analogous method:

Structure	Name	LCMS
 Compound 32-2	(1 <i>S</i> *,5 <i>S</i> *)-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1- <i>a</i>]isoquinoline-3-carbonyl)-5-methyl-2-azabicyclo[3.2.0]heptane-1-carbonitrile	RT (M40) = 3.76 min, [M+H] ⁺ (ESI ⁺) 472.2

* Denotes unknown stereochemistry, isolated from a diastereomeric mixture using SFC chromatography

[00553] Synthetic Method 33

[00554] Scheme for Method 33



[00555] Step 1, Method 33

[00556] Under argon atmosphere, imidazole (10.44 g, 153.38 mmol, 2.2 eq) was added portionwise to a solution of 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (18 g, 69.72 mmol, 1 eq) and *tert*-butylchlorodimethylsilane (15.76 g, 104.58 mmol, 19.46 mL, 1.5 eq) in dry DCM (108 mL, 0.55M) at 0 °C. Then, the reaction was stirred at rt for 16 h. When the starting material was consumed, the reaction mixture was washed with water (100 mL). The aqueous phase was extracted with DCM three times (50 mL). Organics were combined, dried with MgSO₄ and concentrated under vacuum. The crude was purified by flash

chromatography using heptane/ethyl acetate as eluents. 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (23.5 g, 64.06 mmol, 92% yield) was obtained as colorless oil. ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 4.42 (br s, 1H), 4.2-4.1 (m, 1H), 3.7-3.6 (m, 3H), 3.25 (br t, *J* = 11.1 Hz, 1H), 2.1-2.0 (m, 1H), 2.0-1.9 (m, 1H), 1.4-1.3 (m, 9H), 0.83 (s, 9H), 0.05 (d, *J* = 2.1 Hz, 6H).

[00557] Step 2, Method 33

[00558] Under argon atmosphere 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy) pyrrolidine-1,2-dicarboxylate (6 g, 16.69 mmol, 1 eq) was diluted in dry THF (220 mL, 0.05M). The mixture was cooled to -78 °C and LiHMDS (1M in hexanes, 66.75 mmol, 66.75 mL, 4 eq) was added dropwise. The reaction was stirred at that temperature for 4 h. Then iodomethane (18.95 g, 133.51 mmol, 8.31 mL, 8 eq) was added dropwise. The mixture was stirred at -78 °C for 2 h and then at rt for 16 h. The reaction was followed by TLC and LCMS and two diastereoisomers were formed. The reaction was quenched with water and extracted with EtOAc (100 mL x 3). The organics were washed with brine, dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography eluting with heptane:ethyl acetate. The two diastereoisomers were obtained pure.

[00559] F1: Heptane/AcOEt 95:5. 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl- pyrrolidine-1,2-dicarboxylate (780 mg, 2.09 mmol, 12%) was obtained as a colorless oil. RT (M44) = 1.56 min, [M+Na]⁺ 396.2; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 4.44 (quin, *J* = 6.5 Hz, 1H), 3.7-3.6 (m, 3H), 3.58 (s, 1H), 3.0-3.1 (m, 1H), 2.2-1.9 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.32 (s, 6H), 0.84 (s, 9H), 0.1-0.0 (m, 6H).

[00560] F2: Heptane/AcOEt 93:7. 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-pyrrolidine-1,2-dicarboxylate (2.23 g, 5.84 mmol, 35%) was obtained as a colorless oil.

[00561] LCMS: RT (M44) = 1.56 min, [M+Na]⁺ 396.2; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 4.42 (m, 1H), 3.63 (s, 2H), 3.6-3.5 (m, 2H), 3.3-3.2 (m, 1H), 2.3-2.2 (m, 1H), 1.9-1.8 (m, 1H), 1.56 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 0.86 (s, 9H), 0.1-0.0 (m, 6H).

[00562] Step 3, Method 33

[00563] Potassium trimethylsilanolate (1.53 g, 11.94 mmol, 2 eq) was added to a solution of 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpyrrolidine-1,2-dicarboxylate (2.23 g, 5.97 mmol) in dry THF (28 mL, 0.2 M) and stirred at 50 °C for 16 h. The reaction was followed by TLC and LCMS. Water was added and the pH of the mixture was adjusted to 6 by addition of HCl 1N. The crude was diluted with ethyl acetate (60 mL) and washed with water (50mL). The aqueous layer was extracted with CHCl₃:iPrOH (3:1). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. Crude was used in the next step without further purification. RT (M44) = 1.38 min, [M+Na]⁺ 382.2.

[00564] Step 4, Method 33

[00565] HATU (6.66 g, 17.52 mmol, 1.5 eq) was added to a solution of (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylpyrrolidine-2-carboxylic acid (4.2 g, 11.68 mmol, 1 eq), DIPEA (5.28 g, 40.89 mmol, 7.12 mL, 3.5 eq) and NH₄Cl (937.32 mg, 17.52 mmol, 1.5 eq) in DMF (34 mL, 0.28 M) and the reaction was stirred at room temperature for 16 h. The reaction was followed by LCMS. When the starting material was consumed the reaction was diluted with EtOAc (100 mL) and washed with water (30 mLx5). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with heptane:ethyl acetate to give *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-carbamoyl-2-methylpyrrolidine-1-carboxylate (3.41 g, 9.32 mmol, 80% yield) as a white solid. RT (M44) = 1.26 min, [M+Na]⁺ 359.2; ¹H-NMR (DMSO-d₆, 400 MHz) δ 7.1-7.0 (m, 1H), 7.0-6.8 (m, 1H), 4.4-4.3 (m, 1H), 3.68 (br dd, *J* = 5.0, 11.1 Hz, 1H), 3.2-3.2 (m, 1H), 2.2-2.1 (m, 1H), 1.8-1.7 (m, 1H), 1.6-1.5 (m, 3H), 1.4-1.3 (m, 9H), 0.85 (s, 9H), 0.05 (s, 6H).

[00566] Step 5, Method 33

[00567] Hydrogen chloride 4N in dioxane (4 M, 2.90 mmol, 725.15 µL, 2 eq) was added to a solution of *tert*-butyl(2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-carbamoyl-2-methylpyrrolidine-1-carboxylate (520 mg, 1.45 mmol, 1 eq) in DCM (5 mL, 0.25M) and the reaction was stirred at rt for 16 h. Reaction is followed by LCMS and when all the starting material have reacted the solvent

was removed under vacuum and the crude product was used in the next step without further purification. RT (M43) = 0.67 min, $[M-Cl]^+$ 259.2

[00568] Step 6, Method 33

[00569] TCFH (293.26 mg, 1.05 mmol, 1.2 eq) was added to a solution of 8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (320 mg, 0.87 mmol, 1 eq), (2*R*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-methyl-pyrrolidine-2-carboxamide;hydrochloride (385.27 mg, 1.31 mmol, 1.5 eq) and 1-methylimidazole (250.29 mg, 3.05 mmol, 242.76 μ L, 3.5 eq) in DMA (1.7 mL, 0.45 M) and stirred at 70 °C for 16 h. The reaction was followed by LCMS, showing the formation of the expected compound (RT (M43) = 1.65 min, 608.5 $[M+H]^+$) and the product resulting from the Boc cleavage (RT (M43) = 0.85 min, 494.4 $[M+H]^+$). The reaction was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with heptane/EtOAc (0-100%) to give (2*R*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (100 mg, 0.08 mmol, 9% yield, 50% purity) as a yellowish oil (RT (M43) = 1.65 min, $[M+H]^+$ 608.5) and gradient towards DCM/MeOH (0-10%) to obtain (2*R*,4*S*)-4-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (30 mg, 0.06 mmol, 7% yield) as a white solid. RT (M43) = 0.85 min, $[M+H]^+$ 494.4.

[00570] Step 7, Method 33

[00571] Methyl N-(triethylammoniumsulfonyl)carbamate (Burgess reagent) (23.52 mg, 0.10 mmol, 2 eq) was added to a solution of (2*R*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carboxamide (30 mg, 0.05 mmol, 1 eq) in dichloroethane (2 mL, 0.02M) and the reaction was stirred at rt for 16 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (5 mL) and diluted with DCM (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The

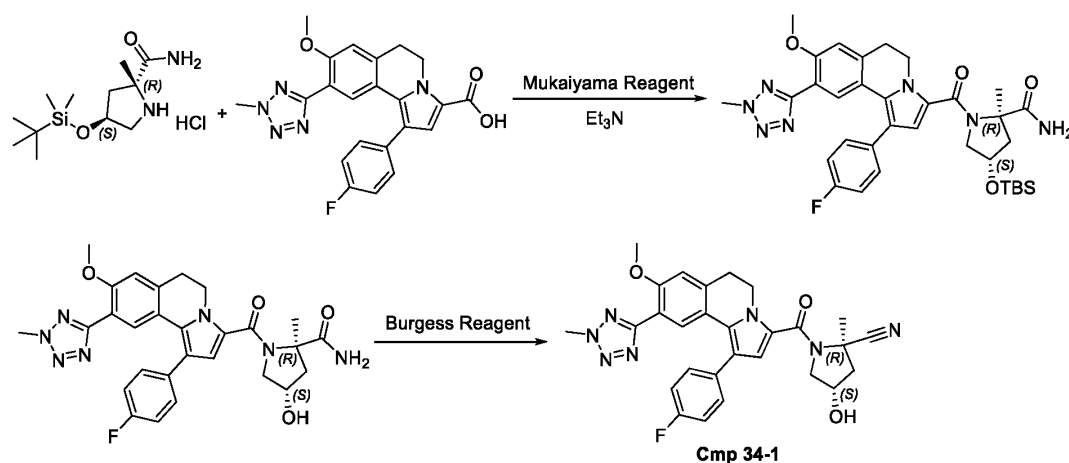
crude product was used in the next step without further purification. RT (M43) = 1.87 min, [M+H]⁺ 590.2.

[00572] Step 8, Method 33

[00573] Tetrabutylammonium fluoride, 1M in THF (1 M, 0.10 mmol, 98.34 μ L, 2 eq) was added to a solution of (2*R*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (29 mg, 0.05 mmol, 1 eq) in dry THF (2 mL) and the reaction was stirred at rt for 16 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (5 mL) and diluted with DCM (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:ethyl acetate to give (2*R*,4*S*)-4-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile (compound 33-1) (12.6 mg, 0.03 mmol, 53% yield) as a white solid. RT (M41) = 3.27 min, [M+H]⁺ (Dual-ESI⁺) 476.2; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 8.09 (s, 1H), 7.24 (s, 1H), 6.59 (s, 1H), 5.42 (br s, 1H), 4.42 (s, 3H), 4.4-4.3 (m, 3H), 4.01 (dd, *J* = 5.4, 10.4 Hz, 1H), 3.89 (s, 3H), 3.64 (dd, *J* = 4.6, 10.3 Hz, 1H), 3.07 (br t, *J* = 6.3 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.61 (dd, *J* = 5.2, 13.0 Hz, 1H), 2.13 (dd, *J* = 5.9, 13.0 Hz, 1H), 1.83 (s, 3H), 1.65 (qd, *J* = 7.4, 15.0 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

[00574] Synthetic Method 34

[00575] Scheme for Method 34



[00576] Step 1, Method 34

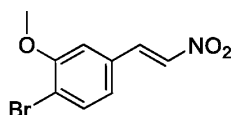
[00577] Triethylamine (289.52 mg, 2.86 mmol, 398.79 μ L, 3 eq) was added to a solution of 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (400 mg, 0.95 mmol, 1 eq), (2R,4S)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-methylpyrrolidine-2-carboxamide; hydrochloride (421.87 mg, 1.43 mmol, 1.5 eq) and 2-chloro-1-methylpyridin-1-ium iodide (365.49 mg, 1.43 mmol, 1.5 eq) in DMA (3 mL, 0.28 M) and stirred at 70 °C for 16 h. The reaction was followed by LCMS showing the formation of the expected product (*m/z* 660) and the TBS deprotected product (*m/z* 546). The reaction was diluted with ethyl acetate (12 mL) and washed with brine (5 mL x 5). The organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The crude product was purified by flash chromatography eluting with dichloromethane:methanol to yield (2R,4S)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl]-4-hydroxy-2-methylpyrrolidine-2-carboxamide (85 mg, 0.15 mmol, 21% yield) as a yellow oil. RT (M43): 0.91 min; [M+H]⁺ 546.4.

[00578] Step 2, Method 34

[00579] Methyl N-(triethylammoniumsulfonyl)carbamate (Burgess reagent) (72.51 mg, 0.30 mmol, 2 eq) was added to a solution of (2*R*,4*S*)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-4-hydroxy-2-methylpyrrolidine-2-carboxamide (83 mg, 0.15 mmol, 1 eq) in DCM (2 mL, 0.08M) and the reaction was stirred at rt for 4 h. The reaction was followed by LCMS. When the starting material was consumed, the reaction was quenched with water (5 mL) and diluted with DCM (10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:ethyl acetate to give (2*R*,4*S*)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-4-hydroxy-2-methylpyrrolidine-2-carbonitrile (compound 34-1) (21 mg, 0.04 mmol, 26% yield) as a white solid. RT (M41): 3.24 min; *m/z* [M+H]⁺ (Dual-ESI⁺) 528.2; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 7.71 (s, 1H), 7.44 (dd, *J* = 5.6, 8.7 Hz, 2H), 7.24 (s, 1H), 7.2-7.2 (m, 2H), 6.74 (s, 1H), 5.42 (br s, 1H), 4.4-4.3 (m, 2H), 4.33 (s, 3H), 4.06 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.87 (s, 3H), 3.70 (dd, *J* = 4.5, 10.3 Hz, 1H), 3.29 (s, 1H), 3.15 (br t, *J* = 6.4 Hz, 2H), 2.62 (dd, *J* = 5.2, 13.1 Hz, 1H), 2.15 (dd, *J* = 5.7, 13.0 Hz, 1H), 1.85 (s, 3H).

[00580] Additional compounds were prepared as described below.

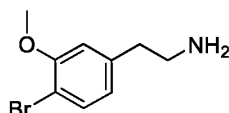
[00581] INTERMEDIATE 1: (E)-1-bromo-2-methoxy-4-(2-nitrovinyl)benzene



[00582] To a solution of 4-bromo-3-methoxy-benzaldehyde (430 g, 2.00 mol) in AcOH (860 mL) was added NH₄OAc (169.55 g, 2.20 mol) and CH₃NO₂ (610.27 g, 10.00 mol, 540.07 mL). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was cooled down to ~25 °C. Three batches were combined to work up. H₂O (1800 mL) was added to the reaction mixture and stirred at 25 °C for 15 min, then it was filtered to afford a filter cake. The filter cake was triturated with MeCN (900 mL) at 25 °C for 15 min, filtered to afford the solid. The solid was triturated with Petroleum ether (1800 mL) at 25 °C for 15 min, filtered to give a cake, which was dried under

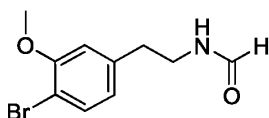
reduced pressure to give the *title compound* (1600 g, 90% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.96 (d, J = 13.7 Hz, 1H), 7.67 - 7.61 (m, 1H), 7.58 (s, 1H), 7.05 (dd, J = 1.8, 8.2 Hz, 1H), 7.00 (d, J = 1.7 Hz, 1H), 4.03 - 3.92 (m, 3H)

[00583] **INTERMEDIATE 2:** 2-(4-bromo-3-methoxyphenyl)ethan-1-amine



[00584] At 0 °C, $\text{BH}_3\cdot\text{THF}$ (1 M, 8.82 L) was added dropwise to a solution of *Intermediate 1* (650 g, 2.52 mol) in THF (6500 mL). Then NaBH_4 (47.64 g, 1.26 mol) was added in portions at 5-8 °C. The mixture was stirring at 65 °C for 18 hr. The reaction mixture was cooled to 0 °C and added dropwise with HCl (4.9 L, 4M). After stirring for 1 h at 70 °C, the reaction mixture was cooled to room temperature and MTBE (1L) was added to the mixture. The aqueous layer was separated and extracted with MTBE (1L x 3). The aqueous layer was adjust to pH=13 with solid NaOH at 0-5°C, then extracted with DCM (5L x 3), The combined organic phase was washed with brine (500 mL x 3), dried with Na_2SO_4 , filtered and concentrated under reduced pressure to give the *title compound* (510 g, 2.13 mol, 88% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.44 (br d, J = 7.9 Hz, 1H), 6.74 (d, J = 1.8 Hz, 1H), 6.68 (dd, J = 1.9, 8.0 Hz, 1H), 3.92 - 3.85 (m, 3H), 3.01 - 2.92 (m, 2H), 2.76 - 2.64 (m, 2H), 1.44 - 1.18 (m, 2H)

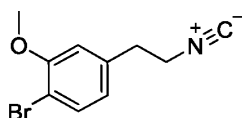
[00585] **INTERMEDIATE 3:** N-(4-bromo-3-methoxyphenethyl)formamide



[00586] To a solution of *Intermediate 2* (40 g, 150.06 mmol, HCl) in ethyl formate (200 mL) was added TEA (45.55 g, 450.18 mmol, 62.66 mL) at 20 °C. The mixture was stirred at 70 °C for 6 hr. Two reactions were combined to work up. The reaction mixture was concentrated under reduced pressure to remove the solvent to give the crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title*

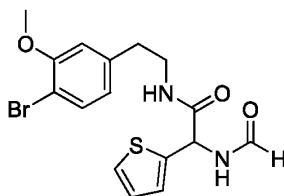
compound (74 g, 88% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.04 (br s, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.50 - 7.42 (m, 1H), 6.97 (d, J = 1.5 Hz, 1H), 6.74 (dd, J = 1.7, 8.0 Hz, 1H), 3.86 - 3.81 (m, 3H), 3.37 - 3.33 (m, 2H), 2.74 - 2.68 (m, 2H).

[00587] **INTERMEDIATE 4:** 1-bromo-4-(2-isocyanoethyl)-2-methoxybenzene



[00588] To a solution of *Intermediate 3* (25 g, 96.86 mmol) in THF (250 mL) was added Burgess Reagent (27.70 g, 116.23 mmol) at 0°C. The mixture was stirred at 20°C for 2 hr. The two reactions was combined to work up. The mixture was added with H₂O (500 mL) and extracted with DCM (200 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title compound* (42 g, 90% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl₃) δ = 7.50 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 6.72 (dd, J = 1.8, 8.0 Hz, 1H), 3.96 - 3.89 (m, 3H), 3.63 (br t, J = 6.9 Hz, 2H), 2.96 (br t, J = 6.8 Hz, 2H).

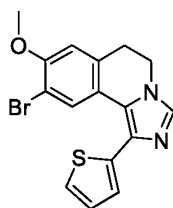
[00589] **INTERMEDIATE 5:** N-(4-bromo-3-methoxyphenethyl)-2-(thiophen-2-yl)acetamide



[00590] To a solution of *Intermediate 4* (20 g, 83.30 mmol) in MeOH (200 mL) was added with ammonium formate (10.51 g, 166.60 mmol) and thiophene-2-carbaldehyde (9.81 g, 87.46 mmol, 8.17 mL) at 20°C. The mixture was stirred at 80°C for 4 hr. The two reactions was combined to work up. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H₂O (500 mL) and extracted with warm EtOAc (200 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude

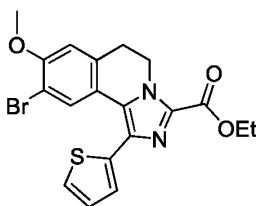
product was triturated by cold EtOAc (100 mL) and filtered to give the *title compound* (38 g, 57% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.86 (br d, J = 8.3 Hz, 1H), 8.46 (br t, J = 5.4 Hz, 1H), 8.02 (s, 1H), 7.47 - 7.36 (m, 2H), 6.98 - 6.85 (m, 3H), 6.66 (dd, J = 0.9, 8.1 Hz, 1H), 5.72 (d, J = 8.3 Hz, 1H), 3.83 - 3.74 (m, 3H), 3.41 - 3.33 (m, 2H), 2.70 (t, J = 6.9 Hz, 2H).

[00591] INTERMEDIATE 6: 9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



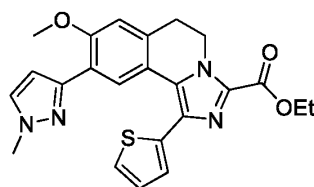
[00592] A solution of P_2O_5 (67.88 g, 478.24 mmol) in methanesulfonic acid (350 mL) at 20 °C was stirred at 75 °C for 0.5 hr. *Intermediate 5* was added into the mixture (38 g, 95.65 mmol) at 75 °C and then it was stirred at 75 °C for 1.5 hr. The reaction was poured into ice- H_2O (1 L) and the mixture was added Na_2CO_3 solid slowly to adjust pH = 8, then it was extracted with EtOAc (400 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (300 mL) and filtered to give the *title compound* (31 g, 89% yield) as a brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 7.84 (s, 1H), 7.78 (s, 1H), 7.54 (br d, J = 4.9 Hz, 1H), 7.26 (br d, J = 2.9 Hz, 1H), 7.18 (s, 1H), 7.15 - 7.09 (m, 1H), 4.15 (br t, J = 6.0 Hz, 2H), 3.91 - 3.84 (m, 3H), 3.05 (br t, J = 5.7 Hz, 2H).

[00593] INTERMEDIATE 7: Ethyl 9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



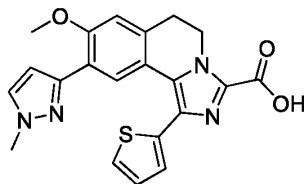
[00594] To a solution of *Intermediate 6* (15 g, 41.52 mmol) in THF (150 mL) was added LDA (2 M, 24.91 mL) at -70 °C. The mixture was added with ethyl chloroformate (22.53 g, 207.61 mmol, 19.76 mL) at -70 °C and the mixture was stirred at -70 °C for 2 hr. The mixture was added with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The organic layers were concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give the *title compound* (9.5 g, 52% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.89 (s, 1H), 7.41 - 7.37 (m, 1H), 7.35 - 7.32 (m, 1H), 7.10 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.82 (s, 1H), 4.69 (t, *J* = 6.6 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.97 - 3.92 (m, 3H), 3.08 (t, *J* = 6.6 Hz, 2H), 1.49 - 1.42 (m, 3H).

[00595] **INTERMEDIATE 8 (From Int 7):** ethyl 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



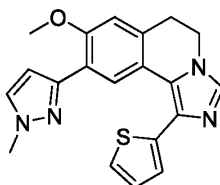
[00596] To a solution of *Intermediate 7* (400 mg, 923.11 μmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (230.48 mg, 1.11 mmol) in dioxane (5 mL) and H₂O (1 mL) was added Xphos-Pd-G₂ (72.63 mg, 92.31 μmol) and Cs₂CO₃ (1.20 g, 3.69 mmol) at 20 °C. The mixture was stirred at 80 °C for 2 hr. The mixture was filtered and the filtrate was added with H₂O (3 mL) and extracted with EtOAc (2 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title compound* (350 mg, 87% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.29 (s, 1H), 7.44 - 7.43 (m, 1H), 7.35 - 7.33 (m, 2H), 7.08 (m, 1H), 6.88 (s, 1H), 6.56 (s, 1H), 4.70 (t, *J* = 6.6 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.12 (t, *J* = 6.6 Hz, 2H), 1.45 (m, 3H).

[00597] **INTERMEDIATE 9:** Potassium 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



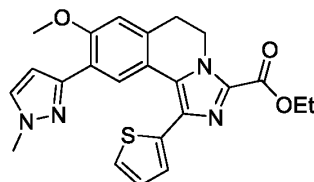
[00598] To a solution of *Intermediate 8* (120 mg, 276.17 μ mol) in THF (1 mL) was added TMSOK (70.86 mg, 552.35 μ mol). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove dioxane to use to next step. The *title compound* (336 mg, crude) was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.46 (s, 1H), 7.65 (s, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.36 (d, J = 4.8 Hz, 1H), 7.08-7.05(m, 2H), 6.63 (s, 1H), 4.61 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 2.96 (t, J = 6.6 Hz, 2H).

[00599] **INTERMEDIATE 10:** 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



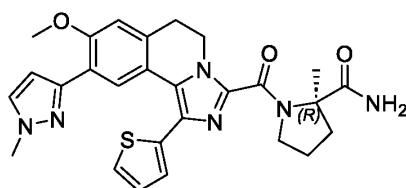
[00600] To a solution of *Intermediate 6* (3 g, 8.30 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (2.07 g, 9.97 mmol) in dioxane (0.5 mL) and H₂O (0.1 mL) was added Xphos-Pd-G2 (653.39 mg, 830.44 μ mol) and Cs₂CO₃ (10.82 g, 33.22 mmol) at 20 °C. The mixture was stirred at 80 °C for 2 hr. The residue was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title compound* (4.5 g, 75% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl₃) δ = 8.47 (s, 1H), 7.69 (s, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 4.8 Hz, 1H), 7.30 (m, 1H), 7.08-7.05(m, 1H), 6.87 (s, 1H), 6.62 (s, 1H), 4.18 (t, J = 6.6 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.12 (t, J = 6.6 Hz, 2H).

[00601] INTERMEDIATE 8 (From Int 10): Ethyl 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00602] To a solution of *Intermediate 9* (1.75 g, 4.83 mmol) in THF (15 mL) was added LDA (2 M, 3.38 mL) at -60 °C. The mixture was added with ethyl chloroformate (1.12 g, 10.32 mmol) at -60 °C and stirred for 2 hr. The mixture was added with H₂O (50 mL) and extracted with EtOAc (20 mL x 3). The organic layers were concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title compound* (1.3 g, 31% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.29 (s, 1H), 7.44 - 7.43 (m, 1H), 7.35 - 7.33 (m, 2H), 7.08 (m, 1H), 6.88 (s, 1H), 6.56 (s, 1H), 4.70 (t, *J* = 6.6 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.12 (t, *J* = 6.6 Hz, 2H), 1.45 (m, 3H).

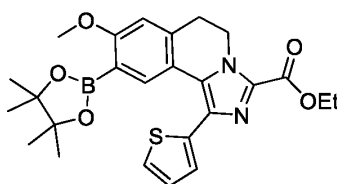
[00603] INTERMEDIATE 11: (R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00604] To a solution of *Intermediate 9* (1.5 g, 3.69 mmol) and (2R)-2-methylpyrrolidine-2-carboxamide (729.08 mg, 4.43 mmol, HCl) in DMF (15 mL) was added DIEA (1.43 g, 11.07 mmol) and HATU (1.68 g, 4.43 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 hr. The mixture was diluted with H₂O (50 mL) and extracted with EtOAc (20 mL x 3). The organic layers

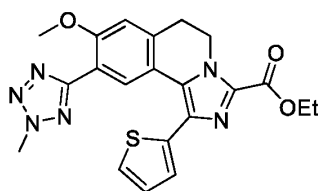
were concentrated under reduced pressure to give a crude product. The crude product was washed by MTBE (5 mL) to give the *title compound* (1.1 g, 57% yield) as a yellow solid.

[00605] INTERMEDIATE 12: Ethyl 8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00606] To a solution of *Intermediate 7* (900 mg, 2.08 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5 g, 19.69 mmol) in n-heptane (10 mL) and dioxane (5 mL) was added KOAc (3.06 g, 31.15 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (424.04 mg, 519.25 μmol) at 20 °C. The mixture was stirred at 80 °C for 2 hr. The reaction was filtered, added with H₂O (15 mL) and extracted with EtOAc (10 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the *title compound* (580 mg, 58% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.07 (s, 1H), 7.39 - 7.35 (m, 2H), 7.07-7.05 (m, 1H), 6.77 (s, 1H), 4.70 (t, *J* = 6.6 Hz, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.32 (t, *J* = 6.6 Hz, 2H), 1.47 (t, *J* = 6.6 Hz, 3H), 1.30 (s, 12H).

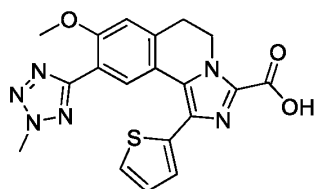
[00607] INTERMEDIATE 13: Ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00608] To a solution of *Intermediate 12* (560 mg, 1.17 mmol) and 5-bromo-2-methyl-tetrazole (208.99 mg, 1.28 mmol) in dioxane (5 mL) and H₂O (1 mL) was added with Xphos-Pd-G₂ (91.72

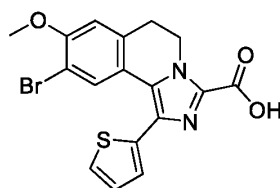
mg, 116.57 μmol) and Cs_2CO_3 (1.14 g, 3.50 mmol) at 20 °C. The mixture was stirred at 80 °C for 2 hr. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (5 mL x 2). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was washed by MTBE (5 mL) and filtered to give the *title compound* (450 mg, 88% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.27 (s, 1H), 7.58-7.57 (m, 1H), 7.35-7.32 (m, 2H), 7.11-7.09 (m, 1H), 4.61 (t, J = 6.6 Hz, 2H), 4.39-4.32 (m, 5H), 3.90 (s, 3H), 3.19 (t, J = 6.6 Hz, 2H), 1.34 (t, J = 6.6 Hz, 3H).

[00609] INTERMEDIATE 14: Potassium 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00610] To a solution of *Intermediate 13* (220 mg, 504.03 μmol) in THF (2.5 mL) was added TMSOK (129.32 mg, 1.01 mmol) at 20 °C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to give a crude product (205 mg, crude) as a yellow solid.

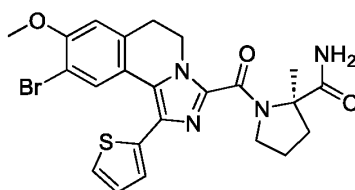
[00611] INTERMEDIATE 15: 9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00612] To a solution of *Intermediate 7* (2 g, 4.62 mmol) in THF (20 mL) was added TMSOK (1.18 g, 9.23 mmol). The mixture was stirred at 20 °C for 1 hr. The mixture was filtered and concentrated under reduced pressure, the crude product was used into the next step. The *title*

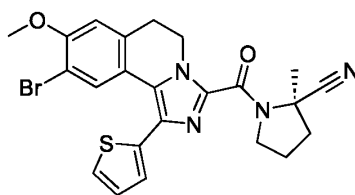
compound (2 g, crude) was obtained as a yellow solid. LCMS (*Method m*, ES⁺, RT=0.390 min) 405.0/407.0 (M+H)⁺

[00613] INTERMEDIATE 16: (R)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00614] To a solution of *Intermediate 15* (2 g, 4.51 mmol) in DMF (20 mL) was added DIEA (2.33 g, 18.04 mmol, 3.14 mL), (2R)-2-methylpyrrolidine-2-carboxamide (965.47 mg, 5.86 mmol, HCl) and HATU (2.57 g, 6.77 mmol). The mixture was stirred at 20 °C for 1 hr. The mixture was poured into water (20 mL) and pH was adjusted to 7 with 1M HCl. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the *title compound* (1.5 g, yield:65%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.36 (t, *J* = 4.1 Hz, 2H), 7.13 - 7.08 (m, 1H), 6.82 (s, 1H), 5.31 (s, 1H), 4.59 (br t, *J* = 5.9 Hz, 2H), 4.40 - 4.20 (m, 2H), 3.93 (s, 4H), 3.04 (br t, *J* = 6.4 Hz, 2H), 2.50 - 2.43 (m, 1H), 2.08 - 1.98 (m, 3H), 1.77 (s, 3H). LCMS (*Method a*, ES⁺, RT=1.671 min) 515.1/517.1 (M+H)⁺

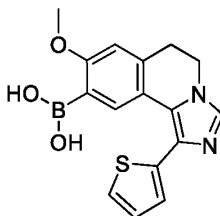
[00615] INTERMEDIATE 17: (R)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



[00616] To a solution of *Intermediate 16* (1.5 g, 2.91 mmol) in pyridine (15 mL) was added TFAA (4.89 g, 23.28 mmol, 3.24 mL). The mixture was stirred at 20 °C for 2 hr. The mixture

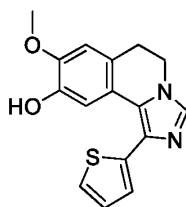
was poured into water (15 mL) and pH was adjusted to 7 with 1M HCl. The aqueous phase was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 0/1) to afford the *title compound* (0.8 g, yield: 55%) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ 8.02 - 7.99 (m, 1H), 7.40 - 7.34 (m, 2H), 7.14 - 7.09 (m, 1H), 6.85 - 6.82 (m, 1H), 4.77 - 4.59 (m, 2H), 4.35 - 4.18 (m, 2H), 3.94 (s, 3H), 3.10 - 3.01 (m, 2H), 2.17 - 2.06 (m, 4H), 1.90 - 1.86 (m, 3H). LCMS (*Method a*, ES⁺, RT=2.039 min) 497.1/498.9 (M+H)⁺

[00617] INTERMEDIATE 18: (8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)boronic acid



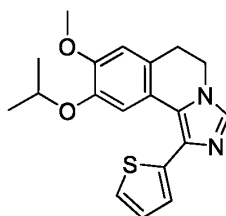
[00618] To a solution of *Intermediate 6* (2.3 g, 6.37 mmol) and hypoboric acid (1.71 g, 19.10 mmol) in EtOH (10 mL) was added DIEA (4.11 g, 31.83 mmol, 5.54 mL) and Pd(dtbpf)Cl₂ (41.49 mg, 63.67 μmol) at 20 °C. The mixture was stirred at 50 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with H₂O (2 mL) and the solid precipitation was filtered. The *title compound* (4.1 g, crude) was obtained as a yellow solid.

[00619] INTERMEDIATE 19: 8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-9-ol



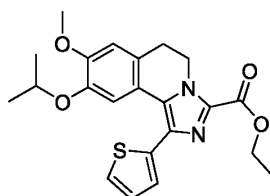
[00620] To a solution *Intermediate 18* (4.1 g, 12.57 mmol) in H₂O (20 mL) was added NaBO₃·4H₂O (1.93 g, 12.57 mmol, 2.42 mL) at 20 °C. The mixture was stirred at 20 °C for 12 hr. The mixture was filtered to give the crude product (1.5 g, 40% yield) as a white solid. ¹HNMR (400 MHz, MeOD-d) δ = 8.13 (s, 1H), 7.85 (d, J = 6.4 Hz, 1H), 7.49 - 7.48 (m, 1H), 7.27 (d, J = 6.4 Hz, 1H), 7.14 - 7.10 (m, 2H), 6.90 (s, 1H), 4.23 - 4.17 (m, 2H), 3.88 (s, 3H), 3.15 (t, J = 6.4 Hz, 1H), 3.04 (t, J = 6.4 Hz, 1H)

[00621] **INTERMEDIATE 20:** 9-isopropoxy-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



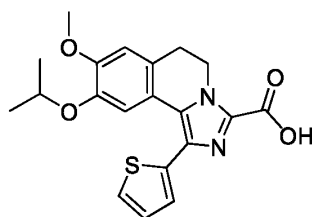
[00622] To a solution of *Intermediate 19* (800 mg, 2.68 mmol) and 2-iodopropane (683.71 mg, 4.02 mmol, 402.18 μ L) in DMF (5 mL) was added K₂CO₃ (741.15 mg, 5.36 mmol) at 20 °C. The mixture was stirred at 80 °C for 12 hr. The residue was diluted with H₂O (15 mL) and extracted with EtOAc (10 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (10 mL) and filtered to give the *title compound* (640 mg, 70% yield) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ 7.60 (s, 1H), 7.35-7.33 (m, 3H), 7.08 - 7.06 (m, 1H), 6.76 (s, 1H), 4.29 - 4.24 (m, 1H), 4.14 (t, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.04 (t, J = 6.4 Hz, 2H), 1.29 (d, J = 4.4 Hz, 6H).

[00623] **INTERMEDIATE 21:** Ethyl 9-isopropoxy-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



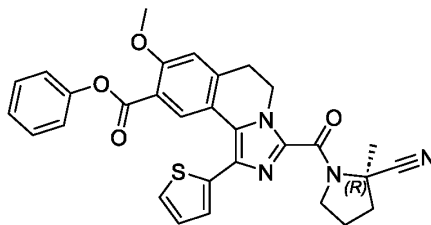
[00624] To a solution of *Intermediate 20* (540 mg, 1.59 mmol) in THF (5 mL) was added *n*-BuLi (2.5 M, 761.37 μ L) at -60 °C. The mixture was added with ethyl chloroformate (587.51 mg, 7.93 mmol, 637.91 μ L) at -60 °C and the mixture was stirred at -60 °C for 2 hr. The mixture was added with H₂O (10 mL) and extracted with EtOAc (5 mL x 3). The organic layers were concentrated under reduced pressure to give the crude product. The crude product was triturated by MTBE (5 mL) to give the *title compound* (270 mg, 41% yield) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 4.8 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.12 (s, 1H), 7.09-7.07 (m, 1H), 6.77 (s, 1H), 4.69 (t, *J* = 6.8 Hz, 1H), 4.46 (q, *J* = 6.8 Hz, 2H), 4.16-4.13 (m, 1H), 3.89 (s, 3H), 3.06 (t, *J* = 6.4 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 4.4 Hz, 6H).

[00625] **INTERMEDIATE 22:** 9-isopropoxy-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



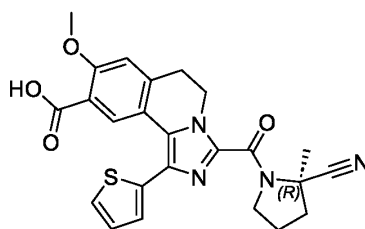
[00626] To a solution of *Intermediate 21* (250 mg, 606.06 μ mol) in THF (3 mL) was added TMSOK (155.50 mg, 1.21 mmol). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure. The *title compound* (233 mg, 100% yield) was obtained as a yellow solid. LCMS (*Method e*, ES⁺, RT=0.358 min) 385.0 (M+H)⁺

[00627] **INTERMEDIATE 23:** Phenyl (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxylate



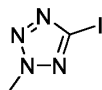
[00628] To a solution of *Intermediate 17* (370 mg, 703.65 μmol) in DMF (5 mL) was added with phenyl formate (515.58 mg, 4.22 mmol, 460.34 μL) and TEA (427.21 mg, 4.22 mmol, 587.63 μL), Pd(dppf)Cl₂.CH₂Cl₂ (143.66 mg, 175.91 μmol) at 20 °C. The mixture was stirred at 120 °C for 12 hr. The reaction mixture was filtered, then the residue was diluted with H₂O (10 mL) and extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 0/1) to give the *title compound* (300 mg, 79.16% yield) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.89 (s, 3 H), 2.06 - 2.18 (m, 3 H), 2.55 - 2.65 (m, 1 H), 3.17 (t, J = 6.50 Hz, 2 H), 3.99 (s, 3 H), 4.30 (br s, 2 H), 4.66 - 4.87 (m, 2 H), 6.98 (s, 1 H), 7.07 (dd, J = 5.13, 3.63 Hz, 1 H), 7.16 (d, J = 7.63 Hz, 2 H), 7.23 - 7.26 (m, 1 H), 7.32 - 7.35 (m, 1 H), 7.38 - 7.44 (m, 3 H), 8.51 - 8.60 (m, 1 H). LCMS (*Method m*. ES⁺, RT=0.58 min) 539.2 (M+H)⁺.

[00629] **INTERMEDIATE 24:** (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxylic acid



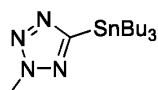
[00630] To a solution of *Intermediate 23* (290 mg, 362.04 μmol) in THF (5 mL) was added TMSOK (92.89 mg, 724.08 μmol) at 20 °C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was added with HCl (0.5 M) to adjust pH=3, then mixture was diluted with H₂O 12 mL and extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (4 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the *title compound* (300 mg, 89.58% yield) as a brown solid. LCMS (*Method m*. ES⁺, RT=0.45 min) 463.2 (M+H)⁺

[00631] **INTERMEDIATE 25:** 5-iodo-2-methyl-2H-tetrazole



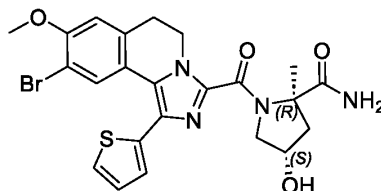
[00632] To a solution of 4-methylbenzenesulfonic acid; hydrate (115.17 g, 605.48 mmol) in ACN (1 L) was added 2-methyltetrazol-5-amine (20 g, 201.83 mmol) at 20 °C. The mixture was cooled to 0-5 °C for 10 min. Then a mixture of KI (83.76 g, 504.57 mmol) and NaNO₂ (27.85 g, 403.66 mmol) dissolved in H₂O (250 mL) was added at 0-5 °C and stirred at 0-5 °C for 2 hr. The mixture was poured into sat. NaHCO₃ (1L), Na₂S₂O₃ (2M, 400 mL) at 0 °C and stirred at 20 °C for 10 min. Then it was extracted with MTBE (200 mL x 2). The combined organic phase was washed with brine (500 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50/1 to 2/1). *The title compound* (15 g, 35.39% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.41 (s, 3 H). LCMS (Method a. ES+, RT = 0.753 min) 211.1 (M+H)

[00633] INTERMEDIATE 26: 2-methyl-5-(tributylstannyl)-2H-tetrazole



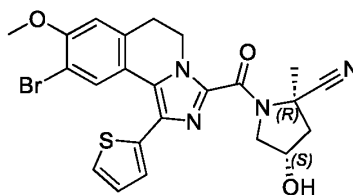
[00634] To a solution of *Intermediate 25* (30 g, 142.87 mmol) in THF (600 mL) was added n-BuLi (2.5 M, 71.44 mL) at -78 °C under N₂ and stirred at -78 °C for 0.5 hr. Then added tributyl(chloro)stannane (53.15 g, 163.28 mmol, 43.93 mL) at -78 °C and stirred at -78 °C for 0.5 hr. Then the mixture was warmed to 15 °C and stirred for 1.5 hr. The mixture was quenched with sat. NH₄Cl solution (200 mL) and extracted with ethyl acetate (300 mL x 3). The combined organic phase was washed with brine (300 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1). *The title compound* (40 g, 75.03% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.36-4.42 (m, 3 H), 1.53-1.65 (m, 6H), 1.28 - 1.41 (m, 7H), 1.19 - 1.26 (m, 5H), 0.89 (t, J=7.3 Hz, 9H)

[00635] **INTERMEDIATE 27:** (2R,4S)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carboxamide



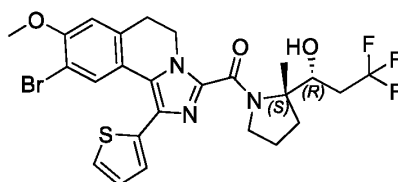
[00636] To a solution of *Intermediate 15* (185 mg, 456.49 μmol) in DMF (2 mL) was added *Intermediate 256* (98.95 mg, 547.79 μmol , HCl salt), DIEA (235.99 mg, 1.83 mmol, 318.05 μL) and HATU (190.93 mg, 502.14 μmol) at 20 °C. The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into the ice water, 1N HCl was added to adjust pH = 5-6. The mixture was extracted with EtOAc (5 mL x 3), then the combined organic layer was washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , PE/EtOAc = 100/1 to 0/1). The title compound (178 mg, 73% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.79 (s, 1H), 7.62 (dd, $J=5.07$, $J=0.81$ Hz, 1H), 7.31 (dd, $J=3.50$, $J=0.88$ Hz, 1H), 7.20 (s, 1H), 7.16 (dd, $J=5.07$, $J=3.56$ Hz, 2H), 6.86 (br s, 1H), 5.13 (d, $J=3.75$ Hz, 1H), 4.40 (br t, $J=6.44$ Hz, 2H), 4.27-4.32 (m, 1H), 4.13-4.19 (m, 1H), 4.02-4.08 (m, 1H), 3.89 (s, 3H), 2.96-3.12 (m, 2H), 2.14-2.25 (m, 1H), 1.77-1.87 (m, 1H), 1.66 (s, 3H) LCMS (*Method e*. ES^+ , RT = 0.435 min) 533.1/533.2 (M+H) $^+$

[00637] **INTERMEDIATE 28:** (2R,4S)-1-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile



[00638] To a solution of *Intermediate 27* (150 mg, 282.26 μmol) in pyridine (1.5 mL) was added TFAA (474.27 mg, 2.26 mmol, 313.88 μL) at 20 °C. The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into the ice water and 1N HCl was added to adjust pH = 2-3. Then suspension was extracted with MTBE (5 mL x 3), combined organic phase was washed with 5 mL brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 0/1). *The title compound* (105 mg, 72.46% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.63 (d, J = 4.50 Hz, 1H), 7.33 (d, J = 2.88 Hz, 1H), 7.22 (s, 1H), 7.17 (dd, J = 5.00, 3.63 Hz, 1H), 5.38 (d, J = 3.38 Hz, 1H), 4.50 (br t, J = 6.32 Hz, 2H), 4.32 - 4.40 (m, 1H), 4.15 - 4.22 (m, 1H), 4.06 (br dd, J = 11.76, 3.13 Hz, 1H), 3.89 (s, 3H), 3.09 (br t, J = 6.38 Hz, 2H), 2.61 (dd, J =13.13, 5.13 Hz, 1H), 2.19 (br dd, J =13.01, 4.13 Hz, 1H), 1.88 (s, 3H) LCMS (*Method e.* ES^+ , RT = 0.555 min) 513.2/515.2 ($\text{M}+\text{H}$) $^+$

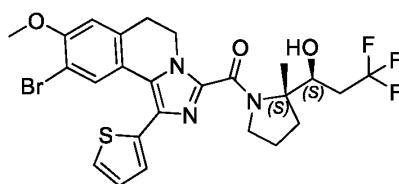
[00639] **INTERMEDIATE 29:** (9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone



[00640] To a solution of *Intermediate 15* (90 mg, 222.08 μmol), *Intermediate 105 A* (62.27 mg, 266.49 μmol , HCl salt) in DMF (2 mL) was added with HATU (92.88 mg, 244.28 μmol) and DIEA (114.80 mg, 888.31 μmol , 154.72 μL). The mixture was stirred at 30 °C for 2 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. *The title compound* (200 mg, 77% yield) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1 H), 7.30 - 7.41 (m, 2 H), 7.11 (m, 1 H), 6.82 (s, 1 H), 6.01 (br s, 1 H), 4.61 - 4.71 (m, 1 H), 4.38 - 4.58 (m, 3 H), 3.94 (s, 4 H), 3.05 (br t,

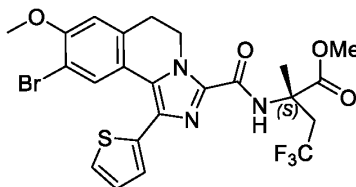
$J=6.44$ Hz, 2 H), 2.24 - 2.38 (m, 2 H), 1.75 - 2.00 (m, 4 H), 1.58 (s, 3 H). LCMS (*Method 1*. ES⁺, RT = 0.589 min) 584/586 (M+H)⁺

[00641] INTERMEDIATE 30: (9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone



[00642] To a solution of *Intermediate 15* (90 mg, 222.08 μ mol), *Intermediate 258* (62.27 mg, 266.49 μ mol, HCl salt) in DMF (0.2 mL) was added HATU (92.88 mg, 244.28 μ mol) and DIEA (114.81 mg, 888.31 μ mol, 154.73 μ L). The mixture was stirred at 25 °C for 1 h. The mixture was poured into ice water and added with 1M HCl to adjust pH=5, and filtered. The filter cake was dissolved with DCM and washed with brine (5 mL x 3), concentrated under reduced pressure to give a crude product. *The title compound* (120 mg, 92 % yield) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79 (s, 1H), 7.60 (dd, $J=5.13$, 0.88 Hz, 1H), 7.30 (d, $J=2.75$ Hz, 1H), 7.21 (s, 1H), 7.15 (dd, $J=5.00$, 3.63 Hz, 1H), 5.31 (d, $J=6.75$ Hz, 1H), 4.71 (br t, $J=8.63$ Hz, 1H), 4.45 - 4.52 (m, 1H), 4.25 - 4.37 (m, 2H), 3.89 (s, 3H), 3.59 - 3.68 (m, 1H), 3.00 - 3.09 (m, 2H), 2.08 - 2.24 (m, 2H), 1.75 - 1.90 (m, 2H), 1.56 - 1.64 (m, 1H), 1.44 (s, 3H) LCMS (*Method e*. ES⁺, RT = 0.404 min) 584.1/586.1 (M+H)⁺

[00643] INTERMEDIATE 31: methyl (S)-2-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoate

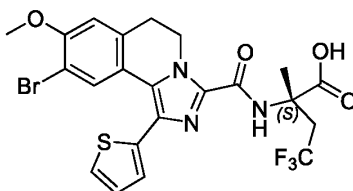


[00644] Step A: To a solution of *Intermediate 15* (2 g, 4.51 mmol) in DMF (20 mL) was added HATU (3.43 g, 9.02 mmol) at 20 °C. The mixture was stirred at 20 °C for 30 min.

[00645] Step B: To a solution of *Intermediate 115* (1.30 g, 5.86 mmol, HCl salt) in DMF (20 mL) was added Na₂CO₃ (1.43 g, 13.53 mmol). The mixture was stirred at 20 °C for 30 min.

[00646] Step C. The mixture of A was added dropwise to the mixture B at 20 °C. The mixture was stirred at 20 °C for 1 hr. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried with Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/ EtOAc =100/1 to 25/1). *The title compound* (1.7 g, 65% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (br s, 1 H), 7.93 (s, 1 H), 7.32 - 7.44 (m, 2 H), 7.13 (m, 1 H), 6.82 (s, 1 H), 4.71 (t, *J*=6.57 Hz, 2 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.26 (m, 1 H), 3.06 (t, *J*=6.57 Hz, 3 H), 1.76 (s, 3 H) LCMS (*Method h*. ES⁺, RT = 2.613 min) 572.1/574.1 (M+H)⁺

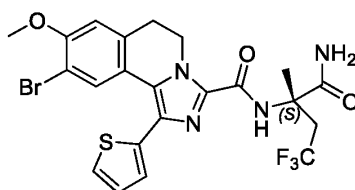
[00647] **INTERMEDIATE 32:** (S)-2-(9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



[00648] To a solution of *Intermediate 31* (1.65 g, 2.88 mmol) in THF (17 mL) was added TMSOK (739.61 mg, 5.77 mmol) at 20 °C. The mixture was stirred at 50 °C for 12 hr. The mixture was added with 1M HCl to adjust pH=3 and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (1.6 g, 99% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.30 (br s, 1 H), 7.84 (br d, *J*=4.41 Hz, 1 H), 7.32 - 7.47 (m, 2 H), 7.13 (br d, *J*=2.98 Hz, 1 H), 6.82 (br d, *J*=4.05 Hz, 1 H), 4.73 (br d,

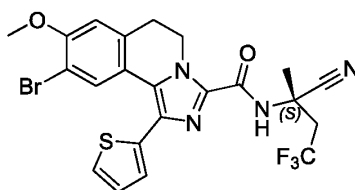
$J=3.93$ Hz, 2 H), 3.93 (br d, $J=4.41$ Hz, 3 H), 3.00 - 3.24 (m, 4 H), 1.79 (br d, $J=3.34$ Hz, 3 H).
LCMS (*Method 1*, ES⁺, RT = 0.563 min) 558.1/560.1 (M+H)⁺

[00649] INTERMEDIATE 33: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-9-bromo-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



[00650] To a solution of *Intermediate 32* (1.5 g, 2.69 mmol) in THF (15 mL) was added CDI (653.40 mg, 4.03 mmol) and NH₃.H₂O (1.13 g, 8.06 mmol, 1.24 mL, 25% purity) at 25 °C. The mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (1.48 g, 98% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.74 (br d, $J=3.75$ Hz, 1H), 7.41-7.45 (m, 1H), 7.31-7.39 (m, 1H), 7.11-7.16 (m, 2H), 6.83 (s, 1H), 6.24-6.39 (m, 1H), 5.34-5.45 (m, 1H), 4.60-4.83 (m, 2H), 3.94 (s, 3 H), 3.39 (m, 1 H), 3.07 (br t, $J=6.57$ Hz, 2 H), 2.90-3.03 (m, 1 H), 1.75 (s, 3 H). LCMS (*Method 1*, ES⁺, RT = 0.529 min) 557.1/559.1 (M+H)⁺

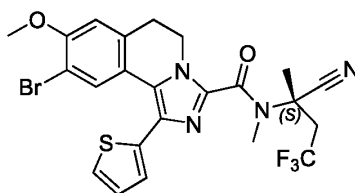
[00651] INTERMEDIATE 34: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



[00652] To a solution of *Intermediate 33* (500 mg, 897.05 μmol) in THF (2.5 mL) was added Burgess reagent (427.54 mg, 1.79 mmol) in DCM (2.5 mL) at 20 °C. The mixture was stirred at

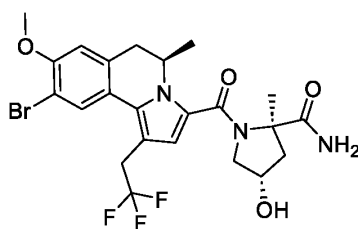
20 °C for 12 hr. The reaction mixture was diluted with H₂O (10 ml) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (400 mg, 82% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.60 (s, 1H), 7.43 (d, *J*=4.65 Hz, 1H), 7.34 (d, *J*=2.81 Hz, 1H), 7.14 (m, 1 H), 6.84 (s, 1 H), 4.60-4.86 (m, 2 H), 3.94 (s, 3 H), 3.01-3.22 (m, 4 H), 1.97 (s, 3 H). LCMS (*Method 1*, ES⁺, RT = 0.593 min) 539.1/541.1 (M+H)⁺

[00653] INTERMEDIATE 35: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



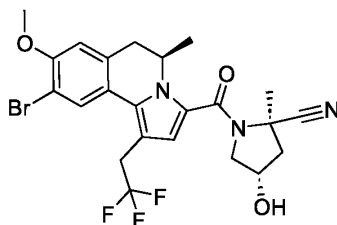
[00654] DMF (1.5 mL) was charged to the three-necked round bottom flask, then *Intermediate 34* (150 mg, 278.10 μmol) was added. At 0 °C inner temperature, NaH (22.25 mg, 556.21 μmol, 60% purity) was added to the reaction mixture at 0 °C. Then CH₃I (59.21 mg, 417.16 μmol, 25.97 μL, 1.5 eq) was added. After the addition, the mixture was stirred at 70 °C for 2 hr. The reaction was cooled and quenched with water (5 mL), extracted with ethyl acetate (5 mL). The organic layer was washed with H₂O (3x2 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 80/20). *The title compound* (70 mg, 45.48% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 7.39 (d, *J*=5.01 Hz, 1H), 7.35 (d, *J*=3.46 Hz, 1H), 7.13 (m, 1H), 6.81-6.86 (m, 1H), 4.66-4.86 (m, 1H), 4.41-4.58 (m, 1H), 3.94 (s, 3H), 3.63 (s, 2H), 3.35 (m, 1H), 2.99-3.22 (m, 4H), 1.96 - 2.08 (m, 2H), 1.98 (s, 1H) LCMS (*Method 1*, ES⁺, RT = 0.601 min) 553.2/555.2 (M+H)⁺

[00655] INTERMEDIATE 36: (2R,4S)-1-((R)-9-bromo-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carboxamide.



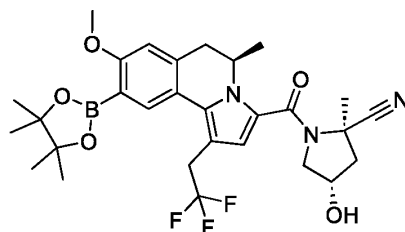
[00656] To a solution of (R)-9-bromo-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (1.7 g, 4.06 mmol) in DMF (10 mL) was added HATU (1.85 g, 4.88 mmol) and DIEA (2.10 g, 16.26 mmol, 2.83 mL). The mixture was stirred at 20 °C for 1 hr. And then the mixture was added *Intermediate 256* (954.55 mg, 5.28 mmol, HCl) and stirred at 20 °C for 2 hr. The reaction mixture was poured into ice-water (50 mL) and added with 1 M HCl to pH = 7. The reaction mixture was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (1.6 g, 72% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.74 - 7.68 (m, 1H), 7.32 - 7.25 (m, 1H), 6.87 - 6.79 (m, 1H), 6.60 - 6.49 (m, 1H), 5.43 - 5.34 (m, 1H), 4.66 - 4.54 (m, 1H), 4.09 - 4.00 (m, 1H), 4.00 - 3.93 (m, 3H), 3.92 - 3.82 (m, 1H), 3.64 - 3.46 (m, 2H), 3.31 (br dd, J = 5.7, 15.5 Hz, 1H), 2.86 - 2.66 (m, 2H), 2.11 - 2.05 (m, 1H), 2.03 - 1.95 (m, 1H), 1.94 - 1.88 (m, 3H), 1.22 - 1.09 (m, 3H). LCMS (*Method I*, ES⁺, RT = 0.441 min) 544.2/546.1 (M+H)⁺.

[00657] INTERMEDIATE 37: (2R,4S)-1-((R)-9-bromo-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile



[00658] To a solution of *Intermediate 36* (2 g, 3.67 mmol) in pyridine (20 mL) was added TFAA (6.17 g, 29.39 mmol, 4.09 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into ice-water (50 mL) and added 1 M HCl to pH = 3-4. The reaction mixture was extracted with MTBE (50 mL × 3). The combined organic phase was washed with brine (50 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (1.75 g, 90% yield) as brown solid. LCMS (*Method 1*, ES⁺, RT = 0.521 min) 526.2/528.2 (M+H)⁺.

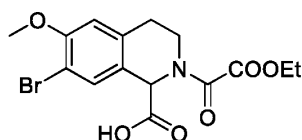
[00659] **INTERMEDIATE 38:** (2R,4S)-4-hydroxy-1-((R)-8-methoxy-5-methyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



[00660] A mixture of *Intermediate 37* (723.68 mg, 2.85 mmol), KOAc (419.53 mg, 4.27 mmol) in n-heptane (2.5 mL) and dioxane (0.5 mL) was degassed and purged with N₂ for 3 times, then the mixture was added with Pd(dppf)Cl₂.CH₂Cl₂ (46.55 mg, 57.00 μmol) and degassed and purged with N₂ for 3 times. The mixture was stirred at 95 °C for 12 hr. The reaction mixture was filtered, added with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum

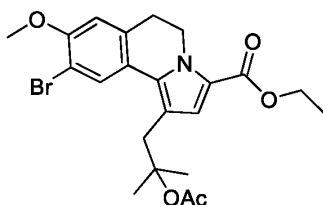
ether/Ethyl acetate=2/1 to 1/1) to give *the title compound* (180 mg, 55% yield) as a brown solid. ^1H NMR (400 MHz, CDCl_3) δ 7.85 - 7.80 (m, 1H), 6.70 (s, 1H), 6.55 - 6.44 (m, 1H), 5.59 - 5.48 (m, 1H), 4.62 - 4.51 (m, 1H), 4.11 - 3.98 (m, 2H), 3.80 (s, 3H), 3.73 - 3.65 (m, 1H), 3.59 - 3.42 (m, 2H), 3.29 (dd, J = 5.7, 15.6 Hz, 1H), 2.78 - 2.60 (m, 2H), 2.14 (dd, J = 6.8, 13.2 Hz, 1H), 1.92 - 1.82 (m, 4H), 1.34 - 1.26 (m, 12H), 1.22 - 1.16 (m, 2H), 1.10 - 0.99 (m, 3H). LCMS (*Method 1*, ES^+ , RT = 0.545 min) 574.3/575.4 ($\text{M}+\text{H}$) $^+$.

[00661] INTERMEDIATE 39: 7-bromo-2-(2-ethoxy-2-oxoacetyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid



[00662] To a solution of 7-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (2.8 g, 8.68 mmol, HCl) in THF (30 mL) was added ethyl 2-chloro-2-oxoacetate (1.54 g, 11.28 mmol, 1.26 mL) at 20 °C. The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a crude product without purification. *The title compound* (3.3 g, crude) was obtained as an orange oil. LCMS (*Method 1*, ES^+ , RT = 0.421 min) 386.1/388.0 ($\text{M}+\text{H}$) $^+$.

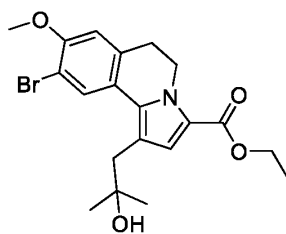
[00663] INTERMEDIATE 40: Ethyl 1-(2-acetoxy-2-methylpropyl)-9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00664] To a solution of *Intermediate 39* (3.3 g, 8.54 mmol) in Ac_2O (35 mL) was added 2-methylpent-4-yn-2-ol (1.01 g, 10.25 mmol) at 20 °C. The mixture was stirred at 140 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove Ac_2O . The residue was

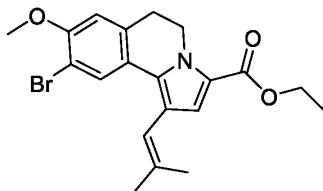
diluted with H₂O (100 mL) and adjusted pH to 8 with aq. Na₂CO₃. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 3/1). *The title compound* (1.7 g, 85.69% yield) were obtained as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 4.60 (t, J = 6.4 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.12 (s, 2H), 2.97 (t, J = 6.4 Hz, 2H), 1.90 (s, 3H), 1.56 (s, 6H), 1.37 (t, J = 7.1 Hz, 3H). LCMS (*Method h*. ES⁺, RT = 2.20 min) 404.2/406.2 (M+H)⁺.

[00665] INTERMEDIATE 41: Ethyl 9-bromo-1-(2-hydroxy-2-methylpropyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



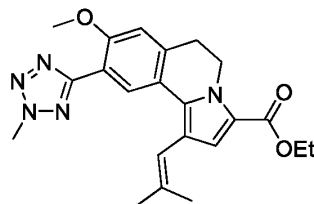
[00666] To a solution of *Intermediate 40* (900 mg, 1.94 mmol) in EtOH (20 mL) was added EtONa (131.90 mg, 1.94 mmol) at 20 °C. The mixture was stirred at 60 °C for 12 hr. The reaction mixture was added with 0.5M HCl (4 mL), then diluted with H₂O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The crude product was triturated with PE (5 mL) at 20 °C for 20 min and filtered. *The title compound* (1.2 g, 73% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.33 (s, 1H), 7.12 (s, 1H), 6.83 (s, 1H), 4.47 (br t, J = 6.4 Hz, 2H), 4.43 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.95 (br t, J = 6.4 Hz, 2H), 2.72 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (s, 6H). LCMS (*Method l*. ES⁺, RT = 0.589 min) 422.2/424.2 (M+H)⁺.

[00667] INTERMEDIATE 42: Ethyl 9-bromo-8-methoxy-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00668] To a solution of *Intermediate 41* (1.2 g, 2.84 mmol) in THF (12 mL) was added Burgess reagent (1.35 g, 5.68 mmol) in DCM (12 mL) at 20 °C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 18*). The title compound (700 mg, 60.93% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.91 (s, 1H), 6.91 (s, 1H), 6.79 (s, 1H), 6.18 (s, 1H), 4.60 (t, J = 6.6 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.00 (t, J = 6.6 Hz, 2H), 1.96 (d, J = 1.0 Hz, 3H), 1.84 (d, J = 0.6 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H). LCMS (*Method 1*, ES⁺, RT = 0.728 min) 404.2/406.1 (M+H)⁺.

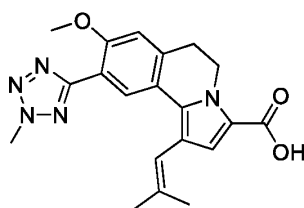
[00669] **INTERMEDIATE 43:** ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00670] To a solution of *Intermediate 42* (700 mg, 1.73 mmol) and *Intermediate 25* (2.58 g, 6.93 mmol) in DMF (7 mL) was added Xphos-Pd-G₂ (272.45 mg, 346.28 μmol) at 20 °C. The mixture was stirred at 120 °C for 1 hr. The reaction mixture was added with H₂O (50 mL) at 0 °C, then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, PE/EtOAc=10/1 to 1/1). The

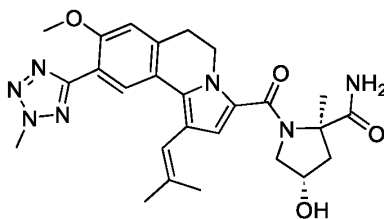
title compound (400 mg, 56%) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.19 (s, 1H), 7.25 (s, 1H), 6.81 (s, 1H), 6.19 (s, 1H), 4.55 (br t, J = 6.5 Hz, 2H), 4.41 (s, 3H), 4.24 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 3.12 (br t, J = 6.5 Hz, 2H), 1.88 (s, 3H), 1.76 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). LCMS (*Method 1*, ES^+ , RT = 0.594 min) 408.2/409.2 ($\text{M}+\text{H}$) $^+$.

[00671] INTERMEDIATE 44: 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00672] To a solution of *Intermediate 43* (50 mg, 122.71 μmol) in THF (0.5 mL) was added TMSOK (62.97 mg, 490.84 μmol) at 20 $^\circ\text{C}$. The mixture was stirred at 70 $^\circ\text{C}$ for 12 hr. The reaction mixture was cooled to room temperature and filtered to give *the title compound* (48 mg, crude) as a yellow solid. LCMS (*Method 1*, ES^+ , RT = 0.455 min) 380.2/381.2 ($\text{M}+\text{H}$) $^+$.

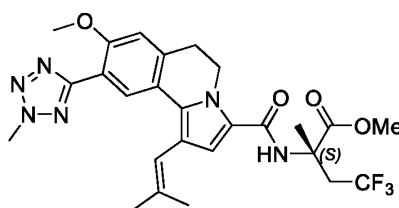
[00673] INTERMEDIATE 45: (2R,4S)-4-hydroxy-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00674] To a solution of *Intermediate 44* (94 mg, 247.75 μmol) and *Intermediate 256* (53.70 mg, 297.30 μmol , HCl) in DMF (1 mL) was added HATU (141.30 mg, 371.63 μmol) and DIEA (128.08 mg, 991.01 μmol , 172.62 μL) at 20 $^\circ\text{C}$. The mixture was stirred at 60 $^\circ\text{C}$ for 12 hr. The reaction mixture was added with H_2O (5 mL) at 0 $^\circ\text{C}$, then extracted with EtOAc (2 mL x 3). The

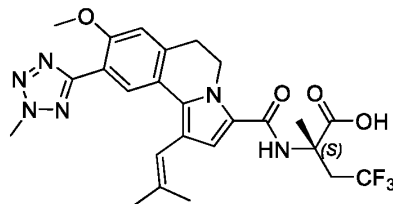
combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the *title compound* (80 mg, 63%) as a brown solid. LCMS (*Method l*. ES⁺, RT = 0.369 min) 506.3/507.3 (M+H)⁺.

[00675] INTERMEDIATE 46: Methyl (S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



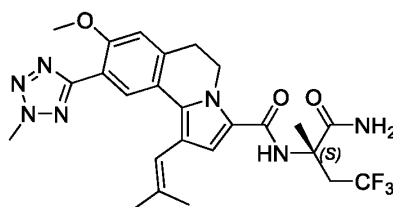
[00676] To a solution of *Intermediate 44* (250 mg, 658.92 μmol) in DMF (2.5 mL) was added with HATU (300 mg, 790.70 μmol) and DIEA (340.64 mg, 2.64 mmol, 459.08 μL) at 20 °C for 1 h. The mixture was added with *Intermediate 115* (189.82 mg, 856.59 μmol, HCl) and stirred at 60 °C for 11 hr. The reaction mixture was added H₂O (20 mL) at 0 °C and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 3/1). The *title compound* (240 mg, 66 %) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.46 (s, 1H), 8.14 (s, 1H), 7.22 (s, 1H), 6.97 (s, 1H), 6.20 (s, 1H), 4.57 - 4.43 (m, 2H), 4.41 (s, 3H), 3.88 (s, 3H), 3.65 (s, 3H), 3.30 - 3.15 (m, 1H), 3.09 - 3.05 (m, 2H), 2.84 (qd, J = 11.3, 15.4 Hz, 1H), 1.89 (s, 3H), 1.81 (s, 3H), 1.57 (s, 3H). LCMS (*Method a*. ES⁺, RT = 1.920 min) 547.3/548.3 (M+H)⁺.

[00677] INTERMEDIATE 47: (S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



[00678] To a solution of *Intermediate 46* (220 mg, 402.53 μmol) in THF (2 mL) was added TMSOK (103.28 mg, 805.06 μmol) at 20°C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with H₂O (10 mL) and adjusted pH to 3-4, which was extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. *The title compound* (200 mg, 93%) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 12.79 (br s, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 7.22 (s, 1H), 6.92 (br s, 1H), 6.20 (s, 1H), 4.61 - 4.37 (m, 5H), 3.88 (s, 3H), 3.30 - 3.16 (m, 1H), 3.06 (br t, J = 6.1 Hz, 2H), 2.92 - 2.74 (m, 1H), 1.89 (s, 3H), 1.81 (s, 3H), 1.60 - 1.50 (m, 3H). LCMS (*Method 1*). ES⁺, RT = 0.482 min) 533.4/534.3 (M+H)⁺.

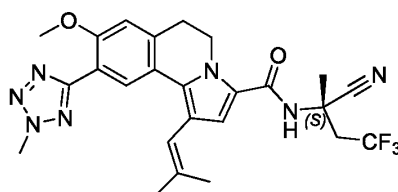
[00679] INTERMEDIATE 48: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00680] To a solution of *Intermediate 47* (180 mg, 338.02 μmol) in THF (2 mL) was added CDI (82.21 mg, 507.03 μmol) at 20 °C and stirred for 1 hr. Then the mixture was added NH₃.H₂O (142.15 mg, 1.01 mmol, 156.21 μL , 25% purity) at 20 °C and stirred for 1 h. The reaction mixture was added H₂O (5 mL) at 0 °C, then extracted with DCM (2 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced

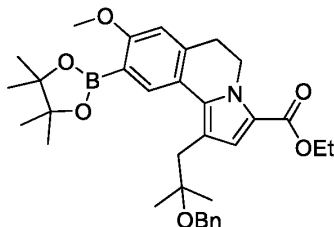
pressure to give a crude product. *The title compound* (200 mg, crude) was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.14 (s, 1H), 8.05 (s, 1H), 7.43 (br s, 1H), 7.22 (s, 1H), 7.10 (br s, 1H), 6.90 (s, 1H), 6.21 (s, 1H), 4.56 - 4.44 (m, 2H), 4.41 (s, 3H), 3.88 (s, 3H), 3.31 - 3.18 (m, 1H), 3.07 (br d, J = 6.4 Hz, 2H), 3.01 - 2.86 (m, 1H), 1.89 (s, 3H), 1.81 (s, 3H), 1.55 (s, 3H). LCMS (*Method I*). ES^+ , RT = 0.467 min) 532.3/533.3 ($\text{M}+\text{H}$) $^+$.

[00681] INTERMEDIATE 49: (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



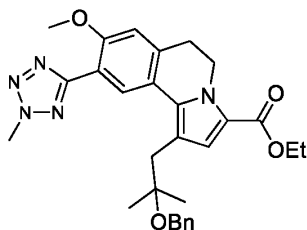
[00682] To a solution of *Intermediate 48* (180 mg, 338.65 μmol) in THF (2 mL) was added Burgess reagent (161.40 mg, 677.29 μmol) in DCM (2 mL) at 20 $^{\circ}\text{C}$. The mixture was stirred at 20 $^{\circ}\text{C}$ for 2 hr. The reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (2 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 1/1) to give *the title compound* (120 mg, 69.01%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.39 (s, 1H), 6.95 (s, 1H), 6.53 (s, 1H), 6.25 (s, 1H), 5.94 (s, 1H), 4.67 (t, J = 6.6 Hz, 2H), 4.44 (s, 3H), 4.01 - 3.97 (m, 3H), 3.23 - 3.04 (m, 4H), 1.95 (s, 6H), 1.80 (s, 3H). LCMS (*Method I*). ES^+ , RT = 0.541 min) 514.3/515.3 ($\text{M}+\text{H}$) $^+$.

[00683] INTERMEDIATE 50: ethyl 1-(2-(benzyloxy)-2-methylpropyl)-8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00684] To a solution of *Intermediate 70* (2.5 g, 4.88 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (12.39 g, 48.79 mmol) in n-heptane (25 mL) and dioxane (5 mL) was added with KOAc (7.18 g, 73.18 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (79.68 mg, 97.57 μmol). The mixture was stirred at 95°C for 12 hr. The mixture was filtered and the filtrate was added with 10 mL H₂O. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=92/1 to 8/1) to give *the title compound* (2.5 g, 91% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.31 (s, 1H), 7.39 - 7.35 (m, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.02 (s, 1H), 6.75 (s, 1H), 5.31 (s, 1H), 4.61 - 4.56 (m, 3H), 4.31 - 4.24 (m, 2H), 3.89 - 3.86 (m, 2H), 3.14 (s, 1H), 3.01 - 2.96 (m, 1H), 1.37 (d, *J* = 2.1 Hz, 2H), 1.34 (s, 4H), 1.33 (s, 8H), 1.27 (d, *J* = 3.5 Hz, 12H), 1.25 (s, 2H). LCMS (*Method 1*, ES⁺, RT = 0.739 min) 506.3 (M+H)⁺

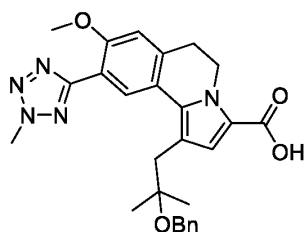
[00685] **INTERMEDIATE 51:** ethyl 1-(2-(benzyloxy)-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00686] To a solution of *Intermediate 50* (2 g, 3.57 mmol), 5-bromo-2-methyl-tetrazole (640.84 mg, 3.93 mmol) in dioxane (2 mL) and H₂O (1 mL) was added with Cs₂CO₃ (3.49 g, 10.72 mmol)

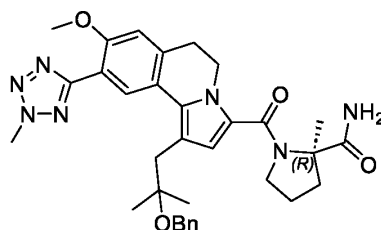
and XPHOS-Pd-G₂ (140.63 mg, 178.73 μ mol). The mixture was stirred at 70 °C for 2 hr under N₂. The mixture was filtered and the filtrate was added with 10 mL H₂O. The aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (15 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=88/1 to 12/1). *The title compound* (1.1 g, 59% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.64 - 8.58 (m, 1H), 7.34 - 7.30 (m, 2H), 7.25 - 7.19 (m, 1H), 7.07 (s, 1H), 6.97 - 6.91 (m, 1H), 5.31 (s, 1H), 4.69 - 4.61 (m, 2H), 4.59 - 4.53 (m, 2H), 4.40 (s, 3H), 4.34 - 4.26 (m, 2H), 3.99 (s, 3H), 3.15 (s, 2H), 3.05 (br t, *J* = 6.3 Hz, 2H), 1.62 - 1.55 (m, 1H), 1.41 - 1.30 (m, 9H). LCMS(*Method 1*, ES⁺, RT = 0.625 min) 516.3/517.3 (M+H)⁺

[00687] INTERMEDIATE 52: 1-(2-(benzyloxy)-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



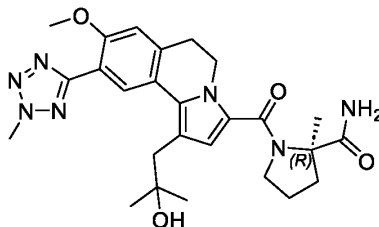
[00688] To a solution of *Intermediate 51* (1.1 g, 2.13 mmol) in EtOH (4 mL), THF (4 mL) and H₂O (4 mL) was added with KOH (359.09 mg, 6.40 mmol). The mixture was stirred at 30 °C for 6 hr. The mixture was added with 1M HCl to adjust pH=5 and added with ethyl acetate (10 mL x 3). The organic layer was washed with brine 10 mL and concentrated under reduced pressure. *The title compound* (0.85 g, 81.72% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.50 - 8.47 (m, 1H), 7.18 (s, 5H), 6.89 - 6.85 (m, 1H), 4.56 - 4.49 (m, 3H), 4.48 - 4.44 (m, 2H), 4.41 (s, 3H), 3.88 (s, 3H), 3.33 (s, 6H), 1.27 (s, 6H). LCMS (*Method 1*, ES⁺, RT = 0.494 min) 488.2 (M+H)⁺

[00689] INTERMEDIATE 53: (R)-1-(1-(2-(benzyloxy)-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



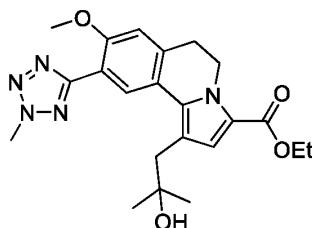
[00690] To a solution of *Intermediate 52* (200 mg, 410.22 μmol), (2R)-2-methylpyrrolidine-2-carboxamide (81.04 mg, 492.26 μmol , HCl) in DMF (2 mL) was added HATU (171.57 mg, 451.24 μmol) and DIEA (212.07 mg, 1.64 mmol, 285.81 μL). The mixture was stirred at 30 °C for 2 hr. The mixture was poured into ice water, filtered and the solid was dissolved with EtOAc (10 mL). The combined organic phase was washed with brine (5 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=70/1 to 30/1). *The title compound* (200 mg, 81% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.42 (s, 1H), 7.25 - 7.18 (m, 6H), 7.13 - 7.07 (m, 1H), 6.81 - 6.75 (m, 1H), 6.58 - 6.54 (m, 1H), 4.48 (s, 2H), 4.41 (s, 3H), 4.28 - 4.20 (m, 2H), 3.87 (s, 3H), 3.59 - 3.51 (m, 1H), 3.06 - 2.96 (m, 4H), 2.06 - 1.97 (m, 2H), 1.84 - 1.75 (m, 3H), 1.49 (s, 3H), 1.28 (br d, J = 1.9 Hz, 6H) LCMS (*Method n*, ES^+ , RT = 0.563 min) 598.5/599.5 ($\text{M}+\text{H}$) $^+$

[00691] INTERMEDIATE 54: (R)-1-(1-(2-hydroxy-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00692] To a solution of *Intermediate 53* (180 mg, 301.15 μmol) in THF (2 mL) was added with Pd/C (360 mg, 338.28 μmol , 10% purity). The mixture was stirred at 50 °C for 12 hr under H_2 (15 psi). The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. *The title compound* (120 mg, 78.50% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.44 - 8.38 (m, 1H), 7.18 (s, 1H), 7.13 - 7.08 (m, 1H), 6.87 (s, 1H), 6.81 - 6.75 (m, 1H), 6.65 - 6.63 (m, 1H), 6.56 - 6.52 (m, 1H), 5.78 - 5.74 (m, 1H), 4.42 (s, 2H), 4.29 - 4.20 (m, 2H), 3.97 - 3.90 (m, 1H), 3.88 - 3.83 (m, 2H), 3.79 - 3.69 (m, 1H), 3.04 - 2.97 (m, 1H), 2.86 - 2.78 (m, 1H), 2.21 - 2.15 (m, 1H), 2.11 - 2.01 (m, 1H), 1.93 - 1.82 (m, 2H), 1.52 (s, 2H), 1.35 (s, 6H), 1.15 (d, J = 5.5 Hz, 5H) LCMS (Method 1, ES+, RT = 0.350 min) 508.3/509.4 (M+H) +

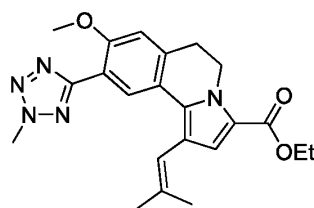
[00693] **INTERMEDIATE 55:** ethyl 1-(2-hydroxy-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00694] To a solution of *Intermediate 51* (1.6 g, 3.10 mmol) in THF (7.5 mL) and EtOH (7.5 mL) was added Pd/C (1.6 g, 1.50 mmol, 10% purity). The mixture was stirred at 45°C for 12 hr under H_2 (15 Psi). The reaction mixture was filtered. The filtrate was and concentrated under reduced pressure to give a residue. *The title compound* (1.1 g, 83.31% yield) was obtained as a gray solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.44-8.50 (m, 1H), 7.19-7.26 (m, 1H), 6.85-6.91 (m,

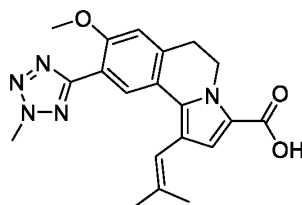
1H), 4.52 (br t, $J=6.25$ Hz, 2H), 4.42 (s, 3H), 4.29 - 4.33 (m, 1H), 4.23 (q, $J=7.09$ Hz, 2H), 3.88 (s, 3H), 3.06 (br t, $J=6.32$ Hz, 2H), 2.76-2.86 (m, 2H), 1.28 (t, $J=7.07$ Hz, 3H), 1.12-1.17 (m, 6H). LCMS (*Method a*. ES^+ , RT = 1.635 min) 425.2/426.2 (M+H)⁺

[00695] INTERMEDIATE 56: Ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



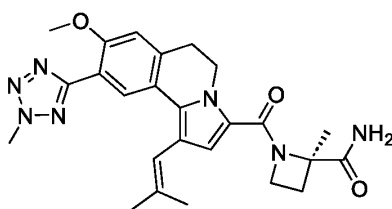
[00696] To a solution of *Intermediate 55* (200 mg, 0.47 mmol) in THF (2 mL) was added with Burgess reagent (224 mg, 0.940 mmol) in DCM (1 mL). The mixture was stirred at 20 °C for 2 h. The mixture was added with H₂O (2 mL) and the pH was adjusted to 5-6 with 1M HCl, extracted with DCM (2 mL x 3). The combined organic phase was washed with brine (2 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EA=10/1 to 0/1) to afford *the title compound* as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.19 (s, 1H), 8.06 - 7.98 (m, 1H), 7.25 (s, 1H), 6.81 (s, 1H), 6.78 - 6.77 (m, 1H), 6.19 (s, 1H), 4.82 - 4.76 (m, 1H), 4.65 (br s, 1H), 4.58 - 4.52 (m, 2H), 4.41 (s, 3H), 4.27 - 4.19 (m, 2H), 3.89 (s, 3H), 3.15 - 3.08 (m, 2H), 1.88 (s, 3H), 1.80 - 1.74 (m, 3H), 1.29 (t, $J = 7.1$ Hz, 3H). LCMS (*Method a*. ES^+ , RT = 2.063 min) 408.2/409.2 (M+H)⁺.

[00697] INTERMEDIATE 57: 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



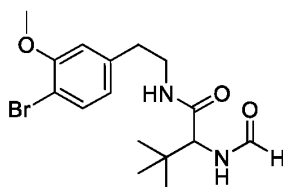
[00698] To a solution of *Intermediate 56* (100 mg, 245.42 μ mol) in THF (1 mL) was added with TMSOK (62.97 mg, 490.84 μ mol). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (102 mg, crude) as a yellow solid. LCMS (*Method g*, ES⁺, RT = 0.450 min) 380.2 (M+H)⁺

[00699] **INTERMEDIATE 58:** (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



[00700] To a solution of *Intermediate 57* (102 mg, 268.84 μ mol) and *Intermediate 124* (60.73 mg, HCl) in DMF (2 mL) was added with HATU (153.33 mg, 403.26 μ mol) and DIEA (138.98 mg, 1.08 mmol, 187.30 μ L) at 20 °C. The mixture was stirred at 20 °C for 1 hr. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc (2 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (2 mL) to give *the title compound* (80 mg, 63% yield) as a yellow solid. LCMS (*Method g*, ES⁺, RT = 0.44 min) 476.3 (M+H)⁺

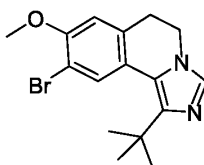
[00701] **INTERMEDIATE 59:** N-(4-bromo-3-methoxyphenethyl)-2-formamido-3,3-dimethylbutanamide



[00702] To a solution of *Intermediate 4* (25.00 g, 104.12 mmol) and 2,2-dimethylpropanal (9.42 g, 109.33 mmol, 12.09 mL) in MeOH (250 mL) was added HCOONH₄ (13.13 g, 208.25 mmol) at

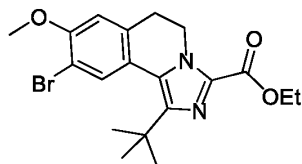
20°C. The mixture was stirred at 80°C for 2 hr. The reaction mixture was diluted with H₂O (500 mL) and extracted with DCM (200 mL×3). The combined organic layers were washed with brine (200 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The crude product was triturated with PE (200 mL) at 20°C for 20 min and filtered. *The title compound* (30 g, 78%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.20 - 8.10 (m, 2H), 8.01 (d, J = 1.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 1.7 Hz, 1H), 6.73 (dd, J = 1.8, 8.1 Hz, 1H), 4.20 (d, J = 9.9 Hz, 1H), 3.83 (s, 3H), 3.41 - 3.33 (m, 1H), 3.31 - 3.22 (m, 1H), 2.70 (dt, J = 2.4, 7.1 Hz, 2H), 0.84 (s, 9H). LCMS (*Method m*. ES⁺, RT = 0.42 min) 371.2/373.2 (M+H)⁺

[00703] INTERMEDIATE 60: 9-bromo-1-(tert-butyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline



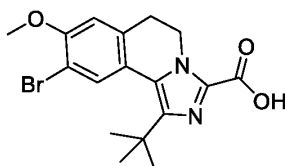
[00704] To a solution of PPA (49.68 g, 107.74 mmol, 85% purity) in toluene (100 mL) was added *Intermediate 59* (10 g, 26.93 mmol) at 20 °C. The mixture was stirred at 110 °C for 2 hr. The reaction mixture was added by H₂O (300 mL) at 20 °C, then adjust pH=8, extracted with DCM (100 mL×3). The combined organic layers were washed with brine (100 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 16*). *The title compound* (4.00 g, 44 %) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.95 (s, 1H), 7.42 (s, 1H), 6.79 (s, 1H), 4.04 (t, J = 6.2 Hz, 2H), 3.92 (s, 3H), 2.96 (t, J = 6.2 Hz, 2H), 1.48 (s, 9H). LCMS (*Method m*. ES⁺, RT = 0.38 min) 335.0/337.0 (M+H)⁺

[00705] INTERMEDIATE 61: Ethyl 9-bromo-1-(tert-butyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



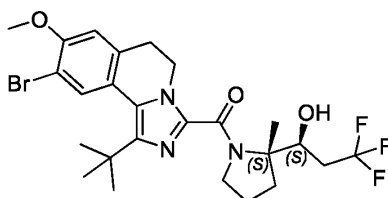
[00706] To a solution of *Intermediate 60* (4 g, 11.93 mmol) in THF (35 mL) was added LDA (2 M, 8.95 mL) at -70°C for 1 hr under N₂. At -70°C, the mixture was added with Ethyl chloroformate (12.95 g, 119.32 mmol, 11.41 mL) and stirred at -70°C for 1 hr. The mixture was poured into H₂O (100 mL) at -70°C and extracted with EtOAc (50 mL×3). The organic layers were washed with brine (100 mL×2), filtered and concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1). *The title compound* (2 g, 82%) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (s, 1H), 6.83 (s, 1H), 4.64 - 4.55 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 2.94 (t, J = 6.4 Hz, 2H), 1.51 (s, 9H), 1.45 (t, J = 7.1 Hz, 3H) LCMS (*Method m*, ES⁺, RT = 0.52 min) 407.0/409.0 (M+H)⁺

[00707] INTERMEDIATE 62: 9-bromo-1-(tert-butyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



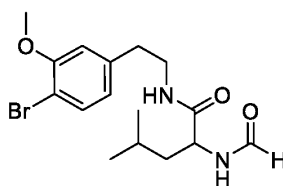
[00708] To a solution of *Intermediate 61* (400 mg, 982.08 μmol) in THF (4 mL) was added TMSOK (251.98 mg, 1.96 mmol) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. *The title compound* (375 mg, crude) was obtained as a yellow solid. LCMS (*Method m*, ES⁺, RT = 0.40 min) 379.0/381.1 (M+H)⁺.

[00709] **INTERMEDIATE 63:** (9-bromo-1-(tert-butyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone



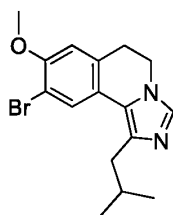
[00710] To a solution of *Intermediate 62* (280.00 mg, 738.30 μmol) and *Intermediate 258* (207.01 mg, 885.96 μmol , HCl) in DMF (3 mL) was added HATU (308.80 mg, 812.13 μmol) and DIEA (381.68 mg, 2.95 mmol, 514.40 μL) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was added with H₂O (30 mL) at 0°C, then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 3/1). *The title compound* (350 mg, 85%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.80 (s, 1H), 7.17 (s, 1H), 5.46 (d, J = 6.6 Hz, 1H), 4.84 - 4.74 (m, 1H), 4.30 - 4.15 (m, 3H), 3.93 - 3.77 (m, 4H), 2.92 (br t, J = 6.1 Hz, 2H), 2.40 - 2.28 (m, 1H), 2.27 - 2.15 (m, 1H), 2.13 - 2.03 (m, 1H), 1.84 - 1.69 (m, 2H), 1.66 - 1.56 (m, 1H), 1.51 (s, 3H), 1.39 (s, 9H). LCMS (*Method m*, ES⁺, RT = 0.55 min) 558.3/560.2 (M+H)⁺

[00711] **INTERMEDIATE 64:** N-(4-bromo-3-methoxyphenethyl)-2-formamido-4-methylpentanamide



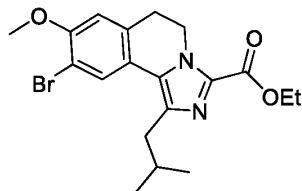
[00712] To a solution of *Intermediate 4* (5.00 g, 20.82 mmol) in MeOH (50 mL) was added with 3-methylbutanal (3.59 g, 41.65 mmol, 4.57 mL), HCOONH₄ (2.63 g, 41.65 mmol) at 20°C. The mixture was stirred at 80°C for 4 hr. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL×3). The combined organic layers were washed with brine (100 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by *Method 6*. *The title compound* (1.50 g, 19%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.37 (br s, 1 H), 4.14 (m, 1 H), 3.33 (br s, 1 H), 2.05 - 2.17 (m, 1 H), 1.68 - 1.80 (m, 3 H), 1.40 (s, 6 H), 1.32 (s, 5 H), 1.25 - 1.29 (m, 3 H) LCMS (*Method i*. ES⁺, RT = 0.42 min) 371.1/373.1 (M+H)⁺

[00713] **INTERMEDIATE 65:** 9-bromo-1-isobutyl-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline



[00714] A solution of P₂O₅ (2.49 g, 17.51 mmol, 1.08 mL) in methanesulfonic acid (13 mL) was heated to 75°C and stirred for 0.5 hr. *Intermediate 64* (1.30 g, 3.50 mmol) was added at 75°C. The mixture was stirred at 75°C for 12 hr. The mixture was cooled, added with sat. NaHCO₃ to adjust pH=8, diluted with H₂O (100 mL) and extracted with DCM (50 mL×3). The combined organic layers were washed with brine (50 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (1 g, 85%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.03 (br s, 1 H), 6.78 (s, 1 H), 6.34 (s, 1 H), 3.83 (br t, J=6.32 Hz, 2 H), 3.45 (s, 3 H), 2.59 (br t, J=6.32 Hz, 2 H), 2.30 (d, J=7.27 Hz, 2 H), 1.64 - 1.76 (m, 1 H), 0.55 (d, J=6.68 Hz, 6 H) LCMS (*Method m*. ES⁺, RT=0.39 min) 335.0/337.0 (M+H)⁺

[00715] **INTERMEDIATE 66:** ethyl 9-bromo-1-isobutyl-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate

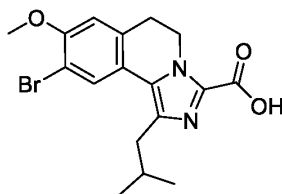


[00716] Step A: To a solution of *Intermediate 65* (800.00 mg, 2.39 mmol) in THF (8 mL) was added LDA (2 M, 1.43 mL) at -70°C for 30 min under N₂.

[00717] Step B: A solution of ethyl chloroformate (1.29 g, 11.93 mmol, 1.14 mL) in THF (8 mL) was stirred at -70°C under N₂.

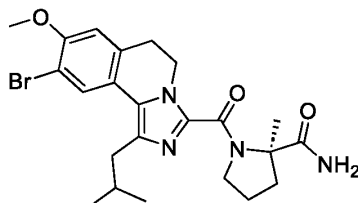
[00718] Step C: The solution A was added dropwise to the solution B mixture at -70°C for 1.5 hr. The mixture was added with NaHCO₃ (10 mL) and extracted with EtOAc (50 mL×3). The organic layers were concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 80/20). *The title compound* (150 mg, 15%) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.85 (s, 1 H), 6.83 (s, 1 H), 4.66 (t, J=6.57 Hz, 2 H), 4.45 (m, 2 H), 3.94 (s, 3 H), 3.02 (br t, J=6.57 Hz, 2 H), 2.78 (d, J=7.25 Hz, 2 H), 2.03 - 2.22 (m, 1 H), 1.44 (t, J=7.13 Hz, 3 H), 1.00 (d, J=6.63 Hz, 6 H) LCMS (*Method a*. ES⁺, RT = 1.57 min) 407.1/409.1 (M+H)⁺

[00719] **INTERMEDIATE 67:** 9-bromo-1-isobutyl-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[00720] To a solution of *Intermediate 66* (130 mg, 319.17 μmol) in THF (1.5 mL) was added TMSOK (81.89 mg, 638.35 μmol). The mixture was stirred at 20°C for 1 hr. The mixture was concentrated under reduced pressure. *The title compound* (130.00 mg, crude) was obtained as a white solid. LCMS (*Method m*. ES⁺, RT = 0.41 min) 379.2/381.2 (M+H)⁺.

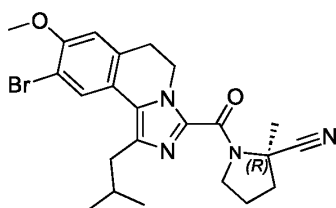
[00721] **INTERMEDIATE 68:** (R)-1-(9-bromo-1-isobutyl-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00722] To a solution 1 of *Intermediate 67* (130 mg, 311.50 μmol) in DMF (1 mL) was added with HATU (130.29 mg, 342.65 μmol) at 20°C. The mixture was stirred at 20°C for 30 min.

[00723] To a solution 2 of (2R)-2-methylpyrrolidine-2-carboxamide (61.54 mg, 373.80 μmol , HCl) in DMF (1 mL) was added with Na_2CO_3 (66.03 mg, 623.00 μmol). The mixture was stirred at 20°C for 30 min. The solution 1 was added dropwise to the solution 2 mixture at 20°C. The mixture was stirred at 20°C for 1 hr. The reaction mixture was poured into ice water (5 ml), filtered and the solid was dissolved with EtOAc (25 ml). The organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. *The title compound* (110 mg, 72%) was obtained as a white solid. LCMS (*Method a*, ES^+ , RT = 1.49 min) 489.4/491.0 (M+H) $^+$.

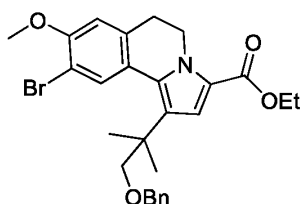
[00724] **INTERMEDIATE 69:** (R)-1-(9-bromo-1-isobutyl-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



[00725] To a solution of *Intermediate 68* (110.00 mg, 224.76 μmol) in THF (1 mL) was added Burgess Reagent (107.12 mg, 449.53 μmol). The mixture was stirred at 20°C for 2 hr. The reaction mixture was diluted with H_2O (5 ml) and extracted with DCM (5 mL $\times$ 3). The combined organic

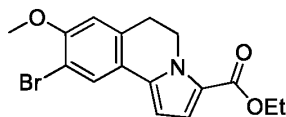
layers were washed with brine (5 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (80 mg, 76%) was obtained as a white solid.

[00726] INTERMEDIATE 70: ethyl 1-(1-(benzyloxy)-2-methylpropan-2-yl)-9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00727] To a solution of *Intermediate 39* (5 g, 12.95 mmol) in Ac₂O (100 mL) was added 2,2-dimethylbut-3-ynoxymethylbenzene (2.92 g, 15.54 mmol). The mixture was stirred at 140°C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O 50 mL and quenched with Na₂CO₃ 100 mL. Then extracted with DCM (100 mL×3). The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 10/1). *The title compound* (5.50 g, 41%) as colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.28 (t, J=7.07 Hz, 3 H), 1.34 (s, 6 H), 2.88 (br t, J=6.13 Hz, 2 H), 3.54 (s, 2 H), 3.89 (s, 3 H), 4.23 (d, J=7.13 Hz, 2 H), 4.37 - 4.43 (m, 2 H), 4.48 (s, 2 H), 6.90 (s, 1 H), 7.13 (s, 1 H), 7.29 (br d, J=4.75 Hz, 5 H), 8.05 (s, 1 H) LCMS (*Method h*. ES⁺, RT = 0.73 min) 408.0/410.0 (M+H)⁺.

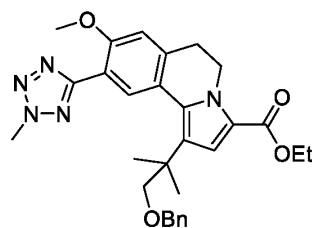
[00728] INTERMEDIATE 71: Ethyl 9-bromo-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00729] To a solution of *Intermediate 39* (23.94 g, 61.99 mmol) in Ac₂O (120 mL) was added ethynyl (trimethyl) silane (7.92 g, 80.59 mmol, 11.16 mL). The mixture was stirred at 140 °C for

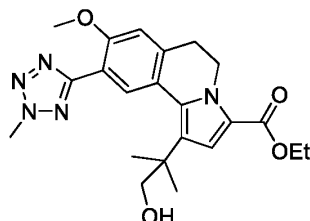
1 hr. The reaction mixture was concentrated to dryness. The residue was diluted with DCM (100 mL) and adjusted to pH 8 with sat. Na₂CO₃, then extracted with DCM (100 mL×2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with PE (200 mL) at 25°C for 10 min, filtered and concentrated under reduced pressure. *The title compound* (18.08 g, 79%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.28 (t, J=7.07 Hz, 3 H) 3.05 (t, J=6.75 Hz, 2 H) 3.87 (s, 3 H) 4.19 - 4.26 (m, 2 H) 4.51 (t, J=6.75 Hz, 2 H) 6.66 - 6.70 (m, 1 H) 6.89 - 6.92 (m, 1 H) 7.09 - 7.13 (m, 1 H) 7.90 (s, 1 H) LCMS (*Method m*. ES⁺, RT = 0.62 min) 350.1/352.1 (M+H)⁺

[00730] INTERMEDIATE 72: Ethyl 1-(1-(benzyloxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



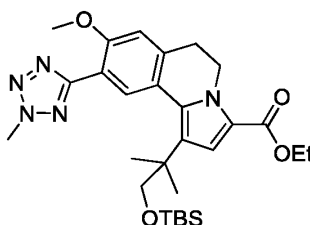
[00731] To a solution of *Intermediate 70* (2.50 g, 4.88 mmol) in DMF (50 mL) was added with *Intermediate 26* (3.64 g, 9.76 mmol) and XPHOS-Pd-G₂ (767.71 mg, 975.74 μmol) at 20°C. The mixture was stirred at 120 °C for 12 h. The reaction mixture was poured into H₂O (80 mL) and extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine (10 mL×3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 0/1). *The title compound* (3.40g, 68 %) as a white solid. ¹H NMR (400 MHz, DMSO--d₆) δ ppm 1.27 - 1.32 (m, 3 H), 1.38 (s, 6 H), 2.98 (br t, J=5.84 Hz, 2 H), 3.60 (s, 2 H), 3.90 (s, 3 H), 4.23 (q, J=7.03 Hz, 2 H), 4.39 (s, 3 H), 4.43 - 4.49 (m, 4 H), 6.92 (s, 1 H), 7.21 - 7.32 (m, 6 H), 8.44 (s, 1 H) LCMS (*Method m*. ES⁺, RT = 0.54 min) 416.4/417.3 (M+H)⁺.

[00732] **INTERMEDIATE 73:** Ethyl 1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00733] To a solution of *Intermediate 72* (3.30 g, 6.40 mmol) in THF (45 mL) and EtOH (45 mL) was added Pd/C (50 mg, 10% purity) under H₂ (15 psi). The mixture was stirred at 45°C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. *The title compound* (2.70 g, 99%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 - 1.41 (m, 3 H), 1.47 (s, 6 H), 1.60 - 1.70 (m, 1 H), 2.96 - 3.04 (m, 2 H), 3.87 (s, 2 H), 4.01 (s, 3 H), 4.31 (q, J=7.13 Hz, 2 H), 4.42 - 4.46 (m, 3 H), 4.54 - 4.65 (m, 2 H), 6.95 (s, 1 H), 7.05 (s, 1 H), 8.52 (s, 1 H) LCMS (*Method m*. ES⁺, RT = 0.48 min) 426.2/427.3 (M+H)⁺.

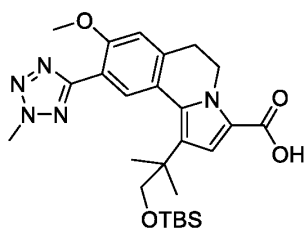
[00734] **INTERMEDIATE 74:** ethyl 1-(((tert-butyl)dimethylsilyl)oxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00735] To a solution of *Intermediate 73* (1.30 g, 3.06 mmol) in DCM (10 mL) was added with imidazole (416.00 mg, 6.11 mmol) and TBSCl (552.61 mg, 3.67 mmol, 451.11 μL) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction was diluted with DCM (20 mL) and washed with H₂O (10 mL ×3). The organic layers were concentrated under reduced pressure. *The title compound* (3.20 g, 97%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 7.09 (s,

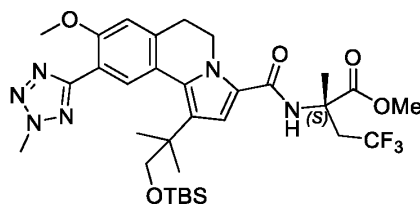
1H), 6.94 (s, 1H), 4.62 - 4.56 (m, 2H), 4.45 - 4.41 (m, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.03 - 3.99 (m, 3H), 3.77 (s, 2H), 2.99 (br t, J = 6.3 Hz, 2H), 1.44 - 1.41 (m, 6H), 1.39 - 1.35 (m, 3H), 0.87 - 0.83 (m, 9H), -0.02 - -0.09 (m, 6H) LCMS (*Method f*, ES⁺, RT = 0.75 min) 540.2/541.2 (M+H)⁺.

[00736] INTERMEDIATE 75: 1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00737] To a solution of *Intermediate 74* (1.00 g, 1.85 mmol) in THF (10 mL) was added with TMSOK (713.07 mg, 5.56 mmol). The mixture was stirred at 20°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give the *title compound* (1.02 g, crude) as a yellow solid. LCMS (*Method f*, ES⁺, RT=0.61 min) 380.2/381.2 (M+H)⁺.

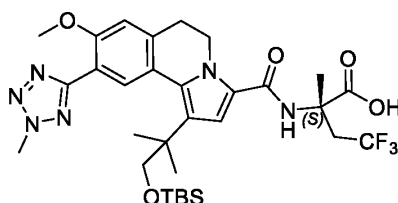
[00738] INTERMEDIATE 76: methyl (S)-2-(1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoate



[00739] To a solution of *Intermediate 75* (1.00 g, 1.95 mmol) and *Intermediate 115* (519.70 mg, 2.35 mmol, HCl) in DMF (10 mL) was added HATU (1.49 g, 3.91 mmol) and DIEA (1.01 g, 7.82 mmol, 1.36 mL) at 80°C. The mixture was stirred at 80°C for 12 hr. The mixture was diluted with H₂O (40 mL) and extracted with EtOAc (20 mL×3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column

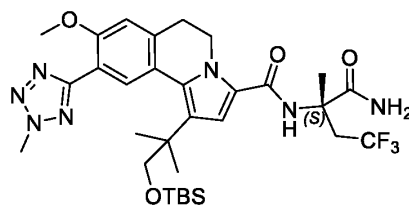
chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1). The *title compound* (550.00 mg, 41%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.49 (s, 1H), 6.93 (s, 1H), 6.81 - 6.71 (m, 2H), 4.51 (s, 2H), 4.45 - 4.42 (m, 3H), 4.03 - 3.99 (m, 3H), 3.87 - 3.83 (m, 3H), 3.80 - 3.75 (m, 2H), 3.48 - 3.39 (m, 1H), 3.02 - 2.93 (m, 3H), 1.76 (s, 3H), 1.44 - 1.42 (m, 6H), 0.87 - 0.85 (m, 9H), -0.02 - -0.07 (m, 6H). LCMS (*Method m*, ES⁺, RT=0.68 min) 679.4/680.4 (M+H)⁺.

[00740] INTERMEDIATE 77: (S)-2-(1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



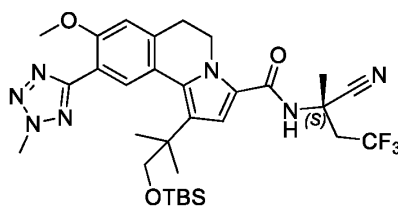
[00741] To a solution of *Intermediate 76* (500.00 mg, 736.58 μmol) in THF (5 mL) was added with TMSOK (283.49 mg, 2.21 mmol). The mixture was stirred at 70°C for 6 hr. The mixture was diluted with H₂O (10 mL) and adjust pH = 6 with 0.5N HCl, then it was extracted with EtOAc (10 mL×3). The organic layers were concentrated under reduced pressure. The *title compound* (480 mg, 98%) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 6.94 (s, 1H), 6.77 (s, 1H), 6.62 (s, 1H), 4.56 - 4.49 (m, 3H), 4.45 - 4.41 (m, 3H), 4.03 - 3.97 (m, 3H), 3.81 - 3.75 (m, 2H), 3.25 - 3.22 (m, 1H), 3.03 - 2.95 (m, 2H), 2.86 - 2.81 (m, 1H), 1.81 (s, 3H), 1.45 - 1.41 (m, 7H), 1.22 - 1.20 (m, 2H), 0.88 - 0.84 (m, 9H), -0.03 - -0.08 (m, 6H) LCMS (*Method m*, ES⁺, RT=0.62 min) 665.5/666.4 (M+H)⁺.

[00742] INTERMEDIATE 78: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00743] To a solution of *Intermediate 77* (430.00 mg, 645.86 μmol) in THF (5 mL) was added with CDI (157.09 mg, 968.79 μmol) at 20°C. The mixture was stirred at 20°C for 0.5 hr. The mixture was added $\text{NH}_3 \cdot \text{H}_2\text{O}$ (271.62 mg, 1.94 mmol, 298.48 μL , 25% purity) at 20°C. The mixture was stirred at 20°C for 1 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL $\times$ 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (3 mL) to give the *title compound* (300.00 mg, 70%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.51 (s, 1H), 6.95 (s, 1H), 6.79 (s, 1H), 6.26 (s, 2H), 4.61 - 4.48 (m, 3H), 4.44 (s, 3H), 4.00 (s, 3H), 3.82 - 3.71 (m, 2H), 3.31 (br dd, J = 11.6, 15.9 Hz, 1H), 3.22 (s, 1H), 3.11 - 2.92 (m, 3H), 1.74 (s, 3H), 1.36 - 1.23 (m, 2H), 1.20 (s, 2H), 0.91 - 0.84 (m, 10H), -0.01 - -0.08 (m, 5H) LCMS (*Method f*, ES^+ , RT = 0.59 min) 664.6/665.4 ($\text{M}+\text{H}$) $^+$.

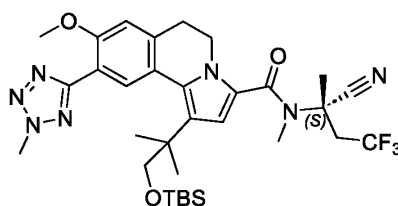
[00744] **INTERMEDIATE 79:** (S)-1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00745] To a solution of *Intermediate 78* (260.00 mg, 391.68 μmol) in THF (3 mL) was added burgess reagent (186.68 mg, 783.36 μmol) at 20°C. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (10 mL) and extracted with MTBE (10 mL $\times$ 3). The organic layers were concentrated under reduced pressure to give the *title*

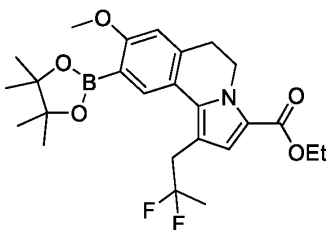
compound (230.00 mg, 91%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.56 (s, 1H), 7.00 (s, 1H), 6.78 (s, 1H), 4.74 - 4.57 (m, 2H), 4.48 (s, 3H), 4.09 - 4.04 (m, 3H), 3.81 (s, 2H), 3.30 - 3.09 (m, 2H), 3.04 (t, J = 6.3 Hz, 2H), 2.00 (s, 3H), 1.60 (s, 4H), 1.50 - 1.45 (m, 7H), 0.93 - 0.89 (m, 8H), 0.03 - -0.02 (m, 6H) LCMS (*Method f*, ES^+ , RT = 0.65 min) 646.4/647.4 ($\text{M}+\text{H}$) $^+$.

[00746] INTERMEDIATE 80: (S)-1-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



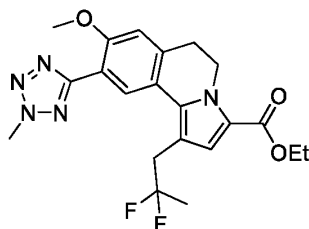
[00747] To a solution of *Intermediate 79* (230.00 mg, 356.15 μmol) in DMF (3 mL) was added NaH (21.37 mg, 534.23 μmol , 60% purity) at 0°C under N_2 . The mixture was stirred at 20°C for 0.5 hr. CH_3I (101.10 mg, 712.31 μmol , 44.34 μL) was dropwise added at 20°C and the mixture was stirred at 70°C for 2 hr under N_2 . The reaction was poured into sat. NH_4Cl (10 mL) at 0°C and extracted with EtOAc (5 mL $\times$ 3). The organic layers were concentrated under reduced pressure to give the title compound (200 mg, 85%) as a yellow solid. LCMS (*Method m*, ES^+ , RT = 1.07 min) 440.3 ($\text{M}+\text{H}$) $^+$.

[00748] INTERMEDIATE 81: ethyl 1-(2,2-difluoropropyl)-8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00749] To a solution of ethyl 9-bromo-1-(2,2-difluoropropyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (2.00 g, 4.67 mmol) in n-heptane (14 mL) and dioxane (7 mL) was added KOAc (6.87 g, 70.05 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (11.86 g, 46.70 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (762.74 mg, 934.00 μmol). The mixture was stirred at 95°C for 12 hr. The residue was poured into water (20 mL). The aqueous phase was extracted with EtOAc (20 mL×3). The combined organic phase was washed with brine (20 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EA=10/1 to 0/1) to give *the title compound* (1.40 g, 63 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.10 - 8.00 (m, 1H), 7.00 - 6.96 (m, 1H), 6.81 - 6.74 (m, 1H), 4.65 - 4.53 (m, 2H), 4.33 - 4.25 (m, 2H), 3.88 (s, 3H), 3.35 (t, J = 15.6 Hz, 2H), 3.00 (br t, J = 6.4 Hz, 2H), 1.74 - 1.56 (m, 3H), 1.36 (s, 12H), 1.29 - 1.24 (m, 3H). LCMS (*Method a*, ES⁺, RT = 2.25 min 476.0/477.2 (M+H)⁺.

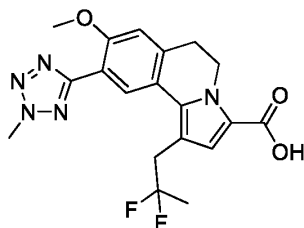
[00750] **INTERMEDIATE 82:** ethyl 1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00751] To a solution of *Intermediate 81* (1.30 g, 2.73 mmol) in dioxane (10 mL) and H₂O (5 mL) was added Cs₂CO₃ (3.56 g, 10.94 mmol), 5-iodo-2-methyl-tetrazole (746.55 mg, 3.56 mmol) and XPHOS-Pd-G₂ (430.37 mg, 546.99 μmol). The mixture was stirred at 80°C for 2 hr. The residue was poured into water (15 mL). The aqueous phase was extracted with EtOAc (15 mL×3). The combined organic phase was washed with brine (15 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EA=10/1 to 0/1) to give *the title compound* (760.00 mg, 64%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (s, 1H), 7.02 - 6.97 (m, 2H), 4.69 - 4.63 (m, 2H), 4.45

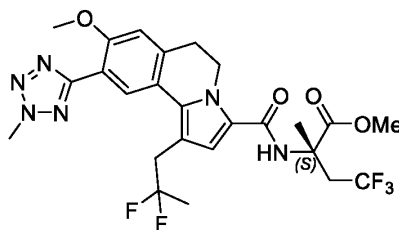
(s, 3H), 4.34 - 4.28 (m, 2H), 4.00 (s, 3H), 3.44 - 3.34 (m, 2H), 3.07 (br t, $J = 6.5$ Hz, 2H), 1.76 - 1.65 (m, 3H), 1.41 - 1.35 (m, 3H). LCMS (*Method m*, ES⁺, 1.64 min) 432.3/433.2 (M+H)⁺.

[00752] INTERMEDIATE 83: 1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo [2,1-a]isoquinoline-3-carboxylic acid



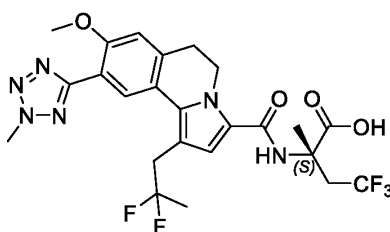
[00753] To a solution of *Intermediate 82* (760 mg, 1.76 mmol) in THF (5 mL) and EtOH (5 mL) was added KOH (296.50 mg, 5.28 mmol) in H₂O (5 mL). The mixture was stirred at 80 °C for 2 hr. The solvent was evaporated and the pH was adjusted to 3-4 with 1M HCl. The aqueous phase was extracted with EtOAc (8 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (650 mg, 91 %) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 12.42 - 12.32 (m, 1H), 8.21 - 8.17 (m, 1H), 7.30 - 7.23 (m, 1H), 6.85 (s, 1H), 4.61 - 4.50 (m, 2H), 4.45 - 4.39 (m, 3H), 3.89 (s, 3H), 3.12 - 3.03 (m, 2H), 1.73 - 1.59 (m, 3H). LCMS (*Method m*, ES⁺ 1.64 min) 432.3/433.2 (M+H)⁺.

[00754] INTERMEDIATE 84: methyl (S)-2-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoate



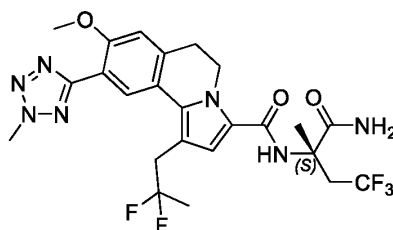
[00755] To a solution of *Intermediate 83* (800 mg, 1.98 mmol) in DMF (8 mL) was added HATU (905 mg, 2.38 mmol) and DIEA (1.03 g, 7.93 mmol, 1.38 mL) at 20°C for 1 hr. Then it was added with *Intermediate 115* (571.34 mg, 2.58 mmol, HCl). The mixture was stirred at 80°C for 4 hr. The residue was poured into water (10 mL) and the pH was adjusted to 5 with 1M HCl. The aqueous phase was extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EA=10/1 to 0/1) to give title compound (600 mg, 53%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.32 (s, 1H), 6.99 - 6.96 (m, 1H), 6.80 (s, 1H), 6.67 (s, 1H), 4.63 - 4.57 (m, 2H), 4.45 (s, 3H), 4.02 - 3.97 (m, 3H), 3.47 - 3.33 (m, 3H), 3.06 (t, *J* = 6.4 Hz, 2H), 2.82 (s, 1H), 2.06 - 2.04 (m, 1H), 1.79 - 1.59 (m, 8H). LCMS (*Method m*, ES+ 0.52 min 571.3./572.3 (M+H)⁺.

[00756] **INTERMEDIATE 85:** (S)-2-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



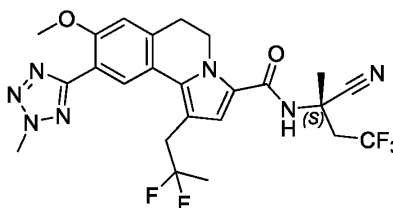
[00757] To a solution of *Intermediate 84* (600 mg, 1.05 mmol) in THF (7 mL) was added TMSOK (269 mg, 2.10 mmol). The mixture was stirred at 50 °C for 3 hr. The residue was added with water (8 mL) and the pH was adjusted to 4-5 with 1M HCl. The aqueous phase was extracted with EtOAc (8 mL×3). The combined organic phase was washed with brine (8 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (620.00 mg, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 12.88 - 12.75 (m, 1H), 8.37 - 8.28 (m, 1H), 8.16 (s, 1H), 7.27 - 7.20 (m, 1H), 7.01 - 6.91 (m, 1H), 4.54 - 4.38 (m, 5H), 3.89 (s, 3H), 3.38 - 3.23 (m, 4H), 3.03 (br t, *J* = 6.0 Hz, 2H), 2.89 - 2.76 (m, 1H), 1.70 (br t, *J* = 18.7 Hz, 3H), 1.56 (s, 3H). LCMS (*Method m*, ES+ RT = 0.46 min 557.3./558.3 (M+H)⁺.

[00758] **INTERMEDIATE 86:** (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



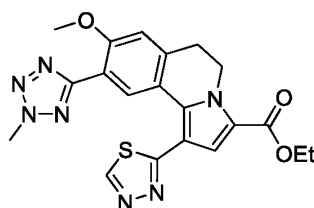
[00759] To a solution of *Intermediate 85* (570 mg, 1.02 mmol) in THF (6 mL) was added CDI (249.13 mg, 1.54 mmol). The mixture was stirred at 25°C for 1 h, then it was added NH₃·H₂O (430 mg, 3.07 mmol, 473.37 µL, 25% purity). The mixture was stirred at 25°C for 1 hr. The mixture was diluted with H₂O (6 mL), extracted with DCM (5 mL×3). The combined organic layer was washed with 5 mL H₂O, 5 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated to give *the title compound* (580.00 mg, crude) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.35 - 8.26 (m, 1H), 7.81 - 7.67 (m, 1H), 7.19 - 7.08 (m, 1H), 7.02 - 6.95 (m, 1H), 6.69 (s, 1H), 6.49 - 6.41 (m, 1H), 5.46 - 5.33 (m, 1H), 4.75 - 4.65 (m, 1H), 4.59 - 4.48 (m, 1H), 4.44 (s, 3H), 3.99 (s, 3H), 3.46 - 3.24 (m, 3H), 3.11 - 2.98 (m, 3H), 1.79 - 1.70 (m, 5H). LCMS (*Method m*, ES⁺ RT = 0.44 min 556.3/557.3 (M+H)⁺.

[00760] **INTERMEDIATE 87:** (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00761] To a solution of *Intermediate 86* (530 mg, 954.10 μ mol) in THF (3 mL) was added with Burgess Reagent (909.46 mg, 3.82 mmol) in DCM (3 mL). The mixture was stirred at 25 °C for 1 hr. The mixture was diluted with H₂O (6 mL), extracted with DCM (5 mL $\times$ 3). The combined organic layer was washed with 5 mL H₂O, 5 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated to give a crude product. The residue was purified by column chromatography (SiO₂, PE/EA=10/1 to 0/1) to give *the title compound* (340 mg, 66 %) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ = 8.31 (s, 1H), 7.03 - 6.96 (m, 1H), 6.65 (s, 1H), 6.04 - 5.99 (m, 1H), 4.70 - 4.61 (m, 2H), 4.45 (s, 3H), 4.05 - 3.97 (m, 3H), 3.44 - 3.32 (m, 2H), 3.21 - 3.05 (m, 4H), 1.96 (s, 2H), 1.71 (br t, J = 18.4 Hz, 3H), 1.57 (br s, 2H). LCMS (*Method m*. ES+ RT 0.51 min 538.3/539.3 (M+H)⁺.

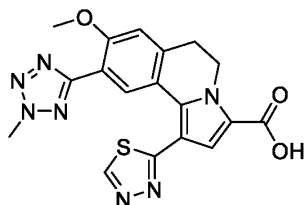
[00762] **INTERMEDIATE 88:** ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00763] To a solution of ethyl 8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (5.00 g, 11.51 mmol) and *Intermediate 26* (8.59 g, 23.03 mmol) in DMF (50 mL) was added XPHOS-Pd-G₂ (1.81 g, 2.30 mmol) at 20°C. The mixture was stirred at 120°C for 12 hr. The reaction mixture was diluted with H₂O (50 mL) and KF (10% w/w, 20 mL). The reaction mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with (50 mL $\times$ 4), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 0/1) to give *the title compound* (2.20 g, 44%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 9.06 - 8.96 (m, 1H), 8.67 - 8.56 (m, 1H), 7.21 - 7.16 (m, 1H), 6.94 - 6.85 (m, 1H), 4.70 - 4.56 (m, 2H), 4.32 (s, 3H),

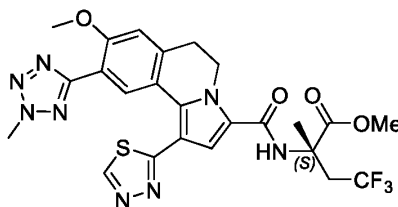
4.27 (q, $J = 7.2$ Hz, 2H), 3.95 - 3.88 (m, 3H), 3.07 (t, $J = 6.6$ Hz, 2H), 1.36 - 1.26 (m, 3H). LCMS (*Method h*. ES+ RT 0.46 min 438.2/439.2 (M+H)⁺).

[00764] INTERMEDIATE 89: 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



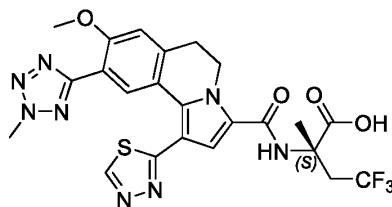
[00765] To a solution of *Intermediate 88* (2.20 g, 5.03 mmol) in THF (10 mL), EtOH (10 mL) and H₂O (10 mL) was added with KOH (846.44 mg, 15.09 mmol) at 20°C. The mixture was stirred at 80°C for 2 hr. The reaction mixture was poured into ice-water (50 mL) and added 1 M HCl to pH=5-6. The reaction mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE (20 mL) at 20°C for 5 min and filtered to give the *title compound* (1.40 g, 68%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.59 (s, 1H), 8.61 - 8.49 (m, 1H), 7.34 - 7.28 (m, 1H), 7.25 - 7.17 (m, 1H), 4.68 - 4.55 (m, 2H), 4.45 - 4.36 (m, 3H), 3.91 (s, 3H), 3.24 - 3.11 (m, 2H), 1.41 - 1.33 (m, 1H). LCMS (*Method m*. ES+ RT 0.34 min 410.2/411.2 (M+H)⁺).

[00766] INTERMEDIATE 90: methyl(S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



[00767] To a solution of *Intermediate 89* (1.10 g, 2.69 mmol) and *Intermediate 115* (774.01 mg, 3.49 mmol, HCl) in DMF (11 mL) was added HATU (1.23 g, 3.22 mmol) and DIEA (1.39 g, 10.75 mmol, 1.87 mL). The mixture was stirred at 20°C for 2 hr. The reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH=5-6. The reaction mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 1/2) to give *the title compound* (1.00 g, 65%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 9.17 (s, 1H), 8.66 - 8.57 (m, 1H), 7.36 - 7.29 (m, 1H), 7.17 - 7.12 (m, 1H), 7.09 - 7.00 (m, 2H), 4.75 - 4.62 (m, 2H), 4.45 (s, 3H), 4.05 (s, 3H), 3.98 - 3.88 (m, 3H), 3.60 - 3.41 (m, 1H), 3.23 - 3.14 (m, 2H), 3.09 - 3.00 (m, 1H), 1.89 - 1.79 (m, 3H). LCMS (*Method m*, ES⁺, RT = 0.46 min 577.3/578.3 (M+H)⁺

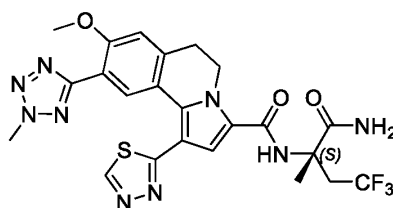
[00768] **INTERMEDIATE 91:** (S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



[00769] To a solution of *Intermediate 90* (800 mg, 1.39 mmol) in THF (4 mL) and MeOH (4 mL) was added LiOH·H₂O (87.33 mg, 2.08 mmol) in H₂O (4 mL) at 20°C. The mixture was stirred at 45°C for 6 hr. The reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH=3-4. The reaction mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (600 mg, 77%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.04 - 8.94 (m, 1H), 8.25 - 8.15 (m, 1H), 7.67 - 7.61 (m, 1H), 7.51 (s, 1H), 6.95 (s, 1H), 4.93 - 4.78 (m, 1H), 4.55 - 4.41 (m, 1H), 4.38 - 4.29 (m, 3H), 3.99 - 3.87 (m, 3H), 3.69 -

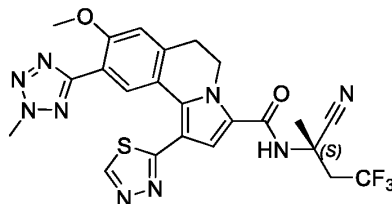
3.51 (m, 1H), 3.17 - 2.99 (m, 2H), 2.97 - 2.82 (m, 1H), 1.86 - 1.79 (m, 3H). LCMS (*Method m*. ES⁺, RT = 0.40 min 563.2/664.3 (M+H)⁺

[00770] INTERMEDIATE 92: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



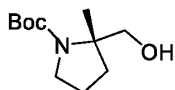
[00771] To a solution of *Intermediate 91* (600 mg, 1.07 mmol) in THF (8 mL) was added CDI (259.43 mg, 1.60 mmol). The mixture was stirred at 20 °C for 2 hr and added with NH₃.H₂O (448.57 mg, 3.20 mmol, 492.93 μL, 25% purity). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH = 5-6. The reaction mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 0/1) to give *the title compound* (400 mg, 67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 9.08 - 8.95 (m, 1H), 8.47 - 8.27 (m, 1H), 7.14 - 7.06 (m, 1H), 6.96 - 6.75 (m, 2H), 4.71 - 4.61 (m, 1H), 4.47 - 4.38 (m, 1H), 4.34 - 4.27 (m, 3H), 3.94 - 3.83 (m, 3H), 3.34 - 3.16 (m, 1H), 3.10 - 2.92 (m, 3H), 1.98 (s, 2H), 1.75 - 1.66 (m, 3H). LCMS (*Method n*. ES⁺, RT = 0.38 min 562.3/563.4 (M+H)⁺

[00772] INTERMEDIATE 93: (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00773] To a solution of *Intermediate 92* (400 mg, 712.33 μ mol) in DCM (2 mL) was added burgess reagent (339.50 mg, 1.42 mmol) in THF (2 mL). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with H₂O 10 mL and extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 1/2) to give *the title compound* (300 mg, 77%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 9.04 (s, 1H), 8.33 (s, 1H), 7.26 (s, 2H), 7.11 - 7.07 (m, 1H), 6.94 - 6.84 (m, 2H), 4.66 - 4.51 (m, 2H), 4.65 - 4.51 (m, 1H), 4.42 - 4.29 (m, 3H), 3.97 - 3.86 (m, 3H), 3.12 - 2.96 (m, 4H), 1.92 - 1.83 (m, 3H) LCMS (*Method m*, ES⁺, RT = 0.44 min 544.3/545.3 (M+H)⁺

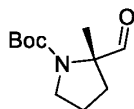
[00774] **INTERMEDIATE 94:** Tert-butyl (S)-2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate



[00775] To a solution of (2S)-1-tert-butoxycarbonyl-2-methyl-pyrrolidine-2-carboxylic acid (20 g, 87.23 mmol) in THF (100 mL) was added with BH₃.THF (1 M, 104.68 mL) dropwise for 0.5 hr at 0 °C. The mixture was stirred at 25 °C for 15 hr. The mixture was quenched by addition MeOH (25 mL) slowly at 0 °C during 0.5 hr. Then the mixture was stirred at 80 °C for 1 hr. The mixture was cooled to 20 °C and concentrated to give the residue, which was dissolved with ethyl acetate (300 mL), washed with saturated NaHCO₃ solution (300 mL), water (300 mL), dried over anhydrous Na₂SO₄ and filtered, the filtrate was concentrated to give *the title compound* (16 g, 85%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.62 - 3.70 (m, 1H), 3.54 - 3.61 (m,

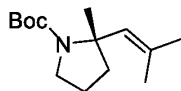
1H), 3.50 (br t, $J = 8.13$ Hz, 1H), 3.25 - 3.37 (m, 1H), 1.72 - 1.91 (m, 2H), 1.62 - 1.71 (m, 2H), 1.45 (s, 9H), 1.35 (br s, 3H).

[00776] **INTERMEDIATE 95:** Tert-butyl (S)-2-formyl-2-methylpyrrolidine-1-carboxylate



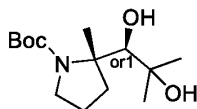
[00777] To a solution of *Intermediate 94* (8 g, 37.16 mmol) in DCM (80 mL) was added Dess-Martin Periodinane (20.49 g, 48.31 mmol) at 20°C. The mixture was stirred at 20°C for 6 hr. The mixture was added with sat. NaHCO₃ solution (300 mL) slowly and filtered using kieselguhr. The filtrate was diluted with H₂O (100 mL) and extracted with DCM (100 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 7/1). *The title compound* (12 g, 76%) was obtained as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.28 - 9.49 (m, 1H), 3.40 - 3.77 (m, 2H), 1.97 (br dd, *J* = 6.36, 4.28 Hz, 3H), 1.62 - 1.71 (m, 1H), 1.46 (s, 3H), 1.36 - 1.44 (m, 9H).

[00778] **INTERMEDIATE 96:** tert-butyl (S)-2-methyl-2-(2-methylprop-1-en-1-yl)pyrrolidine-1-carboxylate



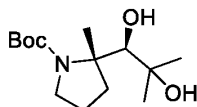
[00779] Isopropyl (triphenyl) phosphonium; bromide (13.55 g, 35.17 mmol) was dissolved with THF (30 mL), then t-BuOK (1 M, 35.17 mL) was added dropwise, then *Intermediate 95* (5 g, 23.44 mmol) was added. The mixture was stirred at 30°C for 12 hr. The mixture was filtered. The filter cake was triturated with MTBE at 20°C for 15 min, then filtered. All of the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 97/3). *The title compound* (8 g, 71%) was obtained as a colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.25 - 5.37 (m, 1H), 3.38 (br dd, *J* = 6.75, 3.75 Hz, 1H), 3.29 (br t, *J* = 8.19 Hz, 1H), 1.69 - 2.00 (m, 4H), 1.61 - 1.67 (m, 3H), 1.54 (s, 3H), 1.30 - 1.40 (m, 12H).

[00780] **INTERMEDIATE 97:** tert-butyl (S)-2-((R)-1,2-dihydroxy-2-methylpropyl)-2-methylpyrrolidine-1-carboxylate



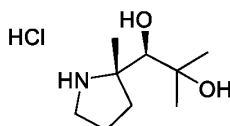
[00781] To a solution of *Intermediate 96* (7 g, 29.25 mmol) in acetone (50 mL) and H₂O (5 mL) was added NMO (5.14 g, 43.87 mmol, 4.63 mL) and K₂OsO₄·2H₂O (323.27 mg, 877.37 μmol) at 0 °C. The mixture was stirred at 20 °C for 12 hr. The mixture was poured into sat. Na₂S₂O₃ (5 mL). The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=70/1 to 30/1) to give *the title compound* (6 g, 75%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.49 - 3.72 (m, 2H), 3.28 (dt, *J* = 10.88, 7.50 Hz, 1H), 2.30 (br d, *J* = 1.63 Hz, 1H), 1.67 - 1.85 (m, 3H), 1.40 - 1.54 (m, 12H), 1.30 (s, 6H). LCMS (*Method t*), ES⁺, RT = 1.74 min) 274.2 (M+H)⁺.

[00782] **INTERMEDIATE 98:** tert-butyl (S)-2-((R)-1,2-dihydroxy-2-methylpropyl)-2-methylpyrrolidine-1-carboxylate



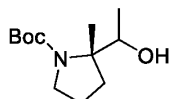
[00783] *Intermediate 97* (6 g, 21.95 mmol) was separated by SFC (*SFC method A*). *The title compound* (0.6 g, 10%) was obtained as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.13 - 5.90 (m, 1H), 3.48 - 3.72 (m, 2H), 3.30 (dt, *J* = 10.91, 7.99 Hz, 1H), 2.44 - 2.60 (m, 1H), 1.78 - 1.86 (m, 2H), 1.67 - 1.75 (m, 1H), 1.37 - 1.55 (m, 12H), 1.32 (s, 3H), 1.25 (s, 3H). LCMS (*Method t*), ES⁺, RT = 1.79 min) 274.2 (M+H)⁺.

[00784] **INTERMEDIATE 99:** (R)-2-methyl-1-((S)-2-methylpyrrolidin-2-yl)propane-1,2-diol



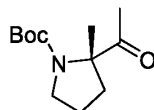
[00785] To a solution of *Intermediate 98* (100 mg, 365.81 μ mol) in MeOH (0.5 mL) was added HCl/MeOH (4 M, 1 mL). The mixture was stirred at 20°C for 1 hr. The reaction was concentrated directly under reduced pressure to give *the title compound* (75 mg, 357.63 μ mol, 97.76% yield, HCl) as a white solid.

[00786] **INTERMEDIATE 100:** tert-butyl (2S)-2-(1-hydroxyethyl)-2-methylpyrrolidine-1-carboxylate



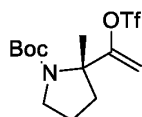
[00787] To a solution of *Intermediate 95* (20 g, 93.78 mmol) in THF (200 mL) was added MeMgBr (3 M, 34.38 mL) at 0°C. The mixture was stirred at 20°C for 2 hr. The reaction was quenched with H₂O (300 mL) and extracted with EtOAc (100 mL x 3). The organic layers were concentrated under reduced pressure to give *the title compound* (20 g, 93%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.39 (s, 1H), 5.09 (br d, J = 9.76 Hz, 1H), 3.88 (q, J = 6.34 Hz, 1H), 3.58 (br t, J = 8.50 Hz, 1H), 3.26 (td, J = 10.22, 7.07 Hz, 1H), 1.63 - 1.90 (m, 4H), 1.46 (s, 9H), 1.26 - 1.40 (m, 3H), 1.10 - 1.15 (m, 3H).

[00788] **INTERMEDIATE 101:** tert-butyl (S)-2-acetyl-2-methylpyrrolidine-1-carboxylate



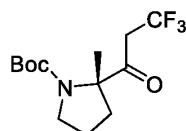
[00789] To a solution of *Intermediate 100* (20 g, 87.22 mmol) in DCM (200 mL) was added Dess-Martin Periodinane (44.39 g, 104.66 mmol) at 20°C. The mixture was stirred at 20°C for 2 hr. The mixture was filtered using kieselguhr. The filtrate was diluted with H₂O (300 mL) and extracted with DCM (100 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 7/1) to give *the title compound* (19 g, 96%) was obtained as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.44 - 3.76 (m, 2H), 2.11 (s, 3H), 1.90 - 2.02 (m, 3H), 1.71 - 1.80 (m, 1H), 1.45 (s, 3H), 1.41 (s, 9H).

[00790] **INTERMEDIATE 102:** tert-butyl (S)-2-methyl-2-(1-(((trifluoromethyl)sulfonyl)oxy)vinyl)pyrrolidine-1-carboxylate



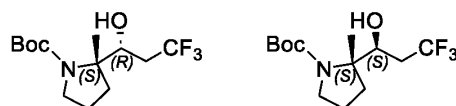
[00791] To a solution of *Intermediate 101* (7 g, 30.80 mmol) in THF (70 mL) was dropwise added with LDA (2 M, 23.10 mL) at -70°C. The mixture was added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl sulfonyl)methanesulfonamide (12.10 g, 33.88 mmol) at -70°C. The mixture was stirred at 50°C for 12 hr. The residue was diluted with H₂O (300 mL) and extracted with EtOAc (200 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give *the title compound* (14 g, 63%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.20 - 5.28 (m, 1H), 5.01 - 5.13 (m, 1H), 3.40 - 3.65 (m, 2H), 2.17 - 2.32 (m, 1H), 1.76 - 1.94 (m, 3H), 1.56 - 1.67 (m, 3H), 1.45 (s, 8H).

[00792] **INTERMEDIATE 103:** tert-butyl (S)-2-methyl-2-(3,3,3-trifluoropropanoyl)pyrrolidine-1-carboxylate



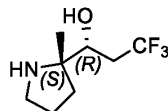
[00793] To a solution of *Intermediate 102* (2.8 g, 7.79 mmol) in t-BuOH (25 mL) and H₂O (25 mL) was added with AgNO₃ (13.24 mg, 77.92 μmol) and (NH₄)₂S₂O₈ (355.61 mg, 1.56 mmol) at 20°C. The reaction was stirred at 30°C for 12 hr. The reaction mixture was diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was washed with EtOAc (3×50 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1) to give *the title compound* (2.1 g, 46%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.60 - 3.80 (m, 1H), 3.35 - 3.55 (m, 2H), 3.17 - 3.29 (m, 1H), 1.94 - 2.11 (m, 3H), 1.72 - 1.89 (m, 1H), 1.37 - 1.53 (m, 12H).

[00794] **INTERMEDIATE 104A&104B:** tert-butyl (S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidine-1-carboxylate; tert-butyl (S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidine-1-carboxylate



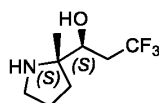
[00795] To a solution of *Intermediate 103* (300 mg, 1.02 mmol) in MeOH (3 mL) was added NaBH₄ (115.30 mg, 3.05 mmol) at 0 °C. The mixture was stirred at 30 °C for 1 hr. 2 batches were combined for work up. The mixture was added with H₂O (5 mL) and extracted with EtOAc (2 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by prep-TLC (SiO₂, PE:EtOAc= 3:1) to give *Intermediate 104A* (50 mg, 66%) with the lower polarity, the other one is *Intermediate 104B* (40 mg, 53%) as a yellow oil.

[00796] **INTERMEDIATE 105A:** (R)-3,3,3-trifluoro-1-((S)-2-methylpyrrolidin-2-yl)propan-1-ol



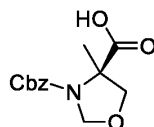
[00797] To a solution of *Intermediate 104A* (50 mg, 168.17 μ mol) in MeOH (0.5 mL) was added HCl/MeOH (4M, 1 mL). The mixture was stirred at 20 °C for 1hr. The mixture was concentrated under reduced pressure to give *the title compound* (39 mg, 99%, HCl) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 4.00 (m, 1H), 3.32 - 3.39 (m, 2H), 2.31 - 2.57 (m, 2H), 2.03 - 2.28 (m, 2H), 1.86 - 1.95 (m, 2H), 1.35 (s, 3H).

[00798] **INTERMEDIATE 105B:** (S)-3,3,3-trifluoro-1-((S)-2-methylpyrrolidin-2-yl)propan-1-ol



[00799] To a solution of *Intermediate 104B* (40 mg, 134.54 μ mol) in MeOH (0.5 mL) was added HCl/MeOH (4M, 1 mL). The mixture was stirred at 20 °C for 1hr. The mixture was concentrated under reduced pressure to give *the title compound* (31 mg, 98%, HCl) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 4.00 (m, 1H), 3.32 - 3.39 (m, 2H), 2.31 - 2.57 (m, 2H), 2.03 - 2.28 (m, 2H), 1.86 - 1.95 (m, 2H), 1.35 (s, 3H).

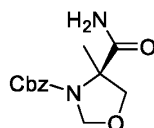
[00800] **INTERMEDIATE 106:** (R)-3-((benzyloxy)carbonyl)-4-methyloxazolidine-4-carboxylic acid



[00801] (2R)-2-amino-3-hydroxy-2-methyl-propanoic acid (2 g, 16.79 mmol) was dissolved in NaOH (2 M, 8.39 mL) at 20 °C. Then, an aqueous solution of formaldehyde (5.45 g, 67.16 mmol, 37% purity) was added dropwise under vigorous stirring and the resulting solution was stirred for 48h at 20°C, after which time the pH was 8-9. NaHCO_3 (3.37 g, 40.08 mmol) and acetone (20 mL) was added to the reaction mixture, and the solution was cooled to 0-5°C. Benzyl carbonochloridate (4.27 g, 25.05 mmol) was added dropwise under vigorous stirring, while the pH was adjusted to 9 with sat. NaHCO_3 . The reaction mixture was stirred at 5°C for 30

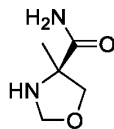
min and at 20°C for 12 hr. Acetone was evaporated, the reaction mixture was diluted with 30 mL H₂O and extracted with MTBE (30 mL x 3). The MTBE phase extracts were discarded. After cooling to 0°C, the solution was acidified with 1N HCl to pH = 2. The suspension was extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (3.3 g, crude) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 - 7.43 (m, 5H), 5.18 (s, 2H), 5.05 (br s, 1H), 4.98 - 5.03 (m, 1H), 4.26 - 4.42 (m, 1H), 3.85 - 3.95 (m, 1H), 1.58 - 1.76 (m, 3H). LCMS (*Method u*) ES⁺, RT=1.164 min) 265.9 (M+H)⁺.

[00802] INTERMEDIATE 107: Benzyl (R)-4-carbamoyl-4-methyloxazolidine-3-carboxylate



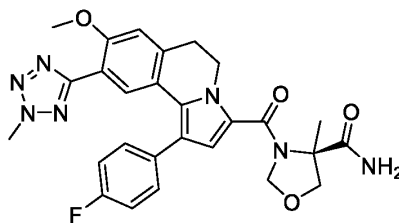
[00803] To a solution of *Intermediate 106* (2.8 g, 10.56 mmol) in THF (28 mL) was added with CDI (2.57 g, 15.83 mmol). The mixture was stirred at 20 °C for 5 hr. Then CDI (855.79 mg, 5.28 mmol) was added to the reaction mixture and stirred at 30 °C for 2 hr. Then NH₃.H₂O (6.61 g, 52.78 mmol, 28% purity) was added to the reaction mixture. The mixture was stirred at 20 °C for 12 hr. 1 N HCl was added to the reaction mixture until the pH was 4-5. Then the reaction mixture was extracted with DCM (30 mL x 3), the combined organic phase was washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/EA = 10/1 to 1/1) to give *the title compound* (2.2 g, 80%) as a colorless oil. ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 7.27 - 7.41 (m, 5H), 5.13 (br s, 3H), 4.95 (d, J=3.81 Hz, 1H), 4.22 (br d, J=8.70 Hz, 1H), 3.85 (br s, 1H), 1.59 (br s, 3H). LCMS (*Method u*. ES⁺, RT=1.00 min) 264.9 (M+H)⁺.

[00804] **INTERMEDIATE 108:** (R)-4-methyloxazolidine-4-carboxamide



[00805] To a solution of *Intermediate 107* (700 mg, 2.65 mmol) in EtOAc (35 mL) was added Pd/C (140.00 mg, 131.55 μ mol, 10% purity) under H₂ (1 atm). The mixture was stirred at 20°C for 2 hr. The reaction mixture was filtered, and the organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (368 mg, 95%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.40 (br s, 1H), 7.12 (br s, 1H), 4.48 (br s, 1H), 4.07 (br s, 1H), 3.83 (d, J=7.75 Hz, 1H), 3.63 (br s, 1H), 3.18 (d, J=7.63 Hz, 1H), 1.30 (s, 3H). LCMS (*Method u.* ES⁺, RT=0.153 min) 130.9 (M+H).

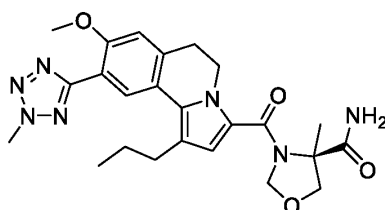
[00806] **INTERMEDIATE 109:** (R)-3-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carboxamide



[00807] To a solution of 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (*Int 109B*) (60 mg, 143.06 μ mol) in DMF (1.2 mL) was added HATU (59.83 mg, 157.36 μ mol) and DIEA (73.96 mg, 572.24 μ mol) stirred at 20°C for 0.5hr. *Intermediate 108* (27.93 mg, 214.59 μ mol) was added at 20°C. The mixture was stirred at 50°C for 12 hr. The reaction was added to ice-water (20 mL), then was filtered. The filter cake was dissolved with EtOAc (10mL). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1 to

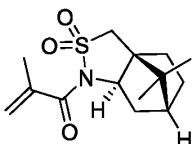
0/1) to give *the title compound* (93 mg, 32%) was a pink solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.75 - 7.85 (m, 1H), 7.39 (ddd, $J = 8.66, 5.47, 3.13$ Hz, 2H), 7.01 - 7.11 (m, 3H), 6.94 (s, 1H), 6.69 - 6.73 (m, 1H), 6.47 (s, 1H), 5.47 - 5.64 (m, 1H), 5.39 (d, $J = 4.25$ Hz, 1H), 5.31 (d, $J = 4.38$ Hz, 1H), 4.52 - 4.72 (m, 2H), 4.41 - 4.48 (m, 1H), 4.34 (s, 3H), 3.94 - 3.98 (m, 3H), 3.86 (d, $J = 9.13$ Hz, 1H), 3.06 - 3.18 (m, 2H), 1.76 - 1.84 (m, 2H), 1.67 (s, 1H). LCMS (*Method a*), ES^+ , RT = 1.476 min 531.2 (M+H) $^+$.

[00808] INTERMEDIATE 110: (R)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carboxamide



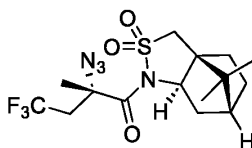
[00809] To a solution of 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (*Int 110B*) (200 mg, 544.36 μmol) in DMF (2 mL) was added HATU (227.68 mg, 598.80 μmol) and DIEA (281.42 mg, 2.18 mmol) at 20°C , stirred at 20°C for 1 hr. The mixture was added *Intermediate 108* (85.02 mg, 653.24 μmol) at 20°C , stirred at 70°C for 11 hr. The reaction mixture was added H_2O (15 mL) at 0°C , and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/ethyl acetate = 5/1 to 1/1) to give *the title compound* (120 mg, 25%, 55% purity) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.07 (br s, 1H), 7.48 (br s, 1H), 7.23 (br s, 2H), 7.02 (br s, 1H), 6.74 (d, $J = 1.2$ Hz, 1H), 6.46 (d, $J = 1.7$ Hz, 1H), 5.36 (br s, 1H), 5.19 (br s, 1H), 4.99 (br d, $J = 2.3$ Hz, 1H), 4.55 - 4.46 (m, 1H), 4.45 - 4.30 (m, 4H), 4.30 - 4.18 (m, 1H), 4.08 (br d, $J = 8.9$ Hz, 1H), 3.88 (s, 3H), 3.80 (br dd, $J = 1.5, 8.3$ Hz, 1H), 3.75 - 3.68 (m, 1H), 3.03 (br s, 3H), 2.72 - 2.61 (m, 2H), 1.72 - 1.58 (m, 2H), 1.51 (br d, $J = 1.8$ Hz, 2H), 1.45 - 1.32 (m, 2H), 1.03 - 0.95 (m, 3H), -0.06 (br s, 1H). LCMS (*Method l*), ES^+ , RT = 0.406 min 480.3 (M+H) $^+$.

[00810] INTERMEDIATE 111: 1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]iso thiazol-1(4H)-yl)-2-methylprop-2-en-1-one



[00811] To a solution of (1S,5R,7R)-10,10-dimethyl-3thia-4-azatricyclo[5.2.1.0^{1,5}]decane 3,3-dioxide (45 g, 209.00 mmol) in THF (450 mL) at -20°C was added LiCl (9.75 g, 229.90 mmol) and TEA (27.49 g, 271.70 mmol). The mixture was stirred for 10 min. 2-methylprop-2-enoyl 2-methylprop-2-enoate (38.66 g, 250.80 mmol) in THF (135 mL) was then added. The thick white mixture was stirred within the cooling bath and allowed to reach 20°C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was poured into 2 L H₂O and stirred for 10 min, then filtered. The filter cake was dissolved with 500 mL DCM, washed with H₂O (300 mL x 2), brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (56 g, 95%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.65 (s, 1H), 5.54 (s, 1H), 3.93 - 4.00 (m, 1H), 3.83 (d, *J* = 14.01 Hz, 1H), 3.61 (d, *J* = 13.88 Hz, 1H), 1.71 - 1.94 (m, 8H), 1.42 - 1.54 (m, 1H), 1.22 - 1.33 (m, 1H), 1.13 (s, 3H), 0.95 (s, 3H). LCMS (*Method a*), ES⁺, RT = 1.675 min 284.2 (M+H)⁺.

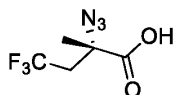
[00812] INTERMEDIATE 112: (S)-2-azido-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methano benzo[c]isothiazol-1(4H)-yl)-4,4,4-trifluoro-2-methylbutan-1-one



[00813] Togni's Reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 101.34 g, 307.00 mmol) and [(CH₃CN)₄Cu]PF₆ (3.81 g, 10.23 mmol) were dissolved in DMA (290 mL). *Intermediate 111* (29 g, 102.33 mmol) and TMSN₃ (23.58 g, 204.67 mmol) were added at 20

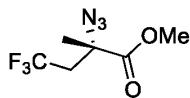
°C~25°C. Under N₂ atmosphere, the mixture was stirred at 50°C for 16 hr. The reaction mixture was diluted with 200 mL MTBE and 500 mL H₂O, the organic layer was extracted with MTBE (200 mL x 3) and the combined organic phase was washed with brine (500 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 19*) to give *the title compound* (25 g, 62%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.02 - 4.12 (m, 1H), 3.55 - 3.65 (m, 1H), 3.44 - 3.52 (m, 1H), 2.77 - 2.94 (m, 2H), 1.84 - 2.07 (m, 5H), 1.72 (s, 3H), 1.30 - 1.45 (m, 2H), 1.19 (s, 3H), 1.00 (s, 3H). LCMS (*Method a*), ES⁺, RT = 1.987 min 417.1 (M+Na)⁺.

[00814] **INTERMEDIATE 113:** (S)-2-azido-4,4,4-trifluoro-2-methylbutanoic acid



[00815] To a solution of *Intermediate 112* (10 g, 25.35 mmol) in THF (50 mL) was added LiOH.H₂O (2.13 g, 50.71 mmol) in H₂O (50 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove THF, then extracted with EtOAc (80 mL x 3), the aqueous layer was acidified to pH = 1 by the addition of 1M HCl and then was extracted with EtOAc (50 mL x 3). The organic layer was washed with 100 mL brine and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (4.5 g, 90%) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.48 - 14.21 (m, 1H), 2.73 - 2.97 (m, 2H), 1.55 (s, 3H).

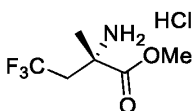
[00816] **INTERMEDIATE 114:** methyl (S)-2-azido-4,4,4-trifluoro-2-methylbutanoate



[00817] To a solution of *Intermediate 113* (4.5 g, 22.83 mmol) in DMF (45 mL) was added CH₃I (6.48 g, 45.66 mmol) and K₂CO₃ (6.31 g, 45.66 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred at 20 °C for 12 hr. The reaction mixture was added to 100 mL ice-water and extracted with EtOAc (80 mL x 3), the combined organic phase was washed with 100 mL

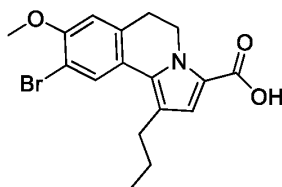
brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (4.1 g, 85%) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.77 (s, 3H), 2.89 - 3.01 (m, 2H), 1.58 (s, 3H).

[00818] INTERMEDIATE 115: methyl (S)-2-amino-4,4,4-trifluoro-2-methylbutanoate



[00819] To a solution of *Intermediate 114* (4.1 g, 19.42 mmol) in THF (82 mL) was added HCl (1 M, 21.36 mL) and Pd/C (1.37 g, 1.28 mmol, 10% purity) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 3 times. The mixture was stirred under H₂ (1 atm) at 20°C for 12 hr. The reaction mixture was filtered under kieselguhr. The filtrate was concentrated under reduced pressure to give a residue. 50 mL of toluene was added to the crude and co-evaporated under reduced pressure to remove H₂O. It was repeated for 6 times. *The title compound* (4 g, crude, HCl) was obtained as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.23 (br s, 3H), 3.77 (s, 3H), 3.02 - 3.24 (m, 2H), 1.63 (s, 3H).

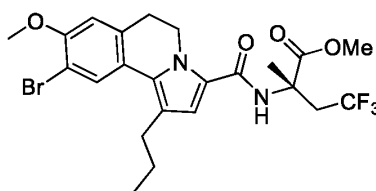
[00820] INTERMEDIATE 116: 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00821] Ethyl 9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (5 g, 12.75 mmol) was dissolved in EtOH (35 mL) and THF (15 mL). Then the mixture was added KOH (2.15 g, 38.24 mmol) in H₂O (15 mL). The mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80°C for 16 hr under N₂ atmosphere. The reaction mixture was added with H₂O 20 mL and adjust pH = 4 with 1M HCl. The reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with

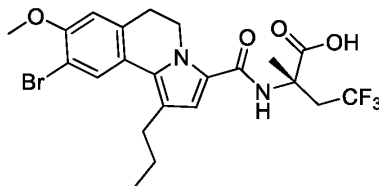
brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (4 g, 86%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.22 (br s, 1H), 7.66 (s, 1H), 7.15 (s, 1H), 6.74 (s, 1H), 4.48 (t, *J* = 6.44 Hz, 2H), 3.88 (s, 3H), 2.97 (br t, *J* = 6.44 Hz, 2H), 2.62 (t, *J* = 7.63 Hz, 2H), 1.54 - 1.68 (m, 2H), 0.97 (t, *J* = 7.32 Hz, 3H). LCMS (Method e), ES⁺, RT = 0.566 min 364.0 (M+H)⁺.

[00822] INTERMEDIATE 117: methyl (S)-2-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido) -4,4,4-trifluoro-2-methylbutanoate



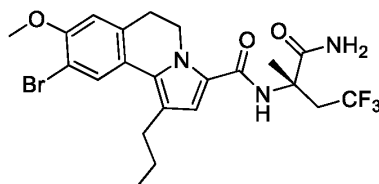
[00823] To a solution of *Intermediate 116* (2 g, 5.49 mmol) in DMF (30 mL) was added HATU (2.71 g, 7.14 mmol) and DIEA (2.84 g, 21.96 mmol). The mixture was stirred at 80°C for 2 hr. Then *Intermediate 115* (1.70 g, 7.69 mmol, HCl) was added and stirred at 80°C for 12 hr. The reaction mixture was cooled and added into H₂O 30 mL, adjust pH = 5 with 1M HCl at 0 - 5°C. The mixture was filtered and the solid was dissolved in EtOAc (30 mL). The organic layer was washed with H₂O (30 mL x 2) and brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 80/20) to give *the title compound* (1.6 g, 55%) as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.37 (s, 1H), 7.64 (s, 1H), 7.13 (s, 1H), 6.91 (s, 1H), 4.31 - 4.47 (m, 2H), 3.87 (s, 3H), 3.63 (s, 3H), 3.22 (br dd, *J* = 15.26, 12.28 Hz, 1H), 2.88 - 3.01 (m, 2H), 2.75 - 2.88 (m, 1H), 2.63 (t, *J* = 7.57 Hz, 2H), 1.60 - 1.71 (m, 2H), 1.53 - 1.58 (m, 3H), 1.00 (t, *J* = 7.33 Hz, 3H). LCMS (Method e), ES⁺, RT = 0.630 min 531.1 (M+H)⁺.

[00824] INTERMEDIATE 118: (S)-2-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



[00825] To a solution of *Intermediate 117* (2 g, 3.76 mmol) in THF (20 mL) was added TMSOK (965.72 mg, 7.53 mmol). The mixture was stirred at 50°C for 12 hr. 1M HCl was added to the reaction solution and adjust pH = 4. The mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (1.65 g, 85%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.20 (s, 1H), 7.64 (s, 1H), 7.13 (s, 1H), 6.89 (s, 1H), 4.38 - 4.49 (m, 2H), 3.87 (s, 3H), 3.27 (br s, 1H), 2.89 - 2.97 (m, 2H), 2.71 - 2.87 (m, 1H), 2.56 - 2.69 (m, 2H), 1.58 - 1.72 (m, 2H), 1.54 (s, 3H), 1.00 (t, *J* = 7.34 Hz, 3H). LCMS (Method *e*), ES⁺, RT = 0.563 min 517.1 (M+H)⁺.

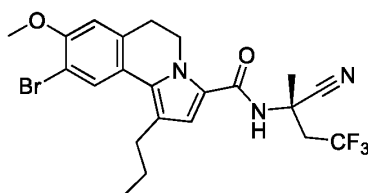
[00826] INTERMEDIATE 119: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00827] To a solution of *Intermediate 118* (1.3 g, 2.51 mmol) in THF (13 mL) was added CDI (611.19 mg, 3.77 mmol) at 25°C for 1 hr, then NH₃.H₂O (1.06 g, 7.54 mmol, 25% purity) was added to the mixture. The mixture was stirred at 25°C for 1 hr. The residue was poured into water (30 mL). The aqueous phase was extracted with DCM (30 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (1.25 g, 96%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.94 (s, 1H), 7.64 (s, 1H), 7.42 (br s, 1H), 7.13 (s, 2H), 6.82 (s, 1H), 4.43 (br d, *J* = 2.88 Hz, 2H), 3.87 (s, 3H), 3.30 (s, 1H), 2.87 - 3.06 (m, 3H), 2.63 (br t, *J* = 7.50 Hz, 2H), 1.65

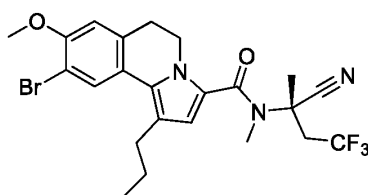
(dq, $J = 14.85, 7.26$ Hz, 2H), 1.54 (s, 3H), 1.00 (br t, $J = 7.25$ Hz, 3H). LCMS (Method *e*), ES^+ , RT = 0.549 min 517.1 (M+H)⁺.

[00828] INTERMEDIATE 120: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00829] To a solution of *Intermediate 119* (1.2 g, 2.32 mmol) in THF (12 mL) was added burgess reagent (1.11 g, 4.65 mmol) in DCM (12 mL). The mixture was stirred at 25 °C for 1 hr. The residue was poured into water (30 mL). The aqueous phase was extracted with DCM (30 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (1 g, 86%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.45 (s, 1H), 7.66 (s, 1H), 7.16 (s, 1H), 6.91 (s, 1H), 4.49 (br t, $J = 6.48$ Hz, 2H), 3.88 (s, 3H), 3.16 - 3.32 (m, 2H), 2.96 (br t, $J = 6.42$ Hz, 2H), 2.63 (t, $J = 7.58$ Hz, 2H), 1.81 (s, 3H), 1.56 - 1.72 (m, 2H), 1.00 (t, $J = 7.34$ Hz, 3H). LCMS (Method *e*), ES^+ , RT = 0.605 min 498.1 (M+H)⁺.

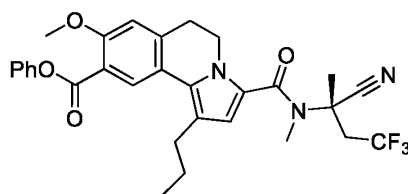
[00830] INTERMEDIATE 121: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00831] DMF (30 mL) was charged to the three-necked round bottom flask, then *Intermediate 120* (1 g, 2.00 mmol) was added to the mixture at 25°C for 5min under Ar balloon. At 0°C inner temperature NaH (120.38 mg, 3.02 mmol, 60% purity) was added in portions to the reaction

mixture at 0°C within 15 min under Ar balloon. Then CH₃I (569.64 mg, 4.02 mmol) was added. After the addition, the mixture was stirred at 70°C for 2 hr. The residue was poured into NH₄Cl (20 mL). The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with H₂O (20 mL x 2) and brine (20 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 84/16) to give *the title compound* (0.70 g, 68%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.76 (s, 1H), 6.80 (s, 1H), 6.41 (s, 1H), 4.23 - 4.39 (m, 2H), 3.93 (s, 1H), 3.39 (s, 3H), 3.12 - 3.37 (m, 2H), 2.98 (t, *J* = 6.50 Hz, 2H), 2.65 - 2.72 (m, 2H), 2.00 - 2.08 (m, 3H), 1.63 - 1.76 (m, 2H), 1.05 (t, *J* = 7.38 Hz, 3H). LCMS (Method e), ES⁺, RT = 0.650 min 512.1 (M+H)⁺.

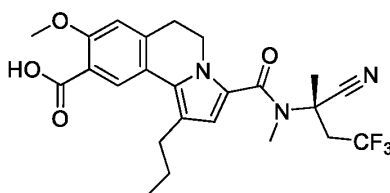
[00832] INTERMEDIATE 122: phenyl (S)-3-((2-cyano-4,4,4-trifluorobutan-2-yl)(methyl)carbamoyl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylate



[00833] A mixture of *Intermediate 121* (400 mg, 780.70 μmol), phenyl formate (572.04 mg, 4.68mmol), TEA (473.99 mg, 4.68 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (63.75 mg, 78.07μmol) in DMF (4 mL) was degassed and purged with N₂ for 3 times at 20°C, and then the mixture was stirred at 120°C for 12 hr under N₂ atmosphere. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2/1 to 1/1) to give *the title compound* (400 mg, 92%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.27 - 8.21 (m, 1H), 7.43 - 7.33 (m, 2H), 7.24 - 7.13 (m, 4H), 6.89 - 6.84(m, 1H), 6.40 - 6.31 (m, 1H), 4.38 - 4.19 (m, 2H), 3.98 - 3.80 (m, 3H), 3.36 - 3.31 (m, 3H), 3.27 - 3.19 (m, 1H), 3.14 -3.07 (m,

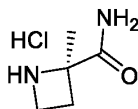
1H), 3.04 - 2.97 (m, 2H), 2.70 - 2.61 (m, 2H), 1.97 (s, 3H), 1.71 - 1.56 (m, 2H), 1.12 (s, 2H), 0.94 (t, $J = 7.3\text{Hz}$, 3H). LCMS (Method I), ES⁺, RT = 0.619 min 554.0 (M+H)⁺.

[00834] INTERMEDIATE 123: (S)-3-((2-cyano-4,4,4-trifluorobutan-2-yl)(methyl)carbamoyl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylic acid



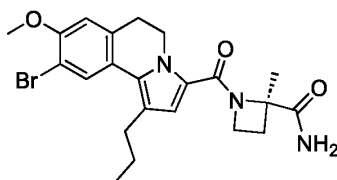
[00835] To a solution of *Intermediate 122* (380 mg, 686.45 μmol) in THF (4 mL) was added TMSOK (176.13 mg, 1.37 mmol) at 20°C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove THF and EtOH, diluted with H₂O (10 mL) and adjusted pH to 3 - 4, which was extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (400 mg, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 12.76 - 12.38 (m, 1H), 9.33 (br s, 1H), 7.92 (s, 1H), 7.20 - 7.11 (m, 3H), 6.80 - 6.71 (m, 2H), 6.50 (s, 1H), 4.31 - 4.10 (m, 2H), 3.85 (s, 3H), 3.28 - 3.16 (m, 4H), 3.09 - 2.98 (m, 2H), 2.70 - 2.60 (m, 2H), 1.92 (s, 3H), 1.63 (sxt, $J = 7.4\text{ Hz}$, 2H), 0.98 (t, $J = 7.3\text{ Hz}$, 3H). LCMS (Method I), ES⁺, RT = 0.510 min 478.0 (M+H)⁺.

[00836] **INTERMEDIATE 124:** (R)-2-methylazetidine-2-carboxamide



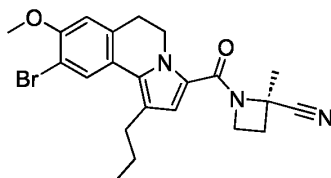
[00837] To a solution of tert-butyl (R)-2-carbamoyl-2-methylazetidine-1-carboxylate (2 g, 9.33 mmol) in EtOAc (10 mL) was added HCl/EtOAc (4M, 20 mL). The mixture was stirred at 20°C for 1 hr. The mixture was concentrated under reduced pressure to give *the title compound* (1.4 g, 99% yield, HCl salt) as a white solid.

[00838] **INTERMEDIATE 125:** (R)-1-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



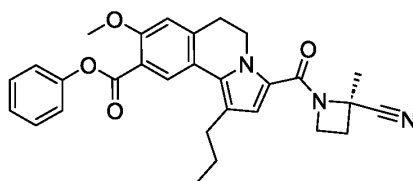
[00839] To a solution of *Intermediate 116* (1 g, 2.75 mmol) in DMF (10 mL) was added *Intermediate 124* (496.19 mg, 3.29 mmol, HCl), DIEA (1.42 g, 10.98 mmol) and HATU (1.15 g, 3.02 mmol). The mixture was stirred at 20°C for 1 hr. The reaction mixture was added to the ice water, 1M HCl was added to adjust the pH was 5 - 6. Filtered and the aqueous phase was extracted with EtOAc(20 mL x 3), the combined organic phase was washed with brine (20 mL x 6) to remove DMF, dried by Na₂SO₄, and filtered, then concentrated under reduced pressure to give the title compound (1.24 g, 98%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.27 - 8.41 (m, 1H), 7.76 (s, 1H), 6.81 (s, 1H), 6.47 (s, 1H), 5.35 (br s, 1H), 4.46 - 4.69 (m, 2H), 4.26 - 4.38 (m, 2H), 3.93 (s, 3H), 2.90 - 3.01 (m, 3H), 2.64 - 2.74 (m, 2H), 2.15 (ddd, *J* = 11.59, 8.97, 5.78 Hz, 1H), 1.88 (s, 3H), 1.65 - 1.74 (m, 2H), 1.05 (t, *J* = 7.33 Hz, 3H). LCMS (Method *e*), ES⁺, RT = 0.525 min 462.0 (M+H)⁺.

[00840] **INTERMEDIATE 126:** (R)-1-(9-bromo-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile



[00841] *Intermediate 125* (1.1 g, 2.39 mmol) was dissolved in THF (6 mL). Then Burgess Reagent (1.14 g, 4.78 mmol) in DCM (6 mL) was added to the mixture. The mixture was stirred at 20°C for 1 hr. The reaction mixture was added with water (10 mL x 3). The organic layers were washed with brine (15 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/EtOAc=20/1 to 1/1) to give *the title compound* (930 mg, 88%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.74 - 7.78 (m, 1H), 6.81 (s, 1H), 6.44 (s, 1H), 4.63 (br t, *J* = 6.48 Hz, 2H), 4.36 - 4.46 (m, 2H), 3.93 (s, 3H), 2.96 (t, *J* = 6.48 Hz, 2H), 2.83 (ddd, *J* = 11.58, 8.89, 5.81 Hz, 1H), 2.69 (t, *J* = 7.70 Hz, 2H), 2.43 (dt, *J* = 11.43, 7.98 Hz, 1H), 1.91 (s, 3H), 1.69 (sxt, *J* = 7.41 Hz, 2H), 1.04 (t, *J* = 7.34 Hz, 3H). LCMS (Method *e*), ES⁺, RT = 0.596 min 444.0 (M+H)⁺.

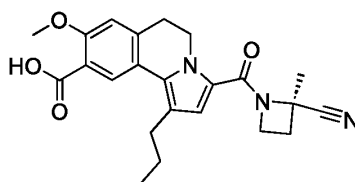
[00842] **INTERMEDIATE 127:** Phenyl(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylate



[00843] To a solution of *Intermediate 126* (400 mg, 904.27 μmol) in DMF (4 mL) was added phenyl formate (662.58 mg, 5.43 mmol) and TEA (549.01 mg, 5.43 mmol). Then the suspension was degassed and purged with a stream of N₂. Then Pd(dppf)Cl₂.CH₂Cl₂ (184.61 mg, 226.07 μmol) was added to the reaction mixture at 20°C. The mixture was stirred at 120°C for 12 hr. The reaction mixture was partitioned between EtOAc 10 mL and H₂O (10 mL). The organic phase was

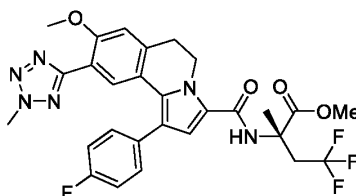
separated, washed with brine (15 mL x 6) to remove DMF, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/EA = 20/1 to 1/1) to give *the title compound* (360 mg, 82%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.33 (s, 1H), 7.40 - 7.48 (m, 2H), 7.29 (s, 1H), 7.25 (d, *J* = 7.58 Hz, 2H), 6.95 (s, 1H), 6.46 (s, 1H), 4.68 (br t, *J* = 6.54 Hz, 2H), 4.37 - 4.47 (m, 2H), 3.98 (s, 3H), 3.07 (t, *J* = 6.48 Hz, 2H), 2.80 - 2.90 (m, 1H), 2.71 - 2.78 (m, 2H), 2.40 - 2.49 (m, 1H), 1.92 (s, 3H), 1.71 (sxt, *J* = 7.51 Hz, 2H), 1.02 (t, *J* = 7.34 Hz, 3H). LCMS (Method I), ES⁺, RT = 0.587 min 484.3 (M+H)⁺.

[00844] INTERMEDIATE 128: (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylic acid



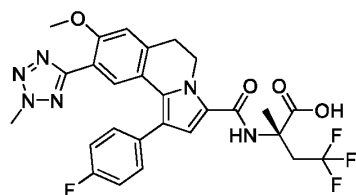
[00845] To a solution of *Intermediate 127* (700 mg, 1.45 mmol) in THF (7 mL) was added TMSOK (371.42 mg, 2.90 mmol). The mixture was stirred at 20°C for 1 hr. The reaction mixture was stirred at 30°C in oil bath for 1 hr. The reaction mixture was added to the ice water, 1M HCl was added to adjust pH = 5 - 6. The reaction mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (630 mg, crude) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.64 (br s, 1H), 8.43 (s, 1H), 6.96 - 6.97 (m, 1H), 6.46 (s, 1H), 4.67 (br t, *J* = 6.63 Hz, 2H), 4.37 - 4.48 (m, 2H), 4.12 (s, 3H), 3.06 (t, *J* = 6.50 Hz, 2H), 2.81 - 2.88 (m, 1H), 2.73 - 2.79 (m, 2H), 2.44 (ddd, *J* = 11.66, 8.72, 7.13 Hz, 1H), 1.92 (s, 3H), 1.66 - 1.75 (m, 2H), 1.05 (t, *J* = 7.38 Hz, 3H). LCMS (Method I), ES⁺, RT = 0.461 min 408.1 (M+H)⁺.

[00846] **INTERMEDIATE 129:** methyl (S)-4,4,4-trifluoro-2-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



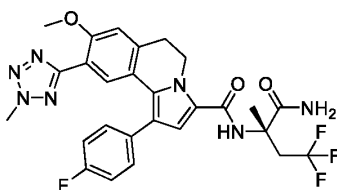
[00847] To a solution of 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (500 mg, 1.19 mmol) and *Intermediate 115* (317.03 mg, 1.43 mmol, HCl) in DMF (10 mL) was added HATU (906.59 mg, 2.38 mmol) and DIEA (616.30 mg, 4.77 mmol) at 80°C. The mixture was stirred at 80°C for 12 hr. The mixture was diluted with H₂O (40 mL) and extracted with EtOAc (20 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1) to give the title compound (1 g, 71%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.48 (s, 1H), 7.70 (s, 1H), 7.43 (dd, *J* = 5.8, 8.2 Hz, 2H), 7.24 - 7.17 (m, 3H), 7.08 (s, 1H), 4.61 - 4.42 (m, 2H), 4.33 (s, 3H), 3.86 (s, 3H), 3.68 - 3.63 (m, 3H), 3.28 - 3.17 (m, 1H), 3.12 (br t, *J* = 6.3 Hz, 2H), 2.93 - 2.78 (m, 1H), 1.56 (s, 3H). LCMS (Method g), ES⁺, RT = 0.553 min 587.3 (M+H)⁺.

[00848] **INTERMEDIATE 130:** (S)-4,4,4-trifluoro-2-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



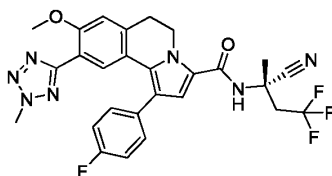
[00849] To a solution of *Intermediate 129* (900 mg, 1.53 mmol) in THF (10 mL) was added TMSOK (393.70 mg, 3.07 mmol) at 20°C. The mixture was stirred at 20°C for 2 hr. The mixture was added with 1N HCl to adjust pH = 5 and the reaction was diluted with H₂O (20 mL) and extracted with EtOAc (10 mL x 3). The organic layers were concentrated under reduced pressure to give *the title compound* (800 mg, 91%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.74 - 12.89 (m, 1H), 8.29 (s, 1H), 7.68 - 7.71 (m, 1H), 7.39 - 7.46 (m, 2H), 7.17 - 7.24 (m, 3H), 7.07 (s, 1H), 4.55 - 4.63 (m, 1H), 4.43 - 4.52 (m, 1H), 4.33 (s, 3H), 3.86 (s, 3H), 3.20 - 3.29 (m, 1H), 3.12 (br t, *J* = 6.44 Hz, 2H), 2.72 - 2.90 (m, 1H), 1.56 (s, 3H). LCMS (Method e), ES⁺, RT = 0.476 min 573.2 (M+H)⁺.

[00850] **INTERMEDIATE 131:** (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



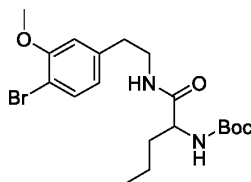
[00851] To a solution of *Intermediate 130* (700 mg, 1.22 mmol) in THF (10 mL) was added CDI (297.39 mg, 1.83 mmol) at 20°C. The mixture was stirred at 20°C for 0.5 hr. The mixture was added NH₃.H₂O (514.26 mg, 3.67 mmol, 25% purity) at 20°C. The mixture was stirred at 20°C for 1 hr. The reaction was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (3 mL) and filtered to give *the title compound* (690 mg, 98%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.81 (s, 1H), 7.74 (s, 1H), 7.42 - 7.36 (m, 2H), 7.13 (d, *J* = 0.6 Hz, 3H), 7.09 - 7.03 (m, 2H), 6.93 (s, 1H), 6.67 (s, 1H), 6.49 (s, 1H), 4.77 - 4.57 (m, 2H), 4.36 - 4.31 (m, 3H), 3.98 - 3.91 (m, 3H), 3.32 - 3.09 (m, 4H), 1.75 (s, 3H). LCMS (Method e), ES⁺, RT = 0.482 min 572.1 (M+H)⁺.

[00852] **INTERMEDIATE 132:** (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00853] To a solution of *Intermediate 131* (340 mg, 594.90 μ mol) in THF (3 mL) was added burgess reagent (354.43 mg, 1.49 mmol) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were concentrated under reduced pressure to give *the title compound* (520 mg, 78%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 - 7.78 (m, 1H), 7.29 - 7.36 (m, 2H), 7.05 (t, J = 8.70 Hz, 2H), 6.93 (s, 1H), 6.53 - 6.58 (m, 1H), 6.22 (s, 1H), 4.68 - 4.77 (m, 1H), 4.51 - 4.61 (m, 1H), 4.35 (s, 3H), 3.96 (s, 3H), 3.00 - 3.26 (m, 4H), 1.96 (s, 3H). LCMS (Method e), ES⁺, RT = 0.5332 min 554.1 (M+H)⁺.

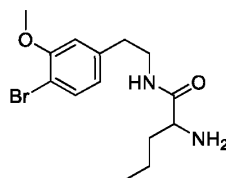
[00854] **INTERMEDIATE 133:** tert-butyl(1-((4-bromo-3-methoxyphenethyl)amino)-1-oxopent-2-yl)carbamate



[00855] To a solution of 2-(tert-butoxycarbonylamino)pentanoic acid (5.19 g, 23.90 mmol) in DCM (50 mL) was added CDI (4.23 g, 26.08 mmol) at 20°C for 10 min, then added with *Intermediate 2* (5 g, 21.73 mmol). The mixture was stirred at 20°C for 30 min. The mixture was added with sat. NaHCO₃ to adjust pH=8. The aqueous phase was extracted with DCM (5 mLx3). The combined organic phase was washed with brine (10 mLx2), dried with anhydrous

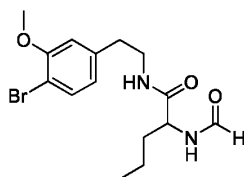
Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=55/1 to 45/1) to give *the title compound* (2.9 g, 46%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 (d, *J*=7.88 Hz, 1 H) 6.75 (d, *J*=1.50 Hz, 1 H) 6.67 (dd, *J*=8.00, 1.63 Hz, 1 H) 6.14 (br s, 1 H) 4.89 (br d, *J*=2.63 Hz, 1 H) 3.94 - 4.01 (m, 1 H) 3.90 (s, 3 H) 3.43 - 3.59 (m, 2 H) 2.79 (t, *J*=7.00 Hz, 2 H) 1.72 - 1.83 (m, 1 H) 1.49 - 1.60 (m, 2 H) 1.43 (s, 8 H) 1.25 - 1.37 (m, 2 H) 0.91 (t, *J*=7.32 Hz, 3 H) LCMS (*Method i*. ES⁺, RT = 0.756 min) 452.3/453.3 (M+Na)⁺

[00856] INTERMEDIATE 134: 2-amino-N-(4-bromo-3-methoxyphenethyl)pentanamide



[00857] To a solution of *Intermediate 133* (5 g, 11.65 mmol) in EtOAc (10 mL) was added HCl/EtOAc (4 M, 50 mL). The mixture was stirred at 20°C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (3.8 g, 99 %) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 - 8.28 (m, 4 H) 7.39 (d, *J*=8.00 Hz, 1 H) 6.81 (s, 1 H) 6.67 (br d, *J*=7.88 Hz, 1 H) 4.20 (br s, 1 H) 3.86 (s, 3 H) 3.59 (br d, *J*=5.75 Hz, 1 H) 3.35 (br s, 1 H) 2.81 (br s, 2 H) 1.81 (br s, 2 H) 1.15 - 1.33 (m, 2 H) 0.84 (br t, *J*=6.88 Hz, 3 H) LCMS (*Method g*. ES⁺, RT = 0.348 min) 329.0/331.0 (M+H)⁺

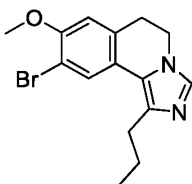
[00858] INTERMEDIATE 135: N-(4-bromo-3-methoxyphenethyl)-2-formamidopentanamide



[00859] To a solution of *Intermediate 134* (500 mg, 1.37 mmol, HCl) in ethyl formate (4.61 g, 62.16 mmol) and MeOH (1 mL) was added Et₃N (276.70 mg, 2.73 mmol). The mixture was stirred

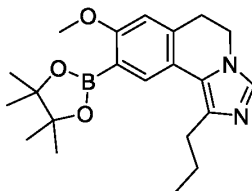
at 70°C for 16 hr. The reaction mixture was added with 2 mL H₂O and adjust pH=5 with HCl (0.5 M). The aqueous layer was extracted with ethyl acetate (5 mL) and the combined phase was washed with brine 10 mL and concentrated under reduced pressure to give *the title compound* (800 mg, 82%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.17 (br d, *J*=8.13 Hz, 1 H) 8.05 (br t, *J*=5.57 Hz, 1 H) 7.98 (d, *J*=0.75 Hz, 1 H) 7.43 (d, *J*=8.00 Hz, 1 H) 6.95 (d, *J*=1.88 Hz, 1 H) 6.72 (dd, *J*=8.07, 1.81 Hz, 1 H) 4.21 - 4.28 (m, 1 H) 3.83 (s, 3 H) 3.34 - 3.39 (m, 1 H) 3.23 - 3.31 (m, 1 H) 2.69 (t, *J*=6.94 Hz, 2 H) 1.33 - 1.53 (m, 2 H) 1.06 - 1.24 (m, 2 H) 0.75 - 0.84 (m, 3 H) LCMS (*Method g*. ES⁺, RT = 0.407 min) 357.0/359.1 (M+H)⁺

[00860] INTERMEDIATE 136: 9-bromo-8-methoxy-1-propyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline



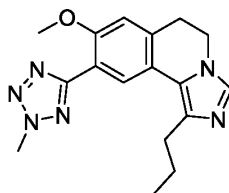
[00861] A mixture of P₂O₅ (794.67 mg, 5.60 mmol) in methanesulfonic acid (2.5 mL) was stirred at 75°C for 0.5 hr, then was added *Intermediate 135* (500 mg, 1.40 mmol). The mixture was stirred at 90°C for 12 hr. The mixture was cooled and quenched with ice water, then added with Na₂CO₃ to adjust pH=8, extracted with EtOAc (5 mL×2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1) to give *the title compound* (280 mg, 62%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.58 (d, *J*=7.88 Hz, 2 H) 7.15 (s, 1 H) 4.05 - 4.13 (m, 2 H) 3.86 (s, 3 H) 2.98 (t, *J*=6.38 Hz, 2 H) 2.67 (t, *J*=7.57 Hz, 2 H) 1.66 (sxt, *J*=7.45 Hz, 2 H) 0.87 - 0.99 (m, 3 H) LCMS (*Method e*. ES⁺, RT = 0.355 min) 322.9/321.9 (M+H)⁺

[00862] INTERMEDIATE 137: 8-methoxy-1-propyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydroimidazo[5,1-*a*]isoquinoline



[00863] To a solution of *Intermediate 136* (3 g, 9.34 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (23.72 g, 93.40 mmol) in DMSO (30 mL) was added KOAc (13.75 g, 140.09 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (152.54 mg, 186.79 μmol) at 20°C. The mixture was stirred at 95°C for 12 hr under N₂ atmosphere. The reaction mixture was diluted with 30 mL EtOAc and filtered, the filtrate was washed with brine (20 mL×6) to remove DMSO, dried by Na₂SO₄, and filtered, then concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give *the title compound* (3.4 g, crude) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.73 - 7.78 (m, 1 H) 6.76 - 6.79 (m, 1 H) 4.56 - 4.66 (m, 2 H) 4.34 - 4.45 (m, 2 H) 3.85 - 3.90 (m, 3 H) 3.59 - 3.74 (m, 2 H) 2.91 - 3.00 (m, 2 H) 1.33 - 1.41 (m, 3 H) LCMS (*Method a*, ES⁺, RT = 1.314 min) 369.4/370.3 (M+H)⁺

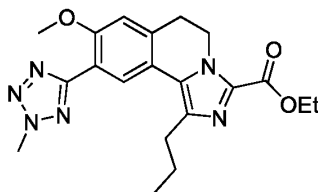
[00864] INTERMEDIATE 138: 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline



[00865] To a solution of *Intermediate 137* (3.38 g, 9.18 mmol) and 5-bromo-2-methyl-tetrazole (1.50 g, 9.18 mmol) in dioxane (30 mL) and H₂O (6 mL) was added Cs₂CO₃ (8.97 g, 27.53 mmol) and XPHOS-Pd-G₂ (361.06 mg, 458.89 μmol) at 20 °C. Then the mixture was stirred at 70°C for 2 hr under N₂ atmosphere. The reaction mixture was added 30 mL water and extracted with DCM (30 mL×3). The combined organic layers were washed with brine (25 mL×3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was

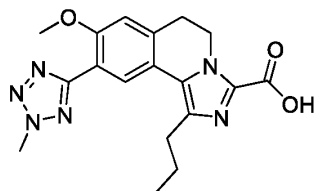
purified by column chromatography (SiO₂, EA/DCM/MeOH) to give *the title compound* (940 mg, 32%) as a brown solid. LCMS (*Method a*. ES⁺, RT = 0.097 min) 325.3/326.2 (M+H)⁺

[00866] INTERMEDIATE 139: ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



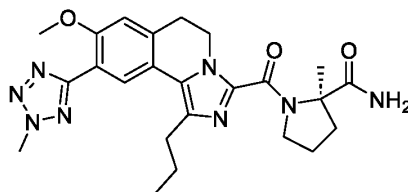
[00867] THF (45 mL) was charged to the 25 mL three-necked round bottom flask, then *Intermediate 138* (1.4 g, 4.32 mmol) was added at 20°C. At -60°C inner temperature, LDA (2 M, 2.81 mL) was added dropwise to the reaction mixture at -60°C within 2 min. The mixture was stirred at -60°C for 0.5 hr. At -60°C inner temperature, ethyl chloroformate (2.34 g, 21.58 mmol) was added dropwise to the reaction mixture. After the addition, the mixture was stirred at -60°C for 0.5 hr. The reaction mixture was stirred at 20°C for 1.5 hr. The reaction mixture was added to 15mL NaHCO₃ at 0°C. The mixture was extracted by DCM (30 mL×2). Then organic phase was washed by brine (15mL×2). The organic layers were dried over Na₂SO₄, filtered. The organic phase was concentrated under reduced pressure at 40°C to give a residue. The residue was purified by column chromatography to give *the title compound* (270 mg, 16%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.33 (s, 1 H) 6.98 - 7.02 (m, 1 H) 4.73 (t, *J*=6.62 Hz, 2 H) 4.42 - 4.51 (m, 5 H) 4.01 (s, 3 H) 3.14 (br t, *J*=6.50 Hz, 2 H) 2.91 - 3.01 (m, 2 H) 1.78 - 1.88 (m, 2 H) 1.44 - 1.48 (m, 4 H) 1.07 (t, *J*=7.33 Hz, 3 H) LCMS (*Method e*. ES⁺, RT = 0.338 min) 397.1/398.1 (M+H)⁺

[00868] **INTERMEDIATE 140:** 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[00869] To a solution of *Intermediate 139* (80 mg, 201.79 μmol) in THF (0.8 mL) was added TMSOK (51.78 mg, 403.59 μmol). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (74 mg, crude) as a yellow solid. LCMS (*Method e*, ES^+ , $\text{RT}=0.302$ min) 369.0/370.0 ($\text{M}+\text{H}^+$)

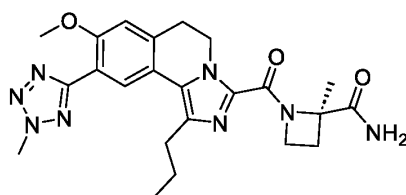
[00870] **INTERMEDIATE 141:** (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00871] To a solution of *Intermediate 140* (120 mg, 325.74 μmol) in DMF (1.2 mL) was added (2R)-2-methylpyrrolidine-2-carboxamide (64.35 mg, 390.89 μmol , HCl), DIEA (168.40 mg, 1.30 mmol) and HATU (136.24 mg, 358.32 μmol). The mixture was stirred at 20°C for 1 hr. The reaction mixture was added to the ice water, 1M HCl was added to adjust $\text{pH} = 5-6$. The reaction mixture was extracted with DCM (5 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give *the title compound* (153 mg, 98%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1 H) 7.00 (s, 1 H) 4.57 (br d, $J=0.98$ Hz, 2 H) 4.46 (s, 3 H) 4.09 - 4.29 (m, 3 H) 4.01 (s, 3 H) 3.12 (br t, $J=5.93$ Hz, 2 H) 2.97 (s, 2 H) 2.88 - 2.93 (m, 3 H) 2.81 (s, 6 H) 2.00 - 2.07 (m, 3

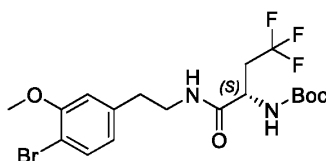
H) 1.76 - 1.83 (m, 5 H) 1.21 - 1.29 (m, 4 H) 1.05 (t, $J=7.34$ Hz, 3 H) LCMS (*Method e.* ES⁺, RT = 0.327 min) 479.2/480.2 (M+H)⁺

[00872] INTERMEDIATE 142: (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



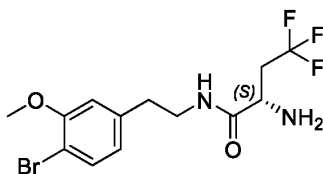
[00873] To a solution of *Intermediate 140* (130 mg, 352.89 μ mol) in DMF (1.3 mL) was added *Intermediate 124* (63.78 mg, 423.47 μ mol, HCl), DIEA (182.43 mg, 1.41 mmol) and HATU (147.60 mg, 388.18 μ mol). The mixture was stirred at 20°C for 1 hr. The reaction mixture was added to the 5 mL ice water, 1M HCl was added to adjust pH = 6. The reaction mixture was extracted with EtOAc (5 mL $\times$ 3), the combined organic phase was washed with brine (5 mL $\times$ 6), dried by Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (177 mg, crude) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.23 - 8.32 (m, 2 H) 8.03 (s, 1 H) 6.96 - 7.01 (m, 1 H) 5.36 - 5.42 (m, 1 H) 4.67 - 4.78 (m, 3 H) 4.56 (td, $J=10.02$, 5.62 Hz, 1 H) 4.46 (s, 3 H) 4.13 (q, $J=7.13$ Hz, 2 H) 4.00 (s, 3 H) 3.07 - 3.15 (m, 2 H) 2.97 (s, 5 H) 2.83 - 2.92 (m, 8 H) 2.81 (s, 6 H) 2.06 (s, 3 H) 1.90 (s, 3 H) 1.79 - 1.87 (m, 2 H) 1.19 - 1.32 (m, 9 H) 1.05 (t, $J=7.40$ Hz, 3 H) 0.81 - 0.91 (m, 3 H) LCMS (*Method e.* ES⁺, RT = 0.357 min) 465.1/466.1 (M+H)⁺

[00874] INTERMEDIATE 143: tert-butyl(S)-(1-((4-bromo-3-methoxyphenethyl)amino)-4,4,4-trifluoro-1-oxobutan-2-yl) carbamate



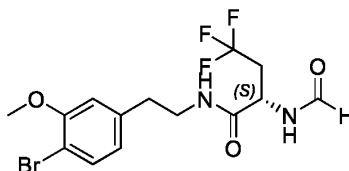
[00875] To a solution of (2S)-2-(tert-butoxycarbonylamino)-4,4,4-trifluoro-butanoic acid (3.82 g, 14.86 mmol) in DCM (30 mL) was added CDI (3.28 g, 20.26 mmol) at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was added *Intermediate 212* (3.6 g, 13.51 mmol, HCl) and DIEA (3.49 g, 27.01 mmol) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction was diluted with H₂O (100 mL) and extracted with DCM (50 mL×3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (20 mL) to give *the title compound* (2.9 g, 46%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (br s, 1 H) 7.43 (d, *J*=8.00 Hz, 1 H) 7.18 (d, *J*=8.75 Hz, 1 H) 6.94 (d, *J*=1.50 Hz, 1 H) 6.72 (dd, *J*=8.00, 1.50 Hz, 1 H) 4.18 - 4.27 (m, 1 H) 3.83 (s, 3 H) 3.27 - 3.31 (m, 2 H) 2.69 (br t, *J*=7.00 Hz, 2 H) 2.53 - 2.62 (m, 1 H) 2.45 (br s, 1 H) 1.37 (s, 9 H) LCMS (*Method e*. ES⁺, RT = 0.528 min) 490.9/492.9 (M+Na)⁺

[00876] **INTERMEDIATE 144:** (S)-2-amino-N-(4-bromo-3-methoxyphenethyl)-4,4,4-trifluorobutanamide



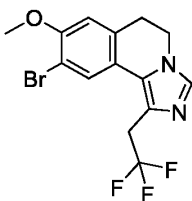
[00877] To a solution of *Intermediate 143* (4.5 g, 9.59 mmol) in EtOAc (50 mL) was added HCl/EtOAc (4M, 50 mL) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (7.7 g, 99%, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (br t, *J* = 5.0 Hz, 1H), 8.66 (br s, 3H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.77 (br d, *J* = 7.9 Hz, 1H), 4.05 (br s, 1H), 3.85 (s, 3H), 3.65 - 3.23 (m, 3H), 2.92 - 2.67 (m, 4H) LCMS (*Method g*. ES⁺, RT = 0.337 min) 369.0/371.0 (M+H)⁺

[00878] **INTERMEDIATE 145:** (S)-N-(4-bromo-3-methoxyphenethyl)-4,4,4-trifluoro-2-formamidobutanamide



[00879] To a solution of *Intermediate 144* (7.7 g, 20.86 mmol) in ethyl formate (69.78 g, 941.91 mmol) was added TEA (6.33 g, 62.57 mmol) and MeOH (5 mL) at 20°C. The mixture was stirred at 75°C for 12 hr. The reaction mixture was concentrated under reduced pressure. The mixture was added with HCl (0.5 mol) to adjust pH=5, then mixture was diluted with H₂O 90 mL and extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine 50 mL (25 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (7.5 g, 91%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 - 8.61 (m, 1 H) 8.31 (br t, *J*=5.26 Hz, 1 H) 8.03 (s, 1 H) 7.44 (d, *J*=8.07 Hz, 1 H) 6.93 (d, *J*=1.71 Hz, 1 H) 6.72 (dd, *J*=8.01, 1.65 Hz, 1 H) 4.51 - 4.70 (m, 1 H) 3.83 (s, 3 H) 3.24 - 3.32 (m, 2 H) 2.57 - 2.76 (m, 4 H) LCMS (*Method g*. ES⁺, RT= 0.413 min) 397.1/399.1 (M+H)⁺

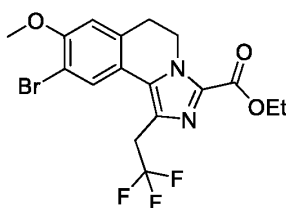
[00880] **INTERMEDIATE 146:** 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline



[00881] A mixture of P₂O₅ (10.72 g, 75.53 mmol) in methanesulfonic acid (60 mL) at 20°C was stirred at 75°C for 0.5 hr. Then *Intermediate 145* (6 g, 15.11 mmol) was added and stirred at 75°C for 1.5 hr. The mixture was cooled and poured into ice-water, then added with NaOH to adjust pH=8, then was extracted with EtOAc (35 mL×3). The combined organic layers were washed with

brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (5.1 g, 93%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.75 (s, 1H), 7.71 (s, 1H), 7.18 (s, 1H), 4.13 (t, J = 6.4 Hz, 2H), 3.88 (s, 3H), 3.84 - 3.75 (m, 2H), 3.00 (br t, J = 6.4 Hz, 2H) LCMS (*Method h*. ES⁺, RT = 1.847 min) 361.0/363.2 (M+H)⁺

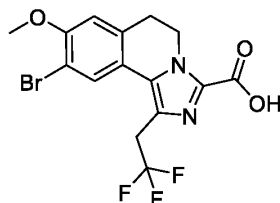
[00882] INTERMEDIATE 147: ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00883] Four batches were carried out in parallel.

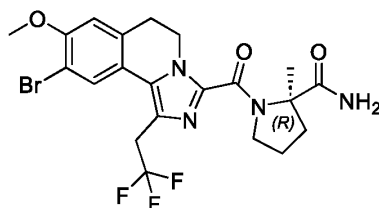
[00884] To a solution of *Intermediate 146* (0.2 g, 553.78 μmol) in THF (3 mL) was added LDA (2 M, 332.27 μL) at -60°C under N₂ and stirred at -60°C for 0.5 hr under N₂. Then added ethyl chloroformate (0.35 g, 3.23 mmol) at -60°C under N₂ and the mixture was stirred at -60°C for 1 hr. The mixture was poured into sat.NaHCO₃ solution (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (0.2 g, 21%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.73 - 7.78 (m, 1 H) 6.76 - 6.79 (m, 1 H) 4.56 - 4.66 (m, 2 H) 4.34 - 4.45 (m, 2 H) 3.85 - 3.90 (m, 3 H) 3.59 - 3.74 (m, 2 H) 2.91 - 3.00 (m, 2 H) 1.33 - 1.41 (m, 3 H). LCMS (*Method a*. ES⁺, RT = 1.808 min) 433.1/435.0 (M+H)⁺

[00885] **INTERMEDIATE 148:** potassium 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00886] To a solution of *Intermediate 147* (130 mg, 300.08 μ mol) in THF (3 mL) was added TMSOK (76.99 mg, 600.16 μ mol) at 20°C and stirred at 20°C for 1 hr. The mixture was concentrated under reduced pressure to give *the title compound* (260 mg, crude) as a brown solid. LCMS (*Method h*, ES^+ , RT = 1.448 min) 405.0/407.0 (M+H)⁺

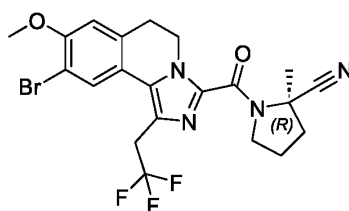
[00887] **INTERMEDIATE 149:** (R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00888] To a solution of *Intermediate 148* (130 mg, 293.28 μ mol) in DMF (2 mL) was added HATU (223.03 mg, 586.57 μ mol), DIEA (227.42 mg, 1.76 mmol) at 20°C and stirred at 20°C for 0.5 hr. Then added (2R)-2-methylpyrrolidine-2-carboxamide (72.43 mg, 439.93 μ mol HCl) at 25°C for 12 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (5 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (120 mg, 79 %) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 0.25 H) 7.72 - 7.80 (m, 1 H) 6.78 - 6.89 (m, 1.7 H) 5.33 - 5.48 (m, 1 H) 4.49 - 4.63 (m, 2.7 H)

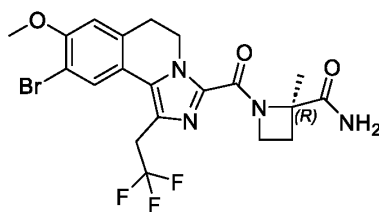
4.07 - 4.35 (m, 4.4 H) 3.91 - 3.96 (m, 4.8 H) 3.60 - 3.74 (m, 2.5 H) 2.93 - 3.05 (m, 3.6 H) 2.39 - 2.52 (m, 1.5 H) 1.86 - 2.03 (m, 4.4 H) 1.77 (br s, 4.8 H) LCMS (*Method a* . ES⁺, RT = 1.588 min) 515.1/517.1 (M+H)⁺

[00889] INTERMEDIATE 150: (R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



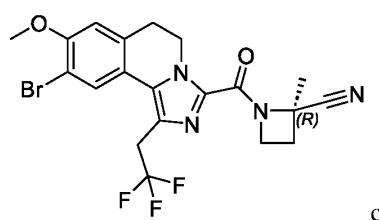
[00890] To a solution of *Intermediate 149* (90 mg, 174.65 μ mol) in THF (1 mL) was added Burgess reagent (83.24 mg, 349.30 μ mol) in DCM (1 mL) at 20°C and stirred at 20°C for 1 hr. The residue was poured into water (5 mL). The aqueous phase was extracted with DCM (5 mL $\times$ 3). The combined organic phase was washed with brine (5 mL $\times$ 2), dried with anhydrous Na₂SO₄. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1//1) to give *the title compound* (70 mg, 81%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (s, 0.2 H) 7.77 (s, 1 H) 6.85 - 6.89 (m, 1 H) 6.81 - 6.84 (m, 0.3 H) 5.38 (d, *J*=5.3 Hz, 0.3 H) 4.68 (br t, *J*=6.5 Hz, 2.4 H) 4.10 - 4.30 (m, 3.6 H) 3.91 - 3.98 (m, 4.5 H) 3.66 (qd, *J*=10.1, 4.6 Hz, 2 H) 3.03 (br t, *J*=6.4 Hz, 3 H) 2.53 - 2.63 (m, 1.5 H) 2.02 - 2.16 (m, 4.6 H) 1.83 - 1.91 (m, 4.4 H) 1.23 - 1.32 (m, 3.6 H) LCMS (*Method s*. ES⁺, RT = 3.247 min) 496.9/498.9 (M+H)⁺

[00891] INTERMEDIATE 151: 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline



[00892] To a solution of *Intermediate 148* (130 mg, 293.28 μ mol) in DMF (2 mL) was added HATU (223.03 mg, 586.57 μ mol), DIEA (227.42 mg, 1.76 mmol) at 20°C and stirred at 20°C for 0.5 hr. Then added *Intermediate 124* (66.26 mg, 439.93 μ mol, HCl) at 25°C for 12 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with EtOAc (5 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (110 mg, 75%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.02 - 8.19 (m, 0.8 H) 7.74 - 7.78 (m, 0.3 H) 7.66 - 7.72 (m, 0.8 H) 6.78 (s, 0.7 H) 6.73 - 6.76 (m, 0.5 H) 5.24 - 5.35 (m, 1 H) 4.57 - 4.76 (m, 3 H) 4.40 - 4.52 (m, 1 H) 4.01 - 4.19 (m, 1 H) 3.83 - 3.92 (m, 4 H) 3.50 - 3.63 (m, 1.8 H) 2.89 - 2.97 (m, 2.4 H) 2.77 - 2.87 (m, 1 H) 2.71 - 2.74 (m, 0.6 H) 2.04 - 2.14 (m, 0.7 H) 1.82 (s, 3 H) LCMS (*Method s*, ES⁺, RT = 2.921 min) 500.9/502.9 (M+H)⁺

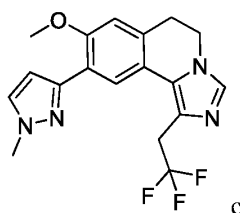
[00893] **INTERMEDIATE 152:** 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline



[00894] To a solution of *Intermediate 151* (90 mg, 179.53 μ mol) in THF (1 mL) was added burgess reagent (85.57 mg, 359.07 μ mol) in DCM (1 mL) at 20°C and stirred at 20°C for 1 hr. The residue was poured into water (5 mL). The aqueous phase was extracted with DCM (5mL $\times$ 3). The combined organic phase was washed with brine (5 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (60 mg, 69%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 0.4 H) 7.79 (s, 0.2 H) 7.76 (s, 1 H) 6.93 - 7.03 (m, 1.5 H) 6.86 (s, 1.3 H) 6.82 (s, 0.5 H) 5.37 (d, *J*=5.4 Hz, 0.4 H) 5.02 (s, 0.6 H) 4.63 - 4.88 (m, 6.7 H) 4.14 - 4.23 (m, 1 H) 3.92 - 3.98 (m, 5.53 H) 3.76 (br t, *J*=6.4 Hz, 2 H) 3.57

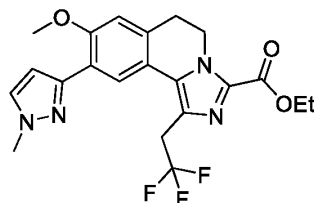
- 3.69 (m, 2.6 H) 2.95 - 3.06 (m, 4 H) 2.86 (ddd, $J=11.5, 8.8, 6.3$ Hz, 1.6 H) 2.38 - 2.47 (m, 1.7 H) 2.28 (s, 1.9 H) 1.92 - 1.98 (m, 4.6 H) 1.84 - 1.90 (m, 2 H) 1.55 (s, 7 H) LCMS (*Method s*. ES^+ , RT = 1.847 min) 361.0/363.2 (M+H)⁺

[00895] INTERMEDIATE 153: 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline



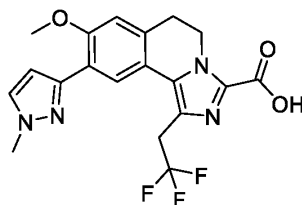
[00896] To a solution of *Intermediate 146* (300 mg, 830.66 μ mol) 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (190.11 mg, 913.73 μ mol) in dioxane (6 mL) and H₂O (1.2 mL) was added XPHOS-Pd-G₂ (65.36 mg, 83.07 μ mol), Cs₂CO₃ (1.08 g, 3.32 mmol) at 20°C and stirred at 80°C for 3 hr. The residue was poured into ice-water (10 mL). The aqueous phase was extracted with EtOAc(5 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (260 mg, 86%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.13 - 8.20 (m, 1 H) 7.52 (s, 1 H) 7.41 (d, $J=2.13$ Hz, 1 H) 6.88 (s, 1 H) 6.72 (d, $J=2.25$ Hz, 1 H) 4.11 - 4.19 (m, 2 H) 3.98 (s, 3 H) 3.93 (s, 3 H) 3.75 (q, $J=10.51$ Hz, 2 H) 3.09 (t, $J=6.38$ Hz, 2 H) LCMS (*Method a*. ES^+ , RT = 1.209 min) 363.3/364.3 (M+H)⁺

[00897] **INTERMEDIATE 154:** ethyl 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[00898] To a solution of *Intermediate 153* (170 mg, 469.16 μ mol) in THF (2 mL) was added LDA (2 M, 351.87 μ L) at -60°C . The mixture was added ethyl formate (173.77 mg, 2.35 mmol) at -60°C and the mixture was stirred at -60°C for 2 hr. The mixture was added H_2O (10 mL) and extracted with EtOAc (5 mL $\times$ 3). The organic layers were concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 1/1) to give *the title compound* (70 mg, 34%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.25 (s, 1H), 7.72 (d, $J = 2.1$ Hz, 1H), 7.18 (s, 1H), 6.70 (d, $J = 2.1$ Hz, 1H), 4.59 (br t, $J = 6.5$ Hz, 2H), 4.33 (q, $J = 7.0$ Hz, 2H), 3.95 - 3.79 (m, 10H), 3.08 (br t, $J = 6.4$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H). LCMS (*Method e*, ES^+ , $\text{RT} = 0.461$ min) 435.2/436.2 ($\text{M}+\text{H}$) $^+$

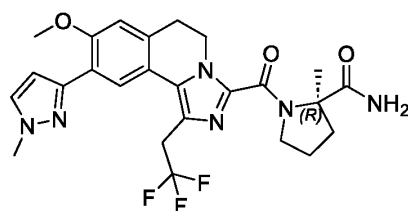
[00899] **INTERMEDIATE 155:** 8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[00900] To a solution of *Intermediate 154* (70 mg, 161.14 μ mol) in THF (1 mL) was added TMSOK (41.34 mg, 322.28 μ mol). The mixture was stirred at 20°C for 2 hr. The reaction

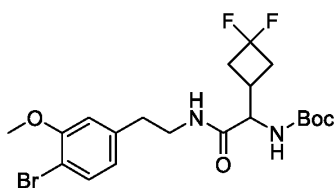
mixture was concentrated under reduced pressure to give *the title compound* (65 mg, crude) as a yellow solid. LCMS (*Method e*. ES⁺, RT = 0.342 min) 407.2/408.2 (M+H)⁺

[00901] INTERMEDIATE 156: (R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00902] To a solution of *Intermediate 155* (65 mg, 159.96 μmol) and (2R)-2-methylpyrrolidine-2-carboxamide (31.60 mg, 191.95 μmol, HCl) in DMF (1 mL) was added HATU (66.90 mg, 175.95 μmol) and DIEA (62.02 mg, 479.87 μmol) at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc (2 mL×3). The organic layers were concentrated under reduced pressure to give *the title compound* (60 mg, crude) as a yellow oil. LCMS (*Method e*. ES⁺, RT = 0.396 min) 517.3/518.3 (M+H)⁺

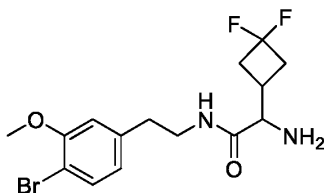
[00903] INTERMEDIATE 157: tert-butyl (2-((4-bromo-3-methoxyphenethyl)amino)-1-(3,3-difluorocyclobutyl)-2-oxoethyl)carbamate



[00904] To a solution of 2-(tert-butoxycarbonylamino)-2-(3,3-difluorocyclobutyl) acetic acid (7.31 g, 27.57 mmol) in DCM (35 mL) was added CDI (6.39 g, 39.39 mmol) at 20°C for 12 hr, and added *Intermediate 212* (7 g, 26.26 mmol, HCl), DIEA (6.79 g, 52.52 mmol). The mixture was stirred at 20°C for 2 hr. The mixture was added with 30 mL H₂O. The aqueous layer was extracted with DCM (20 mL×3). The combined organic phase was washed with brine (10 mL×2),

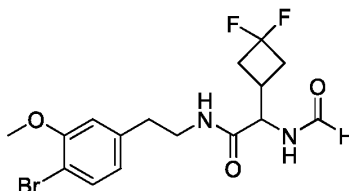
dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=80/1 to 20/1) to give *the title compound* (7 g, 56%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J*=8.00 Hz, 1 H) 6.74 (d, *J*=1.25 Hz, 1 H) 6.67 (dd, *J*=7.94, 1.44 Hz, 1 H) 6.11 - 6.21 (m, 1 H) 5.00 (br s, 1 H) 4.04 (br t, *J*=8.00 Hz, 1 H) 3.90 (s, 3 H) 3.47 - 3.57 (m, 2 H) 2.78 (t, *J*=7.07 Hz, 2 H) 2.54 - 2.71 (m, 2 H) 2.30 - 2.52 (m, 3 H) 1.44 (s, 9 H) LCMS (*Method 1*, ES⁺, RT = 0.521 min) 479.1/477.2 (M+H)⁺

[00905] INTERMEDIATE 158: 2-amino-N-(4-bromo-3-methoxyphenethyl)-2-(3,3-difluorocyclobutyl)acetamide



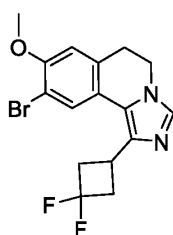
[00906] To a solution of *Intermediate 157* (7 g, 14.66 mmol) in EtOAc (35 mL) was added HCl/EtOAc (4 M, 75.35 mL). The mixture was stirred at 20°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (6 g, 99%, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (br t, *J*=5.44 Hz, 1 H) 8.41 (br s, 3 H) 7.46 (d, *J*=8.00 Hz, 1 H) 7.01 (d, *J*=1.75 Hz, 1 H) 6.76 (dd, *J*=8.00, 1.75 Hz, 1 H) 3.84 (s, 3 H) 3.78 (br d, *J*=7.63 Hz, 1 H) 3.49 (dq, *J*=13.38, 6.88 Hz, 1 H) 3.22 - 3.40 (m, 2 H) 2.72 - 2.76 (m, 1 H) 2.56 - 2.65 (m, 2 H) 2.30 - 2.41 (m, 2 H) LCMS (*Method 1*, ES⁺, RT = 0.357 min) 379.0/377.0 (M+H)⁺

[00907] INTERMEDIATE 159: N-(4-bromo-3-methoxyphenethyl)-2-(3,3-difluorocyclobutyl)-2-formamidoacetamide



[00908] To a solution of *Intermediate 158* (1 g, 2.42 mmol, HCl) in ethyl formate (8.14 g, 109.90 mmol) and MeOH (1 mL) was added Et₃N (489.21 mg, 4.83 mmol). The mixture was stirred at 75°C for 24 hr. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with H₂O (20 mL) and added with HCl (0.5 mol) to adjust pH=5, then the mixture was extracted with EtOAc(10 mL×3). The combined organic layers were washed with brine 10 mL (5 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (0.7 g, 71%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (br d, *J*=8.63 Hz, 1 H) 8.20 (br t, *J*=5.32 Hz, 1 H) 8.05 (s, 1 H) 7.44 (d, *J*=8.13 Hz, 1 H) 6.95 (d, *J*=1.38 Hz, 1 H) 6.73 (dd, *J*=8.00, 1.50 Hz, 1 H) 4.40 (br t, *J*=7.75 Hz, 1 H) 3.83 (s, 3 H) 3.34 - 3.41 (m, 1 H) 3.24 - 3.31 (m, 1 H) 2.69 (br t, *J*=6.94 Hz, 2 H) 2.26 - 2.47 (m, 5 H) LCMS (*Method 1*. ES⁺, RT = 0.413 min) 407.1/405.1 (M+H)⁺

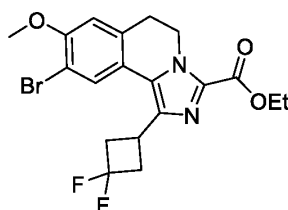
[00909] INTERMEDIATE 160: 9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-*a*]isoquinoline



[00910] A mixture of P₂O₅ (1.23 g, 8.64 mmol) in methanesulfonic acid (7 mL) was stirred at 75°C for 0.5 hr, and was added *Intermediate 159* (0.7 g, 1.73 mmol). The mixture was stirred

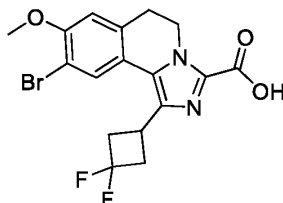
at 75°C for 2 hr. The residue was poured into cooled sat. Na₂CO₃ to pH=8. The aqueous phase was extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated to give *the title compound* (580 mg, 91%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (s, 1 H) 7.59 (s, 1 H) 7.16 (s, 1 H) 4.10 (t, *J*=6.38 Hz, 2 H) 3.87 (s, 3 H) 3.54 - 3.65 (m, 1 H) 2.78 - 3.03 (m, 6 H) LCMS (*Method l*. ES⁺, RT = 0.367 min) 369.0/371.0 (M+H)⁺

[00911] INTERMEDIATE 161: ethyl 9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



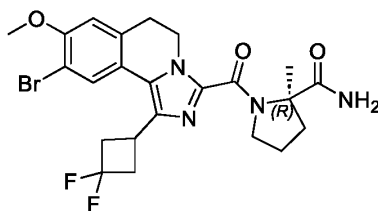
[00912] To a solution of *Intermediate 160* (0.25 g, 677.13 μmol) in THF (2.5 mL) was added LDA (2 M, 406.28 μL) at -60°C under N₂ and stirred at -60°C for 0.5 hr under N₂. Then added ethyl chloroformate (0.37 g, 3.41 mmol) at -60°C under N₂ and the mixture was stirred at -60°C for 2 hr. The mixture was poured into sat. NaHCO₃ solution (5 mL). The aqueous phase was extracted with EtOAc (5 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (0.2 g, 67%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.59 - 7.64 (m, 1 H) 6.83 - 6.88 (m, 1 H) 4.60 - 4.71 (m, 2 H) 4.46 (q, *J*=7.1 Hz, 2 H) 3.92 - 3.99 (m, 3 H) 3.53 - 3.66 (m, 1 H) 2.94 - 3.18 (m, 6 H) 1.46 (t, *J*=7.1 Hz, 3 H) LCMS (*Method a*. ES⁺, RT = 1.945 min) 444.1/443.0 (M+H)⁺

[00913] **INTERMEDIATE 162:** 9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[00914] To a solution of *Intermediate 161* (150 mg, 339.93 μmol) in THF (3 mL) was added TMSOK (87.22 mg, 679.86 μmol) at 20°C and stirred at 20°C for 1 hr. The mixture was concentrated under reduced pressure to give *the title compound* (150 mg, crude) as a brown solid. LCMS (*Method 1*, ES⁺, RT = 0.394 min) 415.0/417.0 (M+H)⁺

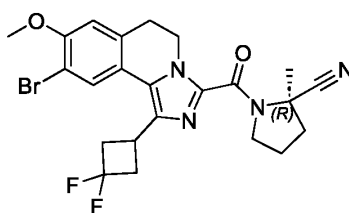
[00915] **INTERMEDIATE 163:** (R)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00916] To a solution of *Intermediate 162* (150 mg, 332.37 μmol), (2R)-2-methylpyrrolidine-2-carboxamide (82.08 mg, 498.56 μmol , HCl) in DMF (3 mL) was added HATU (139.02 mg, 365.61 μmol), DIEA (171.82 mg, 1.33 mmol) at 20°C and stirred at 40°C for 12 hr. Then added (2R)-2-methylpyrrolidine-2-carboxamide (54.72 mg, 332.37 μmol , HCl), HATU (88.46 mg, 232.66 μmol), DIEA (85.91 mg, 664.74 μmol) at 40°C for 2 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with EtOAc (5 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (130 mg, 75%) as a yellow solid.

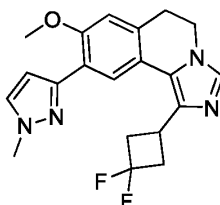
^1H NMR (400 MHz, CDCl_3) δ 7.59 (s, 1 H) 6.84 (s, 1 H) 6.52 (br d, $J=5.9$ Hz, 1 H) 5.35 - 5.51 (m, 1 H) 4.47 - 4.70 (m, 2 H) 4.18 - 4.41 (m, 2 H) 3.90 - 3.97 (m, 3 H) 3.56 - 3.67 (m, 1 H) 2.93 - 3.12 (m, 6 H) 2.48 (dt, $J=12.2, 6.2$ Hz, 1 H) 2.00 - 2.14 (m, 3 H) 1.72 - 1.82 (m, 3 H) LCMS (*Method a* . ES^+ , RT = 1.700 min) 545.1/547.1 (M+H) $^+$

[00917] INTERMEDIATE 164: (R)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



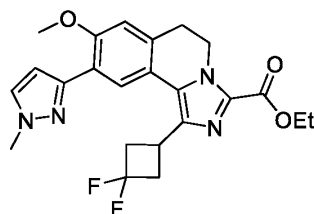
[00918] To a solution of *Intermediate 163* (110 mg, 210.18 μmol) in THF (2 mL) was added burgess reagent (100.17 mg, 420.35 μmol) in DCM (2 mL) at 20°C and stirred at 20°C for 2 hr. The residue was poured into water (5 mL). The aqueous phase was extracted with DCM (5 mL $\times$ 3). The combined organic phase was washed with brine (5 mL $\times$ 2), dried with anhydrous Na_2SO_4 . The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1//1) to give *the title compound* (100 mg, 94%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.57 - 7.65 (m, 1 H) 6.87 - 6.88 (m, 1 H) 4.69 - 4.82 (m, 1 H) 4.58 (dt, $J=14.0, 7.0$ Hz, 1 H) 4.16 - 4.35 (m, 2 H) 3.94 (s, 3 H) 3.61 (td, $J=8.6, 2.7$ Hz, 1 H) 2.95 - 3.07 (m, 6 H) 2.55 - 2.64 (m, 1 H) 2.08 - 2.18 (m, 3 H) 1.89 (s, 3 H) 1.55 (s, 4 H). LCMS (*Method l*. ES^+ , RT = 0.595 min) 507.2/505.2(M+H) $^+$

[00919] **INTERMEDIATE 165:** 1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



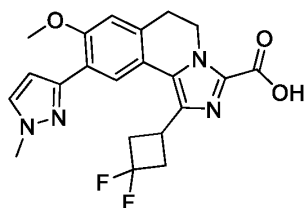
[00920] To a solution of *Intermediate 160* (300 mg, 812.56 μ mol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (185.97 mg, 893.82 μ mol), XPHOS-Pd-G₂ (63.93 mg, 81.26 μ mol), Cs₂CO₃ (1.06 g, 3.25 mmol) in dioxane (2.5 mL) and H₂O (0.5 mL) was degassed and purged with N₂ for 3 min, and then the mixture was stirred at 80°C for 2 hr under N₂ atmosphere. The residue was poured into water (10 mL). The aqueous phase was extracted with DCM (5 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1 to 1/1) to give *the title compound* (200 mg, 66%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 (s, 1 H) 7.71 (d, *J*=1.75 Hz, 1 H) 7.65 (s, 1 H) 7.10 (s, 1 H) 6.70 (d, *J*=2.13 Hz, 1 H) 4.13 (br t, *J*=6.25 Hz, 2 H) 3.86 - 3.96 (m, 6 H) 3.53 - 3.65 (m, 1 H) 2.87 - 3.06 (m, 6 H) LCMS (*Method h*. ES⁺, RT = 1.787 min) 371.2/372.2 (M+H)⁺

[00921] **INTERMEDIATE 166:** ethyl 1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



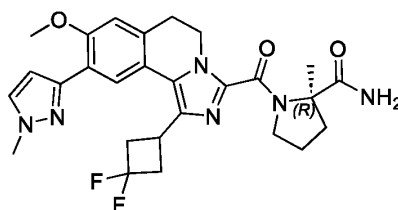
[00922] To a solution of *Intermediate 165* (220 mg, 593.96 μ mol) in THF (2 mL) was added LDA (2 M, 326.68 μ L) at -60°C . The mixture was added ethyl formate (220.00 mg, 2.97 mmol) at -60°C and the mixture was stirred at -60°C for 2 hr. The residue was poured into water (5 mL). The aqueous phase was extracted with EtOAc (5mL $\times$ 3). The combined organic phase was washed with brine (5 mL $\times$ 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 1/1) to give *the title compound* (70 mg, 27%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.09 (s, 1 H) 7.72 (d, $J=2.03$ Hz, 1 H) 7.16 (s, 1 H) 6.72 (d, $J=1.91$ Hz, 1 H) 4.58 (br t, $J=6.56$ Hz, 2 H) 4.30 - 4.39 (m, 2 H) 3.91 (d, $J=3.34$ Hz, 6 H) 2.94 - 3.11 (m, 6 H) 1.34 (t, $J=7.03$ Hz, 3 H) LCMS (*Method e*. ES^+ , RT = 0.498 min) 443.2/444.3 ($\text{M}+\text{H}$) $^+$

[00923] **INTERMEDIATE 167:** 1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



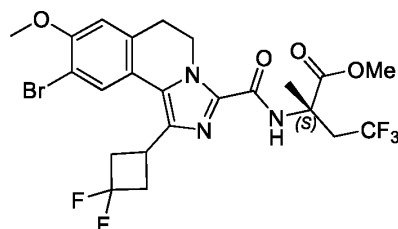
[00924] To a solution of *Intermediate 166* (70 mg, 158.21 μ mol) in THF (1 mL) was added TMSOK (40.59 mg, 316.41 μ mol). The mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give *the title compound* (65 mg, crude) as a yellow solid. LCMS (*Method e*. ES^+ , RT = 0.358 min) 415.2/416.2 ($\text{M}+\text{H}$) $^+$

[00925] **INTERMEDIATE 168:** (R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00926] To a solution of *Intermediate 167* (65 mg, 156.85 μ mol) and (2R)-2-methylpyrrolidine-2-carboxamide (30.99 mg, 188.22 μ mol, HCl) in DMF (1 mL) was added HATU (65.60 mg, 172.54 μ mol) and DIEA (60.81 mg, 470.55 μ mol) at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was added H₂O (10 mL) and extracted with EtOAc (5 mL $\times$ 3). The organic layers were concentrated under reduced pressure to give *the title compound* (60 mg, 73%) as a yellow solid. LCMS (*Method g*, ES⁺, RT = 0.442 min) 525.2/526.2 (M+H)⁺

[00927] **INTERMEDIATE 169:** methyl (S)-2-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoate

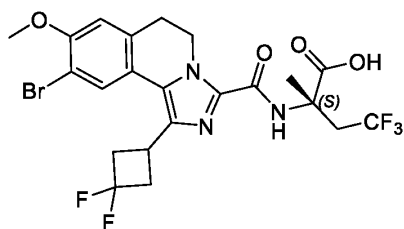


[00928] Step A: To a solution of *Intermediate 168* (1.5 g, 3.32 mmol) in THF (10 mL) was added HATU (2.53 g, 6.65 mmol) at 20°C. The mixture was stirred at 20°C for 30 min.

[00929] Step B: To a solution of *Intermediate 115* (957.51 mg, 4.32 mmol) in DMF (10 mL) was added Na₂CO₃ (1.06 g, 9.97 mmol). The mixture was stirred at 20°C for 30 min.

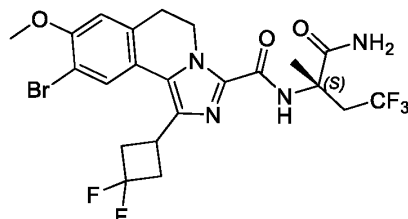
[00930] Step C: The mixture from step A was added dropwise to the mixture B mixture at 20°C. The mixture was stirred at 20°C for 11 hr. The mixture was added with 10 mL H₂O, then it was extracted with EtOAc (15 mL×3), the combined organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EtOAc = 100/0 to 50/50) to give *the title compound* (1.35 g, 70%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.20 - 8.14 (m, 1H), 7.59 (s, 1H), 6.84 (s, 1H), 4.68 (t, J = 6.6 Hz, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.80 (s, 2H), 3.63 - 3.55 (m, 1H), 3.39 - 3.26 (m, 2H), 3.01 - 2.97 (m, 2H), 1.79 (s, 3H), 1.62 (s, 2H) LCMS (*Method l*. ES⁺, RT = 0.623 min) 580.2/582.2 (M+H)⁺

[00931] **INTERMEDIATE 170:** (S)-2-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



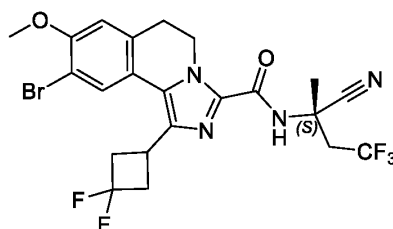
[00932] To a solution of *Intermediate 169* (0.5 g, 861.56 μmol) in THF (5 mL) was added TMSOK (221.05 mg, 1.72 mmol). The mixture was added with HCl (0.5 mol) to adjust pH=5, then mixture was diluted with H₂O (20 mL) and extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine 10 mL (5 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (900 mg, crude) as a yellow foam. LCMS (*Method g*. ES⁺, RT = 0.564 min) 566.1/568.1 (M+H)⁺

[00933] **INTERMEDIATE 171:** (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



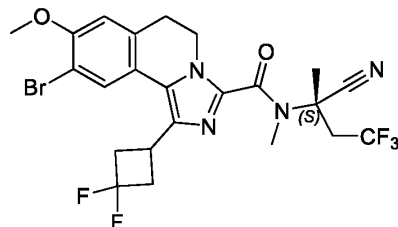
[00934] To a solution of *Intermediate 170* (0.8 g, 1.41 mmol) in THF (1 mL) was added CDI (343.59 mg, 2.12 mmol) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (247.54 mg, 4.24 mmol, 60%). The mixture was stirred at 25°C for 2 h. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give *the title compound* (700 mg, crude) as a yellow solid. LCMS (*Method g*, ES^+ , RT = 0.559 min) 565.1/567.1 (M+H)⁺

[00935] **INTERMEDIATE 172:** (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



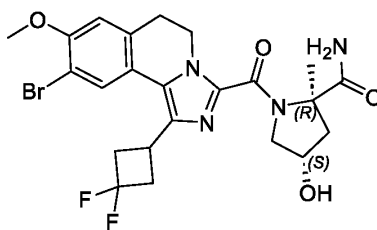
[00936] To a solution of *Intermediate 171* (0.6 g, 1.06 mmol) in THF (3 mL) and DCM (3 mL) was added Burgess reagent (505.84 mg, 2.12 mmol). The mixture was stirred at 30°C for 2 hr. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , PE/EtOAc = 10/1 to 1/1) to give *the title compound* (450 mg, 78%) as a white solid.

[00937] **INTERMEDIATE 173:** (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(3,3-difluorocyclobutyl)-8-methoxy-N-methyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide



[00938] DMF (3 mL) was charged to the three-necked round bottom flask, then starting *Intermediate 172* (0.3 g, 548.13 μ mol) was added to the mixture at 0°C for 10 min. At 0°C inner temperature NaH (32.88 mg, 822.20 μ mol, 60% purity) was added to the reaction mixture at 0°C within 10 min. Then CH₃I (155.60 mg, 1.10 mmol) was added. After the addition, the mixture was stirred at 70°C for 2 hr. The reaction was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EA = 1/0 to 2/1) to give *the title compound* (200 mg, 65%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.04 - 2.10 (m, 3 H) 2.94 - 3.08 (m, 6 H) 3.11 - 3.23 (m, 1 H) 3.25 - 3.36 (m, 1 H) 3.58 - 3.64 (m, 4 H) 3.95 (s, 3 H) 4.37 - 4.55 (m, 2 H) 6.85 (s, 1 H) 7.58 - 7.62 (m, 1 H) LCMS (*Method 1*, ES⁺, RT = 0.600 min) 561.2/563.2 (M+H)⁺

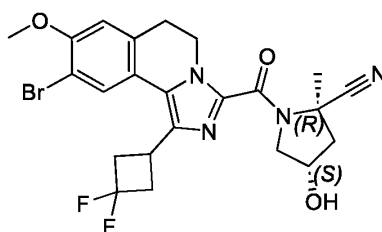
[00939] **INTERMEDIATE 174:** (2R,4S)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carboxamide



[00940] To a solution of *Intermediate 162* (1 g, 2.22 mmol) in DMF (10 mL) was added HATU (1.69 g, 4.43 mmol) at 20°C. The mixture was stirred at 20°C for 30 min (mixture A).

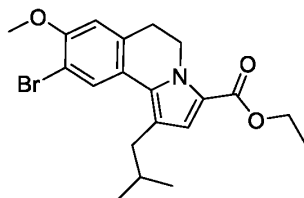
[00941] To a solution of *Intermediate 256* (520.32 mg, 2.88 mmol, HCl) in DMF (10 mL) was added Na₂CO₃ (469.70 mg, 4.43 mmol). The mixture was stirred at 20°C for 30 min (mixture B). The mixture A was added dropwise to the mixture B mixture at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was diluted with H₂O 20 mL and extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine (15 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was triturated with MTBE at 20°C for 30 min to give *the title compound* (700 mg, 59%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.63 (s, 1 H), 7.19 (s, 1 H), 7.11 (br s, 1 H), 6.83 (br s, 1 H), 5.13 (d, J=3.70 Hz, 1 H), 4.27 - 4.45 (m, 3 H), 4.13 - 4.23 (m, 1 H), 4.02 - 4.12 (m, 1 H), 3.88 (s, 3 H), 3.69 (m, 1 H), 2.84 - 3.06 (m, 6 H), 2.19 (m, 1 H), 1.82 (m, 1 H), 1.65 (s, 3 H) LCMS (*Method 1*, ES⁺, RT = 0.426 min) 539.1/541.1 (M+H)⁺

[00942] **INTERMEDIATE 175:** (2R,4S)-1-(9-bromo-1-(3,3-difluorocyclobutyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile



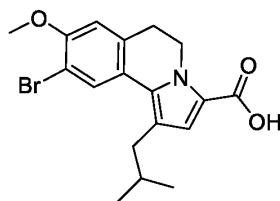
[00943] To a solution of *Intermediate 174* (250 mg, 463.50 μmol) in pyridine (2.5 mL) was added TFAA (778.80 mg, 3.71 mmol) at 20°C. The mixture was stirred at 20°C for 1 hr. The reaction mixture was poured into water, then the mixture was added with 1M HCl to adjust pH=3 and extracted with MTBE (20 mL×3). The combined organic layers were washed with brine (20 mL×3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (200 mg, 83%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 1 H), 6.88 (s, 1 H), 4.65 - 4.70 (m, 1 H), 4.54 - 4.64 (m, 2 H), 4.42 (br d, J=13.35 Hz, 1 H), 4.17 (m, 1 H), 3.94 - 3.99 (m, 3 H), 3.68 (m, 1 H), 3.06 (br t, J=6.32 Hz, 4 H), 2.76 (m, 1 H), 2.35 (m, 1 H), 2.01 (s, 3 H), 1.25 (s, 3 H) LCMS (*Method 1*, ES⁺, RT = 0.519 min) 521.2/523.2 (M+H)⁺

[00944] **INTERMEDIATE 176:** ethyl 9-bromo-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00945] To a solution of *Intermediate 39* (11.97 g, 30.99 mmol) in Ac₂O (70 mL) was added 4-methylpent-1-yne (3.31 g, 40.29 mmol, 4.74 mL) at 20°C. The mixture was stirred at 140°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was added with Na₂CO₃ to adjust pH=8, then mixture was extracted with EtOAc 100 mL (50 mL×2). The combined organic layers were washed with brine 80 mL (40 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1). The crude product was triturated with PE at 20 °C for 30 min. Then it was filtered to give *the title compound* (17 g, 67.49%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.94 (d, J=6.63 Hz, 6 H), 1.28 (t, J=7.07 Hz, 3 H), 1.82 (dt, J=13.26, 6.63 Hz, 1 H), 2.53 (br s, 2 H), 2.99 (br t, J=6.44 Hz, 2 H), 3.88 (s, 3 H), 4.22 (q, J=7.13 Hz, 2 H), 4.37 - 4.59 (m, 2 H), 6.75 (s, 1 H), 7.16 (s, 1 H), 7.69 (s, 1 H). LCMS (*Method 1*, ES⁺, RT = 0.74 min) 406.1/408.1 (M+H)⁺

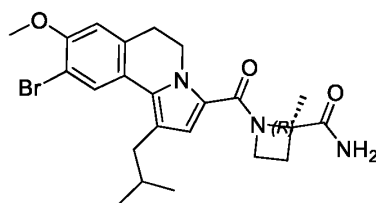
[00946] **INTERMEDIATE 177:** 9-bromo-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00947] To a solution of *Intermediate 176* (2.5 g, 6.15 mmol) in EtOH (10 mL) and THF (10 mL) was added KOH (1.04 g, 18.46 mmol) in H₂O (10 mL). The mixture was stirred at 80

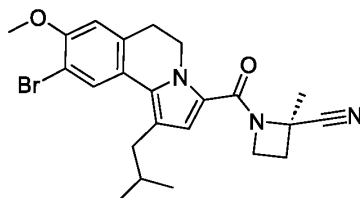
°C for 5hr. The reaction mixture was adjust pH=3 with 1M HCl. The reaction mixture was filtered. The filtrate was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The filter cake was washed three times with toluene and concentrated under reduced pressure to give *the title compound* (2.06 g, crude) was obtained as a pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.25 (br s, 1 H), 7.67 (s, 1 H), 7.15 (s, 1 H), 6.67 - 6.74 (m, 1 H), 4.40 - 4.58 (m, 2 H), 3.82 - 3.93 (m, 4 H), 2.93 - 3.06 (m, 2 H), 2.55 - 2.62 (m, 1 H), 2.52 (br s, 1 H), 1.72 - 1.91 (m, 1 H), 0.92 - 1.00 (m, 6 H), 0.87 - 0.91 (m, 1 H). LCMS (*Method e*. ES⁺, RT = 0.57 min) 378.0/380.0 (M+H)⁺

[00948] INTERMEDIATE 178: (R)-1-(9-bromo-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



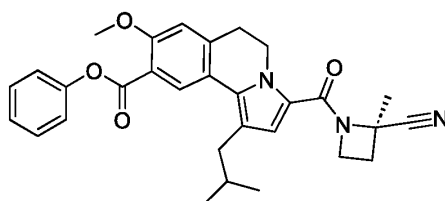
[00949] To a solution of *Intermediate 177* (1.65 g, 4.36 mmol) and *Intermediate 124* (597.49 mg, 5.23 mmol) in DMF (15 mL) was added HATU (1.99 g, 5.23 mmol) and DIEA (2.26 g, 17.45 mmol, 3.04 mL). The mixture was stirred at 20°C for 2 hr. The combined reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH=5-6. The reaction mixture was extracted with EtOAc 60 mL (20 mL×3). The combined organic layers were washed with brine 40 mL (20 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE at 20°C for 10 min. Then filtered, the filter cake was dried under reduced pressure to give *the title compound* (1.8 g, 86.98%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.73 - 7.55 (m, 2H), 7.27 - 7.09 (m, 2H), 6.51 (br s, 1H), 4.56 - 4.24 (m, 4H), 3.90 - 3.83 (m, 3H), 2.99 - 2.87 (m, 2H), 2.55 - 2.52 (m, 2H), 2.48 - 2.39 (m, 1H), 2.10 - 1.98 (m, 1H), 1.88 - 1.76 (m, 1H), 1.67 (br s, 3H), 1.40 (s, 1H), 0.99 - 0.92 (m, 7H). LCMS (*Method I*. ES⁺ RT = 0.563 min) 474.2/476.2 (M+H)⁺.

[00950] **INTERMEDIATE 179:** (R)-1-(9-bromo-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile



[00951] To a solution of *Intermediate 178* (1.8 g, 3.79 mmol) in pyridine (17 mL) was added TFAA (6.38 g, 30.35 mmol, 4.22 mL). The mixture was stirred at 20°C for 2 hr. The combined reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH=2-3. The reaction mixture was extracted with EtOAc 60 mL (20 mL×3). The combined organic layers were washed with brine 40 mL (20 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE at 20°C for 10 min. Then filtered, the filter cake was concentrated under reduced pressure to give *the title compound* (1.6 g, 92%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.72 - 7.64 (m, 1H), 7.19 - 7.11 (m, 1H), 6.57 - 6.47 (m, 1H), 4.57 - 4.34 (m, 4H), 3.88 (s, 3H), 2.96 (t, J = 6.4 Hz, 2H), 2.73 (ddd, J = 6.0, 9.0, 11.5 Hz, 1H), 2.56 - 2.53 (m, 1H), 2.52 (br d, J = 2.0 Hz, 2H), 2.46 - 2.38 (m, 1H), 1.87 - 1.78 (m, 4H), 0.98 - 0.90 (m, 6H). LCMS (*Method 1*, ES⁺ RT = 0.643 min) 456.2/458.1 (M+H)⁺.

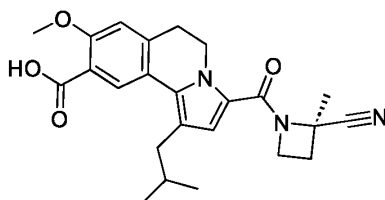
[00952] **INTERMEDIATE 180:** phenyl (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylate



[00953] To a solution of *Intermediate 179* (500 mg, 1.10 mmol), 2-phenylacetaldehyde (789.80 mg, 6.57 mmol, 512.86 μL), TEA (665.17 mg, 6.57 mmol, 914.95 μL), Pd(dppf)Cl₂·CH₂Cl₂ (89.47 mg, 109.56 μmol) in DMF (5 mL) was degassed and purged with N₂ for 3 times at 20°C, and then

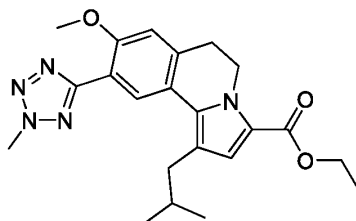
the mixture was stirred at 120°C for 12 h. The combined reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH = 5-6. The reaction mixture was extracted with EtOAc 60 mL (20 mL × 3). The combined organic layers were washed with brine 40 mL (20 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc = 3/1 to 0/1) to give *the title compound* (1.2 g, 73%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.21 (s, 1H), 7.55 - 7.42 (m, 2H), 7.35 - 7.22 (m, 4H), 6.62 - 6.52 (m, 1H), 5.81 - 5.71 (m, 1H), 4.61 - 4.47 (m, 2H), 4.46 - 4.35 (m, 2H), 3.92 (s, 3H), 3.15 - 3.04 (m, 2H), 2.80 - 2.69 (m, 1H), 2.57 (br d, J = 6.8 Hz, 2H), 2.47 - 2.38 (m, 1H), 1.92 - 1.79 (m, 4H), 0.98 - 0.89 (m, 6H). LCMS (*Method g*, ES⁺ RT = 0.609 min) 498.2/499.3 (M+H)⁺.

INTERMEDIATE 181: (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylic acid



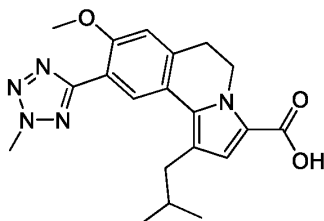
[00954] To a solution of *Intermediate 180* (600 mg, 1.21 mmol) in THF (10 mL) was added TMSOK (309.38 mg, 2.41 mmol). The mixture was stirred at 20°C for 2hr. The combined reaction mixture was poured into ice-water (10 mL) and added 1 M HCl to pH = 5-6. The reaction mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine 40 mL (20 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (450 mg, 88%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.99 (br d, J=6.38 Hz, 6 H), 1.81 (s, 3 H), 1.84 - 1.94 (m, 1 H), 2.39 - 2.47 (m, 1 H), 2.60 (br d, J=6.75 Hz, 2 H), 2.68 - 2.74 (m, 1 H), 3.07 (br t, J=6.25 Hz, 2 H), 4.08 (s, 3 H), 4.37 - 4.60 (m, 4 H), 6.27 (t, J=6.88 Hz, 1 H), 6.56 (s, 1 H), 7.13 (dd, J=6.50, 1.38 Hz, 1 H), 7.29 (s, 1 H), 8.31 - 8.55 (m, 2 H), 10.88 (s, 1 H), 11.99 (br s, 1 H). LCMS (*Method g*, RT = 0.493 min) 422.2/423.2 (M+H)⁺.

[00955] **INTERMEDIATE 182:** ethyl 1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



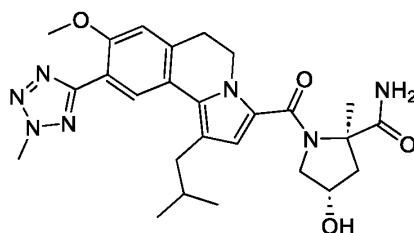
[00956] A mixture of *Intermediate 176* (2 g, 4.92 mmol), *Intermediate 26* (3.67 g, 9.84 mmol) and XPHOS-Pd-G2 (387.29 mg, 492.23 μ mol) in DMF (5 mL) was degassed and purged with Ar for 3 times, and then the mixture was stirred at 120°C for 12 hr under Ar atmosphere. The reaction mixture was poured into H₂O (20 mL) and added 10% KF (20 mL). The mixture was stirred 5 min and filtered. Then it was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 61/39). Then organic layers was concentrated under reduced pressure to give *the title compound* (1.06 g, 53%) was obtained as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.15 (s, 1 H), 7.21 - 7.29 (m, 1 H), 6.73 - 6.80 (m, 1 H), 4.49 - 4.59 (m, 2 H), 4.38 - 4.45 (m, 3 H), 4.17 - 4.28 (m, 2 H), 3.84 - 3.98 (m, 3 H), 3.07 - 3.15 (m, 2 H), 2.52 - 2.62 (m, 2 H), 1.77 - 1.92 (m, 1 H), 1.22 - 1.36 (m, 3 H), 0.91 - 1.00 (m, 6 H). LCMS (*Method a*. RT = 2.144 min) 409.2/410.2 (M+H)⁺

[00957] **INTERMEDIATE 183:** 1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00958] To a solution of *Intermediate 182* (0.8 g, 1.95 mmol) in EtOH (3 mL), THF (3 mL) and H₂O (3 mL) was added KOH (328.84 mg, 5.86 mmol). The mixture was stirred at 90°C for 2 hr. The reaction mixture was poured into H₂O 5 mL and adjust pH=3 with 1M HCl. The reaction mixture was filtered. The filtrate was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The filter cake was dried under reduced pressure to give *the title compound* (0.7 g, 94%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.23 (br s, 1 H), 7.99 - 8.33 (m, 1 H), 7.24 (s, 1 H), 6.63 - 6.85 (m, 1 H), 4.49 - 4.60 (m, 2 H), 4.37 - 4.45 (m, 3 H), 3.85 - 3.94 (m, 3 H), 3.01 - 3.13 (m, 2 H), 2.52 - 2.62 (m, 2 H), 1.78 - 1.93 (m, 1 H), 0.88 - 1.02 (m, 6 H). LCMS (*Method a*. RT = 1.161 min) 381.2/382.2 (M+H)⁺.

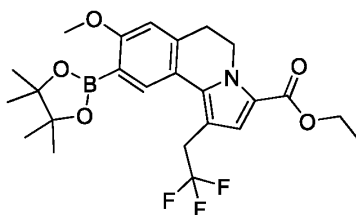
[00959] **INTERMEDIATE 184:** (2R,4S)-4-hydroxy-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[00960] To a solution of *Intermediate 183* (350 mg, 917.61 μmol) in DMF (5 mL) was added HATU (418.68 mg, 1.10 mmol) and TEA (278.55 mg, 2.75 mmol, 383.16 μL). The mixture was

stirred at 25°C for 0.5 hr. Then the mixture was added *Intermediate 256* (215.47 mg, 1.19 mmol, HCl salt). The mixture was stirred at 45°C for 12 hr. The reaction mixture was poured into H₂O 5 mL and adjust pH=7 with 1M HCl. The reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =100/0 to 5/95). *The title compound* (200 mg, 43%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.11 (s, 1 H), 7.21 (s, 1 H), 7.09 (br s, 1 H), 6.76 - 6.86 (m, 1 H), 6.46 (s, 1 H), 4.38 - 4.44 (m, 3 H), 4.29 - 4.33 (m, 1 H), 4.25 (br t, *J*=5.75 Hz, 2 H), 4.04 - 4.14 (m, 1 H), 3.88 (s, 3 H), 3.59 (dd, *J*=10.51, 4.77 Hz, 1 H), 2.97 - 3.07 (m, 2 H), 2.56 (br d, *J*=6.72 Hz, 2 H), 2.19 (dd, *J*=12.78, 5.68 Hz, 1 H), 1.75 - 1.92 (m, 2 H), 1.63 (s, 3 H), 0.98 (dd, *J*=6.36, 1.59 Hz, 6 H). LCMS (*Method a*. RT = 1.306 min.) 507.2/508.2 (M+H)⁺.

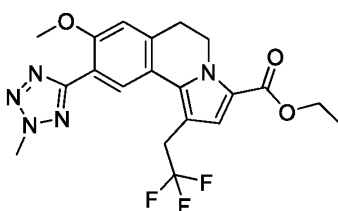
[00961] INTERMEDIATE 185: Ethyl 8-methoxy-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate



[00962] To a solution of ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12 g, 27.76 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (35.25 g, 138.81 mmol) in heptane (100 mL) and dioxane (20 mL) was added KOAc (20.44 g, 208.22 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (453.44 mg, 555.26 μmol) at 20°C. The mixture was stirred at 95°C for 12 hr. The reaction mixture was filtered and then diluted with H₂O 50 mL and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The crude product was triturated with PE (100 mL) at 20 °C for 1 hr. Then was filtered, the filter cake was

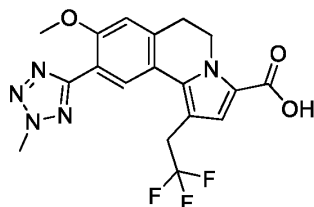
concentrated under reduced pressure to give *the title compound* (8 g, 60%) was obtained as a light brown solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.95 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 4.59 (t, J = 6.5 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.59 (q, J = 10.6 Hz, 2H), 3.01 (t, J = 6.5 Hz, 2H), 1.40 - 1.34 (m, 15H), 1.27 (s, 3H). LCMS (*Method 1*, RT = 0.67 min) 480.2(M+H) $^{+}$.

[00963] INTERMEDIATE 186: ethyl 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



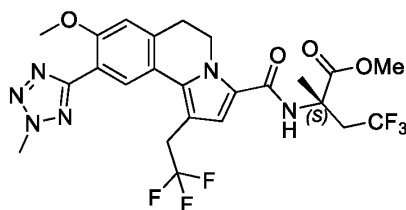
[00964] To a solution of *Intermediate 185* (8 g, 16.69 mmol) and 5-bromo-2-methyl-tetrazole (2.99 g, 18.36 mmol) in dioxane (80 mL) and H_2O (40 mL) was added XPHOS-Pd- G_2 (656.63 mg, 834.56 μmol) and Cs_2CO_3 (16.31 g, 50.07 mmol) at 20°C . The mixture was stirred at 70°C for 3 hr. The reaction mixture was filtered, and then diluted with H_2O 30 mL and extracted with DCM (50 mL $\times$ 2). The combined organic layers were washed with brine (30 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a crude product. The crude product was triturated with PE (50 mL) at 20°C for 15 min. Then was filtered, the filter cake was concentrated under reduced pressure to give *the title compound* (6.3 g, 86%) was obtained as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.11 (s, 1H), 7.29 (s, 1H), 6.94 (s, 1H), 4.61 - 4.47 (m, 2H), 4.43 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.84 - 3.68 (m, 2H), 3.10 (br t, J = 6.1 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H). LCMS (*Method 1*, RT = 0.54 min) 436.2/437.2 (M+H) $^{+}$.

[00965] **INTERMEDIATE 187:** 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[00966] To a solution of *Intermediate 186* (6.3 g, 14.47 mmol) in THF (25 mL), EtOH (25 mL) and H₂O (13 mL) was added KOH (1.62 g, 28.94 mmol) at 20°C. The mixture was stirred at 80°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove THF and EtOH, diluted with H₂O 50 mL and adjusted pH to 3-4, which was filtered and dried under reduced pressure to give a crude product. *The title compound* (5.7 g, 96%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 12.49 (br s, 1H), 8.10 (s, 1H), 7.29 (s, 1H), 6.93 - 6.86 (m, 1H), 4.56 (br t, J = 6.4 Hz, 2H), 4.43 (s, 3H), 3.89 (s, 3H), 3.81 - 3.67 (m, 2H), 3.08 (br t, J = 6.2 Hz, 2H), 1.29 - 1.08 (m, 1H). LCMS (*Method 1*, RT = 0.41 min) 408.2/409.2(M+H) +.

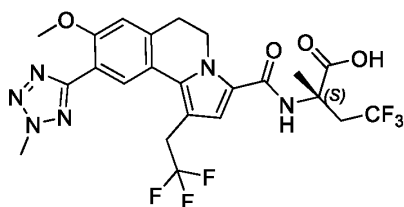
[00967] **INTERMEDIATE 188:** methyl (S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



[00968] To a solution of *Intermediate 187* (1 g, 2.45 mmol) in DMF (10 mL) was added HATU (1.12 g, 2.95 mmol) and DIEA (1.27 g, 9.82 mmol, 1.71 mL) at 25°C for 3h, then it was added *Intermediate 115* (785.81 mg, 3.19 mmol, HCl salt). The mixture was stirred at 80°C for 9 h. Poured into ice water, added with HCl to adjust pH=6 and filtered under reduced pressure. The

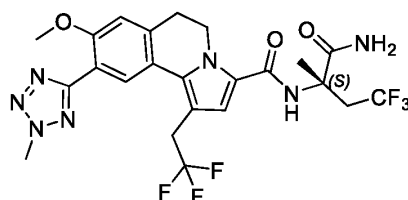
filter cake was dissolved with EtOAc and the organic phase was washed with brine, concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =1/1). *The title compound* (920 mg, 65%) was obtained as a brown solid. ¹HNMR (400 MHz, DMSO-d₆) δ ppm 8.59 (s, 1 H) 8.07 (s, 1 H) 7.27 (s, 1 H) 7.05 (s, 1 H) 4.49 (br t, J=6.38 Hz, 2 H) 4.43 (s, 3 H) 3.89 (s, 3 H) 3.72 (q, J=11.17 Hz, 2 H) 3.65 (s, 3 H) 3.15 - 3.29 (m, 1 H) 3.04 (br t, J=6.25 Hz, 2 H) 2.77 - 2.88 (m, 1 H) 2.65 - 2.71 (m, 5 H) 1.57 (s, 3 H). LCMS (*Method a*, RT = 1.81 min) 575.2/576.2 (M+H)⁺.

[00969] INTERMEDIATE 189: (S)-4,4,4-trifluoro-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



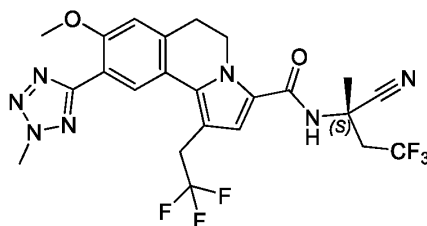
[00970] To a solution of *Intermediate 188* (100 mg, 174.07 μmol) in THF (1 mL) was added TMSOK (44.66 mg, 348.14 μmol). The mixture was stirred at 50 °C for 12 hr. The reaction mixture was adjusted to pH=3 with 1M HCl. The aqueous layer was extracted with EtOAc (3 mL×3). The combined organic phase was washed with brine (5 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (60 mg, 61%) was obtained as a white solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.21 (s, 1 H) 6.99 (s, 1 H) 6.70 (d, J=7.46 Hz, 1 H) 4.55 - 4.66 (m, 2 H) 4.46 (s, 3 H) 4.00 (s, 3 H) 3.75 - 3.80 (m, 1 H) 3.57 - 3.68 (m, 2 H) 3.03 - 3.09 (m, 3 H) 1.78 - 1.85 (m, 3 H) 1.23 - 1.32 (m, 2 H). LCMS (*Method l*, RT = 0.459 min) 561.3/562.3 (M+H)⁺.

[00971] **INTERMEDIATE 190:** (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



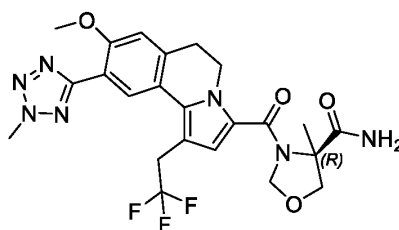
[00972] To a solution of *Intermediate 189* (60 mg, 107.06 μ mol) in THF (1 mL) was added CDI (26.04 mg, 160.59 μ mol) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (45.02 mg, 321.17 μ mol, 49.48 μ L, 25% purity). The mixture was stirred at 25°C for 2 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with DCM (5 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column to give *the title compound* (42.69 mg, 71%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.12 (s, 1 H) 8.07 (s, 1 H) 7.48 (br s, 1 H) 7.27 (s, 1 H) 7.14 (br s, 1 H) 6.96 (s, 1 H) 4.46 - 4.54 (m, 2 H) 4.43 (s, 3 H) 3.89 (s, 3 H) 3.72 (q, $J=11.34$ Hz, 2 H) 3.18 - 3.29 (m, 1 H) 2.93 - 3.07 (m, 3 H) 1.55 (s, 3 H). LCMS (*Method r*. RT = 2.785 min) 560.0/561.0 ($\text{M}+\text{H}$) $^+$.

[00973] **INTERMEDIATE 191:** (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00974] To a solution of *Intermediate* 190 (490 mg, 875.84 μ mol) in THF (5 mL) was added burgess reagent (417.43 mg, 1.75 mmol) in DCM (5 mL). The mixture was stirred at 25°C for 12hr. The reaction mixture was partitioned between H₂O 5 mL and DCM 10 mL. The organic phase was separated, washed with brine 10 mL (5 mL $\times$ 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/EtOAc=1/1). *The title compound* (300 mg, 63%) was obtained as a yellow solid. ¹HNMR (400 MHz, DMSO-d₆) δ ppm 8.60 - 8.68 (m, 1 H) 8.09 (s, 1 H) 7.29 (s, 1 H) 7.05 (s, 1 H) 4.56 (br t, J=6.25 Hz, 2 H) 4.43 (s, 3 H) 3.89 (s, 3 H) 3.73 (q, J=11.34 Hz, 2 H) 3.17 - 3.29 (m, 2 H) 2.99 - 3.13 (m, 3 H) 1.83 (s, 3 H). LCMS (*Method 1*, RT = 0.51 min) 542.2/543.3 (M+H)⁺.

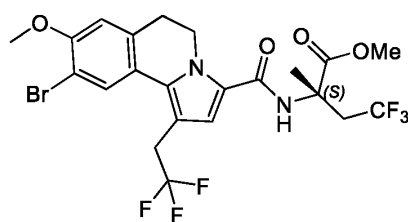
[00975] **INTERMEDIATE 192:** Rel-(R)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carboxamide



[00976] To a solution of *Intermediate* 187 (300 mg, 736.47 μ mol) in DMF (1 mL) was added DIEA (285.55 mg, 2.21 mmol, 384.83 μ L) and HATU (308.03 mg, 810.12 μ mol) at 20°C for 30 min under N₂. Then was added *Intermediate* 10 8 (115.02 mg, 883.77 μ mol) at 20°C. The mixture was stirred at 40°C for 2 h. The solvent was evaporated and the pH was adjusted to 5-6 with 1M HCl. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 mL $\times$ 3). The combined organic phase was washed with brine (5 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EtOAc =10/1 to EtOAc/MeOH=50/1) to give *the title compound* (250 mg, 65%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.13 - 8.06 (m, 1H), 7.35 - 7.23 (m, 2H), 7.07 - 6.97 (m, 1H), 6.60 - 6.54 (m, 1H), 5.38 - 5.32 (m, 1H), 5.21 -

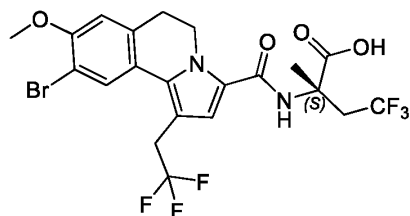
5.14 (m, 1H), 4.42 (s, 3H), 4.38 - 4.20 (m, 2H), 4.09 (d, $J = 8.9$ Hz, 1H), 4.06 - 3.99 (m, 1H), 3.89 (s, 3H), 3.82 (d, $J = 8.9$ Hz, 1H), 3.79 - 3.66 (m, 3H), 3.10 - 2.97 (m, 2H), 1.99 (s, 1H), 1.91 (s, 1H), 1.52 (s, 2H), 1.43 (s, 1H), 1.17 (t, $J = 7.1$ Hz, 1H). LCMS (*Method a.* RT = 1.355 min) 519.2/520.1 (M+H)⁺.

[00977] INTERMEDIATE 193: methyl (S)-2-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoate



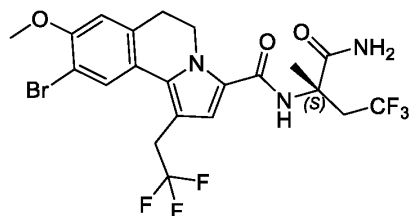
[00978] To a solution of 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (800 mg, 1.98 mmol) in DMF (8 mL) was added DIEA (1.02 g, 7.92 mmol, 1.38 mL) and HATU (903.12 mg, 2.38 mmol). The mixture was stirred at 25 °C for 3 hr. Then was added *Intermediate 115* (526.35 mg, 2.38 mmol, HCl salt) and stirred at 80°C for 9hr. Poured the mixture into ice water, filtered and the solid was collected, dissolved the cake with EtOAc. The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/EtOAc=5/1). *The title compound* (750 mg, 66%) was obtained as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.72 (s, 1 H) 6.83 (s, 2 H) 6.65 (s, 1 H) 4.52 - 4.58 (m, 2 H) 3.94 (s, 3 H) 3.86 (s, 3 H) 3.41 - 3.60 (m, 3 H) 2.88 - 3.04 (m, 3 H) 1.77 (s, 3 H). LCMS (*Method a.* RT = 2.10 min) 571.1/572.9 (M+H)⁺

[00979] INTERMEDIATE 194: (S)-2-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-4,4,4-trifluoro-2-methylbutanoic acid



[00980] To a solution of *Intermediate 193* (650 mg, 1.14 mmol) in THF (7 mL) was added TMSOK (291.92 mg, 2.28 mmol). The mixture was stirred at 50 °C for 12hr. The reaction mixture was adjusted to pH 5-6 with 1M HCl. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (10mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (550 mg, 86%) was obtained as a white solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.72 (s, 1 H) 6.83 (s, 1 H) 6.61 - 6.68 (m, 2 H) 4.55 (br t, J=6.38 Hz, 2 H) 3.92 - 3.95 (m, 3 H) 3.53 (q, J=10.55 Hz, 2 H) 3.21 - 3.38 (m, 1 H) 3.06 - 3.19 (m, 1 H) 2.96 (br t, J=6.44 Hz, 2 H) 1.78 - 1.85 (m, 3 H). LCMS (*Method a*. RT = 1.905 min) 557.2/558.7 (M+H)⁺.

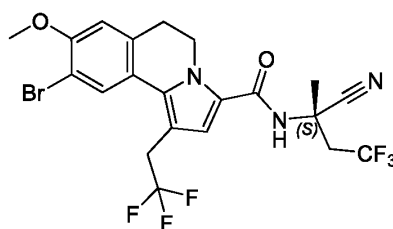
[00981] INTERMEDIATE 195: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00982] To a solution of *Intermediate 194* (550 mg, 986.94 μmol) in THF (6 mL) was added CDI (240.05 mg, 1.48 mmol) at 25°C for 5 min. The mixture was stirred at 25°C for 1h. Then it was added NH₃·H₂O (415.06 mg, 2.96 mmol, 456.11 μL, 25% purity). The mixture was stirred at 25°C for 1h. The residue was poured into water (10 mL). The aqueous phase was extracted with EtOAc (5 mL×3). The combined organic phase was washed with brine (10 mL×2),

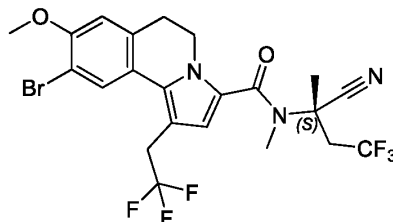
dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. *The title compound* (545 mg, 99%) was obtained as a white solid. ¹HNMR (400 MHz, DMSO-d₆) δ ppm 8.11 (s, 1 H) 7.74 (s, 1 H) 7.47 (br s, 1 H) 7.11 - 7.18 (m, 2 H) 6.92 (s, 1 H) 4.43 (br t, J=6.02 Hz, 2 H) 3.88 (s, 3 H) 3.75 (q, J=11.25 Hz, 3 H) 3.17 - 3.28 (m, 2 H) 2.88 - 3.02 (m, 4 H) 1.55 (s, 3 H). LCMS (*Method a*. RT = 1.819 min) 568.1/570.1 (M+H)⁺

[00983] INTERMEDIATE 196: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



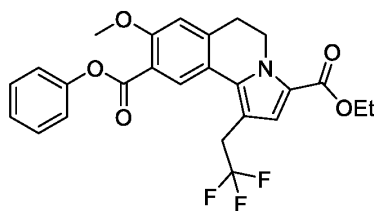
[00984] To a solution of *Intermediate 195* (450 mg, 808.92 μmol) in THF (1 mL) was added burgess reagent (385.54 mg, 1.62 mmol) in DCM (1 mL). The mixture was stirred at 25 °C for 1hr. The residue was poured into water (10 mL). The aqueous phase was extracted with DCM (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column to give *the title compound* (180 mg, 41%) was obtained as a white solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.71 (s, 1 H) 6.85 (s, 1 H) 6.62 (s, 1 H) 5.98 (s, 1 H) 4.54 - 4.68 (m, 2 H) 3.95 (s, 3 H) 3.54 (q, J=10.42 Hz, 2 H) 3.13 - 3.24 (m, 1 H) 3.02 - 3.13 (m, 1 H) 2.98 (t, J=6.44 Hz, 2 H) 1.96 (s, 3 H). LCMS (*Method a*. RT = 2.032 min) 538.1/540.1 (M+H)⁺.

[00985] INTERMEDIATE 197: (S)-9-bromo-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[00986] DMF (10 mL) was charged to the three-necked round bottom flask, then *Intermediate 196* (280 mg, 520.18 μ mol) was added to the mixture at 25°C for 5min. At 0°C, NaH (31.21 mg, 780.26 μ mol, 60% purity) was added to the reaction mixture at 0°C under Ar. Then CH₃I (147.67 mg, 1.04 mmol, 64.77 μ L) was added at 0°C under Ar. After the addition, the mixture was stirred at 70°C for 2hr under Ar. The reaction was quenched with NH₄Cl (10 mL) under Ar and extracted with EtOAc (15 mL). The organic layer was washed with water (10 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc=1/1). *The title compound* (230 mg, 80%) was obtained as a white solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.72 (s, 1 H) 6.84 (s, 1 H) 6.53 (s, 1 H) 4.31 (qt, J=12.62, 6.25 Hz, 2 H) 3.94 (s, 3 H) 3.53 (q, J=10.47 Hz, 2 H) 3.39 (s, 3 H) 3.22 - 3.33 (m, 1 H) 3.14 - 3.22 (m, 1 H) 2.99 (br t, J=6.48 Hz, 2 H) 2.05 (s, 3 H). LCMS (*Method a*, RT = 2.10 min) 552.1/554.0 (M+H)⁺.

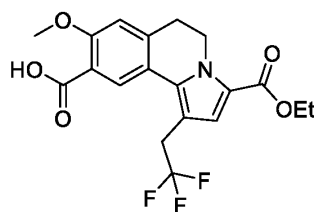
[00987] **INTERMEDIATE 198:** 3-ethyl 9-phenyl 8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3,9-dicarboxylate



[00988] To a solution of ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (8 g, 18.51 mmol) and phenyl formate (15.57 g, 129.56 mmol, 10.11mL) in DMF (40 mL) was added TEA (13.11 g, 129.56 mmol, 18.03

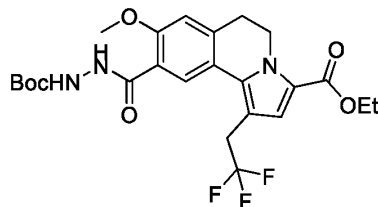
mL) and Pd(dppf)Cl₂. CH₂Cl₂ (3.02 g, 3.70 mmol) at 20°C. The mixture was stirred at 120°C for 12 hr. The reaction mixture was extracted with EtOAc (30 mL×3). The combined organic layers were washed with brine (20 mL×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1 to 4/1). *The title compound* (6 g, 68.47%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.25 (s, 1H), 7.40 - 7.31 (m, 2H), 7.17 (s, 3H), 6.96 - 6.92 (m, 1H), 6.91 - 6.87 (m, 1H), 4.65 - 4.53 (m, 2H), 4.33 - 4.18 (m, 2H), 3.91 (s, 3H), 3.61 - 3.42 (m, 2H), 3.09 - 2.95 (m, 2H), 1.38 - 1.21 (m, 3H). LCMS (*Method l*. RT = 0.63 min) 474.3/475.2 (M+H)⁺.

[00989] INTERMEDIATE 199: 3-(ethoxycarbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylic acid



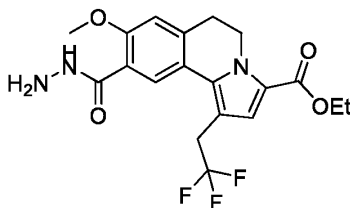
[00990] To a solution of *Intermediate 198* (5.5 g, 11.62 mmol) in THF (100 mL) was added TMSOK (2.98 g, 23.23 mmol). The mixture was stirred at 20 °C for 2hr. The combined reaction mixture was poured into ice-water (20 mL) and added 1 M HCl to pH=5-6. The reaction mixture was extracted with EtOAc 60 mL (20mL ×3). The combined organic layers were washed with brine 60mL (30mL ×2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The title compound (4 g, 86%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 10.57 - 10.42 (m, 1H), 8.32 (s, 1H), 7.19 (s, 1H), 7.02 - 6.83 (m, 2H), 4.66 - 4.50 (m, 2H), 4.31 - 4.19 (m, 2H), 4.05 (s, 3H), 3.62 - 3.48 (m, 2H), 2.99 (s, 2H), 1.35 - 1.24 (m, 3H). LCMS (*Method g*. RT = 0.505 min) 398.1/399.1 (M+H)⁺.

[00991] INTERMEDIATE 200: ethyl 9-(2-(tert-butoxycarbonyl)hydrazine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00992] To a solution of *Intermediate 199* (1 g, 2.52 mmol) in DMF (10 mL) was added HATU (1.15 g, 3.02 mmol), DIEA (1.30 g, 10.07 mmol, 1.75 mL) and tert-butyl N-aminocarbamate (432.39 mg, 3.27 mmol). The mixture was stirred at 20 °C for 1h. The reaction mixture was added to the ice water, white solid appeared, then filtered. The filter cake was dissolved with 30 mL EtOAc and washed with brine (30 mL x 3), the organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (1.2 g, 93%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.51 (br s, 1H), 8.47 (s, 1H), 7.02 (s, 1H), 6.92 (s, 2H), 4.62 (t, *J* = 6.50 Hz, 2H), 4.31 (q, *J* = 7.13 Hz, 2H), 4.05 (s, 3H), 3.63 (q, *J* = 10.59 Hz, 2H), 3.05 (t, *J* = 6.44 Hz, 2H), 1.52 (s, 9H), 1.38 (t, *J* = 7.07 Hz, 3H). LCMS (*Method 1*, RT = 0.550 min) 456.2 (M-t-Bu)⁺.

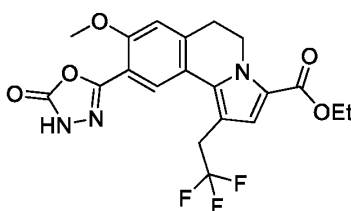
[00993] **INTERMEDIATE 201:** ethyl 9-(hydrazinecarbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[00994] To a solution of *Intermediate 200* (1.26 g, 2.46 mmol) in DCM (15 mL) was added HCl/EtOAc (4M, 15 mL) at 20 °C. The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude was dissolved in 50 mL EtOAc and 10 mL THF, the solution was washed with sat. NaHCO₃ to pH = 9. The organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (950 mg, 93%) was obtained as a

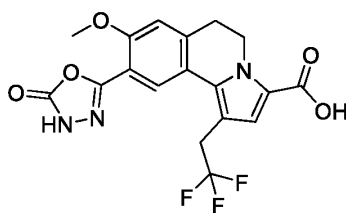
yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 9.26 (br s, 1H), 8.00 (s, 1H), 7.18 (s, 1H), 6.92 (s, 1H), 4.46 - 4.63 (m, 4H), 4.24 (q, $J = 7.05$ Hz, 2H), 3.91 (s, 3H), 3.74 (q, $J = 11.09$ Hz, 2H), 3.05 (br t, $J = 6.31$ Hz, 2H), 1.29 (t, $J = 7.05$ Hz, 3H). LCMS (*Method I*, RT = 0.424 min) 412.2 (M+H) $^+$.

[00995] INTERMEDIATE 202: ethyl 8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



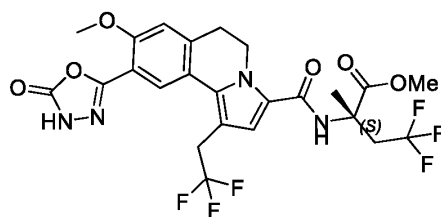
[00996] To a solution of *Intermediate 201* (700 mg, 1.70 mmol) in DCM (7 mL) was added CDI (358.69 mg, 2.21 mmol). The mixture was stirred at 20°C for 2hr. The reaction mixture was washed with H₂O (20 mL x 2), washed with brine (30 mL), the combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (720 mg, 96%) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.51 (br s, 1H), 7.90 (s, 1H), 7.29 (s, 1H), 6.93 (s, 1H), 4.46 - 4.63 (m, 2H), 4.24 (q, $J = 7.09$ Hz, 2H), 3.92 (s, 3H), 3.77 (q, $J = 11.09$ Hz, 2H), 2.98 - 3.18 (m, 2H), 1.19 - 1.40 (m, 3H). LCMS (*Method I*, RT = 0.511 min) 438.2 (M+H) $^+$.

[00997] INTERMEDIATE 203: 8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



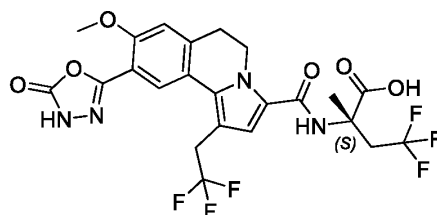
[00998] To a solution of *Intermediate 202* (2.2 g, 4.64 mmol, HCl salt) in THF (20 mL) and EtOH (20 mL) was added LiOH.H₂O (584.51 mg, 13.93 mmol) and H₂O (20 mL) at 20°C. The mixture was stirred at 50°C for 8 hr. The reaction mixture was added to 10 mL ice water and 0.2N HCl was added to adjust pH=3-4, then suspension was filtered to give a residue. *The title compound* (1.85 g, crude) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.27 - 12.72 (m, 2H), 7.84 - 7.93 (m, 1H), 7.28 (s, 1H), 6.88 (s, 1H), 4.55 (br t, J = 6.32 Hz, 2H), 3.92 (s, 3H), 3.75 (q, J = 11.17 Hz, 2H), 3.07 (br t, J = 6.26 Hz, 2H). LCMS (*Method 1*, RT = 0.385 min) 410.1 (M+H)⁺.

[00999] **INTERMEDIATE 204:** methyl (S)-4,4,4-trifluoro-2-(8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



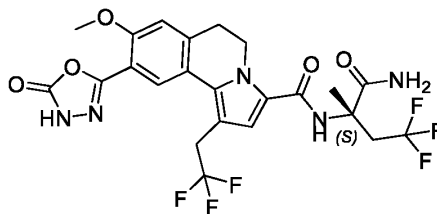
[001000] To a solution of *Intermediate 203* (230 mg, 561.91 μmol) in DMF (2.3 mL) was added HATU (256.39 mg, 674.30 μmol) and DIEA (290.49 mg, 2.25 mmol, 391.50 μL) at 20 °C for 2h. *Intermediate 115* (161.88 mg, 730.49 μmol, HCl salt) was added to the reaction mixture at 20 °C and the mixture was stirred at 80 °C for 6 hr. The reaction mixture was added to ice water and adjust pH = 3-4 by 1M HCl, then the suspension was extracted with EtOAc (15 mLx3), the combined organic phase was washed with brine (10 mLx5), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/ EtOAc = 100/1 to 1/1). *The title compound* (133 mg, 41%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.50 (br s, 1H), 8.60 (s, 1H), 7.86 (s, 1H), 7.27 (s, 1H), 7.04 (s, 1H), 4.47 (br t, J = 6.32 Hz, 2H), 3.91 (s, 3H), 3.74 (q, J = 11.34 Hz, 2H), 3.64 (s, 3H), 3.18 - 3.26 (m, 1H), 3.03 (br t, J = 6.19 Hz, 2H), 2.79 - 2.90 (m, 1H), 1.56 (s, 3H). LCMS (*Method a*, RT = 1.561 min) 577.2 (M+H)⁺.

[001001] INTERMEDIATE 205: (S)-4,4,4-trifluoro-2-(8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



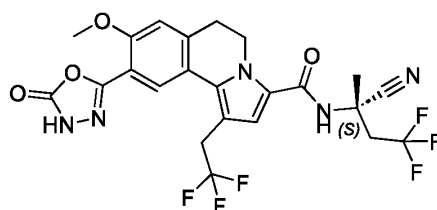
[001002] To a solution of *Intermediate 204* (350 mg, 607.17 μ mol) in THF (3.5 mL) was added TMSOK (155.78 mg, 1.21 mmol) at 20°C. The mixture was stirred at 50°C for 2 hr. Then TMSOK (38.95 mg, 303.59 μ mol) was added and stirred at 50°C for 0.5 hr. The reaction mixture was added to the ice water, 1M HCl was added to adjust pH = 3-4. The reaction mixture was extracted with EtOAc (5 mLx3). The combined organic layers were washed with brine (5 mLx3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (300 mg, 87%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.61 - 13.06 (m, 1H), 12.50 (s, 1H), 8.31 - 8.48 (m, 1H), 7.86 (s, 1H), 7.26 (s, 1H), 7.02 (s, 1H), 4.50 (quin, J = 7.21 Hz, 2H), 3.91 (s, 3H), 3.73 (q, J = 11.25 Hz, 2H), 3.19 - 3.26 (m, 1H), 2.99 - 3.07 (m, 2H), 2.77 - 2.88 (m, 1H), 1.56 (s, 3H). LCMS (*Method e*. RT = 0.437 min) 563.1 (M+H)⁺.

[001003] INTERMEDIATE 206: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[001004] To a solution of *Intermediate 205* (280 mg, 497.85 μ mol) in THF (2.9 mL) was added CDI (121.09 mg, 746.78 μ mol) at 20 °C and stirred for 2 hr. Then $\text{NH}_3 \cdot \text{H}_2\text{O}$ (209.37 mg, 1.49 mmol, 230.08 μ L, 25% purity) was added and stirred at 20 °C for 30 min. The reaction mixture was poured into 5 mL water and 0.2 M HCl was added to the reaction mixture to adjust pH= 6-7. The aqueous phase was extracted with DCM (10 mLx3). The combined organic phase was washed with brine 20 mL, dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. *The title compound* (230 mg, 82%) was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.29 - 12.65 (m, 1H), 8.07 - 8.20 (m, 1H), 7.87 (s, 1H), 7.47 (br s, 1H), 7.26 (s, 1H), 7.11 - 7.18 (m, 1H), 6.95 (s, 1H), 4.41 - 4.54 (m, 2H), 3.89 - 3.94 (m, 3H), 3.64 - 3.78 (m, 2H), 3.25 (br dd, $J = 15.56, 12.34$ Hz, 1H), 3.02 (br d, $J = 3.58$ Hz, 2H), 2.92 - 2.99 (m, 1H), 1.55 (s, 3H). LCMS (*Method e*. RT = 0.417 min) 562.0 (M+H) $^+$.

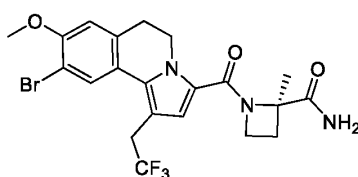
[001005] **INTERMEDIATE 207:** (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-9-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



[001006] To a solution of *Intermediate 206* (95 mg, 169.21 μ mol in pyridine (1.9 mL) was added TFAA (284.32 mg, 1.35 mmol, 188.16 μ L). The mixture was stirred at 20°C for 8 hr. The reaction mixture was added to ice water and 1 M HCl was added to adjust pH = 2-3. The suspension was extracted with EtOAc (15 mL x 3) and washed with 20 mL brine, then the organic phase was concentrated under reduced pressure to give a residue. The residue was dissolved in MeOH (2 mL) and K_2CO_3 (28.06 mg, 203.05 μ mol) was added to the reaction mixture, the suspension was stirred at 20°C for 6 hr. The suspension was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/ EtOAc =1/0 to 0/1). *The title compound* (110 mg, 59%) was obtained as a white

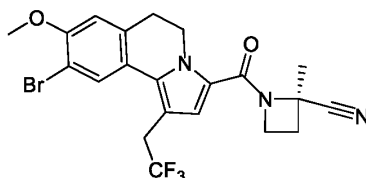
solid (2 batches in total). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.51 (br s, 1H), 8.65 (s, 1H), 7.88 (s, 1H), 7.29 (s, 1H), 7.05 (s, 1H), 4.54 (br t, J = 6.32 Hz, 2H), 3.92 (s, 3H), 3.75 (q, J = 11.17 Hz, 2H), 3.16 - 3.29 (m, 2H), 3.06 (br t, J = 6.19 Hz, 2H), 1.82 (s, 3H). LCMS (*Method g*, RT = 0.489 min) 544.2 (M+H) $^+$.

[001007] INTERMEDIATE 208: (R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



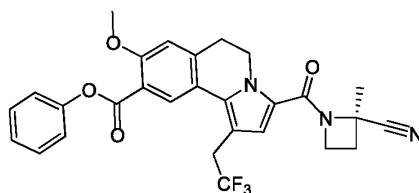
[001008] To a solution of 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (1.6 g, 3.96 mmol) and *Intermediate 124* (715.44 mg, 4.75 mmol, HCl salt) in DMF (16 mL) was added with HATU (1.66 g, 4.35 mmol) and DIEA (2.05 g, 15.83 mmol, 2.76 mL, 4 eq). The mixture was stirred at 25°C for 1 hr under N_2 atmosphere. The mixture was poured into ice-water (50 mL). Filtered and filter cake was dissolved with EtOAc (50 mL), the organic phase was washed with brine (20 mL $\times$ 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. *The title compound* (1.88 g, 94%) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 7.76 (s, 1H), 7.55 (br s, 1H), 7.19 (br s, 1H), 7.16 (s, 1H), 6.67 (br s, 1H), 4.53 - 4.34 (m, 2H), 4.29 (br s, 2H), 3.88 (s, 3H), 3.75 (q, J = 11.2 Hz, 2H), 2.94 (br t, J = 6.4 Hz, 2H), 2.48 - 2.38 (m, 1H), 2.12 - 2.00 (m, 1H), 1.67 (br s, 3H). LCMS (*Method a*, ES^+ , RT = 1.74 min) 500.3/502.0 (M+H) $^+$

[001009] INTERMEDIATE 209: (R)-1-(9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile



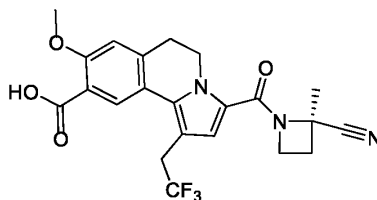
[001010] To a solution of *Intermediate 208* (1.6 g, 3.20 mmol) in THF (16 mL) was added with Burgess reagent (1.52 g, 6.40 mmol) in DCM (16 mL). The mixture was stirred at 25°C for 2 hr under N₂ atmosphere. The mixture was added with 10 mL H₂O. The organic layer was washed with brine 5 mL and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =100/1 to 5/1). *The title compound* (1.5 g, 97.25%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.79 (s, 1H), 7.18 (s, 1H), 6.70 (s, 1H), 4.54 - 4.42 (m, 2H), 4.39 (br t, J = 7.5 Hz, 2H), 3.89 (s, 3H), 3.83 - 3.71 (m, 2H), 2.97 (br t, J = 6.4 Hz, 2H), 2.78 - 2.69 (m, 1H), 2.47 - 2.38 (m, 1H), 1.81 (s, 3H). LCMS (*Method a*. ES⁺, RT =1.99 min) 482.2/484.1 (M+H)⁺

[001011] **INTERMEDIATE 210:** phenyl (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylate



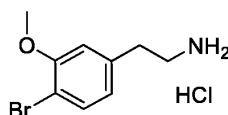
[001012] To a solution of *Intermediate 209* (500 mg, 1.04 mmol) and phenyl formate (1.14 g, 9.33 mmol) in DMF (5 mL) was added with TEA (944.15 mg, 9.33 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (253.99 mg, 311.01 μmol). The mixture was stirred at 120°C for 12 hr under N₂ atmosphere. The mixture was poured into water (10 mL). The aqueous phase was extracted with EtOAc (10 mL×3). The combined organic phase was washed with brine (10 mL×2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =10/1 to 1/1). *The title compound* (450 mg, 82%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.22 (s, 1H), 7.51 - 7.44 (m, 2H), 7.34 - 7.28 (m, 2H), 7.25 (d, J = 7.6 Hz, 2H), 6.73 (s, 1H), 4.54 (br t, J = 6.1 Hz, 2H), 4.41 (br t, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.78 (q, J = 11.1 Hz, 2H), 3.09 (br t, J = 6.3 Hz, 2H), 2.80 - 2.70 (m, 1H), 2.48 - 2.39 (m, 1H), 1.82 (s, 3H). LCMS (*Method a*. ES⁺, RT = 1.99 min) 524.4 (M+H)⁺

[001013] INTERMEDIATE 211: (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxylic acid



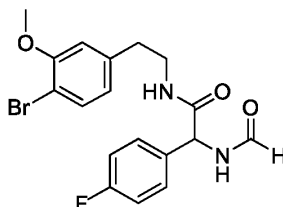
[001014] To a solution of *Intermediate 210* (200 mg, 382.04 μmol) in THF (4 mL) was added with TMSOK (98.02 mg, 764.08 μmol). The mixture was stirred at 15°C for 3 hr under N_2 atmosphere. The reaction mixture was added with H_2O (5 mL) and extracted with MTBE (5 mL). The aqueous phase was acidified with 1 N HCl to pH = 2 and extracted with EtOAc (5 mL $\times$ 3). The organic layers were washed with 5 mL brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. *The title compound* (150 mg, 87.76%) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 12.61 (br s, 1H), 9.31 (s, 1H), 7.97 (s, 1H), 7.20 - 7.12 (m, 3H), 6.78 - 6.69 (m, 4H), 5.75 (s, 1H), 4.50 (br t, J = 6.6 Hz, 2H), 4.39 (br t, J = 8.1 Hz, 2H), 3.86 (s, 3H), 3.72 (q, J = 11.0 Hz, 2H), 3.03 (br t, J = 6.4 Hz, 2H), 2.79 - 2.68 (m, 1H), 2.48 - 2.39 (m, 1H), 1.81 (s, 3H). LCMS (*Method a*, ES^+ , RT = 1.49 min) 448.3 ($\text{M}+\text{H}$) $^+$

[001015] INTERMEDIATE 212: 2-(4-bromo-3-methoxyphenyl)ethan-1-amine (HCl salt)



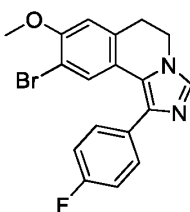
[001016] A solution of *Intermediate 2* (225 g, 977.83 mmol, 1 eq) in HCl/EtOAc (2 M, 2.25 L) was stirred at 20 °C for 1 h. The mixture was filtered, the filter cake was dried under reduced pressure to give the *title compound* (220 g, 825.32 mmol, 84.40% yield, 100% purity, HCl) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.06 (br s, 3H), 7.50 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 1.7 Hz, 1H), 6.79 (dd, J = 1.8, 8.0 Hz, 1H), 3.85 (s, 3H), 3.04 (br s, 2H), 2.93 - 2.84 (m, 2H).

[001017] INTERMEDIATE 213: N-(4-bromo-3-methoxyphenethyl)-2-(4-fluorophenyl)-2-formamidoacetamide



[001018] To a solution of *Intermediate 4* (24 g, 99.96 mmol) in MeOH (240 mL) was added HCOONH₄ (12.61 g, 199.92 mmol) and 4-fluorobenzaldehyde (13.03 g, 104.96 mmol, 11.04 mL) at 20°C. The mixture was stirred at 80°C for 4 hr. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H₂O (100 mL) and extracted with EtOAc (200 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated by MTBE (100 mL) and filtered to give *the title compound* (51 g, 124.62 mmol, 62.33% yield) as a pink solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.84 (br d, *J* = 7.7 Hz, 1H), 8.40 (br t, *J* = 5.3 Hz, 1H), 8.03 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.33 (dd, *J* = 5.6, 8.6 Hz, 2H), 7.13 (t, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.61 (dd, *J* = 1.7, 8.0 Hz, 1H), 5.46 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 3H), 3.40 - 3.34 (m, 1H), 3.32 - 3.26 (m, 1H), 2.67 (t, *J* = 6.8 Hz, 2H). LCMS (*Method 1*, ES⁺, RT = 0.629 min) 431.1/433.1 (M+H)⁺

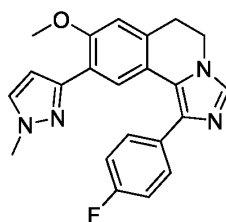
[001019] INTERMEDIATE 214: 9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline



[001020] A solution of P₂O₅ (44.22 g, 311.55 mmol, 19.23 mL) in methanesulfonic Acid (250 mL) was stirred at 75°C for 0.5 hour. The mixture was added *Intermediate 213* (25.5 g, 62.31

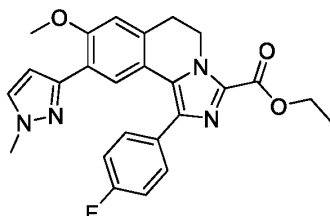
mmol) at 75°C and the mixture was stirred at 75°C for 1.5 hour. The reaction was cooled and poured into cold Na₂CO₃ solution (500 mL) slowly to adjust pH = 8 and extracted with EtOAc (300 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was triturated with MTBE (150 mL) at 20 °C to give *the title compound* (42 g, 90.30%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.79 (s, 1H), 7.63 - 7.56 (m, 2H), 7.49 (s, 1H), 7.30 - 7.22 (m, 2H), 7.18 (s, 1H), 4.15 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.07 (t, *J* = 6.4 Hz, 2H). LCMS (*Method d*. ES⁺, RT = 0.553 min) 373.1/375.1 (M+H)⁺

[001021] INTERMEDIATE 215: 1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



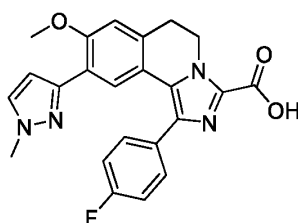
[001022] To a solution of *Intermediate 214* (500 mg, 1.34 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (334.49 mg, 1.61 mmol) in dioxane (2 mL) and H₂O (1 mL) was added XPHOS-Pd-G₂ (105.41 mg, 133.97 μmol) and Cs₂CO₃ (1.75 g, 5.36 mmol) at 20°C. The mixture was stirred at 100°C for 2 hr. The reaction mixture was diluted with H₂O (8 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE (4 mL) at 20°C for 15 min to give *the title compound* (1.5 g, 74.76%) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.09 (s, 1H), 7.76 (s, 1H), 7.70 - 7.60 (m, 3H), 7.27 - 7.17 (m, 2H), 7.10 (s, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 3.92 - 3.84 (m, 3H), 3.76 (s, 3H), 3.09 (t, *J* = 6.3 Hz, 2H). LCMS (*Method a*. ES⁺, RT = 1.146 min) 375.3/376.3 (M+H)⁺

[001023] **INTERMEDIATE 216:** ethyl 1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[001024] To a solution of *Intermediate 215* (400mg, 1.07 mmol) in THF (5 mL) was added n-BuLi (2.5 M, 512.81 μ L) at -60°C . The mixture was added ethyl formate (395.71 mg, 5.34 mmol, 429.65 μ L) at -60°C and the mixture was stirred at -60°C for 2 hrs. The mixture was added H_2O (3 mL) and extracted with EtOAc (5 mL x 3). The organic layers were concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 1/1) to give *the title compound* (310 mg, 32%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.00 (s, 1H), 7.76 - 7.67 (m, 2H), 7.32 (d, J = 2.1 Hz, 1H), 7.10 (t, J = 8.8 Hz, 2H), 6.88 (s, 1H), 6.54 (d, J = 2.1 Hz, 1H), 4.73 (t, J = 6.6 Hz, 2H), 4.48 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). LCMS (*Method g*, ES^+ , RT = 0.480 min) 447.1/448.1 (M+H)

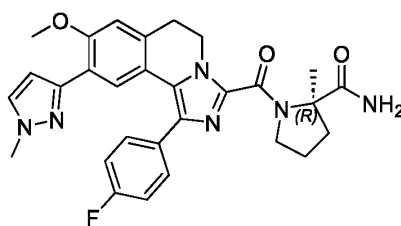
[001025] **INTERMEDIATE 217:** 1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[001026] To a solution of *Intermediate 216* (150 mg, 335.97 μ mol) in THF (1 mL) was added TMSOK (86.20 mg, 671.93 μ mol) at 20°C . The mixture was stirred at 20°C for 2 hr. The reaction

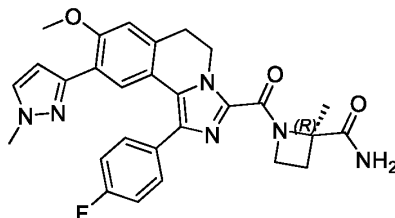
mixture was concentrated under reduced pressure to give *the title compound* (281 mg, crude) as a yellow solid. LCMS (*Method g*, ES⁺, RT = 0.347 min) 419.3/420.1 (M+H)

[001027] INTERMEDIATE 218: (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



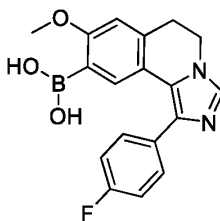
[001028] To a solution of *Intermediate 217* (140 mg, 334.59 μ mol) and (2R)-2-methylpyrrolidine-2-carboxamide (66.10 mg, 401.51 μ mol, HCl) in DMF (1 mL) was added HATU (139.94 mg, 368.05 μ mol) and DIEA (129.73 mg, 1.00 mmol, 174.84 μ L) at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc (2 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was washed by MTBE (5 mL) to give the *the title compound* (110 mg, 62.20%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.07 (s, 1H), 7.75 (br dd, *J* = 5.8, 7.8 Hz, 2H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.15 (br t, *J* = 8.7 Hz, 3H), 6.91 - 6.87 (m, 1H), 6.58 (d, *J* = 2.0 Hz, 1H), 4.66 - 4.50 (m, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.22 (s, 2H), 3.15 (br t, *J* = 5.8 Hz, 3H), 2.56 - 2.41 (m, 1H), 2.21 - 1.90 (m, 4H). LCMS (*Method g*, ES⁺, RT = 0.435 min) 529.2/530.2 (M+H)

[001029] INTERMEDIATE 219: (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



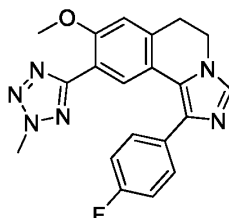
[001030] To a solution of *Intermediate 217* (140 mg, 334.59 μmol) and *Intermediate 124* (60.47 mg, 401.51 μmol , HCl) in DMF (1 mL) was added HATU (139.94 mg, 368.05 μmol) and DIEA (129.73 mg, 1.00 mmol, 174.84 μL) at 20°C. The mixture was stirred at 20°C for 1 hr. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc (2 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was washed by MTBE (5 mL) to give *the title compound* (70 mg, 40.66%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.28 (br s, 1H), 8.08 (s, 1H), 7.72 (dd, J = 5.6, 8.6 Hz, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.15 - 7.06 (m, 2H), 6.92 - 6.86 (m, 1H), 6.60 - 6.53 (m, 1H), 5.40 (br s, 1H), 4.81 - 4.70 (m, 2H), 4.62 (dt, J = 5.8, 10.2 Hz, 1H), 3.98 - 3.91 (m, 3H), 3.91 - 3.83 (m, 3H), 3.22 (s, 1H), 3.20 - 3.06 (m, 3H), 2.22 - 2.13 (m, 1H), 1.20 (s, 3H). LCMS (*Method g*, ES⁺, RT = 0.458 min) 515.2/516.2 (M+H)

[001031] INTERMEDIATE 220: (1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)boronic acid



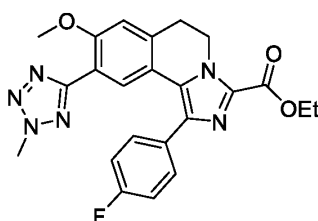
[001032] To a solution of *Intermediate 214* (2.5 g, 6.70 mmol) in EtOH (25 mL) was added hypoboric acid (1.80 g, 20.10 mmol) DIEA (4.33 g, 33.49 mmol, 5.83 mL) and Pd(dtbpf)Cl₂ (218.29 mg, 334.92 μmol). The mixture was stirred at 60 °C for 6 hr. The reaction solution was used directly in next step. LCMS (*Method a*, ES⁺, RT = 0.959 min) 339.3 (M+H)

[001033] INTERMEDIATE 221: 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline



[001034] To a solution of *Intermediate 220* (a solution from the previous step), 5-bromo-2-methyl-tetrazole (697.90 mg, 4.28 mmol) in H₂O (0.3 mL) was added XPHOS-Pd-G₂ (126.35 mg, 160.58 μ mol) and Cs₂CO₃ (5.23 g, 16.06 mmol). The mixture was stirred at 70 °C for 3 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with DCM (5 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EA: MeOH =20/1 to 5/1) to give *the title compound* (850 mg, 42.19%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.16 (s, 1H), 7.74 - 7.63 (m, 3H), 7.09 (t, *J* = 8.7 Hz, 2H), 6.97 (s, 1H), 4.38 (s, 3H), 4.21 (br t, *J* = 5.9 Hz, 2H), 3.97 (s, 3H), 3.19 (br t, *J* = 5.6 Hz, 2H). LCMS (*Method e*, ES⁺, RT = 0.305 min) 377.1/378.1 (M+H)

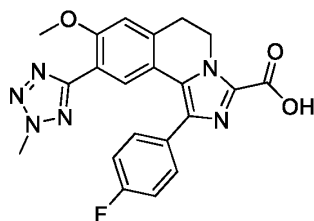
[001035] INTERMEDIATE 222: ethyl 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[001036] THF (75 mL) was charged to the 100 mL three-necked round bottom flask, then *Intermediate 221* (1.3 g, 3.45 mmol) was added at 20°C n. At -65 °C inner temperature, n-BuLi (2.5 M, 2.76 mL) was added dropwise to the reaction mixture at -65°C. After the addition, the

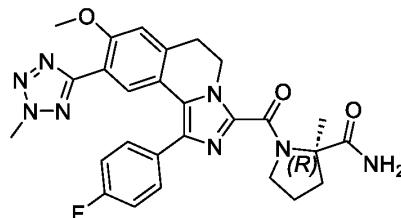
mixture was stirred at -65°C for 1 hr. At -65 °C inner temperature, ethyl chloroformate (1.93 g, 17.78 mmol, 1.70 mL) was added dropwise to the reaction mixture at -65°C. After the addition, the mixture was stirred at -65°C for 0.5 hr, then the mixture was stirred at 0°C for 3.5 hr. The residue was poured into ice water (30 mL) at 0°C. The aqueous phase was extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (50 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1) to give *title compound* (310 mg, 32.50%) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.06 (s, 1H), 7.72 - 7.64 (m, 2H), 7.14 - 7.05 (m, 2H), 6.99 (s, 1H), 4.75 (t, *J* = 6.6 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.37 (s, 3H), 3.98 (s, 3H), 3.20 (t, *J* = 6.6 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). LCMS (*Method a*, ES⁺, RT = 1.543 min) 449.3/450.3 (M+H)

[001037] INTERMEDIATE 223: 1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



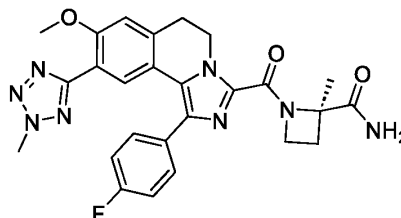
[001038] To a solution of *Intermediate 222* (110 mg, 245.29 μmol) in THF (2 mL) was added TMSOK (62.94 mg, 490.58 μmol) at 20°C. The mixture was stirred at 20°C for 1 h. The mixture was concentrated in vacuo to give *title compound* (100 mg, crude) as a brown solid. LCMS (*Method c*, ES⁺, RT = 0.494 min) 421.1/422.1 (M+H)

[001039] INTERMEDIATE 224: (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[001040] To a solution of *Intermediate 223* (180 mg, 428.17 μmol) in DMF (2 mL) was added HATU (211.64 mg, 556.62 μmol), (2R)-2-methylpyrrolidine-2-carboxamide (98.69 mg, 599.44 μmol , HCl) and DIEA (221.35 mg, 1.71 mmol, 298.32 μL) at 20°C. The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the *title compound* (180 mg, crude) as a white solid. LCMS (*Method e*, ES⁺, RT = 0.387 min) 531.1/532.1 (M+H)⁺.

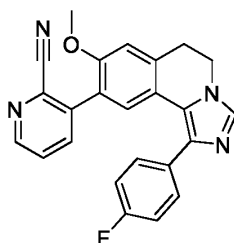
[001041] **INTERMEDIATE 225:** (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



[001042] To a solution of *Intermediate 223* (185 mg, 440.06 μmol) in DMF (3 mL) was added *Intermediate 124* (79.53 mg, 528.07 μmol , HCl), HATU (184.06 mg, 484.07 μmol) DIEA (227.50 mg, 1.76 mmol, 306.60 μL) at 20°C. The mixture was stirred at 20°C for 4 h. Then another batch *Intermediate 124* (19.88 mg, 132.02 μmol , HCl), HATU (50.20 mg, 132.02 μmol), DIEA (56.87 mg, 440.06 μmol , 76.65 μL) at 20°C and stirred at 80°C for 12 h. The residue was poured into water (5 mL), adjusted to pH 5-6 with 1M HCl, filtered, the solid was dissolved in EtOAc (10 mL) and washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under

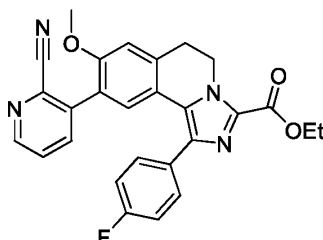
reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give the *title compound* (140 mg, 61.59%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.28 - 8.22 (m, 1H), 8.18 - 8.13 (m, 1H), 7.76 - 7.65 (m, 2H), 7.14 - 7.06 (m, 2H), 7.01 - 6.98 (m, 1H), 5.42 - 5.34 (m, 1H), 4.84 - 4.73 (m, 3H), 4.70 - 4.59 (m, 1H), 4.40 - 4.35 (m, 3H), 4.02 - 3.96 (m, 3H), 3.23 - 3.15 (m, 2H), 2.99 - 2.86 (m, 1H), 2.25 - 2.13 (m, 1H), 1.96 - 1.89 (m, 3H). LCMS (*Method a*, ES⁺, RT = 1.464 min) 517.4/518.4 (M+H)

[001043] INTERMEDIATE 226: (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



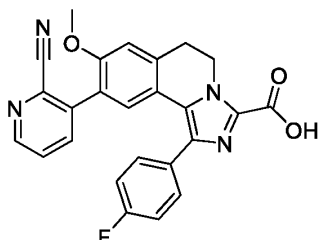
[001044] To a solution of *Intermediate 220* (a solution from previous step), 3-bromopyridine-2-carbonitrile (1.35 g, 7.38 mmol, 1.1 eq) in H₂O (10 mL) was added XPHOS-Pd-G2 (158.46 mg, 201.40 μ mol, 0.03 eq) and Cs₂CO₃ (6.56 g, 20.14 mmol, 3 eq). The mixture was stirred at 70 °C for 3 hr. The residue was poured into water (10 mL). The aqueous phase was extracted with DCM (5 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM/MeOH=1/0 to 0/1) to give the *title compound* (1.9 g, 71.40%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.64 (dd, *J* = 1.6, 4.6 Hz, 1H), 7.72 (dd, *J* = 5.4, 8.8 Hz, 2H), 7.64 - 7.60 (m, 1H), 7.58 (s, 1H), 7.53 - 7.47 (m, 1H), 7.44 (s, 1H), 7.09 (t, *J* = 8.8 Hz, 3H), 6.97 - 6.93 (m, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.20 (t, *J* = 6.3 Hz, 2H). LCMS (*Method h*, ES⁺, RT = 1.831 min) 397.2/398.2 (M+H)

[001045] **INTERMEDIATE 227:** ethyl 9-(2-cyanopyridin-3-yl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



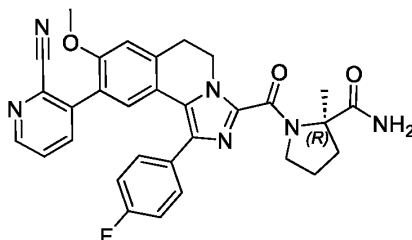
[001046] THF (40 mL) was charged to the 100 mL three-necked round bottom flask, then *Intermediate 226* (1.2 g, 3.03 mmol) was added at 25°C. Then LDA (2 M, 4.54 mL) was added dropwise to the reaction mixture at -60°C. The mixture was stirred at -60°C for 30 min. At -60°C, ethyl chloroformate (1.64 g, 15.14 mmol, 1.45 mL) was added dropwise to the reaction mixture at -60°C. After the addition, the mixture was stirred at -60°C for 30 min. After 1 hr, the reaction mixture was added to ice-water. The mixture was extracted by DCM (20 mL x 2). Then organic phase was washed by H₂O (20 mL x 3), brine (20 mL). The organic layers were dried over Na₂SO₄, filtered. The organic phase was concentrated under reduced pressure at 40°C to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give *the title compound* (600 mg, 42.31%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.64 (d, *J* = 4.5 Hz, 1H), 7.70 (dd, *J* = 5.7, 7.8 Hz, 2H), 7.60 - 7.55 (m, 1H), 7.52 - 7.47 (m, 1H), 7.35 (s, 1H), 7.09 (t, *J* = 8.6 Hz, 2H), 6.98 (s, 1H), 4.76 (t, *J* = 6.5 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 3.21 (br t, *J* = 6.5 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). LCMS (*Method h*. ES⁺, RT = 2.077 min) 469.2/470.2 (M+H)

[001047] **INTERMEDIATE 228:** 9-(2-cyanopyridin-3-yl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[001048] To a solution of *Intermediate 227* (150 mg, 320.19 μmol) in THF (1.5 mL) was added TMSOK (82.15 mg, 640.37 μmol). The mixture was stirred at 25 °C for 2 hr. The reaction solution was concentrated under reduced pressure to give *the title compound* (141 mg, crude) as a brown solid. LCMS (*Method h*, ES^+ , RT = 1.431 min) 441.1/442.1 (M+H)

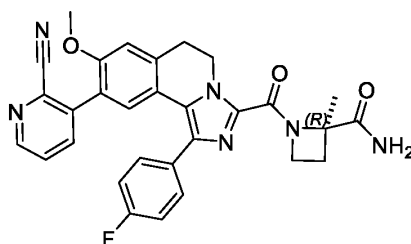
[001049] **INTERMEDIATE 229:** (R)-1-(9-(2-cyanopyridin-3-yl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



[001050] To a solution of *Intermediate 228* (235 mg, 533.58 μmol) and (2R)-2-methylpyrrolidine-2-carboxamide (105.41 mg, 640.29 μmol , HCl) in DMF (2.5 mL) was added HATU (223.17 mg, 586.93 μmol) and DIEA (275.84 mg, 2.13 mmol, 371.76 μL). The mixture was stirred at 25 °C for 1 hr. Pour the mixture into ice water, filtered and the solid was dissolved with EA. The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give *the title compound* (250 mg, 85.10%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.64 (dd, J = 1.6, 4.8 Hz, 1H), 7.74 -

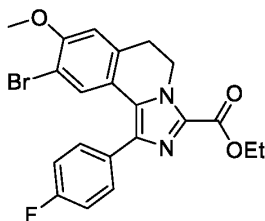
7.67 (m, 2H), 7.61 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.49 (dd, $J = 4.8, 8.0$ Hz, 1H), 7.39 (s, 1H), 7.10 (t, $J = 8.7$ Hz, 2H), 6.97 (s, 1H), 4.75 - 4.55 (m, 2H), 4.40 - 4.18 (m, 2H), 3.87 (s, 3H), 3.16 (br t, $J = 6.4$ Hz, 2H), 2.81 (s, 3H), 2.47 (td, $J = 5.8, 11.9$ Hz, 1H), 2.02 - 1.88 (m, 2H), 1.77 (s, 3H). LCMS (*Method h*. ES⁺, RT = 1.869 min) 551.2/552.2 (M+H)

[001051] INTERMEDIATE 230: (R)-1-(9-(2-cyanopyridin-3-yl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



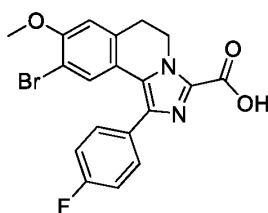
[001052] To a solution of *Intermediate 227* (235 mg, 533.58 μ mol) and *Intermediate 124* (96.43 mg, 640.29 μ mol, HCl) in DMF (2 mL) was added HATU (223.17 mg, 586.93 μ mol) and DIEA (275.84 mg, 2.13 mmol, 371.76 μ L). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was partitioned between H₂O (3 mL) and EtOAc (3 mL). The organic phase was separated, washed with brine (3 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (180 mg, 62.87%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.64 (dd, $J = 1.6, 4.8$ Hz, 1H), 8.23 (br s, 1H), 7.70 (dd, $J = 5.5, 8.6$ Hz, 2H), 7.61 (dd, $J = 1.6, 7.9$ Hz, 1H), 7.50 (dd, $J = 4.8, 7.9$ Hz, 1H), 7.42 (s, 1H), 7.14 - 7.07 (m, 2H), 6.98 (s, 1H), 4.85 - 4.70 (m, 3H), 4.60 (dt, $J = 5.8, 10.3$ Hz, 1H), 3.88 (s, 3H), 3.18 (br t, $J = 6.4$ Hz, 2H), 2.22 - 2.11 (m, 1H), 1.91 (s, 3H), 1.52 - 1.41 (m, 1H). LCMS (*Method h*. ES⁺, RT = 1.928 min) 537.2/538.2 (M+H)

[001053] INTERMEDIATE 231: ethyl 9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylate



[001054] To a solution of *Intermediate 214* (1.00 g, 2.68 mmol) in THF (10 mL) was added LDA (2 M, 1.61 mL) at -70°C. The mixture was stirred at -70°C for 30 min. Then ethyl chloroformate (1.45 g, 13.40 mmol, 1.28 mL) was added the reaction mixture at -70°C. The mixture was stirred at -70°C for 30 min. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1) give *the title compound* (500.00 mg, 42.00%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (t, J=7.15 Hz, 3 H), 3.10 (t, J=6.54 Hz, 2 H), 3.94 (s, 3 H), 4.47 (q, J=7.09 Hz, 2 H), 4.70 (t, J=6.54 Hz, 2 H), 6.83 (s, 1 H), 7.12 (t, J=8.68 Hz, 2 H), 7.59 - 7.72 (m, 3 H). LCMS (*Method g*, ES⁺, RT = 0.338 min) 445.1/447.1 (M+H)

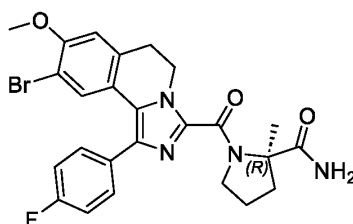
[001055] INTERMEDIATE 232: 9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxylic acid



[001056] To a solution of *Intermediate 231* (530.00 mg, 1.19 mmol) in THF (6 mL) was added TMSOK (305.40 mg, 2.38 mmol) at 20°C. The mixture was stirred at 20°C for 2 h. The reaction

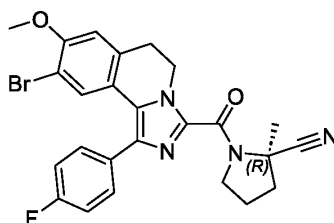
solution was concentrated under reduced pressure to give *the title compound* (541.00 mg, 99.83%) as a white solid. LCMS (*Method I*, ES⁺, RT = 0.40 min) 417.1/419.0 (M+H)

[001057] INTERMEDIATE 233: (R)-1-(9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carboxamide



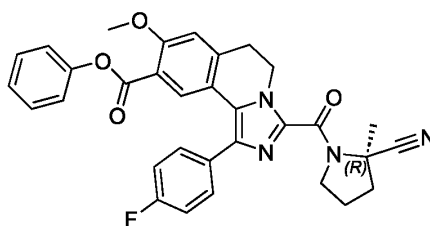
[001058] To a solution of *Intermediate 232* (540.00 mg, 1.19 mmol) in DMF (10 mL) was added (2R)-2-methylpyrrolidine-2-carboxamide (234.30 mg, 1.42 mmol, HCl), HATU (496.04 mg, 1.30 mmol) and DIEA (613.11 mg, 4.74 mmol, 826.29 μ L) at 20°C. The mixture was stirred at 20°C for 2 h. The reaction mixture was poured into H₂O (15 mL) and extracted with EtOAc (4 mL x 3). The combined organic layers were washed with brine (4 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (520.00 mg, 83.14%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.78 (s, 3 H), 1.86 - 2.04 (m, 3 H), 2.48 (dt, J=11.37, 5.81 Hz, 1 H), 3.01 - 3.12 (m, 2 H), 3.93 (s, 3 H), 4.19 - 4.28 (m, 1 H), 4.29 - 4.42 (m, 1 H), 4.49 - 4.60 (m, 1 H), 4.60 - 4.71 (m, 1 H), 5.19 - 5.41 (m, 1 H), 6.46 - 6.63 (m, 1 H), 6.83 (s, 1 H), 7.13 (t, J=8.68 Hz, 2 H), 7.58 - 7.72 (m, 3 H). LCMS (*Method I*, ES⁺, RT = 0.49 min) 527.2/529.2 (M+H)

[001059] INTERMEDIATE 234: (R)-1-(9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



[001060] To a solution of *Intermediate 233* (300 mg, 568.84 μ mol) in THF (3 mL) was added Burgess reagent (271.12 mg, 1.14 mmol) and DCM (3 mL) at 20°C. The mixture was stirred at 20°C for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM (3 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate=10/1 to 0/1) to give *the title compound* (220.00 mg, 75.93%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.89 (s, 3 H), 2.02 - 2.17 (m, 3 H), 2.53 - 2.62 (m, 1 H), 3.02 - 3.16 (m, 2 H), 3.94 (s, 3 H), 4.17 - 4.33 (m, 2 H), 4.52 - 4.62 (m, 1 H), 4.81 (ddd, J=13.23, 7.49, 5.56 Hz, 1 H), 6.84 (s, 1 H), 7.13 (t, J=8.68 Hz, 2 H), 7.58 - 7.70 (m, 3 H). LCMS (*Method 1*, ES⁺, RT = 0.58 min) 509.1/511.1 (M+H)

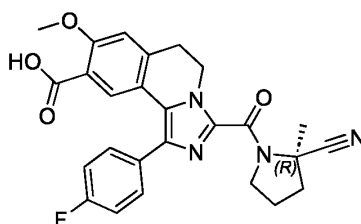
[001061] **INTERMEDIATE 235:** phenyl (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxylate



[001062] To a solution of *Intermediate 234* (220.00 mg, 215.95 μ mol) in DMF (1.5 mL) was added phenyl formate (158.23 mg, 1.30 mmol, 141.28 μ L), TEA (131.11 mg, 1.30 mmol, 180.35 μ L), Pd(dppf)Cl₂.CH₂Cl₂ (44.09 mg, 53.99 μ mol) at 20°C. The mixture was stirred at 120°C for 12 h. The reaction mixture was diluted with H₂O (8 mL) and extracted with DCM (2 mL x 3). The combined organic layers were washed with brine (2 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give *the title compound* (140 mg, 58.87%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.90 (s, 3 H), 2.05 - 2.18 (m, 3 H), 2.54 - 2.67 (m, 1 H), 3.12 - 3.29 (m, 2 H), 3.94 - 4.06 (m, 3 H), 4.20 - 4.38 (m, 2 H), 4.61 - 4.72 (m, 1 H), 4.81 - 4.95 (m, 1 H), 6.98 (s, 1 H), 7.05 - 7.14 (m, 4 H), 7.21 - 7.26 (m, 1 H), 7.36

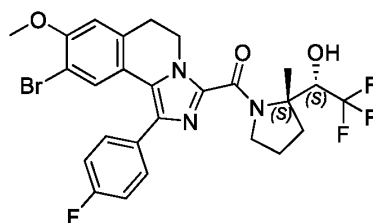
- 7.44 (m, 2 H), 7.67 (br dd, J=8.51, 5.63 Hz, 2 H), 8.20 (s, 1 H). LCMS (*Method 1*, ES⁺, RT = 0.58 min) 551.3/552.3 (M+H)

[001063] INTERMEDIATE 236: (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxylic acid



[001064] To a solution of *Intermediate 235* (120.00 mg, 217.95 μ mol) in THF (2 mL) was added TMSOK (55.92 mg, 435.91 μ mol) at 20°C. The mixture was stirred at 20°C for 2 h. The reaction mixture was added with HCl (0.5 mol) to adjust pH=3, then mixture was diluted with H₂O (5 mL) and extracted with EtOAc(2 mL x 3). The combined organic layers were washed with brine (2 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *the title compound* (103.00 mg, 99.60%) as a white solid. LCMS (*Method 1*, ES⁺, RT = 0.46 min) 475.3/476.3 (M+H)

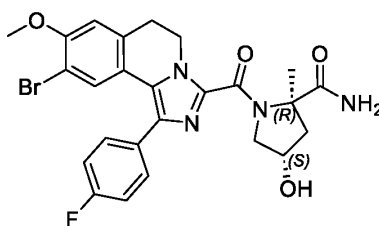
[001065] INTERMEDIATE 237: (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxylic acid



[001066] To a solution of *Intermediate 232* (93 mg, 222.90 μ mol) and (1S)-2,2,2-trifluoro-1-[(2S)-2-methylpyrrolidin-2-yl]ethanol (58.75 mg, 267.48 μ mol, HCl) in DMF (1 mL) was added HATU (93.23 mg, 245.19 μ mol) and DIEA (115.23 mg, 891.60 μ mol, 155.30 μ L) at 20°C.

The mixture was stirred at 20 °C for 2hr. The reaction mixture was added H₂O (5mL) at 0°C, and then extracted with EtOAc (2 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 2/1) to give *the title compound* (23.6 mg, 49.54%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.65 - 7.56 (m, 2H), 7.46 (s, 1H), 7.29 (t, J = 8.9 Hz, 2H), 7.21 (s, 1H), 6.62 (d, J = 6.8 Hz, 1H), 5.22 - 5.10 (m, 1H), 4.53 - 4.42 (m, 1H), 4.38 - 4.21 (m, 2H), 3.88 (s, 3H), 3.67 (dt, J = 6.6, 10.8 Hz, 1H), 3.11 - 3.04 (m, 2H), 2.40 (br dd, J = 4.1, 11.1 Hz, 1H), 1.93 - 1.76 (m, 2H), 1.67 - 1.59 (m, 1H), 1.57 (s, 3H). LCMS (*Method 1*, ES⁺, RT = 0.611 min) 582.1/584.1 (M+H)

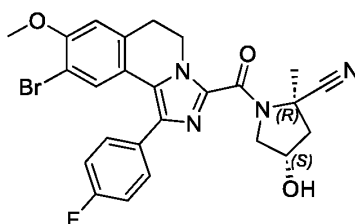
[001067] INTERMEDIATE 238: (2R,4S)-1-(9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carboxamide



[001068] To a solution of *Intermediate 232* (350.00 mg, 419.44 μmol) in DMF (5 mL) was added *Intermediate 256* (90.92 mg, 503.32 μmol, HCl), HATU (175.43 mg, 461.38 μmol) and DIEA (216.83 mg, 1.68 mmol, 292.23 μL) at 20°C. The mixture was stirred at 20°C for 2 h. The reaction mixture was added with HCl (0.5 mol) to adjust pH=3, then mixture was diluted with H₂O (8 mL) and extracted with EtOAc(3 mL x 2). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate: Methanol=10/1 to 0/1) to give *the title compound* (270.00 mg, 59.23% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.26 (s, 3 H), 1.93 (s, 3 H), 1.97 - 2.09 (m, 1 H), 2.07 - 2.13 (m, 1 H), 2.68 (dd, J=13.26, 5.25 Hz, 1 H), 3.06 (t, J=6.38 Hz, 2 H), 3.93 (s, 3 H), 4.32 - 4.41 (m, 1 H), 4.42 -

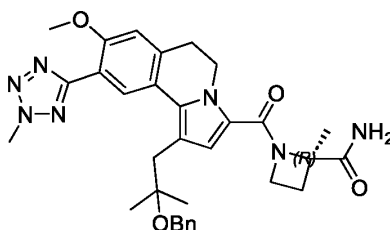
4.51 (m, 1 H), 4.53 - 4.67 (m, 3 H), 6.83 (s, 1 H), 7.13 (t, J=8.63 Hz, 2 H), 7.59 - 7.70 (m, 3 H).
LCMS (*Method 1*, ES⁺, RT = 0.43 min) 443.2/445.2 (M+H)

[001069] INTERMEDIATE 239: (2R,4S)-1-(9-bromo-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile



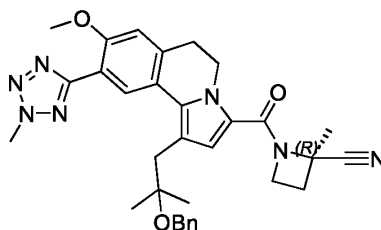
[001070] To a solution of *Intermediate 238* (210.00 mg, 386.47 μ mol) in pyridine (2 mL) was added TFAA (811.70 mg, 3.86 mmol, 537.20 μ L) at 20°C. The mixture was stirred at 30°C for 12 h. The reaction mixture was poured into water, then mixture was added with HCl (0.5 mol) to adjust pH=3 and extracted with MTBE (2mL x 3). The combined organic layers were washed with brine (2mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with K₂CO₃ (30.00 mg) and MeOH (2 mL) at 20°C for 30 min. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give *the title compound* (100.00 mg, 49.25% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.88 (s, 3 H), 2.19 (dd, J=12.87, 3.58 Hz, 1 H), 2.57 - 2.65 (m, 1 H), 3.11 (br s, 2 H), 3.89 (s, 3 H), 4.07 - 4.13 (m, 1 H), 4.16 - 4.26 (m, 1 H), 4.33 - 4.40 (m, 1 H), 4.52 (br d, J=4.65 Hz, 2 H), 5.36 (d, J=3.10 Hz, 1 H), 7.22 (s, 1 H), 7.31 (t, J=8.82 Hz, 2 H), 7.47 (s, 1 H), 7.63 (dd, J=8.64, 5.66 Hz, 2 H). LCMS (*Method 1*, ES⁺, RT = 0.53 min) 525.2/527.2 (M+H)

[001071] INTERMEDIATE 240: (R)-1-(1-(2-(benzyloxy)-2-methylpropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carboxamide



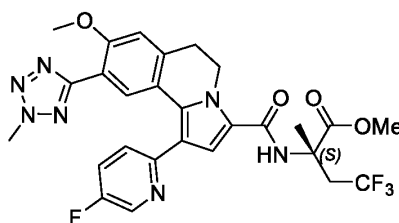
[001072] To a solution of *Intermediate 52* (500 mg, 1.03 mmol) and *Intermediate 124* (185.34 mg, 1.23 mmol, HCl) in DMF (5 mL) was added HATU (428.93 mg, 1.13 mmol) and DIEA (530.17 mg, 4.10 mmol, 714.52 μ L) at 20°C. The mixture was stirred at 20°C for 2hr. The reaction mixture was added H₂O (30 mL) at 0°C, and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. *The title compound* (500 mg, 83.53%) was obtained as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.44 (s, 1H), 7.58 (br s, 1H), 7.21 (br d, J = 3.7 Hz, 7H), 6.59 (br s, 1H), 4.51 (br s, 1H), 4.47 (s, 2H), 4.41 (s, 3H), 4.14 - 3.99 (m, 2H), 3.88 (s, 3H), 3.07 - 2.92 (m, 4H), 2.69 (d, J = 0.7 Hz, 1H), 2.43 - 2.33 (m, 1H), 2.04 - 1.91 (m, 1H), 1.65 (br s, 3H), 1.28 (s, 6H) LCMS (*Method 1*, ES⁺, RT = 0.50 min) 584.3/585.4 (M+H)⁺

[001073] INTERMEDIATE 241: ethyl 9-bromo-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[001074] To a solution of *Intermediate 240* (480 mg, 822.37 μ mol, 1 eq) in THF (2.5 mL) was added burgess reagent (391.95 mg, 1.64 mmol, 2 eq) in DCM (2.5 mL) at 0°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was diluted with H₂O 10 mL and extracted with DCM (3 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ EtOAc =9/1 to 0/1). *The title compound* (400 mg, 85.99%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.45 (s, 1H), 7.21 (s, 5H), 6.60 (s, 1H), 4.56 - 4.44 (m, 4H), 4.41 (s, 3H), 4.20 - 4.08 (m, 2H), 3.88 (s, 3H), 3.06 - 2.98 (m, 4H), 2.71 - 2.62 (m, 2H), 2.39 - 2.32 (m, 1H), 1.79 (s, 3H), 1.27 (s, 6H) LCMS (*Method 1*, ES⁺, RT = 0.56 min) 458.3/459.2 (M+H)⁺

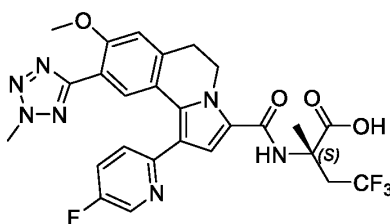
[001075] **INTERMEDIATE 242:** methyl (S)-4,4,4-trifluoro-2-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoate



[001076] To a solution of 1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (1 g, 2.38 mmol) in DMF (10 mL) was added HATU (1.36 g, 3.57 mmol), DIEA (1.23 g, 9.51 mmol, 1.66 mL) and *Intermediate 115* (790.70 mg, 3.57 mmol, HCl) at 20°C. The mixture was stirred at 80°C for 12 hr. The reaction mixture poured into H₂O (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give *title compound* (900 mg, 64.40%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 2.05 (s, 1 H), 2.81 (s, 2 H), 2.94 - 3.06 (m, 1 H), 3.13 (br t, J = 6.38 Hz, 2 H), 3.33 - 3.46 (m, 1 H), 3.85 (s, 3 H), 3.98 (s, 3 H), 4.37 (s, 3 H), 4.58 - 4.70 (m,

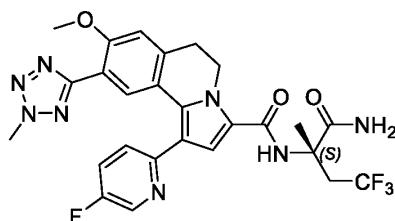
2 H), 6.87 - 6.99 (m, 3 H), 7.45 (td, $J = 8.38, 2.88$ Hz, 1 H), 7.59 (dd, $J = 8.69, 4.32$ Hz, 1 H), 8.08 (s, 1 H), 8.49 (d, $J = 2.88$ Hz, 1 H) LCMS (*Method I*, ES⁺, RT = 0.48 min) 588.4/589.3 (M+H)⁺

[001077] INTERMEDIATE 243: (S)-4,4,4-trifluoro-2-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamido)-2-methylbutanoic acid



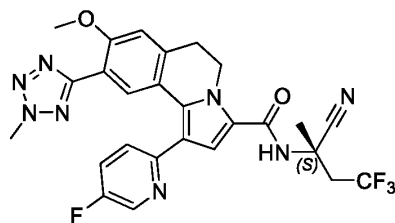
[001078] To a solution of *Intermediate 242* (800 mg, 1.36 mmol) in THF (8 mL) was added TMSOK (349.36 mg, 2.72 mmol) at 20°C. The mixture was stirred at 50°C for 2 hr. The reaction mixture was diluted with 5 mL H₂O, adjusted to pH = 5 with 1M HCl. The aqueous layer was extracted with EtOAc (6 mL x 3), The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give title compound (750 mg, 96.04%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.56 (s, 3 H), 1.99 (s, 1 H), 2.79 - 2.89 (m, 1 H), 3.11 (br t, $J = 6.23$ Hz, 2 H), 3.26 (br dd, $J = 15.28, 12.59$ Hz, 1 H), 3.88 (s, 3 H), 4.36 (s, 3 H), 4.47 - 4.63 (m, 2 H), 7.19 - 7.32 (m, 2 H), 7.59 (dd, $J = 8.80, 4.40$ Hz, 1 H), 7.68 - 7.78 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 8.53 (d, $J = 2.93$ Hz, 1 H). LCMS (*Method I*, ES⁺, RT = 0.43 min) 574.3/575.3 (M+H)⁺

[001079] INTERMEDIATE 244: (S)-N-(1-amino-4,4,4-trifluoro-2-methyl-1-oxobutan-2-yl)-1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



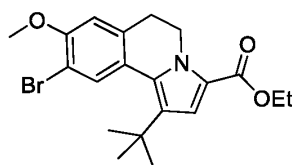
[001080] To a solution of *Intermediate 243* (730.0 mg, 636.45 μmol) in THF (8 mL) was added CDI (154.80 mg, 954.67 μmol) at 20°C for 1 h. The mixture was added $\text{NH}_3 \cdot \text{H}_2\text{O}$ (267.66 mg, 1.91 mmol, 25% purity) at 20°C for 2 hr. The residue was poured into water (20 mL). The aqueous phase was extracted with DCM (5 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give title compound (600 mg, 82.33%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 1.73 (s, 3 H), 3.02 - 3.19 (m, 3 H), 3.31 (br dd, J = 16.01, 11.51 Hz, 1 H), 3.98 (s, 3 H), 4.37 (s, 3 H), 4.57 (ddd, J = 13.35, 8.29, 5.00 Hz, 1 H), 4.53 - 4.63 (m, 1 H), 4.68 - 4.79 (m, 1 H), 6.54 (s, 1 H), 6.97 (d, J = 8.50 Hz, 2 H), 7.13 (s, 1 H), 7.39 (td, J = 8.38, 2.88 Hz, 1 H), 7.55 (dd, J = 8.69, 4.32 Hz, 1 H), 7.75 (s, 1 H), 8.08 (s, 1 H), 8.49 (d, J = 2.75 Hz, 1 H) LCMS (*Method 1*, ES+, RT = 0.42 min) 573.3/574.3 (M+H) +

[001081] INTERMEDIATE 245: (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide



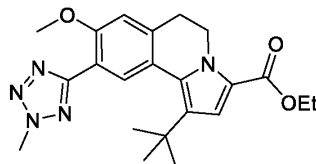
[001082] To a solution of *Intermediate 244* (600 mg, 524.01 μ mol) in THF (6 mL) was added Burgess reagent (249.75 mg, 1.05 mmol) and DCM (6 mL) at 20°C. The mixture was stirred at 20°C for 2 hr. The reaction mixture was diluted with H₂O 20 mL and extracted with DCM 15 mL. The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give *title compound* (500 mg, 86.04%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 1.92 (s, 3 H), 2.05 (s, 1 H), 3.11 - 3.25 (m, 3 H), 3.99 (s, 3 H), 4.38 (s, 3 H), 4.62 - 4.74 (m, 2 H), 6.40 (s, 1 H), 6.98 (d, J = 3.38 Hz, 2 H), 7.40 - 7.50 (m, 1 H), 7.58 (dd, J = 8.76, 4.38 Hz, 1 H), 8.05 (s, 1 H), 8.49 (d, J = 2.88 Hz, 1 H) LCMS (*Method l*. ES⁺, RT = 0.47 min) 555.3/556.4 (M+H)⁺

[001083] **INTERMEDIATE 246:** ethyl 9-bromo-1-(tert-butyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



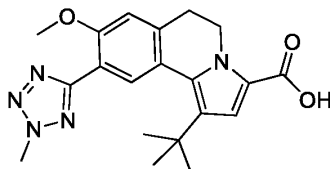
[001084] To a solution of *Intermediate 39* (3.3 g, 8.54 mmol) in Ac₂O (50 mL) was added 3,3-dimethylbut-1-yne (1.40 g, 17.09 mmol) at 20°C. The mixture was stirred at 140°C for 1hr. The reaction mixture was concentrated under reduced pressure to remove Ac₂O. The residue was diluted with H₂O 100 mL and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/EtOAc=10/1 to 0/1). *The title compound* (8 g, 76.81%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.28 (t, J=7.07 Hz, 3 H), 1.37 (s, 9 H), 2.90 (br t, J=6.25 Hz, 2 H), 3.89 (s, 3 H), 4.22 (q, J=7.09 Hz, 2 H), 4.43 (t, J=6.25 Hz, 2 H), 6.88 (s, 1 H), 7.15 (s, 1 H), 7.89 (s, 1 H). LCMS (*Method h*. ES⁺, RT = 2.90 min) 406.1/408.2 (M+H)⁺

[001085] **INTERMEDIATE 247:** ethyl 1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[001086] To a solution of *Intermediate 246* (1 g, 2.46 mmol) in DMF (10 mL) was added *Intermediate 26* (1.84 g, 4.92 mmol) and XPHOS-Pd-G₂ (387.29 mg, 492.23 μ mol) at 20°C. The mixture was stirred at 120°C for 12hr. The reaction mixture was filtered. The residue was diluted with H₂O (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/EtOAc=10/0 to 0/1). The crude product was triturated with MTBE at 20°C for 30 min. *The title compound* (800 mg, 79.38%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.29 (t, J=7.07 Hz, 3 H), 1.40 (s, 9 H), 3.00 (br t, J=6.07 Hz, 2 H), 3.91 (s, 3 H), 4.23 (q, J=7.13 Hz, 2 H), 4.42 (s, 3 H), 4.48 (br t, J=6.19 Hz, 2 H), 6.90 (s, 1 H), 7.25 (s, 1 H), 8.35 - 8.45 (m, 1 H). LCMS (*Method 1*, ES⁺, RT = 0.60 min) 410.2/411.2 (M+H)⁺.

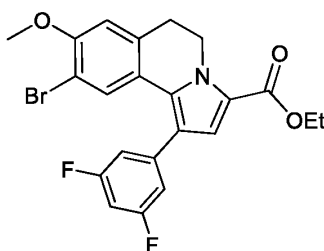
[001087] **INTERMEDIATE 248:** 1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[001088] To a solution of *Intermediate 247* (340 mg, 830.32 μ mol) in EtOH (0.5 mL) and THF (0.5 mL) was added KOH (139.76 mg, 2.49 mmol) in H₂O (0.5 mL) at 20°C. The mixture was stirred at 80°C for 2hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O 10 mL and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. *The title compound* (300 mg, 94.72%) was obtained as

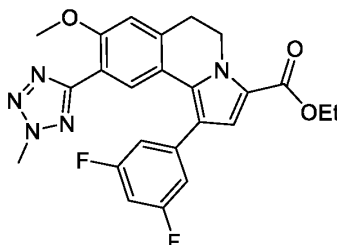
a blue solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 1.40 (s, 9 H), 2.99 (br t, J =5.94 Hz, 2 H), 3.91 (s, 3 H), 4.42 (s, 2 H), 4.47 - 4.52 (m, 2 H), 6.88 (s, 1 H), 7.24 (s, 1 H), 8.39 (s, 1 H), 12.23 (br s, 1 H). LCMS (*Method l*. ES^+ , RT = 0.46 min) 382.1/383.2 ($\text{M}+\text{H}$) $^+$.

[001089] INTERMEDIATE 249: ethyl 9-bromo-1-(3,5-difluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



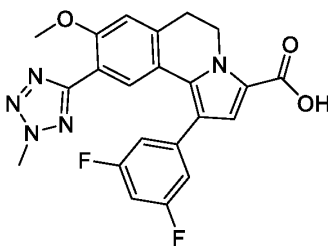
[001090] To a solution of *Intermediate 39* (6 g, 15.54 mmol) in Ac_2O (50 mL) was added 1-ethynyl-3,5-difluoro-benzene (3.22 g, 23.30 mmol, 1.5 eq) at 20°C. The mixture was stirred at 140°C for 1hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The combined reaction mixture was poured into ice-water (100 mL) and added Na_2CO_3 to pH= 8-9. The reaction mixture was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE at 20 °C for 10 min. *The title compound* (5.2 g, 72.40%) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.42 - 7.37 (m, 1H), 7.21 - 7.18 (m, 1H), 6.93 - 6.85 (m, 3H), 6.74 - 6.66 (m, 2H), 4.61 - 4.49 (m, 2H), 4.29 - 4.16 (m, 2H), 3.91 - 3.78 (m, 3H), 2.97 (t, J = 6.5 Hz, 2H), 1.37 - 1.23 (m, 3H). LCMS (*Method g*. ES^+ , RT = 0.70 min) 462.2/464.2 ($\text{M}+\text{H}$) $^+$.

[001091] **INTERMEDIATE 250:** ethyl 1-(3,5-difluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate



[001092] To a solution of *Intermediate 249* (2 g, 4.33 mmol) *Intermediate 26* (3.23 g, 8.65 mmol) in DMF (20 mL) was added XPHOS-Pd-G₂ (680.80 mg, 865.27 μ mol) at 20°C. The mixture was stirred at 120°C for 12hr under Ar. The reaction mixture was diluted in H₂O (50 mL) and added KF (20 mL). The reaction mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layers were washed with (50 mL $\times$ 4), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE at 20 °C for 5 min to give *title compound* (1.3 g, 64.56%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.91 (s, 1H), 6.98 - 6.84 (m, 4H), 6.72 - 6.58 (m, 1H), 4.66 - 4.52 (m, 2H), 4.30 - 4.21 (m, 5H), 3.93 - 3.88 (m, 3H), 3.14 - 2.99 (m, 2H), 1.34 - 1.27 (m, 5H), 0.90 - 0.81 (m, 3H). LCMS (*Method 1*, ES⁺, RT = 0.61 min) 466.2/467.2 (M+H)⁺.

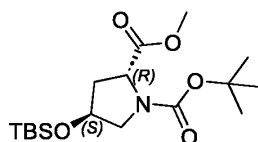
[001093] **INTERMEDIATE 251:** 1-(3,5-difluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid



[001094] To a solution of *Intermediate 250* (1.2 g, 2.58 mmol, 1 eq) in THF (30 mL) was added TMSOK (992.23 mg, 7.73 mmol, 3 eq). The mixture was stirred at 20 °C for 2hr. The reaction

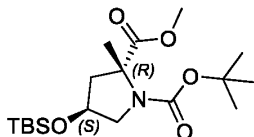
mixture was poured into ice-water (50 mL) and added 1 M HCl to pH=5-6. The reaction mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE at 20 °C for 5 min to give *title compound* (800 mg, 70.94%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.88 - 7.72 (m, 1H), 7.35 - 7.25 (m, 1H), 7.20 - 7.07 (m, 3H), 6.99 (s, 1H), 4.64 - 4.51 (m, 2H), 4.40 - 4.29 (m, 3H), 3.97 - 3.80 (m, 3H), 3.17 (br t, *J* = 6.3 Hz, 2H). LCMS (*Method a.* ES⁺, RT = 1.63 min) 438.2/439.2 (M+H)⁺.

[001095] INTERMEDIATE 252: 1-(tert-butyl) 2-methyl (2R,4S)-4-((tert-butyl)dimethylsilyl)oxy)-pyrrolidine-1,2-dicarboxylate



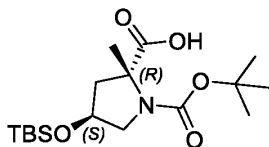
[001096] Under argon atmosphere, imidazole (42.47 g, 623.8 mmol) was added portions to a solution of O1-tert-butyl O2-methyl (2R,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (90 g, 366.94 mmol) and tert-butyl-chloro-dimethyl-silane (82.96 g, 550.41 mmol, 67.72 mL) in DCM (540 mL) at 0°C. Then reaction was stirred at 15°C for 16 hr. The residue was poured into water (500 mL). The aqueous phase was extracted with DCM (500 mL $\times$ 3). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 25/1). *The title compound* (112 g, 84.90% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 4.43 (br s, 1H), 4.25-4.15 (m, 1H), 3.68 - 3.61 (m, 3H), 3.51 - 3.38 (m, 1H), 3.25 (br t, *J* = 10.9 Hz, 1H), 2.16-2.05 (m, 1H), 2.04-1.89 (m, 1H), 1.41 - 1.30 (m, 9H), 0.86 - 0.79 (m, 10H), 0.06 (d, *J* = 2.1 Hz, 6H)

[001097] INTERMEDIATE 253: 1-(tert-butyl) 2-methyl (2R,4S)-4-((tert-butyl)dimethylsilyl)oxy)-2-methylpyrrolidine-1,2-dicarboxylate



[001098] Three batches were carried out in parallel. *Intermediate 252* (30 g, 83.44 mmol) was dissolved in dry THF (300 mL). The mixture was cooled to -78°C and LiHMDS (1 M, 208.60 mL) was added dropwise. Reaction was stirred at that temperature for 30 min. Then MeI (47.37 g, 333.77 mmol, 20.78 mL) was added dropwise. The mixture was stirred at -78°C to 15°C for 12 hr. The residue was poured into water (1000 mL). The aqueous phase was extracted with EtOAc (1000 mL x 3). The combined organic phase was washed with brine (100 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=50/1 to 20/1). *The title compound* (33 g, 70.58% yield) was a colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.43 (qd, $J = 2.3, 4.7$ Hz, 1H), 3.69-3.61 (m, 2H), 3.61-3.54 (m, 2H), 3.31 - 3.25 (m, 1H), 2.33-2.18 (m, 1H), 1.91-1.78 (m, 1H), 1.60-1.52 (m, 3H), 1.40-1.30 (m, 9H), 0.88-0.76 (m, 9H), 0.09-0.02 (m, 6H)

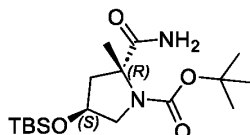
[001099] INTERMEDIATE 254: (2R,4S)-1-(tert-butoxycarbonyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylpyrrolidine-2-carboxylic acid



[001100] To a solution of *Intermediate 253* (17.5 g, 46.85 mmol) in THF (170 mL) was added TMSOK (12.02 g, 93.69 mmol) at 20°C . The mixture was stirred at 50°C for 12 hours. The reaction was added H_2O (500 mL) and the mixture was added 1N HCl solution to make the pH = 6 and the extracted with EtOAc (300 mL x 3). The organic layers were concentrated under reduced pressure to give a product. *The title compound* (33 g, 97.96% yield) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.41 (br s, 1H), 3.54 (br dd, $J=4.5, 11.3$ Hz, 1H), 3.30-3.20 (m,

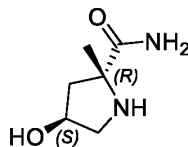
1H), 2.31-2.18 (m, 1H), 1.88-1.73 (m, 1H), 1.52 (s, 3H), 1.40-1.31 (m, 9H), 0.89-0.81 (m, 9H), 0.06 (s, 6H)

[001101] INTERMEDIATE 255: tert-butyl (2R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-carbamoyl-2-methylpyrrolidine-1-carboxylate



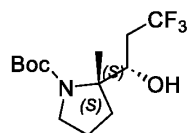
[001102] To a solution of *Intermediate 254* (15 g, 41.72 mmol) in THF (150 mL) was added CDI (10.15 g, 62.58 mmol) at 20°C. The mixture was stirred at 20°C for 0.5 hour. The mixture was added NH₃·H₂O (26.11 g, 208.60 mmol, 28.70 mL, 28% purity) at 20°C. The mixture was stirred at 20°C for 1 hour. The reaction mixture was diluted with H₂O (500 mL) and the reaction was added 1N HCl solution to adjust the pH = 7, the reaction was extracted with MTBE (200 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The crude product was washed by NaHCO₃ solution (300 mL) and the mixture was filtered to give the product as a white solid. The white solid was dissolved by MTBE (500 mL) and the organic layers was washed by H₂O and brine (100 mL). The organic layers was dried over Na₂SO₄ and the mixture was filtered. The organic layers were concentrated under reduced pressure to give a product. *The title compound* (25 g, 83.56% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.11 - 7.00 (m, 1H), 6.98-6.81 (m, 1H), 4.37 (br d, *J* = 2.4 Hz, 1H), 3.68 (br dd, *J* = 4.9, 11.1 Hz, 1H), 3.25-3.16 (m, 1H), 2.20 (br dd, *J* = 5.5, 12.9 Hz, 1H), 1.84-1.70 (m, 1H), 1.56-1.49 (m, 3H), 1.39-1.32 (m, 9H), 0.89-0.82 (m, 9H), 0.08-0.03 (m, 6H)

[001103] INTERMEDIATE 256: (2R,4S)-4-hydroxy-2-methylpyrrolidine-2-carboxamide



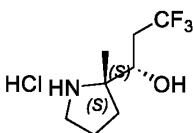
[001104] To a solution of *Intermediate 255* (2 g, 5.58 mmol) in MeOH (4 mL) was added HCl/MeOH (40 mL). The mixture was stirred at 20 °C for 1hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was concentrated under reduced pressure to remove solvent. *The title compound* (1 g, 99.25% yield, HCl) was obtained as a white oil. ¹H NMR (400 MHz, DMSO-d₆) δ 9.97-9.79 (m, 1H), 8.86-8.70 (m, 1H), 8.15-8.03 (m, 1H), 7.83-7.74 (m, 1H), 4.46-4.34 (m, 1H), 3.44-3.30 (m, 1H), 3.17-3.04 (m, 1H), 2.64-2.54 (m, 1H), 2.45-2.33 (m, 1H), 2.17-2.05 (m, 1H), 1.74 (s, 3H)

[001105] **INTERMEDIATE 257:** tert-butyl (S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)-pyrrolidine-1-carboxylate



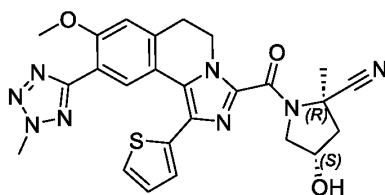
[001106] To a solution of *Intermediate 103* (20 g, 67.73 mmol) in MeOH (100 mL) was added Tetrabutylammonium borohydride (34.85 g, 135.46 mmol) at 0°C. The mixture was stirred at 30°C for 1 hour. The two reactions was combined to work up. The mixture was diluted with H₂O (300 mL) and extracted with EtOAc (100 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 1/1) to give *the title compound* (10.5 g, 52% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.37-6.10 (m, 1H), 4.15 (br d, *J*= 7.5 Hz, 1H), 3.69 - 3.56 (m, 1H), 3.37-3.25 (m, 1H), 2.32-2.11 (m, 2H), 1.89-1.62 (m, 4H), 1.50-1.35 (m, 12H)

[001107] **INTERMEDIATE 258:** tert-butyl (S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)-pyrrolidine-1-carboxylate

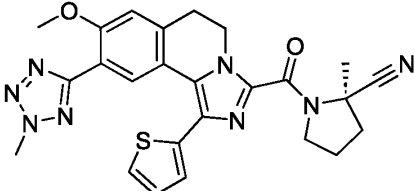
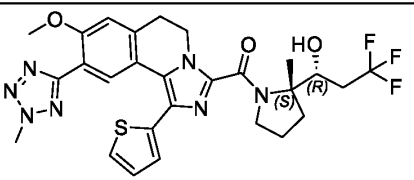


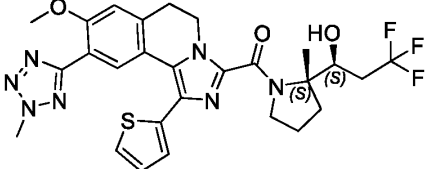
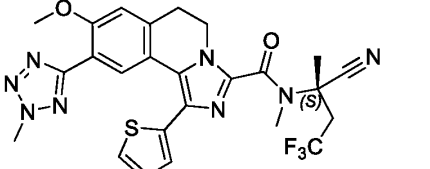
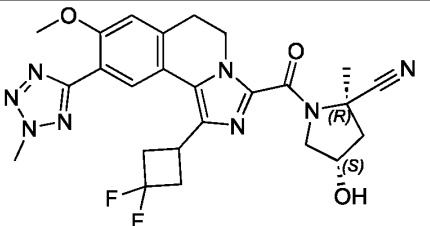
[001108] To a solution of *Intermediate 257* (200 mg, 672.69 μmol) in MeOH (0.5 mL) was added HCl/MeOH (4 M, 5.00 mL, 29.73 eq) at 20°C. The mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove MeOH. *The title compound* (150 mg, 641.96 μmol , 95.43% yield, HCl) was obtained as a white solid. ^1H NMR (400 MHz, MeOD- d_4) δ = 3.98-4.01 (d, J = 9.2 Hz, 1H), 3.37-3.37(m, 2H), 2.39-2.44(m, 2H), 2.10-2.14(m, 2H), 1.89-1.93((m, 2H), 1.35(s, 3H).

[001109] **EXAMPLE 1 (METHOD A):** (2R,4S)-4-hydroxy-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile

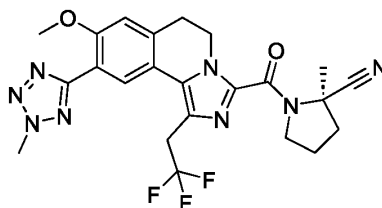


[001110] To a solution of *Intermediate 28* (80 mg, 155.82 μmol) in DMF (0.8 mL) was added *Intermediate 2* (116.28 mg, 311.64 μmol) and XPHOS-Pd- G_2 (12.26 mg, 15.58 μmol) at 20 °C. The mixture was stirred at 120 °C for 12 h. The reaction mixture was added to the ice water and extracted with EtOAc (2 mL x 3), combined organic phase was washed with 3 mL brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 15*). *EXAMPLE 1* (41.38 mg, 51.41% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.32 (s, 1H), 7.56 (dd, J = 5.13, 1.00 Hz, 1H), 7.37 (dd, J = 3.56, 0.94 Hz, 1H), 7.33 (s, 1H), 7.11 (dd, J = 5.13, 3.63 Hz, 1H), 5.39 (d, J = 3.38 Hz, 1H), 4.55 (br t, J = 6.38 Hz, 2H), 4.33-4.43 (m, 4H), 4.17 - 4.28 (m, 1H), 4.08 (dd, J = 11.69, 3.06 Hz, 1H), 3.91 (s, 3H), 3.19 (br t, J = 6.38 Hz, 2H), 2.62 (dd, J = 13.13, 5.13 Hz, 1H), 2.20 (dd, J = 13.07, 3.94 Hz, 1H), 1.89 (s, 3H) LCMS (*Method r*. ES^+ , RT = 2.655 min) 517.0/518.0 (M+H) $^+$

Example No.	Precursor	Structure/Name	LCMS
2	Int. 17	 (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method s.</i> ES ⁺ , RT=2.976 min) 501.0 (M+H) ⁺
3	Int. 29	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method f.</i> ES ⁺ , RT = 3.001 min) 588.2/589.2 (M+H) ⁺

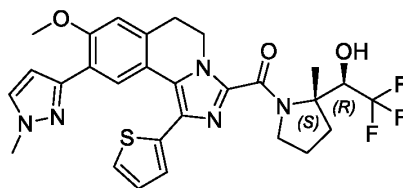
4	Int. 30	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method f.</i> ES ⁺ , RT = 3.110 min) 588.2/589.2 (M+H) ⁺
5	Int. 35	 (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide	LCMS (<i>Method f.</i> ES ⁺ , RT = 3.055 min) 557.0/558.0 (M+H) ⁺
6	Int. 175	 (2R,4S)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method f.</i> ES ⁺ , RT = 2.710 min) 525.2/526.2 (M+H) ⁺

[001111] **EXAMPLE 7 (METHOD B):** (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



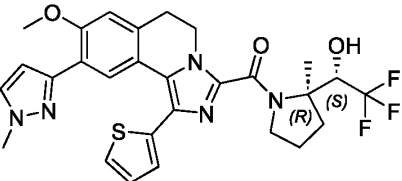
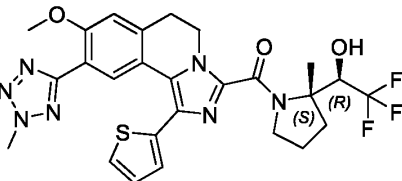
[001112] To a solution of *Intermediate 150* (55 mg, 110.60 μmol), *Intermediate 26* (82.53 mg, 221.19 μmol) in DMF (1 mL) was added XPHOS-Pd-G₂ (8.70 mg, 11.06 μmol) at 20 °C. The mixture was stirred at 110 °C for 60 min. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (*Method 16*). *EXAMPLE 7* (13.12 mg, 23.7% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 - 8.14 (m, 1 H) 7.29 - 7.36 (m, 1 H) 4.53 (br t, J=6.6 Hz, 2 H) 4.43 (s, 3H) 3.99 - 4.09 (m, 2 H) 3.90 (s, 3 H) 3.83 (q, J=11.0 Hz, 2 H) 3.14 (br t, J=6.4 Hz, 2 H) 2.43 - 2.47 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.07 - 2.08 (m, 1 H) 2.07 - 2.08 (m, 1 H) 1.87 - 2.06 (m, 2 H) 1.76 (s, 3 H) LCMS (*Method r*. ES⁺, RT = 2.855 min) 501.1/502.1(M+H)⁺

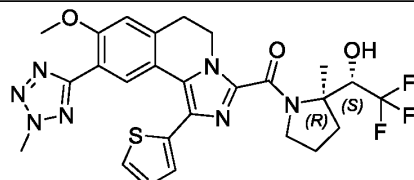
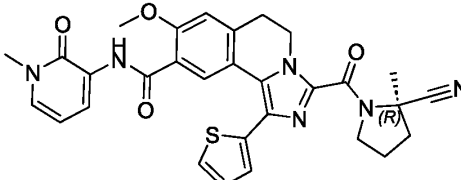
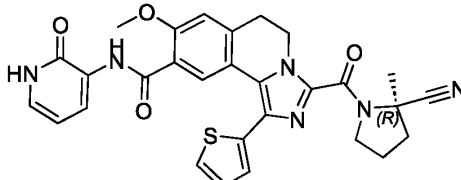
[001113] **EXAMPLE 8 (METHOD C):** (8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone

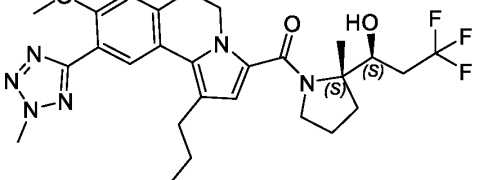
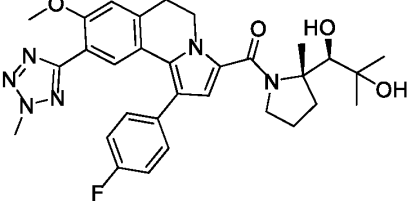


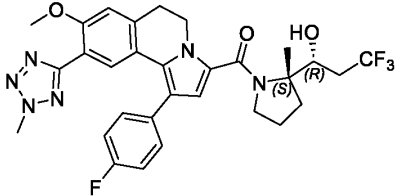
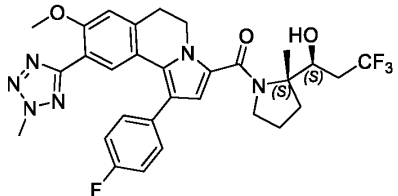
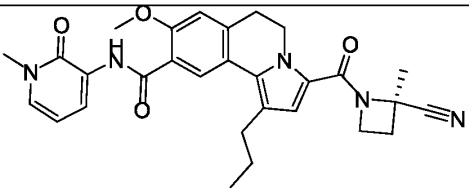
[001114] To a solution of *Intermediate 9* (90 mg, 221.43 μmol) and (1R)-2,2,2-trifluoro-1-[(2S)-2-methylpyrrolidin-2-yl]ethanol (53.50 mg, 243.57 μmol , HCl) in DMF (0.5 mL) was

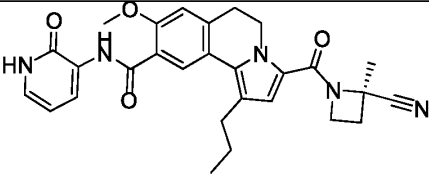
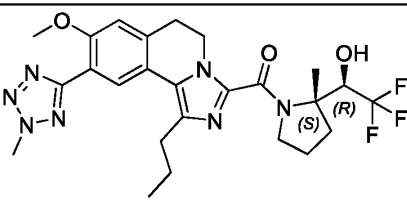
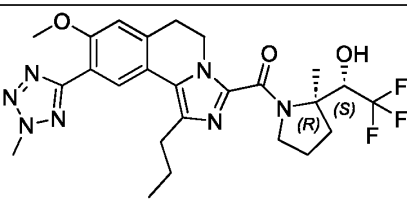
added HATU (92.61 mg, 243.57 μ mol) and DIEA (85.85 mg, 664.28 μ mol) at 20 °C. The mixture was stirred at 20 °C for 2 hr. The organic layers was concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (*Method 15*) to give *EXAMPLE 8* (46.37 mg, 36% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.44 (s, 1H), 7.65 (d, J = 2 Hz, 1H), 7.52 (d, J = 5.2 Hz, 1H), 7.40 (d, J = 2.8 Hz, 1H), 7.13-7.10 (m, 2H), 6.71 (d, J = 7.2 Hz, 1H), 6.63 (s, 1H), 5.04 (t, J = 6.6 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.20 (m, 1H), 3.89 (s, 3H), 3.84-3.81 (m, 4H), 3.07 (t, J = 6.6 Hz, 2H), 2.39-2.36 (m, 1H), 1.84-1.80 (m, 2H), 1.74-1.69 (m, 1H), 1.61 (s, 3H). LCMS (*Method s*. ES $^+$, RT = 3.22 min) 572.3 (M+H) $^+$

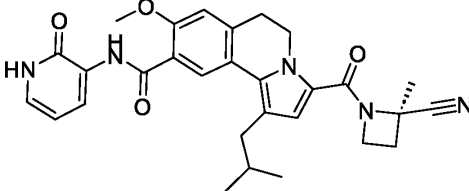
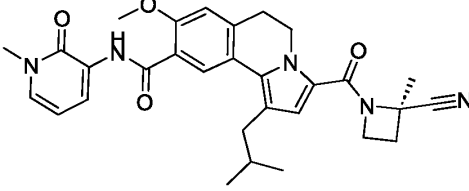
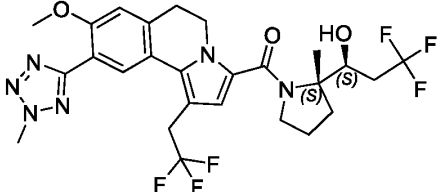
Example No.	Precursor	Structure/Name	LCMS
9	Int. 9	 (8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl) methanone	LCMS (<i>Method s</i> . ES $^+$, RT = 3.224 min) 572.2 (M+H) $^+$
10	Int. 14	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method s</i> . ES $^+$, RT = 3.07 min) 574.3 (M+H) $^+$

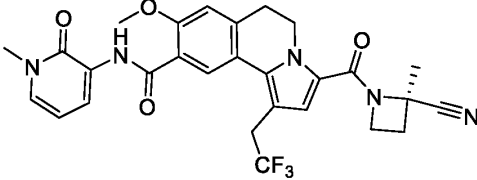
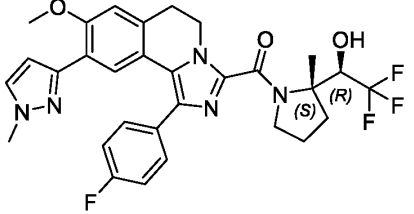
11	Int. 14	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method s.</i> ES ⁺ , RT =3.098 min) 574.3 (M+H) ⁺
12	Int. 24	 (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method s.</i> ES ⁺ , RT = 2.984 min) 569.0 (M+H) ⁺
13	Int. 24	 (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method s.</i> ES ⁺ , RT =2.864 min) 555.0 (M+H) ⁺

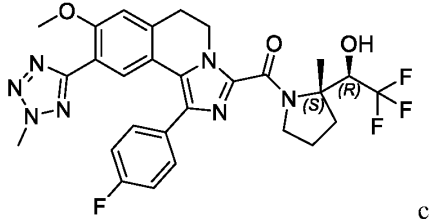
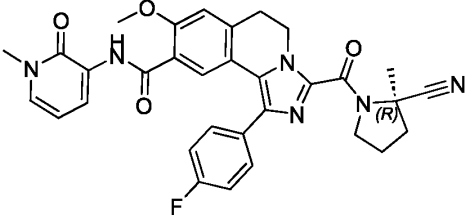
14	Int. 110B	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)431rrolidine-1-yl)methanone	LCMS (<i>Method f.</i> ES⁺, RT = 3.313 min) 547.2 (M+H)⁺.
15	Int. 109B	 ((S)-2-((R)-1,2-dihydroxy-2-methylpropyl)-2-methylpyrrolidin-1-yl)(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)methanone	LCMS (<i>Method r.</i> ES⁺, RT = 2.975 min) 575.1 (M+H)⁺

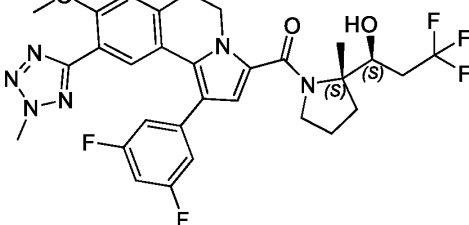
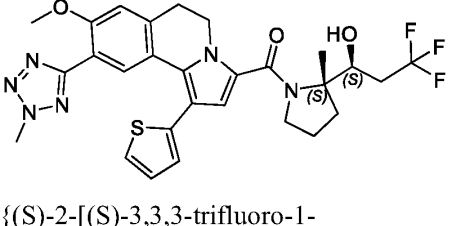
16	Int. 109B	 (1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method f</i>) ES+ RT=3.209 min) 599.2 (M+H)+.
17	Int. 109B	 (1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method b</i>) ES+ RT= 2.965 min) 599.2 (M+H)+.
18	Int. 128	 (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method h</i>) ES ⁺ , RT = 2.084 min) 514.2 (M+H) ⁺ .

19	Int. 128	 (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method r.</i> ES ⁺ , RT =2.913 min) 500.1 (M+H) ⁺
20	Int. 140	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method r.</i> ES ⁺ , RT = 2.980 min) 534.1/535.1 (M+H) ⁺
21	Int. 140	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method k.</i> ES ⁺ , RT =2.495min) 534.4 (M+H) ⁺

22	Int. 181	 (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method r</i> , RT = 3.02 min) 514.2/515.2 (M+H) ⁺ .
23	Int. 181	 (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method q</i> , RT = 2.82 min) 528.3/529.3 (M+H) ⁺ .
24	Int. 187	 (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method f</i> , RT = 3.06 min) 587.3/588.3 (M+H) ⁺ .

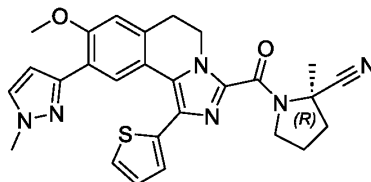
25	Int. 211	 (R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method r.</i>) ES ⁺ , RT = 2.60 min) 554.2 (M+H) ⁺
26	Int. 217	 (1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method s.</i>) ES ⁺ , RT = 3.292 min) 584.3/585.3 (M+H) ⁺

27	Int. 223	 (1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone	LCMS (<i>Method s.</i> ES⁺, RT = 3.107 min) 586.2/587.2 (M+H)⁺
28	Int. 236	 (R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide	LCMS (<i>Method s.</i> ES⁺, RT = 3.051 min) 581.1/582.1 (M+H)⁺

29	Int. 251	 (1-(3,5-difluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>method f</i> . ES ⁺ , RT = 3.25 min) 617.2/618.2 (M+H) ⁺
30	***	 {(S)-2-[(S)-3,3,3-trifluoro-1-hydroxypropyl]-2-methyl-1-pyrrolidinyl} {11-methoxy-12-(2-methyl-2H-tetraazol-5-yl)-3-(2-thienyl)-6-azatricyclo[7.4.0.0^{2,6}]trideca-1(13),2,4,9,11-pentaen-5-yl}methanone	LCMS (<i>method M9</i> . ES ⁺ , RT = 3.87 min) 587.3 (M+H) ⁺

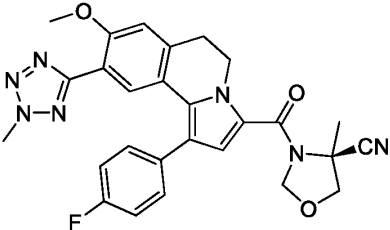
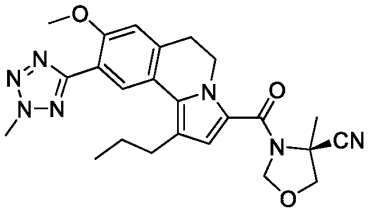
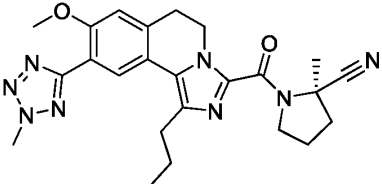
*** = 8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid, prepared in accordance with a method analogous to that of method 19 (steps 1 to 3) using ethyl 9-bromo-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (as described herein) as the starting material.

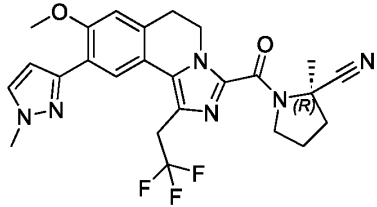
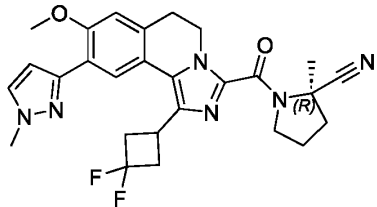
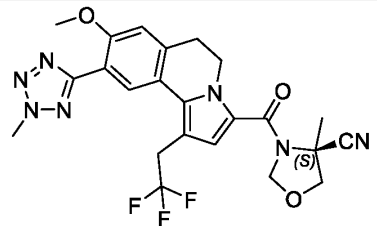
[001115] EXAMPLE 31 (METHOD D): (R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile

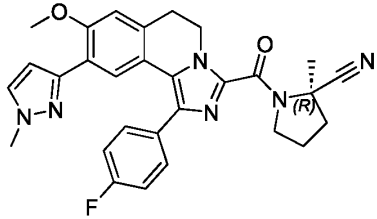
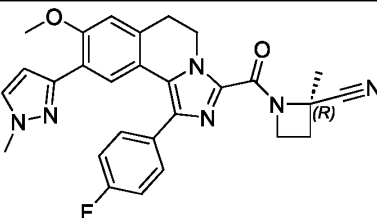
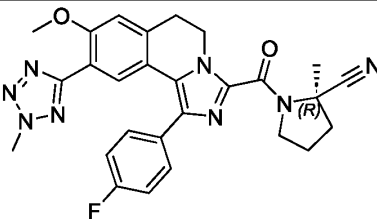


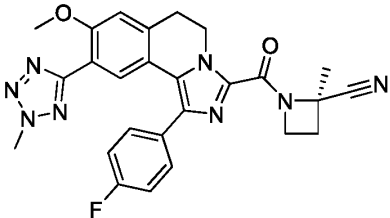
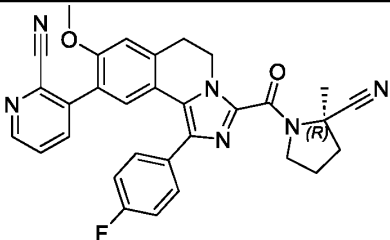
[001116] To a solution of *Intermediate 11* (550 mg, 1.06 mmol) in THF (5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (634.26 mg, 2.66 mmol) in DCM (5 mL) at 20 °C. The mixture was stirred at 20 °C for 2 hr. The residue was diluted with H₂O (30 mL) and extracted with DCM (15 mL x 3). The organic layers were concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 0/1) to give *EXAMPLE 31* (385 mg, 36% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.48 (s, 1H), 7.65 (d, *J* = 2 Hz, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.16(s, 1H), 7.13-7.11 (m, 1H), 6.64 (d, *J* = 7.2 Hz, 1H), 4.50 (t, *J* = 6.6 Hz, 2H), 4.12-4.07 (m, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.11 (t, *J* = 6.6 Hz, 2H), 2.21-2.18 (m, 1H), 2.05-1.94 (m, 2H), 1.78 (s, 3H). LCMS (*Method s*. ES⁺, RT = 3.08 min) 499.2 (M+H)⁺

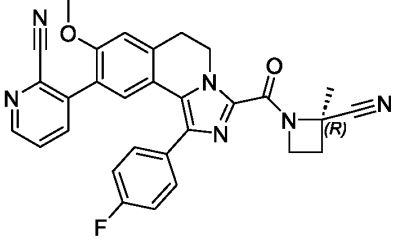
Example No.	Precursor	Structure/Name	LCMS
32	Int. 58	(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	LCMS (<i>Method f</i> . ES ⁺ , RT=3.08 min) 458.2 (M+H) ⁺ .

33	Int. 109	 (S)-3-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile	LCMS (<i>Method r.</i>) ES ⁺ , RT = 3.038 min) 514.0 (M+H) ⁺ .
34	Int. 110	 (S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile	LCMS (<i>Method s.</i>) ES ⁺ , RT=2.991 min) 462.1 (M+H) ⁺
35	Int. 141	 (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method r.</i>) ES ⁺ , RT = 2.846 min) 461.1/462.1 (M+H) ⁺

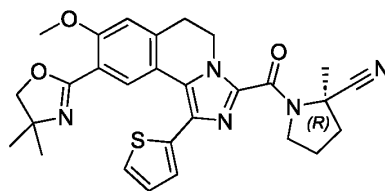
36	Int. 156	 (R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method f.</i> ES ⁺ , RT = 2.996 min) 499.2/500.2 (M+H) ⁺
37	Int. 168	 (R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method f.</i> ES ⁺ , RT = 3.221 min) 507.2/508.2 (M+H) ⁺
38	Int. 192	 (S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile	LCMS (<i>Method r.</i> RT =2.895 min) 501.2/502.0 (M+H) ⁺ .

39	Int. 218	 (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method s.</i> ES ⁺ , RT = 3.178 min) 511.2/512.2 (M+H) ⁺
40	Int. 219	 (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	LCMS (<i>Method s.</i> ES ⁺ , RT=3.208 min) 497.2/498.2 (M+H) ⁺
41	Int. 224	 (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-	LCMS (<i>Method s.</i> ES ⁺ , RT=2.995 min) 513.2/514.2 (M+H) ⁺

		carbonyl)-2-methylpyrrolidine-2-carbonitrile	
42	Int. 225	 (R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile	LCMS (<i>Method s</i> , ES ⁺ , RT=3.019 min) 499.2/500.2 (M+H) ⁺
43	Int. 229	 (R)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile	LCMS (<i>Method f</i> , ES ⁺ , RT=3.218 min) 533.2/534.2 (M+H) ⁺ .

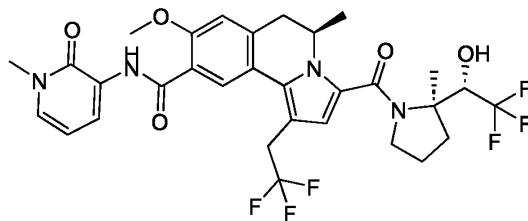
44	Int. 230	 (R)-3-(3-(2-cyano-2-methylazetidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile	LCMS (<i>Method s</i> , ES ⁺ , RT=3.209 min) 519.0/520.0 (M+H) ⁺ .
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[001117] **EXAMPLE 45 (METHOD E):** (R)-1-(9-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



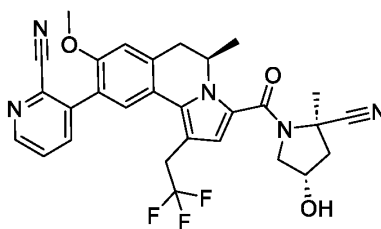
[001118] To a solution of *Intermediate 17* (100 mg, 201.04 μ mol) in dioxane (1 mL) was added 4,4-dimethyl-5H-oxazole (39.86 mg, 402.09 μ mol) and DPPE (4.81 mg, 12.06 μ mol), t-BuOLi (80.47 mg, 1.01 mmol, 90.62 μ L), Pd(OAc)₂ (9.03 mg, 40.21 μ mol) at 20 °C. The mixture was stirred at 110 °C for 12 hr. The reaction mixture was filtered to give the residue. The residue was purified by prep-HPLC (*Method 15*) to give **EXAMPLE 45** (8.06 mg, 7.78% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 1.89 (s, 3 H), 2.06 - 2.18 (m, 3 H), 2.55 - 2.65 (m, 1 H), 3.17 (t, J = 6.50 Hz, 2 H), 3.99 (s, 3 H), 4.30 (br s, 2 H), 4.66 - 4.87 (m, 2 H), 6.98 (s, 1 H), 7.07 (dd, J = 5.13, 3.63 Hz, 1 H), 7.16 (d, J = 7.63 Hz, 2 H), 7.23 - 7.26 (m, 1 H), 7.32 - 7.35 (m, 1 H), 7.38 - 7.44 (m, 3 H), 8.51 - 8.60 (m, 1 H). LCMS (*Method s*, ES⁺, RT = 3.082 min) 516.1 (M+H)⁺

[001119] **EXAMPLE 46 (METHOD F):** (R)-8-methoxy-5-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide



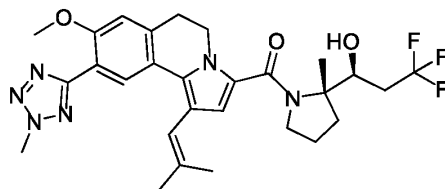
[001120] A mixture of *Intermediate 55B* (93 mg, 190.01 μmol), (1S)-2,2,2-trifluoro-1-[(2R)-2-methylpyrrolidin-2-yl]ethanol (70.95 mg, 323.02 μmol , HCl) and CDI (33.89 mg, 209.01 μmol) in NMP (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 $^{\circ}\text{C}$ for 12 hr under N_2 atmosphere. The residue was purified by prep-HPLC (*Method 15*) to give *EXAMPLE 46*. (19.42 mg, 15.61% yield) as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.96 (s, 1H), 8.46 (br d, J = 6.6 Hz, 1H), 8.37 (s, 1H), 7.44 (br d, J = 6.3 Hz, 1H), 7.32 (s, 1H), 6.69 (br d, J = 5.4 Hz, 1H), 6.48 (s, 1H), 6.30 (br t, J = 7.1 Hz, 1H), 5.10 - 4.96 (m, 2H), 4.10 (s, 3H), 3.84 - 3.60 (m, 3H), 3.56 (s, 4H), 3.27 - 3.18 (m, 1H), 2.98 (br d, J = 15.9 Hz, 1H), 2.43 - 2.32 (m, 1H), 1.86 - 1.84 (m, 1H), 1.85 - 1.66 (m, 2H), 1.61 (s, 3H), 1.08 (br d, J = 6.4 Hz, 3H). LCMS (*Method q*, ES^+ , RT = 2.773 min) 655.3/656.3 ($\text{M}+\text{H}$) $^+$.

[001121] **EXAMPLE 47 (METHOD G):** 3-((R)-3-((2R,4S)-2-cyano-4-hydroxy-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-9-yl)picolinonitrile



[001122] To a solution of *Intermediate 37* (100 mg, 174.40 μ mol) and 3-bromopyridine-2-carbonitrile (38.30 mg, 209.27 μ mol) in dioxane (1 mL) H₂O (0.2 mL) was added Cs₂CO₃ (227.29 mg, 697.58 μ mol) and degassed and purged with N₂ for 3 time. And then the mixture was added XPHOS-Pd-G₂ (13.72 mg, 17.44 μ mol) and stirred at 80 °C for 2 hr. The residue was diluted with H₂O 10 mL and then extracted with EtOAc 30 mL (10 mL $\times$ 3). The combined organic layers were washed with brine 30 mL (10 mL $\times$ 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 15*) to give the *EXAMPLE 47* (45 mg, 46.95% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.81 - 8.70 (m, 1H), 8.14 - 8.08 (m, 1H), 7.87 - 7.79 (m, 1H), 7.67 - 7.61 (m, 1H), 7.33 - 7.27 (m, 1H), 6.71 - 6.66 (m, 1H), 5.45 - 5.39 (m, 1H), 5.26 (quin, J = 6.0 Hz, 1H), 4.39 - 4.32 (m, 1H), 4.04 - 3.97 (m, 1H), 3.92 - 3.76 (m, 5H), 3.68 - 3.61 (m, 1H), 3.31 - 3.24 (m, 1H), 3.05 - 2.94 (m, 1H), 2.66 - 2.60 (m, 1H), 2.55 - 2.46 (m, 14H), 2.23 - 2.15 (m, 1H), 1.91 - 1.85 (m, 3H), 1.21 - 1.14 (m, 3H). LCMS (*Method h*. ES⁺, RT = 1.930 min) 550.2/551.2 (M+H)⁺

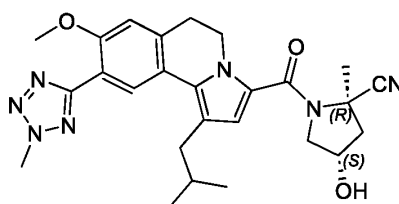
EXAMPLE 48 (METHOD H): (8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone



[001123] To a solution of *Intermediate 57* (48 mg, 126.51 μ mol) and *Intermediate 258* (35.47 mg, 151.81 μ mol, HCl) in DMF (1 mL) was added HATU (62.53 mg, 164.47 μ mol) and DIEA (65.40 mg, 506.05 μ mol, 88.14 μ L) at 20 °C. The mixture was stirred at 80 °C for 2 hr. The reaction mixture was added H₂O (5 mL) at 0 °C, and then extracted with EtOAc (2 mL $\times$ 3). The combined organic layers were washed with brine (3 mL $\times$ 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (*Method 15*). *EXAMPLE 48* (24.09 mg, 34.09% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.12 (s, 1H), 7.20 (s, 1H), 6.50 (s, 1H), 6.21 (s, 1H), 5.47 (d, J =

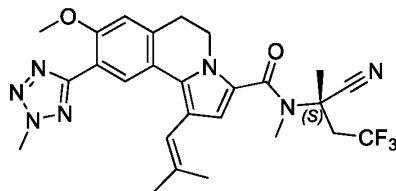
6.5 Hz, 1H), 4.81 - 4.71 (m, 1H), 4.45 - 4.32 (m, 4H), 4.09 (td, $J = 6.5, 13.2$ Hz, 1H), 3.88 (s, 3H), 3.85 - 3.68 (m, 2H), 3.11 - 3.02 (m, 2H), 2.40 - 2.15 (m, 2H), 2.12 - 2.01 (m, 1H), 1.87 (s, 3H), 1.83 - 1.67 (m, 5H), 1.64 - 1.56 (m, 1H), 1.54 (s, 3H). LCMS (*Method s*). ES^+ , RT = 3.238 min) 559.2/560.2 (M+H)⁺

[001124] EXAMPLE 49 (METHOD I): (2R,4S)-4-hydroxy-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



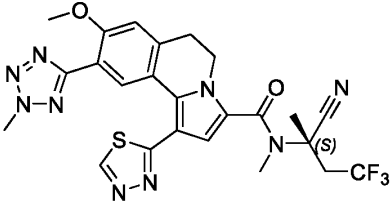
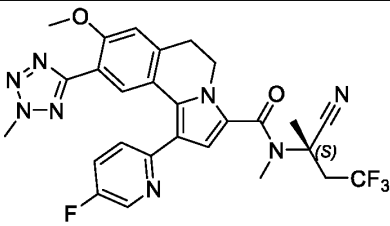
[001125] To a solution of *Intermediate 184* (70 mg, 137.91 μmol) in pyridine (1 mL) was added TFAA (231.72 mg, 1.10 mmol, 153.36 μL) at 20 °C. The mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with H₂O (5 mL), adjusted pH=3-4 with 1M HCl and extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (1 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 15*). *EXAMPLE 49* (23.11 mg, 34.23% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.12 - 8.16 (m, 1 H), 7.22 - 7.26 (m, 1 H), 6.53 - 6.57 (m, 1 H), 5.38 - 5.45 (m, 1 H), 4.41 - 4.44 (m, 3 H), 4.28 - 4.40 (m, 3 H), 3.98 - 4.05 (m, 1 H), 3.87 - 3.93 (m, 3 H), 3.60 - 3.67 (m, 1 H), 3.03 - 3.11 (m, 2 H), 2.54 - 2.64 (m, 3 H), 2.09 - 2.17 (m, 1 H), 1.81 - 1.90 (m, 4 H), 0.95 - 1.00 (m, 6 H). LCMS (*Method r*). ES^+ , RT = 2.833 min) 490.1/491.1 (M+H)⁺.

[001126] EXAMPLE 50 (METHOD J): (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide

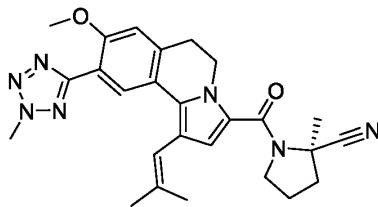


[001127] Equip a 25 mL three-necked round bottom flask, addition funnel and thermometer, Ar balloon etc. DMF (1 mL) was charged to the three-necked round bottom flask, then starting *Intermediate 48* (100 mg, 194.74 μ mol) was added to the mixture at 20 °C under Ar. At 0 °C inner temperature NaH (11.68 mg, 292.11 μ mol, 60% purity) was added in portions to the reaction mixture for 15 min. Then, CH₃I (55.28 mg, 389.47 μ mol, 24.25 μ L) was added at 0 °C. After the addition, the mixture was stirred at 70 °C for 2 h under Ar. When the starting material was consumed the reaction was quenched with water (5 mL) and diluted with ethyl acetate (2 mL x 3). The organic layer was washed with water (3 mL x 2) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. When the starting material was consumed the reaction was quenched with water (5 mL) and diluted with ethyl acetate (2 mL x 3). The organic layer was washed with water (3 mL x 2) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (*Method 15*). The *EXAMPLE 50* (40.92 mg, 39.83% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.16 (s, 1H), 7.24 (s, 1H), 6.53 (s, 1H), 6.21 (s, 1H), 4.42 (s, 3H), 4.34 - 4.16 (m, 2H), 3.89 (s, 3H), 3.47 - 3.35 (m, 1H), 3.29 - 3.20 (m, 4H), 3.10 (br t, J = 6.8 Hz, 2H), 1.93 (s, 3H), 1.89 (s, 3H), 1.77 (s, 3H). LCMS (*Method r*). ES⁺, RT = 3.267 min) 528.1/529.1 (M+H)⁺.

Example No.	Precursor	Structure/Name	LCMS
51	Int. 87		LCMS (<i>Method s</i> , ES ⁺ RT=3.11 min) 552.0/553.0 (M+H) ⁺ .

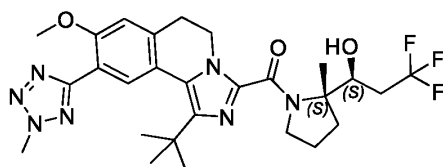
		(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(2,2-difluoropropyl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide	
52	Int. 93	 (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide	LCMS (<i>Method g</i> , ES ⁺ , RT = 2.80 min) 558.1/559.1 (M+H) ⁺
53	Int. 244	 (S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(5-fluoropyridin-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-1,2,3-triazol-4-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide	LCMS (<i>method h</i> , ES ⁺ , RT = 2.07 min) 569.3/570.3 (M+H) ⁺

[001128] **EXAMPLE 54 (METHOD K):** ((R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile



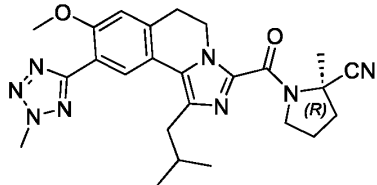
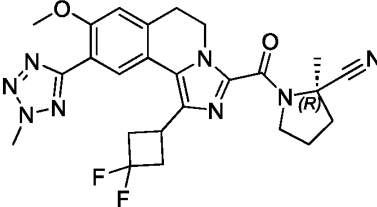
[001129] To a solution of *Intermediate 54* (40 mg, 78.80 μ mol) in THF (0.2 mL) was added Burgess reagent (18.78 mg, 78.80 μ mol) in DCM (0.2 mL). The mixture was stirred at 0 °C for 1 hr. The reaction mixture was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine 10 mL (5 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (*Method 15*). *EXAMPLE 54* (2 mg, 4.09 μ mol, 5.18% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.42 - 8.34 (m, 1H), 7.16 (s, 1H), 6.56 - 6.51 (m, 1H), 4.38 - 4.35 (m, 3H), 4.29 - 4.16 (m, 2H), 3.86 - 3.76 (m, 4H), 3.76 - 3.64 (m, 1H), 3.06 - 2.94 (m, 2H), 2.79 - 2.73 (m, 2H), 2.41 - 2.38 (m, 1H), 2.13 - 2.04 (m, 1H), 1.98 - 1.82 (m, 2H), 1.72 - 1.65 (m, 3H), 1.15 - 1.05 (m, 6H) LCMS (*Method f*. ES⁺, RT = 2.663 min) 490.2/491.2 (M+H)⁺

[001130] **EXAMPLE 55 (METHOD L):** (1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone

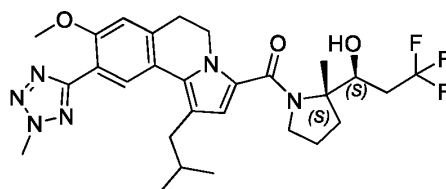


[001131] To a solution of *Intermediate 63* (100.00 mg, 179.07 μ mol) and *Intermediate 26* (133.63 mg, 358.15 μ mol, 2 eq) in DMF (1 mL) was added XPHOS-Pd-G₂ (14.09 mg, 17.91 μ mol) at 20 °C under Ar. The mixture was stirred at 110°C for 5 h. The reaction mixture was added H₂O (5 mL) at 20°C, and then extracted with EtOAc (2 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (*Method 15*). *The title*

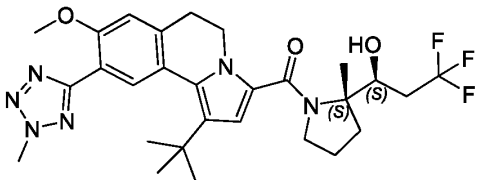
compound (46.93 mg, 47%) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.30 (s, 1H), 7.27 (s, 1H), 5.46 (br d, J = 5.9 Hz, 1H), 4.81 (br dd, J = 5.6, 9.1 Hz, 1H), 4.43 (s, 3H), 4.34 - 4.18 (m, 3H), 3.95 - 3.79 (m, 4H), 3.02 (br t, J = 6.1 Hz, 2H), 2.40 - 2.17 (m, 2H), 2.09 (td, J = 8.5, 12.9 Hz, 1H), 1.88 - 1.70 (m, 2H), 1.65 - 1.56 (m, 1H), 1.52 (s, 3H), 1.42 (s, 9H) LCMS (*Method s*, ES $^+$, RT = 3.18 min) 562.3/563.3 (M+H) $^+$

Example No.	Precursor	Structure/Name	LCMS
56	Int. 69	 (R)-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method g</i> , ES $^+$, RT = 3.00 min) 475.2/476.2 (M+H) $^+$.
57	Int. 164	 (R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method r</i> , ES $^+$, RT = 3.048 min) 509.1/510.1 (M+H) $^+$

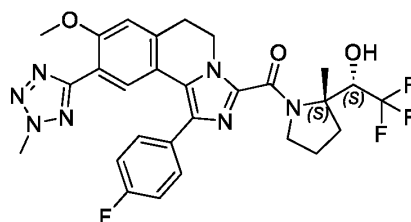
[001132] **EXAMPLE 58 (METHOD N):** (1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone



[001133] To a solution of *Intermediate 183* (100 mg, 262.17 μmol) in DMF (1 mL) was added *Intermediate 258* (73.51 mg, 314.61 μmol , HCl salt), HATU (119.62 mg, 314.61 μmol) and DIEA (203.30 mg, 1.57 mmol, 273.99 μL). The mixture was stirred at 70°C for 16 hr. The mixture was without workup. The residue was purified by prep-HPLC (*Method 15*) to give the *EXAMPLE 58* (45.38 mg, 31%) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.10 (s, 1 H), 7.21 (s, 1 H), 6.42 (s, 1 H), 5.47 (d, $J=6.48$ Hz, 1 H), 4.76 (br dd, $J=8.99, 7.15$ Hz, 1 H), 4.42 (s, 3 H), 4.24 - 4.35 (m, 1 H), 4.15 (s, 1 H), 3.88 (s, 3 H), 3.66 - 3.83 (m, 2 H), 3.04 (s, 2 H), 2.54 (br d, $J=6.97$ Hz, 2 H), 2.26 - 2.40 (m, 1 H), 2.16 - 2.25 (m, 1 H), 2.06 (dt, $J=12.62, 8.60$ Hz, 1 H), 1.68 - 1.91 (m, 3 H), 1.55 - 1.65 (m, 1 H), 1.53 (s, 3 H), 0.96 (dd, $J=6.48, 2.93$ Hz, 6 H). LCMS (*Method f*. RT = 3.330 min) 560.3/561.3 (M+H) $^+$.

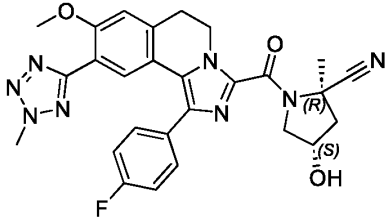
Example No.	Precursor	Structure/Name	LCMS
59	Int. 248	 (1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone	LCMS (<i>method r.</i> ES ⁺ , RT = 3.25 min) 561.3/562.3 (M+H) ⁺

[001134] EXAMPLE 60 (METHOD O): (1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone

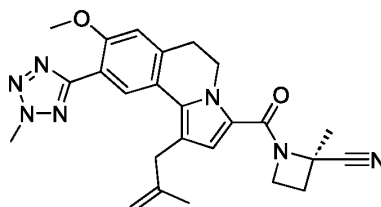


[001135] To a solution of *Intermediate 237* (80 mg, 137.37 μ mol) and *Intermediate 26* (102.51 mg, 274.73 μ mol) in DMF (1 mL) was added XPHOS-Pd-G₂ (21.62 mg, 27.47 μ mol) at 20°C. The mixture was stirred at 130°C for 4hr. The reaction mixture was added H₂O (5 mL), and then extracted with EtOAc (2 mL x 3). The combined organic layers were washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (*Method 15*) to give *EXAMPLE 60* (32.2 mg, 40.03%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.96 (s, 1H), 7.68 - 7.60 (m, 2H), 7.31 (s, 1H), 7.23 (t, J = 8.9 Hz, 2H), 6.62 (d, J = 6.6 Hz, 1H), 5.23 - 5.12 (m, 1H), 4.57 - 4.47 (m, 1H), 4.44 - 4.33 (m, 4H), 4.32 - 4.22 (m, 1H), 3.89 (s, 3H), 3.69 (dt, J = 6.8, 10.8 Hz, 1H), 3.21 - 3.12 (m,

2H), 2.41 (dt, J = 7.4, 11.5 Hz, 1H), 1.94 - 1.76 (m, 2H), 1.67 - 1.54 (m, 4H). LCMS (*Method f*. ES+, RT = 3.195 min) 586.1 (M+H) +

Example No.	Precursor	Structure/Name	LCMS
61	Int. 239	 (2R,4S)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile	LCMS (<i>Method h</i> ES+, RT=1.749 min) 529.2/530.2 (M+H) +

[001136] **EXAMPLE 62 (METHOD P):** (R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylallyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile



[001137] To a solution of *Intermediate 241* (50 mg, 88.39 μ mol) in DCM (0.5 mL) was added BCl₃ (1 M, 441.96 μ L) at -70°C. The mixture was stirred at -70°C for 10 min. The reaction mixture was added H₂O (2 mL) at 0°C, and then extracted with DCM (1 mL x 3). The combined organic layers were washed with brine (2 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (*Method 16*) to give *title compound* (7.02 mg, 17.36%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆)

δ = 8.00 (s, 1H), 7.23 (s, 1H), 6.58 (s, 1H), 4.79 (s, 1H), 4.64 (s, 1H), 4.55 (br t, J = 7.7 Hz, 2H), 4.46 - 4.33 (m, 5H), 3.88 (s, 3H), 3.36 (s, 2H), 3.06 (br t, J = 6.4 Hz, 2H), 2.73 (ddd, J = 6.3, 8.8, 11.4 Hz, 1H), 2.47 - 2.37 (m, 1H), 1.80 (d, J = 8.0 Hz, 6H). LCMS (*Method s*. ES⁺, RT = 3.01 min) 458.1/459.1 (M+H)⁺.

[001138] Biological Activity Assays

[001139] HTRF cAMP Assay in HEK293 cell lines expressing hFSHR/hTSHR/hLHCGR

[001140] As noted above, glycoprotein hormone receptors, FSHR, TSHR and LHR/LHCGR predominantly activate the G_{as} class of intracellular G proteins, resulting in cAMP accumulation. The HTRF assay is based on a competition between native cAMP produced by cells and cAMP labeled with the dye d2 (red acceptor) for binding to a cryptate labeled antibody (Europium donor). The specific energy transfer signal is inversely proportional to the concentration of cAMP in the standard or sample.

[001141] Compounds were tested for agonist activity in cell lines over-expressing human FSHR or TSH or LHR. For each cell line, 5000 cells/well were plated in 5 μ l 1x Stimulation Buffer + 0.5M IBMX by Integra Multichannel Pipet in 384-well, solid white low volume plates (Greiner 784075). These plates contained 100 nl of the test compounds (in concentration-response curve format) in 100% DMSO. Then 5 μ l 1x Stimulation Buffer + 0.5M IBMX were added to a total reaction volume of 10 μ l. Controls (FSK for positive control; 1x Stimulation Buffer + 0.5M IBMX for negative control; EC₁₀₀ of the appropriate hormone) were added in columns 23 and 24. The plates were incubated at 37 °C 5% CO₂ for 45 min. Following stimulation, cAMP was measured using HTRF reagents (CisBio #62AM4PEC) as described by the manufacturer. For detection, 5 μ l cAMP-d2 (Acceptor) and 5 μ l Anti-cAMP-Cryptate (Donor) of HTRF detection reagents were added per well and incubated at room temperature for 1 hour in darkness. The plates were read on EnVision multilabel plate reader (Perkin Elmer, CA) to measure calculated fluorescence ratio (665 nm/620 nm). Dose response curves for rFSH, rTSH, rhCG and test compounds were generated using in-house analysis tool A-plus and GraphPad Prism 7 software. EC₅₀ values and % response of the compounds compared to maximal response of the cognate hormone were calculated for each

compound in the three cell lines. The selectivity ratio for hFSHR over hTSHR was calculated as $\text{hTSHR EC}_{50}/\text{hFSHR EC}_{50}$.

[001142] The data is interpreted according to the following and shown in Tables 3 and 4:

For human FSHR cAMP assay: + : ≥ 10 nM; ++ : 9-1 nM; +++ : 0.9-0.1 nM.

For human TSHR selectivity ratio (EC_{50} TSHR cAMP/ EC_{50} FSHR cAMP): - : less than 1;

+ : 10 to less than 25; ++ : 25 to less than 50; +++ : > 50 .

[001143] Table3

Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
4-1	+++	++
4-2	+++	+++
4-3	++	+++
6-1	+++	++
6-2	++	+++
6-3	+++	+++
6-4	++	+++
6-5	++	+++
6-6	++	+++
6-7	++	+++
6-8	++	+++
7-1	+++	++
7-2	+++	+
7-3	+++	++
7-4	++	+
7-5	++	+
7-6	++	++
7-7	++	++
7-8	+++	+++

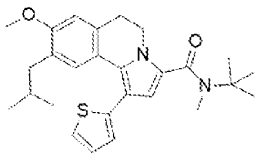
Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
7-9	++	+++
7-10	+++	+++
7-11	++	+++
7-12	++	+++
7-13	++	+++
7-14	++	+++
7-15	+++	++
7-16	++	+++
7-17	++	+++
7-18	+++	+++
7-19	+++	+++
7-20	++	+++
7-21	+++	+++
7-22	++	+++
7-23	++	++
7-24	++	+++
7-25	++	++
7-26	++	++
7-27	++	+++
7-28	+++	++
8-1	+++	++
8-2	+++	+
8-3	++	++
8-4	+	+
8-5	+	+
8-6	+++	+
8-7	+	+

Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
8-8	++	+
8-9	+++	++
8-10	++	+++
8-11	+++	+++
8-12	++	++
8-13	++	+++
8-14	++	+++
8-15	++	++
8-16	++	++
9-1	+++	++
9-2	+++	+++
10-1	+++	++
10-2	++	+
10-3	++	+
10-4	+++	++
10-5	+++	++
10-6	+++	+++
10-7	++	++
10-8	+++	++
10-9	++	+++
10-10	+++	+
10-11	+++	+
10-12	+++	++
10-13	+++	+
10-14	++	++
10-15	+++	++
10-16	+++	+++

Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
10-17	++	++
10-18	++	+
10-19	++	+
10-20	+++	++
10-21	++	+++
10-22	++	+++
10-23	+++	++
10-24	+++	++
10-25	++	+++
10-26	+++	+++
10-27	+++	+++
10-28	+++	++
10-29	+++	++
10-30	+++	+++
10-31	++	+++
10-32	+++	+++
10-33	+++	+++
10-34	+++	+++
10-35	+++	+++
10-36	++	+++
10-37	+++	++
10-38	++	+++
10-39	+++	+++
10-40	++	++
10-41	+++	+++
10-42	++	++
10-43	+++	+++

Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
10-44	+++	+++
10-45	++	+++
10-46	++	+++
10-47	++	++
10-48	++	++
11-1	+++	++
13-1	++	++
13-2	++	+
13-3	++	++
13-4	++	+
13-5	++	+++
13-6	++	+
13-7	++	++
13-8	+++	+++
13-9	+++	++
13-10	+++	+++
13-11	+++	+++
13-12	++	+++
18-1	+++	+++
18-2	+++	+++
18-3	+++	+++
18-4	+++	+++
18-5	+++	++
18-6	++	+++
18-7	+++	+++
20-1	++	+++
20-2	++	++

Compound No.	FSHR cAMP Assay	TSHR Selectivity Ratio
24-1	++	+++
24-2	++	+++
25-1	+++	+++
26-1	++	++
26-2	++	++
32-1	++	+++
32-2	++	+++
33-1	+++	+++
34-1	+++	+++
MK-8389*	++	-



*MK-8389:

[001144] Table 4

Example	FSHR cAMP Assay	TSHR Selectivity Ratio
1	+++	+++
2	++	+++
3	++	+++
4	+++	+++
5	+++	+++
6	++	+++
7	+	+++
8	++	+
9	+	+
10	+++	+++

Example	FSHR cAMP Assay	TSHR Selectivity Ratio
11	+	++
12	+++	+++
13	+++	+++
14	++	+++
15	++	+++
16	++	+
17	++	++
18	++	+++
19	+++	+++
20	++	++
21	+	+
22	+++	+++
23	+++	+++
24	++	+++
25	++	++
26	++	+
27	+++	+++
28	+++	+++
29	++	+
30	+++	++
31	++	+++
32	++	+++
33	++	+++
34	++	+++
35	+	+++
36	+	++
37	++	+

Example	FSHR cAMP Assay	TSHR Selectivity Ratio
38	++	++
39	++	+++
40	+	+++
41	++	+++
42	++	+++
43	+	++
44	+	++
45	++	+++
46	++	++
47	++	++
48	+++	+++
49	+++	+++
50	++	+
51	++	+
52	+	+++
53	++	+++
54	+++	+++
55	++	+++
56	++	+++
57	+++	+++
58	+++	++
59	++	++
60	++	+++
61	+++	+++
62	++	+++

[001145] Progesterone release HTRF assay in GFSHR-17 cells

[001146] As noted above, the immortalized rat steroidogenic granulosa cell line, GFSHR-17 (ABM cat# T0605), stably expresses the rat FSH Receptor and is responsive to FSH stimulation with human FSH. This engineered cell line lacks the aromatase found in primary granulosa cells required for conversion of androgen precursors to estrogens. However it shows a robust progesterone response which can serve as a surrogate to verify the cellular activity of FSHR agonists. The cell-based assay evaluates the ability of compounds to activate FSHR in GFSHR-17 cells by measuring progesterone released into the supernatant using a progesterone HTRF kit from Cisbio. A ratiometric HTRF read-out to assess agonist activity of compounds is described below.

[001147] A concentration response curve was obtained in the following manner. After seeding cells and incubating at 37°C for 20 hours, test compounds were prepared at different concentrations starting at 2.7 μ M with 3-fold dilutions to provide curves as a 10-point series and were dispensed to cells with the CyBi® SELMA 384/25 μ l. After incubation at 37°C and 5% CO₂ for 20 hours, the supernatant was harvested with the CyBi® SELMA 384/25 μ l and 10 μ l supernatant transferred to the assay plate. Afterwards the supernatant was loaded with dyes (detection reagents), antibody labelled with Eu3+-Cryptate, and progesterone labelled with d2. An incubation step at room temperature for 1 hour in the dark followed. The plates were measured with the Envision plate reader. The progesterone present in the sample competes with the binding between the two detection reagents and thereby prevents FRET from occurring. The specific signal is inversely proportional to progesterone concentration. Compounds of the invention showed EC₅₀ in this assay of 1650 nM or lower. Certain compounds of the invention showed EC₅₀ in this assay of 100 nM or lower.

[001148] FSHR activation bioassay (modified Steelman-Pohley)

[001149] As noted above, the activity of the compounds described herein as agonists of the follicle-stimulating hormone receptor is investigated using a modification of the classic follicle-stimulating hormone bioassay (Steelman-Pohley) which is based on the increase in ovarian weight in immature female rats. *See* Steelman, S.L. and F.M. Pohley, Endocrinology, 1953, 53(6):604-16. Immature (25-day old) female Sprague Dawley rats weighing approximately 55-70 grams are

used in the assay. FSH (5 -10 IU per injection) is used as a positive control. Alternatively, pregnant mare serum gonadotropin (PMSG) (30 IU) is used as a positive control as a single subcutaneous injection followed 48 hours later by an injection of human chorionic gonadotropin (hCG).

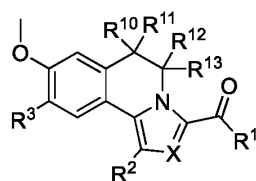
[001150] To stimulate follicle growth, FSH (subcutaneously) or a compound as disclosed herein (oral gavage) is administered twice daily for three days. Urinary hCG (25 IU) is then injected subcutaneously to stimulate ovulation, and animals are euthanized 18 hours later by anesthesia with isoflurane followed by exsanguination. Blood plasma is saved for pharmacokinetic analysis, including estradiol measurement as a marker of FSHR activation, or T4 measurement as a marker of off-target TSHR activation. Uterine tissue is weighed as a reflection of serum estradiol levels, and ovarian weights are measured as a reflection of increased follicular volume and/or corpora lutea formation. One ovary is frozen for tissue analysis and the other ovary is fixed in 4% formalin overnight and then transferred to a vial filled with 70% ethanol for histological analysis. To measure the number of ovulated oocytes, oviducts are collected and placed in a sterile petri dish containing a droplet of 100 μ L of M2 medium supplemented with 300 μ g/mL hyaluronidase under mineral oil. The ampullae of the oviducts is punctured with a fine needle and cumulus enclosed oocytes are released into the media. After 10 minutes, oocytes are transferred via capillary pipette into a new droplet of M2 media without hyaluronidase and enumerated.

[001151] All animal procedures are performed in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the National Research Council and are approved by the Institutional Animal Care and Use Committee of the Ferring Research Institute Inc. Animal Care Program, which has received accreditation from the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and is licensed with the California Department of Health. Studies are conducted under an approved protocol (#FRI 07-0006).

[001152] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology disclosed herein in its broader aspects.

WHAT IS CLAIMED IS:

1. A compound of Formula (A)



Formula (A)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is $-NR^fR^g$, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 13 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or
- (ii) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected

from halogen, nitrile, $-\text{C}(\text{O})\text{NR}^{5a}\text{R}^{5b}$, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, and $\text{C}_1\text{-C}_3$ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and $\text{C}_1\text{-C}_3$ alkyl;

X is CR^{20} or N;

R^{20} is selected from H, halogen, nitrile, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ haloalkyl;

R^3 is selected from $-\text{C}(\text{O})\text{NHR}^6$, $-\text{SO}_2\text{-(C}_1\text{-C}_3 \text{ alkyl)}$, $-\text{SO}_2\text{-(C}_3\text{-C}_6 \text{ cycloalkyl)}$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, and $-\text{C}(\text{O})\text{NH}_2$;

R^6 is selected from:

(i) $-(\text{CR}^7\text{R}^8)_n\text{C}(\text{O})\text{NR}^d\text{R}^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and $\text{C}_1\text{-C}_3$ alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and $\text{C}_1\text{-C}_3$ alkyl;

(ii) $\text{C}_1\text{-C}_6$ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the

heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

2. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein X is CR²⁰.
3. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein X is N.
4. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein R¹ is -NR^fR^g, wherein:

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl; or

- (ii) R^f is C₁-C₆ alkyl; and R^g is C₁-C₆ alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile.

5. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

6. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 5-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

7. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof

according to any one of claims 1 to 4, wherein R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl.

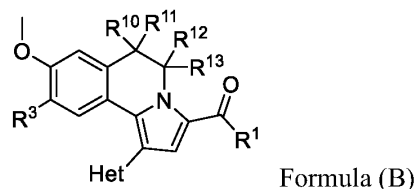
8. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl.
9. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^1 is $-NR^fR^g$, wherein R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile.
10. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is C_1 - C_6 alkyl or C_1 - C_6 alkenyl.
11. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is C_1 - C_6 haloalkyl.
12. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is C_1 - C_6 hydroxyalkyl.
13. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is phenyl optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl.
14. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is 4-fluorophenyl.

15. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is C_4 - C_6 cycloalkyl optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl.

16. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl.

17. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein R^2 is 3,3-difluorocyclobutyl, 5-fluoropyridin-2-yl, 2-thiophenyl, 5-thiazolyl, or 1,3,4-thiadiazolyl.

18. A compound of Formula (B)



Formula (B)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms

to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

Het is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R^5 groups independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

(ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

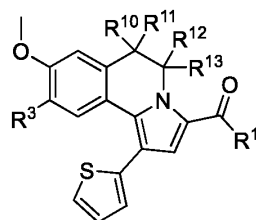
each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

19. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 18, wherein Het is a 5-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl.

20. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 18, wherein Het is a 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, optionally substituted with 1 to 4 R⁵ groups independently selected from halogen, nitrile, -C(O)NR^{5a}R^{5b}, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C₁-C₃ alkyl.

21. A compound of Formula (C)



Formula (C)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or

partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

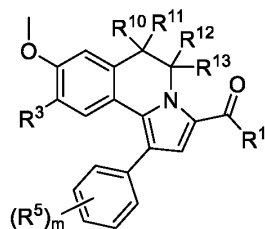
each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

- (ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

22. A compound of Formula (D)



Formula (D)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is , wherein R^1 is substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

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

each R^5 is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

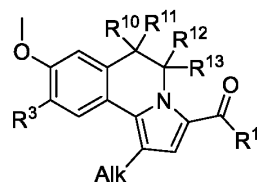
each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

- (ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

23. A compound of Formula (E)



Formula (E)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is , wherein R¹ is substituted with 1 to 4 R⁴ groups, wherein each R⁴ group is independently selected from halogen, hydroxy, nitrile, -NR^{4a}R^{4b}, -SR^{4a}, -S(O)₂R^{4a}, and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy and halogen; optionally wherein 2 R⁴ groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C₁-C₃ alkyl;

R³ is selected from -C(O)NHR⁶, -SO₂-(C₁-C₃ alkyl), -SO₂-(C₃-C₆ cycloalkyl), phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

Alk is C₁-C₆ alkyl or C₁-C₆ alkenyl;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or

partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

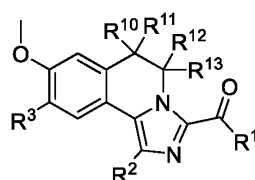
each of R^d and R^e is independently selected from H and C_1 - C_3 alkyl;

- (ii) C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1 - C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1 - C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

24. A compound of Formula (F)



Formula (F)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is $-NR^fR^g$, wherein

- (i) R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl; or
- (i) R^f is C_1 - C_6 alkyl; and R^g is C_1 - C_6 alkyl substituted with 1 to 4 R^{4c} groups, wherein each R^{4c} group is independently selected from halogen, hydroxy, and nitrile;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 alkenyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, 5- to 6-membered heterocycloalkyl ring, and 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heterocycloalkyl ring and the 5- to 6-membered heteroaryl ring contain 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, the 5- to 6-membered heterocycloalkyl ring, and the 5- to 6-membered heteroaryl

ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

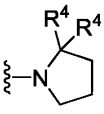
(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens; and

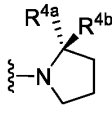
each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected

from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or R¹¹ and R¹² together form a double bond, and R¹⁰ and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

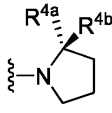
25. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof

according to any one of claims 1 to 4, 6, 7, and 10 to 24 and , wherein R¹ is , wherein each R⁴ is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

26. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof

according to any one of claims 1 to 4, 6, 7, and 10 to 24, wherein R¹ is , wherein R^{4b} is C₁-C₆ alkyl and R^{4a} is selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

27. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof

according to any one of claims 1 to 4, 6, 7 and 10 to 24, wherein R¹ is , wherein R^{4a} is C₁-C₆ alkyl and R^{4b} is selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from C₃-C₆ cycloalkyl, hydroxy, and halogen.

28. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein R³ is a 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and -C(O)NH₂.

29. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein R^3 is 5- to 6-membered heteroaryl ring, wherein the 5- to 6-membered heteroaryl ring contains 1 to 4 ring nitrogens, and wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$.
30. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein R^3 is tetrazole, pyrazole, imidazole, oxazole, or pyridine, wherein R^3 may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$; optionally wherein R^3 is tetrazole optionally substituted with C_1 - C_3 alkyl.
31. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-27, wherein R^3 is $-C(O)NHR^6$.
32. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 31, wherein R^6 is $-(CR^7R^8)_nC(O)NR^dR^e$.
33. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 32, wherein each of R^7 and R^8 is independently selected from H and C_1 - C_3 alkyl.
34. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 32, wherein R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen.
35. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 31, wherein R^6 is C_1 - C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and hydroxy.

36. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 31, wherein R⁶ is C₁-C₆ alkyl optionally substituted with nitrile or tetrazole.

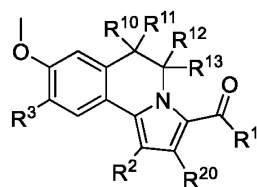
37. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 31, wherein R⁶ is phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C₁-C₃ alkyl optionally substituted with 1 to 7 independently selected halogens, and C₁-C₃ alkoxy optionally substituted with 1 to 7 independently selected halogens.

38. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to claim 31, wherein R⁶ is cyclopropane optionally substituted with nitrile or is cyclobutane optionally substituted with nitrile.

39. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-38, wherein each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

40. The compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any one of claims 1-38, wherein any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl.

41. A compound of Formula (I')



Formula (I')

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R^1 is $-NR^fR^g$, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 8-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 4 R^4 groups, wherein each R^4 group is independently selected from halogen, hydroxy, nitrile, $-NR^{4a}R^{4b}$, $-SR^{4a}$, $-S(O)_2R^{4a}$, and C_1 - C_6 alkyl optionally substituted with 1 to 4 substituents independently selected from C_3 - C_6 cycloalkyl, hydroxy, and halogen; optionally wherein 2 R^4 groups, together with the atoms to which they are attached, form a 4- to 6-membered ring; and each R^{4a} and R^{4b} is independently selected from C_1 - C_3 alkyl;

R^2 is selected from C_1 - C_6 alkyl; C_1 - C_6 haloalkyl; C_1 - C_6 hydroxyalkyl; $-(C_1-C_3 \text{ alkyl})-SO_2CH_3$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with 1 to 13 halogens; $-(C_1-C_6 \text{ alkyl})-NR^{5a}R^{5b}$; phenyl; C_4 - C_6 cycloalkyl; and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl, C_4 - C_6 cycloalkyl, and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 4 R^5 groups, wherein each R^5 group is independently selected from halogen, nitrile, $-C(O)NR^{5a}R^{5b}$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; and each R^{5a} and R^{5b} is independently selected from H and C_1 - C_3 alkyl;

R^{20} is selected from H, halogen, nitrile, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

R^3 is selected from $-C(O)NHR^6$, $-SO_2-(C_1-C_3 \text{ alkyl})$, $-SO_2-(C_3-C_6 \text{ cycloalkyl})$, phenyl, and 5- to 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and $-C(O)NH_2$;

R^6 is selected from:

(i) $-(CR^7R^8)_nC(O)NR^dR^e$, wherein

n is 1 or 2;

each of R^7 and R^8 is independently selected from H and C_1-C_3 alkyl, or R^7 and R^8 together with the carbon to which they are attached form a 3- to 6-membered saturated or partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

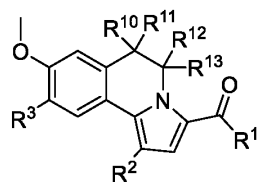
each of R^d and R^e is independently selected from H and C_1-C_3 alkyl;

- (ii) C_1-C_6 alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, and hydroxy; and
- (iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from oxo, halogen, hydroxy, nitrile, C_1-C_3 alkyl optionally substituted with 1 to 7 independently selected halogens, and C_1-C_3 alkoxy optionally substituted with 1 to 7 independently selected halogens; and

each of R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or any two of R^{10} , R^{11} , R^{12} , and R^{13} , together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or R^{11} and R^{12} together form a double bond, and R^{10} and R^{13} are independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

42. A compound of Formula (I)



Formula (I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -NR^fR^g, wherein R^f and R^g together with the nitrogen to which they are attached form a 4- to 6-membered heterocycloalkyl ring optionally containing 1 additional ring heteroatom selected from oxygen, sulfur and nitrogen, and substituted with 1 to 3 R⁴ groups, wherein each R⁴ group is independently selected from nitrile and C₁-C₆ alkyl optionally substituted with 1 to 4 substituents independently selected from hydroxy and halogen;

R² is selected from C₁-C₆ alkyl; C₁-C₆ haloalkyl; phenyl; and 5- to 6-membered heteroaryl ring containing 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the phenyl and the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 or 2 R⁵ groups, wherein each R⁵ group is independently selected from halogen, nitrile, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and C₁-C₃ alkoxy;

R³ is selected from -C(O)NHR⁶ and 5- to 6-membered heteroaryl ring containing 1 to 3 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the 5- to 6-membered heteroaryl ring may be optionally substituted with 1 to 3 substituents independently selected from hydroxy, nitrile, and C₁-C₃ alkyl;

R⁶ is selected from:

(i) -(CR⁷R⁸)_nC(O)NR^dR^e, wherein

n is 1 or 2;

each of R⁷ and R⁸ is independently selected from H and C₁-C₃ alkyl, or R⁷ and R⁸ together with the carbon to which they are attached form a 3- to 6-membered saturated or

partially unsaturated ring optionally containing a ring heteroatom selected from oxygen, sulfur, and nitrogen;

each of R^d and R^e is independently selected from H and C₁-C₃ alkyl;

(ii) C₁-C₆ alkyl optionally substituted with nitrile or 5- or 6-membered heteroaryl ring containing 1 to 4 ring heteroatoms independently selected from oxygen and nitrogen, wherein the ring may be optionally substituted with 1 to 4 substituents independently selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, and hydroxy; and

(iii) phenyl, 3- to 6-membered saturated or partially unsaturated ring, or 5- to 6-membered heteroaryl ring, wherein the saturated or partially unsaturated ring optionally contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the heteroaryl ring contains 1 or 2 ring heteroatoms independently selected from oxygen, sulfur, and nitrogen, and wherein the phenyl, saturated or partially unsaturated ring, and heteroaryl ring may be optionally substituted with 1 or 2 substituents independently selected from halogen, hydroxy, nitrile, and C₁-C₃ alkyl optionally substituted with one or more independently selected halogens; and

each of R¹⁰, R¹¹, R¹², and R¹³ are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl; or any two of R¹⁰, R¹¹, R¹², and R¹³, together with the carbon atom(s) to which they are attached, form a 3- to 6-membered ring, and the remaining two are independently selected from H, C₁-C₆ alkyl, and C₁-C₆ haloalkyl,

wherein 0 to 10 hydrogen atoms attached to one or more carbon atoms are replaced with deuterium atom(s).

43. A compound selected from the group consisting of:

[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-methyl-2-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]pyrrolidin-1-yl]methanone;

(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*S*)-2-methyl-2-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(*R*)-8-methoxy-5-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl) pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(3*S*)-4-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-3-methyl-morpholine-3-carbonitrile;

(2*R*)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(*R*)-1-(1-(1-hydroxy-2-methylpropan-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(*R*)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(*R*)-1-(1-(2,2-difluoropropyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(*R*)-3-(2-cyano-2-methylazetidine-1-carbonyl)-N-(1-cyanocyclobutyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(*R*)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(2*R*)-1-[8-methoxy-9-oxazol-2-yl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

4-[3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]-6-methyl-1*H*-pyridin-2-one;

(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-oxazol-2-yl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

3-[3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]pyridine-2-carbonitrile;

3-[3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]pyridine-2-carbonitrile;

[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

(2*R*)-1-[9-(1*H*-imidazol-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

(2*R*)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

[(5*R*)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-methyl-2-[(1*R*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

[(5*R*)-8-methoxy-5-methyl-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

(2*R*)-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(*R*)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl)-5-(trifluoromethyl)picolinonitrile;

(*R*)-1-(8-methoxy-9-(2-methyl-2*H*-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(8-methoxy-9-(2-methyl-2*H*-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*S*)-2-methyl-2-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(*R*)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2*H*-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(*R*)-1-(8-methoxy-9-(2-methyl-2*H*-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(*R*)-1-(1-(5-fluoropyridin-2-yl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(*R*)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

((*R*)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

5-((*R*)-8-methoxy-5-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl)nicotinamide;

3-((*R*)-8-methoxy-5-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl)picolinonitrile;

((*R*)-8-methoxy-5-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

((1*aR*,9*bR*)-8-methoxy-7-(2-methyl-2H-tetrazol-5-yl)-5-(thiophen-2-yl)-1*a*,9*b*-dihydro-1*H*-cyclopropa[*c*]pyrrolo[2,1-*a*]isoquinolin-3-yl)((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-thiazol-5-yl]-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)methanone;

[8-methoxy-9-(2-methyltetrazol-5-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-methyl-2-[(1*R*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl)methanone;

(2*R*)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*)-1-[8-methoxy-9-(1*H*-pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*)-1-[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*)-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

4-[3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]-1-methyl-pyridin-2-one;

[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1*H*-pyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

6-[8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]-1*H*-pyridin-2-one;

4-[3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]-1-methyl-pyridin-2-one;

3-[3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-9-yl]pyridine-2-carbonitrile;

[(5*R*)-8-methoxy-5-methyl-9-(1-methylpyrazol-3-yl)-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

(*R*)-1-(8-methoxy-9-(1-methyl-1*H*-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(*R*)-1-(8-methoxy-6-methyl-9-(1-methyl-1*H*-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

((*R*)-8-methoxy-5-methyl-9-(1-methyl-1*H*-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

((*R*)-2-((*R*)-1-hydroxyethyl)-2-methylpyrrolidin-1-yl)((*S*)-8-methoxy-5-methyl-9-(1-methyl-1*H*-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)methanone

((1*aR*,9*bR*)-8-methoxy-7-(1-methyl-1*H*-pyrazol-3-yl)-5-(thiophen-2-yl)-1*a*,9*b*-dihydro-1*H*-cyclopropa[*c*]pyrrolo[2,1-*a*]isoquinolin-3-yl)((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(1-methyl-1*H*-pyrazol-3-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)((*S*)-2-methyl-2-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[9-(1*H*-imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

(2*R*)-1-[9-(1*H*-imidazol-2-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-*N*-(2-oxo-1*H*-pyridin-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(2-oxo-1*H*-pyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-[2-(dimethylamino)-2-oxo-ethyl]-3-[(2*R*)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-(2,2-dimethylpyrrolidine-1-carbonyl)-8-methoxy-*N*-(1*H*-tetrazol-5-ylmethyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(2-oxo-1*H*-pyridin-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-1-(4-fluorophenyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-1-(4-fluorophenyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclopropyl)-8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclopropyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-1-(4-fluorophenyl)-8-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(3-cyanooxetan-3-yl)-8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(3-cyanooxetan-3-yl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyano-1-methyl-ethyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-[(3*R*)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-[(3*S*)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-(3-cyanooxetan-3-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclopropyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-(3-cyanooxetan-3-yl)-8-methoxy-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-(3-cyanooxetan-3-yl)-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-*N*-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-*N*-(2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-8-methoxy-3-((*S*)-2-methyl-2-((*R*)-2,2,2-trifluoro-1-hydroxy ethyl) pyrrolidine-1-carbonyl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-3-(2-cyano-2-methylazetidine-1-carbonyl)-*N*-(1-cyanocyclobutyl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-((*R*)-2-((*R*)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-((*R*)-2-cyano-2-methylpyrrolidine-1-carbonyl)-*N*-(1-cyanocyclobutyl)-8-methoxy-6-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-*N*-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*S*)-*N*-(1-cyanocyclobutyl)-3-((*R*)-2-((*R*)-1-hydroxyethyl)-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(4*S*)-*N*-(1-cyanocyclobutyl)-7-methoxy-4-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(thiophen-2-yl)-3*a*,5-dihydro-4*H*-cyclopenta[*a*]naphthalene-8-carboxamide;

(*S*)-3-((*R*)-2-cyano-2-methylpyrrolidine-1-carbonyl)-*N*-(1-cyanocyclobutyl)-8-methoxy-5-methyl-1-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(*R*)-*N*-(1-cyanocyclobutyl)-8-methoxy-5-methyl-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

(1*aR*,9*bR*)-*N*-(1-cyanocyclobutyl)-8-methoxy-3-((*R*)-2-methyl-2-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-5-(thiophen-2-yl)-1*a*,9*b*-dihydro-1*H*-cyclopropa[*c*]pyrrolo[2,1-*a*]isoquinoline-7-carboxamide;

N-[2-(dimethylamino)-2-oxo-ethyl]-3-[(2*S*)-2-ethyl-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

[(2*R*)-2-[(1*S*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-methyl-2-[(1*R*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-[(1*S*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(1-methylpyrazol-3-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-[(1*S*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone;

[(2*S*)-2-[(1*S*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-methyl-2-[(1*R*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidin-1-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-[1-hydroxypropyl]-2-methyl-pyrrolidin-1-yl]methanone;

[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*S*)-2-[(1*S*)-1-hydroxyethyl]-2-methyl-pyrrolidin-1-yl]methanone;

2-cyclopropyl(hydroxy)methyl-2-methylpyrrolidin-1-yl)(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)methanone;

(*R*)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-*N*-(2-cyanopropan-2-yl)-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(1-methyl-2-oxo-3-pyridyl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-*N*-(2-oxo-1*H*-pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-[(3*R* or *S*)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

3-[(2*R*)-2-cyano-2-methyl-pyrrolidine-1-carbonyl]-*N*-[(3*S* or *R*)-3-cyanotetrahydrofuran-3-yl]-8-methoxy-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl]-[(2*R* or *S*)-4,4-difluoro-2-methyl-2-[(1*R* or *S*)-1-hydroxyethyl]pyrrolidin-1-yl]methanone;

N-(1-cyanocyclobutyl)-3-[(2*R*)-2-[(1*R*)-1-hydroxyethyl]-2-methyl-pyrrolidine-1-carbonyl]-8-methoxy-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

N-(1-cyanocyclobutyl)-8-methoxy-3-[(2*R*)-2-methyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]pyrrolidine-1-carbonyl]-1-thiazol-5-yl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-9-carboxamide;

2-ethyl-1-[8-methoxy-9-(1-methylpyrazol-3-yl)-1-(2-thienyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]pyrrolidine-2-carbonitrile;

rel-(2*R*,3*S*)-3-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile;

rel-(2*R*,3*S*)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-3-hydroxy-2-methyl-pyrrolidine-2-carbonitrile;

2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-2-azabicyclo[4.2.0]octane-1-carbonitrile;

(1*S*,5*S*)-2-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl)-5-methyl-2-azabicyclo[3.2.0]heptane-1-carbonitrile;

(2*R*,4*S*)-4-hydroxy-1-[8-methoxy-9-(2-methyltetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-2-methyl-pyrrolidine-2-carbonitrile; and

(2*R*,4*S*)-1-[1-(4-fluorophenyl)-8-methoxy-9-(2-methyltetrazol-5-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carbonyl]-4-hydroxy-2-methyl-pyrrolidine-2-carbonitrile;

(2*R*,4*S*)-4-hydroxy-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(*R*)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-*a*]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-*a*]isoquinolin-3-yl)((*S*)-2-methyl-2-((*R*)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-*a*]isoquinolin-3-yl)((*S*)-2-methyl-2-((*S*)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide;

(2R,4S)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide;

(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

((S)-2-((R)-1,2-dihydroxy-2-methylpropyl)-2-methylpyrrolidin-1-yl)(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)methanone;

(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl) ((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-1-isobutyl-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(R)-3-(2-cyano-2-methylazetidine-1-carbonyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(R)-3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-9-carboxamide;

(1-(3,5-difluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

{(S)-2-[(S)-3,3,3-trifluoro-1-hydroxypropyl]-2-methyl-1-pyrrolidinyl} {11-methoxy-12-(2-methyl-2H-tetraazol-5-yl)-3-(2-thienyl)-6-azatricyclo[7.4.0.0^{2,6}]trideca-1(13),2,4,9,11-pentaen-5-yl} methanone;

(R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(S)-3-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile;

(S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile;

(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-propyl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(S)-3-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-4-methyloxazolidine-4-carbonitrile;

(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(1-methyl-1H-pyrazol-3-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

(R)-3-(3-(2-cyano-2-methylpyrrolidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile;

(R)-3-(3-(2-cyano-2-methylazetidine-1-carbonyl)-1-(4-fluorophenyl)-8-methoxy-5,6-dihydroimidazo[5,1-a]isoquinolin-9-yl)picolinonitrile;

(R)-1-(9-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-8-methoxy-1-(thiophen-2-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-8-methoxy-5-methyl-3-((R)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidine-1-carbonyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-9-carboxamide;

3-((R)-3-((2R,4S)-2-cyano-4-hydroxy-2-methylpyrrolidine-1-carbonyl)-8-methoxy-5-methyl-1-(2,2,2-trifluoroethyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-9-yl)picolinonitrile;

(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(2R,4S)-4-hydroxy-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide;

(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(2,2-difluoropropyl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide;

(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-tetrazol-5-yl)-1-(1,3,4-thiadiazol-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide;

(S)-N-(2-cyano-4,4,4-trifluorobutan-2-yl)-1-(5-fluoropyridin-2-yl)-8-methoxy-N-methyl-9-(2-methyl-2H-1,2,3-triazol-4-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxamide;

((R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylprop-1-en-1-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(R)-1-(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(1-(3,3-difluorocyclobutyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-2-methylpyrrolidine-2-carbonitrile;

(1-isobutyl-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(1-(tert-butyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-3,3,3-trifluoro-1-hydroxypropyl)pyrrolidin-1-yl)methanone;

(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinolin-3-yl)((S)-2-methyl-2-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)methanone;

(2R,4S)-1-(1-(4-fluorophenyl)-8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carbonyl)-4-hydroxy-2-methylpyrrolidine-2-carbonitrile;

(R)-1-(8-methoxy-9-(2-methyl-2H-tetrazol-5-yl)-1-(2-methylallyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carbonyl)-2-methylazetidine-2-carbonitrile;

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

44. A pharmaceutical composition comprising the compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any of one of claims 1-43, and a pharmaceutically acceptable carrier.

45. A method of modulating follicle-stimulating hormone receptor (FSHR) activity in a subject, comprising administering to a subject in need thereof the compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any of one of claims 1-43, or the composition according to claim 44.

46. A method of modulating follicle-stimulating hormone receptor (FSHR) activity in a biological sample, comprising contacting the biological sample with the compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any of one of claims 1-43, or the composition of claim 44.

47. A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof according to any of one of claims 1-43, or the composition of claim 44, optionally wherein the disease or disorder is a fertility disorder.

48. A compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-43, or a composition of claim 44, for use in modulating follicle-stimulating hormone receptor (FSHR) activity in a subject in need thereof.

49. A compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-43, or a composition of claim 44, for use in in treating a disease or disorder in a subject in need thereof, optionally wherein the disease or disorder is a fertility disorder.

50. Use of a compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-43, or a composition of claim 44, in the preparation of a medicament for modulating follicle-stimulating hormone receptor (FSHR) activity in a subject.
51. Use of a compound, stereoisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-43, or a composition of claim 44, in the preparation of a medicament for treating a disease or disorder in a subject in need thereof, optionally wherein the disease or disorder is a fertility disorder.
52. The method of claim 47, the compound for use of claim 49, or the use of claim 51, wherein the disease or disorder is selected from hypogonadotropic hypogonadism, isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, craniopharyngiomas, combined pituitary hormone deficiency, fertile eunuch syndrome, abnormal beta subunit of LH, abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), infiltrative lesions, hemochromatosis, sarcoidosis, histiocytosis, lymphoma, lymphocytic hypophysitis, meningitis, pituitary apoplexy, hyperprolactinemia, hypothyroidism, intentional (iatrogenic) secondary hypogonadism, empty sella, pituitary infarction, Sheehan syndrome, anorexia nervosa, congenital adrenal hyperplasia, and disorders related to GnRH deficiency.