

MC2R MODULATOR COMPOUNDS

This application relates to novel compounds and their use as melanocortin subtype-2 receptor (MC2R) antagonists. Compounds described herein may be useful in the treatment or prevention of diseases in which MC2R is involved. This application is also directed to pharmaceutical compositions comprising these compounds and the manufacture and use of these compounds and compositions in the prevention or treatment of such diseases in which MC2R is involved.

BACKGROUND OF THE INVENTION

Adenocorticotrophic hormone (ACTH) is a 39-amino acid peptide implicated in the regulation of adrenal glucocorticoid synthesis and secretion within the hypothalamic-pituitary-adrenal (HPA) axis, and as such, plays a primary role in regulation of stress responses. ACTH is synthesized by corticotrophic cells in the anterior pituitary via proteolytic cleavage of proopiomelanocortin (POMC). Upon stressful stimuli, ACTH is secreted and acts at the melanocortin 2 receptor (MC2R) in adrenal glands to regulate synthesis and secretion of glucocorticoids and androgens. The secretion of glucocorticoids provides negative feedback to both hypothalamus and anterior pituitary to reduce production and secretion of corticotrophic releasing hormone (CRH) and ACTH respectively – thereby providing a fine balance in regulating stress responses. Diseases linked to ACTH dysfunction range from Cushing's disease to congenital adrenal hyperplasia and polycystic ovarian syndrome (PCOS) (*Microsc. Res. Tech.* 61, 275–287 (2003)).

The MC2R belongs to the melanocortin family of G protein-coupled receptors (GPCRs), of which there are five subtypes - MC1R, MC2R, MC3R, MC4R and MC5R. MC1R is associated with pigmentation regulation, MC2R with glucocorticoid synthesis, MC3R and MC4R with energy homeostasis and MC5R with exocrine gland physiology. MC2R is selectively activated by ACTH, while the remaining receptor subtypes also bind the melanocortin peptides α -, β -, and γ -melanocyte-stimulating hormone (α -MSH, β -MSH, and γ -MSH) (*Am. J. Physiol. Endocrinol. Metab.* 284, E468-74 (2003); *Life Sci.* 59, 797–801 (1996)).

Another unique aspect of the MC2R relative to the other melanocortin receptors is that the accessory protein, MRAP (melanocortin 2 receptor protein), is required for MC2R expression and function. MRAP is a single transmembrane protein which forms an antiparallel homodimer with MC2R to allow trafficking of the receptor to the plasma membrane (*Proc. Natl. Acad. Sci.* 104, 20244 LP – 20249 (2007)) Binding of ACTH to the MC2R/MRAP complex in adrenal cortical cells activates cAMP production via the G_s signalling pathway. Increases in intracellular cAMP in turn

stimulates cortisol synthesis and secretion (*Microsc. Res. Tech.* 61, 275–287 (2003)).

Congenital adrenal hyperplasia (CAH) is a disorder characterised by disruption in adrenal steroidogenesis linked to excessive ACTH and CRH production. Three enzyme deficiencies arising from specific gene mutations are implicated: 21-hydroxylase deficiency from mutations in *CYP21A2* (the most common form), 3 β -hydroxysteroid dehydrogenase (*HSD3B2*) and 11 β -hydroxylase (*CYP11B1*). In CAH, these enzyme deficiencies impair cortisol synthesis, resulting in a loss of cortisol negative feedback on CRH and ACTH. Excess ACTH results in steroidogenesis proximal to the deficient enzyme, leading to the hyperandrogenic pathophysiology associated with the disorder. CAH patients can present with hirsutism, acne, alopecia oligomenorrhea and infertility associated with virilization. Glucocorticoid and mineralocorticoid hormone replacement therapies are mainstay treatments, however require close monitoring to balance overtreatment and undertreatment. Further, 'stress dosing' is required at times of significant stress, illness or surgery (*J. Pediatr. Adolesc. Gynecol.* 30, 520–534 (2017)). Importantly, high doses of glucocorticoid replacement are required to inhibit ACTH production and thereby reduce adrenal androgen levels. This often means that in order to control adrenal androgen levels, patients will suffer from corticosteroid-associated side effects or Cushing's-like symptoms. Thus, there remains a need for better treatments of CAH. As ACTH is elevated in CAH, inhibition of its activity, through antagonism of MC2R, provides an attractive means of modulating the steroidogenesis pathway.

Cushing's disease is another rare disease associated with excess secretion of ACTH caused by adenomas of pituitary corticotropic cells. Clinical presentations include obesity, hirsutism, muscle weakness as well as cardiovascular and metabolic complications associated with hypercortisolism. Treatments for Cushing's disease involve removal of either the ACTH-secreting tumour in the pituitary, or removal of the adrenal glands, however drug treatment is often used in addition to, or before surgery to alleviate symptoms. Current drug therapies aim to inhibit adrenal steroidogenesis, however, are not without adverse effects such as hypothyroidism and hypogonadism (*J. Med. Life* 9, 12–18 (2016)). Inhibition of ACTH activity via MC2R antagonism provides a potential therapeutic option in management of this disease.

In addition to CAH and Cushing's disease, polycystic ovary syndrome (PCOS) may be amenable to MC2 modulation. PCOS is associated with abnormal regulation of steroidogenesis and excess androgen levels. In a subset of patients the androgen excess results from functional adrenal

hyperandrogenism (*Endocr. Rev.* 37, 467–520 (2016)). Modulation of ACTH activity in these patients offers another therapeutic avenue for this multisystem disorder.

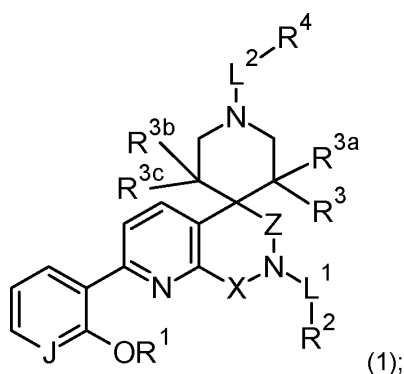
Thus, antagonism of MC2R presents an important therapeutic modality for treatment of diseases associated with ACTH dysfunction. WO2019/23669, WO2021/091788, WO2021/126693 and WO2021/133563 disclose MC2R antagonist compounds.

Long duration of action is a widely sought after feature in drug design, enabling prolonged efficacy and simplified dosing regimes (*British Journal of Pharmacology* 2010, 161(3), 488–508). In the treatment of diseases associated with ACTH dysfunction, in particular diseases with excess ACTH, inhibitors with longer residence times offer the advantage of insurmountable antagonism, whereby receptor inhibition remains in the face of high ACTH concentrations. A means of achieving these favourable drug properties involves developing a compound with slow dissociation (k_{off}) kinetics (*Neurochemistry international* 2007, 51(5), 254–260). This has been demonstrated at various targets, ranging from fevipiprant at the DP2 receptor to NK₁ neurokinin receptor antagonists (*Mol Pharmacol* 2016, 89(5), 593–605; *The Journal of pharmacology and experimental therapeutics* 2007, 322(3), 1286–1293).

THE INVENTION

The present invention provides compounds having activity as melanocortin subtype-2 receptor (MC2R) antagonists.

Provided is a compound of Formula (1):



or a salt thereof, wherein;
J is N or CH;

X is -CO-, -CH₂- or -CH₂CH₂-;

Z is a bond, -CH₂- or -CO-;

L¹ is -(CH₂)_n-, -(CH₂)_nCONH-, -(CH₂)_nCOO-, -CO(CH₂)_nNH- or -CO(CH₂)_n-, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms;

R² is H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹²;

R^{2a} and R^{2b} are independently H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms;

R³ is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R³ is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

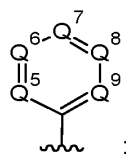
R^{3a} is H or is joined to R³ to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3b} is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R³ and R^{3b} is H;

L² is a bond or -CO- and R⁴ is a group:



wherein Q⁵ is CR⁵ or N; Q⁶ is CR⁶ or N; Q⁷ is CR⁷ or N; Q⁸ is CR⁸ or N; and Q⁹ is CR⁹ or N; where one, two or none of Q⁵, Q⁶, Q⁷, Q⁸ and Q⁹ is N;

or L² is -CO- and R⁴ is -(CH₂)_qNH₂, where q is 0-3;

R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from H, halo, CN, NR¹⁵R¹⁶, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, OC₁₋₃alkyl optionally substituted with 1-3 fluorine atoms,

OCH₂cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH₂CN, CO₂H and SO₂Me;

R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3; R^{13} and R^{14} are independently H or methyl; and

5 R^{15} and R^{16} are independently H or C_{1-3} alkyl.

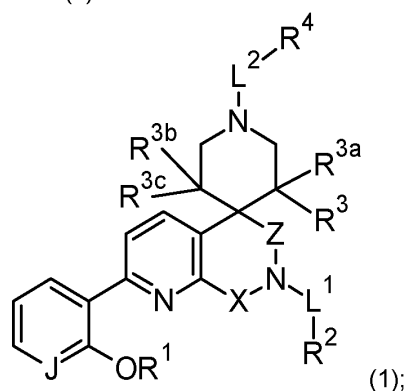
Compounds of the present invention may be used as melanocortin subtype-2 receptor (MC2R) modulators. Compounds of the present invention may be used as MC2R inhibitors. Compounds of the present invention may be used as MC2R antagonists. Compounds of the present invention may be used as MC2R antagonists with a long residence time at the receptor. Compounds of the present invention may be used in the treatment of a disease or disorder associated with MC2R. Compounds of the present invention may be used in the treatment of a disease or disorder that would benefit from the modulation of MC2R activity. Compounds of the present invention may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of diseases or disorders in which MC2R is involved. Compounds of the present invention may be for use as a single agent or in combination with one or more additional pharmaceutical agents.

Compounds of the present invention may be useful in the treatment of congenital adrenal hyperplasia (CAH), Cushing's disease, ectopic ACTH syndrome (or ectopic Cushing's syndrome), polycystic ovary syndrome (PCOS), depressive illness, septic shock, and disorders or symptoms related thereto.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to novel compounds. The invention also relates to the use of novel compounds as modulators of the melanocortin subtype-2 receptor (MC2R), in particular as MC2R antagonists. The invention further relates to novel compounds as MC2R antagonists which have a long residence time at the receptor. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as MC2R antagonists. The invention further relates to compounds, compositions and medicaments that may be useful in the treatment of a disease or disorder characterised by activation of the MC2R receptor.

Provided is a compound of formula (1):



or a salt thereof, wherein;

J is N or CH;

5 X is -CO-, -CH₂- or -CH₂CH₂-;

Z is a bond, -CH₂- or -CO-;

L¹ is -(CH₂)_n-, -(CH₂)_nCONH-, -(CH₂)_nCOO-, -CO(CH₂)_nNH- or -CO(CH₂)_n-, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms;

10 R² is H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹²;

R^{2a} and R^{2b} are independently H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms;

15 R³ is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R³ is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

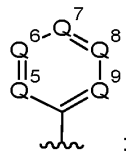
R^{3a} is H or is joined to R³ to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

20 R^{3b} is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

25 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R³ and R^{3b} is H;

L^2 is a bond or $-CO-$ and R^4 is a group:



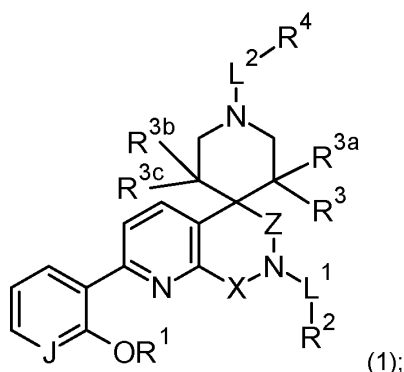
wherein Q⁵ is CR⁵ or N; Q⁶ is CR⁶ or N; Q⁷ is CR⁷ or N; Q⁸ is CR⁸ or N; and Q⁹ is CR⁹ or N; where one, two or none of Q⁵, Q⁶, Q⁷, Q⁸ and Q⁹ is N;

5 or L² is -CO- and R⁴ is -(CH₂)_qNH₂, where q is 0-3;

R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from H, halo, CN, NR¹⁵R¹⁶, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, OC₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, OCH₂cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH₂CN, CO₂H and SO₂Me;

R¹⁰, R¹¹ and R¹² are independently selected from H, OH, oxo, halo, C₁₋₃ alkyl optionally substituted with OH or 1-3 fluorine atoms, SO₂NH₂, OSO₂OH, OSO₂F, B(OH)₂, Bpin, -(CH₂)_gNR¹³R¹⁴, -CH₂(CH₂)_g(OCH₂CH₂O)_yR¹³, -(CH₂)_gCO₂R¹³ and -(CH₂)_gCONR¹³R¹⁴, where g is 0-3 and y is 1-3; R¹³ and R¹⁴ are independently H or methyl; and R¹⁵ and R¹⁶ are independently H or C₁₋₃alkyl.

15 Also provided is a compound of Formula (1):



or a salt thereof, wherein;

J is N or CH;

X is -CO-, -CH₂- or -CH₂CH₂-;

20 Z is a bond, -CH₂- or -CO-;

L¹ is $-(CH_2)_n-$, $-(CH_2)_nCONH-$, $-(CH_2)_nCOO-$, $-CO(CH_2)_nNH-$ or $-CO(CH_2)_n-$, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms;

R^2 is H, CO_2H , OH, $\text{NR}^{2a}\text{R}^{2b}$, $\text{CONR}^{2a}\text{R}^{2b}$, $\text{SO}_2\text{NR}^{2a}\text{R}^{2b}$, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R^{10} , R^{11} and R^{12} , or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R^{10} , R^{11} and R^{12} ;

R^{2a} and R^{2b} are independently H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms;

- 5 R^3 is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or $\text{CH}_2\text{C}_{3-4}$ cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^3 is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

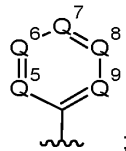
- 10 R^{3a} is H or is joined to R^3 to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3b} is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or $\text{CH}_2\text{C}_{3-4}$ cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

- 15 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R^3 and R^{3b} is H;

L^2 is a bond or $-\text{CO}-$ and R^4 is a group:



- 20 wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where one, two or none of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N;

or L^2 is $-\text{CO}-$ and R^4 is $-(\text{CH}_2)_q\text{NH}_2$, where q is 0-3;

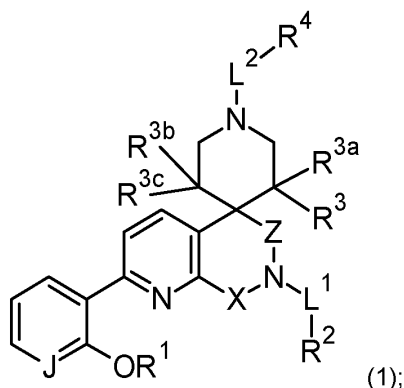
R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $\text{NR}^{15}\text{R}^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms,

- 25 $\text{OCH}_2\text{cyclopropyl}$ optionally substituted with 1-3 fluorine atoms, OCH_2CN and SO_2Me ;

R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $\text{B}(\text{OH})_2$, Bpin, $-(\text{CH}_2)_g\text{NR}^{13}\text{R}^{14}$, $-\text{CH}_2(\text{CH}_2)_g(\text{OCH}_2\text{CH}_2\text{O})_y\text{R}^{13}$, $-(\text{CH}_2)_g\text{CO}_2\text{R}^{13}$ and $-(\text{CH}_2)_g\text{CONR}^{13}\text{R}^{14}$, where g is 0-3 and y is 1-3; R^{13} and R^{14} are independently H or methyl; and

- 30 R^{15} and R^{16} are independently H or C_{1-3} alkyl.

Also provided is a compound of Formula (1):



or a salt thereof, wherein;

J is N or CH;

5 X is -CO-, -CH₂- or -CH₂CH₂-;

Z is a bond, -CH₂- or -CO-;

L¹ is -(CH₂)_n-, -(CH₂)_nCONH-, -(CH₂)_nCOO-, -CO(CH₂)_nNH- or -CO(CH₂)_n-, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms;

10 R² is H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹²;

R^{2a} and R^{2b} are independently H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms;

15 R³ is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R³ is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

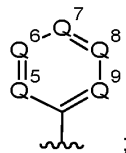
R^{3a} is H or is joined to R³ to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

20 R^{3b} is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

25 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R³ and R^{3b} is H;

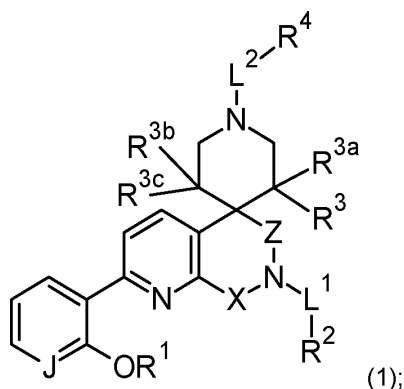
L^2 is a bond or $-\text{CO}-$ and R^4 is a group:



wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where one, two or none of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N;

- 5 R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $\text{NR}^{15}\text{R}^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, $\text{OCH}_2\text{cyclopropyl}$ optionally substituted with 1-3 fluorine atoms, OCH_2CN and SO_2Me ;
- R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $\text{B}(\text{OH})_2$, Bpin, $-(\text{CH}_2)_g\text{NR}^{13}\text{R}^{14}$, -
- 10 $\text{CH}_2(\text{CH}_2)_g(\text{OCH}_2\text{CH}_2\text{O})_y\text{R}^{13}$, $-(\text{CH}_2)_g\text{CO}_2\text{R}^{13}$ and $-(\text{CH}_2)_g\text{CONR}^{13}\text{R}^{14}$, where g is 0-3 and y is 1-3; R^{13} and R^{14} are independently H or methyl; and R^{15} and R^{16} are independently H or C_{1-3} alkyl.

Also provided is a compound of Formula (1):



15

or a salt thereof, wherein;

J is N or CH;

X is $-\text{CO}-$, $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

Z is a bond, $-\text{CH}_2-$ or $-\text{CO}-$;

- 20 L^1 is $-(\text{CH}_2)_n-$, $-(\text{CH}_2)_n\text{CONH}-$, $-(\text{CH}_2)_n\text{COO}-$, $-\text{CO}(\text{CH}_2)_n\text{NH}-$ or $-\text{CO}(\text{CH}_2)_n-$, where n is 0-5;

R^1 is C_{1-4} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or $\text{CH}_2\text{C}_{3-4}$ cycloalkyl optionally substituted with 1-3 fluorine atoms;

R^2 is H, CO_2H , OH, $\text{NR}^{2a}\text{R}^{2b}$, $\text{CONR}^{2a}\text{R}^{2b}$, $\text{SO}_2\text{NR}^{2a}\text{R}^{2b}$, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R^{10} , R^{11} and R^{12} , or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R^{10} , R^{11} and R^{12} ;

R^{2a} and R^{2b} are independently H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms;

- 5 R^3 is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or $\text{CH}_2\text{C}_{3-4}$ cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^3 is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

- 10 R^{3a} is H or is joined to R^3 to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3b} is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or $\text{CH}_2\text{C}_{3-4}$ cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

- 15 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R^3 and R^{3b} is H;

L^2 is $-\text{CO}-$ and R^4 is $-(\text{CH}_2)_q\text{NH}_2$, where q is 0-3;

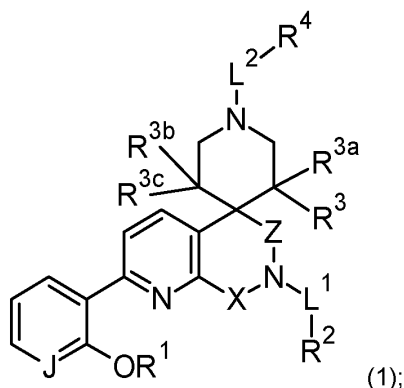
- 20 R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $\text{NR}^{15}\text{R}^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, $\text{OCH}_2\text{cyclopropyl}$ optionally substituted with 1-3 fluorine atoms, OCH_2CN and SO_2Me ;

R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $\text{B}(\text{OH})_2$, Bpin, $-(\text{CH}_2)_g\text{NR}^{13}\text{R}^{14}$, $-\text{CH}_2(\text{CH}_2)_g(\text{OCH}_2\text{CH}_2\text{O})_y\text{R}^{13}$, $-(\text{CH}_2)_g\text{CO}_2\text{R}^{13}$ and $-(\text{CH}_2)_g\text{CONR}^{13}\text{R}^{14}$, where g is 0-3 and y is 1-3;

- 25 R^{13} and R^{14} are independently H or methyl; and

R^{15} and R^{16} are independently H or C_{1-3} alkyl.

Also provided is a compound of Formula (1):



or a salt thereof, wherein;

J is N or CH;

5 X is -CO-, -CH₂- or -CH₂CH₂-;

Z is a bond, -CH₂- or -CO-;

L¹ is -(CH₂)_n-, -(CH₂)_nCONH-, -(CH₂)_nCOO-, -CO(CH₂)_nNH- or -CO(CH₂)_n-, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms;

10 R² is H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹²;

R^{2a} and R^{2b} are independently H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms;

15 R³ is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R³ is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

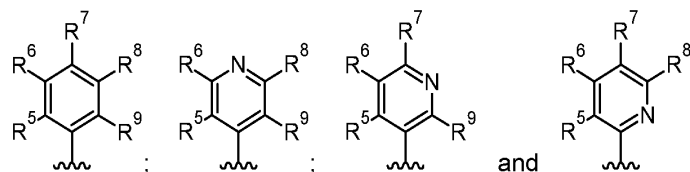
R^{3a} is H or is joined to R³ to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

20 R^{3b} is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

25 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R³ and R^{3b} is H;

L^2 is a bond or $-CO-$ and R^4 is a group selected from:



or L^2 is $-CO-$ and R^4 is $-(CH_2)_qNH_2$, where q is 0-3;

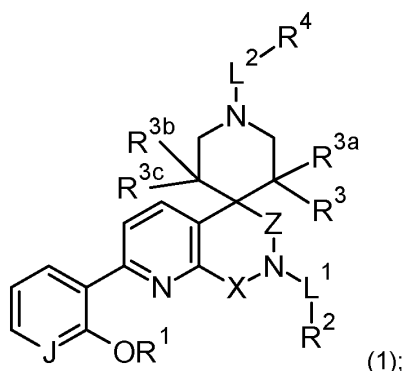
R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $NR^{15}R^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OCH_2 cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH_2CN and SO_2Me ;

R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3;

R^{13} and R^{14} are independently H or methyl; and

R^{15} and R^{16} are independently H or C_{1-3} alkyl.

Also provided is a compound of Formula (1):



or a salt thereof, wherein;

J is N or CH;

X is $-CO-$, $-CH_2-$ or $-CH_2CH_2-$;

Z is a bond, $-CH_2-$ or $-CO-$;

L^1 is $-(CH_2)_n-$, $-(CH_2)_nCONH-$, $-(CH_2)_nCOO-$, $-CO(CH_2)_nNH-$ or $-CO(CH_2)_n-$, where n is 0-5;

R^1 is C_{1-4} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms;

R^2 is H, OH, $NR^{2a}R^{2b}$, $CONR^{2a}R^{2b}$, $SO_2NR^{2a}R^{2b}$, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R^{10} , R^{11} and R^{12} , or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R^{10} , R^{11} and R^{12} ;

R^{2a} and R^{2b} are independently H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms;

- 5 R^3 is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^3 is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

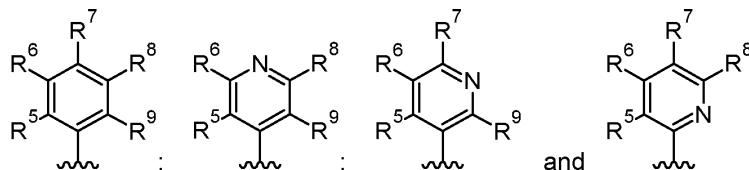
- 10 R^{3a} is H or is joined to R^3 to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3b} is H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

- 15 R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

wherein one or both of R^3 and R^{3b} is H;

L^2 is a bond or -CO- and R^4 is a group selected from:



- 20 or L^2 is -CO- and R^4 is $-(CH_2)_qNH_2$, where q is 0-3;

R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $NR^{15}R^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OCH_2 cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH_2CN and SO_2Me ;

- 25 R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3; R^{13} and R^{14} are independently H or methyl; and R^{15} and R^{16} are independently H or C_{1-3} alkyl.

- 30 In the compounds herein, J can be N or CH. J can be N. J can be CH.

In the compounds herein, X can be -CO-, -CH₂- or -CH₂CH₂-. X can be -CO- or -CH₂-. X can be -CO-. X can be -CH₂-. X can be -CH₂CH₂-.

In the compounds herein, Z can be a bond, -CH₂- or -CO-. Z can be -CH₂- or -CO-. Z can be -CH₂-. Z can be -CO-. Z can be a bond.

In the compounds herein, R¹ can be C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms. R¹ can be C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms. R¹ can be C₁₋₄alkyl. R¹ can be methyl or ethyl. R¹ can be methyl. R¹ can be ethyl. R¹ can be perdeuteroethyl. R¹ can be -CD₂CD₃. R¹ can be trideuteromethyl. R¹ can be -CD₃.

In the compounds herein, L¹ can be -(CH₂)_n-, -(CH₂)_nCONH-, -(CH₂)_nCOO-, -CO(CH₂)_nNH- or -CO(CH₂)_n-, where n is 0-5. L¹ can be a bond, -CH₂CH₂CONH-, -COO-, -CH₂CH₂COO-, -CH₂CH₂CO-, -COCH₂NH-, -COCH₂CH₂NH-, -CO-, -COCH₂-, -CH₂CH₂- or -CH₂-. L¹ can be a bond.

In the compounds herein, R² can be H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹². R² can be H, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹². R² can be H, a piperidine ring which is optionally substituted with R¹⁰, R¹¹ and R¹², a pyrrolidine ring which is optionally substituted with R¹⁰, R¹¹ and R¹², an azetidine ring which is optionally substituted with R¹⁰, R¹¹ and R¹², a hexahydro-1H-pyrrolizine ring system which is optionally substituted with R¹⁰, R¹¹ and R¹², a 2-pyrrolidone ring which is optionally substituted with R¹⁰, R¹¹ and R¹², a 1-azabicyclo[2.2.2]octane ring system which is optionally substituted with R¹⁰, R¹¹ and R¹², a tetrahydrofuran ring which is optionally substituted with R¹⁰, R¹¹ and R¹² or a morpholine ring which is optionally substituted with R¹⁰, R¹¹ and R¹².

In the compounds herein, R^{2a} and R^{2b} can independently be H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms. R^{2a} and R^{2b} can independently be H or C₁₋₃alkyl. R^{2a} and R^{2b} can independently be H or methyl. R^{2a} and R^{2b} can both be H.

R^{2a} can be H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms. R^{2a} can be H or C_{1-3} alkyl. R^{2a} can be H or methyl. R^{2a} can be H.

- 5 R^{2b} can be H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms. R^{2b} can be H or C_{1-3} alkyl. R^{2b} can be H or methyl. R^{2b} can be H.

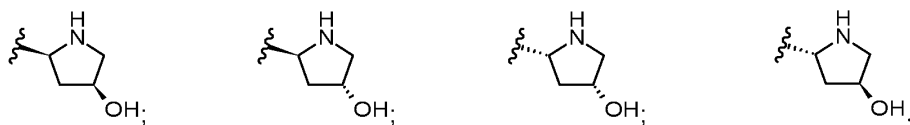
- In the compounds herein, R^{10} , R^{11} and R^{12} can be independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$,
 10 Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3. R^{10} , R^{11} and R^{12} can be independently selected from H, OH, CH_2CH_2OH , CH_2NH_2 and $CH_2CH_2OCH_2CH_2OCH_3$.

- R^{10} can be selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine
 15 atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3. R^{10} can be selected from H, OH, CH_2CH_2OH , CH_2NH_2 and $CH_2CH_2OCH_2CH_2OCH_3$. R^{10} can be H. R^{10} can be OH. R^{10} can be CH_2CH_2OH . R^{10} can be CH_2NH_2 . R^{10} can be $CH_2CH_2OCH_2CH_2OCH_3$.

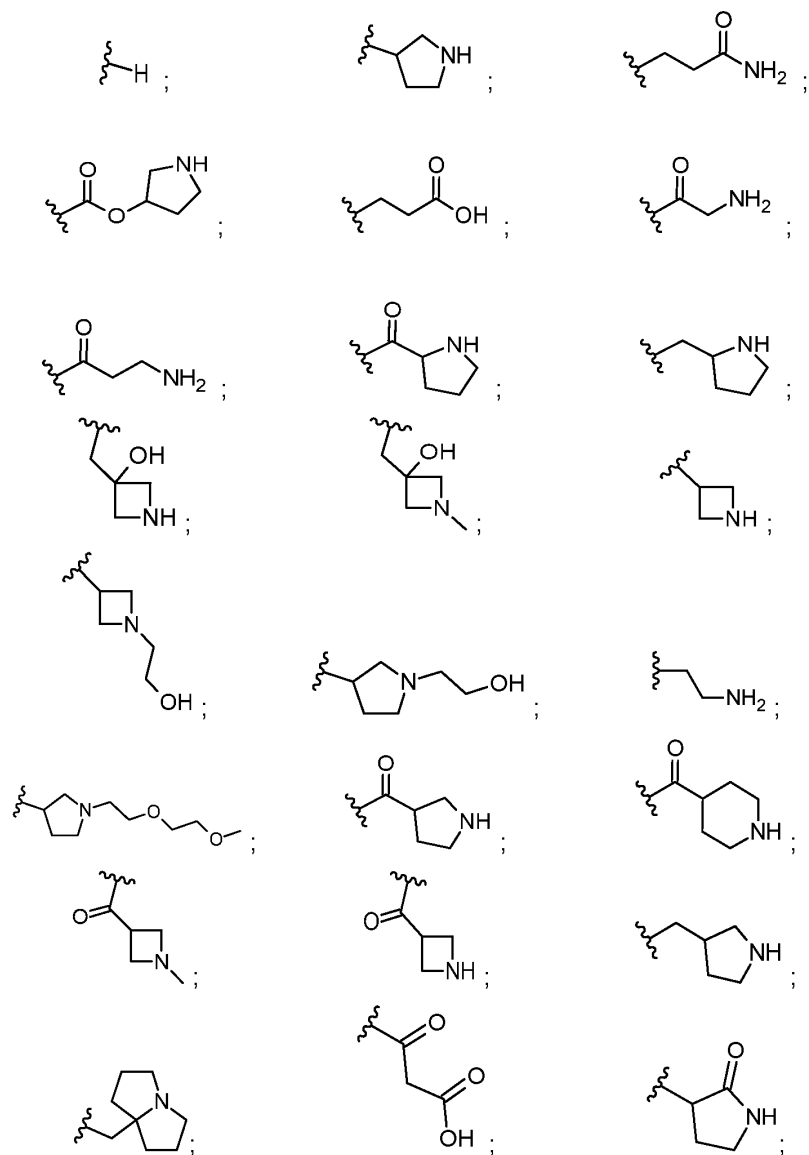
- 20 R^{11} can be selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3. R^{11} can be selected from H, OH, CH_2CH_2OH , CH_2NH_2 and $CH_2CH_2OCH_2CH_2OCH_3$. R^{11} can be H. R^{11} can be OH. R^{11} can be CH_2CH_2OH . R^{11} can be CH_2NH_2 . R^{11} can be $CH_2CH_2OCH_2CH_2OCH_3$.

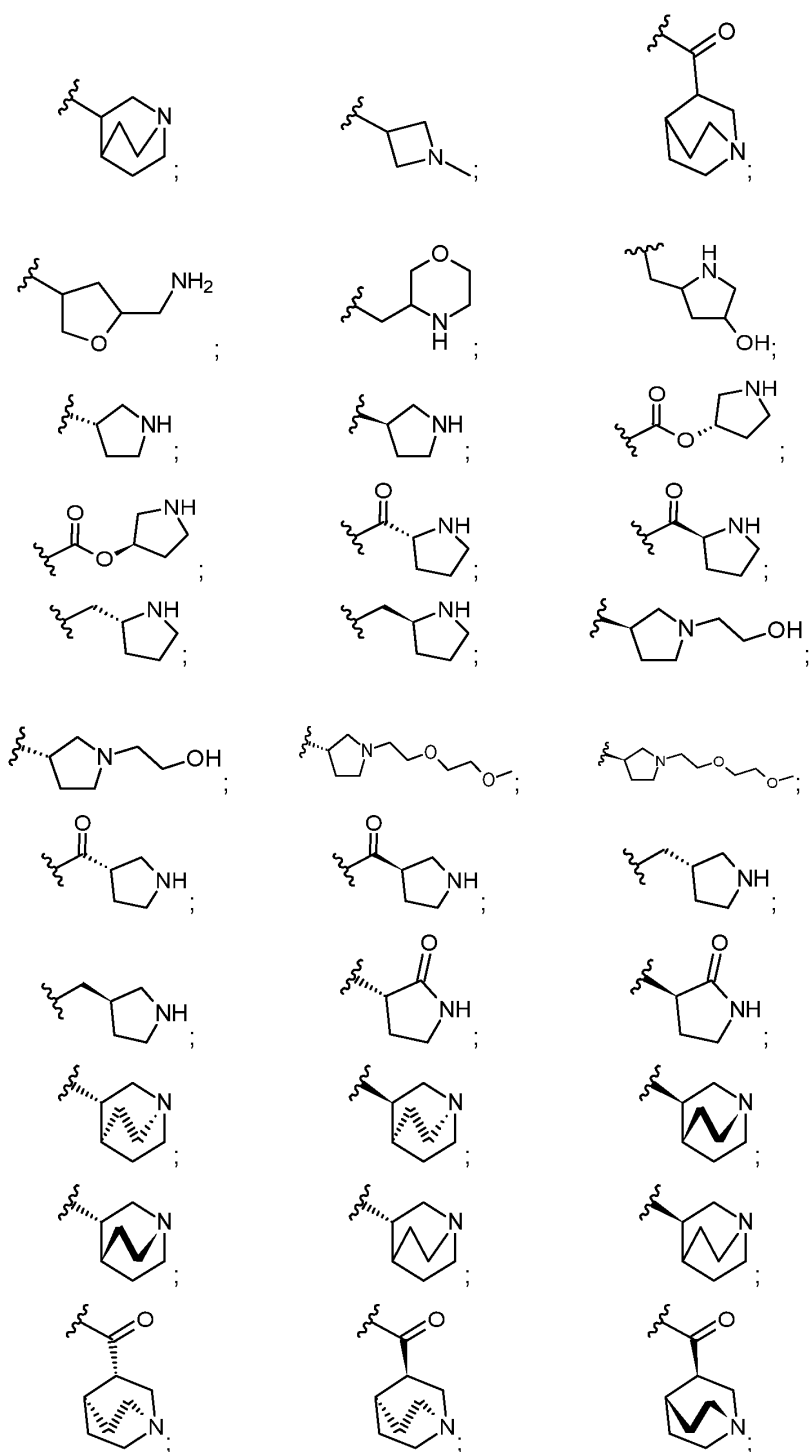
- 25 R^{12} can be selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3. R^{12} can be selected from H, OH, CH_2CH_2OH , CH_2NH_2 and $CH_2CH_2OCH_2CH_2OCH_3$. R^{12} can be H. R^{12} can be OH. R^{12} can be
 30 CH_2CH_2OH . R^{12} can be CH_2NH_2 . R^{12} can be $CH_2CH_2OCH_2CH_2OCH_3$.

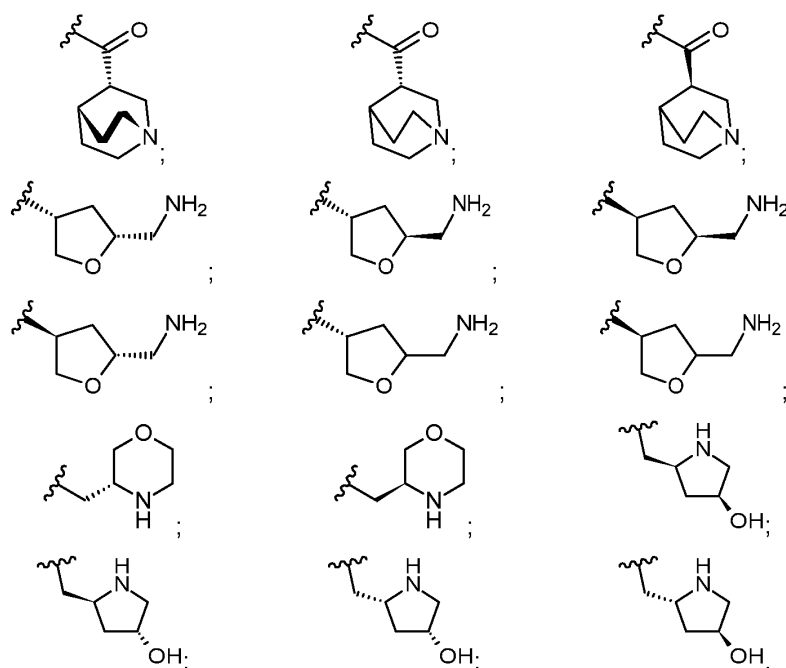
R^{13} and R^{14} can independently be H or methyl. R^{13} can be H or methyl. R^{14} can be H or methyl. R^{13} can be H. R^{13} can be methyl. R^{14} can be H. R^{14} can be methyl.



In the compounds herein, The moiety $-L^1-R^2$ can be selected from:







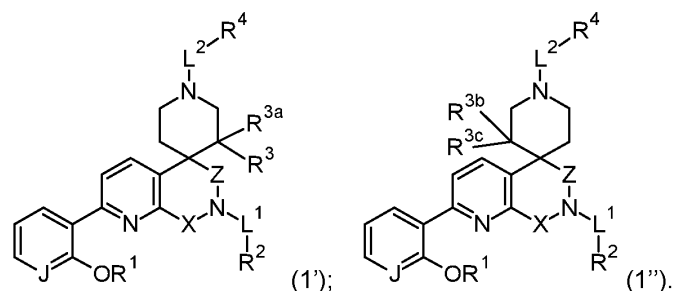
In the compounds herein, R^3 can be H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^3 can be joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms. R^3 can be H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms. R^3 can be H or C_{1-3} alkyl. R^3 can be H, methyl or ethyl.

In the compounds herein, R^{3a} can be H or can be joined to R^3 to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms.

In the compounds herein, R^{3b} can be H, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} can be joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms. R^{3b} can be H or C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms. R^{3b} can be H or C_{1-3} alkyl. R^{3b} can be H, methyl or ethyl.

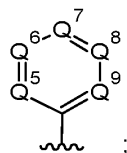
In the compounds herein, R^{3c} can be H or can be joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms.

- In the compounds herein, one or both of R^3 and R^{3b} is H. Thus, for example, the structure of
 5 Formula (1) as defined herein can be effectively viewed as the scope of Formula (1') and (1'') taken together:



- All of R^3 , R^{3a} , R^{3b} and R^{3c} can be H. One of R^3 and R^{3b} can be C_{1-3} alkyl optionally substituted with
 10 1-3 fluorine atoms, C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms or CH_2C_{3-4} cycloalkyl optionally substituted with 1-3 fluorine atoms and the other H. One of R^3 and R^{3b} can be methyl or ethyl and the other H. One of R^3 and R^{3b} can be methyl and the other H. One of R^3 and R^{3b} can be ethyl and the other H.

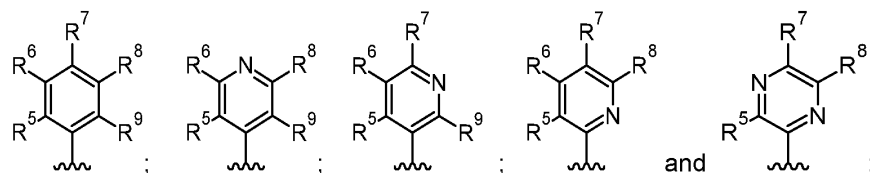
- 15 In the compounds herein, L^2 can be a bond or $-CO-$ and R^4 can be a group:



wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where
 one, two or none of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N;
 or L^2 can be $-CO-$ and R^4 can be $-(CH_2)_qNH_2$, where q is 0-3.

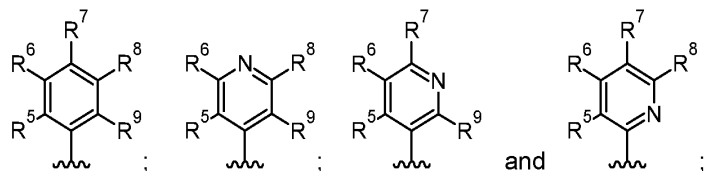
20

L^2 can be a bond or $-CO-$ and R^4 can be a group selected from:



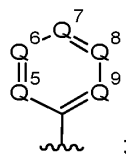
or L^2 can be $-\text{CO}-$ and R^4 can be $-(\text{CH}_2)_q\text{NH}_2$, where q is 0-3.

L^2 can be a bond or $-\text{CO}-$ and R^4 can be a group selected from:



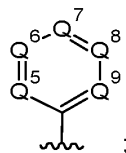
5 or L^2 can be $-\text{CO}-$ and R^4 can be $-(\text{CH}_2)_q\text{NH}_2$, where q is 0-3.

L^2 can be a bond or $-\text{CO}-$ and R^4 can be a group:



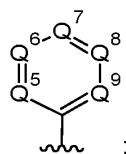
10 wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where one, two or none of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N.

L^2 can be a bond or $-\text{CO}-$ and R^4 can be a group:



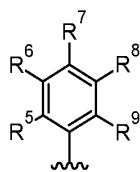
15 wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where one of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N.

L^2 can be a bond or $-\text{CO}-$ and R^4 can be a group:

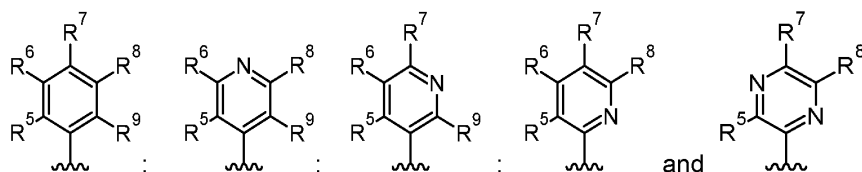


20 wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where two of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 are N.

L^2 can be a bond or $-\text{CO}-$ and R^4 can be a group:

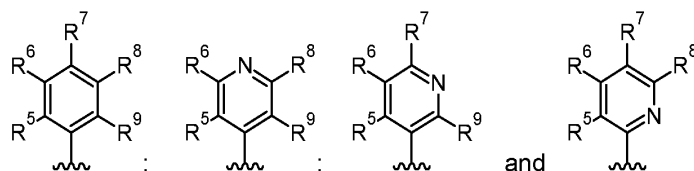


L² can be a bond or -CO- and R⁴ can be a group selected from:



5

L² can be a bond or -CO- and R⁴ can be a group selected from:



L² can be -CO- and R⁴ can be -(CH₂)_qNH₂, where q is 0-3.

10

In the compounds herein, R⁵, R⁶, R⁷, R⁸, and R⁹ can be independently selected from H, halo, CN, NR¹⁵R¹⁶, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, OC₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, OCH₂cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH₂CN and SO₂Me.

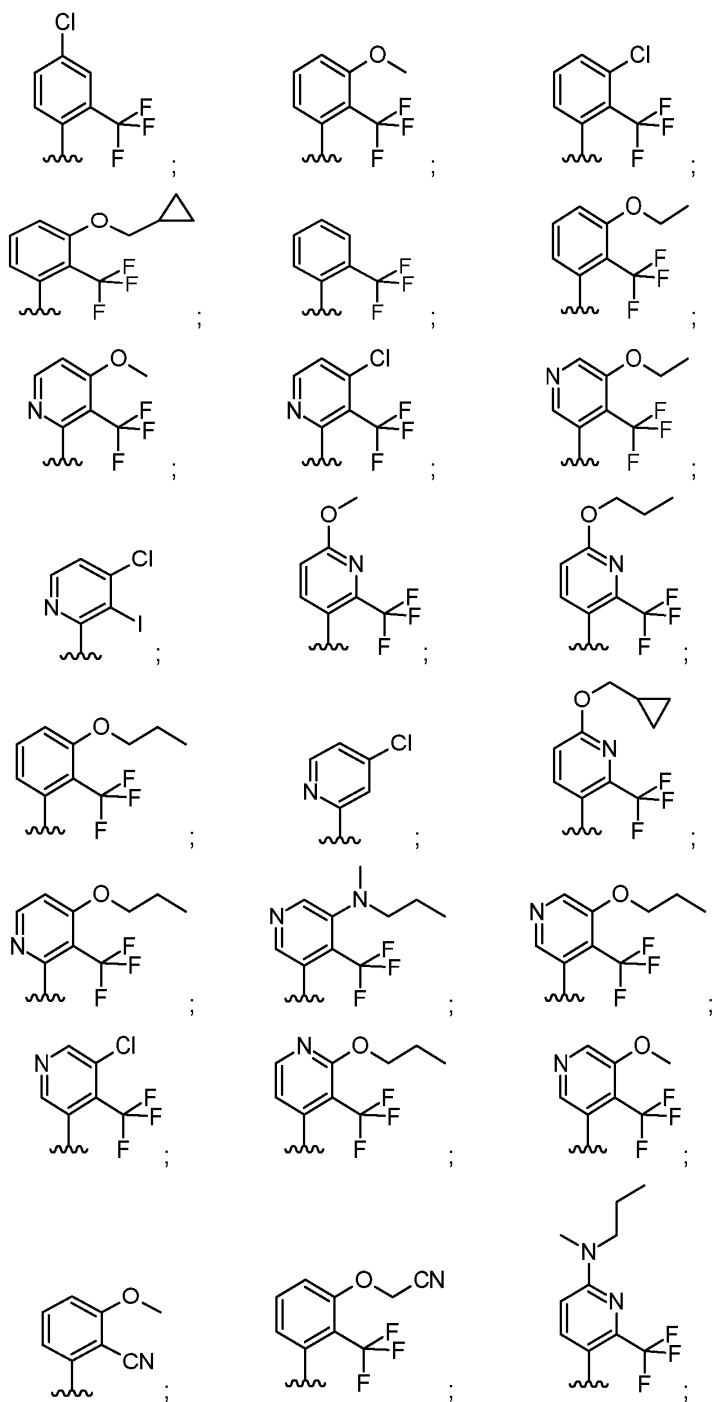
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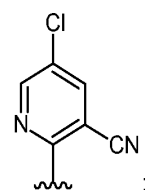
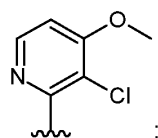
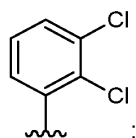
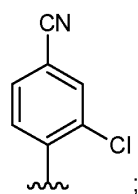
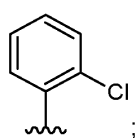
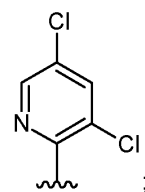
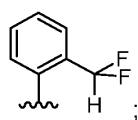
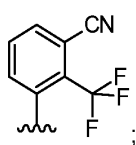
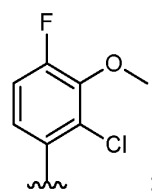
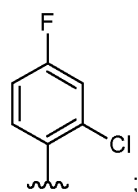
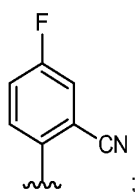
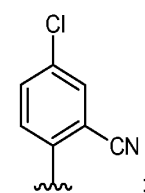
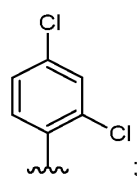
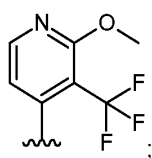
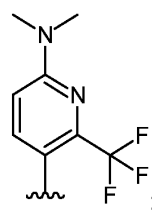
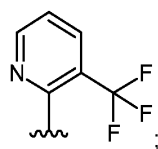
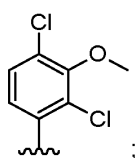
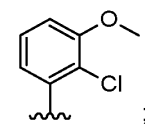
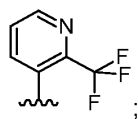
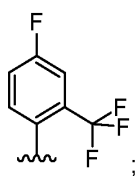
In the compounds herein, R¹⁵ and R¹⁶ can independently be H or C₁₋₃alkyl. R¹⁵ and R¹⁶ can independently be H, methyl, ethyl, *n*-propyl or isopropyl.

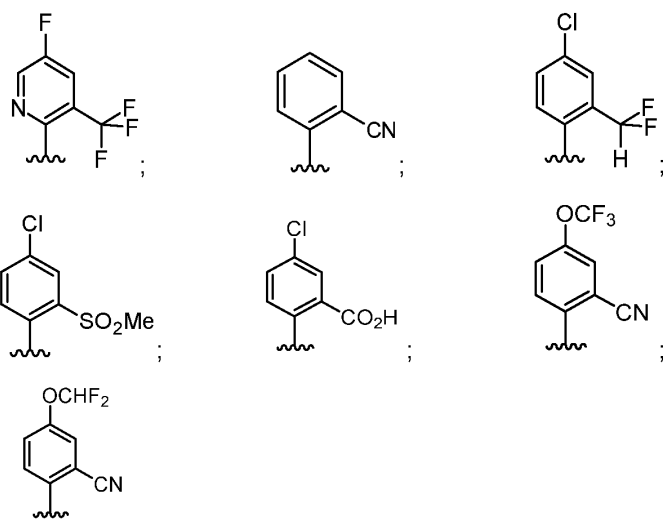
R⁵, R⁶, R⁷, R⁸, and R⁹ can be independently selected from H, Cl, F, I, CN, CF₃, CF₂H, -OMe, -OEt, -O^{*n*}Pr, -N(CH₃)(CH₂CH₂CH₃), -N(CH₃)₂, -OCH₂CN, -OCH₂cyclopropyl, -CO₂H and -SO₂Me.

20

L² can be a bond or -CO- and R⁴ can be a group selected from:

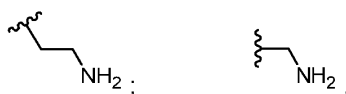






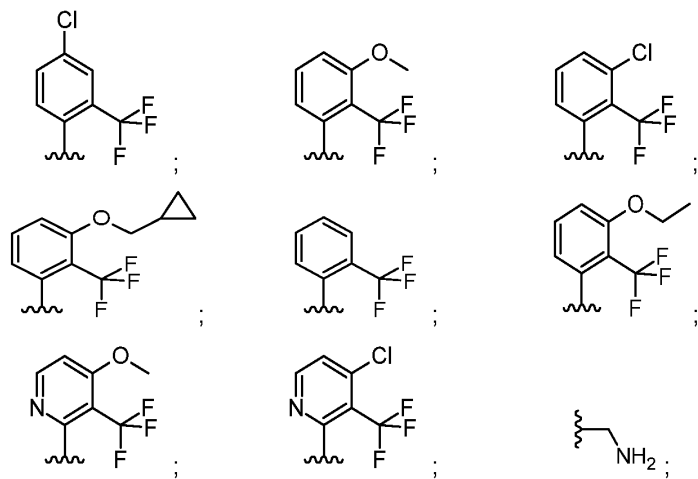
L² can be -CO- and R⁴ can be -(CH₂)_qNH₂, where q is 0-3.

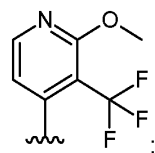
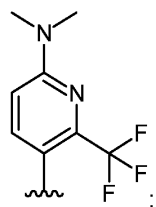
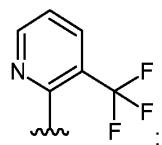
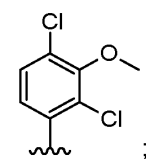
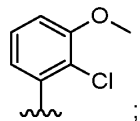
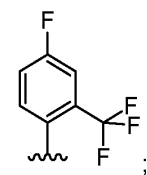
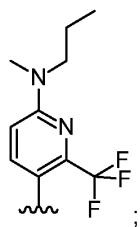
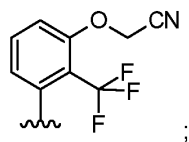
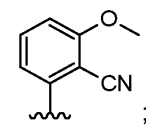
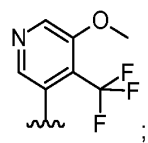
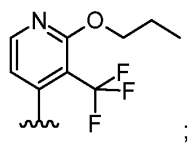
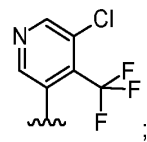
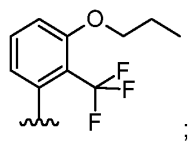
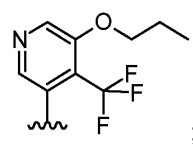
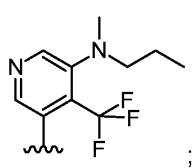
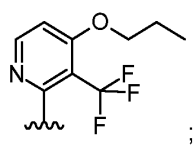
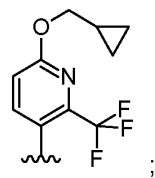
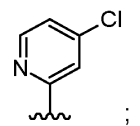
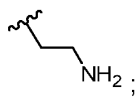
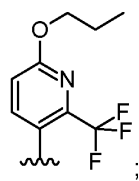
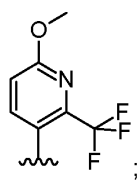
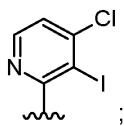
L² can be -CO- and R⁴ can be selected from:

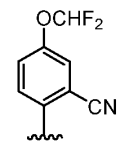
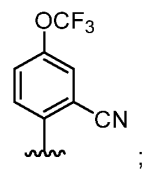
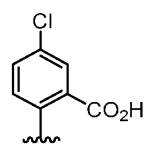
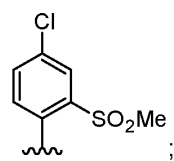
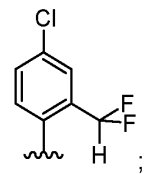
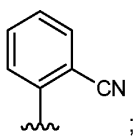
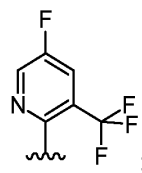
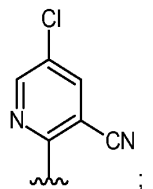
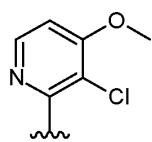
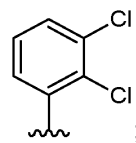
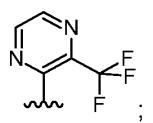
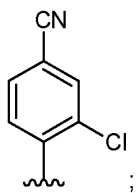
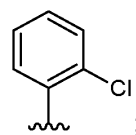
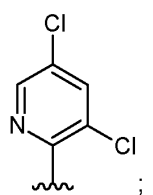
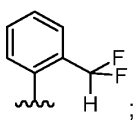
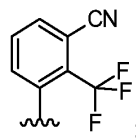
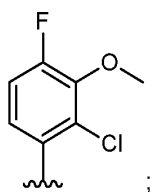
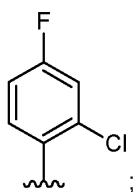
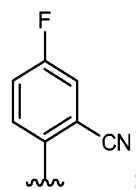
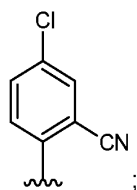
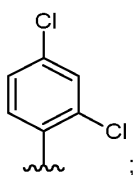


5

R^4 can be a group selected from:





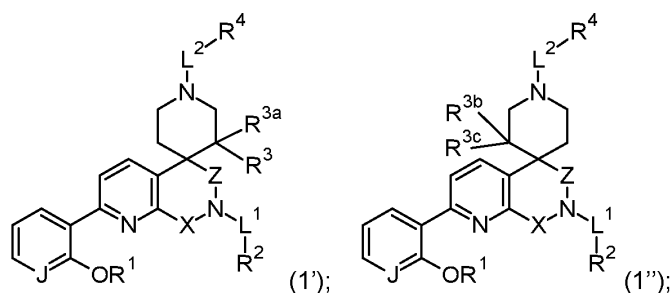


Definitions of L^1 and L^2 herein are provided without limitation to a particular orientation with respect to the rest of the molecule. As such L^1 and L^2 definitions provided include all possible orientations unless stated otherwise. For example, in compounds where L^1 is defined as $-\text{CONH}-$ both of the following may be included:

5



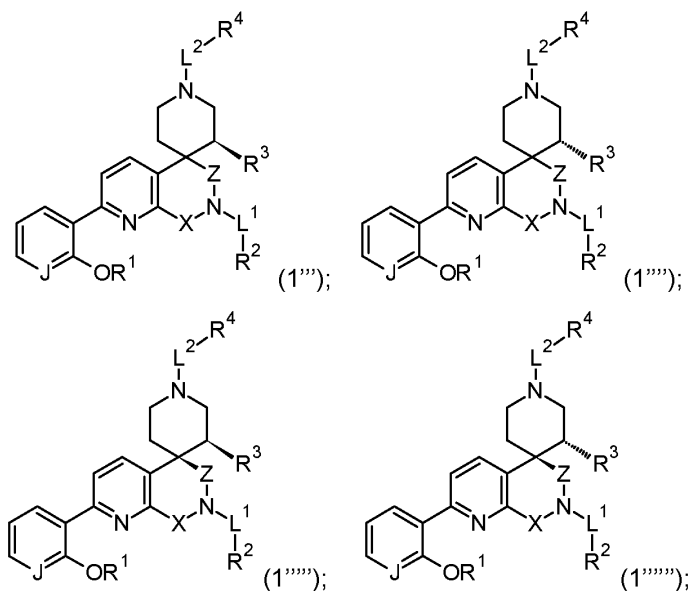
The compound can be a compound of Formula (1') or (1''):

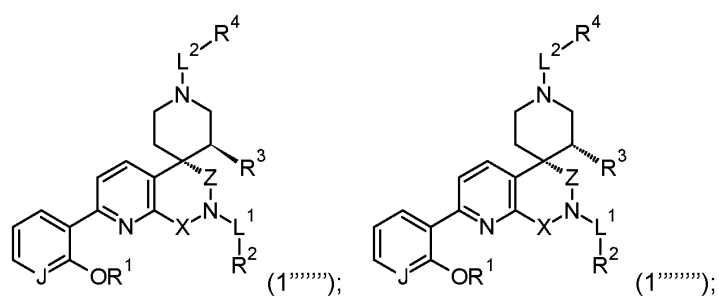


or a salt thereof, wherein J, X, Z, L^1 , L^2 , R^1 , R^2 , R^3 , R^{3a} , R^{3b} , R^{3c} and R^4 are as defined herein.

10

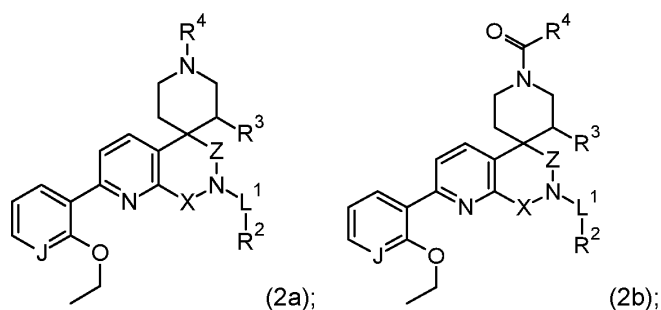
The compound can be a compound of Formula (1'''), (1''''), (1'''), (1'''), (1''') or (1'''):





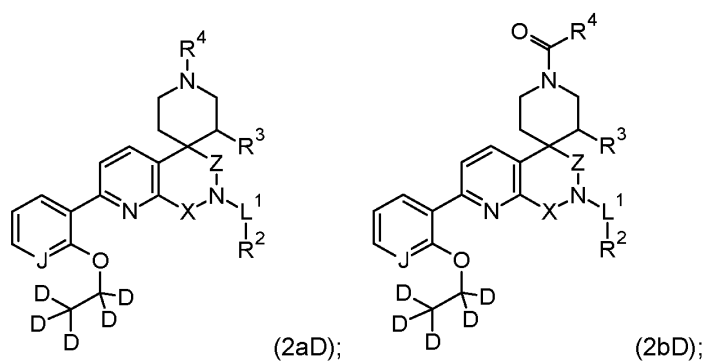
or a salt thereof, wherein J, X, Z, L¹, L², R¹, R², R³ and R⁴ are as defined herein.

The compound can be a compound of Formula (2a) or (2b):



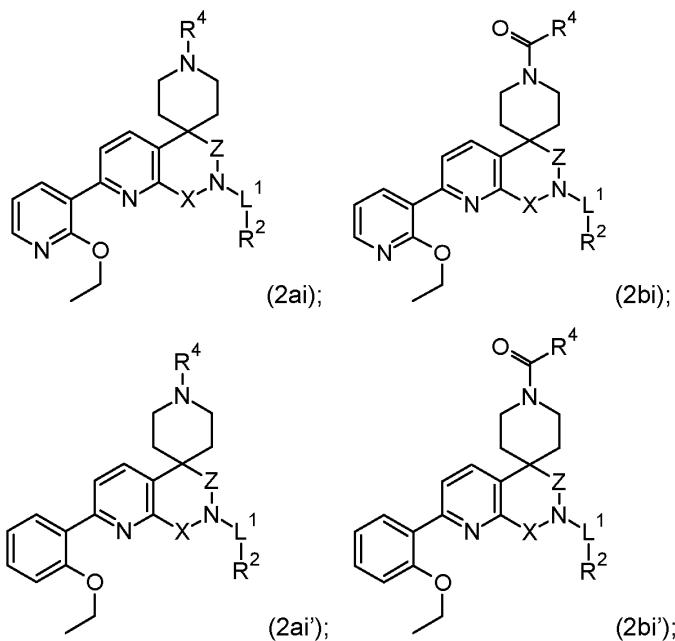
or a salt thereof, wherein X, Z, L¹, R², R³ and R⁴ are as defined herein.

The compound can be a compound of Formula (2aD) or (2bD):



or a salt thereof, wherein X, Z, L¹, R², R³ and R⁴ are as defined herein.

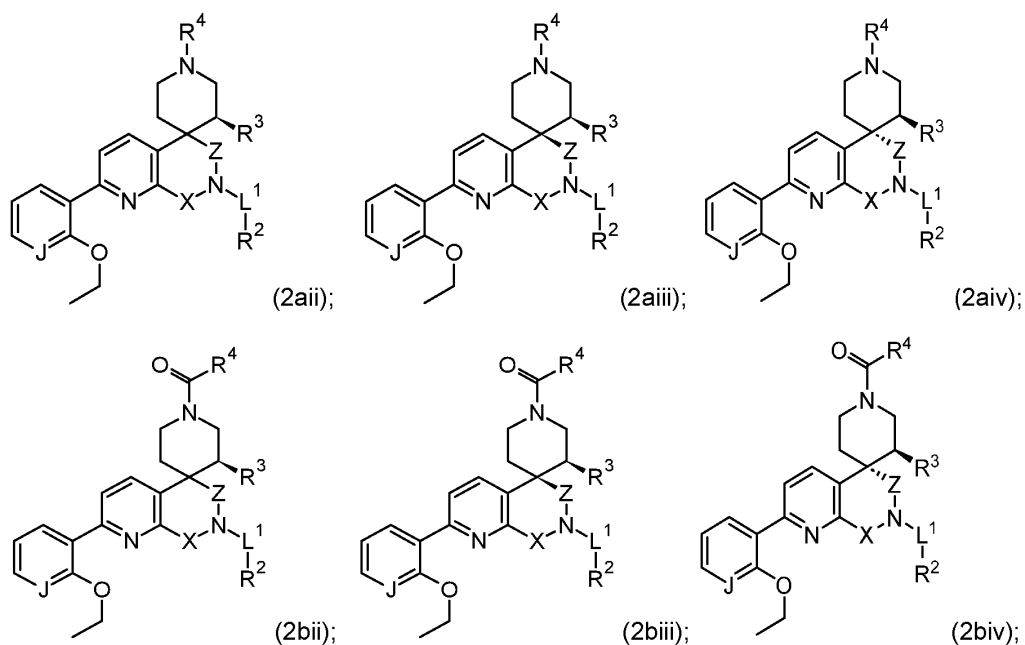
The compound can be a compound of Formula (2ai), (2bi), (2ai') or (2bi'):



or a salt thereof, wherein X , Z , L^1 , R^2 and R^4 are as defined herein.

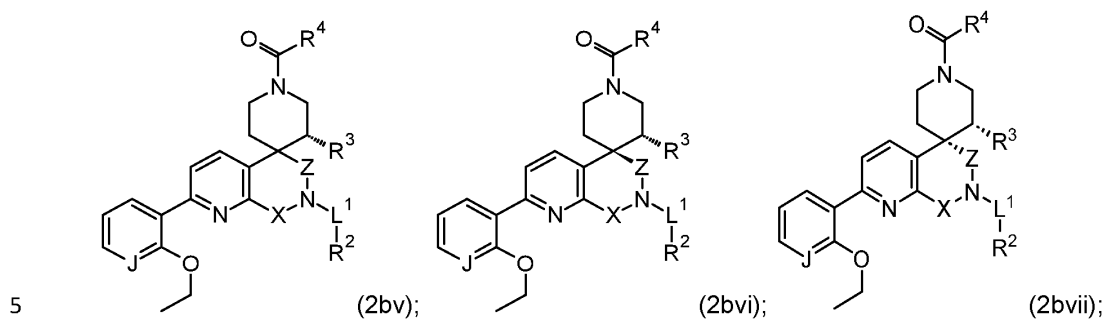
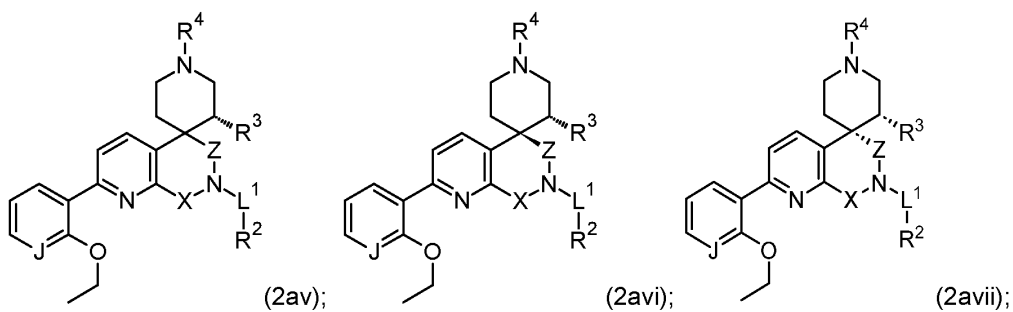
5

The compound can be a compound of Formula (2aii), (2aiii), (2aiv), (2bii), (2biii) or (2biv):



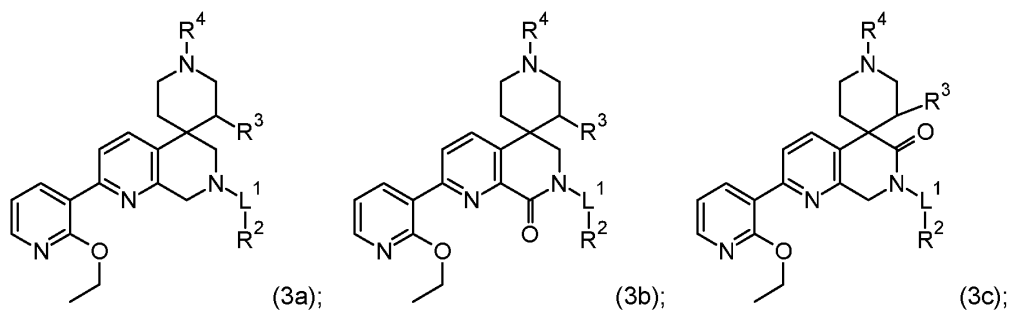
or a salt thereof, wherein X, Z, L¹, R², R³ and R⁴ are as defined herein.

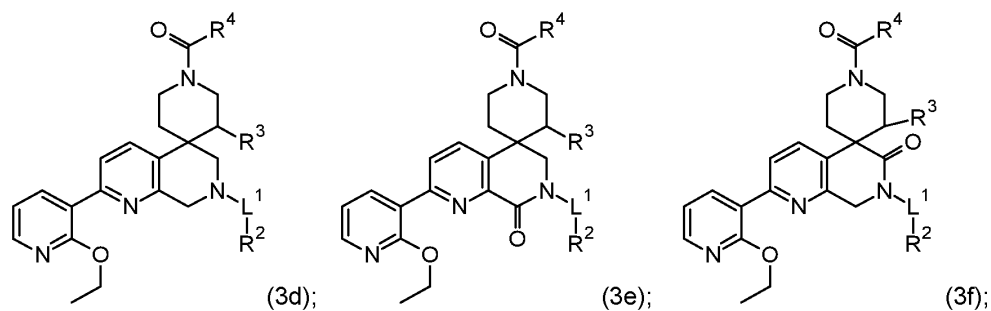
The compound can be a compound of Formula (2av), (2avi), (2avii), (2bv), (2bvi) or (2bvii):



or a salt thereof, wherein X, Z, L¹, R², R³ and R⁴ are as defined herein.

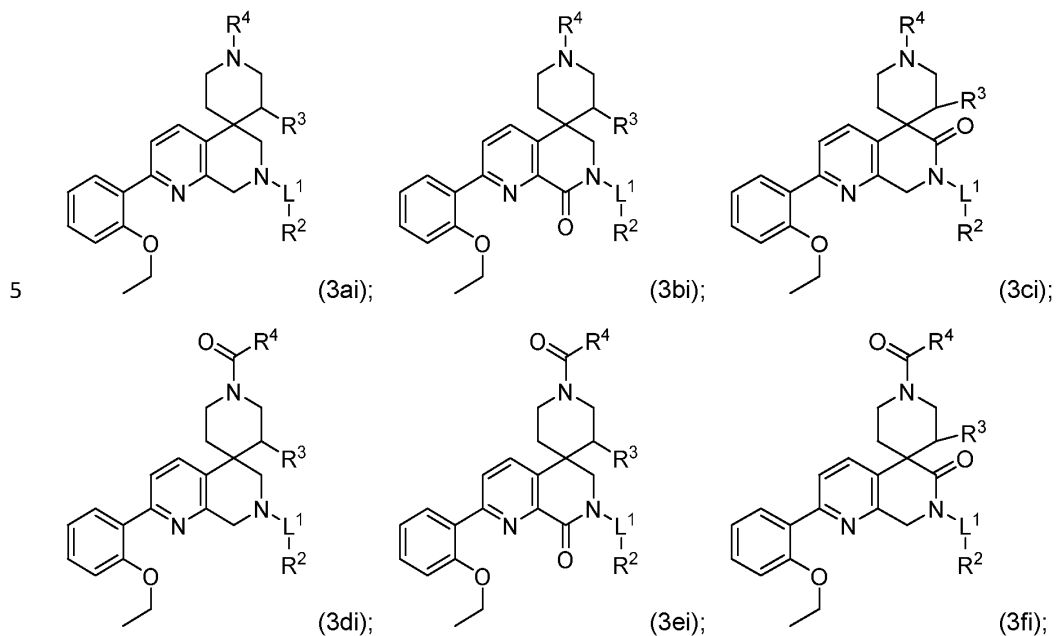
The compound can be a compound of Formula (3a), (3b), (3c), (3d), (3e) or (3f):





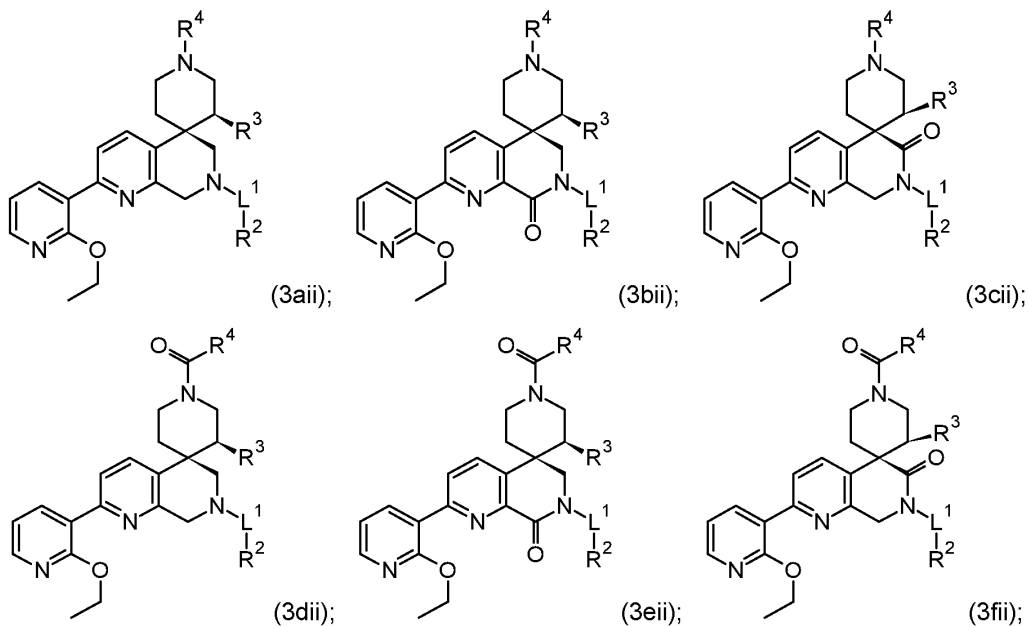
or a salt thereof, wherein L¹, R², R³ and R⁴ are as defined herein.

The compound can be a compound of Formula (3ai), (3bi), (3ci), (3di), (3ei) or (3fi):



or a salt thereof, wherein L^1 , R^2 , R^3 and R^4 are as defined herein.

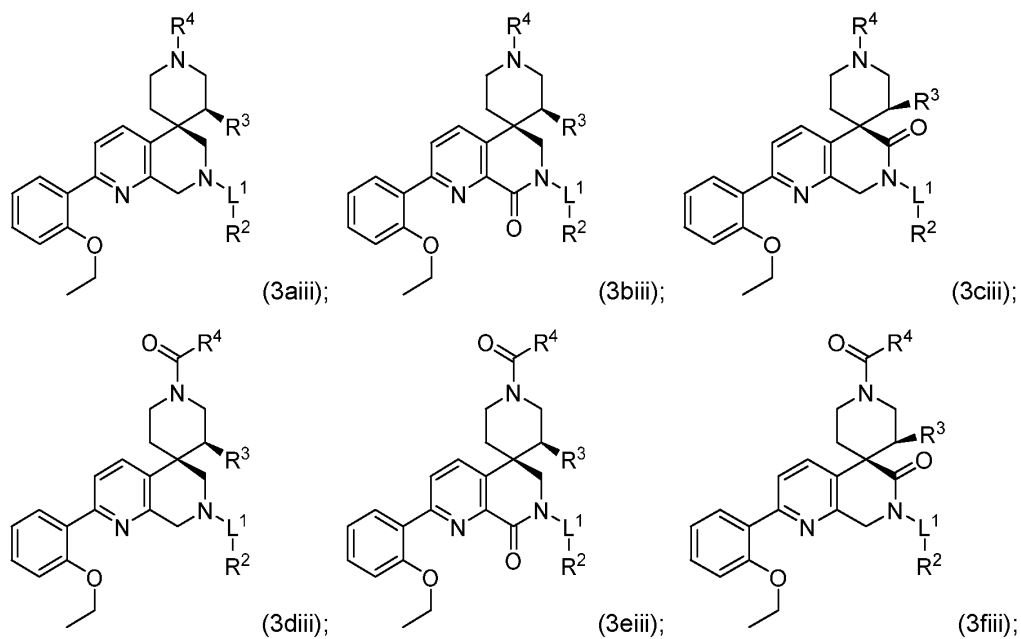
The compound can be a compound of Formula (3aii), (3bii), (3cii), (3dii), (3eii) or (3fii):



or a salt thereof, wherein L^1 , R^2 , R^3 and R^4 are as defined herein.

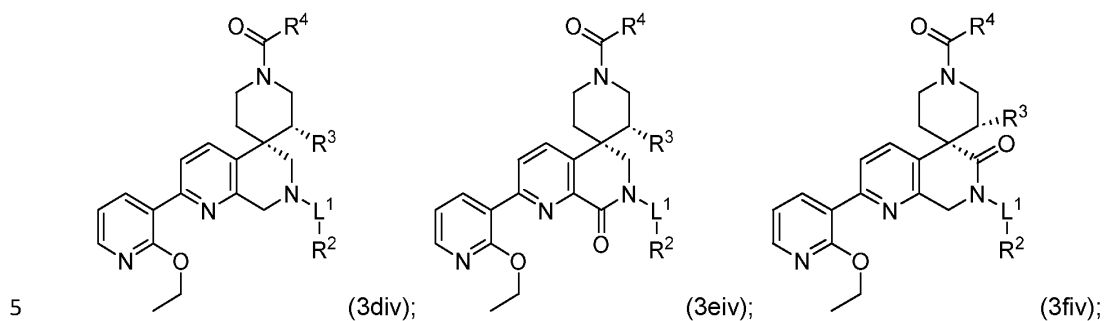
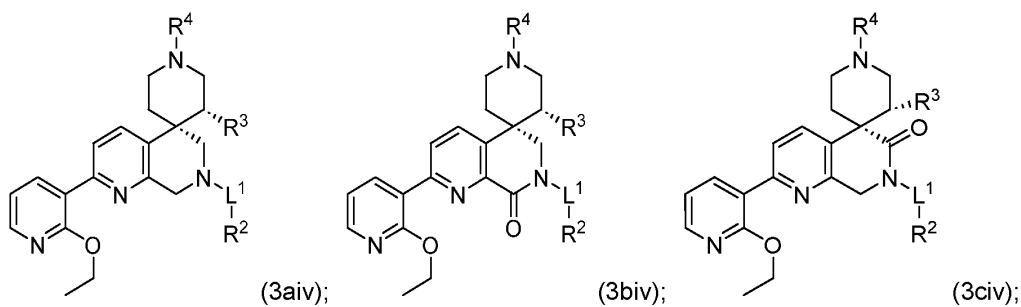
5

The compound can be a compound of Formula (3aiii), (3bihi), (3cii), (3diii), (3eiii) or (3fiii):



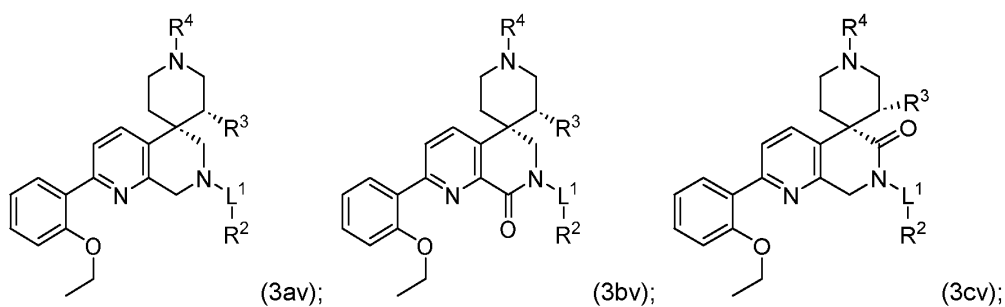
or a salt thereof, wherein L^1 , R^2 , R^3 and R^4 are as defined herein.

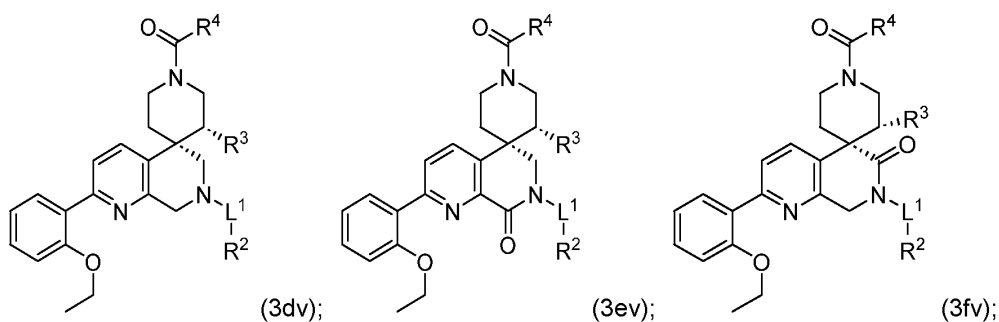
The compound can be a compound of Formula (3aiv), (3biv), (3civ), (3div), (3eiv) or (3fiv):



or a salt thereof, wherein L^1 , R^2 , R^3 and R^4 are as defined herein.

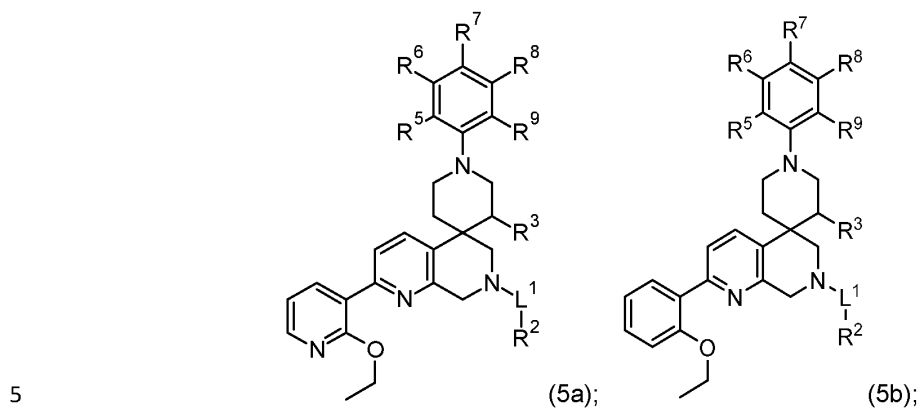
The compound can be a compound of Formula (3av), (3bv), (3cv), (3dv), (3ev) or (3fv):





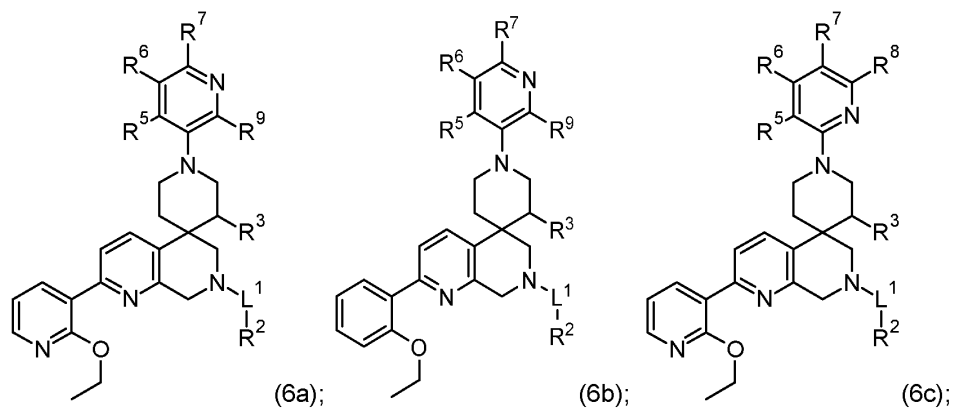
or a salt thereof, wherein L^1 , R^2 , R^3 and R^4 are as defined herein.

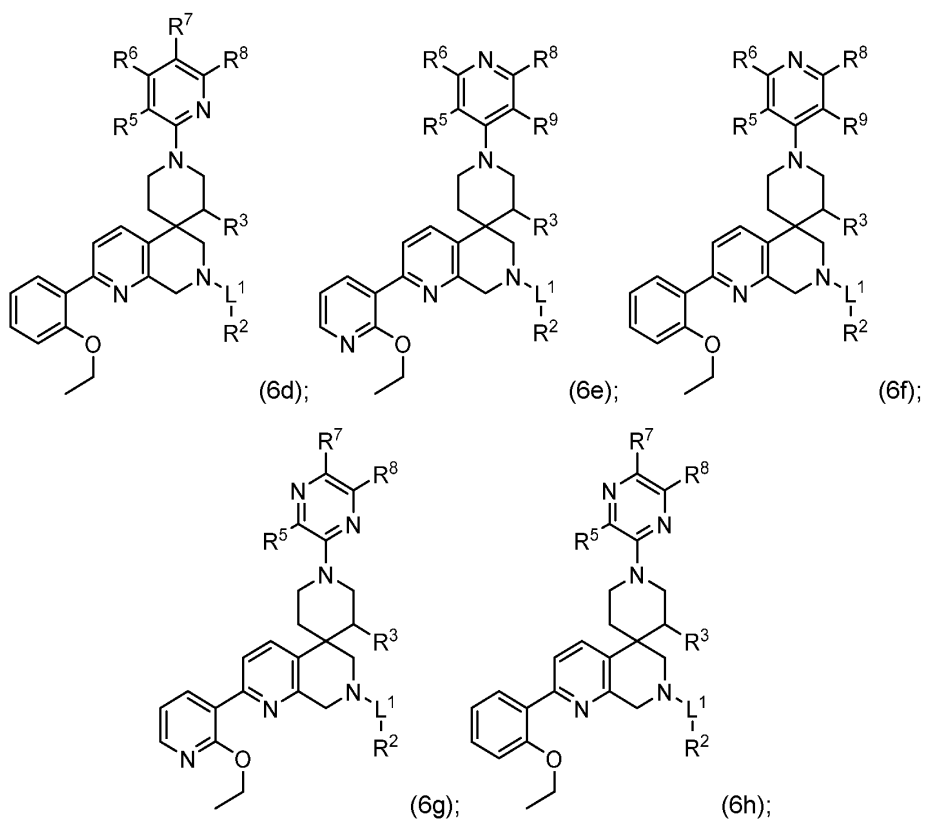
The compound can be a compound of Formula (5a) or (5b):



or a salt thereof, wherein L^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 and R^9 are as defined herein.

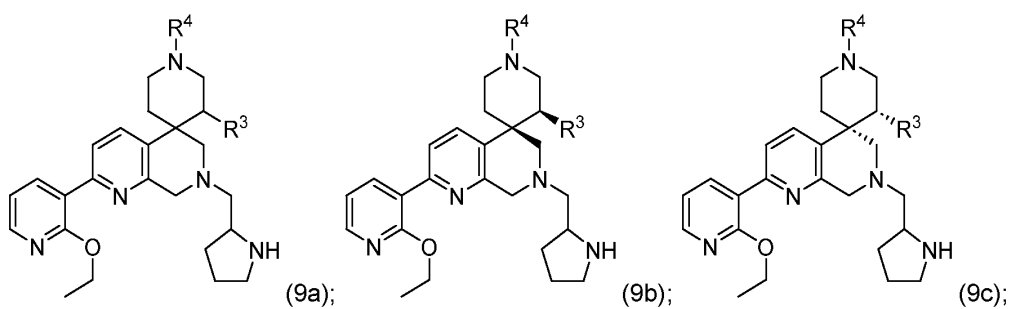
The compound can be a compound of Formula (6a), (6b), (6c), (6d), (6e), (6f), (6g) or (6h):

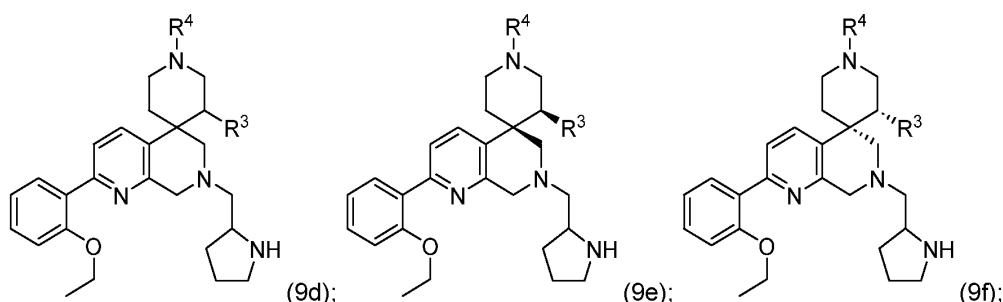




or a salt thereof, wherein L^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 and R^9 are as defined herein.

- 5 The compound can be a compound of Formula (9a), (9b), (9c), (9d), (9e) or (9f):





or a salt thereof, wherein R^3 and R^4 are as defined herein.

The compound can be selected from any one of Examples 1 to 218 as shown in Table 1a or a salt thereof.

The compound can be selected from the group consisting of:

1'-[4-chloro-2-(trifluoromethyl)benzoyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-[1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide;

3-[2-(2-ethoxypyridin-3-yl)-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide;

2-(2-ethoxypyridin-3-yl)-1'-[3-ethoxy-2-(trifluoromethyl)phenyl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[4-chloro-3-(trifluoromethyl)pyridin-2-yl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxypyridin-3-yl)-1'-[3-ethoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-amino-1-[7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]ethanone;

1'-(4-chloro-3-iodopyridin-2-yl)-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridine-3-carbonyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

[2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]methanone;

3-amino-1-[7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]propan-1-one;

[6-(cyclopropylmethoxy)-2-(trifluoromethyl)pyridin-3-yl]-[2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]methanone;

1'-(4-chloropyridin-2-yl)-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[4-chloro-3-(trifluoromethyl)pyridin-2-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

[2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]methanone;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine];

1'-[6-(cyclopropylmethoxy)-2-(trifluoromethyl)pyridine-3-carbonyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-6-oxospiro[8H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide;

2-(2-ethoxypyridin-3-yl)-1'-[6-propoxy-2-(trifluoromethyl)pyridine-3-carbonyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

(S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one;

(R)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-3'-ethylspiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[5-[methyl(propyl)amino]-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[2-(trifluoromethyl)phenyl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-yl)methyl]-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

- 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 7-(azetidin-3-yl)-1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-propoxy-2-(trifluoromethyl)phenyl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-amino-1-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]ethanone;
- 3-amino-1-[1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;
- 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-propoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;
- 2-(2-ethoxypyridin-3-yl)-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;
- 7-(2-aminoethyl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;
- [1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2S)-pyrrolidin-2-yl]methanone;
- [1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2R)-pyrrolidin-2-yl]methanone;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(2S)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

3-amino-1-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-7-[[[(2S)-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-3'-ethylspiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-pyrrolidin-3-yl-1'-[2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3R)-pyrrolidin-3-yl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3S)-pyrrolidin-3-yl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(3R)-pyrrolidin-3-yl]methanone;

[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-piperidin-4-ylmethanone;

[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-(1-methylazetidin-3-yl)methanone;

azetidin-3-yl-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methanone;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

2-(2-ethoxypyridin-3-yl)-1'-[5-ethoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(3R)-pyrrolidin-3-yl]methyl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(3S)-pyrrolidin-3-yl]methyl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

rac-(3'S,5S)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-(pyrrolidin-3-yl)-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[2-propoxy-3-(trifluoromethyl)pyridin-4-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-(pyrrolidin-3-yl)-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidine]-8-one;

(S)-2'-(2-ethoxypyridin-3-yl)-1-(3-propoxy-2-(trifluoromethyl)phenyl)-7'-(pyrrolidin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one;

2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

7-(azetidin-3-yl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one;

2-(2-ethoxypyridin-3-yl)-7-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

azetidin-3-yl 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-carboxylate;

2-[3-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)phenoxy]acetonitrile;

2-(2-ethoxypyridin-3-yl)-1'-[6-[methyl(propyl)amino]-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-6-methoxybenzonitrile;

1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-amino-1-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-6H-spiro[1,7-naphthyridine-5,4'-piperidin]-7(8H)-yl]propan-1-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-(pyrrolidin-3-yl)-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidin]-8-one;

(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-[(3S)-pyrrolidin-3-yl]-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidin]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-(pyrrolidin-3-yl)-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidin]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(3S)-pyrrolidin-3-yl]-1'-[2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(3S)-pyrrolidin-3-yl]-1'-[2-(trifluoromethyl)pyridin-3-yl]-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidin]-8-one;

2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-(pyrrolidin-3-yl)-1'-[2-(trifluoromethyl)pyridin-3-yl]-6,7-dihydro-8H-spiro[1,7-naphthyridine-5,4'-piperidin]-8-one;

[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2R)-pyrrolidin-2-yl]methanone;

[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2S)-pyrrolidin-2-yl]methanone;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

2-[7-(3-aminopropanoyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-6-methoxybenzonitrile;

3-amino-1-[1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

3-amino-1-[1'-(2,4-dichloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(3S)-pyrrolidin-3-yl]-1'-[3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

rac-(3'S,5S)-1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-[(3R)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(3R)-pyrrolidin-3-yl]-1'-[3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-3-oxopropanoic acid;

3-[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]pyrrolidin-2-one;

1'-[6-(dimethylamino)-2-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

7-(1-azabicyclo[2.2.2]octan-3-yl)-2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-fluoro-2-(trifluoromethyl)phenyl]-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-3-amino-1'-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

rac-(3'S,5S)-1'-[4-chloro-3-(trifluoromethyl)pyridin-2-yl]-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2S)-pyrrolidin-2-yl]methanone;

rac-(3'S,5S)-7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

enanti-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethyl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[2-methoxy-3-(trifluoromethyl)pyridin-4-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[2-methoxy-3-(trifluoromethyl)pyridin-4-yl]-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-1-azabicyclo[2.2.2]octan-3-yl-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methanone;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

3-amino-1-[1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rel-[(2R,4S)-4-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]oxolan-2-yl]methanamine;

rac-(2R,4R)-4-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]oxolan-2-yl]methanamine;

2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

rac-(3'S,5S)-7-(azetidin-3-yl)-1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-3-amino-1-[*rac*-(3'S,5S)-1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethylspiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

[2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2R)-pyrrolidin-2-yl]methanone;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

rac-3-amino-1-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[3-(trifluoromethyl)pyridin-2-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

3-amino-1-[2-(2-ethoxyphenyl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one;

1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

2-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-5-fluorobenzonitrile;

2-(2-ethoxyphenyl)-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2-chloro-4-fluoro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxypyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

3-[2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)benzonitrile;

(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'R,5R)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[[2R]-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-[2-(difluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxyphenyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2-chlorophenyl)-2-(2-ethoxy-3-pyridinyl)-7-[[2R]-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxy-3-pyridinyl)-1'-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[(3'S,5S)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

3-chloro-4-[2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]-1'-[3-(trifluoromethyl)pyrazin-2-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxyphenyl)-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2,3-dichlorophenyl)-2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[(3'R,5R)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(3-chloro-4-methoxy-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile;

2-(2-ethoxyphenyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[2(S)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

3-[[2-(2-ethoxy-3-pyridinyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]morpholine;

(3'S,5S)-1'-(2-chlorophenyl)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile;

1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxyphenyl)-1'-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-(2-ethoxy-3-pyridinyl)-1'-[5-fluoro-3-(trifluoromethyl)-2-pyridinyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S)-1'-(2,3-dichlorophenyl)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S)-1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-[[[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile];

1'-(2-chlorophenyl)-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-[2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[[[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile];

5-chloro-2-[[[(3'R,5R)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile];

5-chloro-2-[[[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2S)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile];

1'-[4-chloro-2-(difluoromethyl)phenyl]-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2-(2R)-pyrrolidin-2-yl]methyl]-1'-[3-(trifluoromethyl)pyrazin-2-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

2-[[3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-5-fluorobenzonitrile;

(3'S,5S)-1'-(2-chlorophenyl)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

1'-(4-chloro-2-methylsulfonylphenyl)-2-(2-ethoxyphenyl)-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine];

5-chloro-2-[2-[2-(1,1,2,2,2-pentadeuterioethoxy)phenyl]-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[[3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2-(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2-(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2-(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile;

5-chloro-2-[[3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[2-(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[[3'S,5S)-3'-ethyl-2-[2-(1,1,2,2,2-pentadeuterioethoxy)phenyl]-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile;

(3S,5R)-5-[[1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxyphenyl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]pyrrolidin-3-ol;

(3S,5R)-5-[[1'-(2,4-dichlorophenyl)-2-(2-ethoxyphenyl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]pyrrolidin-3-ol;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2-(2S)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzoic acid;

2-[2-(2-ethoxyphenyl)-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-5-(trifluoromethoxy)benzonitrile;

5-(difluoromethoxy)-2-[2-(2-ethoxyphenyl)-7-[[2-(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile;

or a salt thereof.

The salt thereof can be a pharmaceutically acceptable salt. The salt thereof can be a formate salt, a trifluoroacetic acid (TFA) salt, a mesylate salt or a hydrochloride (HCl) salt. The salt thereof can be a formate salt or a trifluoroacetic acid (TFA) salt.

- 5 The compound can be a salt selected from the group consisting of:

1'-[4-chloro-3-(trifluoromethyl)pyridin-2-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one formate salt;

(S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one formate salt;

(R)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one formate salt;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

7-(azetidin-3-yl)-1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

2-(2-ethoxypyridin-3-yl)-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

7-(2-aminoethyl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3R)-pyrrolidin-3-yl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3S)-pyrrolidin-3-yl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

[2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-(1-methylazetidin-3-yl)methanone TFA salt;

azetidin-3-yl-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methanone TFA salt;

1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(3R)-pyrrolidin-3-yl]methyl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one TFA salt;

1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(3S)-pyrrolidin-3-yl]methyl]spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

7-(azetidin-3-yl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one formate salt;

2-[3-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)phenoxy]acetonitrile formate salt;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

2-[7-(3-aminopropanoyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-6-methoxybenzonitrile formate salt;

3-amino-1-[1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

3-amino-1-[1'-(2,4-dichloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

rac-(3'S,5S)-7-(azetidin-3-yl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one TFA salt;

3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

rac-1-azabicyclo[2.2.2]octan-3-yl-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methanone formate salt;

rac-(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one formate salt;

3-amino-1-[1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

rel-[(2R,4S)-4-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]oxolan-2-yl]methanamine formate salt;

rel-[(2R,4R)-4-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]oxolan-2-yl]methanamine formate salt;

2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

rac-3-amino-1-[*rac*-(3'S,5S)-1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethylspiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

[2-(2-ethoxypyridin-3-yl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-[(2R)-pyrrolidin-2-yl]methanone formate salt;

rac-3-amino-1-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

3-amino-1-[2-(2-ethoxyphenyl)-1'-[4-fluoro-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one formate salt;

1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

5-chloro-2-[2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile formate salt;

2-(2-ethoxyphenyl)-7-[(2R)-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] HCl salt;

2-(2-ethoxyphenyl)-7-[(2R)-pyrrolidin-2-yl]methyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] mesylate salt;

(3'S,5S)-1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

(3'S,5S)-1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;

- (3'S,5S)-1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 1'-(2-chloro-4-fluoro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 2-(2-ethoxypyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 1'-[2-(difluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- (3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 2-(2-ethoxyphenyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 3-chloro-4-[2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile formate salt;
- 1'-(3-chloro-4-methoxy-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 5-chloro-2-[2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile formate salt;
- 3-[[2-(2-ethoxy-3-pyridinyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]morpholine formate salt;
- 1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 2-(2-ethoxy-3-pyridinyl)-1'-[5-fluoro-3-(trifluoromethyl)-2-pyridinyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 1'-[4-chloro-2-(difluoromethyl)phenyl]-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] TFA salt;
- 1'-(4-chloro-2-methylsulfonylphenyl)-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine] formate salt;
- 5-chloro-2-[2-[2-(1,1,2,2,2-pentadeuterioethoxy)phenyl]-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile formate salt;

5-chloro-2-[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile TFA salt;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile TFA salt;

5-chloro-2-[2-(2-ethoxyphenyl)-7-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile TFA salt;

5-chloro-2-[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile TFA salt;

5-chloro-2-[(3'S,5S)-3'-ethyl-2-[2-(1,1,2,2,2-pentadeuterioethoxy)phenyl]-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile formate salt;

(3S,5R)-5-[[1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxyphenyl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]pyrrolidin-3-ol formate salt;

(3S,5R)-5-[[1'-(2,4-dichlorophenyl)-2-(2-ethoxyphenyl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methyl]pyrrolidin-3-ol TFA salt.

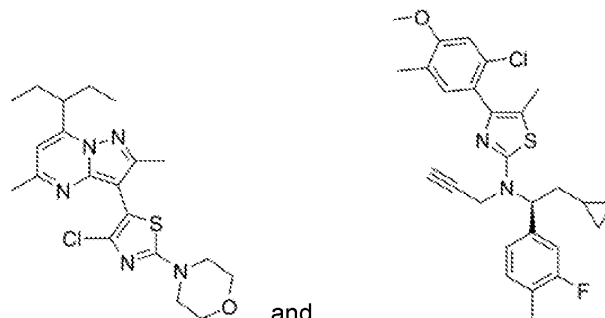
Further embodiments of the invention include the use of a compound of Formula (1) or a salt thereof or a pharmaceutical composition comprising a compound of Formula (1) in medicine. Also included is the use of a compound of Formula (1) or a salt thereof or a pharmaceutical composition comprising a compound of Formula (1) as a melanocortin subtype-2 receptor (MC2R) modulator. Compounds of the present invention may be used as MC2R receptor modulators. Compounds of the present invention may be used as MC2R receptor inhibitors or antagonists. Compounds of the present invention may be used in the treatment of a disease or disorder characterised by activation of MC2R. Compounds of the present invention may be used in the treatment of a disease or disorder associated with MC2R or in the treatment of a disease or disorder that would benefit from the modulation of MC2R activity.

Compounds of the present invention may be used in the treatment of congenital adrenal hyperplasia (CAH), Cushing's disease, ectopic ACTH syndrome, polycystic ovary syndrome (PCOS) depressive illness, septic shock and disorders or symptoms related thereto.

In some embodiments, compounds and compositions detailed herein are used as modulators of MC2R. Provided herein is a method of treating a disease in an individual comprising administering an effective amount of a compound of Formula (1) or any embodiment, variation or aspect thereof.

- 5 Compounds as MC2R modulators as disclosed herein can be useful as a prophylactic or therapeutic agent for MC2R associated diseases. In some embodiments, a compound or salt thereof described herein or a composition described herein may be used in a method of treating Cushing's disease in an individual.
- 10 Also provided are combinations comprising a compound of the present invention and a Corticotropin-releasing factor receptor-1 (CRF₁) antagonist. In the combinations the CRF₁ antagonist may be selected from the group consisting of tildacerfont, crinecerfont, NBI-27914, CP-316,311, NBI-462000, DMP696, pexacerfont, NBI-35965, ONO-2333Ms, antalarmin, NBI-34041, DMP904, NBI-30775, SSR125543, NBI-77860, GSK876008,
- 15 CRA5626/JNJ19567470/R317573, NBI-76169, verucerfont, and CP-154,526.

In the combinations the CRF₁ antagonist may be selected from:



- 20 Also provided are combinations comprising a compound of the present invention and an ACTH antibody. In the combinations the ACTH antibody may be ALD1613 (Feldhaus et al. *Endocrinology*, Jan 2017, 158(1): 1-8).

- The combinations may be used in the treatment of congenital adrenal hyperplasia (CAH),
- 25 Cushing's disease, ectopic ACTH syndrome, polycystic ovary syndrome (PCOS) depressive illness, septic shock and disorders or symptoms related thereto.

Also provided herein are uses of a compound described herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein, in the manufacture of a medicament. In some embodiments, the manufacture of a medicament is for the treatment of a disorder or disease described herein. In some embodiments, the manufacture of a medicament is for the prevention and/or treatment of a disorder or disease mediated by MC2R.

In some embodiments, a compound or salt thereof described herein or a composition described herein may be used in a method as either a stand-alone therapy, or as a conjunctive therapy with other agents that are either palliative (e.g., agents that relieve the symptoms of the disorder to be treated), and/or agents that target the etiology of the disorder. Compounds or compositions of the present invention may be used or administered in combination with a second therapeutic agent.

In some embodiments, (a) a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein and (b) an agent are sequentially administered, concurrently administered or simultaneously administered. In certain embodiments, (a) a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein and (b) an agent are administered with a time separation of about 15 minutes or less, such as about any of 10, 5, or 1 minutes or less. In certain embodiments, (a) a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein and (b) an agent are administered with a time separation of about 15 minutes or more, such as about any of 20, 30, 40, 50, 60, or more minutes. Either (a) a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein and (b) an agent may be administered first. In certain embodiments, (a) a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein and (b) an agent are administered simultaneously.

DEFINITIONS

In this application, the following definitions apply, unless indicated otherwise.

30

The term "MC2R modulator" as used herein refers to any compound which binds to and modulates the function of MC2 receptors. The term "modulator" should be interpreted to include modulation by modalities including, but not limited to antagonists.

The term "treatment", in relation to the uses of any of the compounds described herein, including those of Formula (1) is used to describe any form of intervention where a compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term "treatment" covers both
5 preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

The term "effective therapeutic amount" (for example in relation to methods of treatment of a disease or condition) refers to an amount of the compound which is effective to produce a desired
10 therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

Chemical terms are all used in their conventional sense (e.g. as defined in the IUPAC Gold Book),
15 unless indicated otherwise.

The term "alkyl" as used herein, means straight or branched chain, saturated alkyl groups.

The terms "cycloalkyl" as used herein, means a saturated carbocyclic group containing the
20 indicated number of carbon atoms.

The term "carbocyclic ring" as used herein, means a saturated or unsaturated carbocyclic group containing the indicated number of carbon atoms.

25 The term "heterocyclic ring" as used herein, refers to a saturated or unsaturated ring containing the indicated number of total ring member atoms in which one or more of the ring members is a heteroatom selected from O, S and N, and oxidised forms thereof and the remaining atoms are C.

30 The term "bicyclic" as used herein, means a saturated or unsaturated ring system comprising two joined rings and containing the indicated number of atoms in total. All possible modes of ring junction are included (including spirocyclic, fused and bridged).

The term "heterobicyclic" as used herein, means a saturated or unsaturated heterocyclic ring system comprising two joined rings and containing the indicated number of atoms in total. All possible modes of ring junction are included (including spirocyclic, fused and bridged).

- 5 The number of carbon atoms that are possible in the referenced groups herein may be indicated by subscript " C_{n1-n2} ". Thus, for example, the term " C_{1-3} alkyl" represents an alkyl group having 1, 2 or 3 carbon atoms and includes methyl, ethyl, n-propyl and iso-propyl.

- 10 The term "optionally substituted" as applied to any group means that the said group may if desired be substituted with one or more substituents, which may be the same or different. Thus, for example, the term "optionally substituted with 1-6 fluorine atoms" as applied to a group means that the said group may if desired be substituted with 1, 2, 3, 4, 5 or 6 fluorine atoms.

- 15 To the extent that any of the compounds described have chiral centres, the present invention extends to all optical isomers of such compounds, whether in the form of racemates or resolved enantiomers. The invention described herein relates to all crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said compounds are included herein. In the case of pharmaceutical uses, the salt should
20 be seen as being a pharmaceutically acceptable salt.

- Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with one or more equivalents of an appropriate
25 acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

- 30 Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and p-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, 5 capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and ($\pm$)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic), malonic, ($\pm$)-DL-mandelic, 10 metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g. (+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

15 Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and DMSO. Solvates can be prepared by 20 recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

25 The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West 30 Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

The term "pharmaceutical composition" in the context of this invention means a composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents,

adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

- 10 The compounds of the invention may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^1H , ^2H (D), and ^3H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and ^{16}O and ^{18}O . In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group or an alkoxy group such as a methoxy group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a trideuteromethoxy group). The isotopes may be radioactive or non-radioactive.

- Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

30

The magnitude of an effective dose of a compound will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. The selection of appropriate dosages is within the ability of one of ordinary skill in this art, without undue burden. In general, the daily dose range may be from about 10 μg to about

30 mg per kg body weight of a human and non-human animal, preferably from about 50 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 50 µg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 µg to about 1 mg per kg of body weight of a human and non-human animal.

PHARMACEUTICAL FORMULATIONS

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

Accordingly, in some embodiments of the invention, there is provided a pharmaceutical composition comprising at least one compound of Formula (1) as defined above together with at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

The term “pharmaceutically acceptable” as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the Formula (1) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences,

Mack Publishing Company, Easton, PA, USA. The pharmaceutical compositions can be in any form suitable for oral, parenteral, intravenous, intramuscular, intrathecal, subcutaneous, topical, intranasal, intrabronchial, sublingual, buccal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

5

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

- 10 The composition may be a tablet composition or a capsule composition. Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl
- 15 methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate
- 20 mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

25

- The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or combination of such excipients. Preferably, the compositions comprise from approximately 20% (w/w) to
- 30 approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically acceptable excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention

may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

The composition may be a parenteral composition. Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack.

The compounds of the Formula (1) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

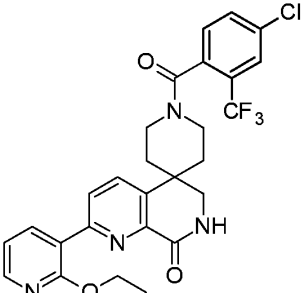
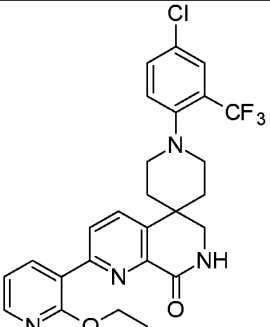
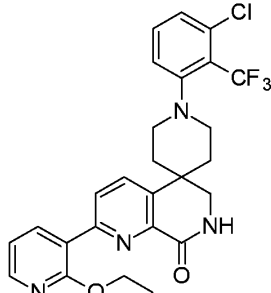
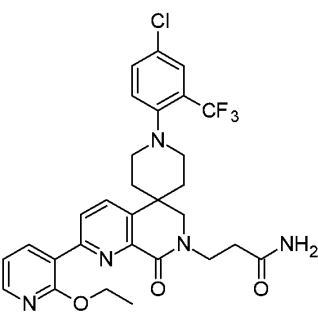
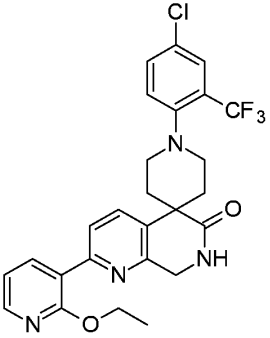
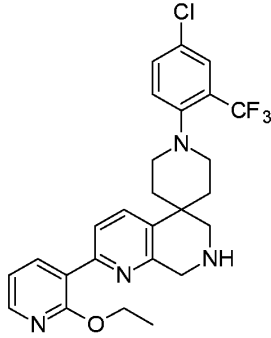
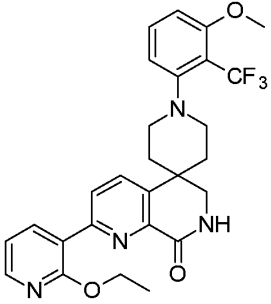
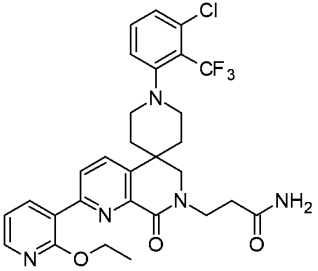
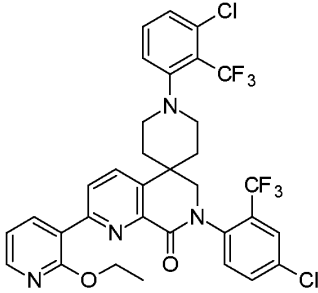
The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

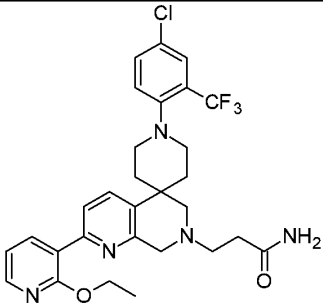
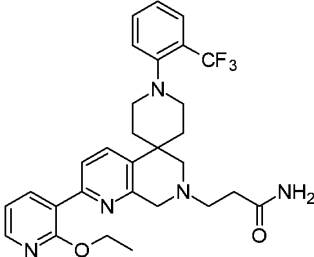
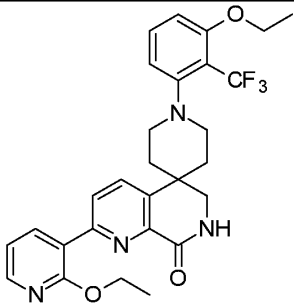
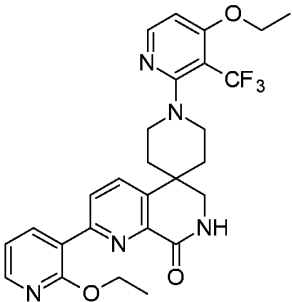
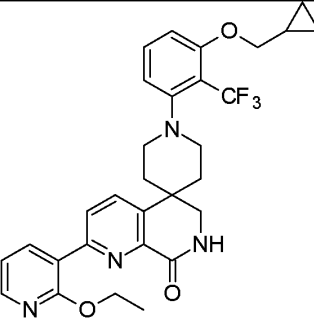
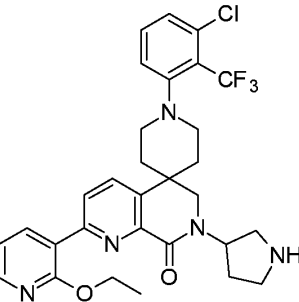
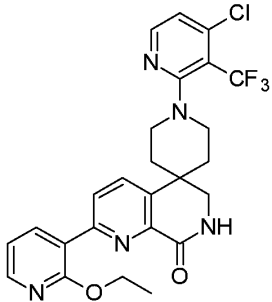
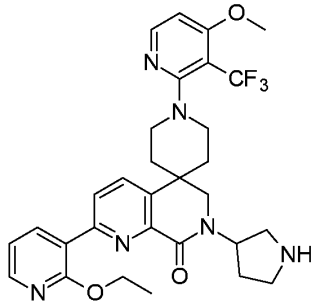
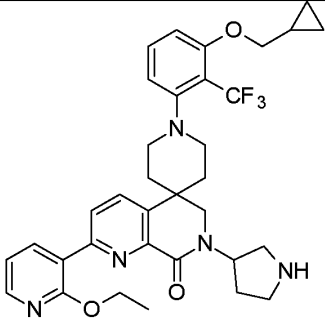
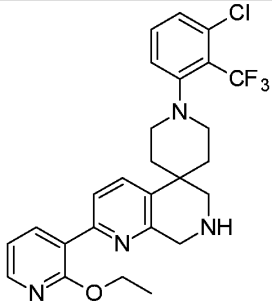
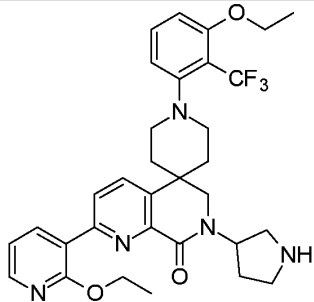
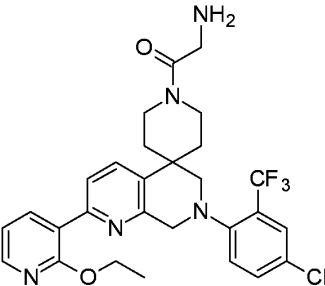
EXAMPLES

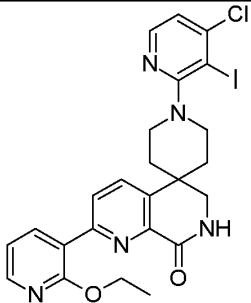
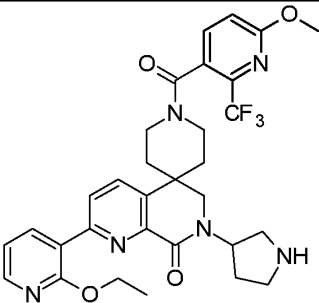
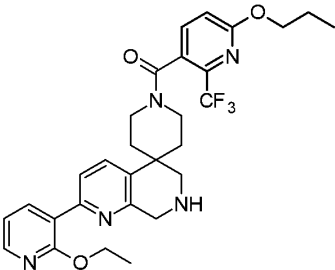
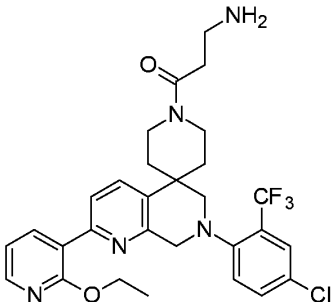
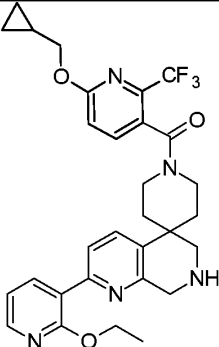
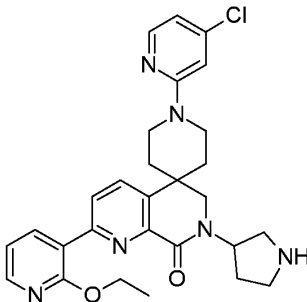
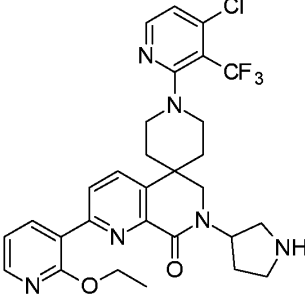
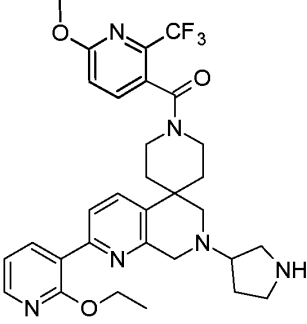
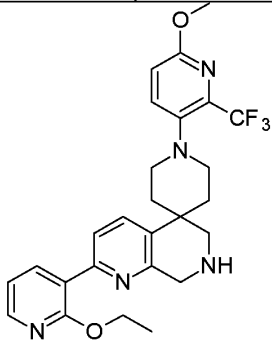
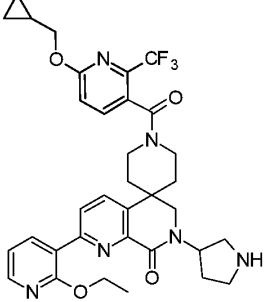
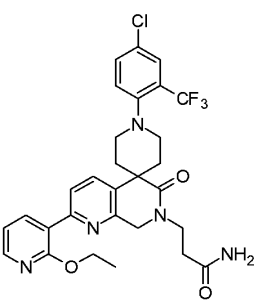
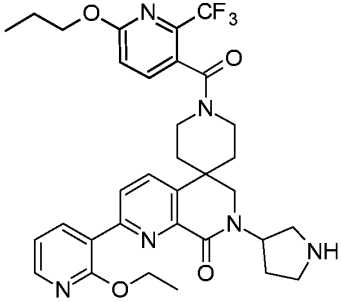
The invention will now be illustrated, but not limited, by reference to the following examples shown in Table 1a.

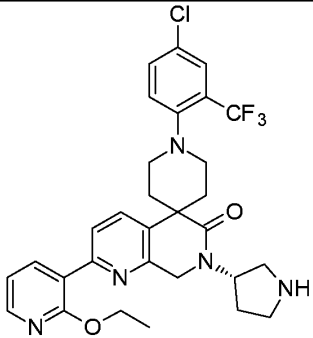
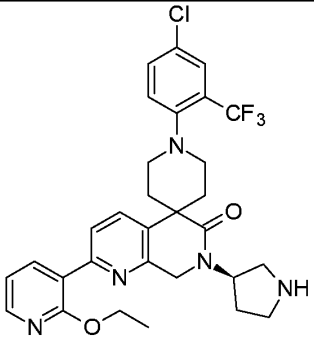
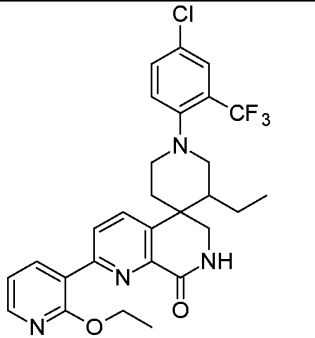
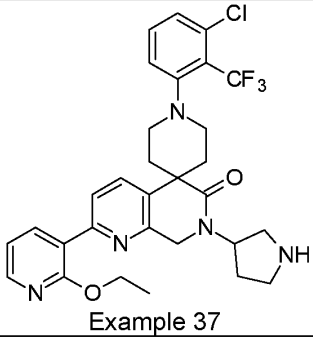
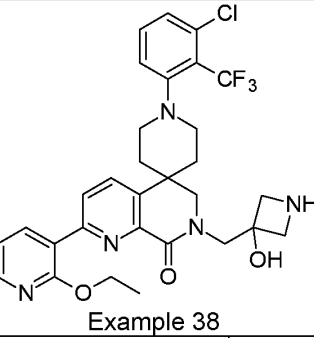
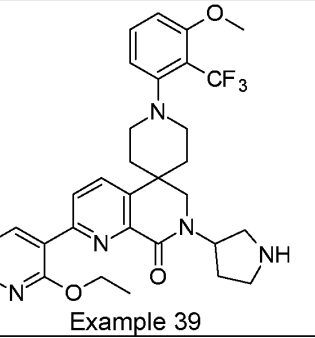
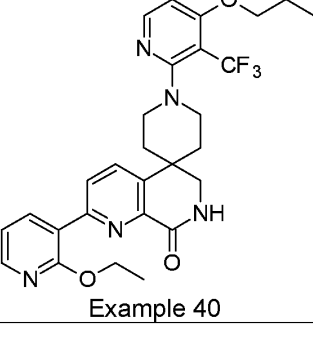
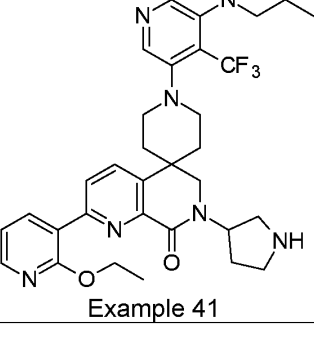
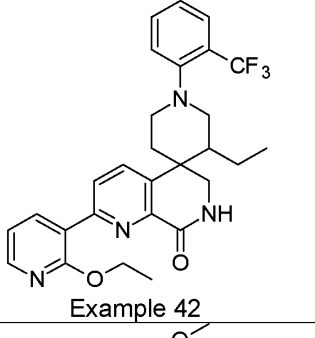
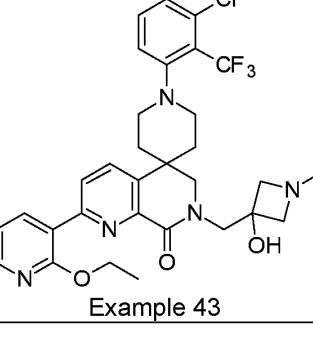
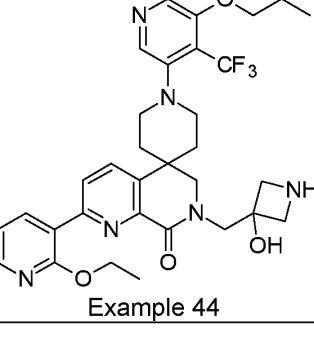
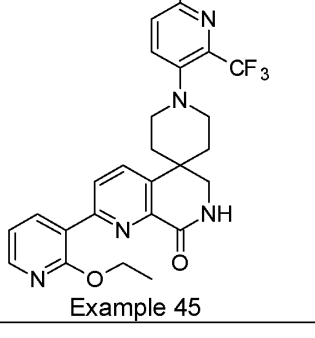
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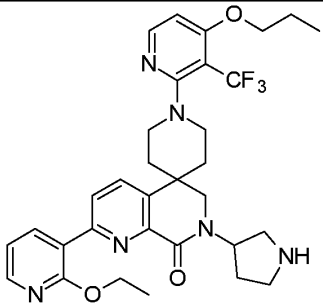
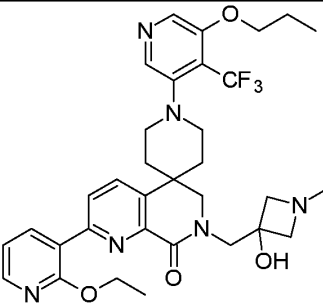
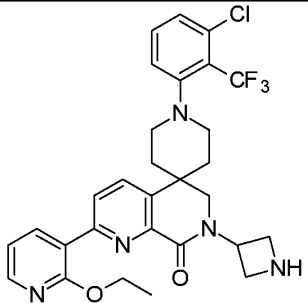
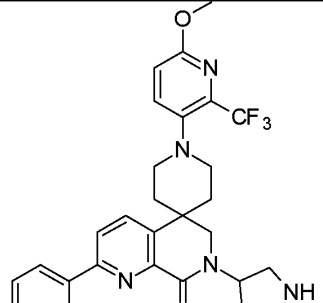
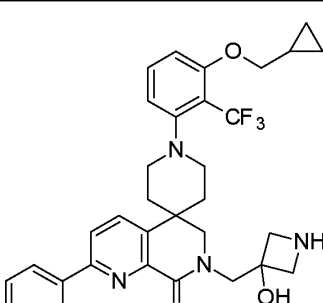
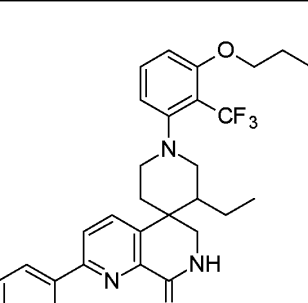
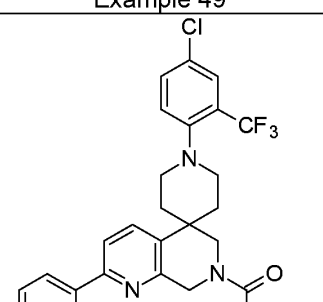
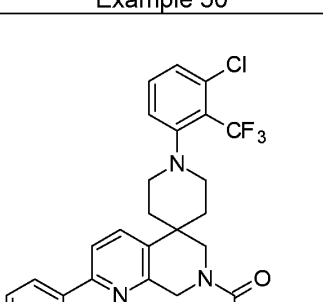
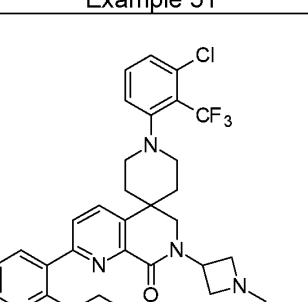
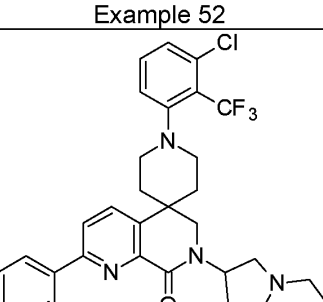
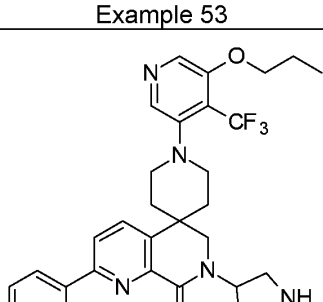
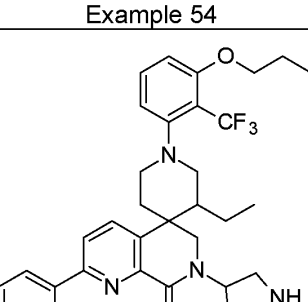
Table 1a – Examples

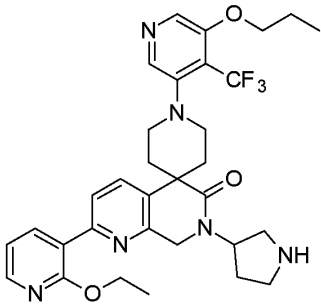
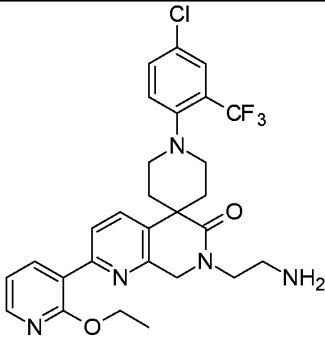
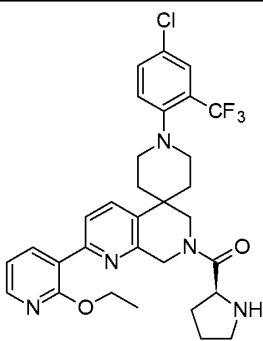
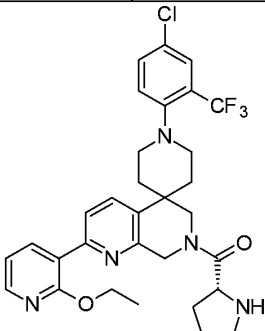
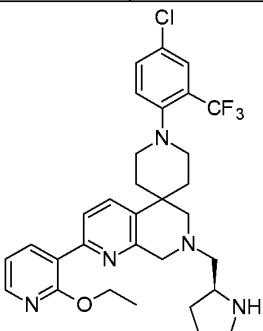
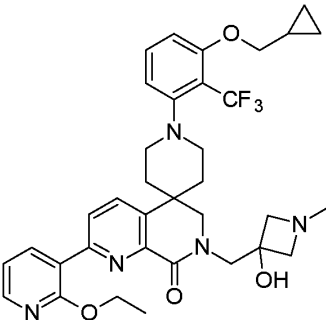
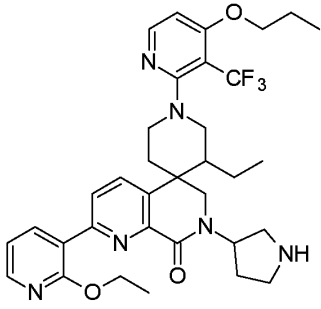
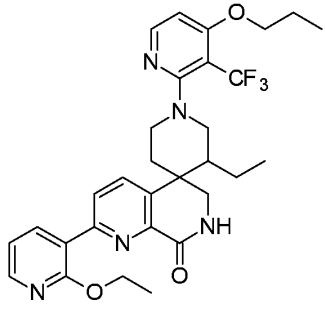
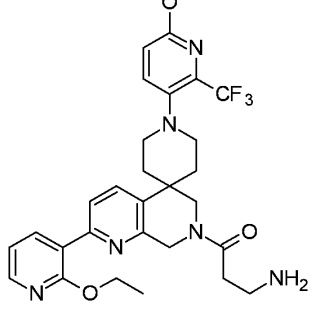
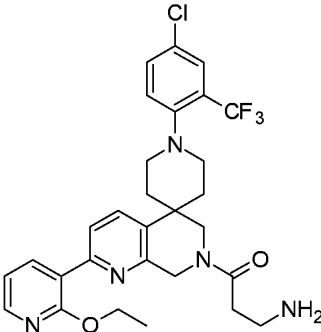
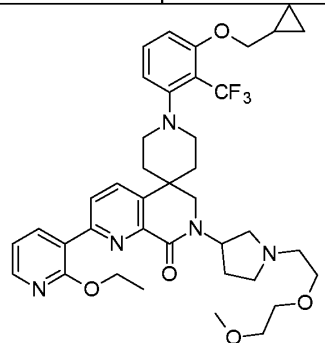
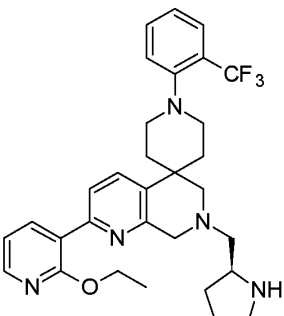
 Example 1	 Example 2	 Example 3
 Example 4	 Example 5	 Example 6
 Example 7	 Example 8	 Example 9

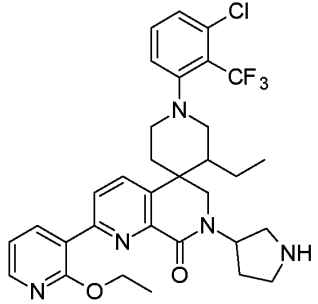
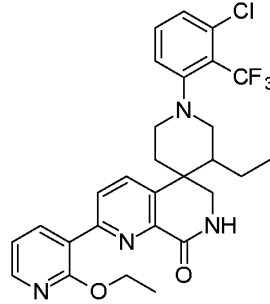
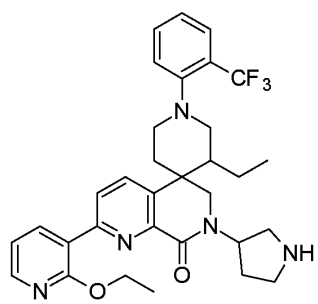
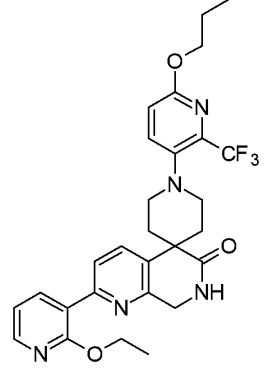
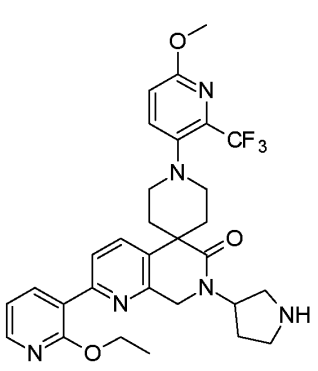
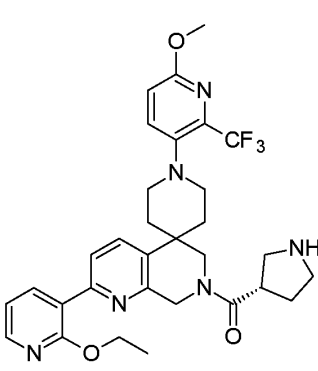
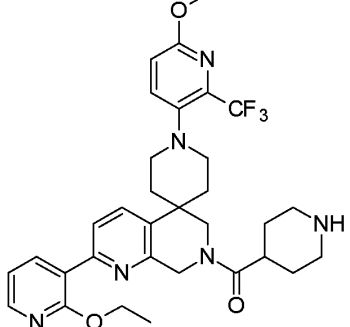
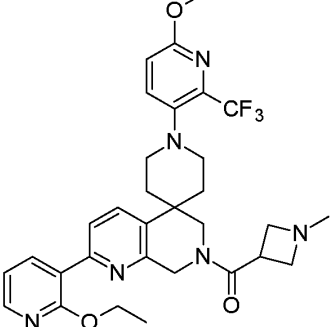
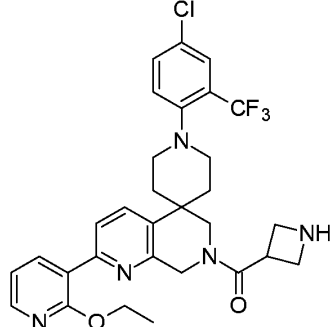
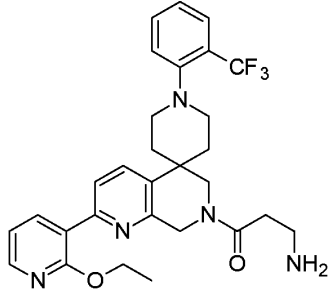
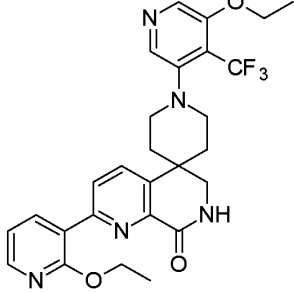
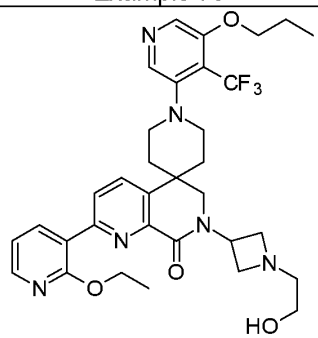
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 Example 13	 Example 14	 Example 15
 Example 16	 Example 17	 Example 18
 Example 19	 Example 20	 Example 21

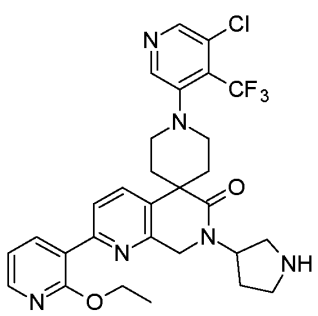
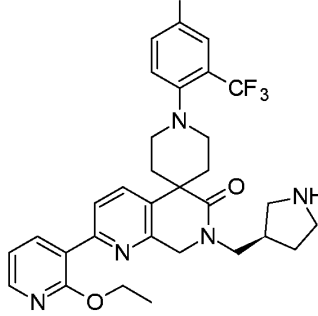
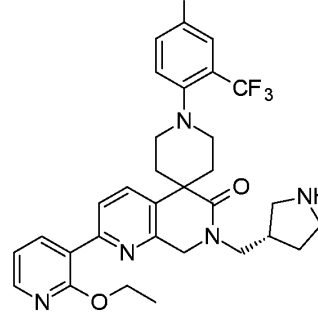
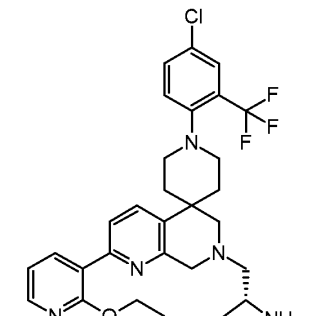
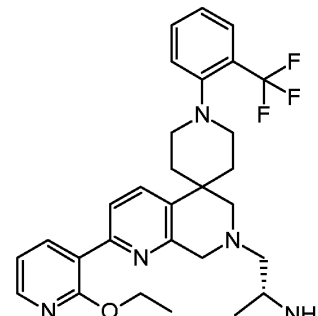
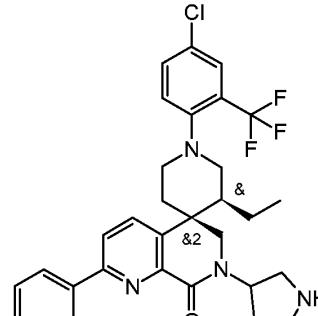
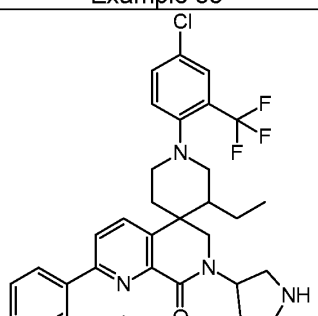
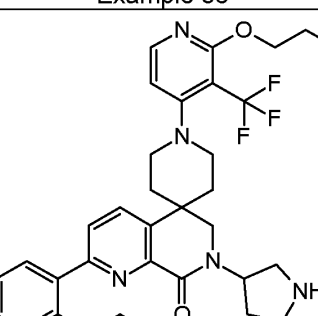
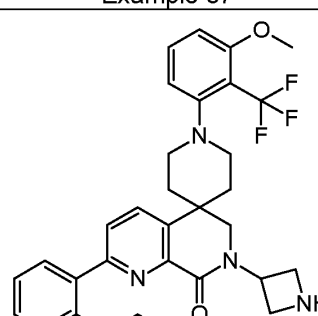
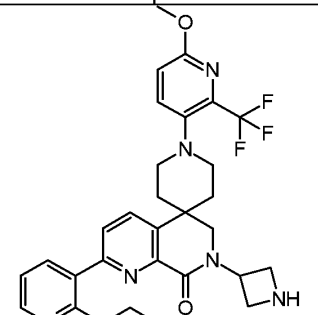
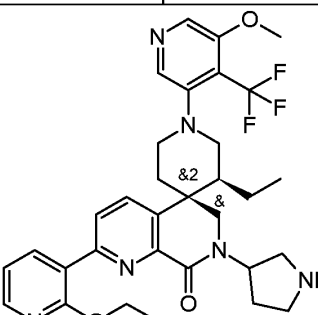
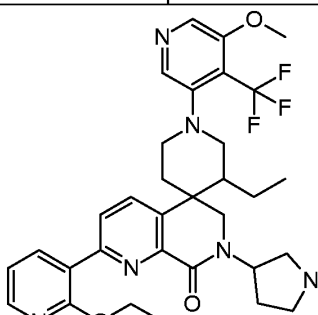
 Example 22	 Example 23	 Example 24
 Example 25	 Example 26	 Example 27
 Example 28	 Example 29	 Example 30
 Example 31	 Example 32	 Example 33

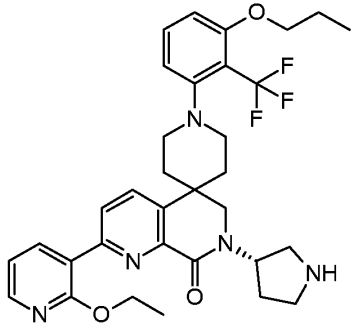
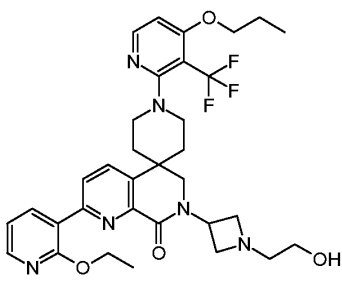
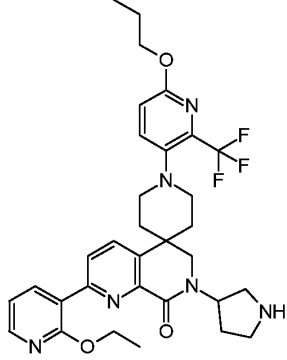
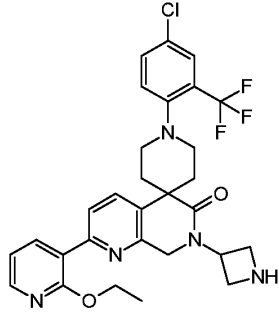
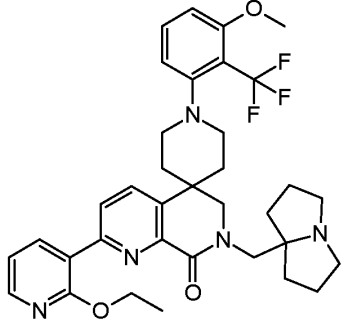
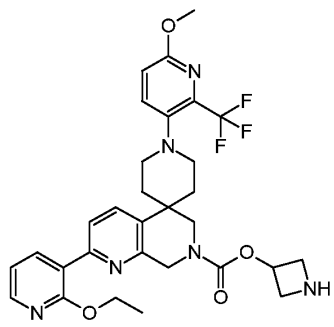
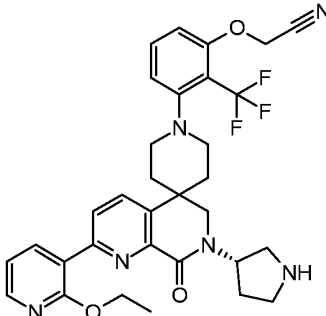
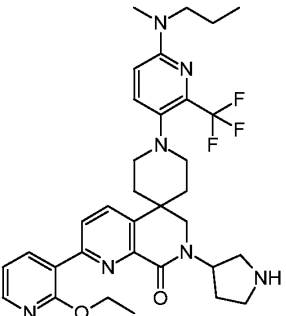
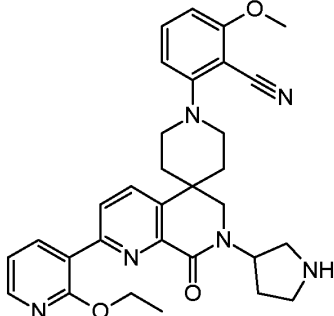
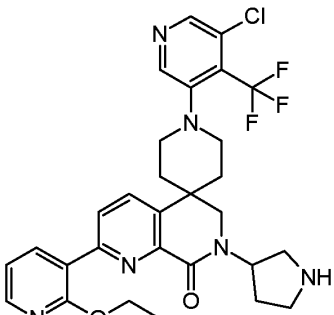
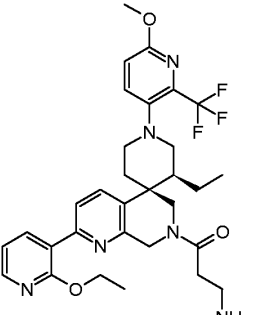
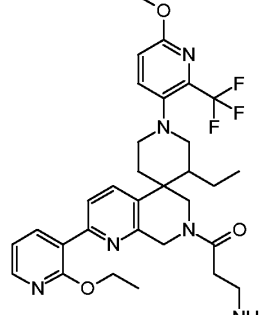
 Example 34	 Example 35	 Example 36
 Example 37	 Example 38	 Example 39
 Example 40	 Example 41	 Example 42
 Example 43	 Example 44	 Example 45

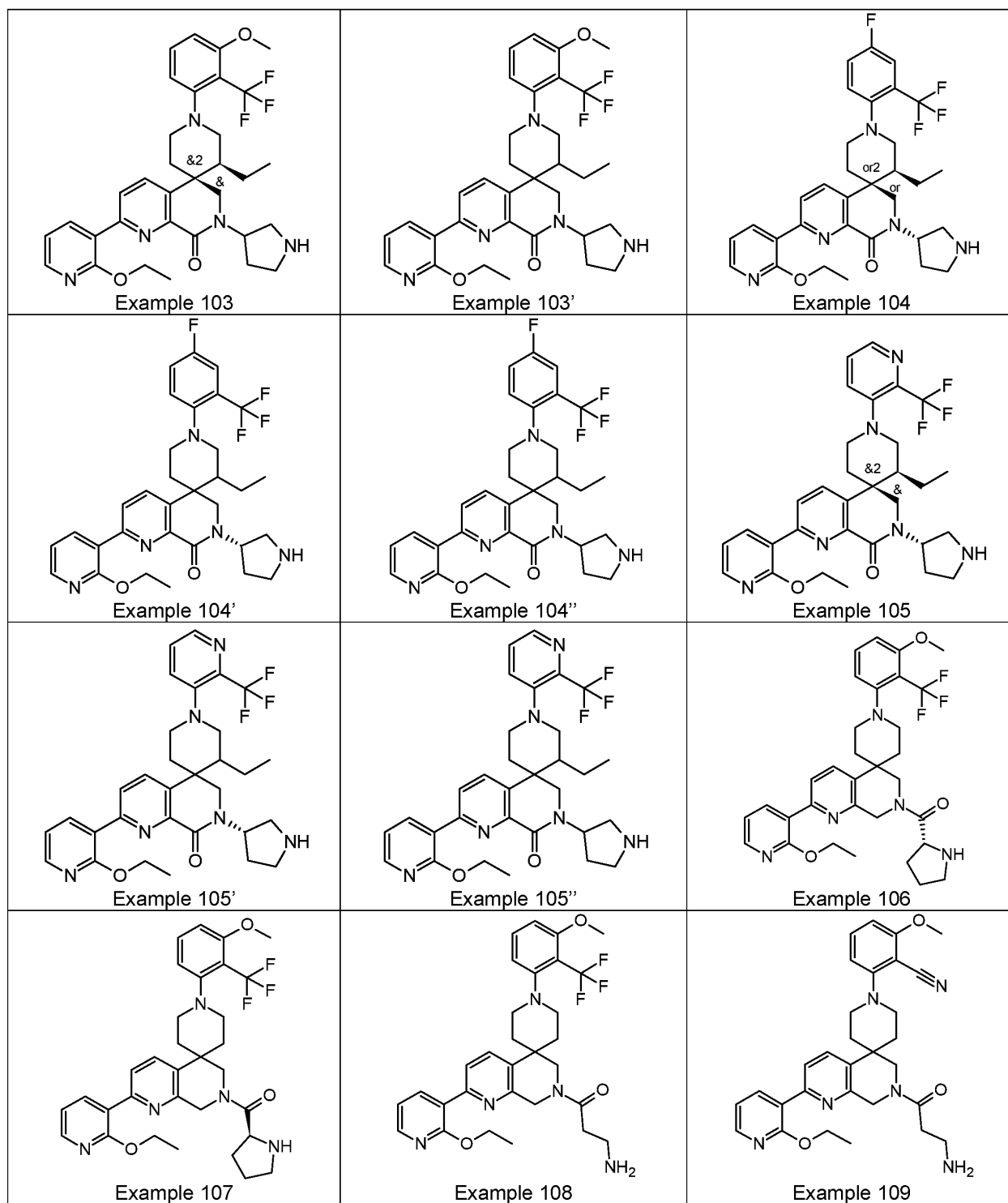
 Example 46	 Example 47	 Example 48
 Example 49	 Example 50	 Example 51
 Example 52	 Example 53	 Example 54
 Example 55	 Example 56	 Example 57

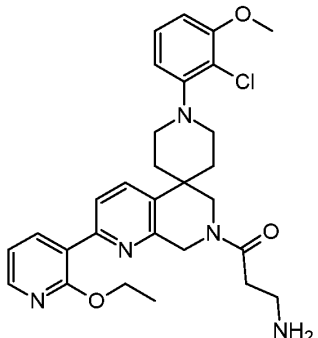
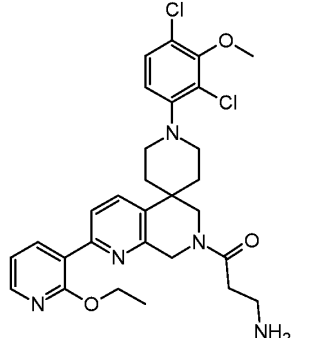
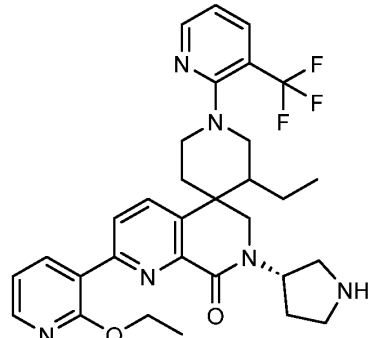
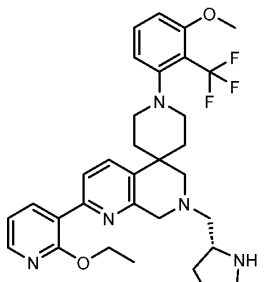
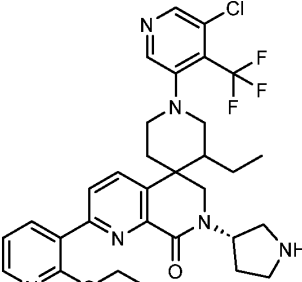
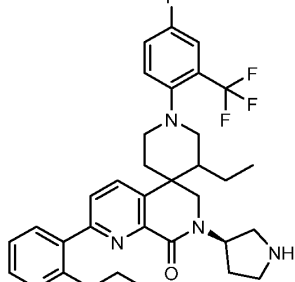
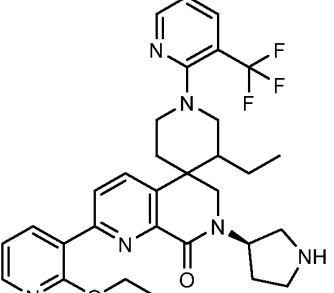
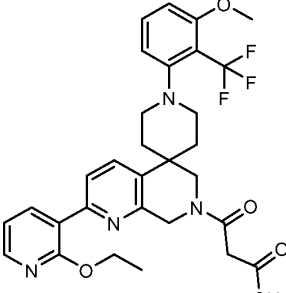
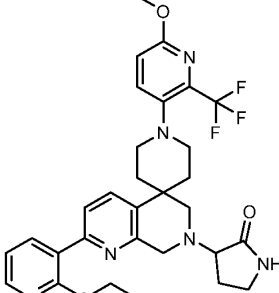
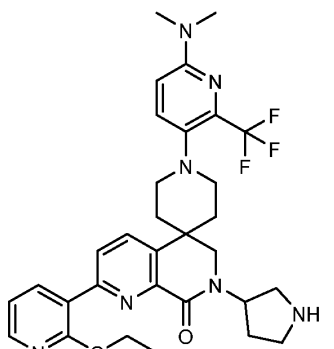
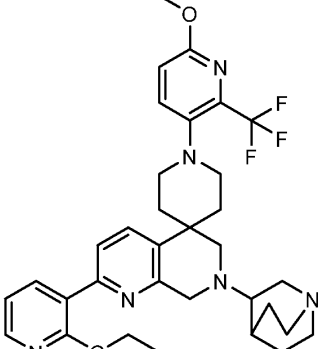
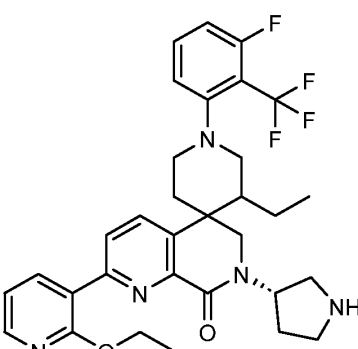
 Example 58	 Example 59	 Example 60
 Example 61	 Example 62	 Example 63
 Example 64	 Example 65	 Example 66
 Example 67	 Example 68	 Example 69

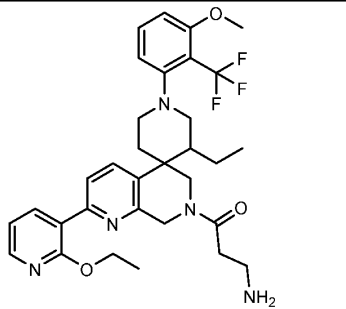
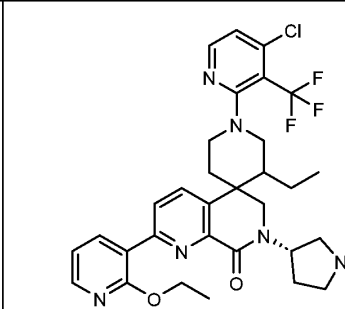
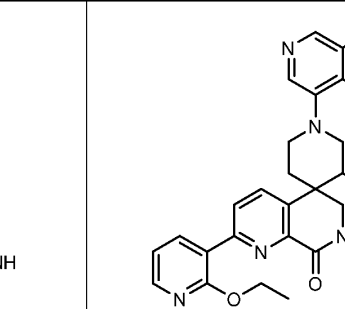
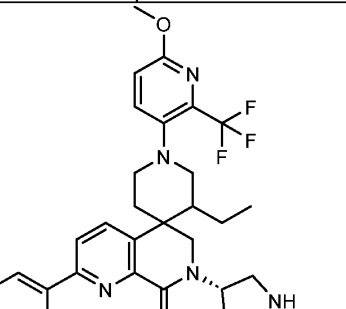
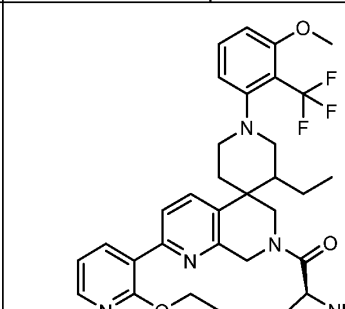
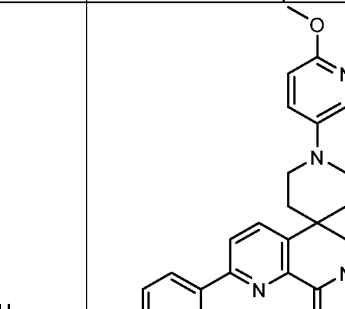
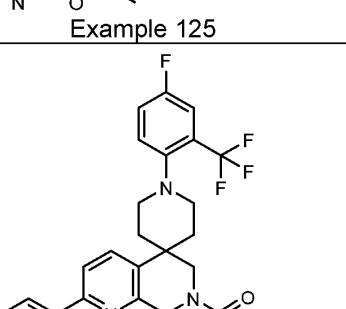
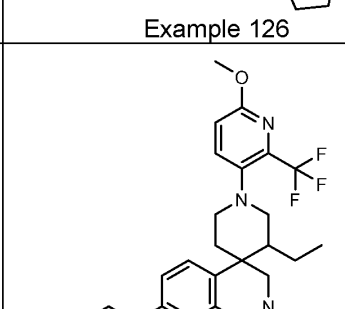
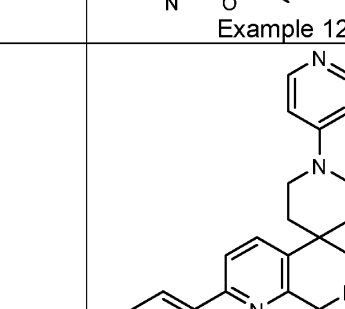
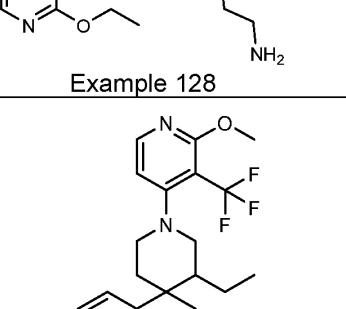
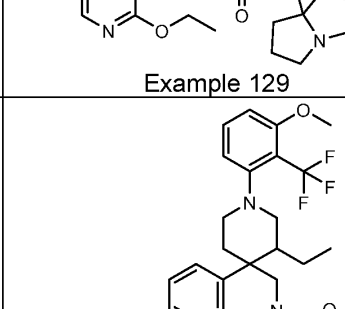
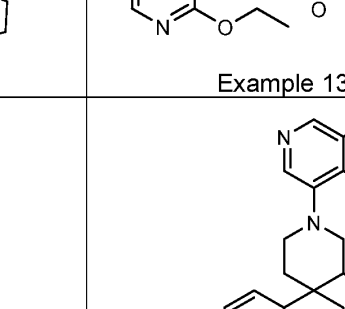
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 Example 73	 Example 74	 Example 75
 Example 76	 Example 77	 Example 78
 Example 79	 Example 80	 Example 81

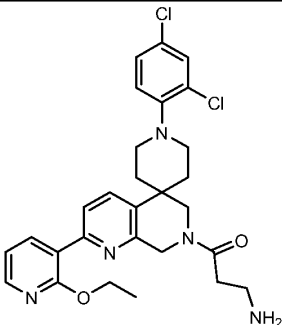
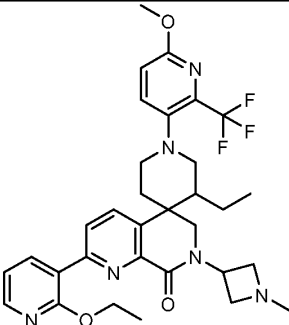
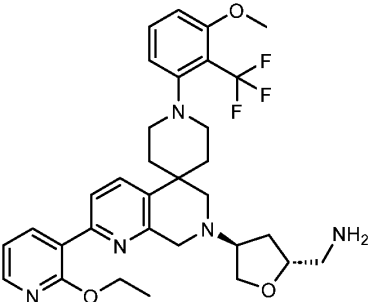
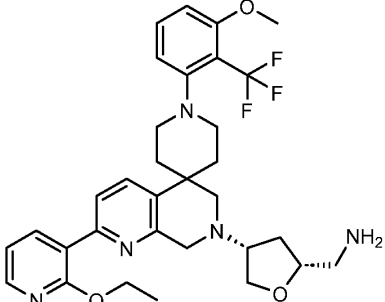
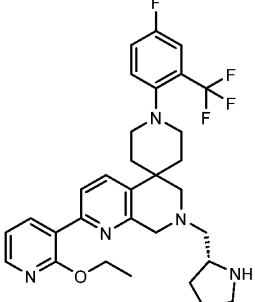
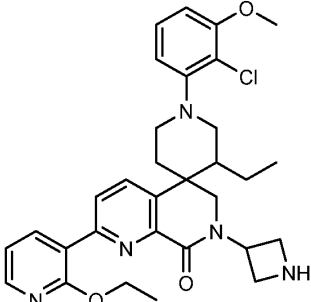
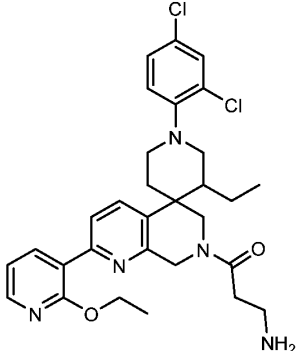
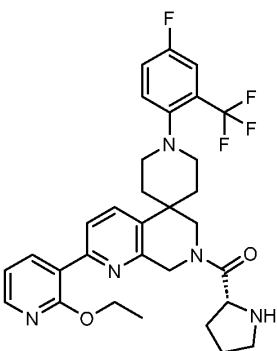
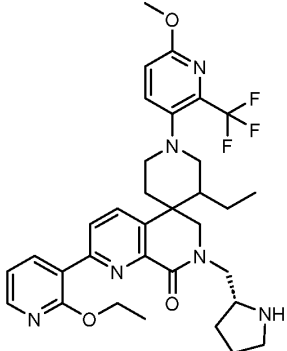
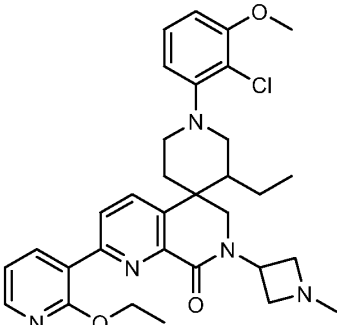
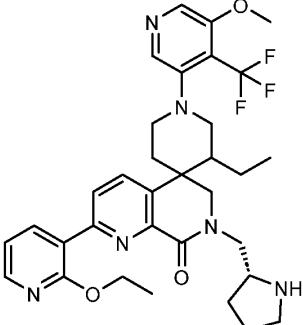
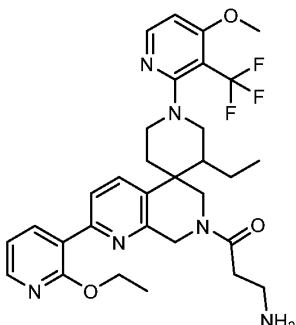
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 Example 85	 Example 86	 Example 87
 Example 87'	 Example 88	 Example 89
 Example 90	 Example 91	 Example 91'

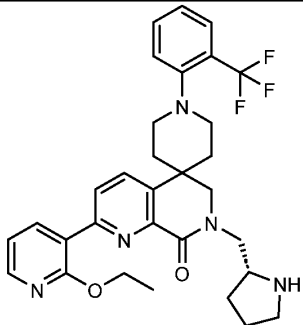
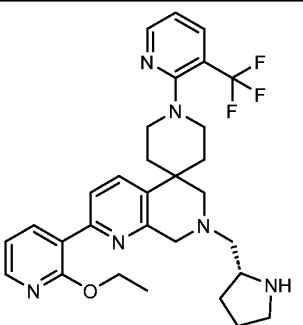
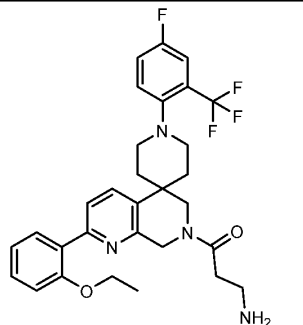
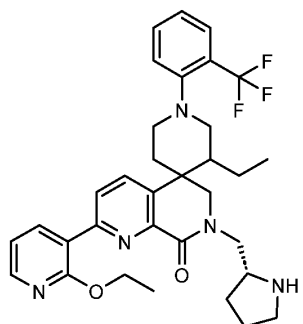
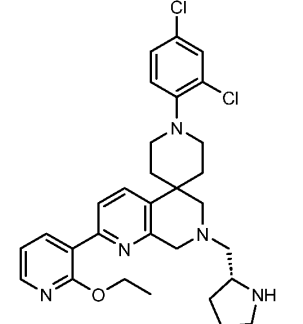
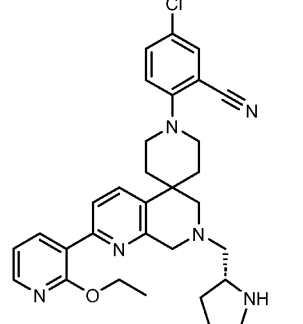
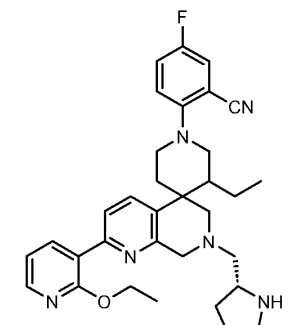
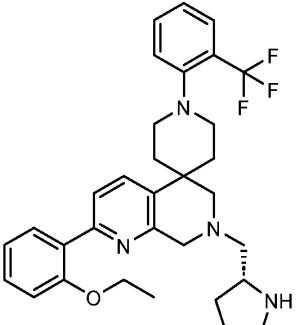
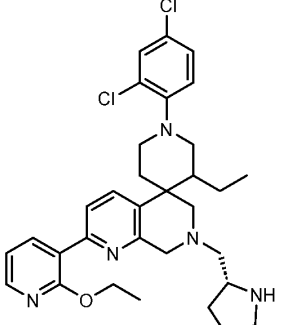
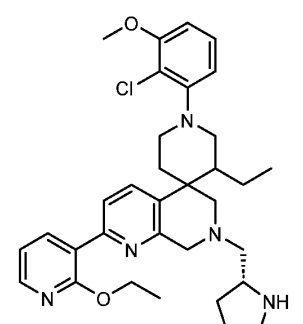
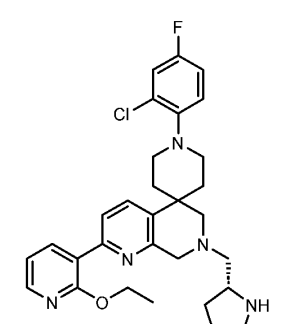
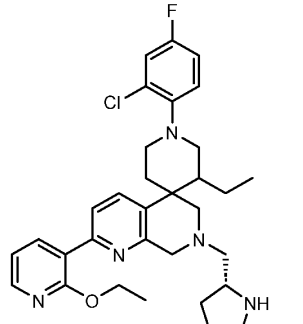
 Example 92	 Example 93	 Example 94
 Example 95	 Example 96	 Example 97
 Example 98	 Example 99	 Example 100
 Example 101	 Example 102	 Example 102'

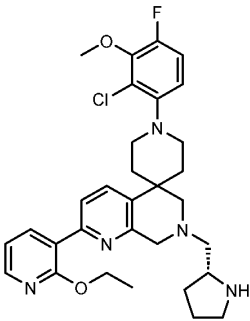
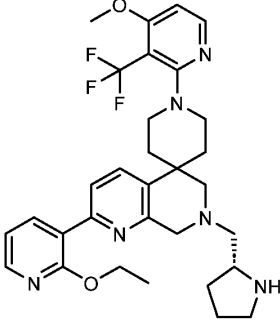
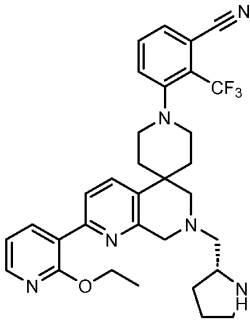
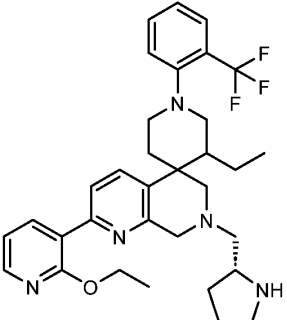
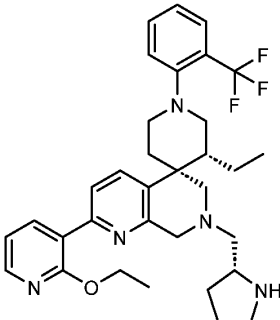
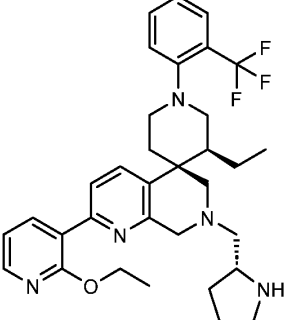
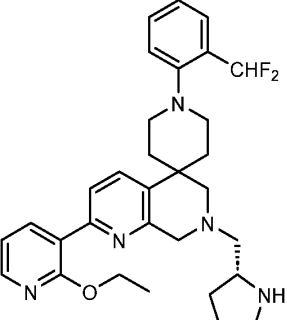
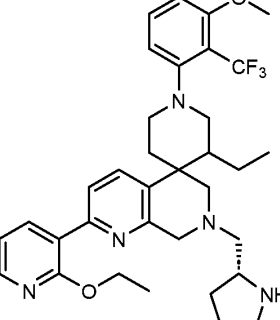
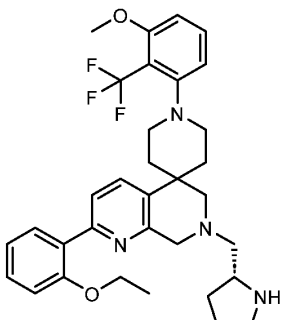
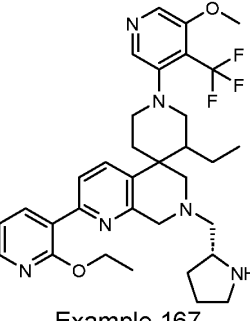
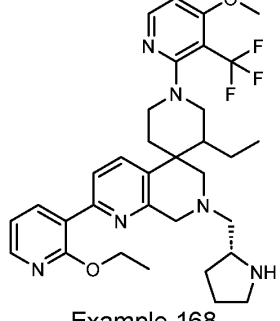
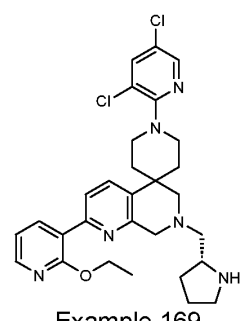


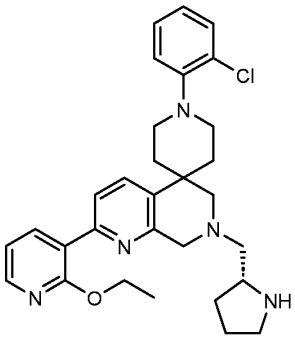
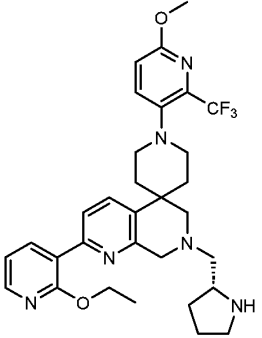
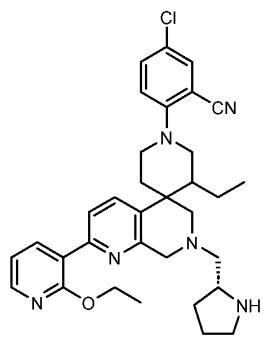
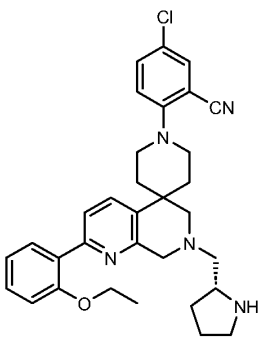
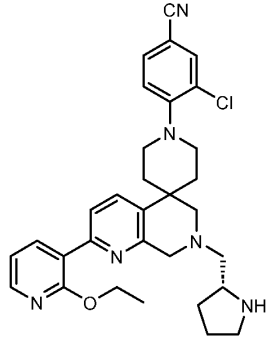
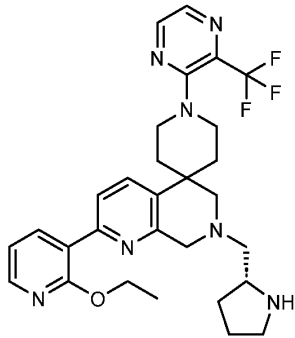
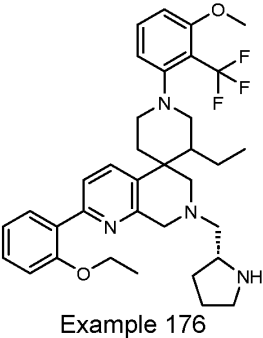
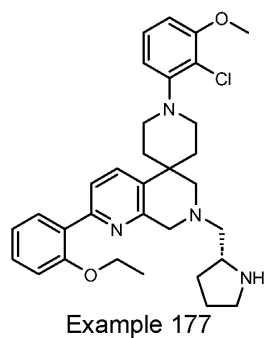
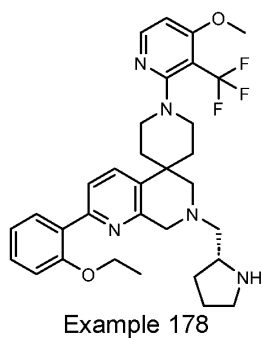
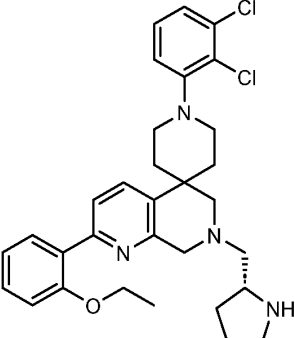
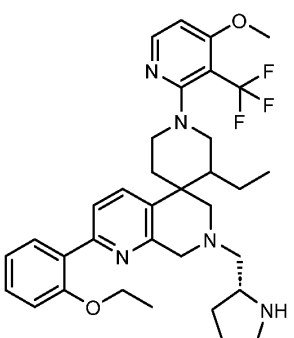
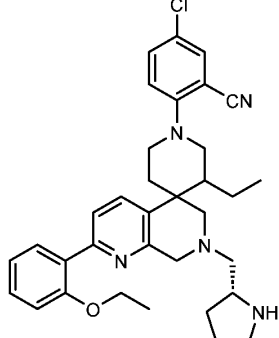
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 Example 113	 Example 114	 Example 115
 Example 116	 Example 117	 Example 118
 Example 119	 Example 120	 Example 121

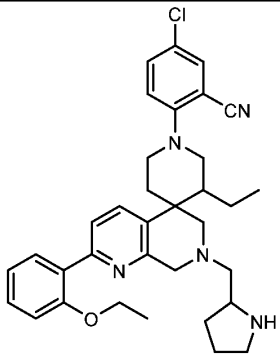
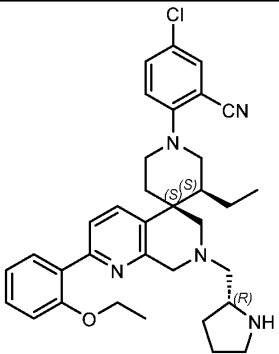
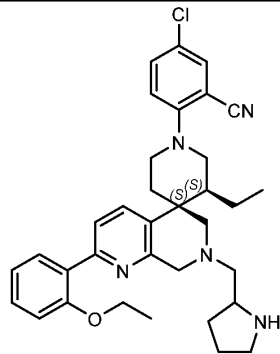
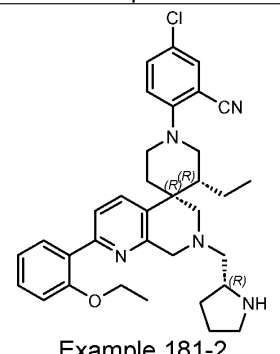
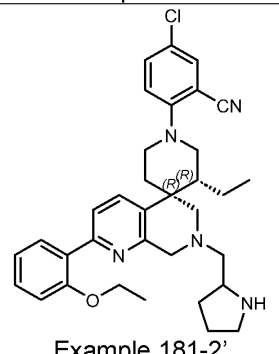
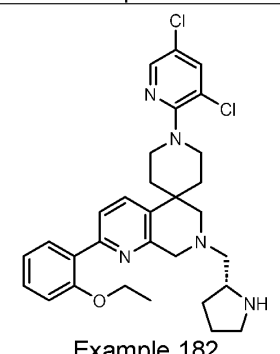
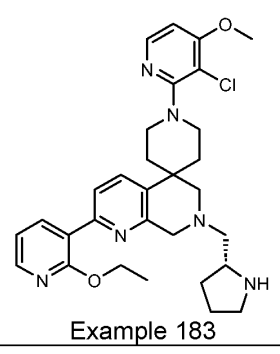
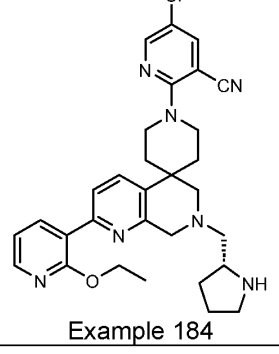
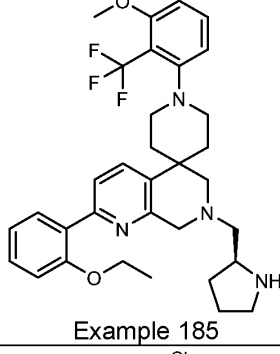
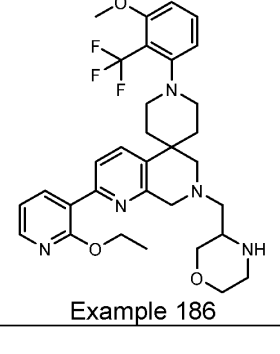
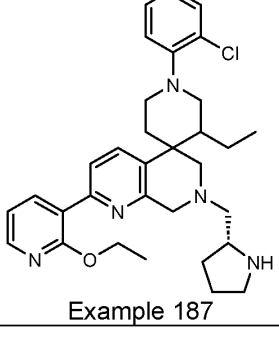
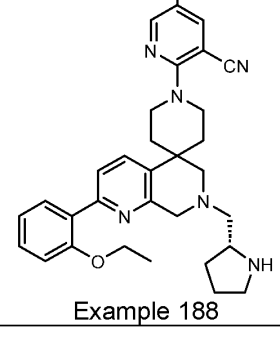
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 Example 125	 Example 126	 Example 127
 Example 128	 Example 129	 Example 130
 Example 131	 Example 132	 Example 133

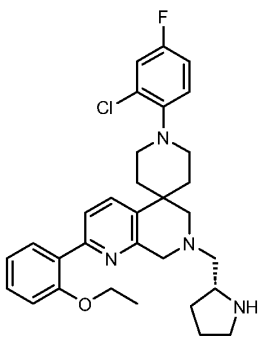
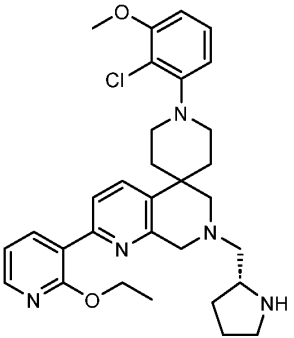
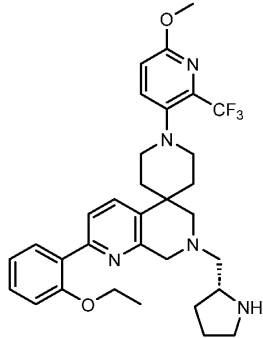
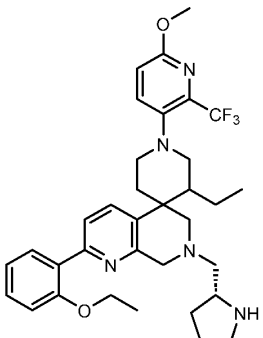
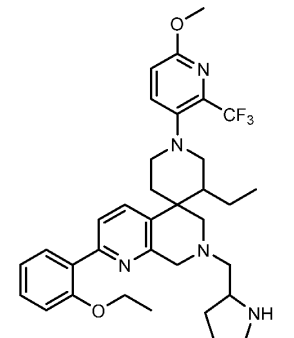
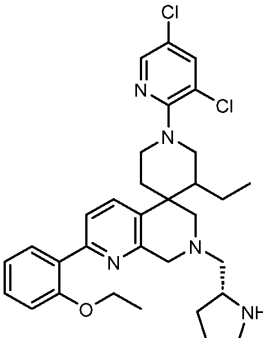
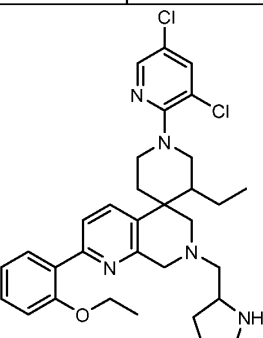
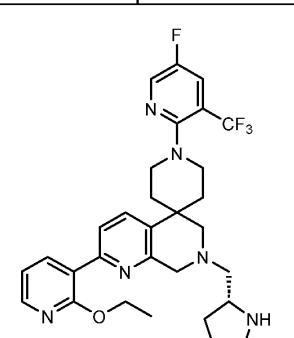
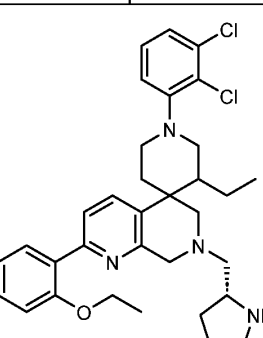
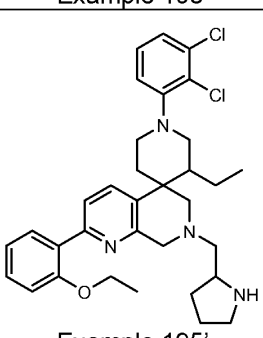
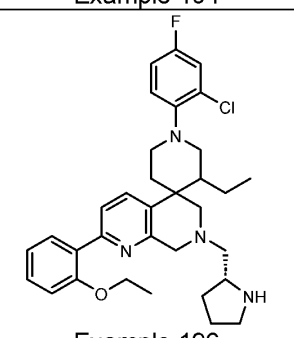
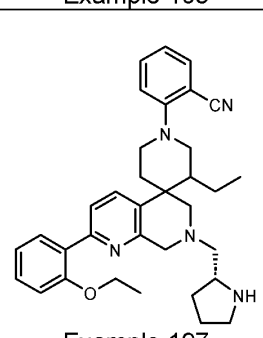
 Example 134	 Example 135	 Example 136
 Example 137	 Example 138	 Example 139
 Example 140	 Example 141	 Example 142
 Example 143	 Example 144	 Example 145

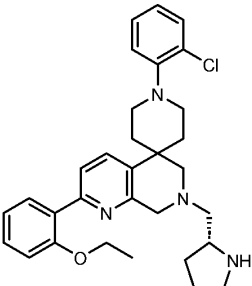
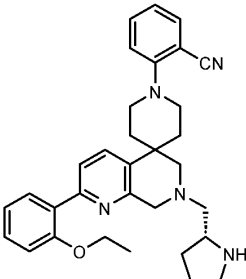
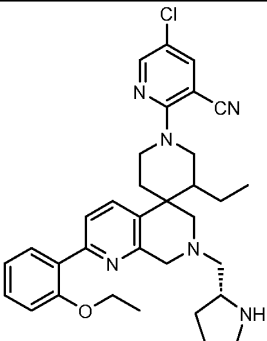
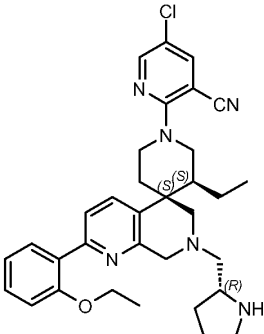
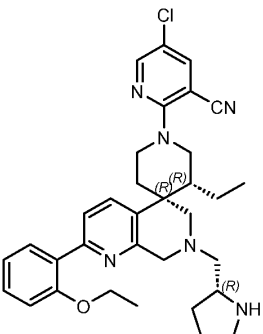
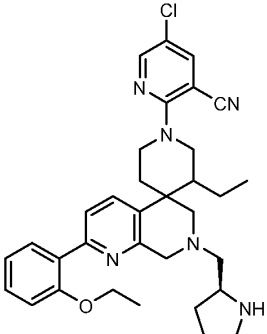
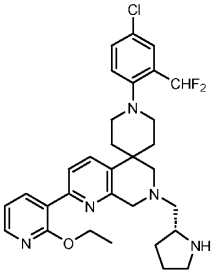
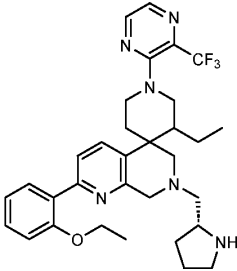
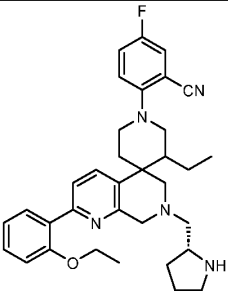
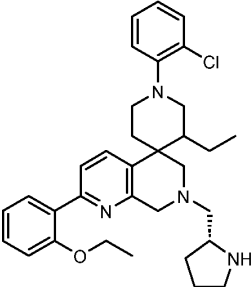
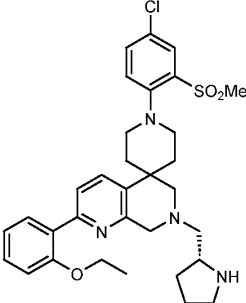
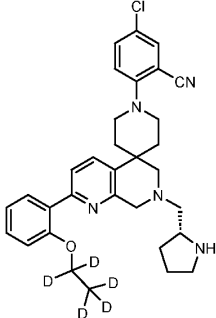
 Example 146	 Example 147	 Example 148
 Example 149	 Example 150	 Example 151
 Example 152	 Example 153	 Example 154
 Example 155	 Example 156	 Example 157

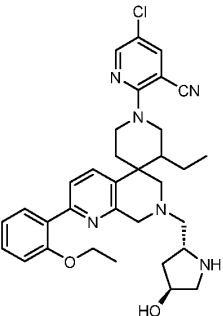
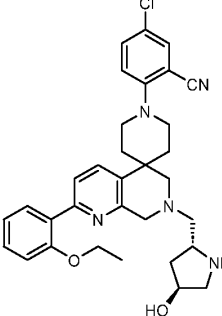
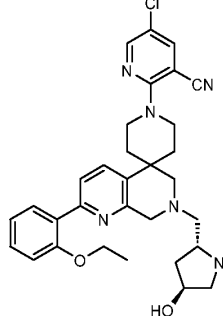
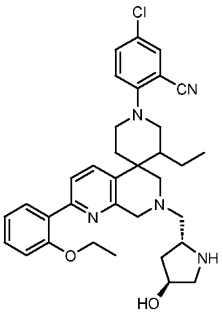
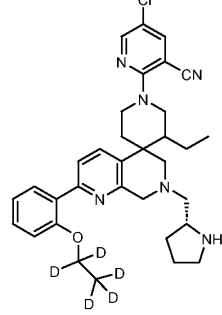
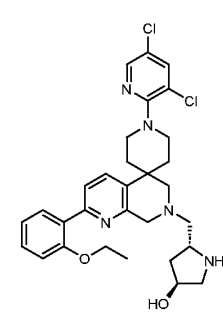
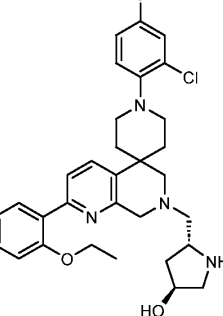
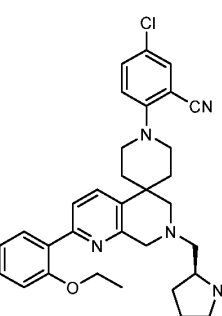
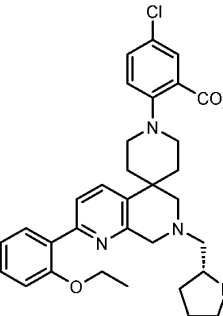
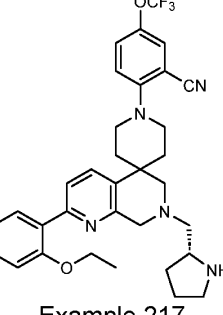
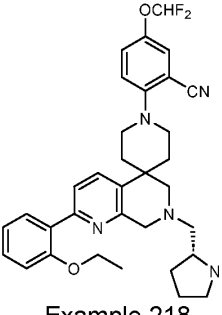
 Example 158	 Example 159	 Example 160
 Example 161	 Example 162	 Example 163
 Example 164	 Example 165	 Example 166
 Example 167	 Example 168	 Example 169

 Example 170	 Example 171	 Example 172
 Example 173	 Example 174	 Example 175
 Example 176	 Example 177	 Example 178
 Example 179	 Example 180	 Example 181

 Example 181	 Example 181-1	 Example 181-1'
 Example 181-2	 Example 181-2'	 Example 182
 Example 183	 Example 184	 Example 185
 Example 186	 Example 187	 Example 188

 Example 189	 Example 190	 Example 191
 Example 192	 Example 192'	 Example 193
 Example 193'	 Example 194	 Example 195
 Example 195'	 Example 196	 Example 197

 Example 198	 Example 199	 Example 200
 Example 200-1	 Example 200-2	 Example 201
 Example 202	 Example 203	 Example 204
 Example 205	 Example 206	 Example 207

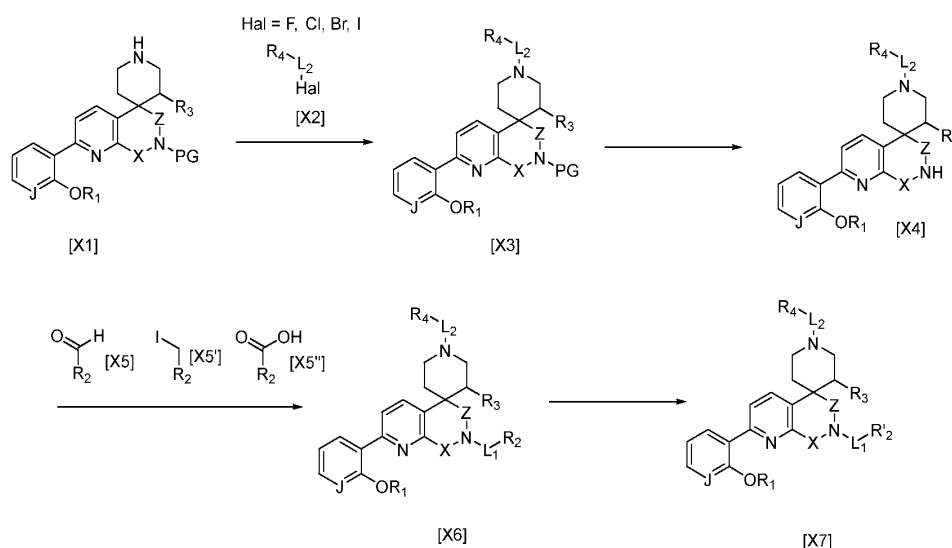
 Example 208	 Example 209	 Example 210
 Example 211	 Example 212	 Example 213
 Example 214	 Example 215	 Example 216
 Example 217	 Example 218	

PREPARATION OF THE COMPOUNDS OF THE INVENTION

Compounds of Formula (1) and derivatives or synthetic intermediates thereof may be prepared in accordance with synthetic methods known to the skilled person. In some embodiments, the invention provides a process for the preparation of a compound as defined in Formula (1) above.

Several methods for the chemical synthesis of spiro[piperidine-4,5'-[1,7]naphthyridine] compounds of the present application are described herein. These and/or other well-known methods may be modified and/or adapted in various ways to facilitate the synthesis of additional compounds within the scope of the present application and claims. Compounds of Formula (1) and derivatives or synthetic intermediates thereof may be prepared in accordance with General Scheme 1.

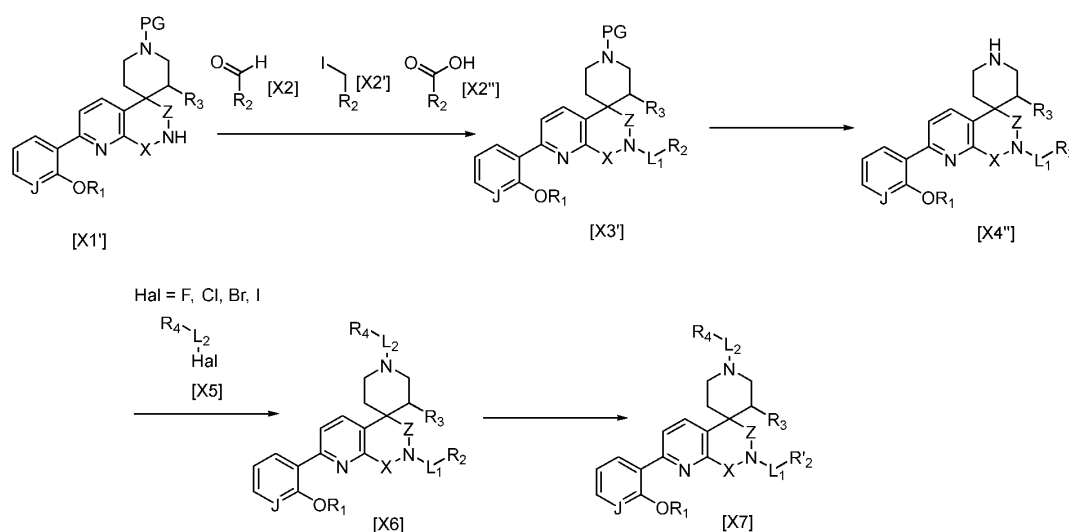
General Scheme 1:



In one approach (General Scheme 1), compounds of formula [X3] may be prepared by the reaction of a compound of formula [X1] with a hetero-aromatic or substituted phenyl-compound of formula [X2] in a transition metal catalysed cross-coupling reaction such as a Buchwald–Hartwig amination with a catalyst such as $Pd(dba)_2$, $Pd(OAc)_2$ or $Pd(o-Tolyl)_3$ with a phosphine ligand such as BINAP, DPPF, XantPhos or JohnPhos, with a base such as $NaOtBu$, K_2CO_3 or Cs_2CO_3 in a suitable solvent such as DMF, THF, dioxane or toluene. The reaction is suitably conducted at elevated temperature. Alternatively, compounds of formula [X3] may also be prepared by the reaction of a compound of formula [X1] with a hetero-aromatic-compound of

formula [X2] in a nucleophilic aromatic substitution (S_NAr) related reaction with a base such as DIPEA, K₂CO₃, Cs₂CO₃ or KOH in a polar solvent such as DMF or THF. The reaction is suitably conducted at elevated temperature. Alternatively, compounds of formula [X3] can be prepared via reaction with a carboxylic acid of formula [X2] in an amide coupling reaction with a coupling agent such as HATU, a solvent such as DCM or DMF and a base such as DIPEA. The reaction is usually conducted at RT. In all cases, after reaction work up, typically by liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC or re-crystallisation. Compounds of formula [X4] may be prepared by standard methods for the removal of the protecting group (PG) with compounds of formula [X3]. In the case of benzyloxycarbonyl (Cbz), a method such as hydrogenation under an atmosphere of hydrogen in the presence of palladium on activated carbon in a polar solvent such as ethanol or methanol. Alternatively, a method using strong base such as KOH in a solvent such as ethanol, suitably conducted at elevated temperature. After reaction work up, typically filtration and/or liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC or re-crystallisation. Compounds of formula [X6] may be prepared by the reaction of a compound of formula [X4] with an aldehyde or ketone derivative of general formula [X5] by a reductive amination reaction with reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride in a polar solvent such as DCM, DCE or methanol. After reaction work up, typically by liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC, chiral preparative SFC or re-crystallisation. Alternatively, they can be prepared with alkyl halides [X5'] or alkyl methanesulfonates via substitution reaction using a strong base such as NaH and a solvent such as DMSO. Alternatively, they can be prepared with carboxylic acids of formula [X5''] via an amide coupling reaction using a coupling agent such as HATU, a solvent such as DCM or DMF and a base such as DIPEA. The reaction is usually conducted at RT. In some examples the compounds of formula [X6] contain an amino group that is protected by nitrogen protecting group such as a tert-butyloxycarbonyl protecting group. In these examples, compounds of formula [X7] are prepared through standard removal of a tert-butyloxycarbonyl protecting group by reaction of a compound of formula [X6] with an acid such as trifluoroacetic acid or phosphoric acid in DCM, HCl in dioxane or formic acid. After reaction work up, typically by liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC, chiral preparative SFC or re-crystallisation.

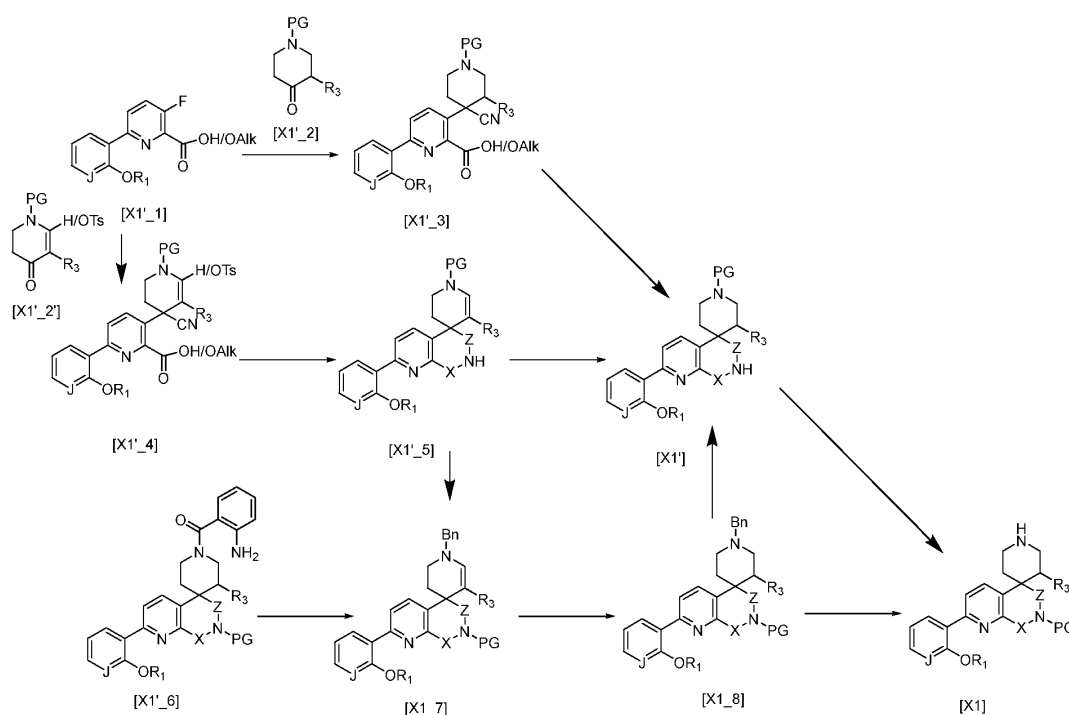
General Scheme 2:



In another approach (General Scheme 2), compounds of formula [X3'] may be prepared by the reaction of compound of formula [X1'] with an aldehyde of formula [X2] by reductive amination reaction with a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride in a polar solvent such as DCM, DCE or methanol. After reaction work up, typically by liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC, chiral preparative SFC or re-crystallisation. Alternatively, they can be prepared with alkyl halides [X2'] or alkyl methanesulfonates via substitution reaction using a strong base such as NaH and a solvent such as DMSO. Alternatively, they can be prepared with carboxylic acids of formula [X2''] via an amide coupling reaction using a coupling agent such as HATU, a solvent such as DCM or DMF and a base such as DIPEA. The reaction is usually conducted at RT. Compounds of formula [X4'] may be prepared by standard methods for the removal of the protecting group (PG) with compounds of formula [X3']. Compounds of formula [X6] may be prepared with compounds of formula [X4'] by the reaction of a hetero-aromatic or substituted phenyl-compound of formula [X5] in a transition metal catalysed cross-coupling reaction such as a Buchwald–Hartwig amination with a catalyst such as $\text{Pd}(\text{dba})_2$, $\text{Pd}(\text{OAc})_2$ or $\text{Pd}(\text{o-Tolyl})_3$ with a phosphine ligand such as BINAP, DPPF, XantPhos or JohnPhos, with a base such as NaOtBu , K_2CO_3 or Cs_2CO_3 in a suitable solvent such as DMF, THF, dioxane or toluene. The reaction is suitably conducted at elevated temperature. Alternatively, compounds of formula [X6] may also be prepared by the reaction of compounds of formula [X4'] with a hetero-aromatic-compound of formula [X5] in a nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) related reaction with a base such as DIPEA, K_2CO_3 , Cs_2CO_3 or KOH in a polar solvent such as DMF or THF, the reaction is suitably conducted at elevated temperature. In some examples the compounds of

formula [X6] contains an amino group that is protected by a nitrogen protecting group such as a tert-butyloxycarbonyl protecting group. In these examples, compounds of formula [X7] are prepared through standard removal of a tert-butyloxycarbonyl protecting group by reaction of compound of formula [X6] with an acid such as trifluoroacetic acid or phosphoric acid in DCM, HCl in dioxane or formic acid. After reaction work up, typically by liquid-liquid extraction, the reaction product is purified by flash column chromatography, reverse phase preparative HPLC, chiral preparative SFC or re-crystallisation.

General Scheme 3:



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Compounds of formula [X1] and [X1'] can be obtained via different methodologies (General Scheme 3). In one approach, compounds of formula [X1'] may be prepared by the reaction-cyclisation of a compound of formula [X1'_3] in one or two steps by reaction with a reducing agent such as Borane-THF complex, LiAlH₄ or RedAl in an anhydrous solvent such as THF or toluene at a suitable temperature. Alternatively, they can be prepared using Raney-Ni in a hydrogen atmosphere with a suitable solvent such as ethanol and water. Compounds of formula [X1'_3] can be prepared via reaction of compounds of formula [X1'_1] with compounds of formula [X1'_2] using a strong base such as KHMDS in a suitable anhydrous solvent such as Toluene and THF

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and a suitable low temperature. Alternatively, compounds of formula [X1'] may be prepared by reduction of a compound of formula [X1'_5] using a suitable reducing agent/s such as PhSH, PhSiH3, Fe(acac)3 or NaBH4, NiCl2 or Pd/C, Ammonium formate or Mn(dpm)3, PhSiH3, TBHP in a suitable solvent, generally alcoholic, and at a suitable temperature. In turn, compounds of formula [X1'_5] may be prepared via the cyclisation reaction of compounds of formula [X1'_4] in one or two steps by reaction with a reducing agent such as Borane-THF complex, LiAlH4 or RedAl in an anhydrous solvent like THF or toluene at a suitable temperature. Alternatively, they can be prepared using Raney-Ni in a hydrogen atmosphere with a suitable solvent such as ethanol and water. Compounds of formula [X1'_4] can be prepared via reaction of compounds of formula [X1'_1] with compounds of formula [X1'_2'] using a strong base such as KHMDS in a suitable anhydrous solvent such as Toluene and THF and a suitable low temperature. Alternatively, compounds of formula [X1'] can be prepared from compounds of formula [X1'_8] via standard deprotection conditions, depending on the nature of PG. Compounds of formula [X1] may be prepared with compounds of formula [X1_8] via typical benzyl deprotection conditions such as NaOH in solvents such as ethanol and water at high temperatures. Alternatively, they can also be prepared via a reduction reaction in a hydrogen atmosphere with a suitable catalyst such as Pd(OH)2 in a suitable solvent such as MeTHF, MeOH or IPA.. Compounds of formula [X1_8] can be prepared by a reduction reaction of compounds of formula [X1_7] with suitable reducing agent/s such as PhSH, PhSiH3, Fe(acac)3 or NaBH4, NiCl2 or Pd/C, Ammonium formate or Mn(dpm)3, PhSiH3, TBHP in a suitable solvent, generally alcoholic, and at a suitable temperature. Compounds of formula [X1_7] can be prepared via reaction of compounds of formula [X1_6] with NaNO2/CuCl/HCl in an alcoholic solvent such as methanol or water, typically at room temperature. This is followed by treatment with aqueous HCl in a suitable solvent such as THF, typically conducted at room temperature. Compounds of formula [X1_7] can also be prepared using compounds of formula [X1'5] via standard protecting group addition reaction conditions.

Compounds of the invention may be prepared according to the methods described below. Note that all the reported yields are based on weight of starting material and product and not their purity.

LCMS methods

No.	Instrument	Mass detector
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1	Agilent 1290 Infinity II	Agilent 6130
2	Agilent 1290 Infinity II	Agilent 6130
3	Agilent 1290 Infinity II	Infinity Lab LC/MSD
4	Agilent 1290 Infinity II	Infinity Lab LC/MSD XT
5	Agilent 1290 Infinity II	Infinity Lab LC/MSD XT
6	Agilent 1290 Infinity II	Infinity Lab LC/MSD
7	Agilent 1200	Agilent 6130
8	Agilent 1290 Infinity II	Agilent 6125
9	Shimadzu LC-20AD&MS 2020	
10	Agilent 1200	Agilent 6110B
11	Agilent 1200	Agilent 6120B

Method Name	Solvent system	Column used	Gradient	UV Range	Mass Range	Column Temp. °C	Flow Rate ml/min
Method A	A=0.1% TFA in H ₂ O: ACN (95:5)	Waters XBridgeC8 3.5 µ, 4.6 x 50 mm	95:5 at 0.0 min, 5:95 at 2.5 min upto 4.0 min, 95: 5 at 4.5 min upto 6.0 min	210 to 400 nm	100-1500 amu	Ambient	1.5
	B=0.1% TFA in ACN						
Method B	A= 0.1% HCOOH in H ₂ O: ACN (95:5)	Atlantis dC18 5µ, 4.6x50mm	95:5 at 0.0 min, 5:95 at 2.5 min upto 4.0 min, 95: 5 at 4.5 min upto 6.0 min	210 to 400 nm	100-1500 amu	Ambient	1.5
	B=ACN						
Method C	A= 0.04% TFA in water and B= 0.02% TFA in acetonitrile	Halo C18 3.0*30mm, 5µm	10-100% B in 0.90 min .10% B in 0.01 min, 10-100% B (0.01-0.50 min) with a hold at 100% B for 0.40 min	210 to 400 nm	50-2000 amu		2.0
Method D	A=770.08 mg of Ammonium acetate in 1000 mL of Milli-Q Water	Zorbax extend C18 5µ, 4.6 x 50mm	90:10 at 0.0 min, 5:95 at 4.0 min upto 5.0 min, 90:10 at 5.0 min upto 6.0 min	210 to 400 nm	100-1500 amu	Ambient	1.2

	B=ACN						
Method E	A=790.06 mg of Ammonium bicarbonate is added to 1000 mL of Milli-Q Water	XBridge C8 3.5µ, 4.6 x 50mm	90:10 at 0.0 min, 5:95 at 4.0 min upto 5.0 min, 90:10 at 5.5 min upto 7.0 min	210 to 400 nm	100-1500 amu	Ambient	1.2
	B=ACN						
Method F	A= 0.037% TFA in water, and B= 0.018% TFA in acetonitrile	Chromolith RP-18e 25-2mm	5-95% B in 1.5 min .5% B in 0.01 min, 5-95% B (0.01-0.7 min), 95% B (0.7 -1.15 min), 5% B in 1.16 min with a hold at 5% B for 0.34 min.	210 to 400 nm	100 – 1000 amu	Ambient	1.5
Method G	A=0.1% HCOOH in H ₂ O: ACN (95:5); Solvent B= ACN	Zorbax eclipse plus C18, (2.1 x 50mm, 1.8µ	Gradient [time (min)/solvent B (%)]:0.0/05, 0.25/05, 2.5/100, 3.0/100, 3.1/05, 4.0/05.	210 to 400 nm		Ambient	0.8
Method H	A=770.08 mg of Ammonium acetate in 1000 mL of Milli-Q Water	Acquity BEH C18, 1.7µ (2.1 x 50mm)	5%B at 0 to 0.25 min, 100% of B at 2.5 min to 3.0min, 5%B at 3.1min and 5%B at 4.0min.	210 to 400 nm		Ambient	0.8
	B=CAN						
Method I	A=0.1% HCOOH in H ₂ O; Solvent B=0.05% HCOOH in ACN	Acquity BEH C18 1.7µ,2.1x30mm	Gradient [time(min)/solvent B (%)]:0.0/5, 0.4/5, 1.8/100,2.4/100,2.6/05,3.0/05.	210 to 400 nm		30 °C	1.0
Method K	A=770.08 mg of Ammonium acetate in 1000 mL of Milli-Q Water	Zorbax XDB C18 5µ, 4.6 x 50mm	10%B at 0 min, 95% B at 3.5 min to 4.5 min, 10%B at 5.0min to 5.5 min.	210 to 400 nm		Ambient	1.2
	B=ACN						
Method L	A=770.08 mg of Ammonium acetate in 1000					Ambient	1.0

	mL of Milli-Q Water	XBridge C8 3.5µ, 4.6 x 50mm	95:5 at 0.0 min, 100 at 2.5 min upto 5.0 min, 95:05 at 5.5 min upto 6.0 min	210 to 400 nm	100-1500 amu		
	B=ACN						
Method M	A=0.1% HCOOH in H ₂ O	Acquity BEH C18, (2.1 x 50mm) 1.7µ	95:5 at 0.0 min upto 0.25 min, 5:95 at 2.5 min upto 3.5 min, 95:05 at 3.6 min upto 4.0 min	210 to 400 nm	100-1500 amu	40 °C	0.8
	B=ACN						
Method N	A=10 mM NH ₄ HCO ₃ in H ₂ O	Xbridge Shield RP18 5 µ 2.1 x 50mm	5-95% B in 2.20 min .5% B in 0.01 min,5-95% B (0.01-1.00 min), 95%-100%B(1.00min-1.80min), 100-5% B (1.80 - 1.81 min) with a hold at 5% B for 0.39min	diode array (DAD)	100-1000 amu		1.0
	B=ACN						
Method O	A=0.037% TFA in H ₂ O	Kinetex C18 5 µ 50 x 2.1mm	5%B in 0.40min and 5-95% B at 0.40-3.00 min , hold on 95% B for 1.00min, and then 95-5%B in 0.01min	diode array (DAD)	100-1000 amu		1.0
	B=0.018% TFA in ACN						
Method P	A= 10mM NH ₄ HCO ₃ in H ₂ O	Xbridge Shield RP18 5 µ 2.1 x 50mm	5%B in 0.40min and 5-95% B at 0.40-3.40 min ,hold on 95% B for 0.45min, and then 95-5%B in 0.01min	diode array (DAD)	100-1000 amu		0.8
	B=ACN						
Method Q	A= 0.01% HCOOH in H ₂ O	LUNA Omega PS 120 C18 3µ 50 x 2.1mm	5.1%B in 0.01 min, 90.5%B in 1.5min, 90%B in 5 min.	210nm			0.6
	B=ACN						
Method R	A= 0.1% HCOOH in H ₂ O: ACN (95:5)	Atlantis dC18 5µ, 4.6x50mm	95:5 at 0.0 min, 5:95 at 8 min upto 8.1 min, 95:5 at 8.5 min upto 10 min	210 to 400 nm	100-1500 amu	25 °C	1.5
	B=ACN						
Method S	A=770.08 mg of Ammonium acetate in 1000 mL of Milli-Q Water	Zorbax Extend C18 5µ, 4.6 x 50mm	90:10 at 0.0 min, 5:95 at 3.5 min upto 4.5 min, 90:10 at 4.5 min upto 5.5 min	210 to 400 nm		Ambient	1.2
	B=ACN						

Method O'	A=0.04% TFA in H ₂ O	Kinetex C18 5 μ 50 x 2.1mm	10%B at 0min, 100%B at 0.9 min, hold to 1min	diode array (DAD)	100-1000 amu	40 °C	2.0
	B=0.02% TFA in ACN						
Method R'	A=0.04% TFA in H ₂ O B=0.02% TFA in ACN	Shimadzu LC-20AD&MS 2020		220 to 254 nm	100 – 2000 amu	40 °C	2.0
Method S'	A= 0.04% TFA in H ₂ O B: 0.02% TFA in ACN	LUNA Omega PS 120 C18 3 μ 50 x 2.1mm	5.1%B in 0.01 min, 90.5%B in 1.5min, 90%B in 5 min.	210nm			0.8
Method W	A= 0.1% Formic acid in H ₂ O; Solvent B= 0.05% Formic acid in CAN	Zorbax Eclipse Plus C18; 2.1x 50 mm, 1.8 μ (Waters Acquity UPLC I class Series with SQD 2 Mass detector)	Gradient [time (min)/solvent B (%): 0.0/5, 0.2/5, 2.5/98, 3.5/98, 3.6/5, 4.0/5	210 to 400 nm		40 °C	0.8
Method Y	A= 10mM Ammonium bicarbonate in H ₂ O; Solvent B = ACN	Acquity UPLC BEH C18; 1.7 μ , 2.1x 50 mm Shimadzu N series UPLC with LCMS 2020 Mass Detector	Gradient [time (min)/solvent B (%): 0.0/5, 0.2/5, 2.5/98, 3.5/98, 3.6/5, 4.0/5	210 to 400 nm		30 °C	0.8

HPLC purification methods for Examples

Method	Solvent system	Column
Method A	A-0.1% TFA in H ₂ O, B-ACN	Sunfire C18 (19 mm x 150 mm) 5 μ m
Method B	A-0.1% HCOOH in H ₂ O, B-ACN	X Bridge C8 (19 mm X 150mm), 5 μ m
Method C	A-10 mM NH ₄ HCO ₃ in H ₂ O, B-ACN	X Bridge C8 (19 mm X 150mm), 5 μ m

Method E	A-0.2% HCOOH in H ₂ O, B-ACN	Phenomenex Luna C18 (75 mm x 30 mm), 3 µm
Method F	A-0.2% HCOOH in H ₂ O, B-ACN	Waters Xbridge BEH C18 (75 mm x 30 mm), 3 µm
Method G	A-0.2% HCOOH in H ₂ O, B-ACN	Phenomenex Luna C18 (80 mm x 40 mm), 3 µm
Method H	A-10 mM NH ₄ HCO ₃ in H ₂ O, B-ACN	Waters Xbridge BEH C18 100*30mm*10µm
Method J	A-0.2% HCOOH in H ₂ O, B-ACN	Waters O-Xbridge C18 (150 mm x 10mm), 5 µm
Method K	A-0.01% TFA in H ₂ O, B-ACN	Gemini C18(250*4.6), 5µm
Method L	A-0.2% HCOOH in H ₂ O, B-ACN	Phenomenex Luna C18 100*40 mm (or 30 mm) *5/3 µm
Method M	A-0.1% TFA in H ₂ O, B-ACN	Phenomenex Luna C18 (75 mm x 30 mm), 3 µm
Method N	A-0.2% HCOOH in H ₂ O, B-ACN	XBridge BEH C18 (19X250mm), 5µm
Method Q	A-0.2% HCOOH in H ₂ O, B-ACN	XBridge BEH C18 (19X150mm), 5µm
Method P	A-0.1% TFA in H ₂ O, B-ACN	XBridge BEH C18 (19X150mm), 5µm
Method U	A-0.2% HCOOH in H ₂ O, B-ACN	XBridge BEH C8 (19X150mm), 5µm
Method Y	A-0.2% HCOOH in H ₂ O, B-ACN	Xselect CSH C18(19X250mm), 5µm
Method AC	A-0.2% HCOOH in H ₂ O, B-ACN	XSelect CSH C18(19X150mm), 5µm
Method AF	A-0.1% TFA in H ₂ O, B-ACN	Shim-pack GIS C18(20X250mm), 5µm
Method AG	A-0.2% HCOOH in H ₂ O, B-ACN	Shim-pack GIS C18(20X250mm), 5µm
Method AK	A-0.2% HCOOH in H ₂ O, B-ACN	Agilent5 prep C18(50*21.2)mm; 5µm
Method AN	A-0.1% TFA in H ₂ O, B-ACN	Atlantis T3 C18(19X250mm), 5µm
Method AO	A-0.2% HCOOH in H ₂ O, B-ACN	Atlantis T3 C18(19X250mm), 5µm
Method AP	A-0.2% HCOOH in H ₂ O, B-ACN	Xtimate,C18(250×21.2mm), 5µm

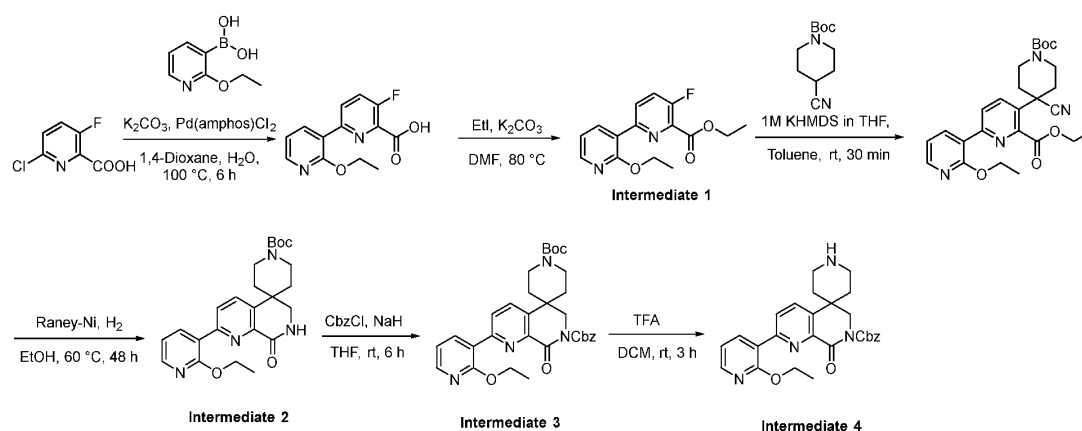
Abbreviations & Acroynms

ACN	acetonitrile
amu	atomic mass unit
atm	Atmospheric units of pressure
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Cbz-Cl	Benzyl chloroformate

DCM	dichloromethane
DMA	dimethylacetamide
DMAP	4-Dimethylaminopyridine
DIPEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
EtOAc	Ethyl Acetate
ESI+	positive electrospray ionization
NMP	<u>N-Methyl-2-pyrrolidone</u>
Ti(OiPr) ₄	<u>Titanium (IV) isopropoxide</u>
HATU	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium,hexafluorophosphate(V)
HPLC	high performance liquid chromatography
IPA	Isopropanol
KHMDS	Potassium hexamethyldisilazide
LCMS	liquid chromatography mass spectrometry
MW	Microwave
NBS	N-Bromosuccinimide
NMR	nuclear magnetic resonance
PET ether	petroleum ether
PIMC	Percentage Inhibition at the maximum concentration
K ₂ CO ₃	Potassium carbonate
Prep	preparative
R _f	retention factor
rt	retention time
RT	Room temperature
NaH	Sodium hydride
Na(OAc) ₃ BH	Sodium triacetoxyborohydride
SFC	supercritical fluid chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography
iPrOAc	Isopropyl acetate

Synthesis of Intermediates:

Procedure for the preparation of benzyl 2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (Intermediate 4)



To a stirred solution of 6-chloro-3-fluoropicolinic acid (10 g, 57.0 mmol) in 1,4-dioxane: H_2O (80:20 mL) were added (2-ethoxypyridin-3-yl)boronic acid (11.4 g, 68.4 mmol) followed by K_2CO_3 (15.8 g, 114 mmol) at RT and solution was purged by nitrogen for 5 minutes. $Pd(amphos)Cl_2$ (0.605 g, 0.854 mmol) was added in reaction mixture and heated at $100^\circ C$ for 16 h. The mixture was filtered through celite bed and bed was washed with EtOAc (100 mL). Combined filtrate was diluted with water (50 mL) and extracted with EtOAc (100 mL x 2). The aqueous layer was acidified with Citric acid (10%) (solid precipitated). The precipitated solid was filtered off to afford 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylic acid (12 g, 44.8 mmol, 79%) as white solid.

LCMS: 2.04 min, 263.1 (M+H)⁺, Method B

To a stirred solution of 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylic acid (12 g, 45.8 mmol) in DMF (80 mL) was added K_2CO_3 (12.65 g, 92 mmol) followed by ethyl iodide (4.44 mL, 54.9 mmol) and reaction mixture was stirred at $80^\circ C$ for 16 h. The reaction mixture was quenched by water (200 mL) and extracted with EtOAc (200 mL x 2). Combined organic extract was washed with brine (100 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get crude. The crude was purified by flash column chromatography. The pure fractions were concentrated under reduced pressure to afford ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (10 g, 34.1 mmol, 75 %) (Intermediate 1) as off white solid.

To a mixture of ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (2.5 g, 8.61 mmol) (Intermediate 1) and tert-butyl 4-cyanopiperidine-1-carboxylate (1.81 g, 8.61 mmol) in toluene (25 mL) was added 1M KHMDS in THF (8.61 mL, 8.61 mmol) and reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched with Saturated NH_4Cl (20 mL) and extracted with EtOAc (2 x 50 mL). Combined organic extracts were dried over sodium sulfate and concentrated

to afford crude. The crude was purified by flash column chromatography using EtOAc-PET ether (0 to 10%) to afford ethyl 5-(1-(tert-butoxycarbonyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (1.2 g, 2.472 mmol, 29%) as a colourless gum.

LCMS: 2.99 min, 481.0 (M+H)⁺, Method B

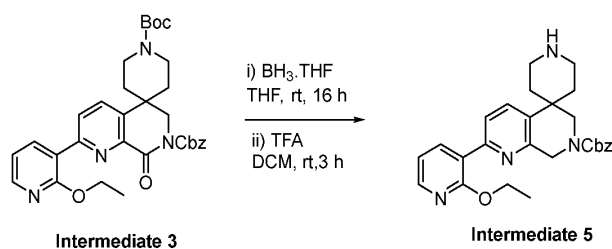
- 5 To a stirred solution of ethyl 5-(1-(tert-butoxycarbonyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (2.5 g, 5.20 mmol) in EtOH:H₂O (20:5 mL) was added Raney nickel (5.47 g, 62.4 mmol) at rt and reaction mixture was stirred under hydrogen gas at 70 psi pressure at 65 °C for 16 h. The reaction mixture was filtered through celite bed, bed was washed with MeOH (20 mL). Combined filtrate was concentrated under reduced pressure to afford crude. The crude was
10 purified by using flash column chromatography to afford tert-butyl 2'-(2-ethoxypyridin-3-yl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (1.5 g, 3.25 mmol, 63 %) (Intermediate 2) as white solid.

- To a stirred solution of tert-butyl 2'-(2-ethoxypyridin-3-yl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (1.5 g, 3.42 mmol) (Intermediate 2) in THF (5 mL) was
15 added NaH (0.274 g, 6.84 mmol) at 0 °C and stirred for 20 min. Cbz-Cl (2.29 mL, 6.84 mmol) was added to the reaction mixture and slowly allowed to stir the reaction mixture at RT for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 2). Combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude. The crude was purified by using
20 flash column chromatography to afford 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (700 mg, 1.198 mmol, 35%) (Intermediate 3) as off white solid.

- To a stirred solution of 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (700 mg, 1.22 mmol) (Intermediate 3) in DCM (5
25 mL) was added TFA (0.471 mL, 6.11 mmol) at 0 °C and reaction mixture was allowed to stir at rt for 2 h. The reaction mixture was concentrated to get crude. The crude was quenched by 1.5 N HCl (5 mL) and extracted with DCM (2 x 10mL). Combined organic extract was washed with water (10 mL) and brine (10 mL). Organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude benzyl 2'-(2-ethoxypyridin-3-yl)-
30 8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate 2,2,2-trifluoroacetate (600 mg, 1.002 mmol, 82%) (Intermediate 4) as gummy solid.

The analytical data for Intermediate 1, 2, 3 and 4 is in Table 1.

Procedure for the preparation of 2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (Intermediate 5)

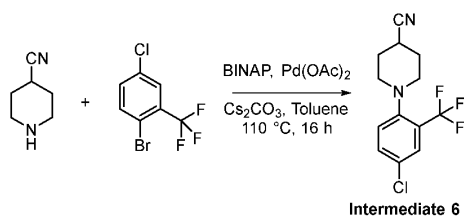


- 5 To a stirred solution of 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (600 mg, 1.048 mmol) (intermediate 3) in THF (10 mL) was added $\text{BH}_3 \cdot \text{THF}$ (4.19 mL, 4.19 mmol) at 0 °C and reaction mixture was stirred at rt for 2 h. After 2 h, excess of $\text{BH}_3 \cdot \text{THF}$ (4.19 mL, 4.19 mmol) was added at 0 °C and reaction mixture was further stirred at rt for 14 h. The reaction was quenched by MeOH (10 mL) at 0 °C and
- 10 concentrated the reaction mixture to afford crude 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (400 mg, 0.716 mmol, 68.3%) as gummy solid. Crude was as such used for next step.

- To a stirred solution of 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (400 mg, 0.716 mmol) in DCM (10 mL) was added TFA
- 15 (82 mg, 0.716 mmol) at 0 °C and reaction mixture was allowed to stir at rt for 3 h. The reaction mixture was directly concentrated and resulted residue was basified by saturated NaHCO_3 solution. The aqueous layer was extracted with EtOAc (2 x 50 mL). Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to afford 2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (700 mg, 1.480 mmol, 207%)
- 20 (Intermediate 5) as a pale yellow gummy solid.

The analytical data for Intermediate 5 is in Table 1.

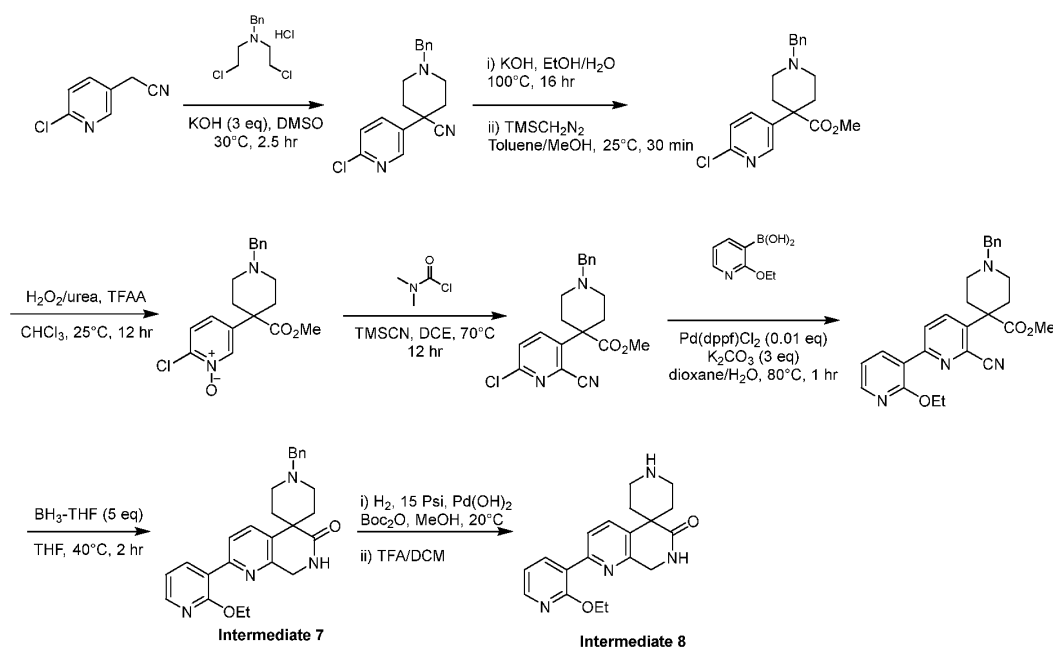
Procedure for the preparation of nitriles as exemplified with the preparation of 1-(4-chloro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (Intermediate 6)



To a stirred solution of piperidine-4-carbonitrile (250 mg, 2.269 mmol) in toluene (2 mL) at RT were added 1-bromo-4-chloro-2-(trifluoromethyl)benzene (883 mg, 3.40 mmol) and Cs_2CO_3 (1.48 g, 4.54 mmol). The reaction mixture was purged with nitrogen for 5 min. BINAP (283 mg, 0.454 mmol) and $\text{Pd}(\text{OAc})_2$ (51 mg, 0.227 mmol) were added, and the reaction mixture was heated at 110 °C for 16 h. The reaction mixture was filtered through celite and washed with EtOAc (10 mL). The filtrate was evaporated, and the crude product was purified via flash column chromatography to afford 1-(4-chloro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (550 mg, 1.87 mmol, 83%) (Intermediate 6) as a yellow gum.

The analytical data for Intermediate 6 is in Table 1.

Procedure for the preparation of lactams as exemplified with the preparation of 2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (Intermediate 8)



To a solution of 2-(6-chloropyridin-3-yl)acetonitrile (10 g, 65.54 mmol) in DMSO (200 mL) were added potassium hydroxide (11.03 g, 196.62 mmol) in portions and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethan-1-amine hydrochloride (17.60 g, 65.54 mmol) at 25 °C. The reaction mixture was stirred at 30 °C for 2.5 hr. After cooling to RT, the reaction mixture was poured into ice-water (600 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phase was washed with brine (500 mL) and dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to get a crude, which was purified by column on silica gel (eluted with PET ether/EtOAc= 100/1 to 20/1) to get 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carbonitrile (11 g, 53.8%) as an orange solid.

¹H NMR (400 MHz, CDCl₃) δ 8.57 - 8.54 (m, 1H), 7.80 (dd, *J* = 2.7, 8.3 Hz, 1H), 7.43 - 7.28 (m, 6H), 3.62 (br s, 2H), 3.10 - 3.00 (m, 2H), 2.54 (br dd, *J* = 5.7, 12.0 Hz, 2H), 2.12 (br s, 4H)

To a solution of 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carbonitrile (5.5 g, 17.64 mmol) in a mixture solvents of ethanol (55 mL) and water (55 mL) was added potassium hydroxide (7.13 g, 127.00 mmol) at 25 °C. The reaction mixture was heated to 100 °C and stirred at 100 °C for 16 hr. One additional vial was set up as described above. After cooling to RT, all two reaction mixtures were combined. The mixture was removed ethanol and acidified to pH 4 with hydrochloric acid (4 N). The suspension was filtered and the filtrate cake was dried under reduced

pressure to get 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carboxylic acid (8 g) as a white solid, which was used to next step directly without further purification.

LCMS: 0.72 min, 331.1 (M+H)⁺, Method O

To a solution of 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carboxylic acid (9.4 g, 28.42 mmol) in a mixture solvents of MeOH (100 mL) and toluene (200 mL) was added (trimethylsilyl)diazomethane in hexane (2 M, 42.62 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was quenched with acetic acid (1 mL) and neutralized with saturation sodium bicarbonate (200 mL) to pH 8 and extracted with EtOAc (3 × 100 mL). The combined organic phase was concentrated under reduced pressure to get a crude, which was purified by flash column chromatography (eluted with PET ether/ EtOAc= 100/5 to 100/20) to afford methyl 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carboxylate (6 g, 61%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.42 (br s, 1H), 7.70 - 7.64 (m, 1H), 7.37 - 7.22 (m, 6H), 3.69 (s, 3H), 3.49 (s, 2H), 2.83 (br d, *J* = 10.4 Hz, 2H), 2.58 (br d, *J* = 12.8 Hz, 2H), 2.21 (br t, *J* = 11.2 Hz, 2H), 2.05 - 1.93 (m, 2H)

To a solution of methyl 1-benzyl-4-(6-chloropyridin-3-yl)piperidine-4-carboxylate (1 g, 2.90 mmol) in chloroform (20 mL) was added hydrogen peroxide urea (545 mg, 5.80 mmol) and trifluoroacetic anhydride (1.22 g, 5.80 mmol, 806.7 uL) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hr. One additional vial was set up as described above. All of two reaction mixtures were combined, quenched by saturation sodium sulfite (200 mL) at 0 °C and extracted with DCM (3 × 100 mL). The combined organic phase was washed with saturation sodium carbonate (200 mL), brine (100 mL) and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to get a crude, which was purified by flash column chromatography (eluted with EtOAc/MeOH= 100 to 100/10) to get 5-(1-benzyl-4-(methoxycarbonyl)piperidin-4-yl)-2-chloropyridine 1-oxide (1 g, 48%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.35 - 7.28 (m, 5H), 7.22 (dd, *J* = 2.1, 8.7 Hz, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 2.79 (br d, *J* = 11.4 Hz, 2H), 2.57 - 2.45 (m, 2H), 2.18 (br t, *J* = 11.0 Hz, 2H), 1.99 - 1.87 (m, 2H).

To a solution of 5-(1-benzyl-4-(methoxycarbonyl)piperidin-4-yl)-2-chloropyridine 1-oxide (1 g, 2.77 mmol) in 1, 2-dichloroethane (15 mL) was added trimethylsilylformonitrile (824.81 mg, 8.31 mmol, 1.04 mL) and N, N-dimethylcarbamoyl chloride (894.1 mg, 8.3 mmol, 764.2 μ L) at 25 °C. The reaction mixture was heated to 70 °C and stirred for 12 hr. Two additional vials were set up as described above. After cooling to RT, all of three reaction mixtures were combined, diluted with the solution of sodium hydroxide (1 N in water, 200 mL) and extracted with EtOAc (3 $\times$ 80 mL). The combined organic layers were washed with brine (80 mL $\times$ 2), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (eluted with PET ether/ EtOAc= 10/1 to 0/1) to get methyl 1-benzyl-4-(6-chloro-2-cyanopyridin-3-yl)piperidine-4-carboxylate (1.5 g, 49%) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.35 - 7.30 (m, 4H), 7.28 (br d, J = 2.4 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 2H), 2.74 - 2.61 (m, 4H), 2.56 - 2.46 (m, 2H), 2.22 - 2.11 (m, 2H)

To a solution of methyl 1-benzyl-4-(6-chloro-2-cyanopyridin-3-yl)piperidine-4-carboxylate (1.3 g, 3.7 mmol) in a mixture solvents of dioxane (20 mL) and water (2 mL) was added (2-ethoxypyridin-3-yl)boronic acid (921.3 mg, 5.6 mmol), K_2CO_3 (1.53 g, 11.04 mmol) and [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (269.2 mg, 367.9 μ mol) at 25 °C under nitrogen. The reaction mixture was heated to 80 °C and stirred at 80 °C for 1 h. After cooling to RT, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to get a crude, which was purified by prep-TLC (EtOAc, R_f = 0.29) to get methyl 1-benzyl-4-(6-cyano-2'-ethoxy-[2,3'-bipyridin]-5-yl)piperidine-4-carboxylate (1.5 g, 3.3 mmol, 89%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 8.43 (dd, J = 1.9, 7.6 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.24 (dd, J = 2.0, 4.9 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 4.3 Hz, 4H), 7.05 (dd, J = 4.9, 7.5 Hz, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.53 (s, 2H), 2.79 - 2.65 (m, 4H), 2.51 (br t, J = 10.1 Hz, 2H), 2.29 - 2.20 (m, 2H), 1.46 (t, J = 7.1 Hz, 3H)

To a solution of methyl 1-benzyl-4-(6-cyano-2'-ethoxy-[2,3'-bipyridin]-5-yl)piperidine-4-carboxylate (700 mg, 1.53 mmol) in THF (14 mL) was added borane THF complex (1 M, 7.67 mL) at 0 °C dropwise under nitrogen. The reaction mixture was heated to 40 °C and stirred at 40 °C for 2 hr. One additional vial was set up as described above. After cooling to 0 °C, all of two reaction mixtures were combined and quenched with MeOH (10 mL). The mixture was heated to 80 °C and stirred at 80 °C for 30 min. After cooling to 25 °C, the resulting mixture was concentrated under reduced pressure to get a residue, which was purified by flash column

chromatography (eluted with PET ether/EtOAc to EtOAc/MeOH= 20/80 to 90/10) to get 1-benzyl-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (700 mg, 53%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, *J* = 1.8, 7.4 Hz, 1H), 8.20 (dd, *J* = 1.9, 4.9 Hz, 1H), 8.00 (s, 1H), 7.84 (br d, *J* = 8.5 Hz, 1H), 7.39 - 7.30 (m, 4H), 7.30 - 7.28 (m, 1H), 7.02 (dd, *J* = 4.9, 7.4 Hz, 1H), 6.09 (br s, 1H), 4.65 (d, *J* = 3.0 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.60 (br s, 2H), 2.79 (br s, 4H), 2.22 (br d, *J* = 13.5 Hz, 2H), 2.11 - 2.01 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H)

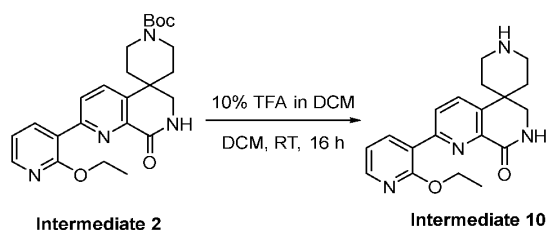
To a solution of 1-benzyl-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (100 mg, 233.4 μmol) in MeOH (5 mL) were added Pd(OH)₂ (100 mg, 142.4 μmol, 20% purity) and di-tert-butylidicarbonate (101.9 mg, 466.7 μmol, 107.2 μL) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The reaction mixture was stirred under hydrogen balloon (15 Psi) at 20 °C for 5 hr. Two additional vials were set up as described above. All of three reaction mixtures were combined, filtered and the filtrate was concentrated under reduced pressure to get a residue, which was purified by prep-TLC to get tert-butyl 2'-(2-ethoxypyridin-3-yl)-6'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (200 mg, 65%) (Intermediate 7) as a colourless oil.

To a solution of tert-butyl 2'-(2-ethoxypyridin-3-yl)-6'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (100 mg, 228.0 μmol) in DCM (1 mL) was added 2,2,2-TFA (154.0 mg, 1.35 mmol, 0.1 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hr. One additional vial was set up as described above. All of two reaction mixtures were combined and concentrated under reduced pressure to get a residue, which was purified by prep-HPLC to get 2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (50 mg, 34%) (Intermediate 8) as a yellow oil.

The analytical data for Intermediate 7 and 8 is in Table 1.

Procedure for the preparation of lactams as exemplified with the preparation of 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Intermediate 10)

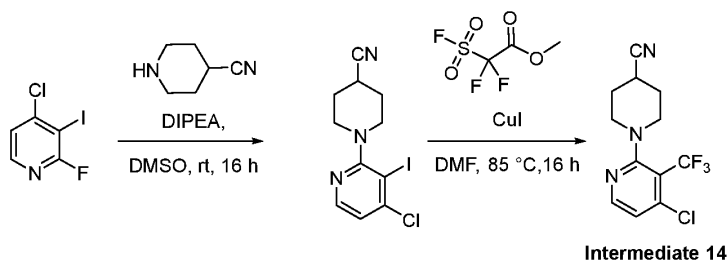
105



To a stirred solution of tert-butyl 2'-(2-ethoxypyridin-3-yl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (200 mg, 0.456 mmol) (Intermediate 2) in DCM (5 mL) at 0 °C were added TFA (0.04 mL, 0.456 mmol) and the reaction mixture was stirred at RT for 16 h. Reaction mixture was evaporated and dried under high vacuum to afford 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one trifluoroacetate (150 mg, 0.400 mmol, 88%) (Intermediate 10) as a brown gum.

The analytical data for Intermediate 10 is in Table 1.

Procedure for the preparation of nitriles as exemplified with the preparation of 1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile (Intermediate 14)



To a stirred solution of piperidine-4-carbonitrile (300 mg, 2.72 mmol) in DMSO (3 mL) were added 4-chloro-2-fluoro-3-iodopyridine (690 mg, 2.68 mmol) followed by DIPEA (1.1 mL, 6.30 mmol) and reaction was heated at 70 °C for 16 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, evaporated, and the crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 50%) to afford 1-(4-chloro-3-iodopyridin-2-yl) piperidine-4-carbonitrile (580 mg, 1.6 mmol, 61%) as a white solid.

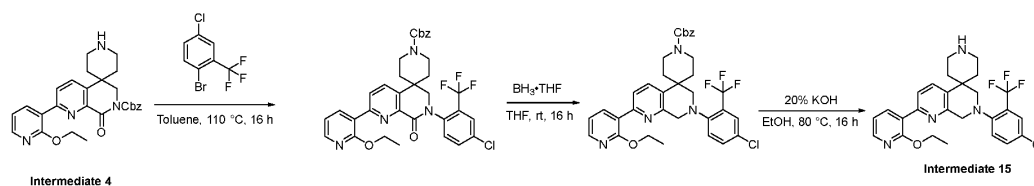
LCMS: 3.21 min, 348.1 (M+H)⁺, Method B

To a stirred solution of 1-(4-chloro-3-iodopyridin-2-yl)piperidine-4-carbonitrile (580 mg, 1.669 mmol) in DMF (1 mL) were added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (390 mg, 2.030 mmol) followed by copper(I) iodide (390 mg, 2.048 mmol) and reaction mixture was heated at 85 °C for 16 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 10mL).

- 5 The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, evaporated, and the crude product was purified by flash column chromatography. The pure fractions were evaporated and dried under a high vacuum to afford 1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile (500 mg, 1.6 mmol, 97%) (Intermediate 14) as a yellow liquid.

- 10 The analytical data for Intermediate 14 is in Table 1.

Procedure for the preparation of amines as exemplified with the preparation of 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 15)



- 15 A stirred solution of benzyl 2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (500 mg, 1.058 mmol) (Intermediate 4) and 1-bromo-4-chloro-2-(trifluoromethyl)benzene (412 mg, 1.587 mmol) in toluene (1 mL) was purged with N₂ for 5 min. Cs₂CO₃ (1034 mg, 3.17 mmol), Pd₂(dba)₃ (48.4 mg, 0.053 mmol) followed by xantphos (42.9 mg, 0.074 mmol) were added and reaction mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated to afford crude. The crude was purified by using flash chromatography in 0 to 70% EtOAc in PET ether to afford benzyl 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (400 mg, 0.608 mmol, 58%) as an off white solid. Note that migration of the Cbz group was observed.

- 25 **LCMS:** 2.89 min, 650.9 (M+H)⁺, Method B

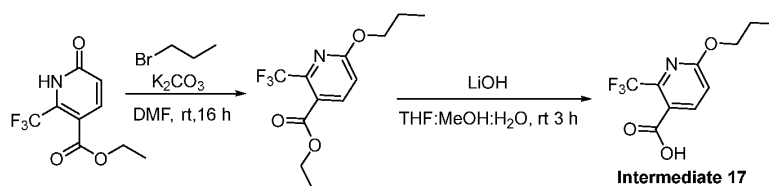
To a stirred solution of benzyl 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (30 mg, 0.046 mmol) in THF (2 mL) was added $\text{BH}_3\cdot\text{THF}$ (0.184 mL, 0.184 mmol) at 0 °C and reaction mixture was stirred at rt for 4 h. The reaction was quenched by MeOH (10 mL) at 0 °C and concentrated the reaction mixture to afford crude benzyl 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (20 mg, 0.031 mmol, 68%) as gummy solid. Crude was as such used for next step.

LCMS: 2.56 min, 637.0 (M+H)⁺, Method A

To a stirred solution of benzyl 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (100 mg, 0.157 mmol) in EtOH (1 mL) was added 20% KOH in water (1 mL, 0.157 mmol) and reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with DCM:MeOH (9:1) (20 mL x 2). Combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (50 mg, 0.089 mmol, 57%) (Intermediate 15) as gummy solid.

The analytical data for Intermediate 15 is in Table 1.

Procedure for the preparation of acids as exemplified with the preparation of 6-propoxy-2-(trifluoromethyl)nicotinic acid (Intermediate 17)



To a stirred solution of ethyl 6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylate (3 g, 12.76 mmol) in DMF (30 mL) were added K_2CO_3 (2.292 g, 16.58 mmol) followed by 1-bromopropane (1.84 mL, 20.28 mmol) and reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (5 mL). The organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate and evaporated to afford crude product. The crude product was purified by flash column chromatography using EtOAc-PET ether

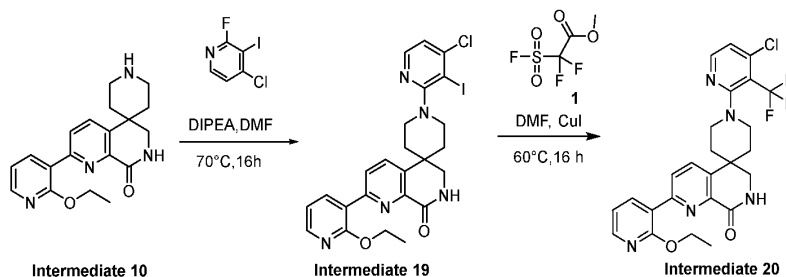
(0 to 30%) to afford ethyl 6-propoxy-2-(trifluoromethyl)nicotinate (3.51 g, 12.54 mmol, 98 %) as a colourless.

LCMS: 2.0 min, 278.1 (M+H)⁺, Method B

A solution of ethyl 6-propoxy-2-(trifluoromethyl)nicotinate (3.5 g, 12.62 mmol) in THF:MeOH:H₂O (15:7.5:0.5 mL) was added LiOH (1.51 g, 63.1 mmol) and reaction mixture was stirred at rt for 16h. The reaction mixture was concentrated and diluted with water (2 mL). The aqueous layer was acidified with 1.5N HCl (1 mL) and extracted with DCM (5 mL x 2). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford 6-propoxy-2-(trifluoromethyl)nicotinic acid (2.8 g, 11.12 mmol, 88%) (Intermediate 17) as white solid.

The analytical data for Intermediate 17 is in Table 1.

Procedure for the preparation of lactams as exemplified with the preparation of (Intermediate 20)



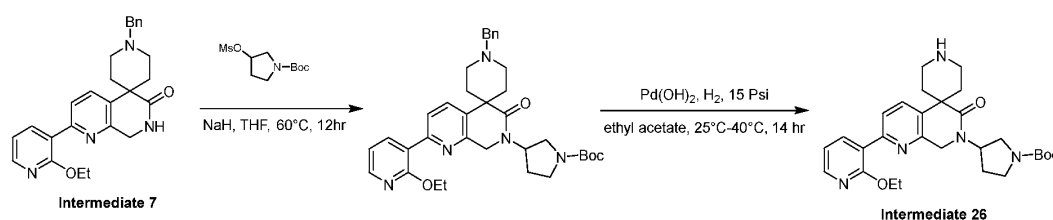
To a stirred solution of 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (300 mg, 0.886 mmol) (Intermediate 10) in DMF (2 mL) were added DIPEA (0.310 mL, 1.773 mmol) and 4-chloro-2-fluoro-3-iodopyridine (342 mg, 1.330 mmol) and reaction mixture was stirred at 70 °C for 16h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 2). combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude. The crude compound was purified by flash column chromatography to afford 1-(4-chloro-3-iodopyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (250 mg, 0.373 mmol, 42 %) (Intermediate 19).

To a stirred solution of 1-(4-chloro-3-iodopyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (100 mg, 0.174 mmol) (Intermediate 19) in DMF (3 ml) were added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (40.0 mg, 0.208 mmol) and copper(I) iodide (39.7 mg, 0.208 mmol) and the reaction mixture was stirred at 60 °C for 16h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). Combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered, and concentrated to afford crude. The crude was purified using prep HPLC. The pure fraction were collected and lyophilized to obtain desired product 1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (22 mg, 0.041 mmol, 23%) (Intermediate 20) as off white solid.

LCMS: 2.33 min, 518.1 (M+H)⁺, Method A

The analytical data for Intermediate 19 and 20 is in Table 1.

Procedure for the preparation of lactams as exemplified with the preparation of tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (Intermediate 26)



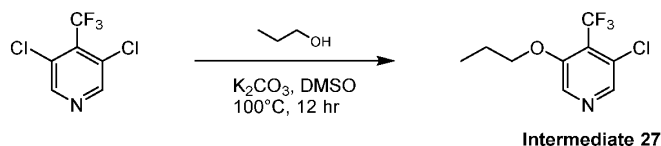
To a solution of 1-benzyl-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (530 mg, 1.24 mmol) (Intermediate 7) in THF (20 mL) was added tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (1.31 g, 4.95 mmol) and NaH (247.34 mg, 6.18 mmol, 60% purity) at 25 °C. After heating to 60 °C, the reaction mixture was stirred at 60 °C for 12 hr. After cooling to RT, the reaction mixture was quenched by water (20 mL) at 0 °C and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography (eluted with PET ether/EtOAc=15/85 to EtOAc/MeOH=95/5, R_f = 0.4) to get tert-butyl 3-(1-benzyl-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (420 mg, 57%) as a yellow oil.

LCMS: 0.69 min, 598.3 (M+H)⁺, Method O

To a solution of tert-butyl 3-(1-benzyl-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (420 mg, 702.64 μmol) in EtOAc (50 mL) was added Pd(OH)₂ (400 mg, 569.66 μmol, 20% purity) at 25 °C under hydrogen (15 Psi). The suspension was degassed under vacuum and purged with hydrogen several times. The reaction mixture was stirred at 25 °C under hydrogen (15 Psi) for 12 hr, then the mixture was heated to 40 °C and stirred at 40 °C for 2 hr. After cooling to RT, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue to get tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (320 mg) (Intermediate 26) as a grey oil, which was used for next step without further purification.

The analytical data for Intermediate 26 is in Table 1.

Procedure for the preparation of pyridines as exemplified with the preparation of 3,5-dichloro-4-(trifluoromethyl)pyridine (Intermediate 27)



15

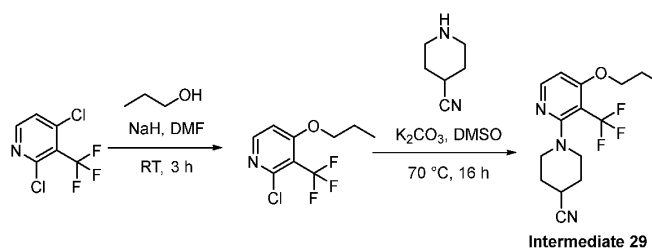
To a solution of 3,5-dichloro-4-(trifluoromethyl)pyridine (0.1 g, 463 μmol) in mixture solvents DMSO (0.5 mL) and propyl alcohol (0.5 mL) was added K₂CO₃ (192 mg, 1.39 mmol) at 25 °C. The reaction mixture was heated to 100 °C and stirred at 100 °C for 12 hr. One additional vial was set up as described above. After cooling to RT, all two reaction mixtures were combined, diluted with brine (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-TLC to give 3-chloro-5-propoxy-4-(trifluoromethyl)pyridine (100 mg, 45%) (Intermediate 27) as colourless oil.

20

The analytical data for Intermediate 27 is in Table 1.

Procedure for the preparation of nitriles as exemplified with the preparation of 1-(4-propoxy-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile (Intermediate 29)

25



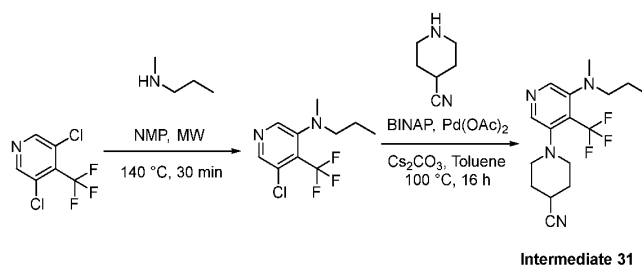
To a stirred suspension of NaH (139 mg, 3.47 mmol) in DMF (2 mL) at 0 °C was added propan-1-ol (153 mg, 2.55 mmol) in DMF (2 mL) and the reaction mixture was stirred at 0 °C for 30 min. 2,4-dichloro-3-(trifluoromethyl)pyridine (500 mg, 2.315 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at RT for 2.5 h. The reaction mixture was quenched cautiously with ice-cold water (20 mL) and extracted with 10% EtOAc in PET ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 15%) to afford 2-chloro-4-propoxy-3-(trifluoromethyl)pyridine (500 mg, 2.044 mmol, 88%) as a colourless liquid.

LCMS: 2.67 min, 239.8 (M+H)⁺, Method B

To a stirred solution of 2-chloro-4-propoxy-3-(trifluoromethyl)pyridine (400 mg, 1.669 mmol) in DMSO (4 mL) at RT were added piperidine-4-carbonitrile (221 mg, 2.003 mmol) and K₂CO₃ (461 mg, 3.34 mmol). The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over sodium sulfate and evaporated. The crude product was purified by flash column chromatography to afford 1-(4-propoxy-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile (310 mg, 0.987 mmol, 59%) (Intermediate 29) as a colourless gum.

The analytical data for Intermediate 29 is in Table 1.

Procedure for the preparation of nitriles as exemplified with the preparation of 1-(5-(methyl(propyl)amino)-4-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile (Intermediate 31)



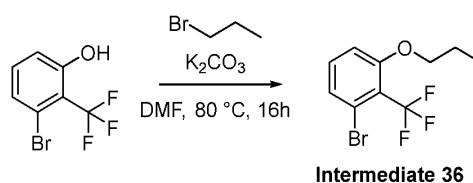
A stirred solution of 3,5-dichloro-4-(trifluoromethyl)pyridine (300 mg, 1.389 mmol) and N-methylpropan-1-amine (508 mg, 6.94 mmol) in NMP (3 mL) was irradiated with MW at 140 °C for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with 20% EtOAc in PET ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated to afford 5-chloro-N-methyl-N-propyl-4-(trifluoromethyl)pyridin-3-amine (280 mg, 0.499 mmol, 36%) as a yellow gum.

LCMS: 2.91 min, 252.9 (M+H)⁺, Method B

A solution of 5-chloro-N-methyl-N-propyl-4-(trifluoromethyl)pyridin-3-amine (350 mg, 1.385 mmol) and piperidine-4-carbonitrile (229 mg, 2.078 mmol) in toluene (8 mL) was degassed with nitrogen for 5 min. Cs₂CO₃ (903 mg, 2.77 mmol), BINAP (173 mg, 0.277 mmol), and Pd(OAc)₂ (31.1 mg, 0.139 mmol) were added. The reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated, and the crude product was purified by flash column chromatography to afford 1-(5-(methyl(propyl)amino)-4-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile (270 mg, 0.780 mmol, 56%) (Intermediate 31) as a pale yellow gum.

The analytical data for Intermediate 31 is in Table 1.

Procedure for the preparation of bromides as exemplified with the preparation of 1-bromo-3-propoxy-2-(trifluoromethyl)benzene (Intermediate 36)

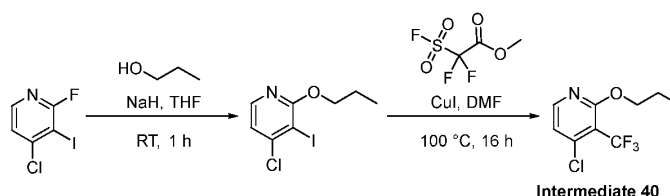


To a stirred solution of 3-bromo-2-(trifluoromethyl)phenol (500 mg, 2.075 mmol) in DMF (10 mL) were added 1-iodopropane (423 mg, 2.490 mmol) and K₂CO₃ (430 mg, 3.11 mmol). The reaction

was heated at 80 °C for 16 h. The reaction was diluted with water (20 mL) and extracted with 20% EtOAc in PET ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and evaporated. The crude product was purified by flash column chromatography to afford 1-bromo-3-propoxy-2-(trifluoromethyl)benzene (380 mg, 1.342 mmol, 65%) (Intermediate 36) as a colourless liquid.

The analytical data for Intermediate 36 is in Table 1.

Procedure for the preparation of chlorides as exemplified with the preparation of 4-chloro-2-propoxy-3-(trifluoromethyl) pyridine (Intermediate 40)



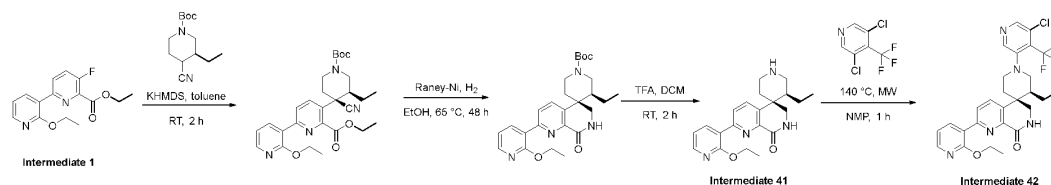
To a stirred suspension of NaH (222 mg, 5.55 mmol) in THF (2 mL) at 0 °C was added propan-1-ol (364 mg, 6.06 mmol) in THF (1 mL) and the reaction mixture was stirred at RT for 30 min. 4-chloro-2-fluoro-3-iodopyridine (1.3 g, 5.05 mmol) in THF (3 mL) was added to the reaction at 0 °C and the reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched cautiously with water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulfate and purified by flash column chromatography using EtOAc in PET ether (0 to 10%) to afford 4-chloro-3-iodo-2-propoxypyridine (1.49 g, 5.01 mmol, 99%) as a yellow gum.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 5.6 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 2H), 1.77 – 1.71 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H).

To a stirred solution of 4-chloro-3-iodo-2-propoxypyridine (750 mg, 2.52 mmol) in DMF (8 mL) at RT were added copper(I) iodide (720 mg, 3.78 mmol) and Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.48 mL, 3.78 mmol). The reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and purified by flash column chromatography to afford 4-chloro-2-propoxy-3-(trifluoromethyl)pyridine (625 mg, 2.294 mmol, 91%) (Intermediate 40) as a yellow liquid.

The analytical data for Intermediate 40 is in Table 1.

Procedure for the preparation of chlorides as exemplified with the preparation of *rac*-(3*S*,4*S*)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Intermediate 42)



- 5 To a stirred solution of ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (1.28 g, 4.41 mmol) (Intermediate 1) and tert-butyl 4-cyano-3-ethylpiperidine-1-carboxylate (700 mg, 2.94 mmol) in Toluene (5 mL) at RT under nitrogen atmosphere was added KHMDS (1M in THF) (3.52 mL, 3.52 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched cautiously with sat NH₄Cl (10 mL) and extracted with EtOAc (2 x 10 mL). Combined organic
- 10 extracts were dried over sodium sulfate and purified by flash column chromatography using EtOAc in PET ether (0 to 30%) to afford *rac*-ethyl 5-((3*S*,4*S*)-1-(tert-butoxycarbonyl)-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (2.2 g, 1.644 mmol, 56%) as a brown gum.

LCMS: 3.19 min, 509.0 (M+H)⁺, Method B

- 15 To a stirred solution of *rac*-ethyl 5-((3*S*,4*S*)-1-(tert-butoxycarbonyl)-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (2 g, 1.573 mmol) in EtOH (10 mL) and water (2 mL) at RT was added Raney nickel (1.38 g, 15.73 mmol). The reaction mixture was stirred at 65 °C for 24 h under 5 atm of hydrogen atmosphere. Another lot of Raney nickel (1.38 g, 15.73 mmol) was added, and the reaction was stirred at 65 °C for 24 h under 5 atm of hydrogen atmosphere. The
- 20 reaction mixture was filtered through celite and washed with 10% MeOH in DCM (200 mL). The filtrate was evaporated, and the crude product was purified by flash column chromatography using MeOH in DCM (0 to 20%) to afford *rac*-tert-butyl (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (650 mg, 1.393 mmol, 89%) as a pale brown gum.

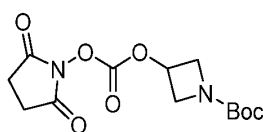
- 25 **LCMS:** 2.55 min, 467.1 (M+H)⁺, Method B

To a stirred solution of *rac-tert*-butyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (650 mg, 1.393 mmol) in DCM (10 mL) at 0 °C was added TFA (1.1 mL, 13.93 mmol). The reaction mixture was stirred at RT for 2 h, then quenched cautiously with 10% NaHCO₃ (10 mL) and extracted with 10% MeOH in DCM (3 x 10 mL). Combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, evaporated, and dried under a high vacuum to afford *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (500 mg, 1.364 mmol, 98%) (Intermediate 41) as a yellow solid.

To a stirred solution of *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (600 mg, 1.637 mmol) in NMP (3 mL) at RT was added 3,5-dichloro-4-(trifluoromethyl)pyridine (884 mg, 4.09 mmol). The reaction mixture was heated in the MW at 140 °C for 1 h. The reaction mixture was evaporated, and the crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 100%). The pure fractions were evaporated and dried under a high vacuum to afford 1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (310 mg, 0.568 mmol, 35) as a yellow solid. 30 mg of the sample was further purified by prep HPLC (Method B). The prep fractions were lyophilized. The residue was dissolved in DCM (10 mL), washed with 10% NaHCO₃ solution (3 mL), water (3 mL), dried over sodium sulfate, evaporated and lyophilized to afford *rac*-(3S,4S)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (8.8 mg) (Intermediate 42) as a white solid.

The analytical data for Intermediate 41 and 42 is in Table 1.

Procedure for the preparation of anhydrides as exemplified with the preparation of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (Intermediate 49)

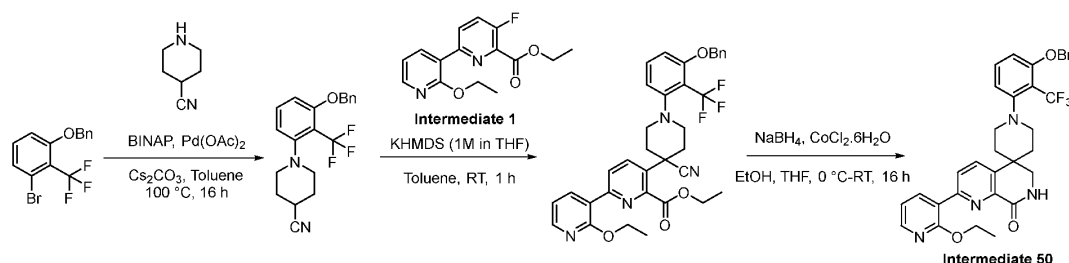


To a stirred solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (200 mg, 1.155 mmol) in acetonitrile (6 mL) were added TEA (0.472 mL, 3.46 mmol) followed by bis(2,5-dioxopyrrolidin-1-yl) carbonate (355 mg, 1.386 mmol) at rt and reaction mixture was stirred at rt for 4 h. The reaction mixture was concentrated under reduce pressure. The crude was diluted by EtOAc (30 mL) and

washed with 10% NaHCO₃ solution (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated and dried under high vacuum to afford tert-butyl 3-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate (300 mg, 0.955 mmol, 83%) (Intermediate 49) as a gum.

- 5 The analytical data for Intermediate 49 is in Table 1.

Procedure for the preparation of amides as exemplified with the preparation of 1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Intermediate 50)



- 10 A solution of 1-(benzyloxy)-3-bromo-2-(trifluoromethyl) benzene (537 mg, 1.622 mmol) and piperidine-4-carbonitrile (214 mg, 1.946 mmol) in toluene (10 mL) was degassed with nitrogen for 5 min. Cs₂CO₃ (1.06 g, 3.24 mmol), BINAP (202 mg, 0.324 mmol), and Pd(OAc)₂ (37 mg, 0.162 mmol) were added, and the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated, and the crude product was purified by flash column chromatography using
- 15 EtOAc in PET ether (0 to 40%) to afford 1-(3-(benzyloxy)-2-(trifluoromethyl) phenyl) piperidine-4-carbonitrile (483 mg, 1.315 mmol, 81%) as a pale yellow gum.

LCMS: 2.85 min, 361.1 (M+H)⁺, Method B

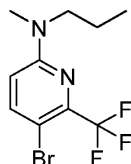
- To a stirred solution of ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (322 mg, 1.109 mmol) and 1-(3-(benzyloxy)-2-(trifluoromethyl) phenyl) piperidine-4-carbonitrile (480 mg, 1.331 mmol) in toluene (5 mL) at RT was added KHMDS (1M in THF) (1.22 mL, 1.220 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with sat NH₄Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 10%) to afford ethyl 5-(1-(3-(benzyloxy)-2-
- 25 (trifluoromethyl) phenyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (236 mg, 0.374 mmol, 34%) as a pale-yellow gum.

LCMS: 3.39 min, 631.2 (M+H)⁺, Method B

To a stirred solution of ethyl 5-(1-(3-(benzyloxy)-2-(trifluoromethyl) phenyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (150 mg, 0.238 mmol) in EtOH (6 mL) and THF (1.50 mL) at RT was added cobalt (II) chloride hexahydrate (566 mg, 2.378 mmol). NaBH₄ (135 mg, 3.57 mmol) was added at 0 °C, and the reaction mixture was stirred at RT for 16 h. The reaction mixture was filtered through celite and washed with 20% MeOH in DCM (2 x 20 mL). The filtrate was evaporated, and the crude product was purified by flash column chromatography using MeOH/DCM (0 to 10%) to afford 38 mg of the product. 18 mg of the compound was further purified by prep-HPLC. The fractions were lyophilized. The residue was dissolved in DCM (5 mL), washed with 10% NaHCO₃ solution (3 mL) and dried over sodium sulfate, evaporated, and lyophilized to afford 1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (4.51 mg, 7.64 μmol, 3%) (intermediate 50) as a white solid.

The analytical data for Intermediate 50 is in Table 1.

15 Procedure for the preparation of bromides as exemplified with the preparation of 5-bromo-*N*-methyl-*N*-propyl-6-(trifluoromethyl)pyridin-2-amine (Intermediate 53)



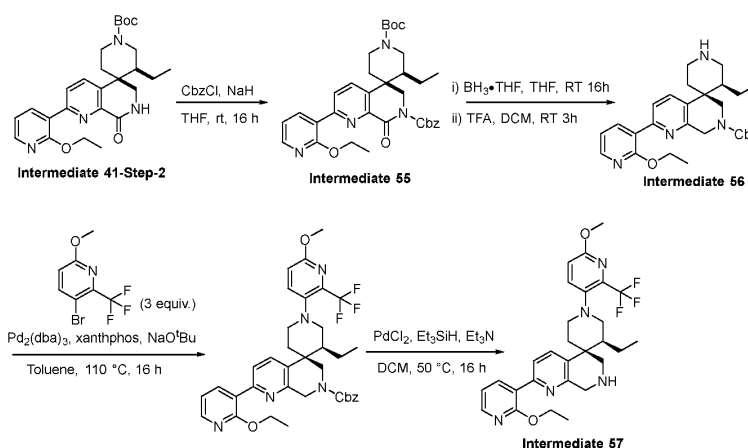
To a stirred solution of 2-chloro-6-(trifluoromethyl)pyridine (2.5 g, 13.77 mmol) in DMSO (15 mL) were added *N*-methylpropan-1-amine (1.511 g, 20.66 mmol) followed by K₂CO₃ (3.81 g, 27.5 mmol) and the reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). Combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford *N*-methyl-*N*-propyl-6-(trifluoromethyl)pyridin-2-amine (2.5 g, 11.46 mmol, 83%) which was used for next step without further purification.

25 LCMS: 2.89 min, 219.2 (M+H)⁺, Method B

To a stirred solution of *N*-methyl-*N*-propyl-6-(trifluoromethyl)pyridin-2-amine (6 g, 27.5 mmol) in MeOH (50 mL) was added NBS (4.40 g, 24.75 mmol) at 0 °C and reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with pet ether (2 x 10 mL), dried over sodium sulfate and concentrated to get crude product. The crude was
 5 purified by flash column chromatography to afford 5-bromo-*N*-methyl-*N*-propyl-6-(trifluoromethyl)pyridin-2-amine (5.5 g, 18.51 mmol, 67%) (Intermediate 53) as a colourless liquid.

The analytical data for Intermediate 53 is in Table 1.

Procedure for the preparation of amines as exemplified with the preparation of 2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 57)
 10



To stirred solution of tert-butyl *rac*-(3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (1.2 g, 2.57 mmol) (see Intermediate 41 synthesis-Step 2) in THF (8 mL) was added NaH (0.206 g, 5.14 mmol) at 0 °C and reaction
 15 was stirred at 0 °C for 20 min followed by 50% Cbz-Cl in toluene (0.439 g, 2.57 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated to get the crude purified by flash column chromatography to afford *rac*-7'-benzyl 1-(tert-butyl) (3*S*,4*S*)-2'-(2-ethoxypyridin-
 20 3-yl)-3-ethyl-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (1.3 g, 2.164 mmol, 84%) (Intermediate 55) as a off white solid.

To a stirred solution of *rac*-7'-benzyl 1-(tert-butyl) (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (1.3 g, 2.164 mmol) in THF (10 mL) was added BH₃.THF (8.66 mL, 8.66 mmol) at 0 °C and the reaction mixture was stirred at rt for 16 h. The mixture was quenched with MeOH (40 mL) and concentrated under reduced pressure to afford crude, which was purified by flash column chromatography in 0 to 50% EtOAc in PET ether to afford *rac*-7'-benzyl 1-(tert-butyl) (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (750 mg, 1.278 mmol, 59%) as an off white solid.

LCMS: 3.41 min, 587.5 (M+H)⁺, Method B

To a stirred solution of *rac*-7'-benzyl 1-(tert-butyl) (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (600 mg, 1.023 mmol) in DCM (10 mL) at 0 °C was added TFA (0.079 mL, 1.023 mmol) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated under reduced pressure, and crude was neutralized with 10% NaHCO₃ solution (50 mL x 1) and extracted with DCM (30 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate and concentrated to get crude *rac*-benzyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (300 mg, 0.617 mmol, 60%) (Intermediate 56) as a brown solid.

A degassed solution (purged with nitrogen gas for 10 min) of *rac*-benzyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (220 mg, 0.452 mmol) and 3-bromo-6-methoxy-2-(trifluoromethyl)pyridine (347 mg, 1.356 mmol) in toluene (3 mL) were added sodium tert-butoxide (130 mg, 1.356 mmol), Xanthphos (26.2 mg, 0.045 mmol) followed by Pd₂(dba)₃ (83 mg, 0.090 mmol) and the reaction mixture was heated at 110 °C for 16 h. The reaction mixture was filtered through a celite bed, and bed was washed with EtOAc. The combined filtrate was concentrated and purified by flash column chromatography using 0 to 20% EtOAc in PET ether to afford *rac*-benzyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (160 mg, 0.242 mmol, 54%) as an off white solid.

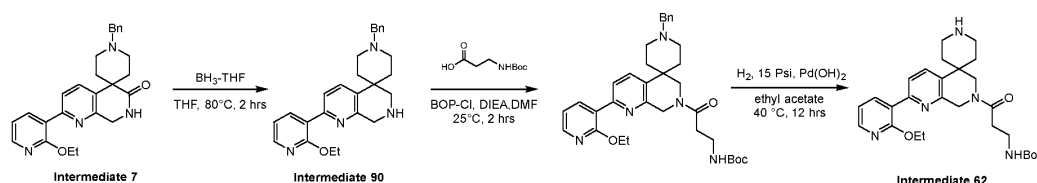
LCMS: 8.09 min, 662.3 (M+H)⁺, Method B

To a stirred solution of *rac*-benzyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (30 mg, 0.045 mmol) in DCM (9 mL) was added Et₃SiH (0.029 mL, 0.181 mmol), Et₃N (0.00338 mL,

0.024 mmol) followed by PdCl₂ (4.82 mg, 0.045 mmol) and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was filtered through celite, and the celite washed with 10% MeOH in DCM (50 mL). The combined filtrate was concentrated to get crude purified by prep-HPLC. The pure fractions were concentrated, and the residue was neutralized with 10% NaHCO₃ solution (20 mL) and extracted with (30 mL). The organic layer was washed with water (20 mL), dried over anhydrous sodium sulfate and lyophilized to afford *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (2.83 mg, 5.36 μmol, 12%) (Intermediate 57) as an off white solid.

The analytical data for Intermediate 55, 56 and 57 is in Table 1.

10 Procedure for the preparation of amines as exemplified with the preparation of tert-butyl (3-(2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (Intermediate 62 and 90)



To a solution of 1-benzyl-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (Intermediate 7) (150 mg, 350.04 μmol) in THF (4 mL) was added BH₃.THF (1 M, 1.75 mL) at 0 °C. The reaction mixture was heated to 80 °C and stirred at 80 °C for 2 h. Four additional vials were set up as described above. After cooling to RT, all five reaction mixture were quenched by addition MeOH (4 mL) at 0 °C and the mixture was refluxed at 80 °C for 2 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-TLC (EtOAc, R_f = 0) to obtain 1-benzyl-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (480 mg, 66%) (intermediate 90) as yellow oil.

The analytical data for Intermediate 90 is in Table 1.

25 To a solution of 3-((tert-butoxycarbonyl)amino)propanoic acid (36.51 mg, 192.98 μmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (**98.25 mg, 385.97 μmol**) in DMF (1 mL) was added N-ethyl-N-isopropylpropan-2-amine (74.83 mg, 578.95 μmol, 100.84 uL) and 1-benzyl-2'-(2-

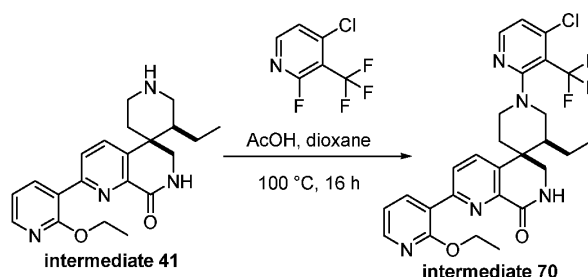
ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (80 mg, 192.98 μ mol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. Four additional vials were set up as described above. All five reaction mixtures were diluted with water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give residue, which was purified by flash column chromatography (eluted with PET ether/EtOAc=1/0 to 0/1 to EtOAc/MeOH=10/1, R_f = 0.3) to obtain tert-butyl (3-(1-benzyl-2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (530 mg, 94%) as yellow oil.

LCMS: 0.44 min, 586.4 [M+H]⁺, Method O'

A mixture of tert-butyl (3-(1-benzyl-2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (520 mg, 887.77 μ mol) and Pd(OH)₂ (520 mg, 3.7 mmol) in EtOAc (10 mL) was degassed and purged with H₂ (15 Psi) for 3 times at 25 °C. The reaction mixture was heated to 40 °C and stirred at 40 °C for 12 hrs under H₂ (15 Psi). After cooling to RT, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give tert-butyl (3-(2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (450 mg) (Intermediate 64) as yellow oil, which was used for next step without purification.

The analytical data for Intermediate 62 is in Table 1.

20 Procedure for the preparation of 4-chloro-2-fluoro-3-(trifluoromethyl)pyridine (Intermediate 70)

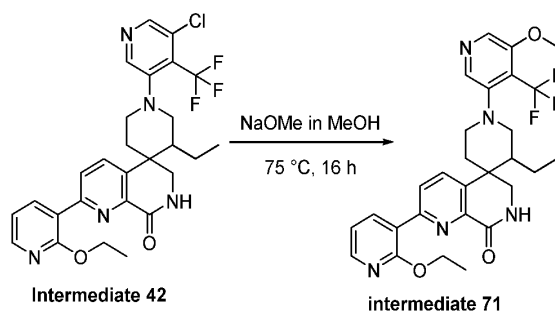


To a stirred solution of 2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8'-one (150 mg, 0.409 mmol) (Intermediate 41) in 1,4 dioxane (2 mL) at RT were added 4-chloro-2-fluoro-3-(trifluoromethyl)pyridine (98 mg, 0.491 mmol) followed by AcOH (50 mg, 0.819 mmol) and reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 $\times$ 10 mL). The combined organic

layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, evaporated and purified by flash column chromatography using MeOH in DCM (0 to 10%) to afford 1-(4-chloro-3-(trifluoromethyl)naphthyl-2-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8'-one (70 mg). 20 mg of the crude product was further purified by Prep HPLC (Method B). The prep fractions were lyophilized. The residue was dissolved in DCM (10 mL), washed with 10% NaHCO₃ solution (3 mL), water (5 mL), dried over sodium sulfate, evaporated and lyophilized to afford 1-(4-chloro-3-(trifluoromethyl)naphthyl-2-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8'-one (3.90 mg, 7.14 μmol, 2%) (Intermediate 70) as a white solid.

10 The analytical data for 70 is in Table 1.

Procedure for the preparation of rac-(3S,4S)-"-(2-ethoxypyridin-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethylnaphthyrn-3-yl)-", "-dihydro-"H-spiro[piperidine-4,"-[1,7naphthyridinen]-"-one (Intermediate 71)

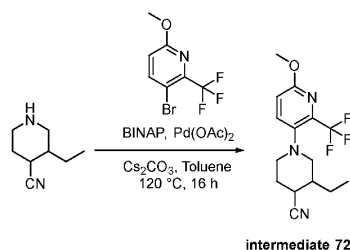


15 To a stirred solution of *rac*-(3S,4S)-1-(5-chloro-4-(trifluoromethylnaphthyrn-3-yl)-2-ethoxypyridin-3-yl)-3-ethyl-2,2'-dihydro-8'H-spiro[piperidine-4,5'-[1,7naphthyridinen]-8'-one (200 mg, 0.366 mmol) (Intermediate 42) in MeOH (5 mL) was added NaOMe (5 mL, 4.50 mmol) and reaction mixture was stirred at 75 °C for 16 h. The reaction mixture was evaporated and crude product was purified by flash column chromatography using MeOH in DCM (0 to 10%) to afford

20 *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (180 mg, 0.366 mmol, 54%) (Intermediate 71) as a white solid.

The analytical data for Intermediate 71 is in Table 1.

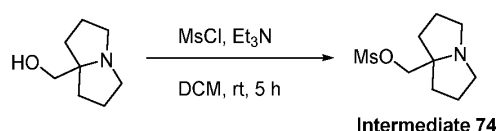
Procedure for the preparation of 3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile (Intermediate 72)



The solution of *rac*-3-ethylpiperidine-4-carbonitrile (0.540 g, 3.91 mmol) in toluene (10 mL) was
 5 purged under nitrogen for 10 min and were added BINAP (0.122 g, 0.195 mmol), Pd(OAc)₂ (0.088
 g, 0.391 mmol), 3-bromo-6-methoxy-2-(trifluoromethyl)pyridine (1.0 g, 3.91 mmol) followed by
 Cs₂CO₃ (2.55 g, 7.81 mmol) and reaction mixture was stirred at 120 °C for 16 h. Reaction mixture
 was diluted with water (40 mL) and extracted with EtOAc (20 mL × 2). The combined organic layer
 10 was washed with brine (20 mL), dried over anhydrous sodium sulphate and purified by flash
 column chromatography using EtOAc in PET-ether (0 to 30%) to afford *rac*-3-ethyl-1-(6-methoxy-
 2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile (900 mg, 2.124 mmol, 54%) (Intermediate
 72) as a colourless liquid.

The analytical data for Intermediate 72 is in Table 1.

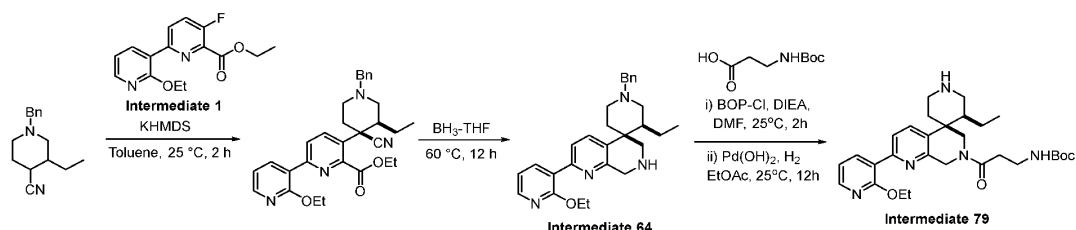
Procedure for the preparation of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl methanesulfonate (intermediate 74)



To a stirred solution of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)MeOH (500 mg, 3.54 mmol) in DCM (5
 mL) was added TEA (537 mg, 5.31 mmol) followed by MsCl (527 mg, 4.60 mmol) and reaction
 mixture was stirred at RT for 5 h. Reaction mixture was diluted with DCM (50 mL) and washed
 20 with 10% NaHCO₃ (20 mL) followed by water (20 mL). The organic layer was dried over anhydrous
 sodium sulfate and evaporated under reduced pressure to afford crude tetrahydro-1H-pyrrolizin-
 7a(5H)-yl)methyl methanesulfonate (270 mg) (Intermediate 74) as yellow gum which was used
 for next step without further purification.

The analytical data for Intermediate 74 is in Table 1.

Procedure for the preparation of *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 79)



- 5 To a solution of 1-benzyl-3-ethylpiperidine-4-carbonitrile (1 g, 4.38 mmol) and ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (1.15 g, 4.38 mmol) (Intermediate 1) in toluene (20 mL) was added KHMDS (1 M, 13.14 mL) at RT and reaction mixture was stirred at RT for 2 h under N₂ atmosphere. Six vials were set up as described above. All seven reaction mixtures were quenched with saturated solution of ammonium chloride (300 mL) at 0 °C and adjusted pH around
- 10 5 with formic acid, then extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulphate and purified by flash column chromatography (PET ether/EtOAc= 7:3) to afford *rac*-ethyl 5-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (3 g, 22%) as a yellow oil.

- ¹H NMR (400 MHz, CDCl₃) δ 8.33 (dd, *J* = 1.9, 7.5 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 8.12 (dd, *J* = 1.9, 4.8 Hz, 1H), 7.92 - 7.79 (m, 1H), 7.27 - 7.25 (m, 3H), 7.25 - 7.16 (m, 2H), 6.94 (dd, *J* = 4.9, 7.5 Hz, 1H), 4.51 - 4.39 (m, 4H), 3.64 - 3.56 (m, 1H), 3.52 - 3.44 (m, 1H), 3.14 - 3.05 (m, 1H), 2.84 (br d, *J* = 12.0 Hz, 1H), 2.45 - 2.26 (m, 3H), 2.21 - 2.14 (m, 1H), 1.62 - 1.41 (m, 1H), 1.37 (dt, *J* = 1.6, 7.1 Hz, 6H), 1.29 - 1.17 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H)

- To a solution of *rac*-ethyl 5-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (200 mg, 401.11 μmol) in THF (2 mL) was added BH₃·THF (1 M, 2.01 mL) at 0 °C under N₂ atmosphere and reaction mixture was stirred at 60 °C for 12 h. Fourteen vials were set up as described above. After cooling to RT, fifteen reaction mixtures were quenched by addition MeOH (40 mL) at 0 °C and the reaction mixture was refluxed at 80 °C for 12 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure to give
- 25 a residue, which was purified by flash column chromatography (EtOAc:MeOH (9:1)) to obtain *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (650 mg, 24%) (Intermediate 64) as yellow oil.

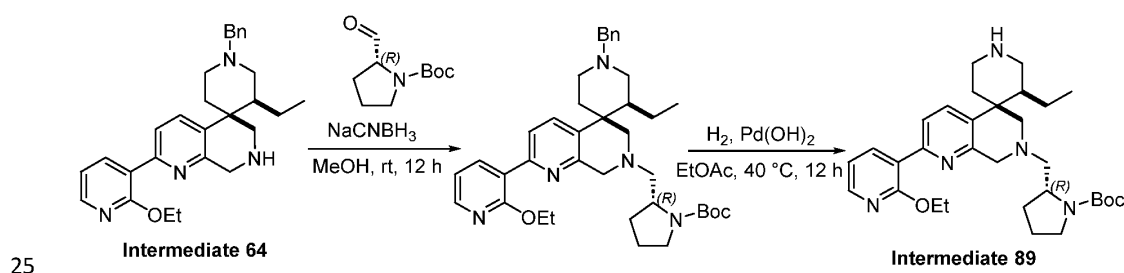
To a solution of 3-((tert-butoxycarbonyl)amino)propanoic acid (42.75 mg, 225.94 μ mol) in DMF (2 mL) was added DIPEA (87.60 mg, 677.82 μ mol, 118.06 μ L) and bis(2-oxooxazolidin-3-yl)phosphinic chloride (115.04 mg, 451.88 μ mol) and stirred at 25 °C for 10 min, the reaction mixture was added *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (100 mg, 225.94 μ mol) (Intermediate 64) and stirred at 25 °C for 2 h. Five additional vials were set up as described above. All six reaction mixtures were quenched with water (30 mL) and extracted with EtOAc (3 $\times$ 15 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulphate and purified by prep-TLC (EtOAc/MeOH= 9/1, R_f = 0.60) to get *rac*-tert-butyl (3-((3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (500 mg, 60%) as a yellow solid.

LCMS: 0.75 min, 614.6 [M+H]⁺, Method O

To a solution of Pd(OH)₂ (290.00 mg, 2.07 mmol) in EtOAc (50 mL) was added *rac*-tert-butyl (3-((3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (290 mg, 472.48 μ mol). After purging with hydrogen for three times, the reaction mixture was stirred at 25 °C for 12 h under hydrogen atmosphere (15 Psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to get *rac*-tert-butyl (3-((3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropyl)carbamate (220 mg, crude) (Intermediate 79) as a grey solid, which was used for next step without further purification.

The analytical data for Intermediate 64 and intermediate 79 is in Table 1

Procedure for the preparation of tert-butyl (*R*)-2-(((3*RS*,4*RS*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (intermediate 89)



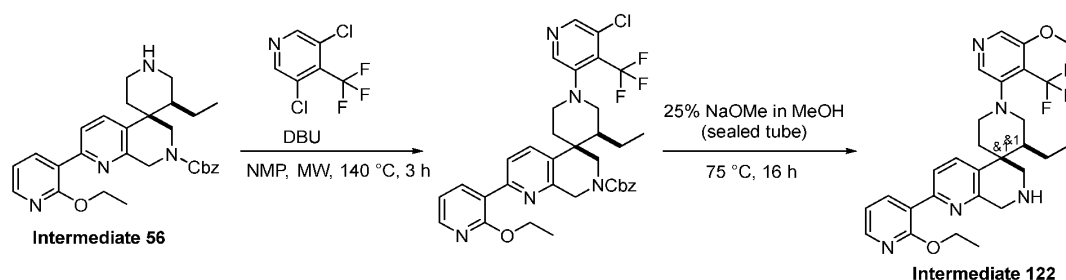
A solution of (3*S*,4*S*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (intermediate 64) (300 mg, 677.82 μ mol) and tert-butyl (*R*)-2-formylpyrrolidine-1-carboxylate (202.58 mg, 1.02 mmol) in MeOH (8 mL) was stirred at RT for 30 mins and NaCNBH₃ (170.38 mg, 2.71 mmol) was added at RT and stirred for 12 h. Nine additional
 5 vials were set up as described above. All ten reaction mixtures were filtered, and the filtrate was concentrated under reduced pressure and purified by flash column chromatography (PET ether/EtOAc= 1/0 to 3/1, *R_f* = 0.40) to get tert-butyl (*R*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (1.8 g, 42%) as a white solid.

10 **LCMS:** 1.57 min, 626.3 [M-H]⁺, Method R'

To a solution of Pd(OH)₂ (1.80 g, 2.56 mmol, 20% purity) in EtOAc (180 mL) was added tert-butyl (*R*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (1.8 g, 2.88 mmol) at RT. After purging with hydrogen (15 Psi) for three times, the reaction mixture was heated to 40 °C and
 15 stirred at 40 °C for 12 h under hydrogen gas pressure (15 Psi). After cooling to RT, the reaction mixture was filtered, concentrated under reduced pressure and purified by prep-TLC (EtOAc/MeOH= 1/1, *R_f* = 0.11) to get tert-butyl (*R*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (1.2 g, 78%) (intermediate 89) as a white solid.

20 The analytical data for Intermediate 89 is in Table 1.

Procedure for the preparation of *rac*-(3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 122)



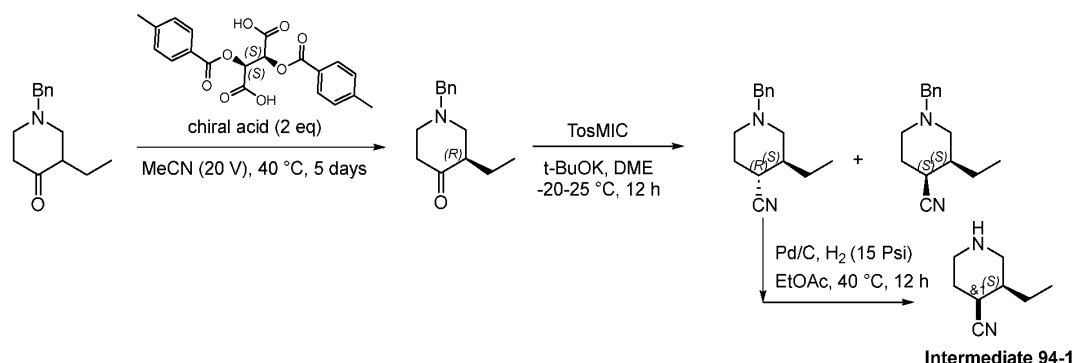
In 10 ml Microwave vial, under nitrogen atmosphere, *rac*-benzyl (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (600 mg, 1.23 mmol) (Intermediate 56) and 3,5-dichloro-4-(trifluoromethyl)pyridine (666 mg, 3.08 mmol) in NMP (5 mL) was added DBU (563 mg, 3.70 mmol) and reaction mixture was heated to 140 °C under microwave for 3 h. Reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, concentrated and purified by flash column chromatography using 10-20% of EtOAc in PET ether to afford *rac*-benzyl (3*S*,4*S*)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (360 mg, 0.495 mmol, 40%) as a light yellow solid.

LCMS: 2.86 min, 666.2 [M+H]⁺, Method G

In 50 ml seal tube, under nitrogen atmosphere, *rac*-benzyl (3*S*,4*S*)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (340 mg, 0.510 mmol) in MeOH (10 mL) was added NaOMe (25% in MeOH) (10 mL, 0.510 mmol) under N₂ at RT. The reaction mixture was stirred at 75 °C for 16 h. The reaction mixture was evaporated to dryness. The crude product was dissolved in water (30 mL), washed with DCM (2 x 25 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulphate and evaporated to get crude (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (300 mg, 0.081 mmol, 16%) (Intermediate 122) as a light yellow gum which was used for next step without further purification.

The analytical data for Intermediate 122 is in Table 1.

Procedure for the preparation of (3*S*,4*R*)-3-ethylpiperidine-4-carbonitrile (intermediate 94-1)



A mixture of 1-benzyl-3-ethylpiperidin-4-one (20 g, 92.04 mmol) and (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid (36.63 g, 94.80 mmol) in ACN (400 mL) was degassed and purged with nitrogen for 3 times. The reaction mixture was stirred at 40 °C for 5 days under nitrogen atmosphere. After cooling to RT, the reaction mixture was filtered, and the filter cake was dried under reduced pressure to give a residue. A 50 mg sample of the material was crystallised and X-Ray analysis performed. The absolute R configuration of (R)-1-benzyl-3-ethylpiperidin-4-one was confirmed. Details can be found after intermediate Table 1

The resulting residue was diluted with water (200 mL). The reaction mixture was adjusted to pH 10 with NH₄OH (30% in water) at 0 °C and extracted with EtOAc (200 mL × 3). The combined organics was washed with brine (300 mL), dried over anhydrous sodium sulphate, filtered, and concentrated to give (R)-1-benzyl-3-ethylpiperidin-4-one (16.5 g) as yellow oil.

SFC Method: R_t=1.347 min, 12.71% purity, R_t=1.523 min, 87.29% purity; Column Name: Chiralpak AD-3, 150×4.6mm I.D., 3μm,; Co-Solvent: 10%; Co-Solvent Name: 0.1% Isopropamide in MeOH; Injected Volume: 3.5 μL; Run time: 5 min. A mixture of (R)-1-benzyl-3-ethylpiperidin-4-one (6.5 g, 29.91 mmol) and 1-(isocyanomethylsulfonyl)-4-methyl-benzene (7.59 g, 38.89 mmol) in glycol dimethyl ether (130 mL) was added KOtBu (8.39 g, 74.78 mmol) at -20 °C under nitrogen. The reaction mixture was stirred at 25 °C for 12 h, then quenched by addition water (50 mL) at 0 °C, and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulphate and purified by flash column chromatography (PET ether/EtOAc = 9/1, R_f = 0.29 and R_f = 0.41) to get (3S,4R)-1-benzyl-3-ethylpiperidine-4-carbonitrile (2.3 g, 34%) as yellow oil and (3S,4S)-1-benzyl-3-ethylpiperidine-4-carbonitrile (3.8 g, 56%) as yellow solid.

(3S,4R)-1-benzyl-3-ethylpiperidine-4-carbonitrile:

¹H NMR (400 MHz, CDCl₃) δ 7.27 (br s, 5H), 3.53 - 3.44 (m, 1H), 3.41 - 3.31 (m, 1H), 2.89 (br d, *J* = 9.4 Hz, 1H), 2.76 (br d, *J* = 10.5 Hz, 1H), 2.10 (dt, *J* = 3.6, 10.2 Hz, 1H), 1.99 - 1.76 (m, 3H), 1.74 - 1.57 (m, 3H), 1.32 - 1.15 (m, 1H), 0.90 - 0.78 (m, 3H)

SFC Method: R_t= 1.312 min, 12.48% purity, R_t=1.426 min, 87.52% purity; Column Name: Chiralpak AD-3, 150×4.6mm I.D., 3µm, Co-Solvent: 10%; Co-Solvent Name: 0.1% isopropamide in MeOH; Injected Volume: 1.5 µL; Run time: 5 min

(3S,4S)-1-benzyl-3-ethylpiperidine-4-carbonitrile:

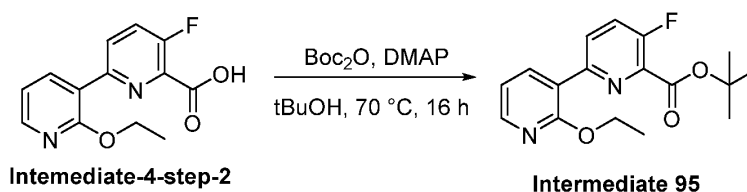
¹H NMR (400 MHz, CDCl₃) δ 7.26 - 7.15 (m, 5H), 3.58 - 3.33 (m, 2H), 2.88 (br d, *J* = 2.6 Hz, 1H), 2.79 - 2.56 (m, 2H), 2.22 (br t, *J* = 10.8 Hz, 1H), 1.96 (br t, *J* = 9.9 Hz, 1H), 1.91 - 1.83 (m, 1H), 1.82 - 1.71 (m, 1H), 1.64 (br s, 1H), 1.45 - 1.29 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H)

SFC Method: R_t = 1.600 min, 15.65% purity, R_t=1.802 min, 84.35% purity; Column Name: Chiralcel OD-3,150×4.6mm I.D., 3um, Co-Solvent: 10%; Co-Solvent Name: isopropanol [0.2% ammonia gas (7M in MeOH)]; Injected Volume: 5.5 µL; Run time: 5 min.

A mixture of (3S,4R)-1-benzyl-3-ethylpiperidine-4-carbonitrile (2.3 g, 10.07 mmol) and Pd/C (7.5 g, 10% purity) in EtOAc (200 mL) was degassed and purged with hydrogen for 3 times. The reaction mixture was stirred at 40 °C for 12 h under hydrogen atmosphere (15 Psi). After cooling to RT, the reaction mixture was filtered and filtrate concentrated under reduced pressure to get (3S,4R)-3-ethylpiperidine-4-carbonitrile (800 mg) as yellow oil.

The analytical data for Intermediate 94-1 is in Table 1.

20 **Procedure for the preparation of tert-butyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-**
carboxylate (intermediate 95)

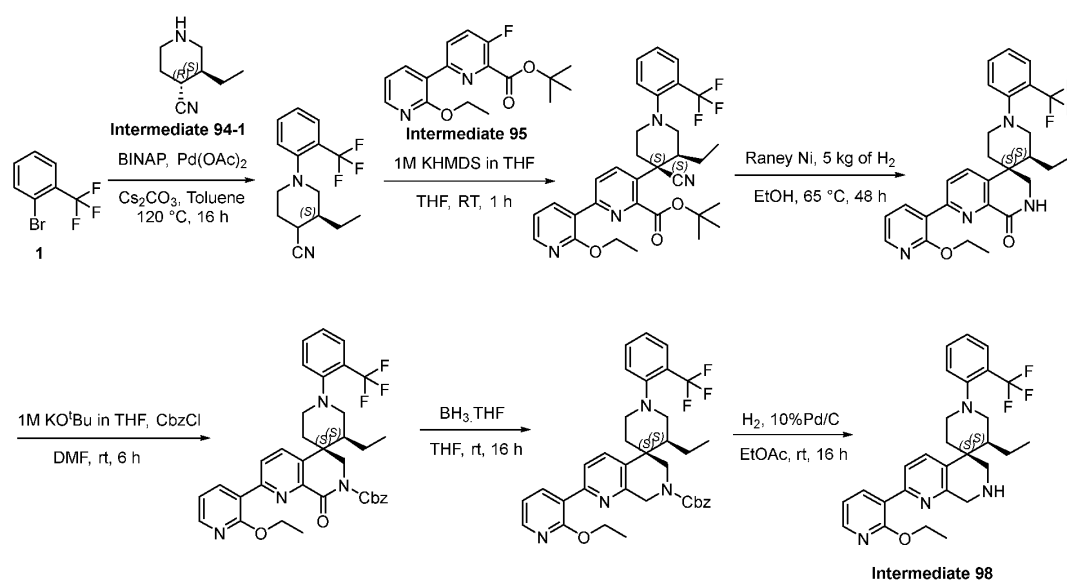


To a stirred solution of 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylic acid (14.5 g, 55.3 mmol) in t-BuOH (200 mL) were added Boc-anhydride (30.2 g, 138 mmol) followed by DMAP (0.676 g, 5.53 mmol) at RT and reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was

basified with 10% NaHCO_3 followed by water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was, dried over anhydrous sodium sulphate and purified by flash column chromatography using EtOAc in PET ether (0 to 30%) to afford tert-butyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (14.5 g, 44.6 mmol, 81%) (intermediate 95) as a pale-yellow solid.

The analytical data for Intermediate 95 is in Table 1.

Procedure for the preparation of (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (intermediate 98)



A solution of (3S, 4R)-3-ethylpiperidine-4-carbonitrile (intermediate 98-1) (300 mg, 2.171 mmol) and 1-bromo-2-(trifluoromethyl)benzene (1465 mg, 6.51 mmol) in toluene (20 mL) was degassed with nitrogen for 5 min and BINAP (135 mg, 0.217 mmol), Cs_2CO_3 (1414 mg, 4.34 mmol) followed by $\text{Pd}(\text{OAc})_2$ (48.7 mg, 0.217 mmol) were added. The reaction mixture was heated at 120 °C for 16 h. The reaction mixture filtered through celite bed, filtrate was evaporated, and crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 20%) to afford (3S)-3-ethyl-1-(2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (400 mg, 1.417 mmol, 65%) as a yellow liquid.

LCMS: 2.28 min, 283.1 $[\text{M}+\text{H}]^+$, Method W

To a stirred solution of KHMDS (1.612 mL, 1.612 mmol) in THF (20 mL) were added a mixture of (3S)-3-ethyl-1-(2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (350 mg, 1.240 mmol) and tert-butyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (474 mg, 1.488 mmol) (Intermediate 99) in THF (20 mL) at RT and reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with saturated NH₄Cl (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and purified by flash column chromatography using EtOAc in PET ether (0 to 90%) to afford tert-butyl 5-((3S,4S)-4-cyano-3-ethyl-1-(2-(trifluoromethyl)phenyl)piperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (580 mg, 0.861 mmol, 79%) as a yellow gum.

10 **LCMS:** 2.84 min, 581.3 [M+H]⁺, Method W

To a solution of tert-butyl 5-((3S,4S)-4-cyano-3-ethyl-1-(2-(trifluoromethyl)phenyl)piperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (580 mg, 0.999 mmol) in EtOH (20 mL) was added Raney Ni (876 mg, 9.99 mmol) and reaction mixture was stirred under 5 kg of hydrogen gas pressure at 65 °C for 48 h. Reaction mixture was filtered through celite bed and washed with 10% MeOH in DCM (100 mL). The filtrate was evaporated and purified by flash column chromatography using MeOH in DCM (0 to 4%) as an eluent. The pure fractions were evaporated and dried under high vacuum to afford (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (170 mg, 0.333 mmol, 33%) as a white solid.

20 **LCMS:** 2.31 min, 511.2 [M+H]⁺, Method W

To a stirred solution of (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (150 mg, 0.294 mmol) in THF (10 mL) was added KOtBu (0.588 mL, 0.588 mmol) at 0 °C and stirred at 0 °C for 15 min. Cbz-Cl (0.063 mL, 0.441 mmol) was added and reaction mixture was stirred at rt for 15 h. The reaction mixture was quenched with saturated NH₄Cl (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and purified by flash column chromatography using EtOAc in PET ether (0 to 50%) to afford get benzyl (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (100 mg, 0.155 mmol, 53%) as a yellow gum.

30 **LCMS:** 2.71 min, 645.2 [M+H]⁺, Method W

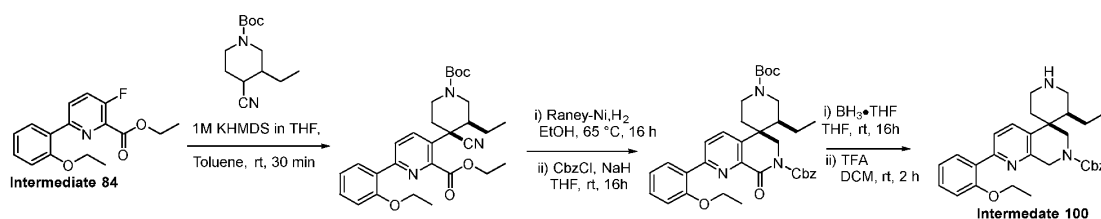
To a stirred solution of benzyl (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (100 mg, 0.155 mmol) in THF (5 mL) was added BH₃·THF (0.233 mL, 0.233 mmol) at 0°C and stirred at RT for 15 h. The reaction mixture was quenched with saturated NH₄Cl (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate and purified by flash column chromatography using EtOAc in PET ether (0 to 50%) as to afford get benzyl (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7] naphthyridine]-7'(8'H)-carboxylate (85 mg, 0.135 mmol, 87%) as a yellow gum.

LCMS: 2.91 min, 631.2 [M+H]⁺, Method W

To a solution of benzyl (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (60 mg, 0.095 mmol) in EtOAc (10 mL) was added 10% Pd-C (10.12 mg, 0.095 mmol) and the mixture was stirred under 5 kg of hydrogen gas pressure at 25 °C for 15 h. Reaction mixture was filtered through celite bed and washed with 10% MeOH in DCM (100 mL). The filtrate was evaporated, and purified by flash column chromatography using MeOH in DCM (0 to 4%) to afford (3*S*,4*S*)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 98) (45 mg, 0.091 mmol, 95%) as a white solid.

The analytical data for Intermediate 98 is in Table 1.

Procedure for the preparation of *rac*-benzyl (3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (Intermediate 100)



To a stirred solution of ethyl 6-(2-ethoxyphenyl)-3-fluoropicolinate (2.91 g, 10.07 mmol) (Intermediate 84) and tert-butyl 4-cyano-3-ethylpiperidine-1-carboxylate (2 g, 8.39 mmol) in toluene (40 mL) was added KHMDS (1.0 M in THF) (8.39 mL, 8.39 mmol) at RT and mixture was stirred at rt for 30 min. Reaction mixture was quenched with saturated NH₄Cl (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous sodium

sulfate and purified by flash column chromatography using 10-20% EtOAc in PET ether to afford cis-racemic ethyl 3-(1-(tert-butoxycarbonyl)-4-cyano-3-ethylpiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (2.5 g, 4.92 mmol, 59%) as yellow solid.

LCMS: 3.15 min, 508.2 [M+H]⁺, Method B

- 5 To a stirred solution of cis-racemic tert-butyl-4-cyano-4-(2-(ethoxycarbonyl)-4-(2-ethoxypyridin-3-yl)phenyl)-3-ethylpiperidine-1-carboxylate (2 g, 3.94 mmol) in EtOH (50 mL) and Water (5 mL) was added Raney Ni (4.88 g, 47.3 mmol) at RT and reaction mixture was stirred under 5 Kg of H₂ gas pressure at 65 °C for 16 h. Reaction mixture was filtered through celite bed and bed was washed with MeOH (20 mL). Filtrate was concentrated and purified by flash column chromatography in 0 to 10% MeOH in DCM to afford cis-racemic of tert-butyl-7-(2-ethoxypyridin-3-yl)-3'-ethyl-1-oxo-2,3-dihydro-1H-spiro[isoquinoline-4,4'-piperidine]-1'-carboxylate (1.3 g, 2.79 mmol, 71%) as a white solid.

LCMS: 2.55 min, 466.3 [M+H]⁺, Method B

- 15 To a stirred solution of tert-butyl-2'-(2-ethoxyphenyl)-3-ethyl-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (2 g, 4.30 mmol) in THF (3 mL) was added NaH (0.344 g, 8.59 mmol) at 0 °C and stirred at 0 °C for 30 min. Cbz-Cl (4.40 g, 12.89 mmol) was added and the mixture was stirred at RT for 16 h. Reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 2). Combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulphate and purified by flash column chromatography in 10-20 30% EtOAc in PET ether to afford 7'-benzyl 1-(tert-butyl)-2'-(2-ethoxyphenyl)-3-ethyl-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (2.1 g, 3.50 mmol, 82%) as gummy solid.

LCMS: 3.05 min, 600.3 [M+H]⁺, Method B

- 25 To a stirred solution of 7'-benzyl 1-(tert-butyl)-2'-(2-ethoxyphenyl)-3-ethyl-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (2 g, 3.33 mmol) in THF (20 mL) was added BH₃.THF (13.34 mL, 13.34 mmol) at 0 °C and mixture stirred at RT for 16 h. Reaction mixture was quenched with MeOH (10 mL) and concentrated under reduced pressure and purified by flash column chromatography using 0 to 50% EtOAc in PET-ether to afford 7'-benzyl 1-(tert-butyl)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (1.2 g, 2.049 mmol, 61%) as an off white solid.

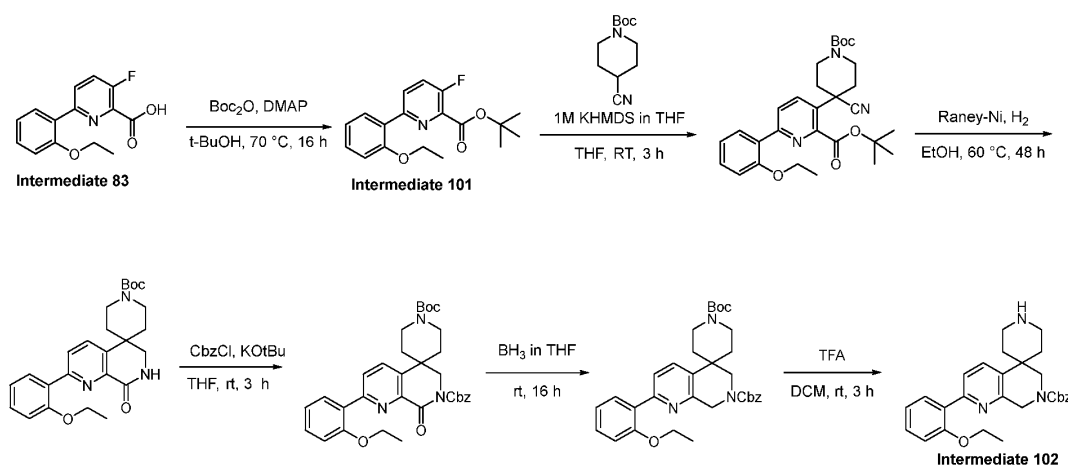
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LCMS: 3.28 min, 586.3 [M+H]⁺, Method B

To stirred solution of 7'-benzyl 1-(tert-butyl)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (1.2 g, 2.049 mmol) in DCM (10 mL) was added TFA (0.676 mL, 8.77 mmol) at 0 °C and reaction mixture was stirred at RT for 2 h. Reaction mixture was concentrated, was quench with 10% NaHCO₃ (20 mL) and extracted with DCM (30 mL x 2). Combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford *rac*-benzyl (3S,4S)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (900 mg, 1.853 mmol, 90%) (intermediate 100) as an off white solid.

The analytical data for intermediate 100 is in Table 1.

Procedure for the preparation of benzyl 2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (Intermediate 102)



To a stirred solution of 6-(2-ethoxyphenyl)-3-fluoropicolinic acid (6.5 g, 24.88 mmol) (Intermediate 83) in t-BuOH were added Boc-anhydride (14.44 mL, 62.2 mmol) followed by DMAP (0.304 g, 2.488 mmol) and reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was basified with 10% NaHCO₃ diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was, dried over anhydrous sodium sulphate, evaporated and purified by flash column chromatography using EtOAc in PET ether (0 to 30%) to afford tert-butyl 6-(2-ethoxyphenyl)-3-fluoropicolinate (6 g, 17.96 mmol, 72%) (intermediate 101) as a pale-yellow solid.

To the stirred solution of the KHMDS (16.39 mL, 16.39 mmol) were added mixture of tert-butyl 6-(2-ethoxyphenyl)-3-fluoropicolinate (4 g, 12.60 mmol) and tert-butyl 4-cyanopiperidine-1-carboxylate (2.65 g, 12.60 mmol) in THF (30 mL) at RT and stirred at RT for 3 h. The reaction mixture was quenched cautiously with sat. NH_4Cl at RT and extracted with EtOAc. The combined organic layer was washed with brine, dried over sodium sulphate and purified by flash column chromatography using EtOAc-PET ether (20 to 50%) to afford tert-butyl 3-(1-(tert-butoxycarbonyl)-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (5 g, 9.85 mmol, 52%) as an off white solid.

LCMS: 2.55 min, 508.3 $[\text{M}+\text{H}]^+$, Method G

To the stirred solution of the tert-butyl 3-(1-(tert-butoxycarbonyl)-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (7.5 g, 14.77 mmol) in EtOH:water (230:40 mL) was added Raney Ni (12.96 g, 148 mmol) and reaction mixture was stirred at 65 °C and under 6 kg of hydrogen gas pressure for 48 h. The reaction mixture was filtered through celite bed and bed was washed with 10% MeOH and DCM. Filtrate was concentrated under reduced pressure (bath temperature: 42 °C) to afford crude gum which was purified by flash column chromatography using 10% MeOH:DCM to obtain tert-butyl 2'-(2-ethoxyphenyl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (5.0 g, 10.74 mmol, 73%) as a white solid.

LCMS: 1.84 min, 438.2 $[\text{M}+\text{H}]^+$, Method G

To the stirred solution of the tert-butyl 2'-(2-ethoxyphenyl)-8'-oxo-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate (8 g, 18.28 mmol) in THF (30 mL) at 0 °C were added t-BuOK (4.10 g, 36.6 mmol) followed by benzyl chloroformate (7.77 g, 45.7 mmol) and reaction mixture was stirred at RT for 3 h. The reaction mixture was quenched cautiously with aq. NH_4Cl solution (100 mL) at 0 °C and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and purified by flash column chromatography using 15% EtOAc in PET ether to obtain 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxyphenyl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (8 g, 13.55 mmol, 74%) as a white solid.

LCMS: 2.37 min, 572.3 $[\text{M}+\text{H}]^+$, Method W

To a stirred solution of 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxyphenyl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (5 g, 8.75 mmol) in THF (25 mL) was added BH_3 in THF (30.6 mL, 30.6 mmol) at 0 °C and reaction mixture was stirred at RT for 16 h. The reaction

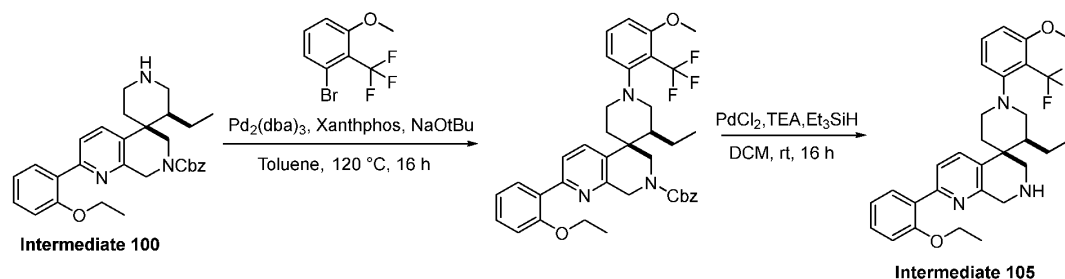
mixture was quenched cautiously with MeOH at 0 °C and evaporated to dryness and purified by flash column chromatography using EtOAc in PET ether (30%) to afford 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (4.2 g, 7.20 mmol, 82%) as an off white solid.

5 **LCMS:** 2.53 min, 558.3 [M+H]⁺, Method G

To the stirred solution of 7'-benzyl 1-(tert-butyl) 2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8'H)-dicarboxylate (6.6 g, 11.83 mmol) in DCM (15 mL) was added TFA (13.49 g, 118 mmol) and reaction mixture was stirred at RT for 16 h. The reaction mixture was concentrated, basified with 10% aq. NaHCO₃ (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate to afford benzyl 2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (4.2 g, 8.70 mmol, 74%) (intermediate 102) as a white solid.

The analytical data for intermediate 101 and 102 is in Table 1.

15 **Procedure for the preparation *rac*-(3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 105)**



To a degassed solution (purged with nitrogen gas for 10 min) of *rac*-benzyl (3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (500 mg, 1.03 mmol) (Intermediate 100) and 1-bromo-3-methoxy-2-(trifluoromethyl)benzene (787.7 mg, 3.09 mmol) in toluene (50 mL) were added NaOtBu (297 mg, 3.09 mmol), Xantphos (119 mg, 0.206 mmol) followed by Pd₂(dba)₃ (94 mg, 0.103 mmol) and reaction mixture was heated at 120 °C for 16 h. The reaction was filtered through celite bed and filtrate was washed with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, and purified by flash column chromatography in 30-35% of EtOAc in PET ether to afford

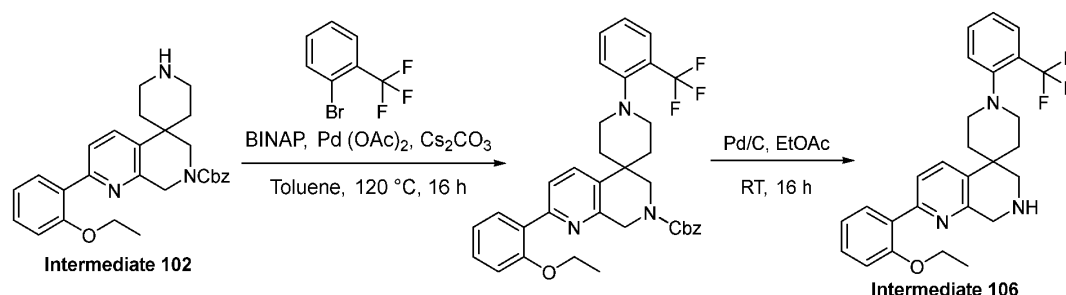
rac-benzyl (3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (220 mg, 0.333 mmol, 32%) as a white solid.

LCMS: 1.99 min, 660.3 [M+H]⁺, Method G.

- 5 To a stirred solution of *rac*-benzyl (3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (220 mg, 0.333 mmol) in DCM (10 mL) were added PdCl₂ (59.1 mg, 0.333 mmol), Et₃SiH (116 mg, 1.000 mmol) followed by Et₃N (67.5 mg, 0.667 mmol) and reaction mixture was stirred at RT for 16 h. The reaction was filtered through celite bed and filtrate was washed with water (10 mL) and
- 10 extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and purified by flash column chromatography using 10% MeOH in DCM to afford *rac*-(3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (60 mg, 0.116 mmol, 34%) (intermediate 105) as a white solid.

- 15 The analytical data for intermediate 105 is in Table 1.

Procedure for the preparation 2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 106)



- A solution of benzyl 2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (2.2 g, 3.94 mmol) and 1-bromo-2-(trifluoromethyl)benzene (1.331 g, 5.91 mmol) in
- 20 Toluene (20 mL) at RT was degassed under nitrogen atmosphere for 10 min. BINAP (491 mg, 0.789 mmol), Cs₂CO₃ (2.6 g, 7.89 mmol), followed by Pd(OAc)₂ (0.089 g, 0.394 mmol) were added and the reaction mixture was heated at 120 °C for 16 h. The reaction mixture was filtered through celite, washed with EtOAc (2 x 10 mL) and the filtrate was evaporated. The crude product was
- 25 purified by flash column chromatography using EtOAc in PET ether (0 - 20%) to afford benzyl 2'-(

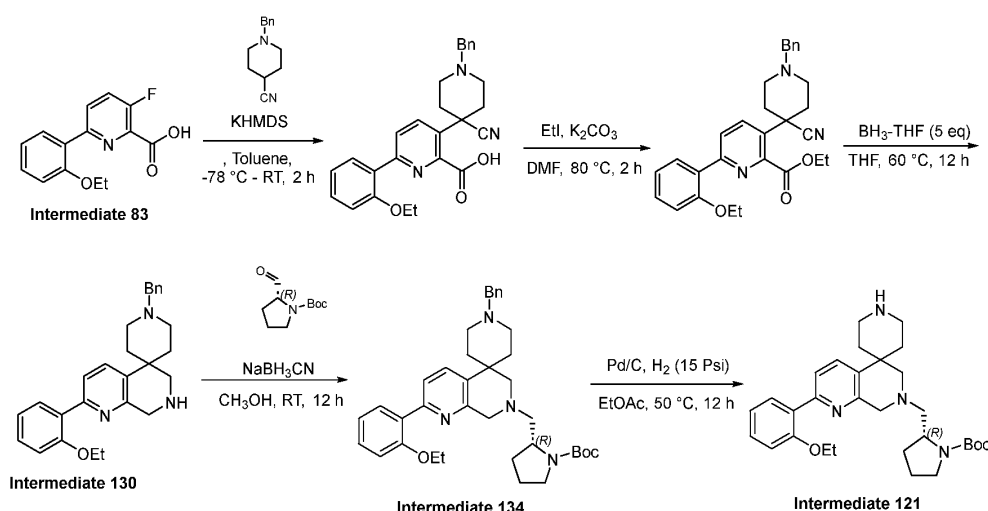
(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (1.75 g, 2.85 mmol, 72%) as a pale yellow solid.

LCMS: 3.43 min, 602.3 [M+H]⁺, Method B

To a stirred solution of benzyl 2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (1.7 g, 2.77 mmol) in EtOAc (18 mL) at RT was added 10% Pd/C (2.95 g, 27.7 mmol). The reaction mixture was stirred at RT under 1 atm of hydrogen for 16 h. The reaction mixture was filtered through celite and washed with EtOAc (2 x 10 mL). The filtrate was evaporated to afford 2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (1 g, 1.925 mmol, 70%) (intermediate 106) as a pale yellow solid.

The analytical data for intermediate 106 is in Table 1.

Procedure for the preparation tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 121)



To a solution of 1-benzylpiperidine-4-carbonitrile (7.67 g, 38.28 mmol) in toluene (200 mL) was added KHMDS (1 M, 74.90 mL) and 6-(2-ethoxyphenyl)-3-fluoropicolinic acid (intermediate 87) (10 g, 38.28 mmol) at -78 °C under N₂. The reaction mixture was warmed to RT and stirred at RT for 2 h under N₂. One additional vial was set up as described above. All of two reaction mixtures were quenched by addition saturated solution of ammonium chloride (200 mL) at 0 °C and adjusted pH 4 - 6 with formic acid. The mixture was diluted with water (100 mL) and extracted

with EtOAc (200 mL × 3). The combined organic layers were washed with brine (400 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give 3-(1-benzyl-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinic acid (40 g, crude) as a yellow solid, which was used to next step without further purification.

5 **LCMS:** 0.39 min, 442.3 [M+H]⁺/ 440.2 [M-H]⁺, Method N

To a solution of 3-(1-benzyl-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinic acid (20 g, 45.30 mmol) in DMF (150 mL) was added K₂CO₃ (18.78 g, 135.89 mmol) and EtI (8.48 g, 54.36 mmol, 4.35 mL) at 0 °C under N₂. The reaction mixture was heated to 80 °C for 2 h under N₂. One additional vial was set up as described above. After cooling to RT, two reaction mixtures were
10 diluted with water (200 mL) and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulphate, and purified by flash column chromatography (**PET ether/EtOAc=1/0 to 0/1, R_f=0.5**) to obtain ethyl 3-(1-benzyl-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (22 g, 52%) as white solid.

LCMS: 1.70 min, 470.2 [M+H]⁺, Method M

15 To a solution of ethyl 3-(1-benzyl-4-cyanopiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (9 g, 19.17 mmol) in THF (180 mL) was added BH₃.THF (1 M, 95.83 mL) at 0 °C under N₂. The reaction mixture was stirred at 60 °C for 12 h under N₂. One additional vial was set up as described above. After cooling to RT, two reaction mixtures were quenched by addition MeOH (100 mL × 2) at 0 °C. The combined mixture was stirred at 80 °C for 12 h. After cooling to RT, the reaction mixture
20 was concentrated under reduced pressure to give a residue (18 g as mixture of 1-benzyl-2'-(2-ethoxyphenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] and precursor amide). To reduce the amide in parallel 2 reactions, the residue (9 g) in THF (180 mL) was added BH₃.THF (1 M, 105.25 mL) at 0 °C under N₂. The reaction mixture was stirred at 60 °C for 2 h under N₂. After cooling to RT, two reaction mixtures were quenched by addition MeOH (100 mL × 2) at 0
25 °C. The combined mixture was stirred at 80 °C for 12 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (**EtOAc/MeOH= 1/0 to 0/1, R_f=0.5**) to obtain 1-benzyl-2'-(2-ethoxyphenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (intermediate 130) (4.2 g, 24%) as white solid.

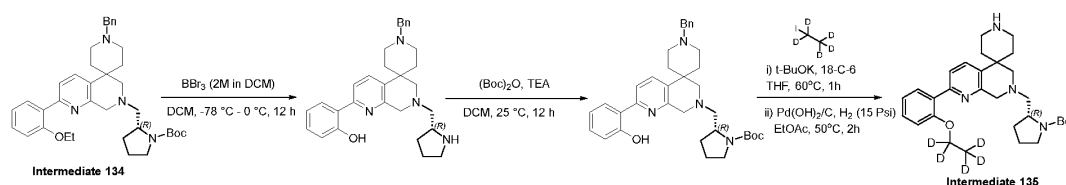
30 To a solution of 1-benzyl-2'-(2-ethoxyphenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (200 mg, 483.61 μmol) and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate (192.72 mg, 967.23 μmol) in MeOH (3 mL) was added NaCNBH₃ (91.17 mg, 1.45 mmol) at RT. The reaction mixture was stirred at RT for 12. Four additional vials were set up as described

above. Five reaction mixtures were concentrated under reduced pressure, and then diluted with water (15 mL) and extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and purified by flash column chromatography (PET ether/EtOAc= 1/0 to 0/1, R_f =0.5) to obtain tert-butyl (R)-2-((1-benzyl-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 134) (1 g, 69%) as a colourless oil.

A mixture of tert-butyl (R)-2-((1-benzyl-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (300 mg, 502.68 μ mol) (Intermediate 138) and 10% Pd/C (1.5 g, 1.41 mmol, 10% purity) in EtOAc (50 mL) was degassed and purged with H₂ (15 Psi) for 3 times at RT. The reaction mixture was stirred at 50 °C for 12 h under H₂ (15 Psi). One additional vial was set up as described above. After cooling to RT, two reaction mixtures were filtered and purified by prep-TLC (EtOAc/MeOH=1/1, R_f =0.2) to obtain tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 121) (220 mg, 43%) as white solid.

The analytical data for intermediate 130, 134 and 121 is in Table 1.

Procedure for the preparation tert-butyl (R)-2-((2'-(2-(ethoxy-d₅)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 135)



To a solution of tert-butyl (R)-2-((1-benzyl-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 138) (500 mg, 837.80 μ mol) in DCM (10 mL) was added BBr₃ (2 M in DCM, 2.09 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Five additional vials were set up as described above. After warming to RT, all six reaction mixtures were quenched with ice water (10 mL) and extracted with DCM (10 mL $\times$ 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate and purified by prep-HPLC method L to obtain (R)-2-(1-benzyl-7'-(pyrrolidin-2-

ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-2'-yl)phenol (1 g, 42%) as a yellow solid.

LCMS: 1.91 min, 469.2 [M+H]⁺, Method O

To a solution of (*R*)-2-(1-benzyl-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-2'-yl)phenol (200 mg, 426.77 μmol) in DCM (5 mL) was added Et₃N (129.56 mg, 1.28 mmol) and Boc₂O (93.14 mg, 426.77 μmol) at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 12 h. Four additional vials were set up as described above. All five reaction mixtures were quenched by addition ice water (40 mL) and then extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate and purified by prep TLC (**PET ether/EtOAc=1/1, R_f = 0.75**) to obtain tert-butyl (*R*)-2-((1-benzyl-2'-(2-hydroxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate ((950 mg, 78%) as a yellow solid.

LCMS: 0.41 min, 569.3 [M+H]⁺, Method C

To a solution of tert-butyl (*R*)-2-((1-benzyl-2'-(2-hydroxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (100 mg, 175.83 μmol) in THF (1.5 mL) was added potassium 2-methylpropan-2-olate (39.46 mg, 351.65 μmol), 1,4,7,10,13,16-hexaoxacyclooctadecane (92.95 mg, 351.65 μmol), and 1-iodoethane-1,1,2,2-*d*₅ (33.97 mg, 210.99 μmol) at 25 °C under nitrogen. The reaction mixture was stirred at 60 °C for 1 h under nitrogen atmosphere. Eight additional vials were set up as described above. After cooling to RT, all nine reaction mixtures were quenched by addition water (20 mL) and extracted with EtOAc (6 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulphate and purified by flash column chromatography (**PET ether/EtOAc =99/11 to 70/30, R_f = 0.5**) to obtain tert-butyl (*R*)-2-((1-benzyl-2'-(2-(ethoxy-*d*₅)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (800 mg, 84%) as a white solid.

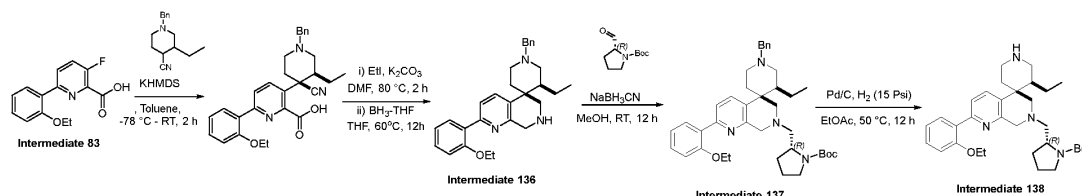
LCMS: 0.41 min, 602.5 [M+H]⁺, Method C

To a solution of tert-butyl (*R*)-2-((1-benzyl-2'-(2-(ethoxy-*d*₅)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (200 mg, 332.32 μmol) in EtOAc (120 mL) was added Pd(OH)₂ (700.04 mg, 20% purity) at 25 °C under nitrogen atmosphere. The reaction mixture was degassed and purged with hydrogen three times. The reaction mixture was stirred at 50 °C for 2 h under hydrogen atmosphere (15 psi). Three additional vials were set up as described above. After cooling to RT, all four reaction mixtures were filtered and concentrated

under reduced pressure to give tert-butyl (*R*)-2-((2'-(2-(ethoxy-*d*₅)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (360 mg, 53%) as a white solid.

The analytical data for intermediate 135 is in Table 1.

Procedure for the preparation tert-butyl (*R*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Intermediate 138)



To a solution of 1-benzyl-3-ethylpiperidine-4-carbonitrile (5g, 21.90 mmol) and 6-(2-ethoxyphenyl)-3-fluoropicolinic acid (intermediate 87) (5.72 g, 21.90 mmol) in toluene (150 mL) was added KHMDS (1 M, 65.69 mL) at -78 °C under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. Four vials were set up as described above. Five reaction mixtures were quenched by addition of saturated NH₄Cl solution (300 mL) at 0 °C and adjusted to pH 4 - 6 with formic acid, then extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain *rac*-3-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-6-(2-ethoxyphenyl)picolinic acid (50 g) as a yellow oil, which was used to next step without further purification.

LCMS: 0.76 min, 468.1 [M-H]⁺, Method R'

To a solution of *rac*-3-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-6-(2-ethoxyphenyl)picolinic acid (10 g, 21.30 mmol) in DMF (200 mL) was added K₂CO₃ (8.83 g, 63.89 mmol) and EtI (3.99 g, 25.56 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 2 h. Four vials were set up as described above. After cooling to RT, five reaction mixtures were quenched by addition water (500 mL) at 0 °C and then extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulphate, filtered and purified by flash column chromatography (PET ether/EtOAc = 1/0 to 8/1, R_f = 0.55) to afford *rac*-ethyl 3-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (32 g, 60%) as yellow oil.

LCMS: 1.78 min, 498.3 [M+H]⁺, Method C

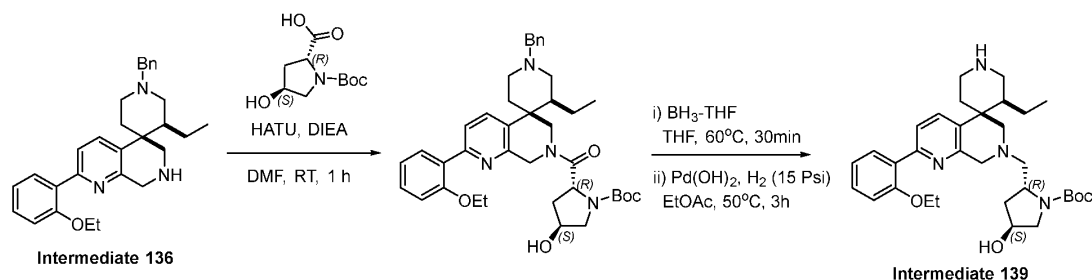
To a solution of *rac*-ethyl 3-((3*S*,4*S*)-1-benzyl-4-cyano-3-ethylpiperidin-4-yl)-6-(2-ethoxyphenyl)picolinate (5 g, 10.05 mmol) in THF (150 mL) was added BH₃.THF (1 M, 50.24 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 12 h. After cooling to RT, reaction mixture was quenched with MeOH (100 mL) at 0 °C and stirred at 80 °C for further 12 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (PET ether/EtOAc= 1/0 to EtOAc/MeOH= 8/1, R_f = 0.40) to obtain *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (1.2 g, 12%) (intermediate 136) as a white solid.

To a solution of *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (230 mg, 520.83 μmol) in MeOH (5 mL) was added tert-butyl (R)-2-formylpyrrolidine-1-carboxylate (207.55 mg, 1.04 mmol) and NaCNBH₃ (130.92 mg, 2.08 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. Four vials were set up as described above. All five reaction mixtures were filtered and the filtrate was concentrated under reduced pressure and purified by flash column chromatography (PET ether/EtOAc = 1/0 to 5/1, R_f = 0.40) to obtain tert-butyl (R)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (intermediate 137) (800 mg, 49%) as yellow oil.

A mixture of tert-butyl (R)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (intermediate 141) (800 mg, 1.28 mmol) and Pd(OH)₂ (800 mg, 5.70 mmol) in EtOAc (20 mL) was degassed and purged with hydrogen (15 Psi) for 3 times at 25 °C. The reaction mixture was stirred at 50 °C for 12 h under hydrogen (15 psi). After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue which was purified by flash column chromatography (eluted with PET ether/EtOAc= 1/0 to EtOAc/MeOH/MeOH= 4/1, R_f = 0.20) to obtain tert-butyl (R)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (600 mg, yield 88%) (intermediate 138) as white solid.

The analytical data for intermediate 136, 137 and 138 is in Table 1.

Procedure for the preparation tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (intermediate 139)



- 5 To a solution of (2*R*,4*S*)-1-tert-butoxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylic acid (178.04 mg, 769.92 μ mol) in DMF (7 mL) were added HATU (439.12 mg, 1.15 mmol), DIPEA (298.52 mg, 2.31 mmol) followed by *rac*-(3*S*,4*S*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (340 mg, 769.92 μ mol) (Intermediate 136) at RT and reaction mixture was stirred at RT for 1 h. Four additional vials were set up as described above.
- 10 All five reaction mixtures were combined, diluted with water (120 mL) and extracted with DCM (3 $\times$ 30 mL). The combined organics were washed with brine (120 mL) and dried over sodium sulfate and purified by flash column chromatography (PET ether/EtOAc = 50/50 to 10/90, R_f = 0.3) to get tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'-carbonyl)-4-hydroxypyrrolidine-1-carboxylate (2.2 g, 87%) as a yellow oil.
- 15

LCMS: 0.44 min, 655.3 (M+H)⁺, Method C

- To a solution of tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'-carbonyl)-4-hydroxypyrrolidine-1-carboxylate (200 mg, 305.42 μ mol) in THF (4 mL) was added a solution of BH₃.THF (1 M, 3.05 mL) dropwise at 0 °C. After warming to RT, the reaction mixture was stirred at 60 °C for 30 min. Five additional vials were set up as described above. After cooling to 0 °C, the reaction mixture was quenched with MeOH (1 mL). All six mixtures were combined and stirred at 60 °C for 1 h. After cooling to RT, the mixture was concentrated under reduced pressure and purified by flash column chromatography (PET ether/EtOAc = 50/50 to 0/100, R_f = 0.29) to get tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (1.2 g, 100%) as a yellow oil.
- 20
- 25

LCMS: 0.40 min, 641.6 (M+H)+, Method C

To a suspension of Pd (OH)₂/C (1.02 g, 1.46 mmol, 20% purity) in EtOAc (20 mL) was added a solution of tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (550
5 mg, 858.23 μmol) in EtOAc (200 mL) at 25 °C under nitrogen. The suspension was degassed and purged with hydrogen for 3 times. The reaction mixture was stirred at 50 °C for 3 h under hydrogen (15 Psi). One additional vial was set up as described above. After cooling to 25 °C, all two reaction mixtures were combined and filtered, the filtrate was concentrated under reduced pressure to get tert-butyl (2*R*,4*S*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-
10 4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (600 mg, crude) (Intermediate 139) as a yellow solid, which was used to next step without further purification.

The analytical data for intermediate 139 is in Table 1.

Table 1

Inter media te	Name	Synthetic Route	Starting Materials	Purification conditions	Data
1	ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate			Flash chromatography: EtOAc- PET ether (0 to 30%)	LCMS: 3.1 min, 291.2 (M+H) ⁺ , Method B
2	tert-butyl spiro[piperidine-4,5'-[1,7]naphthyridine]-1-carboxylate			Flash chromatography: DCM/MeOH (0 to 10%)	LCMS: 2.35 min, 439.2 (M+H) ⁺ , Method B
3	7-benzyl spiro[piperidine-4,5'-[1,7]naphthyridine]-1,7'(8H)-dicarboxylate			Flash chromatography: EtOAc- PET ether (0 to 60%)	LCMS: 2.86 min, 573.0 (M+H) ⁺ , Method B
4	benzyl 2'-(2-ethoxy-pyridin-3-yl)-8'-oxo-7',8'-dihydro-6H-[1,7]naphthyridine-7(8H)-carboxylate			Used crude	LCMS: 1.66 min, 473.2 (M+H) ⁺ , Method A
5	benzyl 2'-(2-ethoxy-pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7(8H)-carboxylate			Used crude	LCMS: 2.37 min, 459.3(M+H) ⁺ , Method B
6	1-(4-chloro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile			Flash chromatography: EtOAc- PET ether (0 to 50%)	LCMS: 2.80 min, 289.1 (M+H) ⁺ , Method B
7	1-benzyl-2'-(2-ethoxy-pyridin-3-yl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]-6-one			Prep-TLC: EtOAc with 0.01% NH ₄ OH - PET ether, Rf = 0.30	LCMS: 0.97 min, 439.2 (M+H) ⁺ , Method O
8	2'-(2-ethoxy-pyridin-3-yl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one			Prep-HPLC : Method H	LCMS: 1.29 min, 339.1 (M+H) ⁺ , Method O
9	1-(3-methoxy-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	piperidine-4-carbonitrile and 1-bromo-3-methoxy-2-(trifluoromethyl)benzene	Flash chromatography: silica gel, EtOAc- PET ether (0 to 25%)	LCMS: 2.59 min, 285.1 (M+H) ⁺ , Method B
10	2'-(2-ethoxy-pyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one				LCMS: 1.12 min, 339.1 (M+H) ⁺ , Method A
11	1-(3-ethoxy-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	piperidine-4-carbonitrile and 1-bromo-3-ethoxy-2-(trifluoromethyl)benzene	Flash chromatography: silica gel, EtOAc- PET ether (0 to 20%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.48 (t, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 2.87 - 2.84 (m, 4H), 2.52 - 2.51 (m, 1H), 2.00 - 1.97 (m, 2H), 1.82 - 1.72 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H).
12	1-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile	As intermediate 6	piperidine-4-carbonitrile and 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine	Flash chromatography: EtOAc- PET ether (0 to 50%)	LCMS: 2.33 min, 286.1 (M+H) ⁺ , Method B
13	1-(3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	piperidine-4-carbonitrile and 1-bromo-3-(cyclopropylmethoxy)-2-(trifluoromethyl)benzene (CAS 1369882-00-7)	Flash chromatography: EtOAc- PET ether (0 to 20%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.46 (t, J = 8.10 Hz, 1H), 6.91 - 6.83 (m, 2H), 3.92 (d, J = 6.6 Hz, 2H), 3.20 - 2.96 (m, 3H), 2.83 - 2.65 (m, 2H), 1.99 - 1.97 (m, 2H), 1.82 - 1.62 (m, 2H), 1.16 - 1.25 (m, 1H), 0.58 - 0.52 (m, 2H), 0.35 - 0.33 (m, 2H).
14	1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile			Flash chromatography:	LCMS: 2.62 min, 290.1 (M+H) ⁺ , Method B

						EIOAc- PET ether (0 to 40%) Used crude				
15	7-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5-[1,7]naphthyridine]									LCMS: 3.80 min, 503.1 (M+H) ⁺ , Method A
16	2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)nicotinoyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one	As Route A			Intermediate 10 and 22	Flash chromatography: DCM/MeOH (0 to 10%)				LCMS: 2.31 min, 542.0 (M+H) ⁺ , Method B
17	6-propoxy-2-(trifluoromethyl)nicotinic acid				1-bromopropane	Used crude				LCMS: 2.34 min, 249.9 (M+H) ⁺ , Method B
18	6-Cyclopropylmethoxy-2-(trifluoromethyl)nicotinic acid	As intermediate 17			(bromomethyl)cyclopropane	Flash chromatography: DCM/MeOH (0 to 10%)				LCMS: 2.32 min, 262.1 (M+H) ⁺ , Method B
19	1-(4-chloro-3-iodopyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one									LCMS: 2.81 min, 575.8 (M+H) ⁺ , Method B
20	1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one					Prep-HPLC: Method E				LCMS: 2.33 min, 518.1 (M+H) ⁺ , Method A
21	2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5-[1,7]naphthyridin]-1-yl-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)methanone	As Route J			Intermediate 5 and 22					LCMS: 1.81 min, 528.0 (M+H) ⁺ , Method B
22	6-methoxy-2-(trifluoromethyl)nicotinic acid	As intermediate 17			Methyl iodide					LCMS: 1.84 min, 222.0 (M+H) ⁺ , Method A
23	2'-(2-ethoxypyridin-3-yl)-1-(6-propoxy-2-(trifluoromethyl)nicotinoyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one	As Route A			Intermediate 10 and 17	Flash chromatography: EIOAc- PET ether (0 to 50%)				LCMS: 2.56 min, 570.0 (M+H) ⁺ , Method B
24	1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5-[1,7]naphthyridin]-6-one	As Route D			Intermediate 8 and 1-bromo-3-chloro-2-(trifluoromethyl)benzene	Prep-TLC: EIOAc- PET ether (1/3), Rf = 0.12				LCMS: 0.939 min, 517.2 (M+H) ⁺ , Method O
25	1-(3-chloro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6			piperidine-4-carbonitrile and 1-bromo-3-chloro-2-(trifluoromethyl)benzene	Flash chromatography: EIOAc- PET ether (0 to 50%)				LCMS: 2.81 min, 289.1 (M+H) ⁺ , Method B
26	tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate					Used crude				¹ H NMR (400 MHz, CDCl ₃) δ 1.42 - 1.49 (m, 12 H), 1.83 - 2.05 (m, 3 H), 2.07 - 2.21 (m, 3 H), 3.06 (br s, 2 H), 3.19 - 3.50 (m, 4 H), 3.64 (br s, 2 H), 4.51 (q, J = 6.92 Hz, 2 H), 4.61 (br s, 2 H), 5.16 - 5.31 (m, 1 H), 7.03 (dd, J = 7.38, 4.88 Hz, 1 H), 7.83 (d, J = 8.38 Hz, 1 H), 8.05 (br d, J = 8.38 Hz, 1 H), 8.21 (dd, J = 4.82, 1.81 Hz, 1 H), 8.24 - 8.29 (m, 1 H)
26-1	tert-butyl (R)-3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate	As intermediate 26			tert-butyl ((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	Used crude				LCMS: 0.43 min, 508.3 (M+H) ⁺ , Method O
26-2	tert-butyl (S)-3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate	As intermediate 26			tert-butyl ((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	Used crude				LCMS: 0.76 min, 508.4 (M+H) ⁺ , Method O (2 min method instead of 1 min)
27	3-chloro-5-propoxy-4-(trifluoromethyl)pyridine					Prep-TLC: EIOAc- PET ether (1/2), Rf = 0.5				¹ H NMR (400 MHz, CDCl ₃) δ 8.33 (d, J = 2.6 Hz, 2H), 4.13 (t, J = 6.2 Hz, 2H), 1.95 - 1.81 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H)
28	3-bromo-6-propoxy-2-(trifluoromethyl)pyridine	As intermediate 27				Prep-TLC: ether, Rf = 0.8				¹ H NMR (400 MHz, CDCl ₃) δ 7.82 (br d, J = 9.4 Hz, 1H), 6.79 (br d, J = 9.3 Hz, 1H), 4.29 (br t, J = 6.8 Hz, 3H), 1.90 - 1.74 (m, 3H), 1.02 (br t, J = 7.6 Hz, 5H)
29	1-(4-propoxy-3-(trifluoromethyl)pyridin-2-yl)piperidine-4-carbonitrile					Flash chromatography: EIOAc- PET ether (0 to 50%)				LCMS: 2.71 min, 314.0 (M+H) ⁺ , Method B

30	2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-1-(5-(methyl(propyl)amino)-4-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 2	Intermediate 1 and 31	Flash chromatography: DCM/MeOH (0 to 6%)	LCMS: 3.47 min, 555.3 (M+H) ⁺ , Method B
31	1-(5-(methyl(propyl)amino)-4-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile			Flash chromatography: EtOAc- PET ether (0 to 40%)	LCMS: 2.69 min, 327 (M+H) ⁺ , Method B
32	2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 2	Intermediate 1 and 33	Flash chromatography: DCM/MeOH (0 to 4%)	LCMS: 2.76 min, 542.3 (M+H) ⁺ , Method B
33	1-(5-propoxy-4-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile	As Intermediate 6	Intermediate 27 and piperidine-4-carbonitrile	Flash chromatography: EtOAc- PET ether (0 to 50%)	LCMS: 2.64 min, 314.2 (M+H) ⁺ , Method B
34	1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile	As Intermediate 6	3-bromo-6-methoxy-2-(trifluoromethyl)pyridine and piperidine-4-carbonitrile	Flash chromatography: EtOAc- PET ether (0 to 30%)	LCMS: 2.69 min, 286.0 (M+H) ⁺ , Method B
35	3-ethyl-1-(3-propoxy-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	Intermediate 36 and 3-ethylpiperidine-4-carbonitrile	Flash chromatography: EtOAc- PET ether (0 to 10%)	LCMS: 3.09 min, 341.2 (M+H) ⁺ , Method B
36	1-bromo-3-propoxy-2-(trifluoromethyl)benzene			Flash chromatography: EtOAc- PET ether (0 to 15%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.48 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.07 (t, J = 6.40 Hz, 2H), 1.79 - 1.70 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H).
37	1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 22 (Route I) using NMP/DPIEA, 140°C 2h.	Intermediate 10 and 3,5-dichloro-4-(trifluoromethyl)pyridine	Flash chromatography: DCM/MeOH (0 to 10%)	LCMS: 2.66 min, 518.2 (M+H) ⁺ , Method B
38	7-(azetidin-3-yl)-2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-1-(5-propoxy-4-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 15 (Route G) using TFA/DCM, RT in the 2 nd Step.	Intermediate 32 and Tert-butyl 3-iodoazetidine-1-carboxylate	Used crude	LCMS: 2.19 min, 597.2 (M+H) ⁺ , Method B
39	2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-1-(2-propoxy-3-(trifluoromethyl)pyridin-4-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 22 (Route I) using K ₂ CO ₃ , DMSO, 70°C, 16h.	Intermediate 10 and Intermediate 40	Flash chromatography: DCM/MeOH (0 to 10%)	LCMS: 2.06 min, 542.1 (M+H) ⁺ , Method A
40	4-chloro-2-propoxy-3-(trifluoromethyl)pyridine			Flash chromatography: EtOAc- PET ether (0 to 10%)	LCMS: 2.32 min, 240.1 (M+H) ⁺ , Method A
41	rac-(3S,4S)-2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-3-ethyl-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one			Used crude	LCMS: 1.43 min, 367.2 (M+H) ⁺ , Method B
42	rac-(3S,4S)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-3-ethyl-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one			Prep-HPLC: Method B	LCMS: 3.61 min, 546.2 (M+H) ⁺ , Method S
43	2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-1-(3-propoxy-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 2 (Route B)	Intermediate 1 and Intermediate 44	Flash chromatography: DCM/MeOH (0 to 20%)	LCMS: 2.16 min, 541.3 (M+H) ⁺ , Method A
44	1-(3-propoxy-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	Intermediate 36 and piperidine-4-carbonitrile	Flash chromatography: EtOAc- PET ether (0 to 20%)	LCMS: 2.84 min, 313.2 (M+H) ⁺ , Method B
45	7-(azetidin-3-yl)-2-(2-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-1-(4-propoxy-3-(trifluoromethyl)pyridin-2-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one 2,2,2-trifluoroacetate	As Example 15 (Route G) using TFA/DCM, RT in the 2 nd Step.	Example 40 and Tert-butyl 3-iodopyrrolidine-1-carboxylate	Prep-HPLC: Method A	LCMS: 1.66 min, 597.0 (M+H) ⁺ , Method A

46	2-(2-ethoxypyridin-3-yl)-1-(6-propoxy-2-(trifluoromethyl)pyridin-3-yl)-6,7-dihydro-8H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one	As Example 2 (Route B)	Intermediate 1 and Intermediate 47	Prep-HPLC: Method B	LCMS: 2.23 min, 542.0 (M+H) ⁺ , Method A
47	1-(6-propoxy-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile	As intermediate 6	piperidine-4-carbonitrile and 3-bromo-6-propoxy-2-(trifluoromethyl)pyridine	Flash chromatography: EtOAc- PEt ether (0 to 80%)	LCMS: 2.87 min, 314.2 (M+H) ⁺ , Method B
48	tert-butyl 3-(2-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8'H)-yl)azetidine-1-carboxylate	As Intermediate 26 using t-BuOK/THF, 80 °C, 4 h in the 1 st Step and H ₂ /Pd(OH) ₂ /EtOAc in the 2 nd Step.	Intermediate 7 and tert-butyl 3-iodoazetidine-1-carboxylate	Used crude	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (dd, J = 7.34, 1.86 Hz, 1 H), 8.19 (dd, J = 4.93, 1.64 Hz, 1 H), 8.00 - 8.05 (m, 1 H), 7.93 - 7.98 (m, 1 H), 7.02 - 7.15 (m, 1 H), 4.97 - 5.16 (m, 1 H), 4.86 (br d, J = 1.53 Hz, 2 H), 4.41 - 4.54 (m, 2 H), 4.18 - 4.27 (m, 2 H), 4.05 - 4.14 (m, 2 H), 3.21 - 3.28 (m, 1 H), 2.96 - 3.05 (m, 1 H), 2.68 - 2.90 (m, 2 H), 2.46 - 2.56 (m, 1 H), 2.14 - 2.31 (m, 2 H), 2.02 - 2.10 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.38 - 1.49 (m, 12 H).
49	tert-butyl 3-(((2,5-dioxypyrrrolidin-1-yl)oxy)carbonyl)azetidine-1-carboxylate			Used crude	LCMS: 2.20 min, 315.1 (M+H) ⁺ , Method B
50	1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2-(2-ethoxypyridin-3-yl)-6,7-dihydro-8H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one			Prep-HPLC: Method B, followed by NaHCO ₃ wash.	LCMS: 2.17 min, 589.2 (M+H) ⁺ , Method A
51	2-(2-ethoxypyridin-3-yl)-1-(6-(methyl(propyl)amino)-2-(trifluoromethyl)pyridin-3-yl)-6,7-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 2	Intermediate 1 and 52	Flash chromatography: DCM/MeOH (0 to 20%)	LCMS: 3.15 min, 555.3 (M+H) ⁺ , Method B
52	1-(6-(methyl(propyl)amino)-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile	As Intermediate 6 using tBuXphos, Pd(dba) ₃ NaOtBu, Toluene, 100°C 16h	piperidine-4-carbonitrile and Intermediate 53	Flash chromatography: EtOAc- PEt ether (0 to 20%)	LCMS: 2.92 min, 327.2 (M+H) ⁺ , Method B
53	5-bromo-N-methyl-N-propyl-6-(trifluoromethyl)pyridin-2-amine			Flash chromatography: EtOAc- PEt ether (0 to 10%)	LCMS: 2.43 min, 299.0 (M+H) ⁺ , Method A
54	2-(2-(2-ethoxypyridin-3-yl)-8'-oxo-7,8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-6-methoxybenzonitrile	As Example 22 (Route I) using DIPEA, DMF, 70°C, 16.	Intermediate 10 and 2-fluoro-6-methoxybenzonitrile	Flash chromatography: EtOAc- PEt ether (0 to 30%)	LCMS: 2.42 min, 470.2 (M+H) ⁺ , Method B
55	rac-7'-benzyl 1-(tert-butyl) (3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1,7'(8'H)-dicarboxylate			Flash chromatography: DCM/MeOH (0 to 5%)	LCMS: 3.06 min, 601.3 (M+H) ⁺ , Method B
56	rac-benzyl spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8'H)-carboxylate			Used crude	LCMS: 2.04 min, 487.3 (M+H) ⁺ , Method B
57	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7,8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]			Prep-HPLC: Method B, followed by NaHCO ₃ wash.	LCMS: 2.30 min, 528.3 (M+H) ⁺ , Method B SFC: (R, R) Wheel-O1; 1.92 min and 2.31 min
57-1	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7,8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin] Enantiomer 1			SFC purification	LCMS: 2.30 min, 528.3 (M+H) ⁺ , Method B SFC: Column: (R, R) Wheel-O1; 1.95 min
57-2	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7,8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin] Enantiomer 2			SFC purification	LCMS: 2.30 min, 528.3 (M+H) ⁺ , Method B SFC: Column: (R, R) Wheel-O1; 2.36 min
58	rac-(3S,4S)-2-(2-ethoxypyridin-3-yl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6,7-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Example 42 (Route N)	3-ethylpiperidine-4-carbonitrile, 1-bromo-3-methoxy-2-(trifluoromethyl)benzene and Intermediate 1	Flash chromatography: DCM/MeOH (0 to 10%)	LCMS: 2.09 min, 541.0 (M+H) ⁺ , Method A

59	(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(4-fluoro-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	As Example 42 (Route N)	3-ethylpiperidine-4-carbonitrile, 1-bromo-4-fluoro-2-(trifluoromethyl)benzene and Intermediate 1	Prep-HPLC: Method B, followed by NaHCO ₃ wash.	LCMS: 3.06 min, 529.4 (M+H) ⁺ , Method B
59-1	(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(4-fluoro-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one Enantiomer 1			SFC purification	LCMS: 3.07 min, 529.2 (M+H) ⁺ , Method B SFC: Column: (R, R) Whelk-01; 2.79 min
59-2	(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(4-fluoro-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one Enantiomer 2			SFC purification	LCMS: 3.03 min, 529.2 (M+H) ⁺ , Method B SFC: Column: (R, R) Whelk-01; 3.49 min
60	(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(2-(trifluoromethyl)pyridin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	As Example 42 (Route N)	3-ethylpiperidine-4-carbonitrile, 3-bromo-2-(trifluoromethyl)pyridine and Intermediate 1	Prep-HPLC: Method B, followed by NaHCO ₃ wash.	LCMS: 2.62 min, 512.2 (M+H) ⁺ , Method B SFC: (R, R) Whelk-01, 2.61 min and 3.15 min
61	2'-(2-ethoxy-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As Example 6 (Route E) with 0°C to 60 °C for 12h	Example 7	Flash chromatography: , EIOAc/MeOH (0 to 25%)	LCMS: 0.48 min, 499.1 (M+H) ⁺ , Method O'
62	tert-butyl (3-(2'-(2-ethoxy-3-yl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8H)-yl)-3-oxopropyl)carbamate			Used crude	LCMS: 0.37 min, 496.3 (M+H) ⁺ , Method O'
63	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(3-(trifluoromethyl)pyridin-2-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	As intermediate 42	2-chloro-3-(trifluoromethyl)pyridine and Intermediate 41	Prep-HPLC: Method B, followed by NaHCO ₃ wash.	LCMS: 1.94 min, 512.3 [M+H] ⁺ , Method A
64	rac-(3S,4S)-1-benzyl-2'-(2-ethoxy-3-yl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]			Flash chromatography: eluted with MeOH/EIOAc (1:9)	LCMS: 0.44 min, 443.3 [M+H] ⁺ , Method R'
65	5-bromo-N,N-dimethyl-6-(trifluoromethyl)pyridin-2-amine	As intermediate 53 using dimethyl amine hydrochloride in the 1 st Step		Flash chromatography: eluted with pet ether	LCMS: 2.84 min, 269.0 (M+H) ⁺ , Method B
66	1-(6-(dimethylamino)-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile			Flash chromatography: eluted with pet ether/EIOAc (8:2)	LCMS: 2.77 min, 299.1 (M+H) ⁺ , Method B
67	1-(6-(dimethylamino)-2-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxy-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	As Example 2 (Route B) with KHMDS in THF at RT in the 1 st step and Raney Ni in the 2 nd step	Intermediate 1 and 66	Flash chromatography: eluted with MeOH/DCM (2:8)	LCMS: 3.02 min, 527.2 (M+H) ⁺ , Method B
68	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(3-fluoro-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	As intermediate 42, using NMP, 120 °C, 2 h	Intermediate 41 and 1,3-difluoro-2-(trifluoromethyl)benzene	Used crude	LCMS: 2.98 min, 529.2 (M+H) ⁺ , Method B
69	rac-benzyl (3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8H)-carboxylate	As intermediate 57	Intermediate 56 and 1-bromo-3-methoxy-2-(trifluoromethyl)benzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.38 min, 527.3 [M+H] ⁺ , Method B

70	rac-(3S,4S)-1-(4-chloro-3-(trifluoromethyl)pyridin-2-yl)-2-(2-ethoxy-3-yl)-3-ethyl-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one			Prep HPLC method B followed by NaHCO ₃ wash	LCMS: 2.21 min, 546.2 (M+H) ⁺ , Method A
71	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethyl)pyridin-3-yl)-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	As Intermediate 42		Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.73 min, 542.2 (M+H) ⁺ , Method B
72	3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)piperidine-4-carbonitrile			Flash chromatography: eluted with EtOAc/PET ether (3:7)	LCMS: 2.85 min, 314.2 [M+H] ⁺ , Method B
73	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	As Example 42 (Route N)	Intermediate 72 and 1	Prep HPLC method B followed by NaHCO ₃ wash	LCMS: 3.00 min, 542.3 [M+H] ⁺ , Method B
74	(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl methanesulfonate			Used as crude	LCMS: 1.43 min, 220.26 (M+H) ⁺ , Method B
75	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(2-methoxy-3-(trifluoromethyl)pyridin-4-yl)-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	As intermediate 70 using K ₂ CO ₃ , DMSO, 70 °C, 16 h	Intermediate 41 and 4-chloro-2-methoxy-3-(trifluoromethyl)pyridine	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.81 min, 542.3 (M+H) ⁺ , Method B
76	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(4-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As Example 6 (Route E)	Intermediate 59 reduced with BH3.THF at 0 to 80 °C, 12 h	Flash chromatography: eluted with MeOH/EtOAc(1:9)	¹ H NMR: (400 MHz, CDCl ₃) δ 8.23 (dd, J = 1.9, 7.4 Hz, 1H), 8.19 (dd, J = 2.0, 4.9 Hz, 1H), 8.00 – 7.94 (m, 1H), 7.91 – 7.86 (m, 1H), 7.45 (dd, J = 4.9, 8.8 Hz, 1H), 7.37 (dd, J = 3.1, 9.1 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.01 (dd, J = 4.9, 7.4 Hz, 1H), 4.50 (q, J = 7.0 Hz, 2H), 4.25 (s, 2H), 3.36 (s, 2H), 3.03 – 2.92 (m, 4H), 2.27 (dt, J = 4.3, 12.6 Hz, 2H), 1.89 (br d, J = 13.8 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H)
77	rac-(3S,4S)-1-(2-chloro-3-methoxyphenyl)-2'-(2-ethoxy-3-yl)-3-ethyl-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	As Example 36 (Route N)	1-bromo-2-chloro-3-methoxybenzene used in 1 st Step	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 6.35 min, 507.1 (M+H) ⁺ , Method B
78	2'-(2-ethoxy-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	As Route B	Intermediate 34 and 1	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.82 min, 514.0 (M+H) ⁺ , Method B
79	rac-tert-butyl (3-((3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8H)-yl)-3-oxopropyl)carbamate			Used crude	LCMS: 0.42 min, 524.4 [M+H] ⁺ , Method C

80	2-(2-ethoxy-3-yl)-1-(2-(trifluoromethyl)phenyl)-6,7-dihydro-8H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one	As intermediate 50 with Raney Ni, H ₂ , EtOH-H ₂ O, 65 °C, 24 h in the 3 rd Step.	1-bromo-2-(trifluoromethyl)benzene in 1 st step (Buchwald)	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.80 min, 483.1 [M+H] ⁺ , Method B
81	2-(2-ethoxy-3-yl)-1-(3-(trifluoromethyl)pyridin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As Example 30 (Route L) using DIPEA, DMF, 80 °C, 16 h in 1 st Step and Et ₃ SiH, PdCl ₂ , Et ₃ N, DCM, 50 °C, 5 h in the 2 nd Step	intermediate 5 and 2-chloro-3-(trifluoromethyl)pyridine	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.68 min, 470.2 [M+H] ⁺ , Method P
82	1-(4-fluoro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile	As intermediate 6	1-bromo-4-fluoro-2-(trifluoromethyl)benzene in the Buchwald reaction	Flash chromatography: eluted with PET ether/EtOAc (8:2)	¹ H NMR (400 MHz, CD ₃ OD): δ 7.60 – 7.50 (m, 1H), 7.43 – 7.32 (m, 2H), 3.06 – 2.97 (m, 2H), -2.94 – -2.80 (m, 3H), 2.10 – 2.01 (m, 2H), 1.97 – 1.86 (m, 2H)
83	6-(2-ethoxyphenyl)-3-fluoropicolinic acid	As intermediate 1 (int 4 synthesis)	(2-ethoxyphenyl)boronic acid in 1 st Step	Solid was isolated by acidification with 1.5 N HCl.	LCMS: 2.17 min, 262.1 [M+H] ⁺ , Method B
84	ethyl 6-(2-ethoxyphenyl)-3-fluoropicolinate	As intermediate 1 (int 4 synthesis)	(2-ethoxyphenyl)boronic acid in 1 st step and ethyl iodide in 2 nd Step	Flash chromatography: eluted with Pet ether/EtOAc (8:2)	LCMS: 2.70 min, 290.1 [M+H] ⁺ , Method B
85	2-(2-ethoxyphenyl)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-6,7-dihydro-8H-spiro[piperidine-4,5-[1,7]naphthyridin]-8-one	As Example 2 (Route B) with KHMDS, in the 1 st Step and Raney Ni, H ₂ , EtOH-H ₂ O, 65 °C, 24 h in the 2 nd Step	Intermediate 84 and 82	Flash chromatography: eluted with Pet ether/EtOAc (8:2)	¹ H NMR (400 MHz, CD ₃ OD): δ 8.13 (s, 2H), 7.77 (dd, J = 1.7, 7.7 Hz, 1H), 7.68 (dd, J = 4.9, 8.2 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.12 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.33 (br s, 1H), 3.28 (s, 1H), 3.15 (br d, J = 12.0 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.45 – 2.35 (m, 2H), 1.47 – 1.38 (m, 8H)
86	2-(2-ethoxyphenyl)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As Route E (Example 6) with BH ₃ ·THF at 0 – 80 °C, 12 h	Intermediate 85	prep-TLC (EtOAc:MeOH R _f = 0.52)	LCMS: 0.50 min, 486.3 [M+H] ⁺ , Method R
87	5-chloro-2-(2-(2-ethoxy-3-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridin]-1-yl)benzonitrile	As Example 30 (Route L) with Pd ₂ (dba) ₃ , NaOtBu, Xanthophos Toluene, 110 °C, 16 h in 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 5 h in 2 nd Step.	Intermediate 5 and 2-bromo-5-chlorobenzonitrile	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 2.14 min, 460.1 [M+H] ⁺ , Method B
88	rac-2-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridin]-1-yl)-5-fluorobenzonitrile	As intermediate 57	Intermediate 56 and 2-bromo-5-fluorobenzonitrile	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.72 min, 472.2 [M+H] ⁺ , Method B

89	<i>tert</i> -butyl (R)-2-((3 <i>S</i> , 4 <i>S</i>)-2'-(2-ethoxy-3- <i>y</i>)-3-ethyl-6 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8 <i>H</i>)- <i>y</i>)methylpyrrolidine-1-carboxylate			prep-TLC eluted with EtOAc/MeOH = 1/1, <i>R</i> _f = 0.11)	LCMS: 1.39/1.41 min, 536.3 [M+H] ⁺ Method C
90	1-benzyl-2'-(2-ethoxypiperidin-3- <i>y</i>)-7',8'-dihydro-6 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridine]		Intermediate 7 reduced with BH ₃ .THF at 0 – 80 °C, 12 h	prep-TLC (EtOAc, <i>R</i> _f = 0)	LCMS: 0.31 min, 415.2 (M+H) ⁺ , Method O'
91	<i>tert</i> -butyl (R)-2-((2'-(2-ethoxypiperidin-3- <i>y</i>)-6 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8 <i>H</i>)- <i>y</i>)methylpyrrolidine-1-carboxylate	As intermediate 89	Intermediate 90 and <i>tert</i> -butyl (R)-2-formylpyrrolidine-1-carboxylate in the 1 st Step.	Used Crude	LCMS: 0.36 min, 508.3 [M+H] ⁺ Method R'
92	2'-(2-ethoxyphenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	As Route B with K ⁺ HMDS in 1 st Step and Raney Ni in 2 nd step	Intermediate 9 and 84 in 1 st Step	Used crude	¹ H NMR (400 MHz, CDCl ₃) δ 8.14 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 – 7.99 (m, 1H), 7.89 (d, <i>J</i> = 8.5 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.38 – 7.33 (m, 1H), 7.08 (t, <i>J</i> = 7.5 Hz, 1H), 6.98 (d, <i>J</i> = 8.3 Hz, 1H), 6.85 (br d, <i>J</i> = 7.9 Hz, 1H), 6.77 (br d, <i>J</i> = 8.4 Hz, 1H), 4.12 (q, <i>J</i> = 6.9 Hz, 2H), 3.90 (s, 3H), 3.72 (br d, <i>J</i> = 1.6 Hz, 2H), 3.15 (br d, <i>J</i> = 11.6 Hz, 2H), 3.01 (br t, <i>J</i> = 11.8 Hz, 2H), 2.38 – 2.20 (m, 2H), 1.99 (br d, <i>J</i> = 12.9 Hz, 2H), 1.42 (t, <i>J</i> = 7.0 Hz, 3H), exchangeable proton not observed.
93	2'-(2-ethoxyphenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridine]	As route E (Example 6) with LAH-THF, THF, 0-25 °C, 6 h and a 15% NaOH:H ₂ O wash	Intermediate 92	Prep HPLC method L	LCMS: 2.46 min, 498.2 [M+H] ⁺ Method O
94-1	(3 <i>S</i> , 4 <i>R</i>)-3-ethylpiperidine-4-carbonitrile			Used crude	VT ¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 3.00 (dd, <i>J</i> = 3.8, 12.6 Hz, 1H), 2.89 (td, <i>J</i> = 3.7, 12.5 Hz, 1H), 2.54 – 2.51 (m, 1H), 2.49 – 2.39 (m, 2H), 2.16 (dd, <i>J</i> = 9.9, 12.5 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.61 – 1.52 (m, 2H), 1.51 – 1.37 (m, 1H), 1.32 – 1.24 (m, 1H), 0.95 – 0.87 (m, 3H)
94-2	(3 <i>R</i> , 4 <i>S</i>)-3-ethylpiperidine-4-carbonitrile	As intermediate 94-1	(2 <i>R</i> , 3 <i>R</i>)-2,3-bis((4-methylbenzoyloxy)butanediolic acid in 1 st Step.	Used crude	VT ¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 3.05 – 2.95 (m, 1H), 2.89 (td, <i>J</i> = 3.5, 12.5 Hz, 1H), 2.54 – 2.50 (m, 1H), 2.48 – 2.44 (m, 1H), 2.43 – 2.38 (m, 1H), 2.16 (dd, <i>J</i> = 9.9, 12.5 Hz, 1H), 1.89 (qd, <i>J</i> = 3.4, 12.9 Hz, 1H), 1.62 – 1.54 (m, 2H), 1.52 – 1.38 (m, 1H), 1.33 – 1.23 (m, 1H), 0.94 – 0.89 (m, 3H)
95	<i>tert</i> -butyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate				LCMS: 2.26 min, 319.1 [M+H] ⁺ , Method W
96	<i>rac</i> -(3 <i>S</i> , 4 <i>S</i>)-2'-(2-ethoxypiperidin-3- <i>y</i>)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 96	<i>rac</i> -3-ethylpiperidine-4-carbonitrile in 1 st Step	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.89 min, 497.2 [M+H] ⁺ , Method I

97	(3R,4R)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]	As intermediate 98	(3R)-3-ethylpiperidine-4-carbonitrile in 1 st Step	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.79 min, 497.2 [M+H] ⁺ , Method G
98	(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]			Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.79 min, 497.2 [M+H] ⁺ , Method W
99	rac-5-chloro-2-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]-1-yl)benzotrile	As intermediate 57	2-bromo-5-chlorobenzotrile in 3 rd Step	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.70 min, 488.2 [M+H] ⁺ , Method G
100	rac-benzyl (3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-6H-spiro[piperidine-4,5-[1',7]naphthyridine]-7(8H)-carboxylate				LCMS: 2.22 min, 486.3 [M+H] ⁺ , Method B
100-1	benzyl (3R,4R)-2'-(2-ethoxy-3-yl)-3-ethyl-6H-spiro[piperidine-4,5-[1',7]naphthyridine]-7(8H)-carboxylate	As intermediate 100 (chirally synthesized) with KOtBu in the 4 th Step	Single enantiomer intermediate 94-2 was used instead of rac-3-ethylpiperidine-4-carbonitrile.	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.46 min, 486.2 [M+H] ⁺ , Method W
101	tert-butyl 6-(2-ethoxy-3-yl)-3-fluoropicolinate	Intermediate 102-step-1			LCMS: 2.27 min, 318.1 [M+H] ⁺ , Method W
102	benzyl 2'-(2-ethoxy-3-yl)-6H-spiro[piperidine-4,5-[1',7]naphthyridine]-7(8H)-carboxylate				LCMS: 1.46 min, 458.2 [M+H] ⁺ , Method G
103	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]	As intermediate 57 with DIPEA, DMF at 80 °C for 16 h in 3 rd Step (SnAr)	Intermediate 58 and 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine in 3 rd Step	Crude used	LCMS: 1.65 min, 528.2 [M+H] ⁺ , Method G
104	2'-(2-ethoxy-3-yl)-1-(3-(trifluoromethyl)pyrazin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]	As route L (Example 30) with using NMP, MW, 140 °C, 2 h in 1 st Step (SnAr) and PdCl ₂ , Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step.	2-chloro-3-(trifluoromethyl)pyrazine and intermediate 5 in the 1 st Step	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.50 min, 471.2 [M+H] ⁺ , Method G.
105	rac-(3S,4S)-2'-(2-ethoxy-3-yl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]				LCMS: 1.81 min, 526.2 [M+H] ⁺ , Method G.
106	2'-(2-ethoxy-3-yl)-1-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]				LCMS: 1.84 min, 468.2 [M+H] ⁺ , Method I
107	3-(2'-(2-ethoxy-3-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1',7]naphthyridine]-1-yl)-2-(trifluoromethyl)benzotrile	As Route L (Example 30) with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step, and H ₂ , 10% Pd/C in EtOAc, rt, 16 h in the 2 nd Step	Intermediate 5 and 3-bromo-2-(trifluoromethyl)benzotrile in 1 st Step	Used crude	LCMS: 2.27 min, 494.7 [M+H] ⁺ , Method Y

108	1-(2-chloro-3-methoxyphenyl)-2-(2-ethoxyphenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step.	Intermediate 102 and 1-bromo-2-chloro-3-methoxybenzene	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.53 min, 464.2 [M+H] ⁺ , Method W
109	2-(2-ethoxyphenyl)-1-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 106 with K ₂ CO ₃ , DMSO, 120 °C, 2 h in the 1 st Step (SnAr), and H ₂ , 10% Pd/C in EtOAc, rt, 16 h in the 2 nd Step.	Intermediate 102 and 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine	Used crude	LCMS: 1.55 min, 499.2 [M+H] ⁺ , Method G
110	1-(2,3-dichlorophenyl)-2-(2-ethoxyphenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step, and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in 2 nd Step.	Intermediate 102 and 1-bromo-2,3-dichlorobenzene	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.77 min, 468.1 [M+H] ⁺ , Method G
111	rac-(3S,4S)-2-(2-ethoxyphenyl)-3-ethyl-1-(4-methoxy-3-(trifluoromethyl)pyridin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 105 with DBU, NMP, 140 °C, MW, 2 h in the 1 st Step (SnAr), and H ₂ , 10% Pd/C in EtOAc, rt, 16 h in the 2 nd Step.	Intermediate 100 and 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine	Used crude	LCMS: 1.74 min, 527.2 [M+H] ⁺ , Method G
112	rac-5-chloro-2-(3S,4S)-2-(2-ethoxyphenyl)-3-ethyl-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]-1-yl)benzonitrile	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step.	Intermediate 100 and 2-bromo-5-chlorobenzonitrile	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.75 min, 487.2 [M+H] ⁺ , Method W
113	1-(3,5-dichloropyridin-2-yl)-2-(2-ethoxyphenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 106 with K ₂ CO ₃ , DMSO, 70 °C, 16 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step.	Intermediate 102 and 3,5-dichloro-2-fluoropyridine	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.67 min, 469.2 [M+H] ⁺ , Method G
114	5-chloro-2-(2'-(2-ethoxyphenyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]-1-yl)nicotinonitrile	As intermediate 106 with K ₂ CO ₃ , DMSO, 120 °C, 16 h in the 1 st Step and PTSA, toluene, 120 °C, 16 h in the 2 nd Step.	Intermediate 102 and 2,5-dichloronicotinonitrile	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.60 min, 460.2 [M+H] ⁺ , Method G
115	2-(2-ethoxyphenyl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and H ₂ , 10% Pd/C in EtOAc, rt, 16 h in the 2 nd Step.	Intermediate 102 and 3-bromo-6-methoxy-2-(trifluoromethyl)pyridine	Used crude	LCMS: 1.57 min, 499.3 [M+H] ⁺ , Method W
116	rac-(3S,4S)-2-(2-ethoxyphenyl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step.	Intermediate 100 and 3-bromo-6-methoxy-2-(trifluoromethyl)pyridine	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.90 min, 527.2 [M+H] ⁺ , Method G
117	rac-(3S,4S)-1-(3,5-dichloropyridin-2-yl)-2-(2-ethoxyphenyl)-3-ethyl-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	As intermediate 105 with K ₂ CO ₃ , DMSO, 80 °C, MW, 2 h in the 1 st Step and	Intermediate 100 and 3,5-dichloro-2-fluoropyridine	Flash chromatography:	LCMS: 1.70 min, 497.1 [M+H] ⁺ , Method W

		PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step		eluted with MeOH/DCM (1:9)		
118	rac-(3S,4S)-1-(2,3-dichlorophenyl)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 100 and 1-bromo-2,3-dichlorobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.85 min, 496.2 [M+H] ⁺ , Method-G	
119	rac-(3S,4S)-1-(2-chloro-4-fluorophenyl)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 5 h in the 2 nd Step	Intermediate 100 and 1-bromo-2-chloro-4-fluorobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.83 min, 480.2 [M+H] ⁺ , Method-G	
120	2-((3S,4S)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin-1-yl]benzonitrile (des-Cl product in step-2 of Example 181)	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 100 chlorobenzonitrile fluorobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.64 min, 453.2 (M+H) ⁺ , Method G	
121	tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin-7'(8H)-yl)methyl]pyrrolidine-1-carboxylate				LCMS: 1.50 min, 507.3 (M+H) ⁺ , Method M	
122	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(5-methoxy-4-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]			Used crude	LCMS: 1.64 min, 528.2 [M+H] ⁺ , Method G	
123	1-(2-chlorophenyl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As Route L (Example 30) with using Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 5 and 1-bromo-2-chlorobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.511 min, 435.1 [M+H] ⁺ , Method G	
124	5-chloro-2-(2'-(2-ethoxyphenyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin-1-yl]benzonitrile	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 102 and 2-bromo-5-chlorobenzonitrile	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.60 min, 459.2 [M+H] ⁺ , Method G	
125	rac-(3S,4S)-1-(2-chlorophenyl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 57 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 56 and 1-chloro-2-iodobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.67 min, 463.2 [M+H] ⁺ , Method G	
126	1-(2-chlorophenyl)-2'-(2-ethoxyphenyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 16 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 102 and 1-bromo-2-chlorobenzene	Flash chromatography: eluted with MeOH/DCM (1:9)	LCMS: 1.62 min, 434.2 [M+H] ⁺ , Method G	

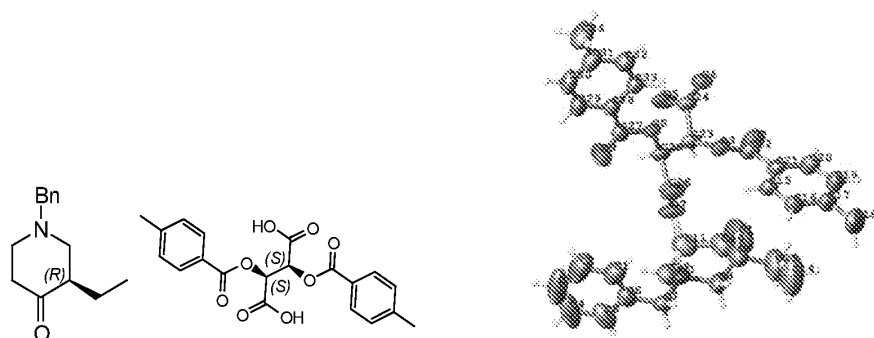
127	2-(2'-(2-ethoxyphenyl)-7,8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-y)benzonitrile	As intermediate 106 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 16 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 102 and 2-bromo-5-chlorobenzonitrile	Flash chromatography: with eluted MeOH/DCM (1:9) (Mixture of intermediate 131 (des-Cl) and its Cl isomer was isolated and used in next step)	LCMS: 1.50 min, 425.2 [M+H] ⁺ and 1.60 min 459.1 [M+H] ⁺ , Method G
128	rac-5-chloro-2'-((3S,4S)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-y)nicotinonitrile	As intermediate 105 with K ₂ CO ₃ , DMSO, 120 °C, 16 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 100 and 2,5-dichloronicotinonitrile	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 2.29 min, 671.3 [M+H] ⁺ , Method W
129	2-((3R,4R)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-y)nicotinonitrile (Chirally synthesized)	As intermediate 105 with K ₂ CO ₃ , DMSO, 120 °C, 16 h in the 1 st Step and PTSA, H ₂ O, toluene 120 °C, 16 h in the 2 nd Step	Intermediate 100-1 and 2,5-dichloronicotinonitrile	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.71 min, 488.2 [M+H] ⁺ , Method W
130	1-benzyl-2'-(2-ethoxyphenyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	Intermediate 121			LCMS: 0.323 min, 414.3 [M+H] ⁺ , Method C
131	rac-(3S,4S)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-(trifluoromethyl)pyrazin-2-yl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 105 with NMP, MW, 140 °C, 4 h in the 1 st Step and H ₂ (1 atm.), 10% Pd/C, EtOAc, rt, 16 h in the 2 nd Step	Intermediate 100 and 2-chloro-3-(trifluoromethyl)pyrazine	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.62 min, 498.3 [M+H] ⁺ , Method W
132	rac-2-((3S,4S)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-y)-5-fluorobenzonitrile	As intermediate 105 with Pd ₂ (dba) ₃ , NaOtBu, Xantphos, Toluene, 110 °C, 24 h in the 1 st Step and PdCl ₂ , Et ₃ SiH, Et ₃ N, DCM, 50 °C, 6 h in the 2 nd Step	Intermediate 100 and 2-bromo-5-fluorobenzonitrile	Flash chromatography: with eluted MeOH/DCM (1:9)	LCMS: 1.58 min, 471.2 [M+H] ⁺ , Method G
133	rac-(3S,4S)-1-(2-chlorophenyl)-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	As intermediate 105 with Cs ₂ CO ₃ , BINAP, Pd(OAc) ₂ , Toluene, 110 °C, 24 h in the 1 st Step and p-TSA, H ₂ O (3 eq), Toluene, 110 °C, 16 h in the 2 nd Step	Intermediate 100 and 1-bromo-2-chlorobenzene	Trituration and washing with n-pentane	LCMS: 1.74 min, 462.2 [M+H] ⁺ , Method G
134	tert-butyl (R)-2-((1-benzyl-2'-(2-ethoxyphenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate	See intermediate 121		Flash chromatography: with eluted Pet ether/EtOAc (1:1)	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 (d, J = 8.3 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.51 (dd, J = 1.4, 7.4 Hz, 1H), 7.42 - 7.33 (m, 5H), 7.32 - 7.27 (m, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.98 - 3.90 (m, 1H), 3.76 (br s, 2H), 3.64 (s, 2H), 3.35 (br s, 2H), 3.14 - 3.04 (m, 1H), 2.87 (br d, J = 9.6 Hz, 2H), 2.56 - 2.45 (m, 2H), 2.41 - 2.27 (m, 2H), 2.24 - 2.15 (m, 1H), 2.04 - 1.84 (m, 6H), 1.79 - 1.67 (m, 2H), 1.50 (s, 9H), 1.34 (t, J = 7.0 Hz, 3H)

135	tert-butyl (R)-2-((2'-(2-(ethoxy-d5)phenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate				LCMS: 0.70 min, 512.3 [M+H] ⁺ , Method F
136	rac-(3S,4S)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	Included in intermediate 138			LCMS: 2.25 min, 442.3 [M+H] ⁺ , Method C
137	tert-butyl (R)-2-(((3SR,4SR)-1-benzyl-2'-(2-ethoxyphenyl)-3-ethyl-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate	Included in intermediate 138			LCMS: 1.60 min, 625.3 [M+H] ⁺ , Method R'
138	tert-butyl (R)-2-(((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate				LCMS: 1.49 min, 535.3 [M+H] ⁺ , Method C
139	tert-butyl (2R,4S)-2-(((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)-4-hydroxypyrrrolidine-1-carboxylate			Used crude	LCMS: 0.43 min, 551.5, [M+H] ⁺ , Method C
140	tert-butyl (2R,4S)-2-((2'-(2-ethoxyphenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)-4-hydroxypyrrrolidine-1-carboxylate	As intermediate 139		Used crude	LCMS: 0.37 min, 523.3 [M+H] ⁺ , Method R'
141	tert-butyl (R)-2-(((3SR,4SR)-2'-(2-(ethoxy-d5)phenyl)-3-ethyl-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate	As intermediate 135		Used crude	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 (br d, J = 8.2 Hz, 1H), 7.68 (dd, J = 3.9, 8.3 Hz, 1H), 7.59 - 7.52 (m, 1H), 7.40 - 7.34 (m, 1H), 7.08 (d, J = 8.2 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 4.06 - 3.94 (m, 1H), 3.84 (br d, J = 15.4 Hz, 1H), 3.61 (br d, J = 18.2 Hz, 1H), 3.40 - 3.33 (m, 2H), 3.19 - 3.08 (m, 1H), 3.02 - 2.82 (m, 3H), 2.77 - 2.56 (m, 2H), 2.36 - 2.34 (m, 2H), 2.23 - 2.04 (m, 2H), 1.99 - 1.81 (m, 4H), 1.78 - 1.61 (m, 1H), 1.54 - 1.47 (m, 9H), 1.16 - 1.01 (m, 2H), 0.80 (br d, J = 7.7 Hz, 3H)
142	tert-butyl (S)-2-((2'-(2-ethoxyphenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidine-1-carboxylate	As intermediate 121	tert-butyl (S)-2-formylpyrrolidine-1-carboxylate	Used crude	LCMS: 0.38 min, 507.4 [M+H] ⁺ , Method c

X-ray crystallographic analysis of (*R*)-1-benzyl-3-ethylpiperidin-4-one complex with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid

X-ray crystal analysis was performed to determine the absolute configuration of (*R*)-1-benzyl-3-ethylpiperidin-4-one as described below.

- 5 **Summary of Results:** The crystal was a colourless block with the following dimensions: 0.20 × 0.20 × 0.03 mm³. The symmetry of the crystal structure was assigned the triclinic space group P1 with the following parameters: $a = 7.45200(10) \text{ \AA}$, $b = 8.45670(10) \text{ \AA}$, $c = 12.9162(2) \text{ \AA}$, $\alpha = 85.7960(10)^\circ$, $\beta = 89.6090(10)^\circ$, $\gamma = 84.8360(10)^\circ$, $V = 808.485(19) \text{ \AA}^3$, $Z = 1$, $D_c = 1.240 \text{ g/cm}^3$, $F(000) = 320.0$, $\mu(\text{CuK}\alpha) = 0.741 \text{ mm}^{-1}$, and $T = 300.15 \text{ K}$. The absolute configuration structure and ORTEP structure are as follows:
- 10



- Description of Equipment and Data Collection:** Rigaku Oxford Diffraction XtaLAB Synergy-S equipped with a HyPix-6000HE area detector Cryogenic system: Oxford Cryostream 800 Cu: $\lambda = 1.54184 \text{ \AA}$, 50W Distance from the crystal to the CCD detector: $d = 35 \text{ mm}$ Tube Voltage: 50
- 15 kV; Tube Current: 1 mA A total of 45334 reflections were collected in the 2θ range from 6.862 to 133.164. The limiting indices were: $-8 \leq h \leq 8$, $-10 \leq k \leq 9$, $-15 \leq l \leq 15$; which yielded 5552 unique reflections ($R_{\text{int}} = 0.0506$). The structure was solved using SHELXT (Sheldrick, G. M. 2015. Acta Cryst. A71, 3-8) and refined using SHELXL (against F^2) (Sheldrick, G. M. 2015. Acta Cryst. C71, 3-8). The total number of refined parameters was 389, compared with 5552 data. All reflections
- 20 were included in the refinement. The goodness of fit on F^2 was 1.051 with a final R value for $[I \geq 2\sigma(I)]$ $R1 = 0.0458$ and $wR2 = 0.1282$. The largest differential peak and hole were 0.27 and -0.20 $\text{\AA}^{-3}$.

Description of Crystal Preparation: 50mg (*R*)-1-benzyl-3-ethylpiperidin-4-one complex with (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid complex was dissolved in 1mL MeOH and kept in a 4mL vial. The solution evaporates slowly at room temperature. Crystals were observed on the second day.

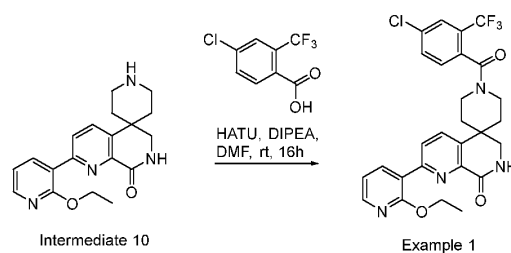
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Synthesis of Examples:

Route A

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-[4-chloro-2-(trifluoromethyl)benzoyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 1)

10



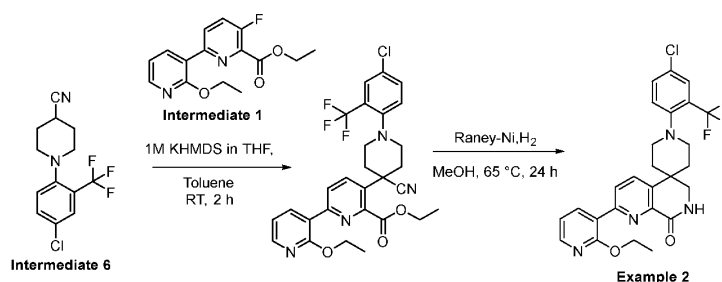
To a stirred solution of 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (50 mg, 0.26 mmol) (Intermediate 10) in DMF (5 mL) under nitrogen at 0°C was added DIPEA (0.1 mL, 0.66 mmol) and HATU (127 mg, 0.33 mmol). The reaction mixture was stirred for 10 min and then added 4-chloro-2-(trifluoromethyl)benzoic acid (80 mg, 0.22 mmol). The reaction mixture was stirred at 25-30°C for 16h. The reaction was quenched with ice-cold water (10 mL) and extracted with DCM (2 x 20 mL). The organic layer was dried over Na₂SO₄ and concentrated to get crude (100 mg) as brown sticky compound which shows 20% of desired product. The crude product was further purified by prep HPLC, followed by lyophilization to afford 1'-[4-chloro-2-(trifluoromethyl)benzoyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (10 mg, 8%) (Example 1) as light pink solid.

20

Analytical data for Example 1 is in Table 2.

Route B

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 2)



To a stirred solution of ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (100 mg, 0.344 mmol) (Intermediate 1) and 1-(4-chloro-2-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (149 mg, 0.517 mmol) (Intermediate 6) in Toluene (5 mL) at RT was added KHMDS (1M in THF) (0.5 mL, 0.500 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was quenched cautiously with Sat NH_4Cl (2 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulfate and evaporated. The crude product was purified by flash column chromatography using EtOAc-PET ether (0 to 10%) to afford ethyl 5-(1-(4-chloro-2-(trifluoromethyl)phenyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (20 mg, 0.031 mmol, 8.9%) as a colourless gum.

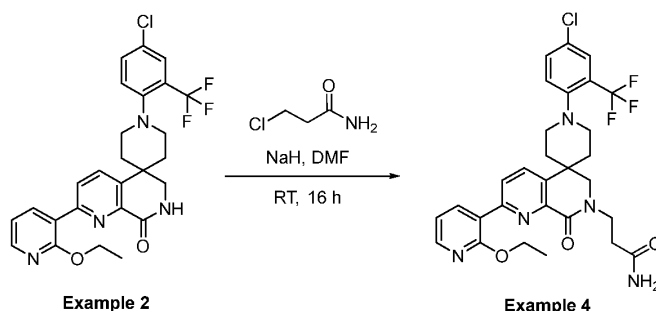
LCMS: 2.94 min, 559.2 (M+H)⁺, Method A

To a stirred solution of ethyl 5-(1-(4-chloro-2-(trifluoromethyl)phenyl)-4-cyanopiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (100 mg, 0.179 mmol) in Ethanol (1 mL) and Water (0.2 mL) at RT was added Raney nickel (188 mg, 2.147 mmol). The reaction mixture was stirred at 65 °C under 75 psi of hydrogen pressure for 24 h. The reaction mixture was filtered through celite and washed with MeOH (20 mL). The filtrate was evaporated, and the crude was purified by prep HPLC. The pure fractions were lyophilized. The residue was dissolved in DCM (20 mL), washed with 10% NaHCO_3 (3 mL), brine (3 mL), dried over sodium sulfate, evaporated and lyophilized to afford 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (40 mg, 0.077 mmol, 43%) (Example 2) as a white solid.

Analytical data for Example 2 is in Table 3.

Route C

Typical procedure for the preparation of lactams as exemplified by the preparation of 3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide (Example 4)



5

To a stirred solution of 1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (20 mg, 0.039 mmol) (Example 2) in DMF (1 mL) at 0 °C was added NaH (2.3 mg, 0.058 mmol) and stirred at RT for 30 min. 3-chloropropanamide (4.99 mg, 0.046 mmol) in DMF (1 mL) was added to the reaction mixture and stirred at RT for 16 h. The reaction mixture was diluted with ice water (20 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by prep HPLC and the fractions were lyophilized. The residue was dissolved in DCM (20 mL), washed with 10% NaHCO₃ (5 mL), water (5 mL), brine (5 mL), dried over sodium sulfate, evaporated and lyophilized to afford 3-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)propanamide as a white solid (8.3 mg, 0.014 mmol, 36%) (Example 4).

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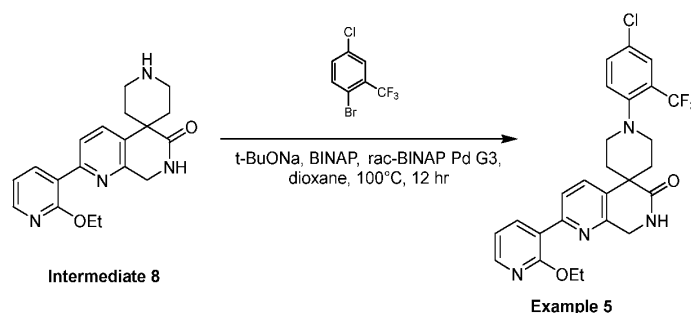
Analytical data for Example 4 is in Table 4.

Route D

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one (Example 5)

20

163

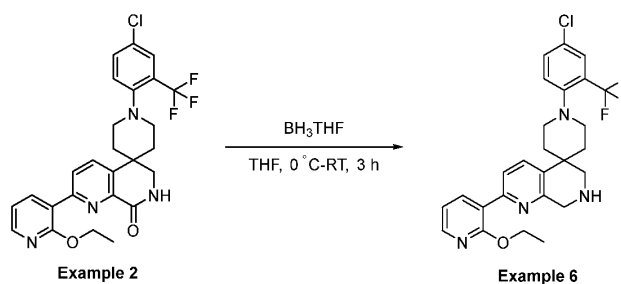


To a solution of 2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6-one (5 mg, 14.78 μmol) (Intermediate 8) and 1-bromo-4-chloro-2-(trifluoromethyl)benzene (4.60 mg, 17.74 μmol , 2.61 μL) in dioxane (0.2 mL) was added sodiumtert-butoxide (7.10 mg, 73.90 μmol), methanesulfonato[2,2-bis(diphenylphosphino)-1,1-binaphthyl](2-amino-1,1-biphenyl-2-yl) palladium(II) (2.93 mg, 2.96 μmol) and ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (1.84 mg, 2.96 μmol) at 25 $^\circ\text{C}$ under nitrogen. The reaction mixture was heated to 100 $^\circ\text{C}$ and stirred at 100 $^\circ\text{C}$ for 12 hr. Three additional vials were set up as described above. After cooling to RT, all of four reaction mixtures were combined, filtered and the filtrate was concentrated under reduced pressure to get a crude, which was purified by prep-TLC (EtOAc/MeOH= 10/1, R_f = 0.57, R_f = 0.00) to get two peaks. Two peaks were purified by prep-HPLC to get 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one (2.7 mg, 12%) (Example 5) as a white solid.

Analytical data for Example 5 is in Table 5.

15 Route E

Typical procedure for the preparation of amines as exemplified with the preparation of 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine] (Example 6)

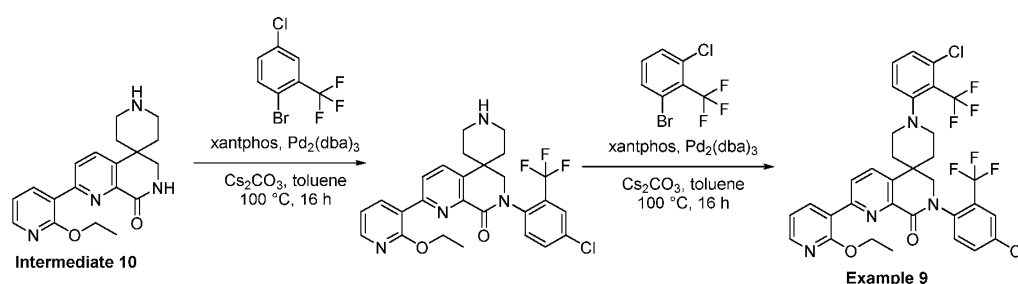


To a stirred solution of 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (20 mg, 0.039 mmol) (Example 2) in THF (1 mL) was added borane THF complex (0.077 mL, 0.077 mmol) at 0 °C and stirred reaction mixture for 3 h at RT. The reaction mixture was quenched with MeOH (10 mL), stirred for 16 h at RT and concentrated under reduced pressure to afford crude. The crude was purified by prep HPLC and the fractions were lyophilized to afford 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine] (2.1 mg, 0.004 mmol, 11%) (Example 6) as white solid.

Analytical data for Example 6 is in Table 6.

10 Route F

Typical procedure for the preparation of lactams as exemplified with the preparation of 1'-[3-chloro-2-(trifluoromethyl)phenyl]-7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 9)



A solution of 1-bromo-4-chloro-2-(trifluoromethyl)benzene (115 mg, 0.443 mmol) and 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (100 mg, 0.295 mmol) (Intermediate 10) in toluene (2 mL) was degassed with nitrogen for 5 min. Cs_2CO_3 (193 mg, 0.591 mmol), xantphos (11.97 mg, 0.021 mmol) and $\text{Pd}_2(\text{dba})_3$ (13.53 mg, 0.015 mmol) were added and the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated and the crude product was purified by prep HPLC (Method B). The fractions were lyophilized. The residue was basified with 10% NaHCO_3 solution and extracted with DCM (3 x 5 mL). The combined organic extracts were evaporated and lyophilized to afford 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (20 mg, 0.04 mmol, 14%) as a white solid.

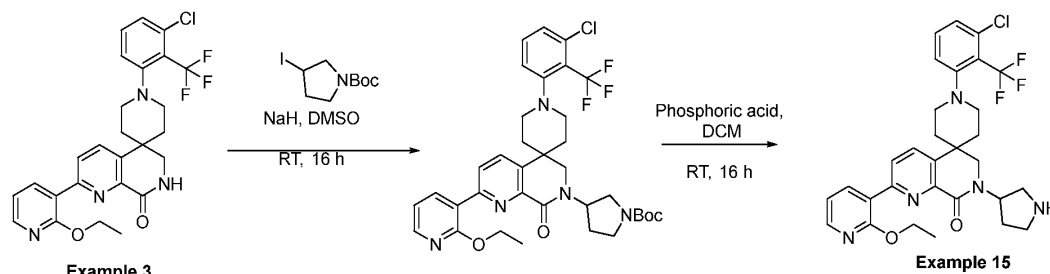
LCMS: 1.51 min, 517.2 (M+H)⁺, Method A

A solution of 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (20 mg, 0.039 mmol) and 1-bromo-3-chloro-2-(trifluoromethyl)benzene (15.1 mg, 0.058 mmol) in toluene (2 mL) was degassed with nitrogen for 5 min. Cs₂CO₃ (25.2 mg, 0.077 mmol), xantphos (1.6 mg, 2.71 μmol) and Pd₂(dba)₃ (1.8 mg, 1.934 μmol) were added and the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated and the crude product was purified by prep HPLC. The fractions were lyophilized. The residue was basified with 10% NaHCO₃ solution and extracted with DCM (3 x 5 mL). The combined organic extracts were evaporated and lyophilized to afford 1'-[3-chloro-2-(trifluoromethyl)phenyl]-7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (4.86 mg, 6.92 μmol, 18%) (Example 9) as an off white solid.

Analytical data for Example 9 is in Table 7.

Route G

Typical procedure for the preparation of amines as exemplified with the preparation of 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 15)



To a stirred solution of 1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (20 mg, 0.039 mmol) (Example 3) in DMSO (1 mL) were added NaH (3.09 mg, 0.077 mmol) at rt and tert-butyl 3-iodopyrrolidine-1-carboxylate (22.99 mg, 0.077 mmol). The reaction mixture was stirred at RT for 16 h, quenched with ice cold water (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organic extracts were washed with brine solution (10 mL), dried over sodium sulfate and evaporated to afford crude product tert-butyl 3-(1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate as red gummy liquid (24 mg, 0.035 mmol, 35%).

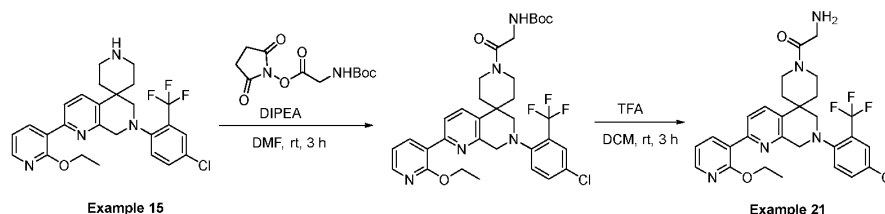
LCMS: 3.90 min, 686.3 (M+H)⁺, Method B

To a stirred solution of tert-butyl 3-(1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (20 mg, 0.029 mmol) in DCM (3 mL). Then added phosphoric acid (14.28 mg, 0.146 mmol) at rt. Reaction mixture was stirred at rt for 16h. The DCM layer was decanted, and the residue was washed with DCM (2 x 10 mL). The crude residue was added 10% NaHCO₃ solution and adjusted to pH ~ 8. The aqueous layer was decanted, triturated with water (2 x 10 mL), decanted and lyophilized to afford as yellow solid. Crude reaction mass was purified by prep HPLC. Sample was lyophilized to afford product 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (1.03 mg, 0.0017 mmol) (Example 15) as a white solid.

Analytical data for Example 15 is in Table 8.

Route H

Typical procedure for the preparation of amines as exemplified by the preparation of 2-amino-1-[7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]ethenone (Example 21)



To a stirred solution of 7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (20 mg, 0.040 mmol) (Example 15) in DMF (1 mL) was added DIPEA (0.01042 mL, 0.060 mmol) followed by 2,5-dioxopyrrolidin-1-yl (tert-butoxycarbonyl)glycinate (16.24 mg, 0.060 mmol) at rt and reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL X 2/3). Combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude tert-butyl (2-(7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-2-oxoethyl)carbamate (20 mg, 0.029 mmol, 74%) as gummy solid which was used for next step without further purification.

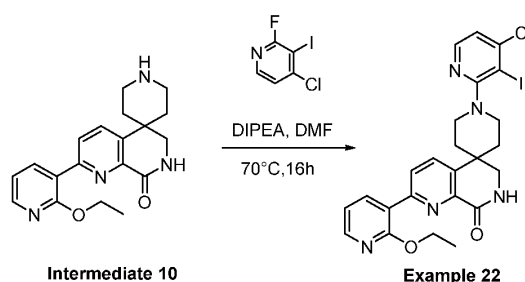
LCMS: 3.25 min, 660.0 (M+H)⁺, Method B

To stirred solution of tert-butyl (2-(7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-2-oxoethyl)carbamate (20 mg, 0.030 mmol) in DCM (1 mL) was added TFA (0.117 mL, 1.515 mmol) at 0 °C and reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated under vacuum and purified by prep HPLC. The pure fractions were lyophilized to afford 2-amino-1-(7'-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)ethan-1-one (4.25 mg, 7.51 μmol, 25%) (Example 21) as white solid.

Analytical data for Example 21 is in Table 9.

10 Route I

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-(4-chloro-3-iodopyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 22)



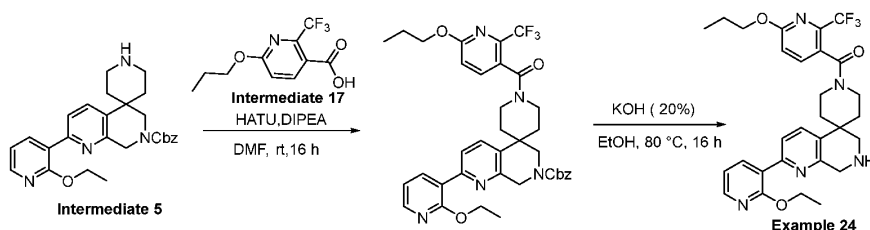
To a stirred solution of 2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (300 mg, 0.886 mmol) (Intermediate 10) in DMF (2 mL) were added DIPEA (0.310 mL, 1.773 mmol) and 4-chloro-2-fluoro-3-iodopyridine (342 mg, 1.330 mmol) and reaction mixture was stirred at 70 °C for 16h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 2). combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude. The crude compound was purified by Biotage-Isolera using 25g silica gel cartridge and eluted with 0 to 10% MeOH in DCM. Pure fractions were concentrated under reduced pressure to afford 1-(4-chloro-3-iodopyridin-2-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (250 mg, 0.373 mmol, 42%). The pure product (15 mg) was purified by prep HPLC. The fraction was collected and lyophilized to obtain 1-(4-chloro-3-iodopyridin-2-

yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one) (4.2 mg) (Example 22) as off white solid.

Analytical data for Example 22 is in Table 10.

Route J

- 5 **Typical procedure for the preparation of amides as exemplified by the preparation of [2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]methanone (Example 24)**



- To a stirred solution of benzyl 2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-
 10 [1,7]naphthyridine]-7'(8'H)-carboxylate (200 mg, 0.436 mmol) (Intermediate 5) in DMF (5 mL) were added DIPEA (282 mg, 2.181 mmol), 6-propoxy-2-(trifluoromethyl)nicotinic acid (130 mg, 0.523 mmol) (Intermediate 17) followed by HATU (249 mg, 0.654 mmol) at RT and reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL x 2). Combined organic extract was washed with brine (30 mL),
 15 dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude. The crude was purified by flash silica column chromatography in 40 to 60% EtOAc in PET ether to afford benzyl 2'-(2-ethoxypyridin-3-yl)-1-(6-propoxy-2-(trifluoromethyl)nicotinoyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (140 mg, 0.151 mmol, 35%) as a brown color gummy.

- 20 **LCMS:** 3.97 min, 690.3 (M+H)⁺, Method B

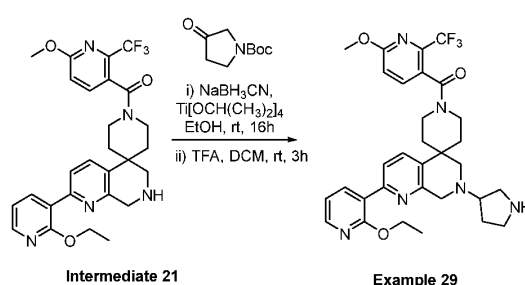
- To a stirred solution of benzyl 2'-(2-ethoxypyridin-3-yl)-1-(6-propoxy-2-(trifluoromethyl)nicotinoyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (50 mg, 0.072 mmol) in EtOH (2 mL) was added 20% KOH in H₂O (40.7 mg, 0.145 mmol) and reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated to get crude. The crude was purified by prep
 25 HPLC. Fractions were collected and lyophilized to obtain (2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-

6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)(6-propoxy-2-(trifluoromethyl)pyridin-3-yl)methanone (20 mg, 0.035 mmol, 49%) (Example 24) as an off white solid.

Analytical data for Example 24 is in Table 11.

Route K

- 5 **Typical procedure for the preparation of amides as exemplified by the preparation of [2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]methanone (Example 29)**



- To a stirred solution of (2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)methanone (50 mg, 0.095 mmol) (Intermediate 21) in ethanol (5 mL) were added tert-butyl 3-oxopyrrolidine-1-carboxylate (35.1 mg, 0.190 mmol), titanium(IV) isopropoxide (26.9 mg, 0.095 mmol) followed by sodium cyanoborohydride (11.91 mg, 0.190 mmol) at 0 °C and reaction was allowed stir at rt for 16 h. The reaction mixture was precipitated using ACN (20 mL) and precipitate filtered off. Solid was washed with ACN (20 mL) and combined filtrate was collected and concentrated to get tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)nicotinoyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (50 mg, 0.030 mmol, 32%) as brown gum.

LCMS: 3.16 min, 697.1 (M+H)⁺, Method B

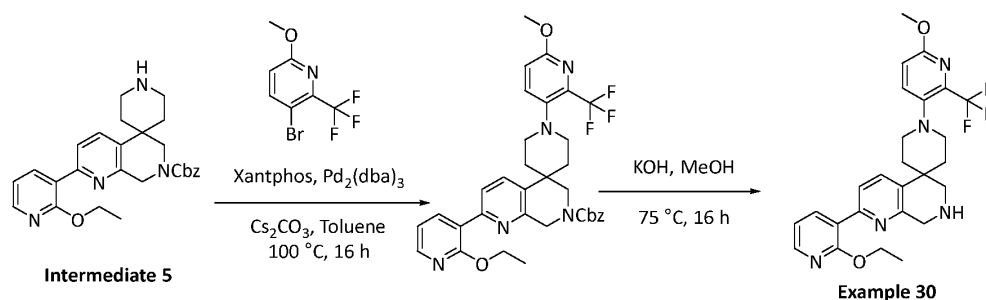
- To a stirred solution of tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)nicotinoyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (50 mg, 0.072 mmol) in DCM (2 mL) was added TFA (8.18 mg, 0.072 mmol) at 0 °C and reaction was allowed to stir at rt for 3 h. The reaction mixture was concentrated to get crude. Crude product was purified by prep HPLC. Fractions were collected and lyophilized. The resulting gum was dissolved in DCM (5 mL) and washed with 10% sodium bicarbonate solution. The

organic layer was dried over anhydrous sodium sulfate and concentrated to get colourless gum which was re-dissolve in ACN:water (1:3) and lyophilized to obtain rac-(2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)methanone (1.34 mg, 2.100 μ mol, 3%) (Example 29) as an off white solid.

Analytical data for Example 29 is in Table 12.

Route L

Typical procedure for the preparation of amines as exemplified by the preparation of 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine] (Example 30)

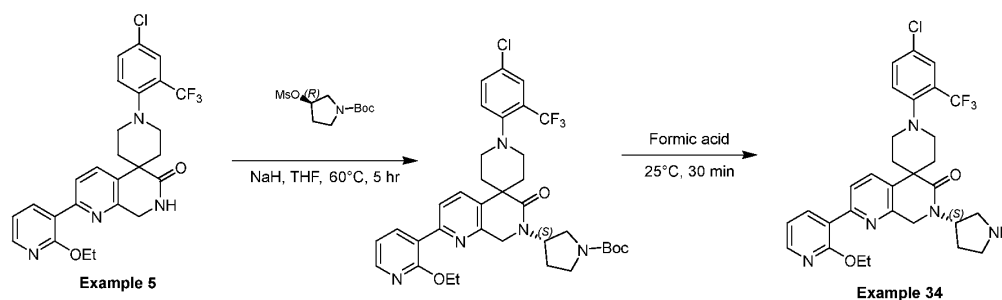


was stirred at 75 °C for 16 h. The reaction mixture was quenched with water (5 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude product was purified by prep HPLC. The fractions were lyophilized. The residue was basified with 10% NaHCO₃ solution and extracted with DCM (3 x 5 mL). The combined organic extracts were evaporated and lyophilized to afford 2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (16.93 mg, 0.031 mmol, 16%) (Example 30) as a white solid.

Analytical data for Example 30 is in Table 13.

Route M

10 **Typical procedure for the preparation of lactams as exemplified by the preparation of (S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (Example 34).**



To a solution of 1'-(4-chloro-2-(trifluoromethyl)phenyl)-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one (35 mg, 67.71 μmol) (Example 5) and tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (71.86 mg, 270.82 μmol) in THF (2 mL) was added NaH (13.54 mg, 338.53 μmol, 60% purity) at 0 °C under nitrogen. The reaction mixture was heated to 60 °C and stirred at 60 °C for 5 hr. After cooling to 0 °C, the reaction mixture was quenched with water (2 mL) and concentrated under reduced pressure to get a crude, which was purified by prep-TLC (PET ether/EtOAc= 2/1, R_f = 0.2) to get tert-butyl (S)-3-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (25 mg, 53%) as a yellow oil.

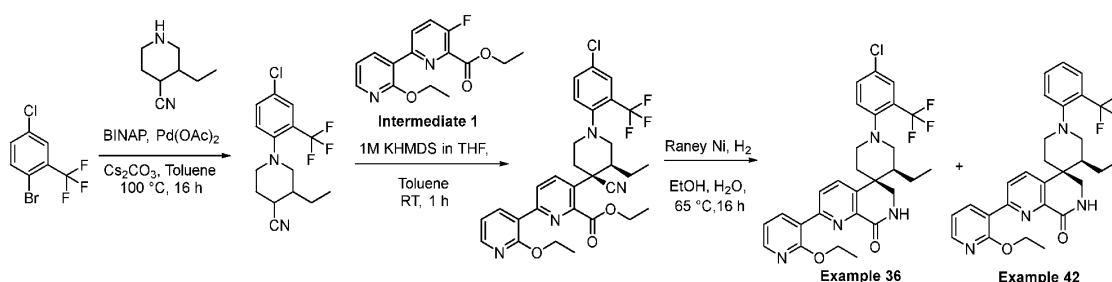
LCMS: 1.16 min, 686.3 (M+H)⁺, Method O

A solution of tert-butyl (S)-3-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (22.00 mg, 32.06 μ mol) in formic acid (0.5 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to get a crude, which was purified by prep-HPLC to get (S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one (9.3 mg, 49%) (Example 34) as a yellow oil.

Analytical data for Example 34 is in Table 14.

Route N

Typical procedure for the preparation of lactams as exemplified by the preparation of *rac*-(3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Example 36) and *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Example 42)



A solution of 1-bromo-4-chloro-2-(trifluoromethyl)benzene (500 mg, 1.927 mmol) and 3-ethylpiperidine-4-carbonitrile (400 mg, 2.89 mmol) in toluene (8 mL) was degassed with nitrogen for 5 min. Cs_2CO_3 (1.3 g, 3.85 mmol), BINAP (240 mg, 0.385 mmol), and $\text{Pd}(\text{OAc})_2$ (44 mg, 0.194 mmol) were added. The reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated, and the crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 10%) to afford 1-(4-chloro-2-(trifluoromethyl)phenyl)-3-ethylpiperidine-4-carbonitrile (510 mg, 1.608 mmol, 83%) as a colourless gum.

LCMS: 3.11 min, 317.0 ($\text{M}+\text{H}$)⁺, Method B

To a stirred solution of ethyl 2'-ethoxy-5-fluoro-[2,3'-bipyridine]-6-carboxylate (470 mg, 1.619 mmol) (Intermediate 1) and 1-(4-chloro-2-(trifluoromethyl)phenyl)-3-ethylpiperidine-4-carbonitrile (513 mg, 1.619 mmol) in toluene (8 mL) at RT was added KHMDS (0.5 M in Toluene) (3.24 mL,

1.619 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with sat NH₄Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash column chromatography using EtOAc in PET ether (0 to 10%) to afford *rac*-ethyl 5-((3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (400 mg, 0.326 mmol, 20%) as a pale yellow gum.

LCMS: 3.70 min, 587.0 (M+H)⁺, Method B

To a stirred solution of *rac*-ethyl 5-((3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-4-cyano-3-ethylpiperidin-4-yl)-2'-ethoxy-[2,3'-bipyridine]-6-carboxylate (400 mg, 0.681 mmol) in EtOH (9 mL) and water (1 mL) was added Raney nickel (1 g, 11.40 mmol). The reaction mixture was stirred under 5 atm of H₂ atmosphere at 65 °C for 16 h. As per LCMS, two compounds were observed. The reaction mixture was filtered through celite and washed with EtOAc (200 mL). The filtrate was evaporated, and the crude product was purified by preparative purification to yield two products. The pure fractions corresponding to *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one were lyophilized. The residue was dissolved in DCM (10 mL), washed with 10% NaHCO₃ solution (5 mL), brine (5 mL), dried over anhydrous sodium sulfate, evaporated and lyophilized to afford *rac*-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (40 mg, 0.076 mmol, 37%) (Example 42) as a white solid.

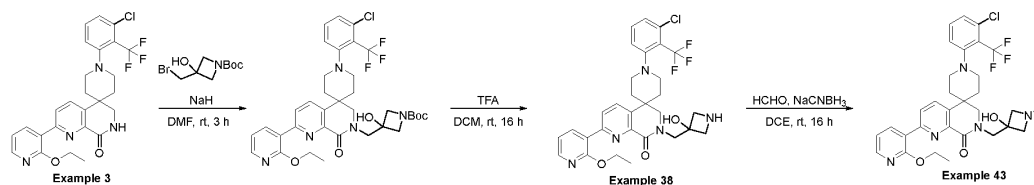
The pure fractions corresponding to *rac*-(3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (Example 36) were lyophilized. The residue was dissolved in DCM (10 mL), washed with 10% NaHCO₃ solution (5 mL), brine (5 mL), dried over anhydrous sodium sulfate, evaporated and lyophilized to afford *rac*-(3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (3.24 mg, 5.79 μmol, 1%) (Example 36) as a white solid.

Analytical data for Example 36 and Example 42 is in Table 15.

Route O

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-

yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 38) and 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 43)



- 5 To a stirred solution of 1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one (50 mg, 0.097 mmol) (Example 3) in DMF (1 mL) was added NaH (7.74 mg, 0.193 mmol) at 0 °C and reaction mixture was stirred for 30 min. tert-butyl 3-(bromomethyl)-3-hydroxyazetidine-1-carboxylate (38.6 mg, 0.145 mmol) in DMF (1 mL) was added to reaction and reaction mixture was slowly allowed to stir at RT for 3 h.
- 10 The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL X 2). Combined organic extract was washed with brine (10 x 2 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude tert-butyl 3-((1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-3-hydroxyazetidine-1-carboxylate (100 mg, 0.074 mmol, 77 %)
- 15 as gummy solid which was used for next step without further purification.

LCMS: 3.14 min, 702.0 (M+H)⁺, Method B

- To a stirred solution of tert-butyl 3-((1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-3-hydroxyazetidine-1-carboxylate (50 mg, 0.071 mmol) in DCM (1 mL) was added TFA at 0 °C (0.027 mL, 0.356 mmol)
- 20 and reaction mixture was allowed to stir at RT for 16 h. The reaction mixture was concentrated to get crude. Crude was purified by prep HPLC. Fractions were concentrated, obtained solid was basified with 10% NaHCO₃ (10 mL), product was extracted with DCM (10 mL x 2). Combined organic extract was dried over sodium sulphate, concentrated and lyophilized to afford 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxyazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (7.91 mg, 0.013 mmol, 18%)
- 25 (Example 38) as white solid.

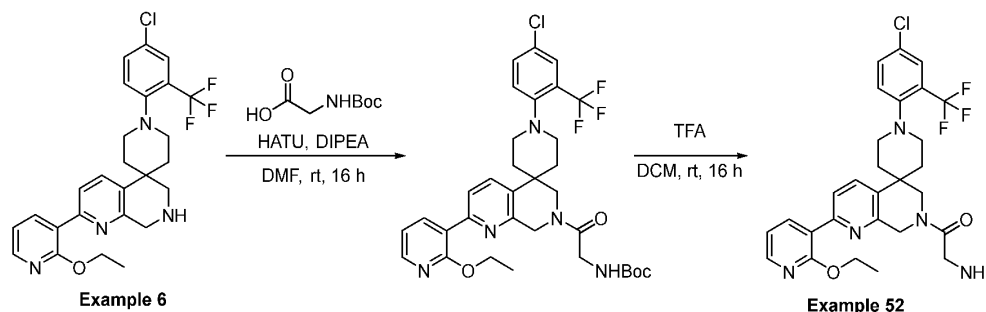
A stirred solution of 1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-[(3-hydroxyazetidin-3-yl)methyl]-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one (40

mg, 0.066 mmol) (Example 38) and formaldehyde (2.394 mg, 0.080 mmol) in DCE (2 mL) was added sodium cyanoborohydride (8.35 mg, 0.133 mmol) at 0 °C and reaction mixture was slowly allowed to stir at rt for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (15 mL x 2). Combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude. Crude was purified by prep HPLC purification in TFA method. The collected fractions were concentrated and obtained solid was dissolved in DCM (10 mL). The organic layer was washed with 10% NaHCO₃ solution and dried over anhydrous sodium sulphate, filtered and concentrated and lyophilized to afford 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (2.49 mg, 3.84 μmol, 6%) (Example 43) as white solid.

Analytical data for Example 38 and Example 43 is in Table 16.

Route P

Typical procedure for the preparation of amines as exemplified by the preparation of 2-amino-1-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]ethanone (Example 52)



To a stirred solution of 1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (25mg, 0.050 mmol) (Example 6) in DMF (8 mL) were added (tert-butoxycarbonyl)glycine (8.71 mg, 0.050 mmol), DIPEA (0.018 ml, 0.099 mmol) followed by HATU (22.68 mg, 0.060 mmol) and reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 2). Combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford crude tert-butyl (2-(1-(4-chloro-2-

(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-2-oxoethyl)carbamate (50 mg, 0.076 mmol) as colourless thick liquid.

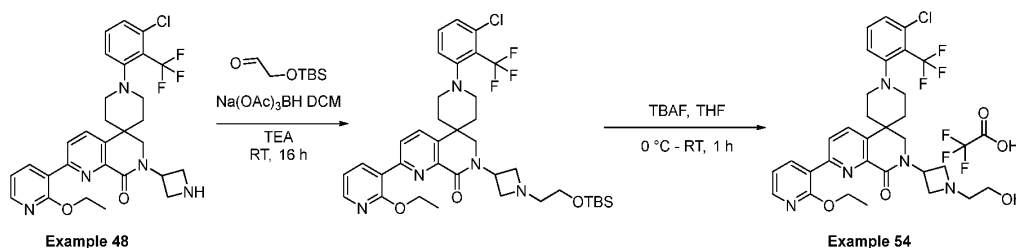
LCMS: 4.01 min, 661.3 (M+H)⁺, Method B

To a stirred solution of tert-butyl (2-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-2-oxoethyl)carbamate (50 mg, 0.076 mmol) in DCM (1 mL) was added TFA (5.84 μ l, 0.076 mmol) and reaction mixture was stirred at RT for 16 h. The reaction mixture was concentrated and neutralized with 10% NaHCO₃ and extracted with EtOAc (20 mL x 2). Combined organic extract was washed with water (20 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford crude. Crude product was purified by Prep-HPLC. Pure fractions were collected and concentrated under reduce pressure to get white solid which was neutralized with aqueous 10% NaHCO₃ (10 mL) and extracted with DCM (20 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated to get white solid which was re-dissolved in ACN:water 1:3 and lyophilized to afford 2-amino-1-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]ethanone (3.94 mg, 0.076 mmol, 9%) (Example 52) as an off white solid.

Analytical data for Example 52 is in Table 17.

Route Q

Typical route for the preparation of aminoalcohol as exemplified by the preparation of 1'-(3-chloro-2-(trifluoromethyl)phenyl)-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one trifluoroacetate (Example 54)



To a stirred solution of 7-(azetidin-3-yl)-1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one (40 mg, 0.070 mmol) (Example 48) and 2-((tert-butyldimethylsilyl)oxy)acetaldehyde (18.28 mg, 0.105 mmol) in DCM (3 mL) at RT were

added TEA (0.05 mL, 0.350 mmol), Na(OAc)₃BH (17.8 mg, 0.084 mmol) and acetic acid (0.400 μL, 6.99 μmol). The reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate and evaporated to afford 7'-(1-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)azetidin-3-yl)-1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (50 mg, 0.068 mmol, 98%)

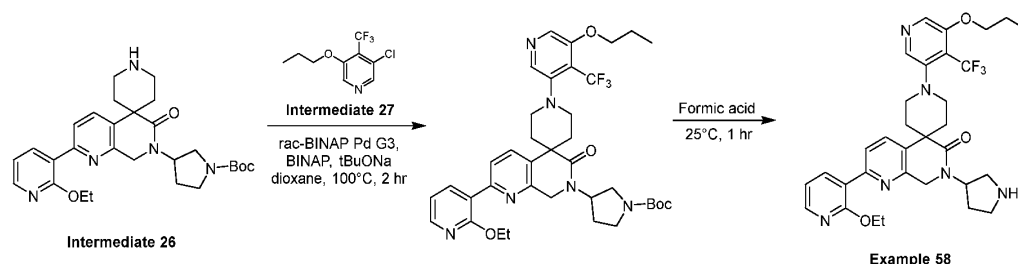
LCMS: 3.20 min, 730.4 (M+H)⁺, Method B

To a stirred solution of 7'-(1-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)azetidin-3-yl)-1-(3-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (40 mg, 0.055 mmol) in THF (3 mL) at 0 °C was added TBAF (0.082 mL, 0.082 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate and evaporated. The crude product was purified by prep-HPLC. The prep fractions were lyophilized to afford 1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one trifluoroacetate (2.08 mg, 6%) (Example 54) as a white solid.

Analytical data for Example 54 is in Table 18.

Route R

Typical procedure for the preparation of lactams as exemplified by the preparation of 2-(2-ethoxypyridin-3-yl)-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one (Example 58)



To a solution of tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (16.95 mg, 33.39 μmol) (Intermediate 26),

3-chloro-5-propoxy-4-(trifluoromethyl)pyridine (10 mg, 41.73 μ mol) (Intermediate 27) and sodium tert-butoxide (12.03 mg, 125.20 μ mol) in dioxane (1 mL) was added bis(diphenylphosphino)-1,1'-binaphthyl (5.20 mg, 8.35 μ mol) and methanesulfonato[2,2-bis(diphenylphosphino)-1,1'-binaphthyl](2-amino-1,1-biphenyl-2-yl)palladium(II) (8.28 mg, 8.35 μ mol) under argon. Then the reaction mixture was heated to 100 °C and stirred at 100 °C for 2 hr. Seven additional vials were set up as described above. After cooling to RT, all eight reaction mixtures were combined, diluted with water (20 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-TLC (eluted with PET ether/EtOAc= 1/2, R_f = 0.49) to give tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-1-(5-propoxy-4-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (21 mg, 9%) as white solid.

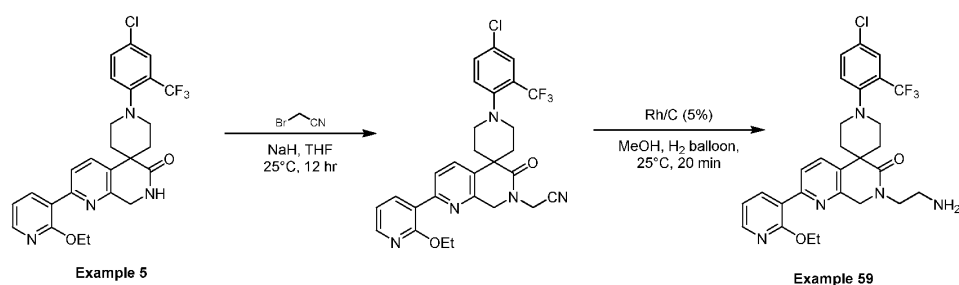
^1H NMR (400 MHz, CD_3OD) δ 8.27 - 8.16 (m, 4H), 8.08 - 7.98 (m, 2H), 7.12 - 7.05 (m, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.20 - 4.10 (m, 2H), 3.70 - 3.47 (m, 5H), 3.44 - 3.33 (m, 4H), 3.27 - 3.21 (m, 2H), 2.40 - 2.31 (m, 2H), 2.24 - 2.13 (m, 4H), 1.87 - 1.81 (m, 2H), 1.46 (s, 12H), 1.42 (t, J = 7.1 Hz, 3H)

A solution of tert-butyl 3-(2'-(2-ethoxypyridin-3-yl)-6'-oxo-1-(5-propoxy-4-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (10 mg, 14.07 μ mol) in formic acid (0.3 mL) was stirred at 25 °C for 1 hr. One additional vial was set up as described above. All two reaction mixtures were combined and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 2-(2-ethoxypyridin-3-yl)-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one (8.2 mg, 47%) (Example 58) as white solid.

Analytical data for Example 58 is in Table 19.

25 Route S

Typical procedure for the preparation of lactams as exemplified by the preparation of 7-(2-aminoethyl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one (Example 59)



To a solution of 1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one (50 mg, 96.72 μ mol) (Example 5) and 2-bromoacetonitrile (11.60 mg, 96.72 μ mol, 6.45 μ L) in THF (2 mL) was added NaH (19.34 mg, 483.60 μ mol, 60% purity) at 0 °C under nitrogen. The reaction mixture was stirred at 25 °C for 12 hr. TLC (PET ether/EtOAc= 2/1, R_f = 0.23) showed starting material was consumed and desired spot was formed. The reaction mixture was quenched with ice-water (2 mL) and extracted with EtOAc (1 mL $\times$ 3). The combine organic phase was concentrated under reduced pressure to get a residue, which was purified by prep-TLC (PET ether/EtOAc= 2/1, R_f = 0.23) to get 2-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)acetonitrile (20 mg, 31%) as a yellow oil.

LCMS: 1.04 min, 556.2 (M+H)⁺, Method O

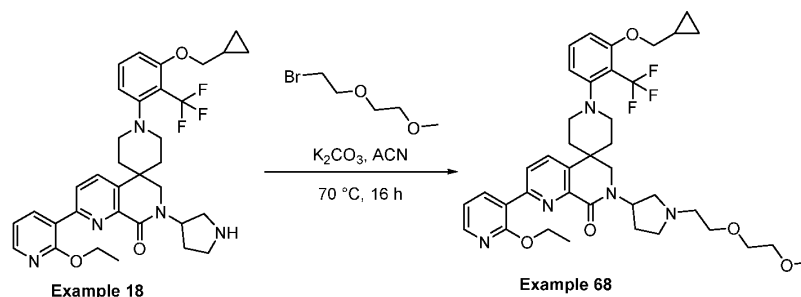
To a solution of 2-(1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)acetonitrile (3 mg, 5.40 μ mol) in MeOH (5 mL) was added Rh/C (3 mg, 1.27 μ mol, 5% purity) and a drop of TFA under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was stirred at 25 °C for 20 min under hydrogen balloon. Four additional vials were set up as described as above. All five reaction mixtures were combined and filtered, the filtrate was concentrated under reduced pressure to get a residue, which was purified by prep-HPLC to get 7-(2-aminoethyl)-1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one g (2.6 mg, 17%) (Example 59) as a white solid.

Analytical data for Example 59 is in Table 20.

Route T

Typical procedure for the preparation of lactams as exemplified by the preparation of 1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-[2-(2-

methoxyethoxy)ethyl]pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one
(Example 68)

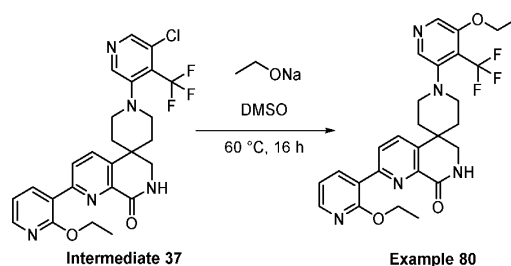


To a stirred solution of 1-(3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (40 mg, 0.046 mmol) (Example 18) in ACN (1 mL) at 0 °C were added 1-bromo-2-(2-methoxyethoxy)ethane (16.96 mg, 0.093 mmol) and K₂CO₃ (9.60 mg, 0.069 mmol). The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was filtered and evaporated. The crude product was purified by flash column chromatography using MeOH in DCM (0 to 10%). The pure fractions were evaporated, and the product was further purified by prep-HPLC. The fractions were lyophilized. The residue was dissolved in DCM (10 mL), washed with 10% NaHCO₃ solution (5 mL), dried over sodium sulfate, evaporated and lyophilized to afford 1-(3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (14.15 mg, 0.019 mmol, 42%) as a white solid.

Analytical data for Example 68 is in Table 21.

Route U

Typical procedure for the preparation of lactams as exemplified by the preparation of 2-(2-ethoxypyridin-3-yl)-1'-[5-ethoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6,7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one (Example 80)

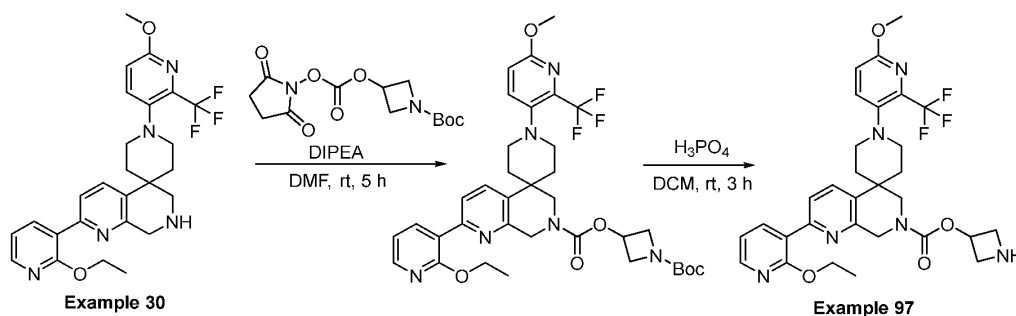


To a stirred solution of 1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (50 mg, 0.097 mmol) (Intermediate 37) in DMSO (0.5 mL) at 0 °C was added sodium ethoxide (33 mg, 0.487 mmol). The reaction mixture was heated at 60 °C for 16 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, and evaporated. The crude product was purified by prep-HPLC and the fractions were lyophilized. The residue was dissolved in DCM (15 mL), basified with 10% NaHCO₃ solution (5 mL), washed with water (5mL), dried over sodium sulfate, evaporated and lyophilized to afford 1-(5-ethoxy-4-(trifluoromethyl)pyridin-3-yl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (6.31 mg, 0.012 mmol, 12%) (Example 80) as a white solid.

Analytical data for Example 80 is in Table 22.

Route V

15 **Typical procedure for the preparation of carbamates as exemplified by the preparation of azetidin-3-yl 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-carboxylate (Example 97)**



To stirred solution of 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7,8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine] (100 mg, 0.200 mmol) (Example 30) in DMF (2.0 mL) were added DIPEA (0.070 mL, 0.400 mmol) followed by tert-butyl 3-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)azetidine-1-carboxylate (94 mg, 0.300 mmol) (Intermediate 50) at 0 °C and reaction mixture was stirred at RT for 5 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to get the 1-(tert-butoxycarbonyl)azetidin-3-yl 2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (50 mg, 0.072 mmol, 36%) as a brown gum.

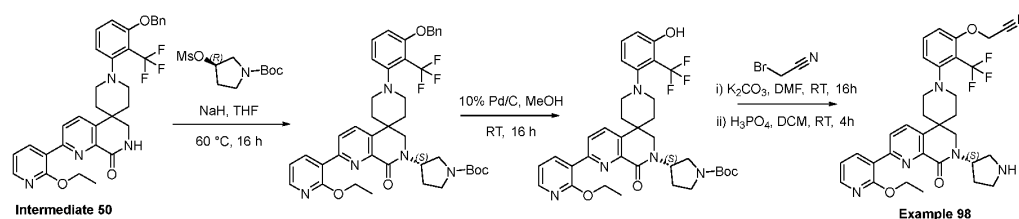
LCMS: 3.49 min, 699.3 (M+H)⁺, Method B

To stirred solution of 1-(tert-butoxycarbonyl)azetidin-3-yl 2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate (50 mg, 0.072 mmol) in DCM (2.0 mL), was added phosphoric acid (85% in water) (7.01 mg, 0.072 mmol) at 0 °C and reaction mixture was stirred at RT for 3 h. The reaction mixture was concentrated, neutralized with 10% NaHCO₃ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated afforded crude compound, which was purified by prep-HPLC. The pure fractions were collected and lyophilized to afford azetidin-3-yl 2'-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7'(8'H)-carboxylate formate salt (5.88 mg, 9.82 μmol, 14%) (Example 97) as a white solid.

Analytical data for Example 97 is in Table 23.

Route W

Typical procedure for the preparation of nitriles as exemplified by the preparation of 2-[3-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)phenoxy]acetonitrile (Example 98)



To a stirred suspension of 1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one (57 mg, 0.097 mmol) (Intermediate 50) in THF (5 mL) at 0 °C was added NaH (20 mg, 0.484 mmol). The reaction mixture was stirred at RT for 30 min. Tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (128 mg, 0.484 mmol) was added at RT. The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was quenched cautiously with saturated ammonium chloride solution (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over sodium sulfate and evaporated. The crude product was purified by flash column chromatography using MeOH in DCM (0 to 10%) to afford tert-butyl (S)-3-(1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (57 mg, 0.062 mmol, 64%) as a yellow gum.

LCMS: 3.32 min, 758.4 (M+H)⁺, Method B

To a stirred solution of tert-butyl (S)-3-(1-(3-(benzyloxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (57 mg, 0.075 mmol) in MeOH (5 mL) at RT was added 10% Pd/C (50 mg, 0.047 mmol) and stirred at RT under 1atm of H₂ pressure for 16h. The reaction mixture was filtered through celite and washed with 20% MeOH-in DCM (20 mL). The filtrate was evaporated and dried under high vacuum to afford tert-butyl (S)-3-(2'-(2-ethoxypyridin-3-yl)-1-(3-hydroxy-2-(trifluoromethyl)phenyl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (38 mg, 0.044 mmol, 59%) as a yellow gum.

LCMS: 2.76 min, 668.3 (M+H)⁺, Method B.

To a stirred solution of tert-butyl (S)-3-(2'-(2-ethoxypyridin-3-yl)-1-(3-hydroxy-2-(trifluoromethyl)phenyl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (35 mg, 0.052 mmol) in DMF (1 mL) at RT were added 2-bromoacetonitrile (13 mg, 0.105 mmol) and K₂CO₃ (11 mg, 0.079 mmol). The reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with water (4 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over sodium sulfate and evaporated to afford tert-butyl (S)-3-(1-(3-(cyanomethoxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (27 mg, 0.029 mmol, 55%) as a yellow gum.

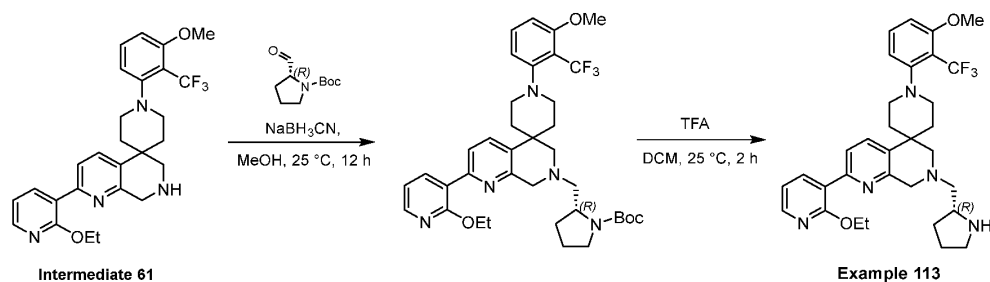
LCMS: 2.88 min, 707.3 (M+H)⁺, Method B

To a stirred solution of tert-butyl (S)-3-(1-(3-(cyanomethoxy)-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-8'-oxo-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)pyrrolidine-1-carboxylate (25 mg, 0.035 mmol) in DCM (1 mL) at 0 °C was added phosphoric acid (25 mg, 0.255 mmol). The reaction mixture was stirred at RT for 4 h. The reaction mixture was basified with 10% NaHCO₃ solution (5 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were dried over sodium sulfate and evaporated. The crude product was purified by prep-HPLC. The prep fractions were lyophilized to afford (S)-2-(3-(2'-(2-ethoxypyridin-3-yl)-8'-oxo-7'-(pyrrolidin-3-yl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-2-(trifluoromethyl)phenoxy)acetonitrile formate (1.25 mg, 1.968 μmol, 6%) (Example 98) as a white solid.

Analytical data for Example 98 is in Table 24.

Route X

Typical procedure for the preparation of methyl pyrrolidine as exemplified (R)-2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 113)



To a solution of 2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (intermediate 61) (20 mg, 40.12 μ mol) in MeOH (1 mL) was added tert-butyl (R)-2-formylpyrrolidine-1-carboxylate (15.99 mg, 80.23 μ mol) and NaCNBH₃ (10.08 mg, 160.47 μ mol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. One additional vial was set up as described above. All two reaction mixtures were diluted with water (10 mL) and extracted with EtOAc (3 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by prep-TLC (PET ether/EtOAc= 1/3, R_f = 0.43) to obtain tert-butyl (R)-2-((2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'-(8'H)-yl)methyl)pyrrolidine-1-carboxylate (25 mg, 46%) as a white solid.

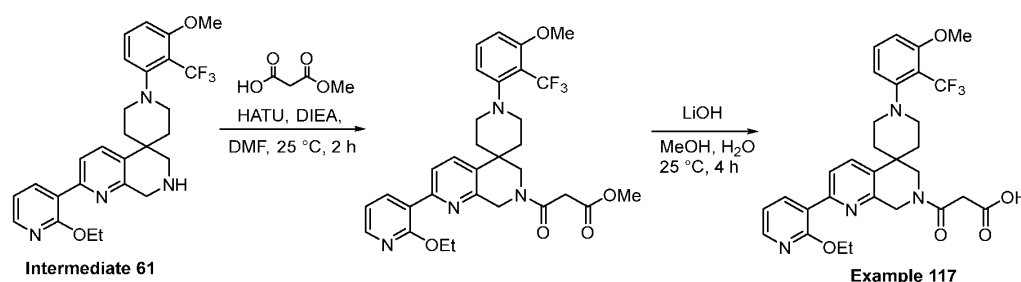
LCMS: 0.59 min, 682.4 [M+H]⁺, Method R'

A solution of tert-butyl (R)-2-((2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (70 mg, 102.67 μmol) in DCM (1 mL) was added TFA (0.2 mL) at 25 °C. The reaction mixture stirred at 25 °C for 2 h and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give (R)-2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (23 mg, 39%) as white solid (Example 113).

Analytical data for Example 113 is in Table 25.

10 Route Y

Typical procedure for the preparation of oxo propionic acid as exemplified by 3-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropanoic acid (Example 117)



- 15 To a solution of 3-methoxy-3-oxopropanoic acid (5.68 mg, 48.14 μmol) and 2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (intermediate 61) (20 mg, 40.12 μmol) in DMF (0.5 mL) were added HATU (30.51 mg, 80.23 μmol) followed by DIPEA (15.55 mg, 120.35 mmol, 20.96 μL) at 25 °C and reaction mixture was stirred at 25 °C for 2 h. One additional vial was set up as described above.
- 20 All two reaction mixtures were diluted with water (2 mL) and extracted with EtOAc (3 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated under reduced pressure and purified by prep-TLC (EtOAc, R_f = 0.6) to obtain methyl 3-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropanoate
- 25 (30 mg, 62%) as white solid.

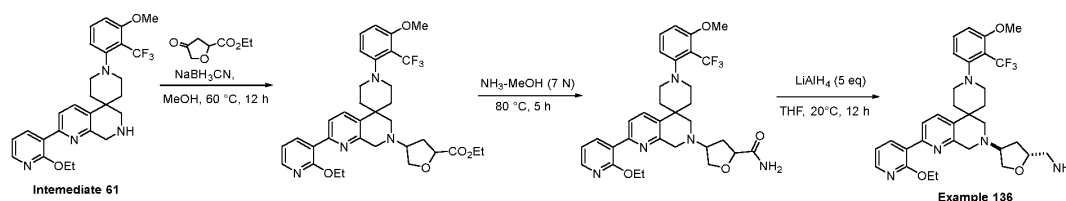
LCMS: 2.23 min, 599.2 [M+H]⁺, Method R'

To a solution of methyl 3-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropanoate (14 mg, 23.39 μmol) in MeOH (0.4 mL) and water (0.2 mL) was added LiOH (2.80 mg, 116.94 μmol) was stirred at 25 °C for 4 h. One additional vial was set up as described above. All two reaction mixtures were concentrated under reduced pressure and purified by prep-HPLC to obtain 3-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)-3-oxopropanoic acid (9.7 mg, 35%) (Example 117) as white solid.

Analytical data for Example 117 is in Table 26.

10 Route Z

Typical procedure for the preparation of *rac*-(2*R*,4*S*)-4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-yl)methanamine (Example 136)



- 15 To a solution of ethyl 4-oxotetrahydrofuran-2-carboxylate (19.03 mg, 120.35 μmol) in MeOH (5 mL) was acidified to pH 4 by acetic acid and stirred at 20 °C for 30 min. The reaction mixture was basified to pH 9 by Et₃N, then added 2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (50 mg, 100.29 μmol) (intermediate 61) and NaCNBH₃ (31.51 mg, 501.47 μmol). The reaction mixture was
- 20 heated to 60 °C and stirred at 60 °C for 12 h. Three additional vials were set up as described above. After cooling to RT, all four reaction mixtures were combined, quenched with water (0.3 mL), concentrated under reduced pressure and was purified by prep-TLC (PET ether/EtOAc= 1/1, peak 1, R_f = 0.36, peak 2, R_f = 0.29) to get ethyl 4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-carboxylate_peak-1 (30 mg, 12%) and ethyl 4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-carboxylate_peak 2 (70 mg, 27%) as colourless oil.
- 25

Peak 1: LCMS: 0.549 min, 641.4(M+H)⁺, Method L

Peak 2: LCMS: 0.547 min, 641.4(M+H)⁺, Method L

A solution of ethyl 4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-carboxylate-Peak-1 (15 mg, 23.41 μmol, 1) in a solution of ammonia in MeOH (0.5 mL, 7 N) was heated to 80 °C and stirred at 80 °C for 5 h. One additional vial was set up as described above. After cooling to RT, all two reaction mixtures were combined and concentrated under reduced pressure to get 4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-carboxamide (25 mg, crude) as a yellow oil, which was used to next step directly without further purification.

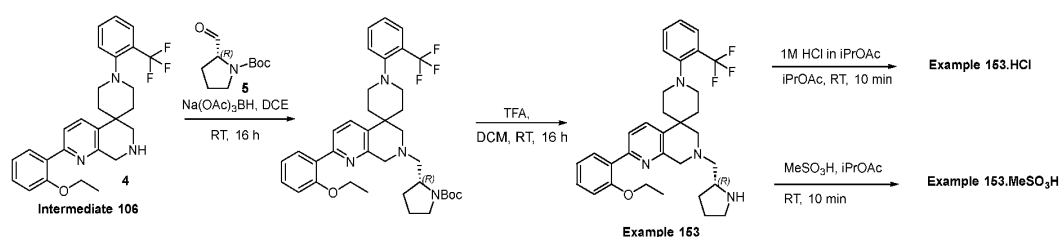
LCMS: 0.47 min, 612.3(M+H)⁺, Method L

To a solution of 4-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)tetrahydrofuran-2-carboxamide (15 mg, 24.52 μmol) in THF (1 mL) was added LAH in THF (2.5 M, 49.05 μL) at 0 °C dropwise. The reaction mixture was stirred at 20 °C for 12 h. One additional vial was set up as described above. After cooling to 0 °C, all two reaction mixtures were combined and quenched with Na₂SO₄ (15 mg) and stirred at 20 °C for 2 h. The suspension was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to get *rel*-[(2R,4S)-4-[2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]oxolan-2-yl]methanamine_peak-1 (5 mg, 13%) (Example 136) as a white solid.

Analytical data for Example 136 is in Table 27.

Route Aa

Typical procedure for the preparation of (*R*)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 153, 153.HCl/MSA)



To a stirred solution of 2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl) phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (1 g, 1.925 mmol) (Intermediate 106) and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate (460 mg, 2.310 mmol) in DCE (10 mL) at 0 °C was added
 5 Na(OAc)₃BH (816 mg, 3.85 mmol). The reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with DCM (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate, evaporated, and purified by flash column chromatography using EtOAc in PET ether (0 to 100%) as an eluent to afford tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (1.1 g, 1.521 mmol, 79%) as a pale white solid.
 10

LCMS: 3.08 min, 651.3 [M+H]⁺, Method B

To a stirred solution of tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (1 g, 1.383 mmol) in DCM (10 mL) at 0 °C was added TFA (1.6 g, 13.83 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was basified cautiously with 10% NaHCO₃ solution (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over sodium sulphate. The resulting residue was purified by prep-HPLC (Method B). The pure prep fractions were lyophilized. The residue was dissolved in DCM (15 mL), washed with 10% NaHCO₃ solution
 15 (5 mL), water (5 mL), dried over sodium sulphate, evaporated and lyophilized to afford (R)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (410 mg, 0.730 mmol, 53%) (Example 153) as an off white solid.
 20

To a stirred solution of (R)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 153) (20 mg, 0.036 mmol) in iPrOAc (1 mL) at 0 °C was added HCl (2M in iPrOAc) (0.02 mL, 0.036 mmol). The reaction mixture was stirred at RT for 10 min. The solid obtained was triturated with
 25

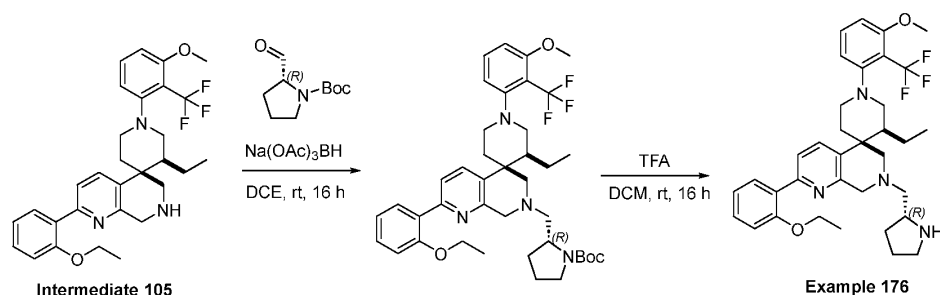
MTBE (2 x 1 mL). The residue was lyophilised to afford (*R*)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] hydrochloride (5.50 mg, 0.00901 mmol, 25%) (Example 153.HCl) as a white solid.

To a stirred solution of (*R*)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 153) (10 mg, 0.018 mmol) in iPrOAc (1 mL) at 0 °C was added MSA (0.2M in iPrOAc) (0.01 mL, 0.018 mmol). The reaction mixture was stirred at RT for 10 min. The reaction mixture was stirred at RT for 10 min. The solid obtained was triturated with MTBE (2 x 1 mL). The residue was purified by prep-HPLC in method I. The prep fractions were lyophilized to afford (*R*)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-1-(2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] methanesulfonate (7.31 mg, 0.011 mmol, 62%) (Example 153.MSA) as a white solid.

Analytical data for Example 153, 153.HCl and 153.MSA is in Table 28.

Route Ab

15 **Typical procedure for the preparation of (3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7'-(*(R)*-pyrrolidin-2-yl)methyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 176)**



To a stirred solution of *rac*-(3*S*,4*S*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Intermediate 105) (55 mg, 0.105 mmol) and tert-butyl (*R*)-2-formylpyrrolidine-1-carboxylate (20.85 mg, 0.105 mmol) in DCE (10 mL) was added Na(OAc)₃BH (44.35 mg, 0.210 mmol) and reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, and the resulting residue purified by flash column chromatography using EtOAc in PET ether (0 to 40%)

to afford [tert-butyl (*R*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (65 mg, 0.091 mmol, 88%) as a white solid.

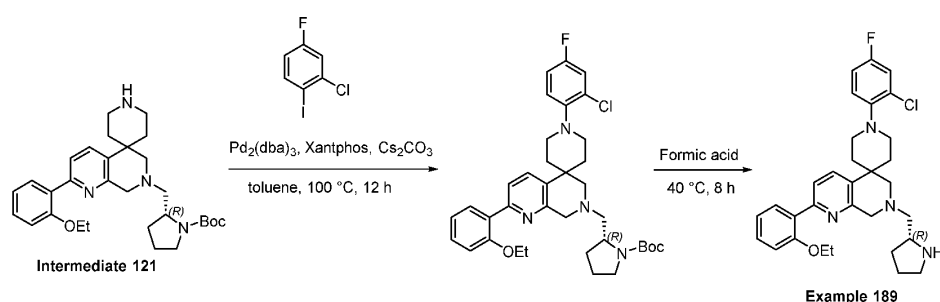
LCMS: 2.22 min, 709.3 [M+H]⁺, Method G.

- 5 To a stirred solution of tert-butyl (*R*)-2-(((3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (65 mg, 0.091 mmol) in DCM (10 mL) was added TFA (0.3 mL) and reaction mixture was stirred at RT for 16 h. The reaction was concentrated and the resulting residue neutralized with aqueous 10% NaHCO₃ solution (10 mL) and extracted with EtOAc (2 x 20 mL). The combined
10 organic layer was dried over anhydrous Na₂SO₄ and purified by Prep. HPLC. The prep fractions were concentrated, and the residue was neutralized with 10% NaHCO₃ solution (10 mL) and extracted with DCM (10 mL). The organic layer was washed with water (10 mL), dried over anhydrous sodium sulphate and lyophilized to afford (3*SR*,4*SR*)-2'-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7'-(((*R*)-pyrrolidin-2-yl)methyl)-7',8'-dihydro-6'H-
15 spiro[piperidine-4,5'-[1,7]naphthyridine] (22 mg, 0.036 mmol, 39%) (Example 176) as a colourless liquid.

Analytical data for Example 176 is in Table 29

Route Ac

- 20 **Typical procedure for the preparation of (*R*)-1-(2-chloro-4-fluorophenyl)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 189):**



To a solution of tert-butyl (*R*)-2-((2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (100 mg, 197.36 μmol) (intermediate 121) and 2-

chloro-4-fluoro-1-iodobenzene (50.61 mg, 197.36 μmol) in toluene (2 mL) was added Cs_2CO_3 (192.91 mg, 592.09 mmol), Xantphos (22.84 mg, 39.47 μmol) and $\text{Pd}_2(\text{dba})_3$ (36.15 mg, 39.47 μmol) at RT and reaction mixture was stirred at 100 °C for 12 h. Four vials were set up as described above. After cooling to RT, all five reaction mixtures were diluted with water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulphate and purified by prep-TLC (PET ether/EtOAc=3/1, R_f = 0.4) to obtain tert-butyl (R)-2-((1-(2-chloro-4-fluorophenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (280 mg, 56%) as white solid.

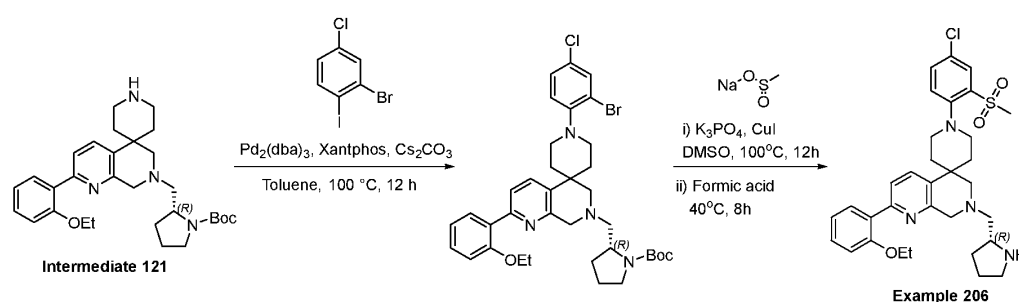
LCMS: 2.42 min, 635.2(M+H)⁺, Method M

A solution of tert-butyl (R)-2-((1-(2-chloro-4-fluorophenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (70 mg, 110.20 μmol) in HCOOH (1 mL) was heated to 40 °C and stirred at 40 °C for 8 h. Three vials were set up as described above. After cooling to RT, all four reaction mixtures were concentrated under reduced pressure and purified by prep-HPLC to obtain (R)-1-(2-chloro-4-fluorophenyl)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (83.7 mg, 36%) (Example 189) as white solid.

Analytical data for Example 189 is in Table 30

Route Ad

Typical procedure for the preparation of (R)-1-(4-chloro-2-(methylsulfonyl)phenyl)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 206):



To a solution of tert-butyl (R)-2-((2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (intermediate 121) (50 mg, 98.68 μmol) and 2-bromo-4-chloro-1-iodobenzene (31.32 mg, 98.68 μmol) in toluene (1 mL) were added Cs_2CO_3 (96.46

mg, 296.05 μ mol), Xantphos (11.42 mg, 19.74 μ mol) followed by $\text{Pd}_2(\text{dba})_3$ (18.07 mg, 19.74 μ mol) and reaction mixture was stirred at 100 °C for 12 h under nitrogen. Five additional vials were set up as described above. After cooling to RT, six reaction mixtures were diluted with water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organics were washed with brine (10 mL), dried over anhydrous sodium sulphate and purified by prep-TLC (PET ether/EtOAc=2/1, R_f = 0.5) to obtain tert-butyl (*R*)-2-((1-(2-bromo-4-chlorophenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (200 mg, 49%) as a white solid.

10 **LCMS:** 2.49 min, 697.1 [M+H]⁺ Method R'

To a solution of tert-butyl (*R*)-2-((1-(2-bromo-4-chlorophenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (50 mg, 71.83 μ mol) and sodium methane sulfinate (9.53 mg, 93.38 μ mol) in DMSO (1 mL) were added K_3PO_4 (15.25 mg, 71.83 μ mol) followed by CuI (13.68 mg, 71.83 μ mol) and reaction mixture was stirred at 110 °C for 12 h under nitrogen. Four additional vials were set up as described above. After cooling to RT, all five reaction mixtures were diluted with water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organics were washed with brine (10 mL), dried over anhydrous sodium sulphate and purified by prep-TLC (PET ether/EtOAc= 4/3, R_f = 0.6) to obtain tert-butyl (*R*)-2-((1-(4-chloro-2-(methylsulfonyl)phenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (70 mg, 28%) as a yellow solid.

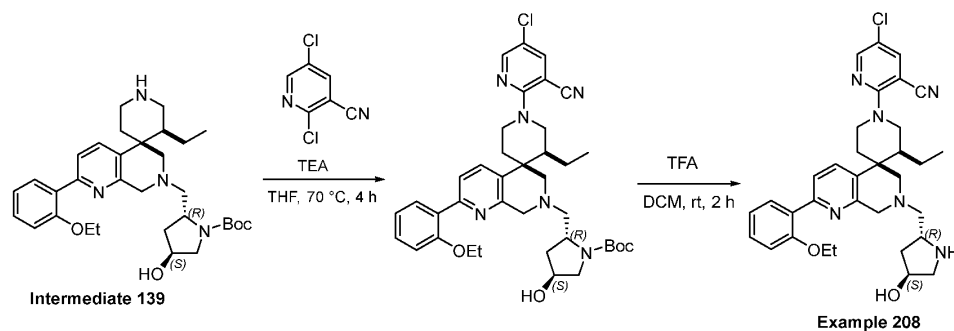
LCMS: 2.16 min, 695.1 [M+H]⁺ Method R'

A solution of (*R*)-2-((1-(4-chloro-2-(methylsulfonyl)phenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (30 mg, 43.15 μ mol) in HCOOH (1 mL) was stirred at 40 °C for 8 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure and purified by prep-HPLC to obtain (*R*)-1-(4-chloro-2-(methylsulfonyl)phenyl)-2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridine] (Example 206) (25.5 mg, 50%) as a white solid.

Analytical data for Example 206 is in Table 31

Route Ae

Typical procedure for the preparation of 5-chloro-2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-7'-(((2R,4S)-4-hydroxypyrrolidin-2-yl)methyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile (Example 208):



5 To a solution of tert-butyl (2R,4S)-2-(((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (50 mg, 90.79 μ mol) (Intermediate 139) in THF (1 mL) were added 2,5 -dichloropyridine-3-carbonitrile (20.42 mg, 118.03 μ mol) followed by Et₃N (27.56 mg, 272.37 μ mol) and reaction mixture was stirred at 70 °C for 4 h. Two additional vials were set up as described above. After cooling to RT,

10 all three mixtures were combined, concentrated and purified by prep-TLC (PET ether/EtOAc= 1/2, R_f = 0.3) to get tert-butyl (2R,4S)-2-(((3SR,4SR)-1-(5-chloro-3-cyanopyridin-2-yl)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (94 mg, 50%) as a white solid.

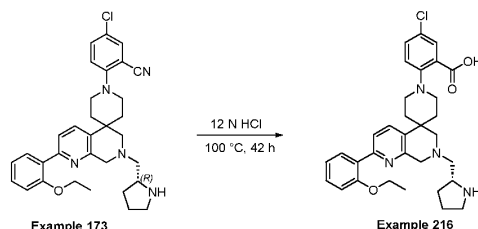
LCMS: 0.62 min, 687.5 (M+H)⁺, Method L

15 To a solution of tert-butyl ((2R,4S)-2-(((3SR,4SR)-1-(5-chloro-3-cyanopyridin-2-yl)-2'-(2-ethoxyphenyl)-3-ethyl-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)-4-hydroxypyrrolidine-1-carboxylate (22.5 mg, 32.74 μ mol) in DCM (1 mL) was added TFA (153.50 mg, 1.35 mmol) and reaction mixture was stirred at RT for 2 h. Three additional vials were set up as described. All four reaction mixtures were combined, concentrated and purified by prep-HPLC
20 to get 5-chloro-2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-7'-(((2R,4S)-4-hydroxypyrrolidin-2-yl)methyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile (39.1 mg, 51%) (Example 208) as a white solid.

Analytical data for Example 208 is in Table 32

Route Af

Typical procedure for the preparation of (*R*)-5-chloro-2-(2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzoic acid (Example 216)



- 5 *tert*-butyl (*R*)-2-((1-(4-chloro-2-cyanophenyl)-2'-(2-ethoxyphenyl)-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7'(8'H)-yl)methyl)pyrrolidine-1-carboxylate (Example 173) (500 mg, 0.779 mmol) was added 10 N HCl (30 mL, 300 mmol) at 25 °C. The reaction mixture was stirred at 100 °C for 42 h. The reaction mixture was cooled to RT and diluted with 10% MeOH in DCM (2 x 20 mL). pH of the reaction mixture was adjusted to ~8 by using 10% sodium hydroxide solution (50 mL) and separated the layers. The aq. layer was extracted with 10% MeOH in DCM (2 x 50 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over Na₂SO₄ and concentrated under vacuum to afford crude compound (100 mg; HPLC purity: 56.0%). The crude was purified by prep- HPLC (Method AP) to afford (*R*)-5-chloro-2-(2'-(2-ethoxyphenyl)-7'-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzoic acid (12 mg, 0.021 mmol, 2.75% yield) (Example 216) as an off-white solid.
- 10
- 15

Analytical data for Example 216 is in Table 33

Table 2 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
1	1'-[4-chloro-2-(trifluoromethyl)benzoyl]-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	A	10 and 4-chloro-2-(trifluoromethyl)benzoic acid		Prep-HPLC: Method K	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 - 8.12 (m, 4H), 7.95 - 7.93 (m, 1H), 7.87 - 7.85 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.20 - 7.15 (m, 1H), 4.48 (q, J = 7.0 Hz, 2H), 3.60 - 3.56 (m, 2H), 3.34 - 3.30 (m, 2H), 2.08 - 1.83 (m, 2H), 1.71 - 1.61 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H).	LCMS: 2.07 min, 545.4 [M+H] ⁺ ; METHOD Q

Table 3 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Purification Method	¹ H NMR	LCMS data
2	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 6	Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 - 8.30 (m, 2H), 8.27-8.26 (m, 1H), 8.23-8.21 (m, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.84 - 7.82 (m, 2H), 7.76 - 7.73 (m, 1H), 7.19 - 7.16 (m, 1H), 4.47 (q, J = 6.8 Hz, 2H), 3.72 - 3.64 (m, 2H), 3.13 - 3.07 (m, 2H), 2.90 - 2.87 (m, 2H), 2.10 - 2.05 (m, 2H), 1.88-1.85 (m, 2H), 1.39 (t, J = 6.8 Hz, 3H).	LCMS: 6.38 min 517.2 [M+H] ⁺ ; METHOD M
3	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 25	Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 - 8.29 (m, 2H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.19 - 7.16 (m, 1H), 4.46 (q, J = 7.0 Hz, 2H), 3.59 - 3.58 (m, 2H), 3.13 - 3.01 (m, 4H), 2.14 - 2.07 (m, 2H), 1.88 - 1.85 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H).	LCMS: 6.45 min, 517.1 [M+H] ⁺ ; METHOD E
7	2-(2-ethoxypyridin-3-yl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 9	Prep-HPLC: Method A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 - 8.25 (m, 3H), 8.21 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.62 - 3.52 (m, 2H), 3.08 - 2.98 (m, 4H), 2.11 - 2.06 (m, 2H), 1.87 - 1.83 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H).	LCMS: 1.97 min, 513.1 [M+H] ⁺ ; METHOD A

12	2-(2-ethoxypyridin-3-yl)-1-[3-ethoxy-2-(trifluoromethyl)phenyl]spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 11	Flash chromatography: DCM/MeOH (0 to 4%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.20 – 8.32 (m, 3H), 8.21 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 4.47 (q, J = 6.8 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.56 (s, 2H), 3.03 – 3.01 (m, 4H), 2.12 – 2.06 (m, 2H), 1.87 – 1.84 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H).	LCMS: 2.25 min, 527.1 (M+H), METHOD A
13	2-(2-ethoxypyridin-3-yl)-1-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 12	Flash chromatography: DCM/MeOH (0 to 10%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.30 – 8.25 (m, 4H), 8.18 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.19 – 7.15 (m, 1H), 6.87 (d, J = 6.0 Hz, 1H), 4.48 – 4.43 (m, 2H), 3.92 – 3.90 (m, 3H), 3.55 – 3.49 (m, 4H), 3.22 – 3.16 (m, 2H), 2.08 – 2.01 (m, 2H), 1.84 – 1.80 (m, 2H), 1.39 – 1.35 (m, 3H).	LCMS: 1.56 min, 514.2 (M+H), METHOD A
14	1-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 13	Flash chromatography: DCM/MeOH (0 to 4%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.25–8.32 (m, 3H), 8.21 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.93 (d, J = 6.8 Hz, 2H), 3.56 (d, J = 2.4 Hz, 2H), 3.33 – 3.03 (m, 4H), 2.12 – 2.08 (m, 2H), 1.87 – 1.83 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.24 – 1.20 (m, 1H), 0.58 – 0.54 (m, 2H), 0.36 – 0.32 (m, 2H).	LCMS: 2.32 min, 553.2 (M+H), METHOD A
16	1-[4-chloro-3-(trifluoromethyl)pyridin-2-yl]-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 14	Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (d, J = 4.8 Hz, 1H), 8.31 – 8.25 (m, 3H), 8.18 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.10 (m, 1H), 4.46 (q, J = 6.8 Hz, 2H), 3.75 – 3.45 (m, 4H), 3.40 – 3.30 (m, 2H), 2.08 – 2.01 (m, 2H), 1.85 – 1.82 (m, 2H), 1.36 (t, J = 6.8 Hz, 3H).	LCMS: 2.95 min, 518.2 (M+H), METHOD K
40	2-(2-ethoxypyridin-3-yl)-1-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 29	Flash chromatography: DCM/MeOH (0 to 10%)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 – 8.24 (m, 4H), 8.18 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.84 (d, J = 5.6 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 4.11 (t, J = 6.4 Hz, 2H), 3.55 – 3.48 (m, 4H), 3.22 – 3.16 (m, 2H), 2.09 – 2.03 (m, 2H), 1.77 – 1.70 (m, 4H), 1.37 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: 1.80 min, 542.2 (M+H), METHOD A
45	2-(2-ethoxypyridin-3-yl)-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	B	1 and 34	Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37 – 8.34 (m, 1H), 8.31 (dd, J = 7.5, 2.0 Hz, 1H), 8.27 – 8.21 (m, 3H), 8.11 (d, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 2H), 4.47 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.64 (d, J = 3.1 Hz, 2H), 3.14 – 3.06 (m, 2H), 2.83 – 2.67 (m, 2H), 2.12 – 2.03 (m, 2H), 1.87 – 1.84 (m, 2H), 1.39 (t, J = 7.0 Hz, 3H).	LCMS: 2.16 min, 514.3 (M+H), METHOD A

Table 4 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
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4	3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide	C	Ex. 2		Prep-HPLC: Method A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 (dd, <i>J</i> = 7.6, 2.0 Hz, 1H), 8.26 (dd, <i>J</i> = 4.8, 2.0 Hz, 1H), 8.21 (d, <i>J</i> = 8.4 Hz, 1H), 8.09 (d, <i>J</i> = 8.4 Hz, 1H), 7.87-7.85 (m, 2H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.44 (br s, 1H), 7.19-7.16 (m, 1H), 6.91 (bs, 1H), 4.47 (q, <i>J</i> = 7.0 Hz, 2H), 3.86 (s, 2H), 3.78 (t, <i>J</i> = 7.2 Hz, 2H), 3.32-3.31 (m, 2H), 3.1-3.15 (m, 2H), 2.8-2.86 (m, 2H), 2.07-2.04 (m, 2H), 1.84-1.81 (m, 2H), 1.39 (t, <i>J</i> = 7.0 Hz, 3H).	LCMS: 2.09 min, 588.2 (M+H), METHOD A
8	3-[1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide	C	Ex. 3		Prep-HPLC: Method A	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.30 (dd, <i>J</i> = 7.5, 2.1 Hz, 1H), 8.26 (dd, <i>J</i> = 4.9, 1.8 Hz, 1H), 8.20 (d, <i>J</i> = 8.4 Hz, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.62 (t, <i>J</i> = 7.8 Hz, 1H), 7.52 (d, <i>J</i> = 8.4 Hz, 1H), 7.43-7.37 (m, 2H), 7.19-7.15 (m, 1H), 6.95-6.87 (m, 1H), 4.46 (q, <i>J</i> = 7.0 Hz, 2H), 3.81 (s, 2H), 3.75 (t, <i>J</i> = 7.2 Hz, 2H), 3.19-3.16 (m, 2H), 3.04-3.00 (m, 2H), 2.50-2.49 (m, 2H), 2.11-2.07 (m, 2H), 1.85-1.80 (m, 2H), 1.38 (t, <i>J</i> = 7.0 Hz, 3H).	LCMS: 5.90 min, 588.2 (M+H), METHOD M
10	3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide	C	Ex. 6	K ₂ CO ₃ , DMF, MW 150 °C 1h	Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.23-8.21 (m, 2H), 7.94 (d, <i>J</i> = 8.0 Hz, 1H), 7.86-7.81 (m, 1H), 7.78-7.73 (m, 3H), 7.38-7.32 (m, 1H), 7.13-7.10 (m, 1H), 6.86-6.75 (m, 1H), 4.44 (q, <i>J</i> = 7.2 Hz, 2H), 3.71 (s, 2H), 3.14-3.08 (m, 2H), 2.88-2.82 (m, 6H), 2.41-2.39 (m, 2H), 2.06-2.00 (m, 2H), 1.84-1.80 (m, 2H), 1.38 (t, <i>J</i> = 7.2 Hz, 3H).	LCMS: 4.53 min, 574.1 (M+H), METHOD A
11	3-[2-(2-ethoxypyridin-3-yl)-1'-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide	C	Ex. 6	K ₂ CO ₃ , DMF, MW 150 °C 1h	Prep-HPLC: Method C (By-product carried through Raney-Ni/H ₂)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.2-8.21 (m, 2H), 7.95 (d, <i>J</i> = 8.4 Hz, 1H), 7.86 (d, <i>J</i> = 8.4 Hz, 1H), 7.77 (d, <i>J</i> = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.37-7.33 (m, 2H), 7.13-7.10 (m, 1H), 6.8-6.79 (m, 1H), 4.44 (q, <i>J</i> = 7.2 Hz, 2H), 3.71 (s, 2H), 3.15-3.09 (m, 2H), 2.88-2.82 (m, 6H), 2.43-2.39 (m, 2H), 2.08-2.02 (m, 2H), 1.84-1.81 (m, 2H), 1.38 (t, <i>J</i> = 7.2 Hz, 3H).	LCMS: 2.24 min, 540.3 (M+H), METHOD B
32	3-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-8-oxospiro[6H-1,7-naphthyridine-5,4'-piperidine]-7-yl]propanamide	C	Ex. 5		Prep-HPLC: Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 (dd, <i>J</i> = 1.9, 7.4 Hz, 1H), 8.19 (dd, <i>J</i> = 1.9, 4.9 Hz, 1H), 8.07-8.03 (m, 1H), 8.02-7.98 (m, 1H), 7.63 (s, 1H), 7.62-7.55 (m, 2H), 7.09 (dd, <i>J</i> = 5.0, 7.5 Hz, 1H), 4.82 (s, 2H), 4.48 (q, <i>J</i> = 7.0 Hz, 2H), 3.86 (t, <i>J</i> = 6.8 Hz, 2H), 3.51-3.42 (m, 2H), 3.03-2.95 (m, 2H), 2.60 (t, <i>J</i> = 6.8 Hz, 2H), 2.33-2.25 (m, 2H), 2.20-2.12 (m, 2H), 1.42 (t, <i>J</i> = 7.1 Hz, 3H) Exchangeable NH ₂ protons were not observed.	LCMS: 2.99 min, 558.2 (M+H), METHOD O
96	2-(2-ethoxypyridin-3-yl)-7-(1,2,3,5,6,7-hexahydro-1H-pyrolizin-7a(5H)-yl)methylmethanesulfonate, piro[6H-1,7-	C	Ex. 7 and (tetrahydro-1H-pyrolizin-7a(5H)-yl)methylmethanesulfonate.	NaH, THF, RT	Prep-HPLC: Method B, followed by NaHCO ₃ wash.	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 (dd, <i>J</i> = 7.2, 2.0 Hz, 1H), 8.26 (dd, <i>J</i> = 4.8, 2.0 Hz, 1H), 8.19 (d, <i>J</i> = 8.4 Hz, 1H), 8.09 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (t, <i>J</i> = 8.4 Hz, 1H), 7.19-7.16 (m, 1H), 7.00-6.94 (m, 2H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.87 (s, 2H), 3.85 (s, 3H), 3.51 (s, 2H), 3.11-3.05 (m, 4H), 2.95-2.93 (m, 2H), 2.60-2.57 (m, 2H), 2.15-2.05 (m, 2H), 1.92-1.82 (m, 4H), 1.77-1.66 (m, 4H), 1.57-1.52 (m, 2H), 1.38 (t, <i>J</i> = 7.2 Hz, 3H).	LCMS: 1.85 min, 636.2 (M+H), METHOD A

	naphthyridine-5,4'-piperidine]-8-one						
118	3-(2-(2-ethoxypyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)pyrrolidin-2-one	C	Ex. 30 and 2-oxopyrrolidin-3-yl methanesulfonate	Et ₃ N, Toluene, MW, 130 °C, 4 h	Prep-HPLC; Method B, followed by NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.24 – 8.15 (m, 3H), 7.94 (d, J = 8.4 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.19 – 7.10 (m, 2H), 4.44 (q, J = 7.0 Hz, 2H), 4.11 (d, J = 15.6 Hz, 1H), 3.88 (s, 3H), 3.80 (d, J = 15.6 Hz, 1H), 3.57 – 3.55 (m, 1H), 3.38 – 3.28 (m, 3H), 3.28 – 3.17 (m, 2H), 2.92 (d, J = 12.0 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.50 – 2.34 (m, 1H), 2.34 – 2.33 (m, 3H), 2.04 – 2.03 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H)	LCMS: 2.84 min, 583.2 (M+H) ⁺ , Method B

Table 5 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
5	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one	D	8		Prep-HPLC; Method H	¹ H NMR (400 MHz, CDCl ₃) δ 8.27 (dd, J = 1.8, 7.4 Hz, 1H), 8.21 (dd, J = 1.8, 4.9 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.03 – 7.02 (m, 1H), 6.05 (br s, 1H), 4.70 (d, J = 2.7 Hz, 2H), 4.52 (q, J = 7.0 Hz, 2H), 3.58 – 3.48 (m, 2H), 3.00 (br d, J = 11.2 Hz, 2H), 2.28 – 2.14 (m, 4H), 1.47 (t, J = 7.0 Hz, 3H)	LCMS: 3.18 min, 517.2 (M+H) ⁺ METHOD O
73	2-(2-ethoxypyridin-3-yl)-1'-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-6-one	D	8 and 28		Prep-HPLC; Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.23 – 8.18 (m, 2H), 8.04 (s, 2H), 7.93 (d, J = 8.9 Hz, 1H), 7.09 (dd, J = 5.0, 7.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.63 (s, 2H), 4.48 (q, J = 7.0 Hz, 2H), 4.26 (t, J = 6.6 Hz, 2H), 3.46 (dt, J = 2.2, 10.8 Hz, 2H), 2.98 – 2.90 (m, 2H), 2.34 – 2.26 (m, 2H), 2.23 – 2.13 (m, 2H), 1.79 (sxt, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H) An exchangeable NH proton was not observed.	LCMS: 3.11 min, 542.1 (M+H) ⁺ METHOD O

Table 6 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
6	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7.8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]	E	Ex. 2		Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.24 - 8.21 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.77 - 7.73 (m, 2H), 7.15 - 7.12 (m, 1H), 6.58 (br s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.01 - 3.98 (m, 1H), 3.89 - 3.82 (m, 2H), 3.12 - 3.01 (m, 2H), 2.89 - 2.83 (m, 2H), 2.74 - 2.71 (m, 1H), 2.34 - 2.33 (m, 1H), 1.78 - 1.70 (m, 1H), 1.68 - 1.65 (m, 2H), 1.38 (t, J = 6.80 Hz, 3H)	LCMS: 5.93 min, 503.3 (M+H), METHOD A
19	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[7.8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]	E	Ex. 3		Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.24 - 8.20 (m, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.15 - 7.12 (m, 1H), 6.59 (br s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.01 - 3.98 (m, 1H), 3.88 - 3.76 (m, 2H), 3.09 - 3.07 (m, 4H), 2.75 - 2.67 (m, 1H), 2.31 - 2.24 (m, 1H), 1.87 - 1.84 (m, 1H), 1.71 - 1.62 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H)	LCMS: 3.14 min, 503.2 (M+H), METHOD B

Table 7 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
9	1'-[3-chloro-2-(trifluoromethyl)phenyl]-7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	F			Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 - 8.22 (m, 4H), 7.98 - 7.93 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.58 - 7.54 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.36 (q, J = 8.0 Hz, 1H), 7.19 - 7.16 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.24 (d, J = 13.2 Hz, 1H), 4.02 (d, J = 12.8 Hz, 1H), 3.17 - 3.09 (m, 2H), 3.02 - 2.99 (m, 2H), 2.25 - 2.19 (m, 2H), 2.04 - 2.01 (m, 2H), 1.39 (t, J = 6.8 Hz, 3H)	LCMS: 3.63 min, 695.1 (M+H), METHOD M

Table 8 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
15	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex. 3		Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 -8.29 (m, 1H), 8.26 (dd, J = 5.0, 2.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.19 -7.16 (m, 1H), 5.14 (t, J = 6.4 Hz, 1H), 4.49-4.44 (m, 2H), 3.76 -3.73 (m, 2H), 3.21 -3.17 (m, 4H), 3.10 -3.08 (m, 4H), 2.34 -2.08 (m, 4 H), 1.93 -1.75 (m, 3H), 1.38 (t, J = 6.8 Hz, 3H).		LCMS: 2.10 min, 586.3 (M+H), METHOD B	SFC: 2.52 min, 100%, Column Name: Chiralpak OX-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
15-1	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1				SFC chiral separation			LCMS: 2.11 min, 586.3 (M+H), METHOD B	SFC: 4.49 min, 99.37%, Column Name: Chiralpak OX-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
15-2	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2				SFC chiral separation			LCMS: 1.69 min, 583.2 (M+H), METHOD A	
17	2-(2-ethoxypyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex. 13		Prep-HPLC: Method C	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.30 -8.25 (m, 3H), 8.18 (d, J = 8.40 Hz, 1H), 8.06 (d, J = 8.40 Hz, 1H), 7.19- 7.16 (m, 1H), 6.88 (d, J = 5.60 Hz, 1H), 5.17- 5.14 (m, 1H), 4.48 -4.43 (m, 2H), 3.93 -3.89 (m, 3H), 3.77 -3.67 (m, 2H), 3.52 (d, J = 12.00 Hz, 2H), 3.28 -3.25 (m, 2H), 3.16 -3.10 (m, 1H), 3.07 -3.05 (m, 1H), 2.96-2.86 (m, 2H), 2.11 -2.03 (m, 4H), 1.85 -1.77 (m, 3H), 1.39 -1.35 (m, 3H).		LCMS: 1.96 min, 622.3 (M+H), METHOD A	
18	1'-[3-(cyclopropylmethoxy)-2-	G	Ex. 14		Prep-HPLC: Method A,	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 -8.25 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.40 Hz, 1H), 7.18 (q,			

	(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one			followed by washing with aq. NaHCO ₃ .	J = 4.80 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.31 -5.01 (m, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.94 (d, J = 6.8 Hz, 2H), 3.74 -3.69 (m, 2H), 3.34 -3.05 (m, 5H), 2.97 -2.96 (m, 1H), 2.94-2.81 (m, 2H), 2.09 -2.02 (m, 3H), 1.84- 1.76 (m, 3H), 1.38 (t, J = 6.8 Hz, 3H), 1.24 -1.22 (m, 2H), 0.58 -0.54 (m, 2H), 0.36 -0.33 (m, 2H).	(M+H), METHOD A	SFC: 2.50 min, 100%, Column Name: YMC Cellulose-SZ, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.	
18-1	1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1			SFC chiral separation				SFC: 3.95 min, 98.02%, Column Name: YMC Cellulose-SZ, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
18-2	1'-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2			SFC chiral separation				
20	2-(2-ethoxypyridin-3-yl)-1'-[3-ethoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex 12	Prep-HPLC: Method B, followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.30 (dd, J = 7.60, 2.0 Hz, 1H), 8.26 (dd, J = 4.80, 2.0 Hz, 1H), 8.24 -8.19 (m, 1H), 8.12 -8.10 (m, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.19 -7.16 (m, 1H), 7.00 -6.98 (m, 1H), 6.95 -6.92 (m, 1H), 5.21 -5.01 (m, 1H), 4.46 (q, J = 6.8 Hz, 2H), 4.11 (q, J = 6.8 Hz, 2H), 3.74 -3.69 (m, 2H), 3.51 -2.86 (m, 6H), 2.84 -2.78 (m, 2H), 2.33 -2.01 (m, 4H), 1.84 -1.79 (m, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H).	LCMS: 1.89 min, 596.3 (M+H), METHOD A		
23	2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridine-3-carbonyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	16	Prep-HPLC: Method B, followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 - 8.25 (m, 2H), 8.21 - 8.13 (m, 2H), 7.97 - 7.88 (m, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.18 - 7.15 (m, 1H), 5.18 - 5.08 (m, 1H), 4.48 - 4.43 (m, 3H), 3.94 (s, 3H), 3.78 - 3.65 (m, 2H), 3.50 - 3.49 (m, 2H), 3.18 - 3.15 (m, 2H), 3.05 - 2.91 (m, 1H), 2.82 - 2.67 (m, 2H), 2.00 - 1.81 (m, 3H), 1.77 - 1.60 (m, 4H), 1.39 - 1.36 (m, 3H).	LCMS: 1.80 min, 611.0 (M+H), METHOD B		
23-1	2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridine-3-carbonyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-			Chiral SFC separation				SFC: 2.79 min, 99.75%, Method: Column Name: YMC Cellulose-SZ, Co-Solvent: 45%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl - Flow

	piperidine]-8-one Enantiomer 1								Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C
23-2	2-(2-ethoxy-3-yl)- 1'-[6-methoxy-2- (trifluoromethyl)pyridine -3-carbonyl]-7- pyrrolidin-3-ylspiro[6H- 1,7-naphthyridine-5,4'- piperidine]-8-one Enantiomer 2	G	19	TFA in 2 nd Step	Flash chromatography: DCM/MeOH (0 to 10%) (Note iodide falls off in NaH step)	Chiral SFC separation		LCMS: 1.58 min, 611.2 (M+H), METHOD A	SFC: 3.73 min, 99.65%, Method: Column Name: YMC Cellulose-SZ, Co-Solvent: 45%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C
27	1'-(4-chloropyridin-2-yl)- 2-(2-ethoxy-3-yl)- 7-pyrrolidin-3- ylspiro[6H-1,7- naphthyridine-5,4'- piperidine]-8-one	G	19	TFA in 2 nd Step	Flash chromatography: DCM/MeOH (0 to 10%) (Note iodide falls off in NaH step)			LCMS: 3.32 min, 519 (M+H), METHOD L	
28	1'-(4-chloro-3- (trifluoromethyl)pyridin- 2-yl)-2-(2-ethoxy-3-yl)- 7-pyrrolidin-3- ylspiro[6H-1,7- naphthyridine-5,4'- piperidine]-8-one	G	20	TFA in 2 nd Step	Prep-HPLC: Method B		Formate	LCMS: 2.04 min, 587.0 (M+H), METHOD B	
31	1'-[6- (cyclopropylmethoxy)-2- (trifluoromethyl)pyridine -3-carbonyl]-2-(2- ethoxy-3-yl)-7- pyrrolidin-3-ylspiro[6H- 1,7-naphthyridine-5,4'- piperidine]-8-one		Ex. 26		Prep-HPLC: Method B, followed by washing with aq. NaHCO ₃			LCMS: 1.75 min, 651.5 (M+H), METHOD A	
31-1	1'-[6- (cyclopropylmethoxy)-2- (trifluoromethyl)pyridine -3-carbonyl]-2-(2- ethoxy-3-yl)-7- pyrrolidin-3-ylspiro[6H- 1,7-naphthyridine-5,4'- piperidine]-8-one							LCMS: 2.07 min, 651.5 (M+H), METHOD B	SFC: 1.68 min, 100%, Method: Column Name: Chiralcel OD-H, Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in IPA; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C

[illegible]

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39-1	2-(2-ethoxypyridin-3-yl)-1-[3-methoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1			SFC chiral separation			LCMS: 1.79 min, 582.1 (M+H), METHOD A	SFC: 2.79 min, 100%, Method: Column Name: YMC Cellulose-SC, Co-Solvent: 50% Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 12 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C
39-2	2-(2-ethoxypyridin-3-yl)-1-[3-methoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2			SFC chiral separation			LCMS: 1.79 min, 582.2 (M+H), METHOD A	SFC: 5.73 min, 100%, Method: Column Name: YMC Cellulose-SC, Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 12 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C
41	2-(2-ethoxypyridin-3-yl)-1-[5-[methyl(propyl)amino]-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 30	Prep-HPLC: Method B; followed by washing with aq. NaHCO ₃	TFA in the 2 nd Step		LCMS: 2.05 min, 624.3 (M+H), METHOD B	
46	2-(2-ethoxypyridin-3-yl)-1-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex. 40	Prep-HPLC: Method B; followed by washing with aq. NaHCO ₃			LCMS: 4.02 min, 611.3 (M+H), METHOD A	
46-1	2-(2-ethoxypyridin-3-yl)-1-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1			SFC chiral separation			LCMS: 1.75 min, 611.2 (M+H), METHOD A	SFC: 1.12 min, 100%, Column Name: Chiralpak AS-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in IPA, Injected Volume: 15 µL, Flowrate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C.
46-2	2-(2-ethoxypyridin-3-yl)-1-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]-7-pyrrolidin-3-			SFC chiral separation			LCMS: 1.75 min, 611.2 (M+H), METHOD A	SFC: 1.90 min, 99.07%, Column Name: Chiralpak AS-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl

	ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2	G	Ex. 3	Using tert-butyl iodopyrrolidine-1-carboxylate and TFA in the 2 nd Step	Prep-HPLC: Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.66 (br s, 1H), 8.32 – 8.25 (m, 3H), 8.17 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.20-7.17 (m, 1H), 5.16 (t, J = 8.0 Hz, 1H), 4.49 – 4.45 (m, 2H), 4.34 – 4.26 (m, 4H), 3.83 (s, 2H), 3.23 – 3.17 (m, 2H), 3.09 – 3.06 (m, 2H), 2.18 – 2.13 (m, 2H), 1.90 – 1.87 (m, 2H), 1.41 (t, J = 5.6 Hz, 3H).	TFA	LCMS: 1.93 min, 572.1 (M ⁺ H), METHOD A	Amine in IPA, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
48	7-(azetidin-3-yl)-1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex. 3	Using tert-butyl iodopyrrolidine-1-carboxylate and TFA in the 2 nd Step	Prep-HPLC: Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.66 (br s, 1H), 8.32 – 8.25 (m, 3H), 8.17 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.20-7.17 (m, 1H), 5.16 (t, J = 8.0 Hz, 1H), 4.49 – 4.45 (m, 2H), 4.34 – 4.26 (m, 4H), 3.83 (s, 2H), 3.23 – 3.17 (m, 2H), 3.09 – 3.06 (m, 2H), 2.18 – 2.13 (m, 2H), 1.90 – 1.87 (m, 2H), 1.41 (t, J = 5.6 Hz, 3H).	TFA	LCMS: 1.93 min, 572.1 (M ⁺ H), METHOD A	Amine in IPA, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
49	2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Ex. 45	TFA in the 2 nd Step	Prep-HPLC: Method B; followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 (dd, J = 7.4, 2.0 Hz, 1H), 8.26 (dd, J = 5.2, 2.0 Hz, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 7.22 - 7.16 (m, 2H), 5.28 - 5.18 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 3.82 - 3.71 (m, 2H), 3.14 - 3.09 (m, 3H), 2.98 - 2.96 (m, 1H), 2.88 - 2.80 (m, 4H), 2.13 - 2.01 (m, 3H), 1.85 - 1.78 (m, 3H), 1.39 (t, J = 7.2 Hz, 3H). An Exchangeable NH proton was not observed.		LCMS: 2.18 min, 583.0 (M ⁺ H), METHOD B	SFC: 2.58 min, 100%, Column Name: Chiralpak OX-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
49-1	2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1				SFC chiral separation			LCMS: 2.20 min, 583.3 (M ⁺ H), METHOD B	SFC: 2.58 min, 100%, Column Name: Chiralpak OX-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
49-2	2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2				SFC chiral separation			LCMS: 2.21 min, 583.3 (M ⁺ H), METHOD B	SFC: 4.31 min, 100%, Column Name: Chiralpak OX-H, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH, Injected Volume: 15 µl, Flowrate: 5 ml/min, Outlet Pressure: 100 bar, 35 °C.
57	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(3-propoxy-2-(trifluoromethyl)phenyl)-7-(pyrrolidin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-	G	Ex. 51	TFA in 2 nd Step	Prep-HPLC: Method B; followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.34 (dd, J = 7.2, 2.0 Hz, 1H), 8.27 - 8.24 (m, 2H), 8.04 (d, J = 8.8 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.18 - 5.05 (m, 1H), 4.50 - 4.46 (m, 2H), 4.01 (t, J = 6.0 Hz, 2H), 3.85 - 3.75 (m, 1H), 3.62 - 3.48 (m, 1H), 3.04 - 2.99 (m, 5H), 2.92 - 2.80 (m, 2H), 2.79 - 2.76 (m, 2H), 1.96 - 1.95 (m, 2H), 1.85 - 1.78 (m, 1H), 1.75 - 1.71 (m, 4H), 1.40 (t, J = 7.2 Hz, 3H), 1.01 - 0.98 (m, 5H), 0.92 - 0.89 (m, 3H).		LCMS: 2.07 min, 638.2 (M ⁺ H), METHOD A	

[illegible]

112	rac-(3S,5S)-2-(2-ethoxy-3-yl)-3-ethyl-7-[(3S)-pyrrolidin-3-yl]-1-[3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 63 and tert-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	NaH in THF at 60 °C in 1 st step, followed by boc deprotection using TFA.	Prep HPLC method B	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.56 – 8.36 (m, 1H), 8.35 – 8.34 (m, 1H), 8.33 – 8.26 (m, 2H), 8.25 – 8.24 (m, 1H), 8.10 – 8.08 (m, 1H), 7.21 – 7.16 (m, 2H), 5.30 – 5.20 (m, 1H), 4.49 – 4.47 (m, 2H), 3.62 – 3.56 (m, 1H), 3.53 – 3.52 (m, 3H), 3.33 – 3.28 (m, 2H), 3.05 – 3.02 (m, 2H), 2.93 – 2.91 (m, 1H), 2.80 – 2.77 (m, 1H), 2.66 – 2.67 (m, 2H), 1.97 (m, 2H), 1.41 – 1.39 (m, 2H), 1.37 – 1.24 (m, 3H), 1.20 – 1.19 (m, 1H), 0.92 (m, 1H), 0.91 – 0.90 (m, 3H).	LCMS: 1.75 min, 581.3 [M+H] ⁺ , Method A	SFC: 4.78 min and 6.64 min Column Name : YMC Cellulose-SC Co-Solvent : 50% Co-Solvent Name : 0.5% Isopropylamine in IPA Injected Volume : 15 µl FlowRate : 5 ml/min Outlet Pressure: 100 bar Temperature : 35 °C
116	(3SR,4SR)-2-(2-ethoxy-3-yl)-3-ethyl-7-[(R)-pyrrolidin-3-yl]-1-[3-(trifluoromethyl)pyridin-2-yl]-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	G	Int. 63 and tert-butyl (S)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	NaH in THF at 60 °C in 1 st step, followed by boc deprotection using TFA, acid	Prep HPLC method B	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.56 – 8.54 (m, 1H), 8.36 – 8.34 (m, 1H), 8.33 – 8.26 (m, 2H), 8.11 – 8.10 (m, 1H), 8.08 – 8.02 (m, 1H), 7.21 – 7.16 (m, 2H), 5.20 – 5.05 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.84 – 3.81 (m, 1H), 3.80 – 3.52 (m, 4H), 3.11 – 3.09 (m, 2H), 3.08 – 3.06 (m, 1H), 2.95 – 2.85 (m, 2H), 2.50 – 2.50 (m, 1H), 2.01 – 1.98 (m, 3H), 1.67 (m, 1H), 1.67 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.27 – 1.24 (m, 1H), 1.23 – 1.21 (m, 1H), 0.94 – 0.90 (m, 3H).	LCMS: 2.26 min, 581.3 [M+H] ⁺ , Method B	SCF: 4.32 min and 5.7 min Column Name : YMC Cellulose-SCCo-Solvent : 50% Co-Solvent Name : 0.5% Isopropylamine in MeOH Injected Volume : 15 µl FlowRate : 5 ml/min Outlet Pressure: 100 bar Temperature : 35 °C
114	rac-(3S,4S)-1-(5-chloro-4-(trifluoromethyl)pyridin-3-yl)-2-(2-ethoxy-3-yl)-3-ethyl-7-(pyrrolidin-3-yl)-6,7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one	G	Int. 42 and rac-tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	NaH in THF at 60 °C in 1 st step and TFA in the 2 nd Step	Prep-HPLC Method B, followed by washing with aq. NaHCO ₃ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.77 (s, 1H), 8.55 (s, 1H), 8.35 (d, J = 1.2 Hz, 1H), 8.30 – 8.26 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 4.8, 7.4 Hz, 1H), 5.31 – 5.15 (m, 1H), 4.49 (q, J = 7.2 Hz, 2H), 3.86 – 3.80 (m, 2H), 3.37 – 3.17 (m, 1H), 3.16 – 3.09 (m, 3H), 3.16 – 3.09 (m, 2H), 3.13 – 2.92 (m, 2H), 2.50 – 2.44 (m, 1H), 2.01 – 1.70 (m, 4H), 1.70 – 1.40 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.26 – 1.22 (m, 1H), 1.22 – 1.16 (m, 1H), 0.93 – 0.90 (m, 3H).	LCMS: 2.37 min, 615.2 (M+H) ⁺ , Method B	SFC: 4.06, 5.22 min and 6.31, 7.86 min, Column Name : YMC Cellulose-SC Co-Solvent : 50% Sample Co-Solvent Name : 0.5% Isopropylamine in MeOH Injected Volume : 15 µl FlowRate : 5 ml/min; Outlet Pressure: 100 bar Temperature : 35 °C
124	rac-(3S,5S)-7-(azetidin-3-yl)-2-(2-ethoxy-3-yl)-3-ethyl-1-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 71 and tert-butyl 3-iodoazetidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method B, followed by washing with aq. NaHCO ₃ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.43 (s, 1H), 8.37 – 8.32 (m, 2H), 8.28 – 8.26 (m, 2H), 8.08 (d, J = 8.8 Hz, 1H), 7.19 – 7.16 (m, 1H), 5.38 – 5.30 (m, 1H), 4.46 (q, J = 6.8 Hz, 2H), 4.02 – 3.99 (m, 5H), 3.83 – 3.73 (m, 2H), 3.70 – 3.62 (m, 3H), 3.33 – 3.31 (m, 2H), 3.16 – 3.13 (m, 2H), 2.34 – 2.33 (m, 1H), 2.01 – 1.98 (m, 1H), 1.74 – 1.73 (m, 1H), 1.39 (t, J = 6.8 Hz, 3H), 1.24 – 1.18 (m, 1H), 1.16 – 1.05 (m, 1H), 0.90 (t, J = 7.6 Hz, 3H).	LCMS: 1.73 min, 597.8 (M+H) ⁺ , Method A	

127	rac-(3S,5S)-7-(azetidin-3-yl)-2-(2-ethoxy-3-yl)-3-ethyl-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 73 and tert-butyl 3-iodoazetidine-1-carboxylate	TFA, DCM in 2 nd step	Prep HPLC method B	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.35 – 8.31 (m, 4H), 8.31 – 8.28 (m, 1H), 7.21 – 7.18 (m, 2H), 5.35 – 5.20 (m, 1H), 4.48 (q, J = 6.8 Hz, 2H), 4.48 – 4.46 (m, 3H), 4.07 – 3.98 (m, 4H), 3.87 – 3.74 (m, 1H), 3.25 – 3.18 (m, 2H), 3.02 (d, J = 7.6 Hz, 2H), 2.73 (d, J = 2.0 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.33 (d, J = 2.0 Hz, 1H), 1.94 (t, J = 2.2 Hz, 1H), 1.40 (t, J = 6.8 Hz, 3H), 1.15 – 0.89 (m, 2H), .86 (t, J = 7.2 Hz, 3H).	LCMS: 2.40 min, 597.3 (M+H) ⁺ Method B	SFC: 1.31 and 2.22 min, 80.94%, 18.01% Column Name : Chiralpak IG; Co-Solvent : 50% Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
130	rac-(3'S,5S)-7-(azetidin-3-yl)-1-(2-ethoxy-3-yl)-2-(2-ethoxy-3-yl)-3-ethyl-1-[2-(trifluoromethyl)pyridin-4-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 75 and tert-butyl 3-iodoazetidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.33 (dd, J = 7.6, 2.0 Hz, 1H), 8.27 – 8.25 (m, 2H), 8.14 (d, J = 6.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.92 (d, J = 6.0 Hz, 1H), 5.31 – 5.27 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.97 – 3.92 (m, 1H), 3.90 (s, 3H), 3.80 – 3.64 (m, 5H), 3.48 – 3.46 (m, 1H), 3.18 – 3.12 (m, 1H), 2.69 – 2.55 (m, 2H), 2.45 – 2.35 (m, 2H), 2.02 – 1.92 (m, 1H), 1.75 – 1.65 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.24 – 1.16 (m, 1H), 1.10 – 0.98 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H).	LCMS: 2.10 min, 597.3 (M+H) ⁺ Method B.	
139	rac-(3S,4S)-7-(azetidin-3-yl)-1-(2-chloro-3-methoxyphenyl)-2-(2-ethoxy-3-yl)-3-ethyl-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	G	Int. 77 and tert-butyl 3-iodoazetidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.34 – 8.32 (m, 1H), 8.27 – 8.26 (m, 2H), 8.25 – 8.12 (m, 1H), 7.32 – 7.19 (m, 1H), 7.19 – 7.16 (m, 1H), 6.93 – 6.87 (m, 2H), 5.45 – 5.30 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 4.05 – 4.01 (m, 1H), 3.85 (s, 3H), 3.70 – 3.63 (m, 4H), 3.52 (m, 1H), 3.47 – 3.42 (m, 2H), 3.40 – 3.33 (m, 3H), 3.22 – 3.10 (m, 1H), 2.87 – 2.84 (m, 1H), 2.02 (m, 2H), 1.82 – 1.81 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 0.95 – 0.84 (m, 3H).	LCMS: 2.11 min, 562.2 (M+H) ⁺ Method B	SFC: 7.46 min, 97.03%, Column: YMC Cellulose-SC, Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
144	rac-(3'S,5S)-2-(2-ethoxy-3-yl)-2-(2-ethoxy-3-yl)-3-ethyl-1-[5-methoxy-4-(trifluoromethyl)pyridin-2-yl]methylpyrrolidine-2-yl]methylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	G	Int. 71 and tert-butyl (R)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.42 – 8.41 (m, 1H), 8.36 – 8.34 (m, 2H), 8.27 – 8.23 (m, 2H), 8.05 – 8.03 (m, 1H), 7.19 – 7.16 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.97 – 3.89 (m, 1H), 3.80 – 3.63 (m, 2H), 3.42 – 3.33 (m, 2H), 3.25 – 3.22 (m, 1H), 3.08 – 3.05 (m, 2H), 2.86 – 2.67 (m, 2H), 2.37 – 2.34 (m, 1H), 2.18 – 1.98 (m, 1H), 1.85 – 1.55 (m, 4H), 1.48 – 1.32 (t, J = 7.2 Hz, 3H), 3.30 – 3.27 (m, 1H), 1.25 – 1.15 (m, 2H), 1.05 – 0.95 (m, 1H), 0.90 – 0.89 (m, 3H). Exchangeable NH proton was not observed.	LCMS: 1.77 min, 625.3 (M+H) ⁺ Method A	SFC: 2.25 min and 3.03 min, Column Name : YMC Cellulose-SZ; Co-Solvent : 40%; Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
146	2-(2-ethoxy-3-yl)-7-[(2R)-pyrrolidin-2-yl]methyl-1'-[2-(trifluoromethyl)phenyl]s	G	Int. 80 and tert-butyl (R)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method B; followed by washing	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.33 – 8.31 (m, 3H), 8.15 (d, J = 8.0 Hz, 1H), 7.79 – 7.70 (m, 3H), 7.38 (t, J = 8.0 Hz, 1H), 7.19 (dd, J = 4.0, 8.0 Hz, 1H), 4.47 (q, J = 8 Hz, 2H), 4.06 – 4.03 (m, 3H), 3.95 – 3.90 (m, 2H), 3.68 – 3.18 (m, 4H), 3.16 – 2.93 (m, 2H), 2.26 –	LCMS: 2.64 min, 566.3	SFC: 2.34 min, 99.14%, Column: Chiralpak OX-H; Co-Solvent : 50%; Co-Solvent Name : 0.5% Isopropylamine in

	piro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one		)pyrrolidine-1-carboxylate		with aq. NaHCO ₃ .	2.07 (m, 3H), 1.98 – 1.74 (m, 5H), 1.91 – 1.74 (m, 1H), 1.39 (t, J = 8.0 Hz, 3H).	[M+H] ⁺ , Method B	MeOH ⁺ ; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
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Table 9 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Purification Method	¹ H NMR	LCMS data
21	2-amino-1-[7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]ethanone	H	15	Prep-HPLC; Method C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.22-8.16 (m, 2H), 7.99-7.90 (m, 4H), 7.81 (s, 1H), 7.12-7.09 (m, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.35-4.31 (m, 2H), 4.10 (s, 2H), 3.66-3.65 (m, 1H), 3.57-3.53 (m, 2H), 3.47-3.42 (m, 2H), 3.21-3.16 (m, 1H), 2.68-2.67 (m, 1H), 2.09-1.86 (m, 3H), 1.36 (t, J = 7.2 Hz, 3H). Exchangeable NH ₂ protons not observed	LCMS: 2.04 min, 560.0 (M+H), METHOD B
25	3-amino-1-[7-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]propan-1-one	H	15 and 3-(tert-butoxycarbonyl)amino)propanoic acid and HATU	Prep-HPLC; Method A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.22 - 8.16 (m, 1H), 8.00 - 7.98 (m, 1H), 7.94 - 7.87 (m, 3H), 7.80 (s, 1H), 7.12-7.08 (m, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.37 - 4.34 (m, 2H), 4.10 (s, 2H), 3.82 - 3.79 (m, 1H), 3.43 - 3.39 (m, 3H), 3.21 - 3.19 (m, 2H), 2.77 - 2.68 (m, 2H), 2.43 - 2.36 (m, 3H), 1.98 - 1.75 (m, 4H), 1.37 (t, J = 6.8 Hz, 3H).	LCMS: 2.07 min, 574.0 (M+H), METHOD B

Table 10 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
22	1'-(4-chloro-3-iodopyridin-2-yl)-2-(2-ethoxypyridin-3-yl)spiro[6.7-dihydro-1,7-naphthyridine-5,4'-piperidine]-8-one	I	10		Prep-HPLC; Method E	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 – 8.30 (m, 1H), 8.27 – 8.25 (m, 2H), 8.22 – 8.20 (m, 2H), 8.09 (d, J = 8.40 Hz, 1H), 7.27 (d, J = 5.20 Hz, 1H), 7.19 – 7.16 (m, 1H), 4.46 (d, J = 7.2 Hz, 2H), 3.57 (t, J = 3.2 Hz, 4H), 3.09 (t, J = 11.6 Hz, 2H), 2.18 - 2.12 (m, 2H), 1.90 (d, J = 13.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).	LCMS: 2.81 min, 575.8 (M+H), METHOD B

Table 11 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
24	[2-(2-ethoxypyridin-3-yl)spiro[7.8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]methanone	J	5 and 17		Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.21 (s, 3H), 8.20-8.08 (m, 2H), 7.26-7.24 (m, 1H), 7.12-7.09 (m, 1H), 4.46-4.41 (m, 3H), 4.30-4.26 (m, 2H), 3.93 (d, J = 4.4 Hz, 2H), 3.33-3.06 (m, 5H), 2.60-2.55 (m, 1H), 1.88-1.74 (m, 6H), 1.36 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: 1.94 min, 556.1 (M+H), METHOD B
26	[6-(cyclopropylmethoxy)-2-(trifluoromethyl)pyridin-3-yl]-[2-(2-ethoxypyridin-3-yl)spiro[7.8-dihydro-6H-1,7'-naphthyridine-5,4'-piperidine]-1'-yl]methanone	J	5 and 18		Prep-HPLC: Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.19-8.08 (m, 3H), 7.88-7.86 (m, 2H), 7.27-7.25 (m, 1H), 7.12-7.11 (m, 1H), 4.46-4.42 (m, 3H), 4.18-4.16 (m, 2H), 3.93-3.92 (m, 2H), 3.22-2.68 (m, 5H), 2.34-2.00 (m, 5H), 1.87-1.38 (m, 3H), 1.35 (s, 1H), 0.58 (q, J = 2.0 Hz, 2H), 0.38 (q, J = 1.2 Hz, 2H)	LCMS: 1.95 min, 568.0 (M+H), METHOD B

Table 12 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data	Chiral Analysis
29	[2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]methanone	K	21		Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.23-8.10 (m, 3H), 7.93-7.88 (m, 2H), 7.27-7.25 (m, 1H), 7.12-7.10 (m, 1H), 4.46-4.41 (m, 3H), 3.94 (s, 3H), 3.66 (m, 4H), 3.33-3.23 (m, 2H), 2.93-2.91 (m, 3H), 2.69-2.61 (m, 2H), 2.34-1.38 (m, 4H), 1.36 (t, J = 4.0 Hz, 3H), 1.24-1.18 (m, 3H). Exchangeable NH proton not observed	LCMS: 1.88 min, 597.0 (M+H), METHOD B	

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62	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[2-(S)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	K	Ex. 6 and tert-butyl (S)-2-formylpyrrolidine-1-carboxylate	1st Step: NaBH(OAc) ₃ , DCE, RT.	Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 – 8.20 (m, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.40 Hz, 1H), 7.78 (m, 2H), 7.73 (q, J = 5.2 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.74 (s, 2H), 3.51 – 3.29 (m, 3H), 3.24 – 3.06 (m, 2H), 2.85 – 2.61 (m, 6H), 2.33 – 2.03 (m, 2H), 1.84 – 1.65 (m, 4H), 1.65 – 1.63 (m, 2H), 1.37 (t, J = 6.8 Hz, 4H).	LCMS: 2.47 min, 586.0 (M+H), METHOD B	SFC: 2.25 min, 100%, Column Name: Lux C2, Co-Solvent : 40%; Co-Solvent Name: 0.5% Isopropylamine in MeOH; Injected Volume: 15 µl; FlowRate: 4 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
69	2-(2-ethoxypyridin-3-yl)-7-[[2-(S)-pyrrolidin-2-ylmethyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	K	Ex. 6 and tert-butyl (S)-2-formylpyrrolidine-1-carboxylate	1st Step: NaBH(OAc) ₃ , DCE, RT.	Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃ . Note Ex. 69 was isolated from impurity carried through.	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.23 – 8.21 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.40 Hz, 1H), 7.75 – 7.67 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.12 (q, J = 5.2 Hz, 1H), 4.44 (q, J = 6.80 Hz, 2H), 3.75 (s, 2H), 3.40 – 3.33 (m, 4H), 3.13 – 3.07 (m, 2H), 2.97 – 2.88 (m, 4H), 2.84 – 2.75 (m, 1H), 2.08 – 2.03 (m, 2H), 1.86 – 1.71 (m, 4H), 1.67 – 1.63 (m, 2H), 1.40 – 1.24 (m, 4H).	LCMS: 1.79 min, 552.2 (M+H), METHOD B	SFC: 1.61 min, 97.70% Column Name: (R,R) Wheelk-01, Co-Solvent : 50%; Co-Solvent Name: 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl ; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
85	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[2-(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	K	Ex. 6 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	1st Step: NaBH(OAc) ₃ , DCE, RT	Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.23 – 8.21 (m, 2H), 7.95 – 7.93 (m, 1H), 7.86 – 7.84 (m, 1H), 7.77 – 7.72 (m, 2H), 7.73 – 7.72 (m, 1H), 7.12 – 7.11 (m, 1H), 4.44 (q, J = 6.8 Hz, 2H), 3.74 (m, 2H), 3.20 – 3.05 (m, 2H), 2.89 – 2.73 (m, 6H), 2.68 – 2.67 (m, 2H), 2.50 – 2.46 (m, 2H), 2.05 – 2.03 (m, 2H), 1.86 – 1.80 (m, 3H), 1.66 – 1.64 (m, 2H), 1.39 – 1.36 (m, 3H). Exchangeable proton not observed.	LCMS: 2.48 min, 596 (M+H), METHOD B	SFC: 1.56 min, 99.79%; Column Name: Lux A1, Co-Solvent : 50%; Co-Solvent Name: 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl ; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
86	2-(2-ethoxypyridin-3-yl)-7-[[2-(R)-pyrrolidin-2-ylmethyl]-1'-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	K	Ex. 6 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	1st Step: NaBH(OAc) ₃ , DCE, RT	Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃ . Note Ex. 86 was isolated from impurity carried through.	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 – 8.21 (m, 2H), 7.96 – 7.94 (m, 1H), 7.87 – 7.85 (m, 1H), 7.80 – 7.12 (m, 3H), 7.13 – 7.12 (m, 1H), 7.12 – 7.10 (m, 1H), 4.44 (q, J = 6.8 Hz, 2H), 3.75 (m, 1H), 3.61 (m, 1H), 3.14 – 3.08 (m, 2H), 2.92 – 2.67 (m, 5H), 2.59 – 2.50 (m, 4H), 2.50 – 2.34 (m, 3H), 2.07 – 2.05 (m, 2H), 1.84 – 1.81 (m, 3H), 1.39 – 1.38 (m, 1H), 1.38 – 1.24 (m, 3H).	LCMS: 4.65 min, 552 (M+H), METHOD L	SFC: 1.46 min, 100% Column Name: Lux A1, Co-Solvent : 45%; Co-Solvent Name: 0.5% Isopropylamine in IPA; Injected Volume : 15 µl ; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C

Table 13 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
30	2-(2-ethoxypyridin-3-yl)-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[7.8-dihydro-6H-1,7-naphthyridine-5,4'-piperidine]	L	5		Prep-HPLC: Method A, followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 - 8.20 (m, 3H), 7.92 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.17 - 7.10 (m, 2H), 4.45 (q, J = 7.2 Hz, 2H), 3.95 (s, 2H), 3.89 (s, 3H), 3.16 (s, 2H), 3.11 - 3.05 (m, 2H), 2.76 - 2.73 (m, 2H), 2.07 - 2.01 (m, 2H), 1.86 - 1.82 (m, 2H), 1.38 (t, J = 4.0 Hz, 3H). Exchangeable NH proton was not observed.	LCMS: 1.91 min, 500.1 (M+H), METHOD A

Table 14 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
34	(S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7'-hydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-6'-one	M	Ex. 5 and tert-butyl ((R)-3-(methylsulfonyl)oxy)pyrrolidine-1-carboxylate		Prep-HPLC: Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.24 (dd, J = 1.9, 7.4 Hz, 1H), 8.20 (dd, J = 1.9, 4.9 Hz, 1H), 8.08 - 8.01 (m, 2H), 7.65 - 7.60 (m, 2H), 7.57 - 7.53 (m, 1H), 7.09 (dd, J = 5.0, 7.5 Hz, 1H), 4.81 (s, 2H), 4.74 (br d, J = 3.5 Hz, 1H), 4.49 (q, J = 7.0 Hz, 2H), 3.62 - 3.54 (m, 1H), 3.46 - 3.36 (m, 4H), 3.18 (td, J = 8.6, 11.4 Hz, 1H), 3.06 - 2.98 (m, 2H), 2.41 (dt, J = 4.5, 8.8 Hz, 1H), 2.37 - 2.30 (m, 2H), 2.22 - 2.13 (m, 3H), 1.42 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.64 min, 586.1 (M+H), METHOD O	SFC: 1.22 min, 100%, Column Name: YMC Cellulose-SZ, Co-Solvent: 40%; Co-Solvent Name: Isopropyl Amine in MeOH; Injected Volume: 4.1 µL; Run time: 3 min.
35	(R)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2'-(2-ethoxypyridin-3-yl)-7'-(pyrrolidin-3-yl)-7'-hydro-6H-spiro[piperidine-4,5'-	M	Ex. 5 and tert-butyl ((S)-3-(methylsulfonyl)oxy)pyrrolidine-1-carboxylate		Prep-HPLC: Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.24 (dd, J = 1.9, 7.4 Hz, 1H), 8.20 (dd, J = 1.9, 4.9 Hz, 1H), 8.09 - 8.01 (m, 2H), 7.67 - 7.60 (m, 2H), 7.58 - 7.53 (m, 1H), 7.09 (dd, J = 5.0, 7.5 Hz, 1H), 4.81 (s, 2H), 4.77 - 4.73 (m, 1H), 4.49 (q, J = 7.0 Hz, 2H), 3.60 - 3.52 (m, 1H), 3.46 - 3.38 (m, 3H), 3.37 - 3.35 (m, 1H), 3.21 - 3.13 (m, 1H), 3.06 - 2.98 (m, 2H), 2.46 - 2.37 (m, 1H), 2.37 - 2.29 (m, 2H), 2.23 - 2.12 (m, 3H), 1.42 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.64 min, 586.1 (M+H), METHOD O	SFC: 1.22 min, 100%, Column Name: YMC Cellulose-SZ, Co-Solvent: 40%; Co-Solvent Name: Isopropyl Amine in MeOH; Injected

	[1,7]naphthyridin]-6-one											Volume: 4.1 µL; Run time: 3 min.
37	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	M	Int. 24 and tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate		Prep-HPLC: Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 - 8.18 (m, 2H), 8.09 - 8.00 (m, 2H), 7.51 - 7.45 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.09 (dd, J = 5.0, 7.4 Hz, 1H), 4.82 (br s, 2H), 4.70 - 4.67 (m, 1H), 4.49 (q, J = 7.0 Hz, 2H), 3.66 - 3.58 (m, 1H), 3.49 - 3.40 (m, 4H), 3.25 - 3.17 (m, 1H), 3.15 - 3.09 (m, 2H), 2.50 - 2.39 (m, 1H), 2.38 - 2.28 (m, 2H), 2.25 - 2.14 (m, 3H), 1.42 (t, J = 7.1 Hz, 3H) Exchangeable proton not observed	Formate		LCMS: 2.59 min, 586.1 (M+H), METHOD O	SFC: 1.26 min, 100%, Column Name: DAICEL Chiralcel OD-3, 50×4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 3.4 µL; Run time: 3 min.	
83	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3R)-pyrrolidin-3-yl]methylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	M	Ex. 5 and tert-butyl (R)-3-((methylsulfonyl)oxy)methylpyrrolidine-1-carboxylate	2 nd Step. TFA/DCM 25°C, 30 min	Prep-HPLC: Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 1.42 (t, J = 7.07 Hz, 3 H), 1.68 - 1.84 (m, 1 H), 2.07 - 2.27 (m, 3 H), 2.28 - 2.44 (m, 2 H), 2.77 (d, J = 15.20, 7.54 Hz, 1 H), 2.91 - 3.08 (m, 3 H), 3.13 - 3.22 (m, 1 H), 3.27 (br d, J = 7.63 Hz, 1 H), 3.34 - 3.52 (m, 3 H), 3.59 - 3.83 (m, 2 H), 4.49 (q, J = 7.13 Hz, 2 H), 4.81 (s, 2 H), 7.09 (dd, J = 7.38, 5.00 Hz, 1 H), 7.49 - 7.59 (m, 1 H), 7.59 - 7.69 (m, 2 H), 8.06 (d, J = 0.75 Hz, 2 H), 8.14 - 8.28 (m, 2 H), 8.55 (s, 1 H)	TFA		LCMS: 2.63 min, 600.2 (M+H), METHOD O		
84	1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[(3S)-pyrrolidin-3-yl]methylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	M	Ex. 5 and tert-butyl (S)-3-((methylsulfonyl)oxy)methylpyrrolidine-1-carboxylate		Prep-HPLC: Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.26 - 8.18 (m, 2H), 8.06 (s, 2H), 7.68 - 7.59 (m, 2H), 7.57 - 7.51 (m, 1H), 7.10 (dd, J = 5.0, 7.4 Hz, 1H), 4.81 (s, 2H), 4.49 (q, J = 7.0 Hz, 2H), 3.70 (s, 2H), 3.50 - 3.37 (m, 4H), 3.20 (td, J = 8.2, 11.4 Hz, 1H), 3.09 - 2.95 (m, 3H), 2.87 - 2.70 (m, 1H), 2.37 - 2.30 (m, 2H), 2.27 - 2.10 (m, 3H), 1.83 - 1.72 (m, 1H), 1.43 (t, J = 7.1 Hz, 3H)	Formate		LCMS: 2.64 min, 600.1 (M+H), METHOD O	SFC: 1.26 min, 100%, Column Name: DAICEL Chiralcel OD-3, 50×4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 4.4 µL; Run time: 3 min.	
91	rac-(3S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethoxy-1-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	M	Int 71	Using tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate in the 1 st step and H ₃ PO ₄ /DCM RT in the 2 nd step	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .		¹ H NMR (400 MHz, DMSO-d ₆ , 80°C) δ 8.38 - 8.36 (m, 2H), 8.30 (s, 1 H), 8.23 - 8.20 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.14 - 7.12 (m, 1H), 5.08 - 4.95 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.78 - 3.74 (m, 1H), 3.62 - 3.52 (m, 2H), 3.32 - 3.24 (m, 1H), 3.15 - 3.02 (m, 4H), 2.95 - 2.92 (m, 1H), 2.85 - 2.75 (m, 2H), 2.45 - 2.35 (m, 1H), 2.05 - 1.95 (m, 2H), 1.85 - 1.65 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.22 - 1.15 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H).			LCMS: 1.69 min, 611.1 (M+H), METHOD A		
92	(S)-2-(2-ethoxypyridin-3-yl)-1-(3-propoxy-2-	M	43	TFA/DCM 25°C, 30 min	Prep-HPLC Method B;		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.30 (dd, J = 7.4, 2.0 Hz, 1H), 8.26 (dd, J = 5.0, 1.6 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.11 (d, J			LCMS: 1.99 min, 610.1		

	(trifluoromethyl)phenyl)-7-(pyrrolidin-3-yl)-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridine]-8-one			min in the 2 nd Step	by following washing with aq. NaHCO ₃ .	= 8.4 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.18 – 5.08 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.01 (t, J = 6.4 Hz, 2H), 3.74 – 3.33 (m, 2H), 3.09 – 2.93 (m, 6H), 2.83 – 2.75 (m, 2H), 2.25 – 1.98 (m, 3H), 1.84 – 1.71 (m, 5H), 1.38 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H). Exchangeable NH proton not observed		(MH+), METHOD A	
94	2-(2-ethoxypyridin-3-yl)-1-[6-propoxy-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 46	Using tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 (dd, J = 7.2, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.24 – 8.19 (m, 2H), 8.11 (d, J = 3.2 Hz, 1H), 7.20 – 7.16 (m, 2H), 5.25 – 5.10 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.78 – 3.74 (m, 2H), 3.13 – 3.10 (m, 3H), 2.97 – 2.94 (m, 1H), 2.84 – 2.78 (m, 4H), 2.15 – 2.01 (m, 3H), 1.79 – 1.72 (m, 5H), 1.39 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H). Exchangeable NH proton was not observed.		LCMS: 2.01 min, (MH+), METHOD A	
99	2-(2-ethoxypyridin-3-yl)-1-[6-[methyl(propyl)amino]-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 51	2 nd Step. TFA/DCM 30 min	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.32 – 8.31 (m, 1H), 8.30 – 8.29 (m, 1H), 8.25 – 8.22 (m, 1H), 8.20 – 8.12 (m, 1H), 7.96 – 7.94 (m, 1H), 7.19 – 7.16 (m, 1H), 6.94 – 6.91 (m, 1H), 5.16 – 5.13 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.81 – 3.71 (m, 2H), 3.52 – 3.45 (m, 2H), 3.32 – 3.02 (m, 3H), 3.01 – 2.89 (m, 4H), 2.87 – 2.82 (m, 4H), 2.05 – 2.04 (m, 3H), 1.82 – 1.77 (m, 3H), 1.59 – 1.53 (m, 2H), 1.41 – 1.37 (m, 3H), 0.89 (m, 3H) exchangeable proton was not observed.		LCMS: 2.58 min, 624.4 (MH+), METHOD B	
99-1	2-(2-ethoxypyridin-3-yl)-1-[6-[methyl(propyl)amino]-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1				SFC chiral separation			LCMS: 2.04 min, 624.3 (MH+), METHOD A	SFC: 2.40 min, Column Name: YMC Cellulose-SC, Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar; 35 °C
99-2	2-(2-ethoxypyridin-3-yl)-1-[6-[methyl(propyl)amino]-2-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2				SFC chiral separation			LCMS: (ESI+): rt= 2.04 min, 624.3 (MH+), METHOD A	SFC: 4.72 min, Column Name: YMC Cellulose-SC, Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar; 35 °C
100	2-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-pyrrolidin-3-	M	Int. 54	2 nd Step. TFA/DCM	Prep-HPLC Method B;	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 – 8.25 (m, 2H), 8.20 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.19		LCMS: 1.86 min, 539.2	

	ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-6-methoxybenzonitrile			25°C, 30 min	by washing with aq. NaHCO ₃ .	– 7.16 (m, 1H), 6.84 – 6.79 (m, 2H), 5.03 (m, 1H), 4.49 – 4.43 (m, 2H), 3.89 (s, 3H), 3.74 – 3.71 (m, 2H), 3.49 – 3.46 (m, 3H), 3.33 (s, 3H), 2.68 – 2.67 (m, 1H), 2.52 – 2.51 (m, 2H), 2.50 – 2.33 (m, 2H), 2.33 – 2.33 (m, 1H), 2.08 – 1.39 (m, 3H), 1.39 – 1.36 (m, 3H).	(M+H), METHOD B	
101	1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxy-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 37	Using tert-butyl ((methylsulfonyl)oxy)pyrrolidine-1-carboxylate in the 1 st step and H ₃ PO ₄ /DCM RT in the 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.77 (s, 1H), 8.56 (s, 1H), 8.30 (dd, J = 7.6, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.19 – 7.16 (m, 1H), 5.18 – 5.10 (m, 1H), 4.47 (q, J = 6.8 Hz, 2H), 3.75 – 3.71 (m, 2H), 3.61 – 3.60 (m, 1H), 3.24 – 3.17 (m, 2H), 3.07 – 3.06 (m, 1H), 2.99 – 2.94 (m, 1H), 2.85 – 2.81 (m, 2H), 2.17 – 2.14 (m, 3H), 2.02 – 2.00 (m, 1H), 1.87 – 1.84 (m, 2H), 1.78 – 1.75 (m, 2H), 1.41 (t, J = 5.6 Hz, 3H).	LCMS: 1.99 min, 587.2 (M+H), METHOD B	
101-1	1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxy-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 1				SFC chiral separation		LCMS: 1.72 min, 587.2 (M+H), METHOD A	SFC: 5.11 min, 100%, Column Name: YMC Cellulose-SC, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C.
101-2	1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxy-3-yl)-7-pyrrolidin-3-ylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one Enantiomer 2				SFC chiral separation		LCMS: 1.72 min, 587.1 (M+H), METHOD A	SFC: 11.42 min, 100%, Column Name: YMC Cellulose-SC, Co-Solvent: 50%, Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar, 35 °C.
103	<i>rac</i> -(3'S,5S)-2-(2-ethoxy-1-[3-methoxy-2-(trifluoromethyl)phenyl]-7-pyrrolidin-3-ylspiro[6H-1,7-	M	Int. 58	Using tert-butyl ((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (dd, J = 7.6, 2.0 Hz, 1H), 8.27 – 8.24 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.22 – 5.02 (m, 1H), 4.50 – 4.45 (m, 2H), 3.85 – 3.81 (m, 4H), 3.62 – 3.52 (m, 1H), 3.33 – 2.98 (m, 4H), 2.91 – 2.89 (m, 2H), 2.78 – 2.75 (m, 2H), 2.50 – 2.43 (m, 2H), 2.08 – 1.92 (m, 2H), 1.88 –	LCMS: 1.86 min, 610.2 (M+H), METHOD A	

	naphthyridine-5,4'-piperidine]-8-one			in the 1 st step and H ₃ PO ₄ /DCM, RT in the 2 nd step		1.78 (m, 1H), 1.72 – 1.58 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.22 – 1.12 (m, 1H), 1.08 – 0.98 (m, 1H), 0.92 – 0.89 (m, 3H).			
104	(3'S,5S)-2-(2-ethoxy-5-yl)-3'-(trifluoromethyl)phenyl]-7-(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one diastereomer 1	M	Int. 59-1	Using TFA/DCM, RT in the 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (dd, J = 2.0, 7.6 Hz, 1H), 8.28 – 8.25 (m, 2H), 8.03 (d, J = 8.8 Hz, 1H), 7.85 – 7.83 (m, 1H), 7.63 – 7.56 (m, 2H), 7.18 (q, J = 4.8 Hz, 1H), 5.09 (m, 1H), 4.51 – 4.45 (m, 2H), 3.90 (d, J = 13.6 Hz, 1H), 3.62 (d, J = 13.6 Hz, 1H), 3.52 (s, 1H), 3.16 – 3.00 (m, 2H), 2.97 – 2.93 (m, 3H), 2.84 – 2.80 (m, 1H), 2.51 – 2.50 (m, 1H), 2.03 (m, 1H), 1.98 (m, 1H), 1.95 (m, 1H), 1.87 (m, 1H), 1.42 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.24 – 1.18 (m, 1H), 1.17 – 1.15 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H). Exchangeable NH proton not observed	LCMS: 2.37 min, 598.3 (M+H) ⁺ METHOD B		SFC: 0.91 min, 99.44%; Column: Chiralpak AS-H, Co-Solvent : 50%, Co-Solvent Name : Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
105	rac-(3'S,5S)-2-(2-ethoxy-5-yl)-3'-(trifluoromethyl)phenyl]-7-(3S)-pyrrolidin-3-yl]-1'-[2-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 60	Using TFA/DCM, RT in the 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.48 – 8.47 (m, 1H), 8.36 – 8.34 (m, 1H), 8.28 – 8.26 (m, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.75 – 7.74 (m, 1H), 7.18 (q, J = 4.8 Hz, 1H), 4.50 (s, 1H), 4.49 – 4.46 (m, 2H), 3.78 (t, J = 8.4 Hz, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.17 – 3.09 (m, 2H), 3.11 (m, 1H), 3.00 – 2.94 (m, 3H), 2.82 – 2.79 (m, 1H), 2.51 – 2.50 (m, 1H), 2.01 – 2.01 (m, 2H), 1.98 – 1.97 (m, 2H), 1.67 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.24 – 1.16 (m, 2H), 1.16 – 0.91 (m, 1H), 0.89 (t, J = 6.0 Hz, 3H).	LCMS: 2.12 min, 581.3 (M+H) ⁺ METHOD B		SFC: 2.86 min and 4.60 min, 49.29%, 49.34%; Column: Chiralpak OX-H, Co-Solvent : 40%; Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
115	rac-(3'S,5S)-2-(2-ethoxy-5-yl)-3'-(trifluoromethyl)phenyl]-7-(3R)-pyrrolidin-3-yl]-1'-[3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 59	TFA/DCM, RT in 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.38 – 8.36 (m, 1H), 8.30 – 8.20 (m, 2H), 8.03 (d, J = 16.0 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.67 – 7.59 (m, 2H), 7.19 (dd, J = 16.0, 12.4 Hz, 1H), 5.26 – 4.99 (m, 1H), 4.49 (a, J = 7.2 Hz, 2H), 3.93 – 3.89 (m, 1H), 3.62 – 3.58 (m, 1H), 3.12 – 3.03 (m, 2H), 3.00 – 2.90 (m, 3H), 2.84 – 2.80 (m, 3H), 2.34 – 2.33 (m, 1H), 1.99 – 1.95 (m, 3H), 1.81 – 1.80 (m, 1H), 1.65 – 1.60 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.20 – 1.15 (m, 1H), 1.09 – 1.01 (m, 1H), 0.86 (t, J = 6.4 Hz, 3H)	LCMS: 2.40 min, 598.3 (M+H) ⁺ Method B		
119	1'-[6-(dimethylamino)-2-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxy-5-yl)-3-yl]-7-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 67 and tert-butyl 3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.30 (dd, J = 7.6, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.96 (d, J = 9.2 Hz, 1H), 5.18 – 5.08 (m, 1H), 4.47 (q, J = 7.0 Hz, 2H), 3.81 – 3.71 (m, 2H), 3.12 – 3.02 (m, 10H), 2.88 – 2.76 (m, 4H), 2.04 – 2.01 (m, 3H), 1.82 – 1.78 (m, 3H), 1.39 (t, J = 7.0 Hz, 3H). An exchangeable NH proton was not observed.	LCMS: 2.45 min, 596.3 (M+H) ⁺ Method B		

121	rac-(3'S,5'S)-2-(2-ethoxypyridin-3-yl)-3'-ethoxy-1-[3-fluoro-2-(trifluoromethyl)phenyl]-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 68 and tert-butyl ((R)-3-(methylsulfonyl)oxy)pyrrolidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.34 (dd, J = 2.0, 7.2 Hz, 1H), 8.28 – 8.25 (m, 2H), 8.06 (d, J = 8.8 Hz, 1H), 7.68 (q, J = 7.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.19 – 7.13 (m, 2H), 5.23 – 5.10 (m, 1H), 4.49 (s, J = 6.8 Hz, 2H), 3.82 (t, J = 10.4 Hz, 1H), 3.62 – 3.52 (m, 2H), 3.23 – 3.17 (m, 2H), 3.06 – 2.92 (m, 4H), 2.80 – 2.78 (m, 1H), 2.51 – 2.42 (m, 2H), 2.01 – 1.97 (m, 2H), 1.90 – 1.65 (m, 2H), 1.40 (t, J = 6.8 Hz, 3H), 1.24 – 1.16 (m, 1H), 1.16 – 1.09 (m, 1H), 0.90 (t, J = 5.6 Hz, 3H).	LCMS: 2.37 min, 598.3 (M+H) ⁺ , Method B	SFC: 3.89 min, and 5.58 min, Column: YMC Cellulose-SC, 50.08% and 47.13% Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
123	rac-(3'S,5'S)-1'-[4-chloro-3-(2-yl)-2-(2-ethoxypyridin-3-yl)-3'-ethoxy-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-3'-ethyl-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 70 and tert-butyl ((R)-3-(methylsulfonyl)oxy)pyrrolidine-1-carboxylate	TFA, DCM in 2 nd step	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.38 (d, J = 5.0 Hz, 1H), 8.33 (dd, J = 7.4, 2.0 Hz, 1H), 8.27 – 8.22 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 7.19 – 7.16 (m, 1H), 5.20 – 5.10 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.80 – 3.78 (m, 1H), 3.72 – 3.67 (m, 2H), 3.62 – 3.55 (m, 1H), 3.16 – 2.88 (m, 3H), 2.85 – 2.75 (m, 1H), 2.48 – 2.38 (m, 2H), 2.08 – 1.78 (m, 3H), 1.72 – 1.58 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.24 – 1.21 (m, 1H), 1.08 – 0.98 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H). Exchangeable NH proton was not observed in ¹ H NMR.	LCMS: 1.96 min, 615.6 (M+H) ⁺ , Method A	
125	rac-(3'S,5'S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	Int. 73 and tert-butyl ((R)-3-(methylsulfonyl)oxy)pyrrolidine-1-carboxylate		Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.36 – 8.32 (m, 1H), 8.30 – 8.26 (m, 1H), 8.28 – 8.25 (m, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.23 – 7.17 (m, 2H), 5.15 – 5.00 (m, 1H), 4.50 (q, J = 7.2 Hz, 2H), 3.93 – 3.90 (m, 1H), 3.88 (s, 3H), 3.89 – 3.34 (m, 2H), 3.20 – 3.16 (m, 4H), 2.97 – 2.94 (m, 3H), 2.81 – 2.78 (m, 1H), 2.53 – 2.52 (m, 1H), 1.99 – 1.96 (m, 3H), 1.99 – 1.42 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.40 – 1.38 (m, 1H), 1.38 – 1.17 (m, 1H), 0.87 (t, J = 7.6 Hz, 3H).	LCMS: 2.35 min, 611.3 (M+H) ⁺ , Method B	SFC: 1.92 min and 2.27 min, 59.66%, 44.33%, Column: YMC Cellulose-SC, Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
129	rac-(3'S,4'S)-2-(2-ethoxypyridin-3-yl)-3'-ethoxy-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7'-[(tetrahydro-1H-pyrolizin-7a(5H)-yl)methyl]-6',7'-dihydro-8'H-spiro[piperidine-	M	Int. 73 and Int. 74	NaH, DMSO, RT, 16 h	Prep-HPLC Method followed by washing with aq. NaHCO ₃	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.38 (dd, J = 7.6, 2.0 Hz, 1H), 8.27 – 8.25 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.23 – 7.16 (m, 2H), 4.50 (q, J = 7.2 Hz, 2H), 4.08 – 3.89 (m, 1H), 3.89 (s, 3H), 3.75 – 3.53 (m, 1H), 3.75 – 3.50 (m, 2H), 3.33 – 3.02 (m, 2H), 3.01 – 2.83 (m, 1H), 2.83 – 2.68 (m, 2H), 2.80 – 2.55 (m, 1H), 2.53 (s, 3H), 2.33 – 1.73 (m, 3H), 1.98 – 1.70 (m, 5H).	LCMS: 2.03 min, 665.2 (M+H) ⁺ , Method A	SFC: 2.47 and 3.25 min; 50.65%, 49.34%; Column: Chiralpak (G, Co-Solvent : 45%, Co-Solvent Name : 0.5% Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min;

	4,5'-[1,7]naphthyridin]-8'-one						1.70 – 1.67 (m, 2H), 1.55 (t, J = 7.2 Hz, 3H), 1.54 – 1.42 (m, 1H), 1.42 – 0.89 (m, 1H), 0.89 – 0.85 (m, 3H).			Outlet Pressure: 100 bar; Temperature : 35 °C
129-1	Enant1-(3S,4S)-2'-(2-ethoxy)pyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7'-(tetrahydro-1H-pyrolizin-7a(5H)-yl)methyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one Enantiomer 1	M	SFC purification				¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.38 (dd, J = 2.0, 7.6 Hz, 1H), 8.27 – 8.25 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.23 – 7.16 (m, 2H), 4.50 (q, J = 7.2 Hz, 2H), 4.08 – 3.89 (m, 1H), 3.89 (s, 3H), 3.75 – 3.53 (m, 1H), 3.75 – 3.50 (m, 2H), 3.33 – 3.02 (m, 2H), 3.01 – 2.83 (m, 1H), 2.83 – 2.68 (m, 2H), 2.80 – 2.55 (m, 1H), 2.53 (s, 3H), 2.33 – 1.73 (m, 3H), 1.98 – 1.70 (m, 5H), 1.70 – 1.67 (m, 2H), 1.55 (t, J = 7.2 Hz, 3H), 1.54 – 1.42 (m, 1H), 1.42 – 0.89 (m, 1H), 0.89 – 0.85 (m, 3H).	LCMS: 2.50 min, 665.3 (M+H) ⁺ , Method B	SFC: 2.49 min; 100%; Column: Chiralpak IG, Co-Solvent : 45%, Co-Solvent Name : 0.5% Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C	
129-2	Enant2-(3S,4S)-2'-(2-ethoxy)pyridin-3-yl)-3-ethyl-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7'-(tetrahydro-1H-pyrolizin-7a(5H)-yl)methyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one Enantiomer 2	M	SFC purification				¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.36 (dd, J = 2.0, 7.6 Hz, 1H), 8.27 – 8.25 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.23 – 7.16 (m, 2H), 4.50 – (q, J = 7.2 Hz, 2H), 4.08 – 3.89 (m, 1H), 3.89 (s, 3H), 3.75 – 3.53 (m, 1H), 3.75 – 3.50 (m, 2H), 3.33 – 3.02 (m, 2H), 3.01 – 2.83 (m, 1H), 2.83 – 2.68 (m, 2H), 2.80 – 2.55 (m, 1H), 2.53 (s, 3H), 2.33 – 1.73 (m, 3H), 1.98 – 1.70 (m, 5H), 1.70 – 1.67 (m, 2H), 1.55 (t, J = 7.2 Hz, 3H), 1.54 – 1.42 (m, 1H), 1.42 – 0.89 (m, 1H), 0.89 – 0.85 (m, 3H).	LCMS: 2.54 min, 665.3 (M+H) ⁺ , Method B	SFC: 3.27 min; 100%; Column: Chiralpak IG, Co-Solvent : 45%, Co-Solvent Name : 0.5% Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C	
142	(R)-2'-(2-ethoxy)pyridin-3-yl)-1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7'-(pyrrolidin-2-yl)methyl)-6',7'-dihydro-8'H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	M	NaH, THF, 60 °C, in the 1 st Step and TFA/DCM in the 2 nd Step	tert-butyl ((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate	Prep-HPLC Method followed by washing with aq. NaHCO ₃		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.30 – 8.32 (m, 2H), 8.25 – 8.27 (m, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.16 – 7.22 (m, 2H), 4.47 (q, J = 7.2 Hz, 2H), 3.88 – 3.91 (m, 5H), 3.65 – 3.67 (m, 1H), 3.44 – 3.46 (m, 2H), 3.25 – 3.10 (m, 2H), 2.87 – 2.89 (m, 1H), 2.75 – 2.81 (m, 3H), 2.06 (q, J = 8.0 Hz, 2H), 1.72 – 1.85 (m, 4H), 1.62 – 1.64 (m, 1H), 1.50 – 1.40 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), exchangeable proton not observed.	LCMS: 2.24 min, 597.2 (M+H) ⁺ , Method B	SFC: 1.80 min, 100%; Column: YMC-Cellulose-SC, Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C	
149	rac-(3'S,5'S)-2'-(2-ethoxy)pyridin-3-yl)-3-ethyl-7-[(2R)-pyrrolidin-2-yl)methyl]-1-[2-(trifluoromethyl)phenyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	M	NaH, THF, 60 °C, in the 1 st Step and TFA/DCM in the 2 nd Step	tert-butyl ((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate	Prep-HPLC Method followed by washing with aq. NaHCO ₃		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.37 – 8.35 (m, 1H), 8.35 – 8.25 (m, 2H), 8.04 – 8.01 (m, 1H), 7.82 – 7.80 (m, 1H), 7.73 – 7.69 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.19 – 7.16 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 4.00 – 3.83 (m, 1H), 3.83 – 3.72 (m, 2H), 3.41 – 3.40 (m, 2H), 3.33 – 3.29 (m, 1H), 3.12 – 3.02 (m, 1H), 2.92 – 2.85 (m, 4H), 2.42 – 2.32 (m, 1H), 2.12 – 1.98 (m, 1H), 1.73 – 1.65 (m, 4H), 1.40 (t, J = 7.0 Hz, 3H), - 1.39 – 1.36 (m, 1H), 1.28 – 1.12	LCMS: 2.32 min, 594.3 [M+H] ⁺ , Method B		

							(m, 1H), 1.08 - 0.92 (m, 1H), 0.88 - 0.85 (m, 3H). Exchangeable NH proton was not observed.		
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Table 15 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data	Chiral Analysis
36	<i>rac</i> -(3S,4S)-1-(4-chloro-2-(trifluoromethyl)phenyl)-2-(2-ethoxypyridin-3-yl)-3-ethyl-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	N	1		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.37 - 8.34 (m, 1H), 8.28 - 8.23 (m, 3H), 8.03 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 1.2 Hz, 2H), 7.73 (s, 1H), 7.19 - 7.16 (m, 1H), 4.51 - 4.46 (m, 2H), 3.75 - 3.71 (m, 1H), 3.53 - 3.49 (m, 1H), 3.12 - 3.04 (m, 2H), 2.90 - 2.84 (m, 2H), 2.38 - 2.28 (m, 1H), 2.08 - 2.03 (m, 1H), 1.66 - 1.65 (m, 1H), 1.40 (t, J = 6.8 Hz, 3H), 1.24 - 1.18 (m, 1H), 1.07 - 1.05 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H).	LCMS: 3.19 min, 545.2 (M+H), METHOD B	
42	<i>rac</i> -(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(2-(trifluoromethyl)phenyl)-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	N	1		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.36 (dd, J = 7.6, 2.0 Hz, 1H), 8.29 - 8.23 (m, 3H), 8.04 (d, J = 8.4 Hz, 1H), 7.74 - 7.68 (m, 3H), 7.38 - 7.34 (m, 1H), 7.20 - 7.17 (m, 1H), 4.51 - 4.46 (m, 2H), 3.75 - 3.71 (m, 1H), 3.53 - 3.49 (m, 1H), 3.13 - 3.05 (m, 2H), 2.90 - 2.84 (m, 2H), 2.50 - 2.33 (m, 1H), 2.07 - 2.04 (m, 1H), 1.67 - 1.66 (m, 1H), 1.40 (t, J = 3.2 Hz, 3H), 1.24 - 1.20 (m, 1H), 1.08 - 1.07 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H).	LCMS: 3.01 min, 511.2 (M+H), METHOD B	
51	<i>rac</i> -(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(3-propoxy-2-(trifluoromethyl)phenyl)-6,7-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8'-one	N	1 and 36		Flash chromatography; DCM/MeOH (0 to 10%)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.35 (dd, J = 7.2, 2.0 Hz, 1H), 8.27 - 8.25 (m, 2H), 8.18 (d, J = 3.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.19 - 7.16 (m, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.49 (q, J = 6.4 Hz, 2H), 4.01 (t, J = 6.0 Hz, 2H), 3.60 - 3.59 (m, 1H), 3.49 - 3.45 (m, 1H), 3.18 - 3.16 (m, 1H), 3.04 - 3.01 (m, 2H), 2.85 - 2.75 (m, 1H), 2.37 - 2.33 (m, 1H), 2.06 - 2.02 (m, 1H), 1.76 - 1.67 (m, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.24 - 1.20 (m, 1H), 1.01 - 0.96 (m, 4H), 0.91 - 0.88 (m, 3H).	LCMS: 7.2 min, 569.3 (M+H), METHOD R	
51-1	<i>rel</i> -(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1-(3-propoxy-2-(trifluoromethyl)phenyl)-6,7-dihydro-8H-spiro[piperidine-4,5'-				Chiral SFC separation		LCMS: 3.24 min, 569.0 (M+H), METHOD B	SFC: 1.82 min, 99.93%, Column Name: YMC Cellulose-SB, Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume:

	[1,7]naphthyridin]-8-one Enantiomer 1								15 μ L; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar; 35 $^{\circ}$ C	
51-2	<i>rel</i> -(3 <i>S</i> ,4 <i>S</i>)-2'-(2-ethoxy-1-(3-propoxy-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one Enantiomer 2				Chiral SFC separation				SFC: 2.14 min, 98.29%, Column Name: YMC Cellulose-SB; Co-Solvent: 50%; Co-Solvent Name: 0.5% Isopropyl Amine in MeOH; Injected Volume: 15 μ L; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar; 35 $^{\circ}$ C	LCMS: 3.23 min, 569.0 (M+H), METHOD B
65	<i>rac</i> -(3 <i>S</i> ,4 <i>S</i>)-2'-(2-ethoxy-1-(4-propoxy-3-(trifluoromethyl)pyridin-2-yl)-6',7'-dihydro-8 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	N	1 and 29		Flash chromatography: DCM/MeOH (0 to 10%)			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (dd, <i>J</i> = 7.6, 2.0 Hz, 1H), 8.29 - 8.23 (m, 3H), 8.16 (d, <i>J</i> = 3.6 Hz, 1H), 8.00 (d, <i>J</i> = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 6.85 (d, <i>J</i> = 6.0 Hz, 1H), 4.50 - 4.45 (m, 2H), 4.12 (t, <i>J</i> = 6.4 Hz, 2H), 3.62 - 3.57 (m, 2H), 3.51 - 3.45 (m, 2H), 3.18 - 3.08 (m, 1H), 2.98 - 2.85 (m, 1H), 2.34 - 2.33 (m, 1H), 2.03 - 2.00 (m, 1H), 1.77 - 1.72 (m, 3H), 1.39 (t, <i>J</i> = 7.2 Hz, 3H), 1.32 - 1.18 (m, 1H), 1.04 - 0.97 (m, 4H), 0.93 - 0.89 (m, 3H).		LCMS: 3.10 min, 570.1 (M+H), METHOD B
71	<i>rac</i> -(3 <i>S</i> ,4 <i>S</i>)-1'-(3-chloro-2'-(2-ethoxy-1-(3-propoxy-2-(trifluoromethyl)phenyl)-3-ethyl-6',7'-dihydro-8 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	N	1 and 1-bromo-3-chloro-2-(trifluoromethyl)b enzene		Prep-HPLC Method B			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.35 (dd, <i>J</i> = 7.5, 2.0 Hz, 1H), 8.26 (d, <i>J</i> = 6.3 Hz, 2H), 8.21 (d, <i>J</i> = 4.0 Hz, 1H), 8.05 (d, <i>J</i> = 8.5 Hz, 1H), 7.60 (t, <i>J</i> = 8.2 Hz, 1H), 7.47 (d, <i>J</i> = 8.3 Hz, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 1H), 7.20 - 7.17 (m, 1H), 4.52 - 4.44 (m, 2H), 3.64 - 3.62 (m, 1H), 3.50 - 3.47 (m, 1H), 3.41 - 3.37 (m, 2H), 3.30 - 3.23 (m, 1H), 3.06 - 2.98 (m, 1H), 2.42 - 2.35 (m, 1H), 2.07 - 2.04 (m, 1H), 1.75 - 1.65 (m, 1H), 1.40 (t, <i>J</i> = 7.0 Hz, 3H), 1.29 - 1.14 (m, 1H), 1.24 - 1.19 (m, 1H), 0.90 (t, <i>J</i> = 7.6 Hz, 3H).		LCMS: 2.25 min, 545.2 (M+H), METHOD A

Table 16 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
38	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxy-1-(3-propoxy-2-(trifluoromethyl)phenyl)-6',7'-dihydro-8 <i>H</i> -spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	O	Ex. 3		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 (dd, <i>J</i> = 7.2 Hz, 2.0 Hz, 1H), 8.26 (dd, <i>J</i> = 4.8 Hz, 2.0 Hz, 1H), 8.20 (d, <i>J</i> = 8.0 Hz, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.61 (t, <i>J</i> = 8.0 Hz, 1H), 7.46 (d, <i>J</i> = 8.0 Hz, 1H), 7.37 (d, <i>J</i> = 8.0 Hz, 1H), 7.19 - 7.16 (m, 1H), 5.77 (s, 1H), 4.47 (q, <i>J</i> = 7.20 Hz, 2H), 3.93 - 3.91 (m, 4H).		LCMS: 2.20 min, 602.3	

	y)methylspiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one				3.78 – 3.58 (m, 4H), 3.19 – 3.16 (m, 2H), 3.03 – 3.00 (m, 2H), 2.13 – 2.08 (m, 2H), 1.85 – 1.82 (m, 2H), 1.38 (t, J = 6.8 Hz, 3H) (exchangeable NH proton was not observed).		(M+H), METHOD B	
43	1-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypropyl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	O	Ex. 3	Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 (dd, J = 7.6 Hz, 2.0, 1H), 8.26 (dd, J = 4.8 Hz, 2.0, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.20 – 7.17 (m, 1H), 5.67 (s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.92 – 3.88 (m, 4H), 3.51 – 3.47 (m, 2H), 3.21 – 3.18 (m, 2H), 3.03 – 3.00 (m, 2H), 2.92 – 2.83 (m, 2H), 2.27 (s, 3H), 2.13 – 2.08 (m, 2H), 1.91 – 1.82 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H).		LCMS: 2.21 min, 616.3 (M+H), METHOD B	
44	2-(2-ethoxypropyl)-7-[(3-hydroxyazetidin-3-yl)methyl]-1-[5-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	O	Int. 32	Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 – 8.30 (m, 3H), 8.27 – 8.25 (m, 1H), 8.25 – 8.18 (m, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.18 (q, J = 4.8 Hz, 1H), 5.74 (s, 1H), 4.49 – 4.44 (m, 2H), 4.18 (t, J = 6.4 Hz, 2H), 3.80 – 3.77 (m, 4H), 3.44 – 3.40 (m, 4H), 3.38 – 3.29 (m, 2H), 3.26 – 3.08 (m, 2H), 2.10 – 2.09 (m, 2H), 1.84 (dd, J = 14.0, Hz, 2H), 1.78 – 1.73 (m, 2H), 1.38 (t, J = 2.4 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H) (Exchangeable NH proton was not observed in ¹ H NMR).		LCMS: 2.71 min, 627.3 (M+H), METHOD B	
47	2-(2-ethoxypropyl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]-1-[5-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	O	Int. 32	Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 – 8.31 (m, 2H), 8.30 – 8.30 (m, 1H), 8.27 – 8.26 (m, 1H), 8.25 – 8.18 (m, 1H), 8.11 – 8.09 (m, 1H), 7.18 (q, J = 4.8 Hz, 1H), 5.66 (s, 1H), 4.48 – 4.46 (m, 2H), 4.19 – 4.16 (m, 2H), 4.16 – 3.88 (m, 4H), 3.51 – 3.43 (m, 4H), 3.43 – 3.33 (m, 1H), 2.82 – 2.80 (m, 1H), 2.82 – 2.69 (m, 2H), 2.68 – 2.67 (m, 1H), 2.34 – 2.33 (m, 3H), 2.28 – 2.26 (m, 1H), 1.40 – 1.38 (m, 2H), 1.36 – 1.24 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H), 0.86 (t, J = 4.0 Hz, 3H).		LCMS: 2.18 min, 641.0 (M+H), METHOD B	
50	1-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypropyl)-7-[(3-hydroxyazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	O	Ex. 14	Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.76 (br s, 1H), 8.30 – 8.26 (m, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.20 – 7.17 (m, 1H), 6.98–6.91 (m, 2H), 6.44 (s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.18–4.17 (m, 2H), 4.16–3.93 (m, 6H), 3.92–3.83 (m, 2H), 3.10–3.00 (m, 4H), 2.11–2.09 (m, 2H), 1.84–1.81 (m, 2H), 1.38 (t, J = 6.8 Hz, 3H), 1.22 (m, 1H), 0.58–0.54 (m, 2H), 0.36–0.34 (m, 2H).	TFA	LCMS: 1.96 min, 638.2 (M+H), METHOD A	
63	1-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypropyl)-7-[(3-hydroxy-1-methylazetidin-3-yl)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	O	Ex. 14	Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 (dd, J = 7.6, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.64 (s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.94 – 3.88 (m, 6H), 3.45 – 3.43 (m, 2H), 3.11 – 3.01 (m, 2H), 2.81 – 2.79 (m, 2H), 2.68 – 2.67		LCMS: 1.92 min, 652.3 (M+H), METHOD A	

	y)methyl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one		the 2 nd Step		(m, 2H), 2.25 (s, 3H), 2.15 – 2.02 (m, 2H), 1.83 – 1.80 (m, 2H), 1.38 (t, J = 6.8 Hz, 3H), 1.24 – 1.22 (m, 1H), 0.57 – 0.55 (m, 2H), 0.36 – 0.33 (m, 2H).		
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Table 17 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
52	2-amino-1-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]ethanone	P	Ex. 6		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.25 – 8.22 (m, 2H), 8.01 – 7.95 (m, 2H), 7.80 – 7.77 (m, 1H), 7.74 – 7.74 (m, 1H), 7.71 – 7.69 (m, 1H), 7.15 – 7.12 (m, 1H), 4.75 (s, 2H), 4.47 – 4.42 (m, 2H), 4.00 (s, 2H), 3.54 (t, J = 10.0 Hz, 2H), 3.17 (t, J = 11.6 Hz, 2H), 2.91 – 2.88 (m, 2H), 2.09 – 2.03 (m, 2H), 1.67 – 1.64 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H) Exchangeable NH ₂ protons not observed.		LCMS: 1.99 min, 561.3 (M+H), METHOD A	
53	3-amino-1-[1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	P	Ex. 19 and 3-(tert-butoxycarbonyl)amino propanoic acid		Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.26 – 8.23 (m, 2H), 7.98 – 7.95 (m, 2H), 7.65 – 7.59 (m, 1H), 7.55 – 7.53 (m, 1H), 7.40 – 7.36 (m, 1H), 7.15 – 7.12 (m, 1H), 4.74 (s, 2H), 4.53 (q, J = 7.2 Hz, 2H), 4.42 (s, 2H), 3.16 – 3.15 (m, 2H), 3.09 – 3.05 (m, 2H), 2.84 – 2.80 (m, 2H), 2.69 – 2.68 (m, 2H), 2.12 – 2.06 (m, 2H), 1.79 – 1.62 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H). [2 exchangeable (NH ₂) Protons were not observed]		LCMS: 2.29 min, 573.9 (M+H), METHOD B	
60	[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-(2S)-pyrrolidin-2-yl]methanone	P	Ex. 6 and (tert-butoxycarbonyl)-L-proline		Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.23 – 8.26 (m, 2H), 7.98 (q, J = 8.4 Hz, 2H), 7.69 – 7.79 (m, 3H), 7.14 (dd, J = 5.2, 7.4 Hz, 1H), 4.85 (q, J = 17.6 Hz, 2H), 4.44 (q, J = 6.8 Hz, 2H), 3.15 – 3.29 (m, 3H), 3.10 – 2.80 (m, 3H), 3.15 – 3.29 (m, 3H), 2.09 – 2.03 (m, 3H), 1.56 – 1.62 (m, 6H), 1.34 (t, J = 6.8 Hz, 3H).		LCMS: 2.05 min, 600.5 (M+H), METHOD A	SFC: 1.72min, 99.74%; Column Name: YMC Anylose-SA, Co-Solvent : 40% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
61	[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]-(2R)-	P	Ex. 6 and (tert-butoxycarbonyl)-D-proline		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.26 – 8.23 (m, 2H), 7.98 (q, J = 8.4 Hz, 2H), 7.77 – 7.69 (m, 3H), 7.16 – 7.13 (m, 1H), 4.95 – 4.91 (m, 1H), 4.84 – 4.80 (m, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.03 (m, 3H), 3.33 – 3.15 (m, 2H), 2.94 – 2.87 (m, 4H), 2.09 – 2.03 (m, 3H), 1.66 – 1.57 (m, 6H), 1.38 (t, J = 6.8 Hz, 3H).		LCMS: 2.36 min, 600.0 (M+H), METHOD B	SFC: 3.05 min, 100%, Column Name: YMC Cellulose-SC, Co-Solvent : 40% Isopropylamine in MeOH; Injected Volume

78	azetidin-3-yl-[1'-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]methanone	P	Ex. 6 and 1-(tert-butoxycarbonyl)azetidin-3-carboxylic acid	Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.76 – 8.67 (m, 1H), 8.27 – 8.25 (m, 2H), 8.03 – 7.99 (m, 2H), 7.85 – 7.75 (m, 3H), 7.15 – 7.13 (m, 1H), 4.81 – 4.45 (m, 2H), 4.31 (q, J = 6.0 Hz, 2H), 4.16 – 4.13 (m, 5H), 4.08 (s, 1H), 3.18 – 3.15 (m, 3H), 2.91 – 2.68 (m, 1H), 2.09 – 2.08 (m, 1H), 2.08 – 2.07 (m, 2H), 1.68 – 1.65 (m, 2H), 1.39 – 1.36 (m, 3H). TFA salt	TFA	LCMS: 1.95 min, 586.5 (M+H), METHOD A	
79	3-amino-1-[2-(2-ethoxypyridin-3-yl)-1'-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	P		Prep-HPLC Method A (By-product resulting from impurity in starting materials from Ex 67 synthesis described in this Table)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.27 – 8.23 (m, 2H), 8.02 – 7.95 (m, 2H), 7.71 – 7.64 (m, 3H), 7.38 – 7.36 (m, 1H), 7.14 (q, J = 4.8 Hz, 1H), 4.82 – 4.75 (m, 2H), 4.45 (q, J = 7.2 Hz, 2H), 4.00 – 3.94 (m, 2H), 3.43 – 3.21 (m, 2H), 3.18 – 3.15 (m, 2H), 2.96 – 2.83 (m, 2H), 2.62 – 2.59 (m, 2H), 2.11 – 2.08 (m, 2H), 1.65 (m, 1H), 1.62 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H) (exchangeable amine protons showed less integration)		LCMS: 2.05 min, 540.3 (M+H), METHOD B	
102-1	3-amino-1-[(3S,5S)-2-(2-ethoxypyridin-3-yl)-3-ethyl-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one Enantiomer 1	P	Int. 57-1 and 3-(tert-butoxycarbonyl)amino propanoic acid	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.33 – 8.31 (m, 1H), 8.24 – 8.23 (m, 1H), 8.12 – 8.06 (m, 2H), 7.96 – 7.92 (m, 1H), 7.22 – 7.14 (m, 2H), 4.90 – 4.86 (m, 1H), 4.74 – 4.73 (m, 1H), 4.69 – 4.47 (m, 2H), 3.89 (s, 3H), 3.52 (m, 2H), 3.32 – 3.23 (m, 2H), 2.98 – 2.84 (m, 3H), 2.80 – 2.75 (m, 2H), 2.68 – 2.60 (m, 1H), 2.33 (m, 1H), 2.29 – 1.69 (m, 3H), 1.41 – 1.39 (m, 3H), 1.03 – 1.02 (m, 2H), 1.00 – 0.74 (m, 3H). one proton observed less due to partial exchange of NH ₂ proton.		LCMS: 2.39 min, 599.3 (M+H), METHOD B	SFC: 2.57 min, 100%, Column: (R, R) wheel-O1, Co-Solvent : 40%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
102-2	3-amino-1-[(3S,5S)-2-(2-ethoxypyridin-3-yl)-3-ethyl-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one Enantiomer 2	P	Int 57-2 and 3-(tert-butoxycarbonyl)amino propanoic acid	Prep-HPLC Method B; followed by washing with aq. NaHCO ₃ .	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.33 – 8.30 (m, 1H), 8.24 (d, J = 2.0 Hz, 1H), 8.08 (dd, J = 8.0, 21.8 Hz, 2H), 7.96 – 7.94 (m, 1H), 7.20 – 7.13 (m, 2H), 5.07 (s, 1H), 4.87 (d, J = 17.2 Hz, 2H), 4.74 – 4.73 (m, 2H), 3.89 (s, 3H), 3.52 (s, 1H), 3.19 (s, 1H), 2.98 (m, 2H), 2.90 (m, 1H), 2.87 – 2.86 (s, 2H), 2.79 – 2.78 (m, 1H), 2.74 (m, 1H), 2.30 (m, 1H), 1.80 (s, 2H), 1.41 – 1.39 (m, 3H), 1.02 (t, J = 7.2 Hz, 2H), 0.78 – 0.74 (m, 3H), exchangeable proton not observed.		LCMS: 5.14 min, 599.2 (M+H), METHOD R	SFC: 2.91 min, 100%, Column: (R, R) wheel-O1, Co-Solvent : 40%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume: 15 µl; FlowRate: 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C

106	[2-(2-ethoxy-2-(trifluoromethyl)phenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-3-yl]-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-2-ylmethanone	Int. 61 and (tert-butoxycarbonyl)-L-proline	Using Formic acid, RT 1 h in the 2 nd Step.	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.22 - 8.15 (m, 2H), 8.02 - 7.94 (m, 2H), 7.48 (t, J = 8.3 Hz, 1H), 7.09 (dd, J = 5.0, 7.4 Hz, 1H), 7.04 - 6.97 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.84 - 4.79 (m, 2H), 4.47 (q, J = 7.0 Hz, 2H), 4.39 (t, J = 7.6 Hz, 1H), 4.17 - 4.02 (m, 2H), 3.87 (s, 3H), 3.28 - 3.23 (m, 1H), 3.22 (m, 2H), 3.12 - 3.05 (m, 2H), 3.04 - 2.95 (m, 1H), 2.45 - 2.35 (m, 1H), 2.34 - 2.15 (m, 2H), 2.00 - 1.92 (m, 1H), 1.91 - 1.76 (m, 2H), 1.76 - 1.61 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H)	LCMS: 2.51 min, 596.2 (M+H) ⁺ METHOD O	SFC: 1.31 min, 100% Column: Chiralcel OD-3, 50x4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: 0.1% Isopropyl Amine in MeOH, Injected Volume: 2.1 µL
107	[2-(2-ethoxy-2-(trifluoromethyl)phenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-3-yl]-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-2-ylmethanone	Int. 61 and (tert-butoxycarbonyl)-L-proline	Using Formic acid, RT 2 h in the 2 nd Step.	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.23 - 8.13 (m, 2H), 8.03 - 7.92 (m, 2H), 7.48 (t, J = 8.3 Hz, 1H), 7.11 - 7.06 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.82 (br s, 2H), 4.51 - 4.43 (m, 2H), 4.36 (br t, J = 7.6 Hz, 1H), 4.10 (d, J = 1.5 Hz, 2H), 3.87 (s, 3H), 3.28 - 3.23 (m, 1H), 3.23 - 3.14 (m, 2H), 3.08 (br d, J = 11.5 Hz, 2H), 3.03 - 2.95 (m, 1H), 2.44 - 2.34 (m, 1H), 2.34 - 2.18 (m, 2H), 1.97 - 1.84 (m, 2H), 1.83 - 1.75 (m, 1H), 1.75 - 1.60 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H)	LCMS: 2.51 min, 596.2 (M+H) ⁺ METHOD O	SFC: 1.29 min, 100% Column: Chiralcel OD-3, 50x4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: 0.1% Isopropyl Amine in MeOH, Injected Volume: 2.1 µL
108	3-amino-1-[2-(2-ethoxy-2-(trifluoromethyl)phenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-3-yl]-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-2-ylpropan-1-one	Int. 61 and 3-(tert-butoxycarbonyl)-L-propanoic acid	Using Formic acid, RT 1 h in the 2 nd Step.	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 0.54H), 8.20 - 8.19 (dd, J = 1.9, 4.9 Hz, 1H), 8.16 - 8.14 (dd, J = 1.8, 7.4 Hz, 1H), 8.01 - 7.99 (m, 1H), 7.95 - 7.93 (m, 1H), 7.51 - 7.46 (m, 1H), 7.10 - 7.07 (dd, J = 4.9, 7.3 Hz, 1H), 7.03 - 6.98 (m, 1H), 6.92 - 6.88 (m, 1H), 4.83 (s, 2H), 4.50 - 4.45 (q, J = 7.1 Hz, 2H), 4.07 (s, 1.5H), 3.90 (s, 0.5H), 3.87 (s, 3H), 3.24 - 3.20 (m, 2H), 3.19 - 3.13 (m, 2H), 3.11 - 3.05 (m, 2H), 2.95 - 2.87 (m, 2H), 2.33 - 2.20 (m, 2H), 1.83 - 1.76 (m, 0.5H), 1.70 (d, J = 13.4 Hz, 1H), 1.42 - 1.39 (t, J = 7.1 Hz, 3H)	LCMS: 2.44 min, 570.3 (M+H) ⁺ METHOD O	
122	rac-3-amino-1-((3S,4S)-2-(2-ethoxy-2-(trifluoromethyl)phenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-6H-spiro[piperidine-4,5-[1,1']naphthyridine]-7-yl)propan-1-one	Int. 69 and 3-(tert-butoxycarbonyl)-L-propanoic acid	Using TFA, RT, 4 h in the 2 nd step	Prep-HPLC Method B followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.30 - 8.32 (m, 1H), 8.23 - 8.24 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.14 (dd, J = 5.2, 7.4 Hz, 1H), 7.10 - 6.90 (m, 2H), 4.63 - 4.90 (m, 3H), 4.46 (q, J = 7.0 Hz, 2H), 4.10 - 4.40 (m, 1H), 3.85 (s, 3H), 3.13 - 3.33 (m, 4H), 2.80 - 3.01 (m, 1H), 2.76 - 2.85 (m, 3H), 2.55 - 2.82 (m, 2H), 1.85 - 1.60 (m, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.00 - 1.01 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H)	LCMS: 2.18 min, 598.2 (M+H) ⁺ Method B	SFC: 2.64 min, and 3.26 min, 49.95%, 47.87%; Column Name: (R, R) Wheelk-01, Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in Methanol; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
126	rac-[(3S,5S)-2-(2-ethoxy-2-(trifluoromethyl)phenyl)-3-(trifluoromethyl)phenyl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-3-yl]-1-(3-methoxy-2-(trifluoromethyl)phenyl)pyrrolidin-2-ylmethanone	Int. 69 and (tert-butoxycarbonyl)-L-proline	Using TFA, DCM, RT, 4 h in the 2 nd step	Prep-HPLC Method B followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.29 - 8.32 (m, 1H), 8.24 - 8.26 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.15 (dd, J = 4.8, 7.2 Hz, 1H), 6.94 (d, J = 8.4 Hz, 2H), 4.73 - 4.99 (m, 2H), 4.60 - 4.63 (m, 1H), 4.47 (q, J = 7.0 Hz, 2H), 4.12 - 4.32 (m, 1H), 3.85 (s, 3H), 3.29 - 3.33 (m, 1H), 3.21 - 3.26 (m, 2H), 2.99 (m, 1H), 2.82 - 2.97 (m, 3H), 2.50 - 2.50 (m, 1H), 2.0 - 2.02 (m, 1H), 1.74 - 1.91 (m, 4H), 1.50 - 1.69 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.2 Hz, 2H), 0.80 (t, J = 7.6 Hz, 3H), exchangeable proton not observed.	LCMS: 2.52 min, 624.4 (M+H) ⁺ Method B	SFC: 2.96 min, and 4.06 min, 71.87%, 1.62%; Column: YMC Cellulose-SC; Co-Solvent : 50%; Co-Solvent Name : 0.5% Isopropylamine in IPA; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C

132	rac-1-azabicyclo[2.2.2]octan-3-yl(3S,5S)-2-(2-ethoxy-1-[3-methoxy-2-(trifluoromethyl)phenyl]piro[6,5-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl)methanone	P	Int. 69 and quinucidine-3-carbonyl chloride	DIPEA, DMF, rt, 16 h (No HATU used), 2 nd step not required	Prep-HPLC Method B	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.31 – 8.23 (m, 2H), 8.10 – 7.90 (m, 2H), 7.55 (t, J = 8.4 Hz, 1H), 7.14 (dd, J = 4.8, 7.6 Hz, 1H), 7.05 – 6.85 (m, 2H), 4.87 – 4.65 (m, 2H), 4.51 – 4.40 (m, 3H), 3.86 (s, 3H), 3.39 (m, 1H), 3.23 – 3.17 (m, 3H), 3.12 – 2.92 (m, 2H), 2.90 – 2.80 (m, 2H), 2.78 – 2.68 (m, 4H), 2.39 – 2.26 (m, 1H), 1.93 (s, 1H), 1.69 – 1.65 (m, 3H), 1.55 – 1.52 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 0.24 (m, 1H), 1.02 – 0.98 (m, 2H), 0.82 – 0.75 (m, 3H).	Formate	LCMS: 2.49 min, 664.3 (M+H) ⁺ , Method B	SFC: 2.50, 2.86 min and 3.23, 4.27 min Column: YMC Cellulose-SZ, Co-Solvent : 50%; Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure : 100 bar; Temperature : 35 °C
141	(R)-2'-(2-ethoxypyridin-3-yl)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-7-propyl-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	P	Int. 76 and (tert-butoxycarbonyl)-D-proline	HATU, DIEA, DCM, 25 °C, 2 h formic acid in 2 nd step	Prep-HPLC Method E	¹ H-NMR (400 MHz, CD ₃ OD) δ 8.54 (br s, 1H), 8.22 – 8.15 (m, 2H), 8.03 – 7.96 (m, 2H), 7.72 (dd, J = 4.9, 8.2 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.08 (dd, J = 5.1, 7.3 Hz, 1H), 4.87 (br d, J = 5.8 Hz, 2H), 4.62 (dd, J = 7.2, 8.5 Hz, 1H), 4.48 (q, J = 7.0 Hz, 2H), 4.27 – 4.17 (m, 1H), 4.16 – 4.06 (m, 1H), 3.39 – 3.34 (m, 1H), 3.29 – 3.04 (m, 3H), 2.97 – 2.87 (m, 2H), 2.55 – 2.44 (m, 1H), 2.35 – 2.14 (m, 2H), 2.07 (br s, 2H), 1.93 – 1.83 (m, 1H), 1.79 – 1.70 (m, 1H), 1.66 (br d, J = 13.2 Hz, 1H), 1.41 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.59 min, 584.3 (M+H) ⁺ , Method S	SFC: 1.20 min, 100% purity; Column Name: Chiralcel OD-3, 50x4.6 mm I.D, 3.0 µm, Co-Solvent: 50%; Co-Solvent Name: 0.2% Ammonia gas in MeOH; Injected Volume: 2.10 µL; Run time: 3.0 min.
148	3-amino-1-[2-(2-ethoxyphenyl)-1-(4-fluoro-2-(trifluoromethyl)phenyl]piro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	P	Int. 86 and 3-((tert-butoxycarbonyl)amino)propanoic acid	BOP-Cl, DIEA, THF, 25 °C, 2 h formic acid in 2 nd step	Prep-HPLC Method F	¹ H-NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.78 – 7.68 (m, 1H), 7.60 (dd, J = 1.6, 7.6 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.14 – 7.08 (m, 1H), 7.05 (t, J = 7.5 Hz, 1H), 4.82 (s, 2H), 4.16 – 4.09 (m, 4H), 3.95 (s, 1H), 3.28 – 3.11 (m, 4H), 3.06 – 2.96 (m, 1H), 2.92 (br t, J = 6.1 Hz, 3H), 2.36 – 2.20 (m, 2H), 1.86 – 1.69 (m, 2H), 1.37 (t, J = 6.9 Hz, 3H)	Formate	LCMS: 2.46 min, 557.2 (M+H) ⁺ , Method O	

Table 18 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
54	1-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-	Q	Ex. 48		Prep-HPLC Method A	¹ H-NMR (400 MHz, DMSO-d ₆) δ 9.77 (br s, 1H), 8.32 – 8.25 (m, 3H), 8.18 (t, J = 8.4 Hz, 1H), 7.63 (t, J = 4.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.38 – 7.09 (m, 1H), 5.38 – 5.22 (m, 1H), 4.95 – 4.85 (m, 1H), 4.52 – 4.45 (m, 6H), 3.87 (s, 1H), 3.73 – 3.66 (m, 2H), 3.45 – 3.39 (m, 2H), 3.21 – 3.16 (m, 3H), 3.11 – 3.04	TFA	LCMS: 2.07 min, 616.3 (M+H) ⁺ , METHOD B	

	yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one				(m, 2H), 2.18 - 2.08 (m, 2H), 1.91 - 1.88 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H). TFA salt			
55	1'-[3-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	Q	Ex. 15	Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 (dd, J = 7.6, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.19 - 7.16 (m, 1H), 5.45 - 5.30 (m, 1H), 4.53 - 4.49 (m, 1H), 4.48 - 4.44 (m, 2H), 3.97 - 3.95 (m, 1H), 3.80 - 3.77 (m, 1H), 3.55 (q, J = 6.0 Hz, 2H), 3.09 - 3.05 (m, 5H), 2.88 - 2.87 (m, 1H), 2.61 - 2.55 (m, 3H), 2.33 - 2.19 (m, 3H), 2.17 - 1.97 (m, 1H), 1.80 - 1.80 (m, 1H), 1.77 - 1.76 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H).	LCMS: 3.70 min, 630.2 (M+H), METHOD D		
81	2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]-1'-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	Q	Int. 38	Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (d, J = 10.0 Hz, 2H), 8.30 - 8.26 (m, 2H), 8.25 - 8.20 (m, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.17 (q, J = 4.8 Hz, 1H), 4.98 - 4.99 (m, 1H), 4.49 - 4.43 (m, 3H), 4.18 (t, J = 6.0 Hz, 2H), 3.89 (s, 2H), 3.63 - 3.59 (m, 2H), 3.40 - 3.28 (m, 4H), 3.22 - 3.18 (m, 6H), 2.34 - 2.33 (m, 2H), 2.11 (d, J = 7.2 Hz, 2H), 1.77 - 1.75 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.60 Hz, 3H).	LCMS: 2.14 min, 641.0 (M+H), METHOD B		
93	2-(2-ethoxypyridin-3-yl)-7-[1-(2-hydroxyethyl)azetidin-3-yl]-1'-[4-propoxy-3-(trifluoromethyl)pyridin-2-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	Q	Int. 45	Prep-HPLC Method A	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 - 8.26 (m, 3H), 8.19 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.18 - 7.15 (m, 1H), 6.86 (d, J = 5.6 Hz, 1H), 4.96 - 4.93 (m, 1H), 4.48 - 4.41 (m, 3H), 4.12 (t, J = 6.0 Hz, 2H), 3.85 (s, 2H), 3.63 - 3.53 (m, 4H), 3.39 - 3.36 (m, 2H), 3.27 - 3.24 (m, 2H), 3.19 - 3.16 (m, 2H), 2.53 - 2.52 (m, 2H), 2.11 - 2.08 (m, 2H), 1.85 - 1.72 (m, 4H), 1.37 (t, J = 6.8 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: 1.65 min, 641.1 (M+H), METHOD A		
131	rac-(3S,4S)-2'-(2-ethoxypyridin-3-yl)-3-ethyl-1'-(2-methoxy-3-(trifluoromethyl)pyridin-4-yl)-7'-(1-methylazetidin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	Q	Ex. 130	Prep-HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.33 (dd, J = 7.4, 2.0 Hz, 1H), 8.27 - 8.24 (m, 2H), 8.14 (d, J = 6.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 6.92 (d, J = 6.2 Hz, 1H), 4.86 - 4.82 (m, 1H), 4.50 - 4.47 (m, 2H), 3.92 - 3.90 (m, 4H), 3.72 - 3.48 (m, 4H), 3.48 - 3.42 (m, 1H), 3.38 - 3.33 (m, 1H), 3.17 - 3.07 (m, 3H), 2.45 - 2.35 (m, 1H), 2.29 (s, 3H), 2.03 - 2.00 (m, 1H), 1.72 - 1.71 (m, 1H), 1.39 (t, J = 6.8 Hz, 3H), 1.20 - 1.17 (m, 1H), 1.12 - 0.98 (m, 1H), 0.92 (t, J = 7.6 Hz, 3H).	LCMS: 1.79 min, 611.7 (M+H) ⁺ , Method A		
133	rac-(3'S,5'S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7'-(1-methylazetidin-3-yl)spiro[6H-1,7-	Q	Ex. 124	Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.43 (s, 1H), 8.37 (s, 1H), 8.33 (dd, J = 7.6, 2.0 Hz, 1H), 8.27 - 8.25 (m, 2H), 8.24 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.19 - 7.16 (m, 1H), 4.85 - 4.81 (m, 1H), 4.51 - 4.45 (m, 2H), 4.00 (s, 3H), 3.96 - 3.92 (m, 1H), 3.69 - 3.55 (m, 3H), 3.33 - 3.31 (m, 2H), 3.16 - 3.13 (m, 4H), 2.52 - 2.50 (m, 1H), 2.33 (s, 3H).	LCMS: 1.88 min, 611.2 (M+H) ⁺ , Method A	Formate	

	naphthyridine-5,4'-piperidine]-8-one					2.04 - 2.01 (m, 1H), 1.74 - 1.73 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.24 - 1.18 (m, 1H), 1.16 - 1.05 (m, 1H), 0.90 (t, J = 7.6 Hz, 3H).			SFC: 4.22 and 4.84 min; 49.87% and 50.12%, Column: (R,R) Whelk-O1, Co-Solvent : 50%, Co-Solvent Name : 0.5%, Isopropylamine in MeOH; Injected Volume : 15 µl; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C
135	rac-(3'S,5S)-2-(2-ethoxy-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]-7-(1-methylazetidin-3-yl)spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	Q	Ex.127	Aq. HCHO (instead 2-(tert-butyl)dimethylsilyloxy)acetaldehyde), Na(OAc) ₃ BH, DCE, rt, 16 h (2 nd step not required)	Prep-HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.34 (dd, J = 2.0, 7.2 Hz, 1H), 8.34 - 8.27 (m, 2H), 8.19 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.23 - 7.20 (m, 2H), 4.82 - 4.79 (m, 1H), 4.50 (q, J = 6.8 Hz, 2 H), 3.99 (d, J = 13.6 Hz, 1H), 3.89 (s, 3H), 3.70 - 3.33 (m, 3H), 3.20 - 3.14 (m, 3H), 3.03 - 3.02 (m, 2H), 2.98 - 2.83 (m, 1H), 2.52 - 2.51 (m, 1H), 2.36 (s, 3H), 2.03 - 2.00 (m, 1H), 2.03 - 9.00 (m, 1H), 1.40 (t, J = 6.8 Hz, 3H), 1.38 - 0.89 (m, 2H), 0.89 - 0.85 (m, 3H).	LCMS: 2.38 min, 611.3 (M+H) ⁺ , Method B		SFC: 2.77 min Column: YMC Cellulose-SB, FlowRate : 5 ml/min; Co-Solvent : 50%, Co-Solvent Name: 0.5% Isopropylamine in MeOH; Outlet Pressure: 100 bar Injected Volume : 15 µl; Temperature : 35 °C
143	Enant2: (3S,4S)-1-(2-chloro-3-methoxyphenyl)-2'-(2-ethoxy-1-[6-methoxy-3-yl]-7-(1-methylazetidin-3-yl)-6',7'-dihydro-8H-spiro[piperidine-4,5'-[1,7]naphthyridin]-8-one	Q	Ex. 139	Aq. HCHO (instead 2-(tert-butyl)dimethylsilyloxy)acetaldehyde), Na(OAc) ₃ BH, DCE, rt, 16 h (2 nd step not required)	Prep-HPLC Method B followed by 10% aq. NaHCO ₃ wash and lyophilization followed by SFC purification to get enantiomer 2	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.34 - 8.32 (m, 1H), 8.27 - 8.26 (m, 2H), 8.13 - 8.11 (m, 1H), 7.32 - 7.28 (m, 1H), 7.19 - 7.17 (m, 1H), 6.94 - 6.88 (m, 2H), 4.90 - 4.86 (m, 1H), 4.48 (q, J = 6.8 Hz, 2H), 4.46 - 4.09 (m, 2H), 3.99 - 3.96 (m, 1H), 3.85 (s, 3H), 3.54 - 3.53 (m, 1H), 3.52 - 3.46 (m, 1H), 3.33 - 3.17 (m, 1H), 3.14 - 3.13 (m, 1H), 3.04 (m, 4H), 2.81 (m, 1H), 2.89 (m, 1H), 2.50 - 2.29 (m, 3H), 2.05 (m, 1H), 2.01 (m, 1H), 1.39 (t, J = 6.8 Hz, 3H), 0.93 (t, J = 6.8 Hz, 3H).	LCMS: 2.19 min, 576.3 (M+H) ⁺ , Method B		SFC: 2.77 min Column: YMC Cellulose-SB, FlowRate : 5 ml/min; Co-Solvent : 50%, Co-Solvent Name: 0.5% Isopropylamine in MeOH; Outlet Pressure: 100 bar Injected Volume : 15 µl; Temperature : 35 °C

Table 19 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
58	2-(2-ethoxypyridin-3-yl)-1-[5-propoxy-4-(trifluoromethyl)pyridin-3-yl]-7-pyrrolidin-3-ylspiro[8H-1,7-yl]	R	26 and 27		Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.23 (dd, J = 1.9, 7.4 Hz, 1H), 8.22 - 8.15 (m, 3H), 8.09 - 7.99 (m, 2H), 7.09 (dd, J = 4.9, 7.4 Hz, 1H), 4.81 (s, 2H), 4.75 (br s, 1H), 4.48 (q, J = 7.0 Hz, 2H), 4.15 (t, J = 6.2 Hz, 2H), 3.60 - 3.48 (m, 3H), 3.41 - 3.32 (m, 2H), 3.26 - 3.19 (m, 2H), 3.14 (td,	Formate	LCMS: 2.47 min , 611.2 (M+H), METHOD O	

	naphthyridine-5,4'-piperidine]-6-one	R	26 and 3-bromo-6-methoxy-2-(trifluoromethyl)pyr idine			¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 - 8.55 (s, 1H), 8.24 (dd, J = 1.9, 7.4 Hz, 1H), 8.20 (dd, J = 1.9, 4.9 Hz, 1H), 8.09 - 8.01 (m, 2H), 7.94 (d, J = 8.9 Hz, 1H), 7.09 (dd, J = 4.9, 7.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.82 - 4.78 (m, 3H), 4.49 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.52 - 3.34 (m, 4H), 3.27 - 3.21 (m, 1H), 3.12 (td, J = 8.2, 11.5 Hz, 1H), 3.00 - 2.91 (m, 2H), 2.39 - 2.28 (m, 3H), 2.22 - 2.05 (m, 3H), 1.42 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.59 min, 583.2 (M+H), METHOD O	SFC: 1.20 min, 98.3% Column Name: Chiralcel OJ-3, 50x4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 7.5 µL Run time: 3 min.
74	2-(2-ethoxy-6-(1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7'-naphthyridine-5,4'-piperidine]-6-one	R	26 and 3-bromo-6-methoxy-2-(trifluoromethyl)pyr idine	Prep-HPLC Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 - 8.19 (m, 2H), 8.08 - 8.03 (m, 2H), 7.95 - 7.92 (d, J = 8.9 Hz, 1H), 7.11 - 7.08 (dd, J = 5.0, 7.4 Hz, 1H), 7.03-7.01 (d, J = 8.9 Hz, 1H), 4.83 (s, 2H), 4.68 - 4.62 (m, 1H), 4.52-4.46 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 3.76 - 3.67 (m, 1H), 3.58 - 3.47 (m, 2H), 3.47 - 3.39 (m, 2H), 3.30 - 3.21 (m, 1H), 2.98-2.94 (m, 2H), 2.51 (m, 1H), 2.41 - 2.30 (m, 2H), 2.19 - 2.14 (m, 3H), 1.44-1.40 (t, J = 7.1 Hz, 3H)	Formate	LCMS: (2.53 min 583.2 (M+H), METHOD O	SFC: 1.21 min, 91.34% purity, RI=1.31 min, 8.66%. Column Name: Chiralpak IH-3, 50x4.6 mm I.D., 3 µm, Co-Solvent: 50%; Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 7.5 µL;
74-2	2-(2-ethoxy-6-(1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7-(3S)-pyrrolidin-3-ylspiro[8H-1,7'-naphthyridine-5,4'-piperidine]-6-one	R	26-2 and 3-bromo-6-methoxy-2-(trifluoromethyl)pyr idine	Prep-HPLC Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 - 8.14 (m, 2H), 8.09 - 7.98 (m, 2H), 7.94 (d, J = 8.6 Hz, 1H), 7.13 - 7.05 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.78 (br s, 2H), 4.49 (br d, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.40 (br t, J = 10.3 Hz, 4H), 3.19 - 3.05 (m, 3H), 3.00 - 2.91 (m, 2H), 2.35 - 2.26 (m, 3H), 2.21 - 2.13 (m, 2H), 2.10 - 2.02 (m, 1H), 1.45 - 1.39 (m, 3H)	Formate	LCMS: 2.54 min, 583.2 (M+H), METHOD O	SFC: 1.21 min, 91.34% purity, RI=1.31 min, 8.66%. Column Name: Chiralpak IH-3, 50x4.6 mm I.D., 3 µm, Co-Solvent: 50%; Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 7.5 µL;
82	1'-[5-chloro-4-(trifluoromethyl)pyridin-3-yl]-2-(2-ethoxy-6-(1-(6-methoxy-2-(trifluoromethyl)pyridin-3-yl)-7-pyrrolidin-3-ylspiro[8H-1,7'-naphthyridine-5,4'-piperidine]-6-one	R	26 and 3,5-dichloro-4-(trifluoromethyl)pyr idine	Prep-HPLC Method G	1 st Step: K ₂ CO ₃ , DMSO, 100°C, 12h. 2 nd Step: DMSO, 100°C, 12h. Formic acid, 25°C, 1h.	¹ H NMR (400 MHz, CD ₃ OD) δ 8.59 (s, 1H), 8.57 (s, 1H), 8.44 (s, 1H), 8.26 (dd, J = 1.9, 7.4 Hz, 1H), 8.22 (dd, J = 1.9, 4.9 Hz, 1H), 8.11 - 8.00 (m, 2H), 7.11 (dd, J = 4.9, 7.4 Hz, 1H), 4.82 (br d, J = 1.6 Hz, 3H), 4.50 (q, J = 7.0 Hz, 2H), 3.65 (br t, J = 10.7 Hz, 2H), 3.53 - 3.42 (m, 2H), 3.30 - 3.23 (m, 3H), 3.12 (td, J = 8.2, 11.6 Hz, 1H), 2.41 - 2.31 (m, 3H), 2.27 - 2.18 (m, 2H), 2.17 - 2.05 (m, 1H), 1.43 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.53 min, 587.2 (M+H), METHOD O	SFC: 1.21 min, 91.34% purity, RI=1.31 min, 8.66%. Column Name: Chiralpak IH-3, 50x4.6 mm I.D., 3 µm, Co-Solvent: 50%; Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 7.5 µL;

95	7-(azetidin-3-yl)-1-[4-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	R	Int. 48 and 1-bromo-4-chloro-2-(trifluoromethyl)benzene		Prep-HPLC Method Q	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.25 (dd, J = 7.38, 1.88 Hz, 1H), 8.20 (dd, J = 4.94, 1.94 Hz, 1H), 8.04 - 8.16 (m, 2H), 7.60 - 7.68 (m, 2H), 7.54 - 7.59 (m, 1H), 7.09 (dd, J = 7.38, 5.00 Hz, 1H), 4.90 - 4.95 (m, 1H), 4.54 - 4.63 (m, 2H), 4.50 (q, J = 7.13 Hz, 2H), 3.99 - 4.11 (m, 2H), 3.92 (br d, J = 11.88 Hz, 1H), 3.78 - 3.87 (m, 1H), 3.70 (dd, J = 11.94, 3.56 Hz, 1H), 3.47 - 3.56 (m, 1H), 3.15 - 3.24 (m, 1H), 3.05 - 3.14 (m, 1H), 2.91 - 2.99 (m, 1H), 2.55 (ddd, J = 13.38, 8.94, 4.19 Hz, 1H), 2.30 - 2.43 (m, 2H), 2.01 - 2.11 (m, 1H), 1.43 (t, J = 7.07 Hz, 3H). Formate salt	Formate	LCMS: 2.53 min, 572.12 (M+H) ⁺ , METHOD O	
109	2-[7-(3-aminopropanoyl)-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-6-methoxybenzonitrile	R	Int. 62 and 2-bromo-6-methoxybenzonitrile		Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.21 - 8.12 (m, 2H), 8.09 - 8.02 (m, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.57 - 7.49 (m, 1H), 7.09 (dd, J = 5.0, 7.4 Hz, 1H), 6.85 - 6.74 (m, 2H), 4.84 (br s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 4.07 (s, 1H), 3.97 - 3.90 (m, 3H), 3.60 - 3.48 (m, 2H), 3.26 - 3.19 (m, 4H), 2.96 - 2.87 (m, 2H), 2.40 - 2.25 (m, 2H), 1.90 - 1.74 (m, 2H), 1.40 - 1.39 (m, 1H), 1.40 (t, J = 7.1 Hz, 2H). Exchangeable NH ₂ ; protons not observed	Formate	LCMS: 2.22 min, 527.3 (M+H) ⁺ , METHOD O	
110	3-amino-1-[1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	R	Int. 62 and 1-bromo-2-chloro-3-methoxybenzene	1 st Step Ru-Phos Pd G4 (0.2eq), Cs ₂ CO ₃ (3eq), dioxane, 100°C, 2 h	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.20 (br d, J = 4.4 Hz, 1H), 8.15 (br d, J = 7.3 Hz, 1H), 8.07 (br d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.12 - 7.05 (m, 1H), 6.94 - 6.86 (m, 1H), 6.85 - 6.80 (m, 1H), 4.85 (br s, 2H), 4.48 (q, J = 7.1 Hz, 2H), 4.08 (s, 1H), 3.92 (s, 1H), 3.88 (s, 3H), 3.49 - 3.37 (m, 2H), 3.18 (br t, J = 6.3 Hz, 2H), 3.15 - 3.07 (m, 2H), 2.94 - 2.87 (m, 2H), 2.41 - 2.28 (m, 2H), 1.87 - 1.71 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.30 min, 536.3 (M+H) ⁺ , METHOD O	
111	3-amino-1-[1'-(2,4-dichloro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	R	Int. 62 and 1-bromo-2,4-dichloro-3-methoxybenzene		Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.23 - 8.18 (m, 1H), 8.15 (dd, J = 1.9, 7.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.98 - 7.92 (m, 1H), 7.39 - 7.31 (m, 1H), 7.11 - 7.07 (m, 1H), 7.03 (d, J = 8.9 Hz, 1H), 4.84 (br s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 4.08 (s, 1H), 3.94 - 3.90 (m, 1H), 3.87 (s, 3H), 3.50 - 3.35 (m, 2H), 3.22 (t, J = 6.2 Hz, 2H), 3.09 (br s, 2H), 2.96 - 2.90 (m, 2H), 2.43 - 2.26 (m, 2H), 1.89 - 1.71 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.47 min, 570.2 (M+H) ⁺ , METHOD O	
128	3-amino-1-(2'-(2-ethoxypyridin-3-yl)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]-7(8H)-yl)propan-1-one	R	Int. 62 and 1-bromo-4-fluoro-2-(trifluoromethyl)benzene	1 st step t-BuONa, BINAP, dioxane, rac-BINAP Pd G3, 100 °C, 2 h	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.21 - 8.17 (m, 1H), 8.15 (dd, J = 1.8, 7.4 Hz, 1H), 8.03 - 7.98 (m, 1H), 7.98 - 7.93 (m, 1H), 7.78 - 7.69 (m, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.37 (m, 1H), 7.08 (dd, J = 5.0, 7.4 Hz, 1H), 4.84 (br s, 2H), 4.47 (q, J = 7.1 Hz, 2H), 4.12 (s, 2H), 3.96 (s, 1H), 3.27 - 3.09 (m, 4H), 3.07 - 2.88 (m, 4H), 2.35 - 2.19 (m, 2H), 1.85 - 1.68 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.52 min, 558.2 (M+H) ⁺ , METHOD O	
134	3-amino-1-[1'-(2,4-dichlorophenyl)-2-(2-ethoxypyridin-3-yl)spiro[6.8-dihydro-1,7-naphthyridine-5,4'-	R	Int. 62 and 2,4-dichloro-1-iodobenzene	1 st step XantPhos, Cs ₂ CO ₃ , Pd ₂ (dba) ₃	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 8.22 - 8.11 (m, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.47 - 7.41 (m, 1H), 7.34 - 7.28 (m, 1H), 7.28 - 7.20 (m, 1H), 7.09 (dd, J = 4.9, 7.4 Hz, 1H), 4.84 (s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 4.08 (s, 2H), 3.43 - 3.32 (m, 1H), 3.28 (br s, 1H), 3.26 - 3.18 (m, 2H), 3.17 - 3.02 (m, 2H), 2.99 -	formate	LCMS: 2.42 min, 540.2 (M+H) ⁺ , Method O	

	piperidine]-7-yl]propan-1-one			toluene, 100 °C, 12 hrs			2.86 (m, 2H), 2.46 - 2.19 (m, 2H), 1.90 - 1.70 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H), exchangeable protons not observed.	Formate		SFC: 1.29 min and 1.66 min. Column Name: Chiralpak OD-3, 150x4.6 mm I.D., 3 µm, Co-Solvent: 50% MeOH [0.2% ammonia (7 M in MeOH)]; injected Volume: 7.50 µL; Run time: 8.0 min.
140	rac-3-amino-1-[rac-(3S,5S)-1-(2,4-dichlorophenyl)-2-(2-ethoxy-3-yl)-3'-ethoxy-3-yl]-6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-yl]propan-1-one	R	Int. 79 and 2,4-dichloro-1-iodobenzene	1 st Step Cs ₂ CO ₃ , Xanphos, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method G		¹ H NMR (400 MHz, CD ₃ OD) δ 8.53 (s, 1H), 8.26 - 8.14 (m, 2H), 8.06 - 7.95 (m, 2H), 7.50 - 7.40 (m, 1H), 7.34 - 7.29 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (dd, J = 5.1, 7.3 Hz, 1H), 4.90 (br s, 1H), 4.82 - 4.72 (m, 1H), 4.49 (q, J = 7.1 Hz, 2H), 3.73 - 3.38 (m, 2H), 3.37 - 3.33 (m, 1H), 3.25 (br dd, J = 6.5, 11.6 Hz, 4H), 3.18 - 2.96 (m, 1H), 2.92 (q, J = 6.5 Hz, 1H), 2.78 (br t, J = 11.5 Hz, 1H), 2.58 - 2.45 (m, 1H), 1.95 (dt, J = 4.9, 12.2 Hz, 1H), 1.89 - 1.67 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.20 - 1.09 (m, 2H), 0.96 - 0.86 (m, 3H), exchangeable protons not observed.	Formate	LCMS: 2.65 min, 568.2 [M+H] ⁺ Method Q	
150	1'-(2,4-dichlorophenyl)-2-(2-ethoxy-3-yl)-pyrrolidin-7-yl]-(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 91 and 2,4-dichloro-1-iodobenzene	Pd ₂ (dba) ₃ , Xanphos, Cs ₂ CO ₃ , Toluene, 100 °C, 12 h	Prep-HPLC Method L		¹ H NMR (400 MHz, CD ₃ OD) δ 8.56 (s, 1H), 8.20 (dd, J = 1.9, 5.0 Hz, 1H), 8.11 - 7.99 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.27 - 7.20 (m, 1H), 7.09 (dd, J = 5.0, 7.4 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 4.05 - 3.93 (m, 2H), 3.78 (d, J = 15.4 Hz, 1H), 3.39 - 3.34 (m, 2H), 3.31 - 3.25 (m, 2H), 3.12 - 2.99 (m, 3H), 2.94 (br d, J = 12.0 Hz, 1H), 2.90 - 2.81 (m, 2H), 2.37 - 2.23 (m, 3H), 2.17 - 2.06 (m, 2H), 2.05 - 1.93 (m, 2H), 1.84 - 1.70 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), exchangeable protons not observed.	Formate	LCMS: 2.61 min, 552.3 [M+H] ⁺ Method S	SFC: 1.57 min. Column Chiralpak IH-3, 50x4.6 mm I.D., 3 µm; Co-Solvent: 50% Co-Solvent Name: Isopropyl Alcohol [0.2% ammonia gas (7 M in MeOH)]; injected Volume: 7.5 µL; Run time: 3 min.
154	(3S,5S)-1-(2,4-dichlorophenyl)-2-(2-ethoxy-3-yl)-pyrrolidin-ethyl-7-yl]-(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 89 and 2,4-dichloro-1-iodobenzene	Cs ₂ CO ₃ , Xanphos, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L		¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.19 (dd, J = 1.5, 4.9 Hz, 1H), 8.08 (ddd, J = 2.0, 3.2, 7.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.26 - 7.19 (m, 1H), 7.08 (dd, J = 4.9, 7.4 Hz, 1H), 4.47 (q, J = 7.0 Hz, 2H), 4.09 (d, J = 15.3 Hz, 1H), 3.98 - 3.84 (m, 1H), 3.71 (d, J = 15.3 Hz, 1H), 3.51 - 3.42 (m, 1H), 3.36 (br s, 1H), 3.29 - 3.19 (m, 3H), 3.16 - 3.06 (m, 1H), 2.84 - 2.64 (m, 3H), 2.47 - 2.37 (m, 2H), 2.13 - 1.94 (m, 3H), 1.77 - 1.65 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.20 - 1.07 (m, 2H), 0.91 - 0.82 (m, 3H), exchangeable protons not observed.	Formate	LCMS: 2.74 min, 580.2 [M+H] ⁺ Method Q	SFC: 0.439 min and 0.863 min. Column name: Chiralpak (G-3, 50x4.6 mm I.D., 3 µm; Co-Solvent: 50% Co-Solvent Name: MeOH [0.2% ammonia gas (7 M in MeOH)]; injected Volume: 1.80 µL; Run time: 2 min.
155	(3S,5S)-1-(2-chloro-3-methoxyphenyl)-2-(2-ethoxy-3-yl)-pyrrolidin-ethyl-7-yl]-(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 89 and 1-bromo-2-chloro-3-methoxybenzene	Cs ₂ CO ₃ (3 eq), Ruphos, Pd G3, dioxane, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L		¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.18 (dd, J = 1.6, 4.9 Hz, 1H), 8.08 (td, J = 2.2, 7.4 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.24 (t, J = 8.2 Hz, 1H), 7.08 (dd, J = 5.0, 7.4 Hz, 1H), 6.88 (dd, J = 8.2, 10.6 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 4.47 (q, J = 7.0 Hz, 2H), 4.07 - 3.70 (m, 2H), 3.88 (s, 3H), 3.85 - 3.77 (m, 1H), 3.51 - 3.45 (m, 2H), 3.34 (br s, 1H), 3.26 - 3.19 (m, 2H), 3.18 - 3.04 (m, 2H), 2.79 - 2.72 (m, 2H), 2.70 - 2.62 (m, 2H), 2.48 - 2.38 (m, 1H), 2.31 (br d, J = 13.4 Hz, 1H), 2.08 - 1.95 (m, 3H), 1.73 - 1.62 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.19 - 1.06 (m, 2H), 0.90 - 0.83 (m, 3H)	Formate	LCMS: 2.40 min, 576.3 [M+H] ⁺ Method O	SFC: 0.838 min and 1.462 min. Column name: Chiralpak (G-3, 50x4.6 mm I.D., 3 µm; Co-Solvent: 50% Co-Solvent Name: MeOH [0.1% isopropanol]; injected Volume: 0.90 µL; Run time: 2 min.

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156	1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 91 and 2-chloro-4-fluoro-1-iodobenzene	Xanphos Pd G4, Cs ₂ CO ₃ , toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.39 (s, 1H), 8.26 - 8.10 (m, 2H), 7.97 - 7.85 (m, 2H), 7.42 (dd, J = 2.9, 8.6 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.21 (dt, J = 2.9, 8.5 Hz, 2H), 7.11 (dd, J = 5.0, 7.3 Hz, 1H), 4.43 (q, J = 7.0 Hz, 2H), 3.77 (br d, J = 12.5 Hz, 2H), 3.67 - 3.58 (m, 2H), 3.10 (br d, J = 11.0 Hz, 2H), 2.95 (br d, J = 11.6 Hz, 4H), 2.81 (br d, J = 12.0 Hz, 1H), 2.74 - 2.67 (m, 1H), 2.64 - 2.52 (m, 1H), 2.14 - 2.05 (m, 2H), 1.92 (br s, 1H), 1.88 (br d, J = 12.9 Hz, 2H), 1.83 - 1.69 (m, 2H), 1.55 - 1.43 (m, 1H), 1.36 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.42 min, 536.3 [M+H] ⁺ Method Q	SFC: 1.10 min; Column name: Chiralpak IH-3, 50x4.6mm I.D., 3 μm; Co-Solvent: 50%; MeOH [0.2% ammonia gas (7M in MeOH)]; Injected Volume: 7.5 μL; Run time: 3 min.
157	(3'S,5S)-1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 89 and 2-chloro-4-fluoro-1-iodobenzene	Cs ₂ CO ₃ , Xanphos, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.19 (dd, J = 1.4, 9 Hz, 1H), 8.08 (ddd, J = 2.0, 3.1, 7.4 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.32 - 7.21 (m, 2H), 7.11 - 7.04 (m, 2H), 4.47 (q, J = 7.1 Hz, 2H), 4.09 (br d, J = 15.4 Hz, 1H), 3.97 - 3.83 (m, 2H), 3.71 (d, J = 15.4 Hz, 1H), 3.49 (d, J = 15.4 Hz, 1H), 3.40 (br s, 1H), 3.33 (br s, 1H), 3.27 - 3.18 (m, 3H), 3.15 - 3.06 (m, 1H), 2.85 - 2.76 (m, 2H), 2.75 - 2.65 (m, 2H), 2.26 - 2.16 (m, 2H), 2.10 - 1.95 (m, 3H), 1.77 - 1.65 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.20 - 1.07 (m, 2H), 0.90 - 0.82 (m, 3H)	Formate	LCMS: 5.28 and 5.35 min, 564.3 [M+H] ⁺ Method R	SFC: 2.38 min and 3.144 min, Column: Chiralpak IG-3, 100x4.6mm I.D., 3 μm; Co-Solvent: 50%; MeOH [0.2% ammonia gas (7M in MeOH)]; Injected Volume: 2.30 μL; Run time: 4 min.
158	1'-(2-chloro-4-fluoro-3-methoxyphenyl)-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 91 and 1-bromo-2-chloro-4-fluoro-3-methoxybenzene	rac-BINAP Pd G3 (0.2 eq), BINAP (0.2 eq), t-BuONa (3 eq), toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.21 - 8.18 (m, 1H), 8.06 - 7.98 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.14 - 7.10 (m, 1H), 7.09 - 7.05 (m, 1H), 6.99 (dd, J = 4.9, 9.0 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 4.00 - 3.91 (m, 5H), 3.76 (d, J = 15.4 Hz, 1H), 3.30 - 3.19 (m, 4H), 3.10 - 2.96 (m, 3H), 2.96 - 2.89 (m, 1H), 2.86 - 2.80 (m, 2H), 2.37 - 2.21 (m, 3H), 2.16 - 2.03 (m, 2H), 2.03 - 1.89 (m, 2H), 1.81 - 1.68 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.36 min, 566.2 [M+H] ⁺ Method O	SFC: 1.20 min, Column Name: Chiralcel OD-3, 50x4.6 mm I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: 0.2% ammonia gas in MeOH; Injected Volume: 1.30 μL; Run time: 3.0 min.
164	1'-12-(difluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 91 and 1-bromo-2-(difluoromethyl)benzene	Pd ₂ (dba) ₃ , BINAP, t-BuONa, toluene, 100 °C, 12 h	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.19 (dd, J = 1.9, 5.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.04 (dd, J = 1.9, 7.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.55 - 7.38 (m, 2H), 7.28 - 7.25 (m, 1H), 7.25 - 7.21 (m, 1H), 7.10 (s, 1H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 3.99 - 3.89 (m, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.29 - 3.12 (m, 2H), 3.09 (br d, J = 11.6 Hz, 1H), 3.06 - 3.00 (m, 2H), 2.93 (d, J = 12.0 Hz, 1H), 2.87 - 2.79 (m, 2H), 2.36 - 2.26 (m, 2H), 2.26 - 2.16 (m, 1H), 2.16 - 2.03 (m, 2H), 2.02 - 1.90 (m, 2H), 1.79 - 1.68 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 5.53 min, 534.3 [M+H] ⁺ Method C	SFC: 1.18 min, Column Chiralcel OD-3, 50x4.6 mm I.D., 3 μm, Co-Solvent: 50%; Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 6.40 μL; Run time: 3.0 min.
165	(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-	R	Int. 89 and 1-bromo-3-methoxy-2-(trifluoromethyl)benzene	Cs ₂ CO ₃ , Xanphos, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.18 (dd, J = 1.7, 4.9 Hz, 1H), 8.07 (dd, J = 2.3, 7.4 Hz, 1H), 7.96 - 7.91 (m, 1H), 7.90 - 7.84 (m, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.08 (dd, J = 4.9, 7.4 Hz, 1H), 6.97 (dd, J = 8.3, 12.2 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 4.47 (q, J = 7.0 Hz, 2H), 4.07 (d, J = 15.0 Hz, 1H), 3.95 - 3.90 (m, 1H), 3.87 (s, 3H), 3.69 (d, J = 15.3 Hz, 1H), 3.51 - 3.46 (m, 1H), 3.27 - 3.04 (m, 4H), 2.80 - 2.61 (m, 3H), 2.52 (br d, J = 12.0 Hz, 1H), 2.38	Formate	LCMS: 2.54 min, 610.3 [M+H] ⁺ Method O	SFC: 1.67 min, 2.30 min; Column name: Chiralpak IG-3, 50x4.6mm I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: ethanol [0.2%Ammonia gas

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	naphthyridine-5,4'-piperidine]				(br d, J = 10.0 Hz, 1H), 2.28 (br d, J = 13.4 Hz, 1H), 2.23 - 2.12 (m, 1H), 2.06 - 1.89 (m, 3H), 1.73 - 1.61 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.30 - 1.10 (m, 2H), 0.87 - 0.80 (m, 3H)				
190	1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxy-3-pyridinyl)-7-[[[2R]-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int. 91 and 1-bromo-2-chloro-3-methoxybenzene	Cs ₂ CO ₃ , Xantphos, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.17 (dd, J = 1.9, 4.9 Hz, 1H), 8.05 (dd, J = 1.9, 7.4 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 8.2 Hz, 1H), (dd, J = 4.9, 7.4 Hz, 1H), 6.88 (dd, J = 1.1, 8.2 Hz, 1H), 6.83 - 6.79 (m, 1H), 4.45 (q, J = 7.0 Hz, 2H), 3.90 - 3.82 (m, 4H), 3.79 - 3.70 (m, 1H), 3.50 - 3.42 (m, 1H), 3.28 (br s, 2H), 3.05 - 2.92 (m, 4H), 2.92 - 2.82 (m, 2H), 2.71 - 2.62 (m, 1H), 2.62 - 2.53 (m, 1H), 2.36 - 2.23 (m, 2H), 2.04 - 1.91 (m, 3H), 1.90 - 1.74 (m, 2H), 1.58 - 1.46 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.31 min, 548.2 [M+H] ⁺ , Method O	SFC: 1.21 min, Column: Chiralpak IH-3, 50x4.6mm I.D., 3 μm, Co-Solvent: 50%, Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 7.50 μL; Run time: 3.0 min
194	2-(2-ethoxy-3-pyridinyl)-1'-[5-fluoro-3-(trifluoromethyl)-2-pyridinyl]-7-[[[2R]-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int 91 and 2-chloro-5-fluoro-3-(trifluoromethyl)pyridine	t-BuONa (3 eq), Ruphos (0.2 eq), Ruphos Pd G3 (0.2 eq), THF (0.2 mL), 80 °C, 12 h and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 8.48 (d, J = 2.9 Hz, 1H), 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.03 (dd, J = 1.9, 7.4 Hz, 1H), 7.97 - 7.91 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 4.9, 7.4 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 3.99 - 3.87 (m, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.24 (s, 3H), 3.26 - 3.18 (m, 2H), 3.10 - 3.03 (m, 1H), 2.99 - 2.92 (m, 1H), 2.88 - 2.77 (m, 2H), 2.30 - 2.17 (m, 3H), 2.15 - 1.80 (m, 4H), 1.80 - 1.65 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H).	Formate	LCMS: 2.40 min, 571.2 [M+H] ⁺ , Method O	SFC: 1.01 min, Column: Chiralcel OD-3, 50x4.6mm I.D., 3 μm, Co-Solvent: 50%, Co-Solvent Name: 0.2% Ammonia gas in MeOH; Injected Volume: 8.00 μL; Run time: 3.0 min.
202	1'-[4-chloro-2-(difluoromethyl)phenyl]-2-(2-ethoxy-3-pyridinyl)-7-[[[2R]-pyrrolidin-2-ylmethyl]spiro[6.8]dihydro-1,7-naphthyridine-5,4'-piperidine]	R	Int 91 and 1-bromo-4-chloro-2-(difluoromethyl)benzene	Pd(OAc) ₂ (0.2 eq), BINAP (0.2 eq), Cs ₂ CO ₃ (3 eq), toluene, 100 °C, 12 h and TFA, DCM in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.08 - 8.01 (m, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.3 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.46 - 7.40 (m, 1H), 7.36 - 7.03 (m, 2H), 4.46 (q, J = 7.0 Hz, 2H), 3.93 - 3.84 (m, 1H), 3.79 - 3.71 (m, 1H), 3.70 - 3.60 (m, 1H), 3.17 - 3.07 (m, 3H), 3.06 - 2.95 (m, 4H), 2.94 - 2.87 (m, 1H), 2.78 - 2.64 (m, 2H), 2.35 - 2.23 (m, 2H), 2.14 - 2.04 (m, 1H), 2.02 - 1.85 (m, 4H), 1.66 - 1.55 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H).	TFA	LCMS: 2.49 min, 568.2 [M+H] ⁺ , Method O	SFC: 1.58 min, Column: Chiralpak IH-3, 100x4.6 mm I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 7.50 μL; Run time: 4.0 min.

Table 20 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
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59	7-(2-aminoethyl)-1-[4-chloro-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)spiro[8H-1,7-naphthyridine-5,4'-piperidine]-6-one	S	Ex. 5	Prep-HPLC Method G	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.26 - 8.18 (m, 2H), 8.09 - 8.01 (m, 2H), 7.66 - 7.60 (m, 2H), 7.57 - 7.53 (m, 1H), 7.09 (dd, J = 5.0, 7.3 Hz, 1H), 4.81 (s, 2H), 4.48 (q, J = 7.0 Hz, 2H), 3.74 (t, J = 6.3 Hz, 2H), 3.47 - 3.42 (m, 2H), 3.08 - 2.98 (m, 4H), 2.33 (br d, J = 14.0 Hz, 2H), 2.24 - 2.13 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H). Exchangeable NH proton not observed.	Formate	LCMS: 2.56 min, 560.1 (M+H). METHOD O
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Table 21 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
68	1-[3-(cyclopropylmethoxy)-2-(trifluoromethyl)phenyl]-2-(2-ethoxypyridin-3-yl)-7-[1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-8-one	T	Ex. 18		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 - 8.25 (m, 2H), 8.20 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 6.95 - 6.90 (m, 2H), 5.32 - 5.19 (m, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.95 - 3.93 (m, 3H), 3.54 - 3.52 (m, 1H), 3.51 - 3.40 (m, 2H), 3.39 - 3.38 (m, 2H), 3.35 - 3.35 (m, 2H), 3.31 - 3.19 (m, 3H), 3.07 - 3.05 (m, 5H), 2.68 - 2.67 (m, 1H), 2.53 - 2.53 (m, 2H), 2.51 - 2.50 (m, 1H), 2.34 - 2.33 (m, 3H), 2.33 - 2.19 (m, 1H), 1.90 - 1.80 (m, 1H), 1.79 - 1.70 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.25 - 1.15 (m, 1H), 0.57 - 0.55 (m, 2H), 0.35 - 0.33 (m, 2H).		LCMS: 2.01 min, 724.2 (M+H). METHOD A	

Table 22 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
80	2-(2-ethoxypyridin-3-yl)-1-[5-ethoxy-4-(trifluoromethyl)pyridin-3-yl]spiro[6,7-dihydro-	U	37		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.36 - 8.31 (m, 2H), 8.31 - 8.29 (m, 2H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.19 - 7.16 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 6.8 Hz, 2H), 3.59 - 3.51 (m,		LCMS: 1.77 min, 528.4 (M+H). METHOD A	

	1,7-naphthyridine-5,4'- piperidine]-8-one					2H), 3.23 - 3.18 (m, 2H), 3.12 - 3.10 (m, 2H), 2.14 - 2.06 (m, 2H), 1.88 - 1.85 (m, 2H), 1.40 - 1.35 (m, 6H).		
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Table 23 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LCMS data
97	azetidin-3-yl 2-(2-ethoxypyridin-3-yl)-1'-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-7-carboxylate	V	Ex. 30 and Int 49		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.26 – 8.21 (m, 3H), 8.02 – 7.99 (m, 2H), 7.19 – 7.15 (m, 1H), 7.14 – 7.12 (m, 1H), 5.14 (t, J = 6.0 Hz, 1H), 4.79 – 4.68 (m, 2H), 4.45 (q, J = 6.8 Hz, 2H), 3.97 (s, 1H), 3.89 – 3.85 (m, 4H), 3.80 (m, 2H), 3.68 (m, 2H), 3.18 – 3.16 (m, 2H), 3.06 – 2.84 (m, 2H), 2.18 – 2.05 (m, 2 H), 1.69 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H). Exchangeable proton not observed	LCMS: 2.35 min, 599.3 (M+H), METHOD B

Table 24 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
98	2-[3-[2-(2-ethoxypyridin-3-yl)-8-oxo-7-[(3S)-pyrrolidin-3-yl]spiro[6H-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)phenoxy]acetoneitrile	W	Int. 50		Prep-HPLC Method B	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.38 (s, 1H), 8.30 (dd, J = 7.6, 2.0 Hz, 1H), 8.26 (dd, J = 4.8, 2.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.40 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.19 – 7.15 (m, 2H), 7.09 (d, J = 8.4 Hz, 1H), 5.31 (s, 2H), 5.15 (br s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.75 – 3.70 (m, 2H), 3.09 – 2.99 (m, 6H), 2.88 – 2.80 (m, 2H), 2.25 – 1.95 (m, 3H), 1.85 – 1.73 (m, 3H), 1.38 (t, J = 7.2 Hz, 3H). Exchangeable NH and COOH proton were not observed.	Formate	LCMS: 1.97 min, 607.3 (M+H), METHOD B	SFC: 3.63 min, 98.5% Column Name: Lux C2 Co-Solvent: 4 0%; Co-Solvent Name: 0.5% isopropyl Amine in MeOH; Injected Volume: 15 µL; Flow Rate: 5 mL/min, Outlet Pressure: 100 bar; 35 °C.

Table 25 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
113	(R)-2'-((2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7-(pyrrolidin-2-ylmethyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7-naphthyridine]	X	Int. 61		Prep-HPLC Method: Column: Phenomenex Luna C18 100*30 mm*3 um; Mobile phase: [water (0.2% formic acid) - acetonitrile]; B%: 30%-60%, 8 min	¹ H-NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.04 (dd, J = 1.9, 7.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 4.01 - 3.92 (m, 2H), 3.87 (s, 3H), 3.75 (d, J = 15.4 Hz, 1H), 3.36 - 3.32 (m, 1H), 3.30 - 3.22 (m, 1H), 3.09 (br d, J = 6.8 Hz, 4H), 3.06 - 3.02 (m, 1H), 2.90 (d, J = 11.8 Hz, 1H), 2.88 - 2.78 (m, 2H), 2.32 - 2.24 (m, 2H), 2.24 - 2.19 (m, 1H), 2.15 - 2.01 (m, 2H), 1.99 - 1.86 (m, 2H), 1.74 - 1.60 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.13 min, 582.3 [M+H], Method O	SFC: 1.159 min, 100.00% purity; Column Name: Chiralcel OJ-3, 50x4.6mm I.D., 3um; Co-Solvent: 50% Co-Solvent Name: 0.1% Isopropyl Amine in MeOH; Injected Volume: 1.4 µL; Run time: 3 min.
120	7-(1-azabicyclo[2.2.2]octan-3-yl)-2-(2-ethoxypyridin-3-yl)-1-[6-methoxy-2-(trifluoromethyl)pyridin-3-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Ex. 30 (Route L) and quinuclidin-3-one	Ti(OiPr) ₄ , NaCNBH ₃ , MeOH, rt, 16 h	Prep HPLC Method B	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.25 - 8.19 (m, 3H), 7.95 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.13 - 7.10 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.70 (abq, J = 15.6 Hz, 2H), 3.33 - 3.25 (m, 1H), 3.10 - 3.05 (m, 2H), 2.84 - 2.68 (m, 9H), 2.43 - 2.37 (m, 2H), 2.13 - 2.03 (m, 3H), 2.02 - 1.82 (m, 3H), 1.82 - 1.79 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.39 - 1.37 (m, 1H); ¹ H-NMR showed boron peaks, indicating BH ₃ complex	Formate	LCMS: 2.48 min, 609.3 [M+H] ⁺ , Method B	SFC: 2.59 min & 2.98 min; Column: YMC Cellulose-SC; Co-Solvent: 50% Co-Solvent Name: 0.5% Isopropylamine in MeOH; Injected Volume: 15 µl; FlowRate: 5 ml/min; Outlet Pressure: 100 bar; Temperature: 35 °C.

138	(R)-2'-(2-ethoxypyridin-3-yl)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-1,7-naphthyridine]	X	Int. 76	tert-butyl (R)-2-formylpyrrolidin e-1-carboxylate, NaCNBH ₃ , MeOH, rt, 1 h followed by boc deprotection using formic acid.	Prep HPLC Method E	¹ H-NMR (400 MHz, CD ₃ OD) δ = 5.1 (s, 1H), 8.18 (dd, J = 1.7, 4.9 Hz, 1H), 8.04 (dd, J = 1.8, 7.4 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.71 (dd, J = 5.1, 8.5 Hz, 1H), 7.46 - 7.36 (m, 2H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 4.08 - 3.99 (m, 1H), 3.96 (d, J = 15.3 Hz, 1H), 3.77 (d, J = 15.3 Hz, 1H), 3.35 (br d, J = 4.5 Hz, 1H), 3.28 (br s, 1H), 3.18 - 3.06 (m, 3H), 3.00 - 2.82 (m, 5H), 2.33 - 2.18 (m, 3H), 2.18 - 2.03 (m, 2H), 1.93 (br dd, J = 13.6, 19.3 Hz, 2H), 1.84 - 1.72 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 570.3 (M+H) ⁺ Method O	SFC: 1.01 min, 100% Column Name: Chiralcel OD-3, 50x4.6 mm I.D.; 3.0 μm, Co-Solvent: 50%; Co-Solvent Name: 0.2% Ammonia gas in MeOH; Injected Volume: 2.90 μL; Run time: 3.0 min.
147	2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-ylmethyl]-1'-[3-(trifluoromethyl)pyridin-2-yl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int. 80	tert-butyl (R)-2-formylpyrrolidin e-1-carboxylate, Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA/DCM in 2nd step.	Prep HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.55 - 8.50 (m, 1H), 8.25 - 8.15 (m, 2H), 8.08 (dd, J = 1.6, 7.8 Hz, 1H), 7.91 (d, J = 8.4, Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 4.8, 7.2 Hz, 1H), 7.13 - 7.05 (m, 1H), 4.43 (q, J = 6.8 Hz, 2H), 3.74 (s, 2H), 3.45 (d, J = 11.6 Hz, 2H), 3.33 (s, 1H), 3.20 (t, J = 11.6 Hz, 2H), 2.83 - 2.89 (m, 3H), 2.72 - 2.76 (m, 1H), 2.53 - 2.57 (m, 2H), 2.04 (t, J = 12.0 Hz, 2H), 1.80 - 1.87 (m, 3H), 1.66 - 1.66 (m, 2H), 1.40 - 1.30 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), exchangeable proton not observed.		LCMS: 2.22 min, 553.3 (M+H) ⁺ , Method B	SFC: 1.34 min, 100% Column Name: YMC-Cellulose-SC, Co-Solvent : 50%, Co-Solvent Name : 0.5% Isopropylamine in MeOH ; Injected Volume: 10 μL; FlowRate : 5 ml/min; Outlet Pressure: 100 bar; Temperature : 35 °C.
151	5-chloro-2-[2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	X	Int. 87	tert-butyl (R)-2-formylpyrrolidin e-1-carboxylate, Na(OAc) ₃ BH ₄ , DCE, rt, 16 h in the 1 st Step and TFA/DCM in 2 nd step	Prep HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.21 (d, J = 6.0 Hz, 2H), 7.95 - 7.82 (m, 3H), 7.70 - 7.60 (m, 1H), 7.27 (d, J = 9.2 Hz, 1H), 7.11 - 7.10 (m, 1H), 4.44 (q, J = 6.8 Hz, 2H), 3.54 (s, 2H), 3.34 - 3.31 (m, 2H), 3.18 - 3.15 (m, 2H), 3.12 (m, 2H), 2.91 - 2.76 (m, 3H), 2.74 - 2.72 (m, 1H), 2.68 - 2.51 (m, 2H), 2.34 - 2.13 (m, 2H), 1.92 - 1.82 (m, 2H), 1.81 - 1.79 (m, 1H), 1.68 - 1.63 (m, 2H), 1.40 - 1.30 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H).		LCMS: 2.42 min, 543.3 [M+H] ⁺ Method B	SFC: 3.79 min, 100% Column: (R,R) Whelk-O1, Co-Solvent : 40%, Co-Solvent Name : 0.5% Isopropylamine in MeOH; Injected Volume : 15 μL; Outlet Pressure: 100 bar; Temperature : 35 °C

152	2-[(3'S,5S)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-5-fluorobenzonitrile	X	Int. 88	tert-butyl (R)-2-formylpyrrolidine-1-carboxylate, Na(OAc) ₃ BH ₄ , DCE, rt, 16 h in 1 st step and TFA/DCM in 2 nd step	Prep HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.29 (d, J = 5.2 Hz, 1H), 8.20 – 8.216 (m, 1H), δ 7.96 (d, J = 20.4 Hz, 1H), 7.78 (d, J = 5.2 Hz, 1H), 7.72 (m, 1H), 7.55 – 7.53 (m, 1H), 7.35 – 7.34 (m, 1H), 7.13 – 7.10 (m, 1H), δ 4.47 (q, J = 6.8 Hz, 2H), 3.83 (m, 1H), 3.57 – 3.53 (m, 2H), 3.49 – 3.30 (m, 3H), 3.18 – 3.15 (m, 2H), 2.87 – 2.84 (m, 2H), 2.83 – 2.68 (m, 1H), 2.51 – 2.50 (m, 3H), 2.46 – 2.45 (m, 1H), 2.34 – 2.33 (m, 1H), 1.81 – 1.79 (m, 2H), 1.77 – 1.63 (m, 2H), 1.40 – 1.40 – 1.30 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), 1.36 (m, 2H), 0.82 – 0.78 (m, 3H).	LCMS: 2.44 min, 555.3 [M+H] ⁺ Method B	SFC: 2.25 min and 4.19 min, 46.82% and 51.53% Column: Chiralpak IG, Co-Solvent : 40%; Co-Solvent Name : 0.5% isopropylamine in MeOH; Injected Volume: 15 µl, FlowRate: 4 ml/min, Outlet Pressure: 100 bar, Temperature : 35 °C.
160	3-[2-(2-ethoxypyridin-3-yl)-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]-2-(trifluoromethyl)benzotriazole	X	Int. 107	tert-butyl (R)-2-formylpyrrolidine-1-carboxylate, Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA/DCM in 2 nd step	Prep HPLC Method AG followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.22 – 8.21 (m, 2H), 8.06 – 8.02 (m, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.86 – 7.84 (m, 3H), 7.13 – 7.10 (m, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.79 – 3.68 (m, 2H), 3.51 – 3.28 (m, 2H), 3.183 – 12 (m, 2H), 2.93 – 2.83 (m, 5H), 2.77 – 2.74 (m, 1H), 2.51 – 2.48 (m, 1H), 2.06 – 2.05 (m, 2H), 1.86 – 8.64 (m, 3H), 1.69 – 1.61 (m, 2H), 1.40 – 1.35 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H), exchangeable proton was not observed.	LCMS: 1.732 min, 577.3 [M+H] ⁺ Method G	SFC: 1.67 min, 96.75%, Column: I-cellulose Z; Cosolvent: 0.5% IPAm in MeOH Injection Volume : 10 µL; 0.5% IPAm in MeOH; Flow : 4.0000 mL/min; Co-Solvent: 40.0 %;; Oven Temperature: 40;; BPR Pressure : 102.0 kgf/cm2
161	(3SR,5SR)-2-(2-ethoxypyridin-3-yl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]-1-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int. 96 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in step-2	Prep HPLC Method B followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.29 (dd, J = 7.4, 1.6 Hz, 1H), 8.21 (dd, J = 4.8, 2.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.74 – 7.67 (m, 3H), 7.35 (t, J = 7.2 Hz, 1H), 7.13 – 7.10 (m, 1H), 4.45 (q, J = 6.8 Hz, 2H), 3.90 – 3.80 (m, 1H), 3.57 – 3.52 (m, 1H), 3.40 – 3.30 (m, 1H), 3.27 – 3.18 (m, 2H), 3.05 – 2.98 (m, 1H), 2.82 – 2.67 (m, 4H), 2.57 – 2.55 (m, 2H), 2.46 – 2.45 (m, 2H), 2.29 – 2.10 (m, 2H), 1.90 – 1.72 (m, 2H), 1.70 – 1.60 (m, 2H), 1.41 – 1.37 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), 1.15 – 0.92 (m, 2H), 0.71 (t, J = 7.6 Hz, 3H), exchangeable proton was not observed	LCMS: 1.97 min, 580.6 [M+H] ⁺ Method A	

162	(3'R,5'R)-2-(2-ethoxy-3-pyridinyl)-3-ethyl-7-yl[(2R)-pyrrolidin-2-yl]methyl-1-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int 97 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in step-2	Prep HPLC Method AK followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.29 (dd, J = 2.0, 7.6 Hz, 1H), 8.21 (dd, J = 2.0, 5.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.6 Hz, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.14 - 7.10 (m, 1H), 4.46 (q, J = 6.8 Hz, 2H), 3.85 (d, J = 15.2 Hz, 1H), 3.58 - 3.51 (m, 1H), 3.16 (d, J = 12.0 Hz, 3H), 3.00 (d, J = 8.8 Hz, 1H), 2.85 - 2.73 (m, 4H), 2.68 (t, J = 1.6 Hz, 2H), 2.51 - 2.48 (m, 2H), 2.21 - 2.10 (m, 1H), 2.12 (d, J = 13.2 Hz, 1H), 1.82 - 1.64 (m, 4H), 1.40 - 1.35 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), 1.07 - 1.05 (m, 2H), 0.70 (t, J = 7.6 Hz, 3H).	LCMS: 1.84 min, 580.3 [M+H] ⁺ , Method G	SFC: 3.49 min, 100%, Column: Lux I-Amylose-3, 0.5% IPAm in MeOH; InjecGon Volume : 12 uL Flow : 4.0 mL/min; Co-Solvent : 20.0 %, BPR Pressure : 102.0 kgf/cm ² Oven Temperature : 40
163	(3'S,5'S)-2-(2-ethoxy-3-pyridinyl)-3-ethyl-7-yl[(2R)-pyrrolidin-2-yl]methyl-1-[2-(trifluoromethyl)phenyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int 98 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in step-2	Prep HPLC Method AK followed by 10% aq. NaHCO ₃ wash and SFC purification to remove minor enantiomer	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.29 (d, J = 7.6 Hz, 1H), 8.22 - 8.20 (m, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.70 - 7.67 (m, 3H), 7.36 - 7.33 (m, 1H), 7.13 - 7.10 (m, 1H), 4.45 (q, J = 7.2 Hz, 2H), 3.56 - 3.51 (m, 1H), 3.43 - 2.99 (m, 2H), 2.84 - 2.68 (m, 3H), 2.68 - 2.67 (m, 1H), 2.52 - 2.50 (m, 4H), 2.34 - 2.14 (m, 3H), 1.80 - 1.66 (m, 5H), 1.41 - 1.35 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.06 - 1.00 (m, 3H), 0.76 (t, J = 7.6 Hz, 3H).	LCMS: 1.80 min, 580.3 [M+H] ⁺ , Method W	SFC: 4.88 min, Column: Lux I-Amylose-3; Co-Solvent : 20.0 %, IPAm in MeOH; Injection Volume : 10 uL; Flow : 4.0000 mL/min; Pressure : 102.0 kgf/cm ² ; Temperature : 40
166	2-(2-ethoxyphenyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[(2R)-pyrrolidin-2-yl]methylspiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int 93	tert-butyl (R)-2-formylpyrrolidine-1-carboxylate, NaBH ₃ CN, MeOH, 25 °C, 2 h in 1 st Step and formic acid in 2 nd step	Prep HPLC method E	¹ H NMR (400 MHz, CD ₃ OD) δ 8.48 (br s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.51 (dd, J = 1.7, 7.6 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.07 - 7.01 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 4.05 - 3.97 (m, 1H), 3.94 (d, J = 15.3 Hz, 1H), 3.87 (s, 3H), 3.73 (d, J = 15.4 Hz, 1H), 3.39 - 3.32 (m, 1H), 3.30 - 3.24 (m, 1H), 3.14 - 2.99 (m, 5H), 2.91 (d, J = 12.0 Hz, 1H), 2.88 - 2.76 (m, 2H), 2.32 - 2.18 (m, 3H), 2.16 - 2.02 (m, 2H), 2.00 - 1.85 (m, 2H), 1.82 - 1.68 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H).	LCMS: 2.35 min, 581.3 [M+H] ⁺ , Method O	SFC: 1.23 min, Column: Chiralcel OD - 3, 50 x 4.6 mm I.D., 3 um, Co-Solvent: 50%, Co-Solvent Name: Methyl alcohol [0.2% ammonia (7 M in MeOH), v/v]; Injected Volume: 5.30 uL; Run time: 3.0 min.
167	(3'SR,5'SR)-2-(2-ethoxy-3-yl)-3'-ethyl-1'-[5-methoxy-4-(trifluoromethyl)pyridin-3-yl]-7-[(2R)-pyrrolidin-2-yl]methylspiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int. 122 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in step-2	Prep HPLC Method AK followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.38 (s, 1H), 8.34 (s, 1H), 8.28 (dd, J = 2.0, 7.6 Hz, 1H), 8.22 - 8.21 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.14 - 7.11 (m, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.84 - 3.86 (m, 1H), 3.59 - 3.50 (m, 3H), 3.20 - 3.25 (m, 5H), 2.94 - 2.91 (m, 3H), 2.69 - 2.67 (m, 2H), 2.34 - 2.33 (m, 2H), 1.90 - 1.72 (m, 4H), 1.38 (t, J = 7.2 Hz, 4H), 1.24 - 1.03 (m, 2H), 0.75 (t, J = 7.6 Hz, 3H).	LCMS: 1.71 min, 611.3 [M+H] ⁺ , Method G	SFC: 1.86 min and 2.17 min; 55.74% and 43.96% Column: I-cellulose-B; Co-Solvent : 25.0 %, 0.5% IPAm in MeOH; Injection Volume : 10 uL; Flow : 4.0 mL/min.

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								Pressure : 102.0 kgf/cm ² ; Temperature : 40 °C
168	(3'S,5S)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[[[(2R)-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int 103 and tert-butyl (R)- 2- formylpyrrol dine-1- carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in step-2	Prep HPLC Method AG followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.32 - 8.28 (m, 2H), 8.22 - 8.20 (m, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.13 - 7.10 (m, 1H), 6.85 (d, J = 6.0 Hz, 1H), 4.46 (q, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.90 - 3.87 (m, 1H), 3.58 - 3.51 (m, 3H), 3.17 - 3.13 (m, 3H), 3.00 - 2.8 (m, 3H), 2.89 - 2.85 (m, 2H), 2.72 - 2.70 (m, 1H), 2.51 - 2.51 (m, 2H), 2.45 - 2.40 (m, 2H), 1.77 - 1.62 (m, 4H), 1.38 (t, J = 6.8 Hz, 3H), 1.04 - 1.01 (m, 2H), 0.78 - 0.74 (m, 3H).	LCMS: 1.70 min, 611.3 [M+H] ⁺ , Method G	SFC: 3.98 min and 5.04 min, Lux I- Amylose-3; Co- Solvent : 30.0 %, 0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min Pressure : 102.0 kgf/cm ² ; Temperature : 40 °C
170	1'-[(2-chlorophenyl)-2-(2-ethoxy-3-pyridinyl)-7-[[[(2R)-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int 123 and tert-butyl (R)- 2- formylpyrrol dine-1- carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep HPLC Method Y followed by 10% aq. NaHCO ₃ workup	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.56 (s, 1H), 8.22 - 8.20 (m, 2H), 7.92 (q, J = 8.4 Hz, 2H), 7.43 (d, J = 1.2 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.13 - 7.10 (m, 1H), 7.05 (t, J = 1.6 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.74 (s, 2H), 3.30 - 3.29 (m, 2H), 3.22 - 3.19 (m, 2H), 3.00 - 2.97 (m, 2H), 2.83 - 2.75 (m, 2H), 2.73 - 2.72 (m, 1H), 2.56 - 2.55 (m, 2H), 2.13 - 2.09 (m, 2H), 1.89 - 1.79 (m, 4H), 1.65 - 1.58 (m, 2H), 1.39 - 1.35 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H)	LCMS: 1.663 min, 581.3 [M+H] ⁺ , Method G	SFC: 5.93 min, 99.30% Column: R-R-Whelk; Co- Solvent : 40.0 %, 0.5% IPAm in MeOH; Injection Volume : 10 uL Flow : 4.0 mL/min; Oven Pressure : 102.0 kgf/cm ² ; Temperature : 40 °C,
171	2-(2-ethoxy-3-pyridinyl)-1-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[[[(2R)-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Ex. 30 and tert-butyl (R)- 2- formylpyrrol dine-1- carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	prep-HPLC using Method- G followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.25 - 8.20 (m, 3H), 7.94-7.85 (m, 2H), 7.40 (d, J = 2.8 Hz, 1H), 7.18 - 7.10 (m, 2H), 4.44 (t, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.74 (s, 2H), 3.35 - 3.32 (m, 2H), 3.07 (t, J = 7.2 Hz, 1H), 2.93-2.84 (m, 3H), 2.76 - 2.74 (m, 3H), 2.06 - 2.04 (m, 2H), 2.59 - 2.51 (m, 1H), 2.07 - 2.01 (m, 2H), 1.84 - 1.81 (m, 3H), 1.67-1.63 (m, 2H), 1.45 (t, J = 7.2 Hz, 3H).	LCMS: 1.76 min, 583.3 [M+H] ⁺ , Method W	
172	5-chloro-2-[(3'SR,5SR)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[[[(2R)-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzotriazole	X	Int. 99 and tert-butyl (R)- 2- formylpyrrol dine-1- carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	Prep HPLC Method Y followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.28 (d, J = 1.6 Hz, 1H), 8.22 - 8.20 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 2.8 Hz, 1H), 7.68 - 7.65 (m, 1H), 7.30 - 7.27 (m, 1H), 7.13 - 7.10 (m, 1H), 4.46 (q, J = 7.0 Hz, 2H), 3.90 - 3.80 (m, 1H), 3.62 - 3.52 (m, 2H), 3.41 - 3.38 (m, 1H), 3.32 (s, 1H), 3.29 - 3.15 (m, 2H), 2.87 - 2.85 (m, 2H), 2.74 - 2.67 (m, 1H), 2.52 - 2.50 (m, 3H), 2.45 (s, 1H), 2.31 (s, 1H), 2.18 (d, J = 11.6 Hz, 1H), 1.80 - 1.78 (m, 2H), 1.65 - 1.62 (m, 2H), 1.39 - 1.30 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.03 (m,	LCMS: 1.78 min, 571.3 [M+H] ⁺ , Method G	SFC: 2.95 min and 6.13 min, Column: Lux I-Amylose-3; Co-Solvent : 40.0 %, 0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² ,

						2H), 0.81 (t, J = 7.2 Hz, 3H). Exchangeable proton was not observed						Oven Temperature : 40 °C.
175	2-(2-ethoxy-3-pyridinyl)-7-[(2R)-pyrrolidin-2-ylmethyl]-1'-[3-(trifluoromethyl)pyrazin-2-yl]spirol[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	X	Int. 104 and tert-butyl 1'-2-formylpyrrolidine-1'-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	Prep HPLC Method AK followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.53 (s, 1H), 8.28 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 6.0 Hz, 2H), 7.90 - 7.82 (m, 2H), 7.11 (t, J = 6.0 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 3.74 - 3.70 (m, 4H), 3.51 (s, 2H), 2.91 - 2.84 (m, 3H), 2.74 - 2.71 (m, 1H), 2.06 - 2.01 (m, 2H), 1.88 - 1.85 (m, 3H), 1.65 - 1.57 (m, 3H), 1.35 (t, J = 7.2 Hz, 3H).		LCMS: 1.60 min, 554.2 [M+H] ⁺ , Method G		SFC: 2.87 min, 94.61% Column: I-cellulose-C; Co-Solvent : 40.0 %; 0.5% IPAm in MeOH Injection Volume : 10 µL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , Ov242temperature : 40 °C.		
185	2-(2-ethoxyphenyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]-7-[(2S)-pyrrolidin-2-ylmethyl]spirol[6.8-dihydro-1,7-naphthyridine-4'-piperidine]	X	Int 93	tert-butyl (S)-2-formylpyrrolidine-1'-carboxylate, NaBH ₃ CN, MeOH, 60 °C, 2 h followed by formic acid in 2 nd step	Prep HPLC method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.51 (dd, J = 1.7, 7.6 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.1 - 7.35 (m, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.04 (dt, J = 0.8, 7.5 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.6 - 3.88 (m, 2H), 3.87 (s, 3H), 3.73 (d, J = 15.4 Hz, 1H), 3.9 - 3.18 (m, 5H), 3.3 - 3.00 (m, 5H), 2.3 - 2.88 (m, 1H), 2.6 - 2.75 (m, 2H), 2.1 - 2.18 (m, 3H), 2.2 - 2.00 (m, 2H), 1.9 - 1.87 (m, 2H), 1.75 - 1.60 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.34 min, 581.3 [M+H] ⁺ , Method O	SFC: 1.29 min, Column: Chiralpak IG-3, 100x4.6mm I.D., 3µm; Co-Solvent: 50%; Co-Solvent Name: MeOH [0.2% ammonia gas (7M in MeOH)]; injected Volume: 2.0 µL. Run time: 5.0 min.			
186	3-[[2-(2-ethoxy-3-pyridinyl)-1'-[3-methoxy-2-(trifluoromethyl)phenyl]spirol[6.8-dihydro-1,7-naphthyridine-4'-piperidine]-7-yl]methyl]morpholine	X	Int 61 and tert-butyl 3-formylmorpholine-4'-carboxylate	NaBH ₃ CN, MeOH, 60 °C, 12 h followed by formic acid in 2 nd step	Prep HPLC method E	¹ H NMR (400 MHz, CD ₃ OD) δ 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.05 (dd, J = 2.0, 7.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.07 (dd, J = 5.0, 7.5 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 4.1 - 3.92 (m, 2H), 3.90 (s, 1H), 3.87 (s, 4H), 3.0 - 3.65 (m, 1H), 3.5 - 3.59 (m, 1H), 3.2 - 3.35 (m, 2H), 3.4 - 3.05 (m, 4H), 3.5 - 2.98 (m, 3H), 2.83 (d, J = 12.0 Hz, 1H), 2.2 - 2.59 (m, 2H), 2.40 - 2.30 (m, 1H), 2.25 - 2.15 (m, 1H), 2.01 (dd, J = 1.6, 13.1 Hz, 1H), 1.86 (dd, J = 1.6, 13.1 Hz, 1H), 1.39 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.43 min, 598.2 [M+H] ⁺ , Method O				
187 (3SR,5SR)-1'-(2-chlorophenyl)-2-(2-ethoxy-3-pyridinyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spirol[6.8-dihydro-1,7-naphthyridine-4'-piperidine]	X	Int 125 and tert-butyl(R)-2-formylpyrrolidine-1'-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	Prep HPLC Method AC followed by 10% aq. NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.28 (dd, J = 2.0, 7.4 Hz, 1H), 8.21 (dd, J = 2.0, 4.8 Hz, 1H), 7.99 - 7.92 (m, 2H), 7.43 (dd, J = 1.6, 7.4 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.14-7.03 (m, 2H), 4.45 (q, J = 7.2 Hz, 2H), 3.86 - 3.80 (m, 1H), 3.57 - 3.52 (m, 1H), 3.33 - 3.17 (m, 2H), 3.02 - 2.83 (m, 2H), 2.74 - 2.67 (m, 2H), 2.53 - 2.51 (m, 2H), 2.47 - 2.46 (m, 2H), 2.34 - 2.14 (m, 3H), 1.81 - 1.78 (m, 2H), 1.65 (d, J =	Formate	LCMS: 1.79 min, 546.2 [M+H] ⁺ , Method G	SFC: 1.83 min and 3.00 min, 49.41% and 49.27%, Column: I-cellulose-J; Co-Solvent : 25.0 %; 0.5% IPAm in MeOH Injection Volume: 10 µL;				

					Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, Oven Temperature : 40 °C.
				3.6 Hz, 2H), 1.40 – 1.38 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H) – 1.21 – 0.94 (m, 2H), 0.78 (t, J = 7.6 Hz, 3H).	

Table 26 – NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	LC/MS data
11 ¹	3-(2'-(2-ethoxypyridin-3-yl)-1-(3-methoxy-2-(trifluoromethyl)phenoxy)-6H-spiro[piperidine-4,5'-[1,7]naphthyridine-7'(8H)-yl]-3-oxopropanoic acid	Y	Int. 61		Method of prep-HPLC: Column: Phenomenex luna C18 100-40 mm*5 um; Mobile phase: [water (formic acid) - acetonitrile]; B%: 35%-75%, 8 min	¹ H NMR (400 MHz, CD ₃ OD) δ 8.21 - 8.15 (m, 2H), 7.99 - 7.92 (m, 2H), 7.52 - 7.44 (m, 1H), 7.08 (dd, J = 5.2, 7.3 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 4.87 (br s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 4.08 (s, 2H), 3.96-3.87 (s, 3H), 3.72 - 3.60 (m, 2H), 3.24 - 3.13 (m, 2H), 3.12 - 3.04 (m, 2H), 2.31 - 2.18 (m, 2H), 1.85 - 1.75 (m, 2H), 1.41 (t, J = 7.0 Hz, 3H)	LCMS: 2.70 min, 585.2 (M+H) ⁺ . Method O

Table 27 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediates	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
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136	rel-[(2R,4S)-4-[(2-(ethoxypyridin-3-yl)-1'-(3-methoxy-2-(trifluoromethyl)phenyls)piro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidin]-7-yl]oxolan-2-yl]methanamine	Z	Int 61	prep-HPLC method E	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.04 (dd, J = 1.9, 7.4 Hz, 1H), 7.95 - 7.90 (m, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 4.31 - 4.18 (m, 2H), 3.87 (s, 3H), 3.81 (s, 2H), 3.77 - 3.69 (m, 1H), 3.41 - 3.34 (m, 1H), 3.14 - 3.06 (m, 2H), 3.06 - 2.93 (m, 4H), 2.91 - 2.83 (m, 1H), 2.78 (d, J = 11.8 Hz, 1H), 2.31 - 2.16 (m, 3H), 2.04 - 1.86 (m, 3H), 1.39 (t, J = 7.1 Hz, 3H) ¹⁹ F NMR: (400 MHz, CD ₃ OD) δ = -56.983 (s, 3F)	Formate	LCMS: 2.33 min, 598.3 (M+H) ⁺ Method Q	SFC: 1.65min, 100% ; Column Name: OZ-3, 50x4.6 mm I.D; 3.0 um, Co-Solvent: 50% ; Co-Solvent Name: 0.2% Ammonia gas in MeOH; Injected Volume: 5.00 µL; Run time: 3.0 min.
137	rel-[(2R,4R)-4-[(2-(ethoxypyridin-3-yl)-1'-(3-methoxy-2-(trifluoromethyl)phenyls)piro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidin]-7-yl]oxolan-2-yl]methanamine	Z	Int 61	From step-1 peak 2 was used for further synthesis prep-HPLC method E	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.20 - 8.14 (m, 1H), 8.05 (dd, J = 1.6, 7.3 Hz, 1H), 7.94 - 7.89 (m, 1H), 7.86 - 7.80 (m, 1H), 7.46 (t, J = 8.3 Hz, 1H), 7.06 (dd, J = 5.1, 7.3 Hz, 1H), 6.95 (br d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 4.20 - 4.05 (m, 2H), 3.94 - 3.88 (m, 1H), 3.86 (s, 3H), 3.81 (s, 1H), 3.76 - 3.69 (m, 1H), 3.41 - 3.34 (m, 1H), 3.12 - 2.96 (m, 6H), 2.93 (br d, J = 12.5 Hz, 1H), 2.87 - 2.78 (m, 1H), 2.42 (td, J = 6.5, 12.5 Hz, 1H), 2.29 - 2.19 (m, 2H), 1.93 - 1.88 (m, 2H), 1.75 - 1.70 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.36 min, 598.3 (M+H) ⁺ Method O	SFC: 1.63 min, 55% ; Rt = 1.798 min, 45% purity Column Name: OZ- 3, 50x4.6 mm I.D; 3.0 um, Co- Solvent: 50% ; Co- Solvent Name: 0.2% ammonia gas in MeOH; Injected Volume: 4.00 µL; Run time: 3.0 min.

Table 28 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermedia tes	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
153	2-(2-ethoxyphenyl)-7- [[[(2R)-pyrrolidin-2- yl]methyl]-1'-[2- (trifluoromethyl)phenyls] piro[6.8-dihydro-1,7- naphthyridine-5,4'- piperidine]]	Aa	Int. 106		prep-HPLC Method B followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.85 - 7.79 (m, 2H), 7.74 - 7.67 (m, 4H), 7.39 - 7.33 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.03 (td, J = 7.6, 0.8 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.76 - 3.70 (m, 2H), 3.60 - 3.40 (m, 1H), 3.33 - 3.11 (m, 2H), 3.15 - 3.05 (m, 1H), 2.98 - 2.82 (m, 6H), 2.58 - 2.48 (m, 2H), 2.09 - 2.01 (m, 2H), 1.92 - 1.84 (m, 3H), 1.73 - 1.70 (m, 2H), 1.49 - 1.41 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H).		LCMS: 1.78 min, 551.3 [M+H] ⁺ , Method A	SFC: 2.67 min, 99.26% ; Column: (R,R) Whelk-O1, Co-Solvent : 40.0 %; 0.5% IPAm in MeOH ; Injection Volume : 10 µL; Flow : 4.0 mL/min, BPR Pressure : 100 bar, Temperature : 35 °C.

153. HCl	2-(2-ethoxyphenyl)-7- [[2(R)-pyrrolidin-2- ylmethyl]-1'-[2- (trifluoromethyl)phenyls piro[6,8-dihydro-1,7- naphthyridine-5,4'- piperidine]hydrochloride salt	Aa	Ex. 153				¹ H-NMR (400 MHz, DMSO-d ₆) δ 9.02 (br s, 1H), 8.35 (br s, 1H), δ 7.85 – 7.79 (m, 2H), 7.74 – 7.67 (m, 4H), 7.42 – 7.33 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.08 – 7.04 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.96 – 3.70 (m, 3H), 3.28 – 3.10 (m, 5H), 2.95 – 2.75 (m, 5H), 2.15 – 1.85 (m, 7H), 1.72 – 1.58 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H).	HCl	LCMS: 1.77 min, 551.2 [M+H] ⁺ , Method A	SFC: 2.70 min, 98.74%, Column: (R,R) Whelk-O1, Co-Solvent : 40.0 %; 0.5% IPAm in MeOH, Injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 100 bar, Temperature : 35 °C.
153. MSA	2-(2-ethoxyphenyl)-7- [[2(R)-pyrrolidin-2- ylmethyl]-1'-[2- (trifluoromethyl)phenyls piro[6,8-dihydro-1,7- naphthyridine-5,4'- piperidine]methane sulfonic acid salt	Aa	Ex. 153				¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.35 (br s, 1H), 7.87 – 7.81 (m, 2H), 7.75 – 7.70 (m, 4H), 7.39 – 7.34 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.06 – 7.02 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.75 – 3.68 (m, 2H), 3.32 – 3.06 (m, 6H), 2.86 – 2.80 (m, 3H), 2.73 – 2.68 (m, 1H), 2.30 (s, 3H), 2.11 – 2.03 (m, 3H), 1.96 – 1.86 (m, 4H), 1.69 – 1.52 (m, 1H), 1.36 (t, J = 7.0 Hz, 3H).	MSA	LCMS: 1.77 min, 551.3 [M+H] ⁺ , Method A	SFC: 2.69 min, 99.95%, Column: (R,R) Whelk-O1, Co-Solvent : 40.0 %; 0.5% IPAm in MeOH, Injection Volume : 15 uL, Flow : 4.0 mL/min, BPR Pressure : 100 bar, Temperature : 35 °C.
173	5-chloro-2-[2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	Aa	Int 124 and tert-butyl (R)-2-formylpyrrolidine -1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method AP followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 – 7.80 (m, 3H), 7.78 – 7.72 (m, 1H), 7.68 – 7.65 (m, 1H), 7.38 – 7.34 (m, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.73 (s, 2H), 3.45 (d, J = 12.0 Hz, 2H), 3.35 (s, 3H), 3.15 (t, J = 12.0 Hz, 2H), 2.88 – 2.82 (m, 3H), 2.40 – 2.34 (m, 1H), 2.28 – 2.24 (m, 2H), 1.90 (d, J = 13.2 Hz, 4H), 1.65 – 1.62 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.32 – 1.36 (m, 1H)		LCMS: 1.65 min, 542.3 [M+H] ⁺ , Method G	SFC: 3.22 min, 96.91%, Column: R,R-Whelk, Co-Solvent : 40.0 %; 0.5% IPAm in MeOH, Injection Volume : 15 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kg/cm2, temperature : 40 °C.
177	1'-(2-chloro-3-methoxyphenyl)-2-(2-ethoxyphenyl)-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Aa	Int 108 and tert-butyl (R)-2-formylpyrrolidine -1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method Y followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.89 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.74 – 7.72 (m, 1H), 7.39 – 7.37 (m, 1H), 7.29 – 7.25 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.89 – 6.85 (m, 2H), 4.14 – 4.09 (m, 2H), 3.84 (s, 3H), 3.73 (s, 2H), 3.33 (s, 2H), 3.21 – 3.18 (m, 2H), 2.97 – 2.86 (m, 6H), 2.68 – 2.67 (m, 1H), 2.13 – 2.08 (m, 2H), 1.87 – 1.82 (m, 4H), 1.67 – 1.64 (m, 2H), 1.36 – 1.33 (m, 4H).		LCMS: 1.634 min, 547.3 [M+H] ⁺ , Method G	
178	2-(2-ethoxyphenyl)-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Aa	Int 109 and tert-butyl (R)-2-formylpyrrolidine -1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method AG followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.31 – 8.30 (m, 1H), 7.79 – 7.71 (m, 3H), 7.37 – 7.33 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.88 – 6.84 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.92 (s, 3H), 3.72 – 3.68 (m, 2H), 3.50 – 3.45 (m, 2H), 3.47 – 3.13 (m, 4H), 2.75 – 2.67 (m, 3H), 2.59 – 2.51 (m, 2H), 2.49 – 2.41 (m, 1H), 2.02 – 1.99 (m, 2H), 1.83 – 1.63 (m, 6H), 1.34 (t, J = 6.8 Hz, 3H)		LCMS: 1.607 min, 582.3 [M+H] ⁺ , Method G	SFC: 2.06 min, 98.68%, Column: I-cellulose-Z, Co-Solvent : 40.0 %; 0.5% IPAm in MeOH, Injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 100 bar, Temperature : 35 °C.

								102.0 kgf/cm2, temperature : 40 °C.	
179	1'-[2,3-dichlorophenyl]-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]]	Aa	Int 110 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₃ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method AK followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.38 (s, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 7.27 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 4.14 - 4.09 (m, 2H), 3.73 (s, 2H), 3.38 (s, 2H), 3.20 (d, J = 11.2 Hz, 2H), 2.99 (t, J = 11.2 Hz, 2H), 2.88 (t, J = 5.2 Hz, 2H), 2.76 - 2.75 (m, 2H), 2.68 (s, 1H), 2.51 (s, 1H), 2.51 (t, J = 1.6 Hz, 1H), 1.89 - 1.80 (m, 4H), 1.68 - 1.62 (m, 2H), 1.40 (d, J = 6.0 Hz, 1H), 1.37 (t, J = 6.8 Hz, 3H).	LCMS: 1.79 min, 551.2 [M+H] ⁺ , Method G	SFC: 3.34 min, 98.62%, Column: R, R-Whelk, Co-Solvent : 40.0%, 0.5% IPAm in MeOH injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.
182	1'-[3,5-dichloro-2-pyridinyl]-2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]]	Aa	Int 113 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₃ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method AK followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.31 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.80 - 7.71 (m, 3H), 7.38 - 7.34 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.03 (m, J = 8.0 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.70 (d, J = 15.2 Hz, 4H), 3.42 (s, 2H), 3.09 (t, J = 11.6 Hz, 2H), 2.91 - 2.82 (m, 2H), 2.75 - 2.67 (m, 1H), 2.51 (s, 2H), 2.08 (t, J = 11.6 Hz, 2H), 1.87 - 1.77 (m, 3H), 1.65 - 1.61 (m, 4H), 1.34 (t, J = 6.8 Hz, 3H).	LCMS: 1.76 min, 552.2 [M+H] ⁺ , Method G	SFC: 2.35 min, 97.31%, Column: I-cellulose-Z, Co-Solvent : 30.0 %, 0.5% IPAm in MeOH injection Volume : 18 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.
188	5-chloro-2-[2-(2-ethoxyphenyl)-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile	Aa	Int 114 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₃ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method AC followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.46 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.81 - 7.71 (m, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 4.23 (d, J = 7.2 Hz, 2H), 4.13 - 4.08 (m, 2H), 3.51 (s, 2H), 3.39 - 3.32 (m, 5H), 2.88 - 2.80 (m, 3H), 2.78 - 2.74 (m, 1H), 2.59 - 2.55 (m, 1H), 1.89 - 1.85 (m, 2H), 2.00 - 1.80 (m, 3H), 1.70 - 1.63 (m, 2H), 1.39 (t, J = 7.2 Hz, 4H).	LCMS: 1.64 min, 543.3 [M+H] ⁺ , Method G	SFC: 2.36 min, 100%, Column: I-cellulose-Z, Co-Solvent : 45.0 %, 0.5% IPAm in MeOH injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.
191	2-(2-ethoxyphenyl)-1'-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[[[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]]	Aa	Int 115 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₃ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method Y followed by 10% NaHCO ₃ wash		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.24 (d, J = 8.8 Hz, 1H), 7.84 - 7.79 (m, 2H), 7.74 - 7.72 (dd, J = 1.6, 7.6 Hz, 1H), 7.38 - 7.34 (m, 1H), 7.18 - 7.11 (m, 2H), 7.03 (t, J = 7.2 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.88 (s, 3H), 3.73 (s, 2H), 3.38 - 3.35 (m, 2H), 3.15 - 3.05 (m, 2H), 2.92 - 2.91 (m, 3H), 2.77 - 2.74 (m, 3H), 2.56 - 2.53 (m, 2H), 2.10 - 1.97 (m, 2H), 1.90 - 1.78 (m, 3H), 1.67 - 1.63 (m, 2H), 1.38 - 1.36 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H).	LCMS: 1.80 min, 582.3 [M+H] ⁺ , Method G	SFC: 2.63 min, 98.31%, Wheelk- (R,R), Co-Solvent : 35.0%, 0.5% IPAm in MeOH injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 100

								bar, temperature : 40 °C.
198	(R)-1-(2-(chlorophenyl)-2-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine])	Aa	Int 126 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method N, followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.0, 1.5 Hz, 1H), 7.43 (dd, J = 8.0, 1.5 Hz, 1H), 7.40 – 7.24 (m, 3H), 7.12 (dd, J = 8.5, 1.1 Hz, 1H), 7.08 – 6.99 (m, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.73 (s, 2H), 3.50 – 3.35 (m, 1H), 3.25 – 3.09 (m, 2H), 3.05 – 2.81 (m, 5H), 2.79 – 2.63 (m, 2H), 2.37 – 2.24 (m, 1H), 2.18 – 2.04 (m, 2H), 1.98 – 1.75 (m, 4H), 1.72 – 1.55 (m, 2H), 1.47 – 1.45 (m, 1H), 1.44 (t, J = 7.0 Hz, 3H).	LCMS: 1.67 min, [M+H] ⁺ , 517.3 Method G	
199	(R)-2-(2-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzonitrile	Aa	Int 127 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd step	prep-HPLC Method Y followed by 10% NaHCO ₃ wash	¹ H-NMR : (400 MHz, DMSO-d ₆) δ 7.86 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.68 – 7.57 (m, 1H), 7.41 – 7.34 (m, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.16 – 7.07 (m, 2H), 7.06 – 7.00 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.83 – 3.69 (m, 2H), 3.55 – 3.39 (m, 3H), 3.21 – 3.08 (m, 2H), 2.99 – 2.74 (m, 4H), 2.73 – 2.49 (m, 2H), 2.40 – 2.30 (m, 1H), 2.21 – 2.05 (m, 2H), 2.02 – 1.81 (m, 3H), 1.78 – 1.61 (m, 2H), 1.37 – 1.36 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H).	LCMS: 1.50 min, [M+H] ⁺ , 508.3 Method G	
209	5-chloro-2-(2-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzonitrile	Aa	Int 124 and tert-butyl (2R,4S)-4-(tert-butyl)di(phenyl)silyloxy)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TBAF and TFA in 2 nd step	prep-HPLC Method AC followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.88 – 7.78 (m, 3H), 7.73 (dd, J = 2.0, 7.6 Hz, 1H), 7.73 (dd, J = 2.0, 7.6 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 1.2 Hz, 1H), 4.58 (d, J = 3.2 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.73 (s, 2H), 3.56 – 3.52 (m, 1H), 3.46 – 3.44 (m, 2H), 3.15 (t, J = 11.2 Hz, 2H), 2.98 – 2.91 (m, 2H), 2.81 (d, J = 11.2 Hz, 1H), 2.68 – 2.62 (m, 1H), 2.54 – 2.53 (m, 2H), 2.50 – 2.47 (m, 1H), 2.12 – 2.08 (m, 2H), 1.93 – 1.88 (m, 2H), 1.76 – 1.71 (m, 1H), 1.54 – 1.48 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H).	LCMS: 1.59 min, [M+H] ⁺ , 558.3 Method G	

Table 29 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermedia tes	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
176	(3SR,4SR)-2-(2-ethoxyphenyl)-3-ethyl-1-(3-methoxy-2-(trifluoromethyl)phenyl)-7-(((R)-pyrrolidin-2-yl)methyl)-7,8-dihydro-	Ab	Int 105		Prep. HPLC method AP followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.86 (d, J = 8.4 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.55 – 7.51 (m, 1H), 7.39 – 7.35 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.93 (d, J = 8.4 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.82 – 3.80 (m, 1H), 3.59 – 3.47 (m, 2H), 3.13 (m, 3H), 2.96 – 2.85 (m, 2H), 2.75 – 2.68 (m, 2H).		LCMS: 1.86 min, 609.3, [M+H] ⁺ , Method G.	SFC: 3.17 min and 3.65 min, 51.50% and 46.72%, Column: I-cellulose-C; Co-solvent : 30.0 %.

	6H-spiro[piperidine-4,5'-1',7naphthyridine]					2.51 (s, 3H), 2.22 – 1.90 (m, 2H), 1.90 – 1.76 (m, 4H), 1.35 (t, J = 7.2 Hz, 3H), 1.01 (s, 2H), 0.88 – 0.85 (m, 1H), 0.74 (t, J = 7.2 Hz, 3H), exchangeable proton was not observed.			0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.
180	rac-(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-1'-[4-methoxy-3-(trifluoromethyl)-2-pyridinyl]-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ab	Int 111 and tert-butyl (R)-2-formylpyrro lidine-1-carboxylat e	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AF followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.31 (d, J = 5.6 Hz, 1H), 7.83 – 7.73 (m, 3H), 7.38 – 7.33 (m, 1H), 7.12 – 7.10 (m, 1H), 7.05 – 7.01 (m, 1H), 6.84 (d, J = 6.0 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.83 – 3.79 (m, 1H), 3.54 – 3.48 (m, 3H), 3.20 – 3.12 (m, 3H), 2.88 – 2.85 (m, 2H), 2.68 – 2.63 (m, 1H), 2.45 – 2.40 (m, 3H), 2.30 – 2.05 (m, 2H), 1.84 – 1.55 (m, 5H), 1.37 – 1.35 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.03 – 1.01 (m, 2H), 0.75 (t, J = 7.2 Hz, 3H).	LCMS: 1.72 min, 610.3 [M+H] ⁺ , Method G	SFC: 3.00 min and 4.56 min, 45.67% and 47.32%, Column: AMYLOSE-A, Co-Solvent : 20.0%, 0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.	
181	5-chloro-2-[(3'S,5SR)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	Ab	Int 112 and tert-butyl (R)-2-formylpyrro lidine-1-carboxylat e	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AP followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 – 7.84 (m, 3H), 7.79 (dd, J = 1.20, 7.8 Hz, 1H), 7.66 (dd, J = 2.8, 9.0 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.28 (dd, J = 2.8, 8.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 4.15 – 4.10 (m, 2H), 3.83 – 3.70 (m, 1H), 3.59 – 3.51 (m, 3H), 3.41 – 3.37 (m, 2H), 3.19 – 3.15 (m, 2H), 2.89 – 2.85 (m, 2H), 2.68 – 2.67 (m, 1H), 2.47 – 2.45 (m, 3H), 2.34 – 2.33 (m, 1H), 2.22 – 2.17 (m, 1H), 1.81 – 1.80 (m, 4H), 1.38 – 1.36 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.08–1.04 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H).	LCMS: 1.766 min, 570.3 (M+H) ⁺ , Method G		
181-1	5-chloro-2-[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile (Absolute stereochemistry determined by small molecule X-Ray. Details can be found after Table 14)				Diastereomer separation using SFC. Column: I-CELLULOSE-J, 0.5% IPAm in MeOH	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 – 7.84 (m, 3H), 7.80 – 7.78 (m, 1H), 7.68 – 7.65 (m, 1H), 7.36 (t, J = 1.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.86 – 3.82 (m, 1H), 3.62 – 3.50 (m, 3H), 3.18 – 3.15 (m, 2H), 2.89 – 2.83 (m, 2H), 2.74 – 2.72 (m, 1H), 2.50 – 2.43 (m, 3H), 2.20 (m, 1H), 2.17 (m, 1H), 1.80 – 1.77 (m, 3H), 1.65 – 1.61 (m, 2H), 1.36 – 1.35 (m, 1H), 1.34 (t, J = 6.8 Hz, 3H), 1.08 – 1.04 (m, 2H), 0.80 (t, J = 7.6 Hz, 3H). Exchangeable proton not observed	LCMS: 1.78 min, 570.3 [M+H] ⁺ , Method G	SFC: 2.40 min, 99.63%, Column: I-CELLULOSE-J, Co-Solvent : 20.0 %, 0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.	

181-2	5-chloro-2-[(3R,5R)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	Ab	Int 116 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Diastereomer separation using SFC. Column: I-CELLULOSE-J. 0.5% IPAm in MeOH	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 – 7.80 (m, 3H), 7.78 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.38 (t, J = 6.8 Hz, 1H), 7.31 (q, J = 9.2 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.04 (t, J = 6.8 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.86 – 3.82 (m, 1H), 3.56 – 3.52 (m, 3H), 3.33 – 2.90 (m, 2H), 2.90 – 2.84 (m, 2H), 2.73 – 2.71 (m, 1H), 2.52 – 2.50 (m, 3H), 2.46 – 2.16 (m, 3H), 1.81 – 1.77 (m, 3H), 1.64 – 1.62 (m, 2H), 1.36 – 1.35 (m, 1H), 1.34 (t, J = 6.8 Hz, 3H), 1.08 – 1.04 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H).	LCMS: 1.78 min, 570.3 [M+H] ⁺ , Method G	SFC: 3.11 min, 98.76%, Column: I-CELLULOSE-J. Co-Solvent : 20.0 %; 0.5% IPAm in MeOH Injection Volume : 10 uL; Flow : 4.0 mL/min; BPR Pressure : 102.0 kgf/cm ² ; temperature : 40 °C.
192	(3'SR,5'SR)-2-(2-ethoxyphenyl)-3'-ethyl-1'-[6-methoxy-2-(trifluoromethyl)-3-pyridinyl]-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ab	Int 116 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AK followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.22 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.38 – 7.34 (m, 1H), 7.18 – 7.11 (m, 2H), 7.05 – 7.02 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.86 – 3.80 (m, 1H), 3.55 – 3.51 (m, 1H), 3.18 – 3.12 (m, 2H), 3.05 – 2.67 (m, 6H), 2.45 – 2.40 (m, 2H), 2.22 – 2.05 (m, 2H), 1.90 – 1.45 (m, 5H), 1.37 – 1.36 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.24 (m, 5H), 1.08 – 0.95 (m, 2H), 0.69 (t, J = 7.2 Hz, 3H).	LCMS: 1.84 min, 610.3 [M+H] ⁺ , Method G	SFC: 1.53 min and 2.00 min; 46.65% and 51.33%, Column: I-CELLULOSE-J. Co-Solvent : 20.0 %; 0.5% IPAm in MeOH Injection Volume : 15 uL; Flow : 4.0 mL/min; BPR Pressure : 102.0 kgf/cm ² ; temperature : 40 °C.
193	(3'SR,5'SR)-1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ab	Int 117 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AF followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.30 (s, 1H), 8.06 (s, 1H), 7.82 – 7.78 (m, 3H), 7.38 – 7.34 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 4.14 – 4.09 (m, 2H), 3.90 – 3.80 (m, 2H), 3.68 – 3.65 (m, 2H), 3.55 – 3.52 (m, 1H), 3.19 – 3.16 (m, 2H), 2.85 – 2.72 (m, 3H), 2.51 – 2.45 (m, 2H), 2.22 – 2.14 (m, 2H), 1.80 – 1.64 (m, 5H), 1.36 – 1.32 (m, 5H), 1.09 – 1.03 (m, 2H), 0.80 – 0.76 (m, 3H).	LCMS: 1.81 min, 580.2 [M+H] ⁺ , Method G	SFC: 2.41 and 3.48 min; 46.98% and 48.61%, Column: I-CELLULOSE-J. Co-Solvent : 20.0 %; 0.5% IPAm in MeOH Injection Volume : 15 uL; Flow : 4.0 mL/min; BPR Pressure : 102.0 kgf/cm ² ; temperature : 40 °C.
195	(3'SR,4'SR)-1-(2,3-dichlorophenyl)-2-(2-ethoxyphenyl)-3-ethyl-7-[(R)-pyrrolidin-2-ylmethyl]-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridine]	Ab	Int 118 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AC followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.88 – 7.83 (m, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.39 – 7.26 (m, 4H), 7.13 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 8.4 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.87 – 3.82 (m, 1H), 3.58 – 3.33 (m, 2H), 3.19 – 3.16 (m, 2H), 3.09 – 3.06 (m, 1H), 2.90 – 2.82 (m, 1H), 2.74 – 2.67 (m, 2H), 2.61 – 2.56 (m, 2H), 2.51 – 2.45 (m, 2H), 2.34 – 2.34 (m, 1H), 2.33 – 2.27 (m, 1H), 1.89 – 1.81 (m, 2H), 1.69 – 1.67 (m, 2H), 1.37 – 1.35 (m, 1H), 1.34 (t, J = 6.8 Hz, 3H), 1.07 – 1.03 (m, 1H).	LCMS: 1.90 min, 579.3 [M+H] ⁺ , Method G.	SFC: 5.50 min and 9.67 min, 45.94% and 48.46%, Column: I-cellulose-J. Co-Solvent : 15%; 0.5% IPAm in MeOH Injection Volume : 18 uL; Flow : 4.0 mL/min; BPR Pressure :

						2H), 0.80 – 0.76 (m, 3H), exchangeable proton was not observed.				102.0 kgf/cm2 temperature : 40 °C.
196	(3SR,4SR)-1-(2-chloro-4-fluorophenyl)-2-(2-ethoxyphenyl)-3-ethyl-7-(((R)-pyrrolidin-2-yl)methyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	Ab	Int 119 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH, DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method Q followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 – 7.85 (m, 2H), 7.72 – 7.82 (m, 1H), 7.44 – 7.41 (m, 1H), 7.39 – 7.31 (m, 2H), 7.23 – 7.18 (m, 1H), 7.19 – 7.12 (m, 1H), 7.06 – 7.02 (m, 1H), 4.15 (q, J = 6.8 Hz, 2H), 3.85 – 3.81 (m, 1H), 3.56 – 3.50 (m, 1H), 3.26 – 3.00 (m, 4H), 2.91 – 2.85 (m, 1H), 2.75 – 2.67 (m, 1H), 2.47 – 2.45 (m, 1H), 2.28 – 2.21 (m, 1H), 2.18 – 2.12 (m, 1H), 1.90 – 1.75 (m, 2H), 1.68 – 1.58 (m, 2H), 1.36 (t, J = 6.8 Hz, 3H), 1.09 – 0.75 (m, 9H), 0.61 – 0.47 (m, 1H), exchangeable proton was not observed.		LCMS: 1.82 min, 563.3 [M+H] ⁺ , Method-F.	SFC: 3.07 min and 4.98 min, 41.26% and 51.83%, Column: I-cellulose-J, Co-solvent : 15%, 0.5% iPAmin MeOH injection Volume : 18 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.	
197	2-[(3SR,5SR)-2-(2-ethoxyphenyl)-3-ethyl-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	Ab	Int 120 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH, DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AO followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.85 – 7.80 (m, 3H), 7.73 (d, J = 1.6 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 1.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.14 – 7.02 (m, 3H), 4.12 (q, J = 6.8 Hz, 2H), 3.86 – 3.82 (m, 1H), 3.60 – 3.50 (m, 2H), 3.42 – 3.32 (m, 2H), 3.21 (m, 1H), 3.18 – 3.13 (m, 2H), 2.87 – 2.85 (m, 2H), 2.77 – 2.75 (m, 1H), 2.68 – 2.50 (m, 1H), 2.46 (m, 2H), 2.34 – 2.18 (m, 2H), 1.89 – 1.81 (m, 2H), 1.66 (m, 2H), 1.37 – 1.36 (m, 1H), 1.33 (t, J = 6.8 Hz, 3H), 1.24 – 1.05 (m, 2H), 0.83 – 0.79 (m, 3H).		LCMS: 1.66 min, 536.3 [M+H] ⁺ , Method G	SFC: 1.37 min and 2.43 min, 51.38% and 43.34%, Column: I-CELLULOSE-J, Co-Solvent : 30.0 %, 0.5% iPAmin MeOH injection Volume : 5 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.	
200	5-chloro-2-[(3SR,5SR)-2-(2-ethoxyphenyl)-3'-ethyl-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]pyridine-3-carbonitrile	Ab	Int 128 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH, DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. HPLC method AO followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.81 - 7.77 (m, 3H), 7.38 - 7.34 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 4.45 – 4.35 (m, 1H), 4.25 - 4.18 (m, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.80 – 3.70 (m, 1H), 3.65 – 3.40 (m, 5H), 3.25 – 3.25 (m, 1H), 3.10 – 2.80 (m, 3H), 2.22 – 2.10 (m, 2H), 1.90 – 1.60 (m, 4H), 1.45 – 1.35 (m, 2H), 1.34 (t, J = 6.8 Hz, 3H), 1.15 – 1.00 (m, 2H), 0.85 – 0.78 (m, 4H).		LCMS: 1.72 min, 571.3 [M+H] ⁺ , Method W	SFC: 2.85 min and 5.76 min, 49.68% and 46.61%, Column: I-cellulose-J, Co-solvent : 20%, 0.5% iPAmin MeOH injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm2, temperature : 40 °C.	

									102.0 kgf/cm ² temperature: 40 °C.
200-1	Enant1-5-chloro-2- [[3(R,5R)-2-(2-ethoxyphenyl)-3-ethyl-7- [[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidin]-1'-yl]pyridine-3-carbonitrile				SFC chiral separation	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.85 - 7.75 (m, 3H), 7.38 - 7.34 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.08 - 6.95 (m, 1H), 4.45 - 4.30 (m, 1H), 4.23 - 4.18 (m, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.85 - 3.75 (m, 1H), 3.58 - 3.53 (m, 1H), 3.48 - 3.46 (m, Hz, 2H), 3.25 - 3.00 (m, 2H), 2.90 - 2.65 (m, 2H), 2.60 - 2.40 (m, 4H), 2.35 - 2.05 (m, 2H), 1.90 - 1.60 (m, 4H), 1.40 - 1.37 (m, 1H), 1.35 (t, J = 6.8 Hz, 3H), 1.20 - 1.00 (m, 2H), 0.82 - 0.78 (m, 3H).		LCMS: 1.75 min, 571.3 [M+H] ⁺ , Method W	SFC: 2.70 min, 98.59% Column: I-Celulose-J, Co-Solvent: 20%, 0.5% iPA in MeOH Injection Volume: 10 uL, Flow: 4.0 mL/min, BPR Pressure: 102.0 kgf/cm ² , temperature: 40 °C.
200-2	Enant2-5-chloro-2- [[3(R,5R)-2-(2-ethoxyphenyl)-3-ethyl-7- [[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidin]-1'-yl]pyridine-3-carbonitrile				SFC chiral separation	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.85 - 7.75 (m, 3H), 7.38 - 7.34 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.08 - 6.95 (m, 1H), 4.45 - 4.30 (m, 1H), 4.23 - 4.18 (m, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.85 - 3.75 (m, 1H), 3.58 - 3.53 (m, 1H), 3.48 - 3.46 (m, Hz, 2H), 3.25 - 3.00 (m, 2H), 2.90 - 2.65 (m, 2H), 2.60 - 2.40 (m, 4H), 2.35 - 2.05 (m, 2H), 1.90 - 1.60 (m, 4H), 1.40 - 1.37 (m, 1H), 1.35 (t, J = 6.8 Hz, 3H), 1.20 - 1.00 (m, 2H), 0.82 - 0.78 (m, 3H).		LCMS: 1.74 min, 571.3 [M+H] ⁺ , Method W	SFC: 5.65 min, 98.88% Column: I-Celulose-J, Co-Solvent: 20.0%, 0.5% iPA in MeOH Injection Volume: 10 uL, Flow: 4.0 mL/min, BPR Pressure: 102.0 kgf/cm ² , temperature: 40 °C.
200-2	5-chloro-2-[(3R,5R)-2-(2-ethoxyphenyl)-3-ethyl-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidin]-1'-yl]pyridine-3-carbonitrile	Ab	Int 129 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH, DCM, rt, 16 h followed by TFA in 2 nd Step	Prep. method followed by 10% NaHCO ₃ wash and SFC purification (i-Celulose-J, 0.5% iPA in MeOH)	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.83 - 7.75 (m, 3H), 7.38 - 7.34 (m, 1H), 7.15 - 7.08 (m, 1H), 7.05 - 6.98 (m, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.20 (d, J = 11.6 Hz, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.82 (d, 15.6 Hz, 1H), 3.55 (d, J = 15.6 Hz, 1H), 3.43 - 3.33 (m, 2H), 3.20 - 3.00 (m, 2H), 2.92 - 2.85 (m, 1H), 2.70 - 2.60 (m, 1H), 2.60 - 2.40 (m, 4H), 2.20 - 2.20 (m, 2H), 1.90 - 1.60 (m, 4H), 1.42 - 1.37 (m, 1H), 1.34 (t, J = 6.8 Hz, 3H), 1.15 - 1.00 (m, 2H), 0.82 - 0.78 (m, 3H).		LCMS: 1.74 min, 571.3 [M+H] ⁺ , Method W	SFC: 5.91 min, 99.02% Column: I-Celulose-J, Co-Solvent: 20%, 0.5% iPA in MeOH Injection Volume: 10 uL, Flow: 4.0 mL/min, BPR Pressure: 102.0 kgf/cm ² , temperature: 40 °C.

201	5-chloro-2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethoxy-7-(((S)-pyrrolidin-2-yl)methyl)-7,8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile	Ab	Int 128 and tert-butyl (S)-2-formylpyrrolidine-1-carboxylate instead of tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. method followed by 10% NaHCO ₃ wash	HPLC AK	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.86 – 7.73 (m, 3H), 7.40 – 7.32 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.07 – 6.99 (m, 1H), 4.43 – 4.33 (m, 1H), 4.26 – 4.16 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.91 – 3.77 (m, 1H), 3.64 – 3.46 (m, 1H), 3.47 – 3.34 (m, 4H), 3.26 – 3.15 (m, 1H), 3.11 – 2.98 (m, 1H), 2.97 – 2.84 (m, 1H), 2.85 – 2.72 (m, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.39 (m, 1H), 2.24 – 2.09 (m, 2H), 1.92 – 1.56 (m, 4H), 1.46 – 1.38 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H), 1.19 – 0.97 (m, 2H), 0.81 (t, J = 7.0 Hz, 3H)	LCMS: 1.63 min, 571.3 [M+H] ⁺ , Method G	SFC: 2.53 min and 3.07 min, 48.45% and 48.60% Column: I-Cellulose-Z, Co-Solvent : 45%, 0.5% IPAm in MeOH injection Volume : 10 µL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.
201-1	Enanti-5-chloro-2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethoxy-7-(((S)-pyrrolidin-2-yl)methyl)-7,8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile				SFC: Column: I-Cellulose-Z, 0.5% IPAm in MeOH.		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.86 – 7.73 (m, 3H), 7.40 – 7.32 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.07 – 6.99 (m, 1H), 4.37 (d, 11.4 Hz, 1H), 4.20 (d, J = 11.4 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.82 (d, J = 15.6 Hz, 1H), 3.54 (d, J = 15.6 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.26 – 3.15 (m, 1H), 3.11 – 2.98 (m, 1H), 2.97 – 2.84 (m, 1H), 2.85 – 2.72 (m, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.39 (m, 1H), 2.24 – 2.09 (m, 2H), 1.92 – 1.56 (m, 4H), 1.46 – 1.38 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H), 1.19 – 0.97 (m, 2H), 0.81 (t, J = 7.0 Hz, 3H)	LCMS: 1.69 min, 571.3 (M+H) ⁺ , Method G	SFC: 2.93 min, 100%, Column: I-Cellulose-J, Co-Solvent : 20%, 0.5% IPAm in MeOH injection Volume : 10 µL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.
201-2	Enanti-5-chloro-2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethoxy-7-(((S)-pyrrolidin-2-yl)methyl)-7,8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile				SFC: Column: I-Cellulose-Z, 0.5% IPAm in MeOH.		¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.47 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.86 – 7.73 (m, 3H), 7.40 – 7.32 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.07 – 6.99 (m, 1H), 4.37 (d, 11.4 Hz, 1H), 4.20 (d, J = 11.4 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.82 (d, J = 15.6 Hz, 1H), 3.54 (d, J = 15.6 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.26 – 3.15 (m, 1H), 3.11 – 2.98 (m, 1H), 2.97 – 2.84 (m, 1H), 2.85 – 2.72 (m, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.39 (m, 1H), 2.24 – 2.09 (m, 2H), 1.92 – 1.56 (m, 4H), 1.46 – 1.38 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H), 1.19 – 0.97 (m, 2H), 0.81 (t, J = 7.0 Hz, 3H)	LCMS: 1.73 min, 571.3 (M+H) ⁺ , Method G	SFC: 5.11 min, 98.00%, Column: I-Cellulose-J, 0.5% Co-Solvent : 35%, 0.5% IPAm in MeOH injection Volume : 10 µL; Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.

203	(3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-7-(((R)-pyrrolidin-2-yl)methyl)-1-(3-(trifluoromethyl)pyrazin-2-yl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	Ab	Int 131 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. method followed by 10% NaHCO ₃ wash	HPLC AN	¹ H-NMR (400 MHz, DMSO-d ₆) δ 8.53 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.83 – 7.76 (m, 3H), 7.38 – 7.34 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.05 – 7.01 (m, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.85 – 3.73 (m, 3H), 3.57 – 3.50 (m, 1H), 3.32 (m, 2H), 3.19 (m, 2H), 3.04 (m, 1H), 2.87 – 2.85 (m, 1H), 2.76 (m, 1H), 2.52 – 2.50 (m, 2H), 2.17 – 2.14 (m, 2H), 1.74 – 1.64 (m, 5H), 1.40 – 1.36 (m, 1H), 1.34 (t, J = 6.8 Hz, 3H), 1.07 – 1.04 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H).		LCMS: 1.68 min, 581.3 [M+H] ⁺ , Method G	SFC: 2.65 and 3.99 min, 49.30% and 48.11%, Column: CELLULOSE-J ₂ , Co-Solvent : 15%, 0.5% IPAm in MeOH Injection Volume : 15 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.
204	2-((3SR,4SR)-2'-(2-ethoxyphenyl)-3-ethyl-7-(((R)-pyrrolidin-2-yl)methyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-5-fluorobenzonitrile	Ab	Int 132 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. method followed by 10% NaHCO ₃ wash	HPLC AC	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.88 – 7.81 (m, 2H), 7.79 (dd, J = 7.8, 1.8 Hz, 1H), 7.73 (dd, J = 8.5, 3.1 Hz, 1H), 7.53 (m, 1H), 7.40 – 7.29 (m, 2H), 7.12 (d, 1H), 7.07 – 7.01 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.89 – 3.77 (m, 1H), 3.61 – 3.46 (m, 2H), 3.32 – 3.21 (m, 4H), 3.21 – 3.05 (m, 2H), 2.92 – 2.66 (m, 3H), 2.49 – 2.38 (m, 2H), 2.32 – 2.11 (m, 2H), 1.94 – 1.75 (m, 2H), 1.72 – 1.56 (m, 2H), 1.40 – 1.36 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H) 1.16 – 0.97 (m, 2H), 0.80 (t, J = 7.0 Hz, 3H).		LCMS: 1.720 min, 554.3 [M+H] ⁺ , Method G	SFC: 1.47 min, and 2.84 min, 50.76% and 43.79%, Column: I-cellulose-J ₂ , Co-Solvent : 25%, 0.5% IPAm in MeOH Injection Volume : 15 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.
205	(3SR,4SR)-1-(2-chlorophenyl)-2'-(2-ethoxyphenyl)-3-ethyl-7-(((R)-pyrrolidin-2-yl)methyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridine]	Ab	Int 133 and tert-butyl (R)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₄ , DCE, rt, 16 h followed by TFA in 2 nd Step	Prep. method P followed by 10% NaHCO ₃ wash	HPLC	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.85 (d, J = 1.5 Hz, 2H), 7.82 – 7.75 (m, 1H), 7.43 (dd, J = 8.0, 1.5 Hz, 1H), 7.40 – 7.26 (m, 3H), 7.15 – 7.10 (m, 1H), 7.08 – 7.01 (m, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.90 – 3.80 (m, 1H), 3.62 – 3.47 (m, 1H), 3.44 – 3.34 (m, 2H), 3.24 – 3.13 (m, 2H), 3.08 – 2.98 (m, 1H), 2.94 – 2.84 (m, 1H), 2.83 – 2.65 (m, 2H), 2.60 – 2.52 (m, 2H), 2.49 – 2.39 (m, 1H), 2.39 – 2.21 (m, 1H), 2.22 – 2.12 (m, 1H), 1.93 – 1.77 (m, 2H), 1.76 – 1.61 (m, 2H), 1.46 – 1.37 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.16 – 0.96 (m, 2H), 0.78 (t, J = 7.0 Hz, 3H) and exchangeable proton.		LCMS: 1.78 min, 545.3 [M+H] ⁺ , Method G	SFC: 3.41 min and 3.47 min, 53.27% and 43.07%, Column: R ₂ -WHELK, Co-Solvent : 35%, 0.5% IPAm in MeOH Injection Volume : 10 uL, Flow : 4.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , temperature : 40 °C.

211	5-chloro-2-((3SR 4SR)-2-(2-ethoxyphenyl)-3-ethyl-7-((2R,4S)-4-hydroxypyrrolidin-2-yl)methyl)-7,8-dihydro-6H-spiro[piperidine-4,5-[1,7]naphthyridin]-1-yl]benzonitrile	Ab	Int. 112 and tert-butyl (2R,4S)-4-((tert-butylidiphenyl)silyloxy)-2-formylpyrrolidine-1-carboxylate	Na(OAc) ₃ BH ₃ , DCM, rt, 16 h in the 1 st Step and TBAF and TFA in the 2 nd step	Prep. method followed by 10% NaHCO ₃ wash	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.87 - 7.82 (m, 3H), 7.79 (d, J = 7.2 Hz, 1H), 7.68 - 7.65 (m, 1H), 7.38 - 7.34 (m, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 4.17 (d, J = 15.2 Hz, 1H), 4.20 (d, J = 15.2 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.83 - 3.61 (m, 1H), 3.58 - 3.51 (m, 4H), 3.42 - 3.17 (m, 3H), 2.89 - 2.89 (m, 2H), 2.68 - 2.65 (m, 1H), 2.51 - 2.47 (m, 2H), 2.34 - 2.17 (m, 2H), 1.81 - 1.77 (m, 3H), 1.52 - 1.50 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H), 1.08 - 1.01 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H).	LCMS: 1.67 min, 586.3 [M+H] ⁺ , Method W	SFC: 1.29 min and 2.96 min, Column: I-CELLULOSE-J, Co-Solvent : 30%, 0.5% IPAm in MeOH Injection Volume : 15 µL, Flow : 5.0 mL/min, BPR Pressure : 102.0 kgf/cm ² , Temperature : 40 °C.
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Table 30 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermedia tes	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
189	1'-(2-chloro-4-fluorophenyl)-2-(2-ethoxyphenyl)-7-[(2R)-pyrrolidin-2-ylmethyl]spiro[6,8]-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ac	Int 121		Method E	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 1.8, 7.5 Hz, 1H), 7.41 - 7.36 (m, 1H), 7.29 - 7.26 (m, 1H), 7.23 (dd, J = 3.1, 8.6 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.08 - 7.05 (m, 1H), 7.05 - 7.02 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.03 - 3.95 (m, 1H), 3.93 (d, J = 15.3 Hz, 1H), 3.74 (d, J = 15.3 Hz, 1H), 3.36 - 3.32 (m, 1H), 3.30 - 3.21 (m, 3H), 3.08 - 3.01 (m, 2H), 3.01 - 2.89 (m, 2H), 2.89 - 2.79 (m, 2H), 2.21 (s, 3H), 2.16 - 2.04 (m, 2H), 2.04 - 1.98 (m, 1H), 1.93 (br dd, J = 1.8, 13.4 Hz, 1H), 1.75 - 1.60 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H).	Formate	LCMS: 2.32 min, 535.2 [M+H] ⁺ , Method O	SFC: 1.83 min, Column: Chiralpak IH-3, 100×4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: 0.2% Ammonia in MeOH; Injected Volume: 5.0 µL; Run time: 4 min.
207	(R)-5-chloro-2-(2'-(2-(ethoxy-d5)phenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl]benzonitrile	Ac	Int 135 and 5-chloro-2-fluorobenzonitrile	CS ₂ CO ₃ (2 eq), DMF, 85 °C, 6 h followed by TFA/DCM, rt, 3 h in 2 nd Step	Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 2.5, 8.9 Hz, 1H), 7.51 (dd, J = 1.6, 7.6 Hz, 1H), 7.41 - 7.36 (m, 1H), 7.23 (d, J = 8.9 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.04 (dt, J = 0.8, 7.5 Hz, 1H), 3.95 (br d, J = 15.3 Hz, 2H), 3.76 (s, 1H), 3.57 - 3.49 (m, 2H), 3.38 - 3.32 (m, 1H), 3.28 (br s, 1H), 3.25 - 3.13 (m, 2H), 3.07 - 3.02 (m, 1H), 2.95 - 2.90 (m, 1H), 2.90 - 2.80 (m, 2H), 2.38 - 2.20 (m, 3H), 2.18 - 2.02 (m, 3H), 1.98 (br d, J = 13.0 Hz, 1H), 1.75 (dd, J = 8.0, 13.0 Hz, 1H).	Formate	LCMS: 2.27 min, 547.2 [M+H] ⁺ , Method O	SFC: 1.31 min, Column: Chiralcel OD-3, 50×4.6mm I.D., 3µm; Co-Solvent: 50%; Co-Solvent Name: 0.2% Ammonia gas in MeOH; Injected Volume: 2.20 µL; Run time: 3.0 min.

214	(3S,5R)-5-((1-(2,4-dichlorophenyl)-2-(2-ethoxyphenyl)-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-7(8H)-yl)methyl)pyrrolidin-3-ol	Ac	Int. 140 and 2,4-dichloro-1-iodobenzene	Cs ₂ CO ₃ , tBuXPhos Pd G3, dioxane, 90 °C.	Method M	¹ H NMR (400 MHz, CD ₃ OD) δ 8.62 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.63 - 7.53 (m, 2H), 7.45 (d, J = 2.4 Hz, 1H), 7.34 - 7.28 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 4.60 (br s, 1H), 4.30 - 4.22 (m, 1H), 4.19 (q, J = 6.9 Hz, 2H), 4.11 - 4.01 (m, 2H), 3.41 (dd, J = 3.6, 12.2 Hz, 1H), 3.38 - 3.33 (m, 3H), 3.28 - 3.23 (m, 1H), 3.09 - 3.00 (m, 2H), 2.97 - 2.89 (m, 2H), 2.85 (br d, J = 12.4 Hz, 1H), 2.40 (dt, J = 4.3, 12.6 Hz, 1H), 2.35 - 2.22 (m, 2H), 2.06 (br d, J = 13.1 Hz, 1H), 1.99 (br d, J = 13.4 Hz, 1H), 1.86 (ddd, J = 4.1, 10.2, 13.8 Hz, 1H), 1.39 (t, J = 6.9 Hz, 3H)	TFA	LCMS: 2.40 min, 567.2 [M+H] ⁺ , Method L	SFC: 1.41 min, Column: Chiralcel OD-3, 50×4.6 mm, I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 7.50 μL; Run time: 3.0 min.
217	(R)-2-(2-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)-(trifluoromethoxy)benzonitrile	Ac	Int. 121 and 2-bromo-5-(trifluoromethoxy)benzonitrile	Cs ₂ CO ₃ , RuPhos Pd G4, dioxane, 100 °C, 12 h and formic acid in 2 nd step	Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.43 - 7.35 (m, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 4.03 - 3.92 (m, 1H), 3.97 (d, J = 15.4 Hz, 1H), 3.75 (d, J = 15.4 Hz, 1H), 3.57 (br d, J = 12.0 Hz, 2H), 3.36 - 3.32 (m, 1H), 3.29 - 3.16 (m, 3H), 3.10 - 3.02 (m, 1H), 2.93 (d, J = 11.9 Hz, 1H), 2.84 (d, J = 7.6 Hz, 2H), 2.40 - 2.28 (m, 2H), 2.28 - 2.20 (m, 1H), 2.17 - 2.02 (m, 3H), 1.99 (br d, J = 12.9 Hz, 1H), 1.81 - 1.68 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.27 min, 592.3 [M+H] ⁺ , Method O	SFC: 3.57 min, 97.35% Column: Chiralcel OD-3, 50×4.6 mm, I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: isopropamide [0.2% ammonia (7 M in MeOH)]; Injected Volume: 2.60 μL; Run time: 5.0 min.
218	(R)-5-(difluoromethoxy)-2-(2-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzonitrile	Ac	Int. 121 and 2-bromo-5-(difluoromethoxy)benzonitrile	Cs ₂ CO ₃ , BINAP, Pd ₂ (dba) ₃ , Toluene, 100 °C, 12 h in the 1 st Step and formic acid in 2 nd Step	Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.44 - 7.36 (m, 2H), 7.28 (d, J = 9.1 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 73.5 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 4.03 - 3.91 (m, 2H), 3.74 (d, J = 15.4 Hz, 1H), 3.54 - 3.45 (m, 2H), 3.37 - 3.32 (m, 1H), 3.29 - 3.25 (m, 1H), 3.24 - 3.13 (m, 2H), 3.09 - 3.01 (m, 1H), 2.97 - 2.89 (m, 1H), 2.89 - 2.79 (m, 2H), 2.40 - 2.19 (m, 3H), 2.17 - 1.94 (m, 4H), 1.80 - 1.68 (m, 1H), 1.35 (t, J = 6.9 Hz, 3H)	Formate	LCMS: 2.16 min, 574.3 [M+H] ⁺ , Method O	SFC: 1.53 min, 97.84% Column: Chiralpak IH-3, 100×4.6 mm I.D., 3 μm; Co-Solvent: 50%; Co-Solvent Name: MeOH [0.2% ammonia gas (7 M in MeOH)]; Injected Volume: 0.80 μL; Run time: 4.0 min.

Table 31 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermedia tes	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
206	(R)-1-(4-chloro-2- (methylsulfonyl)phenyl)- 2-(2-ethoxyphenyl)-7'- (pyrrolidin-2-ylmethyl)- 7',8'-dihydro-6'H- spiro[piperidine-4,5'- [1,7]naphthyridine]	Ad	Int 121		Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.57 - 8.53 (m, 1H), 8.00 - 7.95 (m, 2H), 7.75 - 7.72 (m, 1H), 7.71 (d, J = 3.3 Hz, 1H), 7.70 - 7.66 (m, 1H), 7.53 (dd, J = 1.7, 7.6 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.07 - 7.02 (m, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.97 - 3.89 (m, 2H), 3.75 (d, J = 15.4 Hz, 1H), 3.52 (s, 3H), 3.29 - 3.25 (m, 1H), 3.24 - 3.18 (m, 3H), 3.17 - 3.08 (m, 3H), 2.96 (d, J = 12.0 Hz, 1H), 2.86 - 2.79 (m, 2H), 2.37 - 2.27 (m, 2H), 2.25 - 2.18 (m, 1H), 2.11 - 2.02 (m, 2H), 2.02 - 1.92 (m, 2H), 1.77 - 1.68 (m, 1H), 1.36 (t, J = 6.9 Hz, 3H)	Formate	LCMS: 2.16 min, 595.2 [M+H] Method O	SFC Method: 1.09 min, Column: Chiralpak IH-3, 50x4.6 mm I.D., 3 μm, Co-Solvent: 50%; Co-Solvent Name: 0.2% Ammonia in MeOH; Injected Volume: 3.2 μL; Run Time: 3 min.

Table 32 –NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermedia tes	Conditions	Purific ation Method	¹ H NMR	Salt Form	LCMS data	Chiral Analysis
145	rac-3-amino-1- [(3'S,5S)-2-(2- ethoxypyridin-3-yl)-3'- ethyl-1'-[4-methoxy-3- (trifluoromethyl)pyridin -2-yl]spiro[6.8- dihydro-1,7- naphthyridine-5,4'- piperidine]-7- yl]propan-1-one	Ae	Int 79 and 2-chloro-4- methoxy- 3- (trifluorom ethyl)pyridi ne	K ₂ CO ₃ , DMSO, 80 °C, 12 h in the 1 st Step (SNAI) and formic acid in 2 nd step	Prep- HPLC Method L	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.40 (s, 1H), 8.34 - 8.27 (m, 2H), 8.23 (dd, J = 1.9, 4.8 Hz, 1H), 8.05 - 7.96 (m, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 4.9, 7.4 Hz, 1H), 6.91 - 6.82 (m, 1H), 4.88 - 4.81 (m, 1H), 4.74 - 4.64 (m, 2H), 4.45 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.63 (br d, J = 10.4 Hz, 2H), 3.48 - 3.42 (m, 2H), 3.11 (br d, J = 13.1 Hz, 1H), 2.99 - 2.86 (m, 3H), 2.79 - 2.60 (m, 2H), 2.34 - 2.24 (m, 1H), 1.84 - 1.56 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H), 1.08 - 0.95 (m, 2H), 0.82 (br t, J = 6.4 Hz, 3H)	Formate	LCMS: 2.38 min, 599.3 [M+H] ⁺ , Method Q	SFC: 1.01 min and 1.54 min, Column Name: (S, S)-WHELK-O1, 50x4.6 mm I.D., 3.5 μm, Co-Solvent: 60%; Co-Solvent Name: Ethyl Alcohol [0.2% ammonia (7 M in MeOH)]; Injected Volume: 7.50 μL; Run time: 6.0 min.

159	2-(2-ethoxy-3-pyridin-3-yl)-1'-[4-methoxy-3-(trifluoromethyl)pyridin-2-yl]-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ae	Int 91 and 2-chloro-4-methoxy-3-(trifluoromethyl)pyridine	DIEA, i-PrOH, 110 °C in 1 st Step (SNAr) and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.41 (s, 1H), 8.30 (d, J = 5.8 Hz, 1H), 8.22 - 8.16 (m, 2H), 7.93 - 7.86 (m, 1H), 7.85 - 7.77 (m, 1H), 7.11 (dd, J = 5.0, 7.4 Hz, 1H), 6.85 (d, J = 5.0 Hz, 1H), 4.42 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.81 - 3.69 (m, 2H), 3.50 (br s, 2H), 3.17 (br s, 2H), 3.00 (td, J = 7.1, 10.5 Hz, 2H), 2.90 (br d, J = 10.6 Hz, 2H), 2.84 - 2.80 (m, 1H), 2.67 - 2.61 (m, 1H), 2.56 (br dd, J = 5.4, 12.8 Hz, 1H), 2.01 (br t, J = 12.0 Hz, 2H), 1.91 (br dd, J = 5.1, 12.7 Hz, 1H), 1.84 - 1.70 (m, 4H), 1.50 - 1.41 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.17 min, 583.3 [M+H] ⁺ Method S'	SFC: 1.17 min, Column: Chiralpak IH-3, 50x4.6mm I.D., 3µm, Co-Solvent: 50%, MeOH [0.2% ammonia gas (7M in MeOH)], injected Volume: 7.5 µL, Run time: 3 min.
169	1'-(3,5-dichloro-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ae	Int 91 and 3,5-dichloro-2-fluoropyridine	DIEA, i-PrOH, 110 °C in 1 st Step (SNAr) and formic acid in 2 nd step		¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (s, 1H), 8.20 - 8.16 (m, 2H), 8.04 (dd, J = 2.0, 7.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.85 - 7.80 (m, 2H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 4.01 - 3.90 (m, 2H), 3.80 (br d, J = 1.8 Hz, 1H), 3.78 - 3.73 (m, 2H), 3.33 (br d, J = 4.1 Hz, 1H), 3.30 - 3.23 (m, 1H), 3.22 - 3.10 (m, 2H), 3.09 - 2.91 (m, 2H), 2.90 - 2.78 (m, 2H), 2.32 - 2.26 (m, 1H), 2.26 - 2.19 (m, 2H), 2.17 - 2.03 (m, 2H), 2.03 - 1.89 (m, 2H), 1.74 (qd, J = 8.0, 13.1 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.40 min, 553.2 [M+H] ⁺ Method O	SFC: 3.55 min, Column Name: Chiralcel OJ-3, 150x4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)], Injected Volume: 2.6 µL; Run time: 5 min.
174	3-chloro-4-[2-(2-ethoxy-3-pyridinyl)-7-[[2(R)-pyrrolidin-2-ylmethyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile	Ae	Int 91 and 3-chloro-4-fluorobenzonitrile	DIEA, i-PrOH, 110 °C in 1 st Step (SNAr) and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.05 (dd, J = 1.9, 7.5 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 1.9, 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.98 - 3.90 (m, 1H), 3.87 - 3.79 (m, 1H), 3.79 - 3.74 (m, 1H), 3.50 (br d, J = 11.6 Hz, 2H), 3.27 - 3.19 (m, 1H), 3.19 - 3.07 (m, 3H), 3.05 (d, J = 12.0 Hz, 1H), 2.92 (d, J = 12.0 Hz, 1H), 2.81 - 2.75 (m, 2H), 2.36 - 2.25 (m, 2H), 2.23 - 2.13 (m, 1H), 2.09 - 1.94 (m, 4H), 1.74 - 1.62 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H)	Formate	LCMS: 2.35 min, 543.2 [M+H] ⁺ Method O	SFC: 3.40 min, Column: Chiralpak OJ-3, 150x4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: MeOH [0.2% ammonia gas (7M in MeOH)], injected Volume: 3.20 µL; Run time: 5 min.

183	1'-(3-chloro-4-methoxy-2-pyridinyl)-2-(2-ethoxy-3-pyridinyl)-7-[(2R)-pyrrolidin-2-yl]methylspiro[6.8]-dihydro-1,7-naphthyridine-5,4'-piperidine]	Ae	Int 91 and 2,3-dichloro-4-methoxy-pyridine	DIEA, i-PrOH, 110 °C in 1 st Step (SNAR) and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.18 (dd, J = 1.8, 4.9 Hz, 1H), 8.10 (d, J = 5.8 Hz, 1H), 8.04 (dd, J = 1.8, 7.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 5.0, 7.4 Hz, 1H), 6.84 (d, J = 5.8 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 3.97 (s, 3H), 3.95 - 3.85 (m, 1H), 3.77 (d, J = 15.4 Hz, 1H), 3.67 (br d, J = 15.4 Hz, 2H), 3.28 - 3.21 (m, 2H), 3.13 (ddd, J = 7.6, 10.7, 12.5 Hz, 2H), 3.06 (br d, J = 12.1 Hz, 1H), 2.92 (br d, J = 11.9 Hz, 1H), 2.88 - 2.77 (m, 2H), 2.32 - 2.18 (m, 3H), 2.12 - 2.01 (m, 2H), 1.95 (br dd, J = 13.8, 19.3 Hz, 2H), 1.79 - 1.67 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.05 min, 549.2 [M+H] ⁺ , Method O	SFC: 1.29 min, Column: Chiralcel OJ-3, 150x4.6 mm I.D., 3 µm, Co-Solvent: 50%, Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 2.80 µL; Run time: 3.0 min.
184	5-chloro-2-[2-(2-ethoxy-3-pyridinyl)-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6.8]-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-piperidine-3-carbonitrile	Ae	Int 91 and 2,3-dichloro-4-methoxy-pyridine	DIEA, i-PrOH, 110 °C in 1 st Step (SNAR) and formic acid in 2 nd step	Prep-HPLC Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.48 (br s, 1H), 8.36 (d, J = 2.6 Hz, 1H), 8.18 (dd, J = 1.9, 4.9 Hz, 1H), 8.04 (dd, J = 1.8, 7.4 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.92 - 7.87 (m, 1H), 7.84 - 7.79 (m, 1H), 7.06 (dd, J = 5.0, 7.4 Hz, 1H), 4.44 (q, J = 7.0 Hz, 2H), 4.39 - 4.29 (m, 2H), 4.05 - 3.95 (m, 2H), 3.78 - 3.70 (m, 1H), 3.46 - 3.36 (m, 2H), 3.36 - 3.32 (m, 1H), 3.30 - 3.26 (m, 1H), 3.11 - 3.04 (m, 1H), 3.01 - 2.94 (m, 1H), 2.93 - 2.81 (m, 2H), 2.31 - 2.12 (m, 4H), 2.10 - 2.00 (m, 2H), 1.98 - 1.89 (m, 1H), 1.76 (qd, J = 8.0, 13.0 Hz, 1H), 1.37 (t, J = 7.0 Hz, 3H)	Formate	LCMS: 2.32 min, 544.2 [M+H] ⁺ , Method O	SFC: 3.693 min, Column: Chiralcel OJ-3, 150x4.6 mm I.D., 3 µm, Co-Solvent: 50%, Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume: 3.20 µL; Run time: 5.0 min.
208	5-chloro-2-[(3SR,4SR)-2-(2-ethoxyphenyl)-3-ethyl-7'-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl]-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl]nicotinonitrile	Ae	Int 139		Method M	¹ H NMR (400 MHz, CD ₃ OD) δ 8.40 - 8.36 (m, 1H), 8.20 - 8.11 (m, 1H), 8.06 - 8.03 (m, 1H), 7.86 - 7.81 (m, 1H), 7.60 - 7.54 (m, 1H), 7.50 - 7.43 (m, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.13 - 7.07 (m, 1H), 4.59 (br d, J = 3.5 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.38 - 4.29 (m, 1H), 4.29 - 4.18 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.08 (br d, J = 16.0 Hz, 1H), 3.79 (d, J = 16 Hz, 1H), 3.60 - 3.50 (m, 1H), 3.48 - 3.43 (m, 1H), 3.39 - 3.34 (m, 1H), 3.28 - 3.21 (m, 1H), 3.11 - 2.98 (m, 1H), 2.93 - 2.87 (m, 1H), 2.86 - 2.81 (m, 1H), 2.78 - 2.56 (m, 1H), 2.42 - 2.29 (m, 2H), 2.29 - 2.20 (m, 1H), 1.98 - 1.78 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.26 - 1.08 (m, 2H), 0.98 - 0.88 (m, 3H)	TFA	LCMS: 2.34 min, 587.3 [M+H] ⁺ , Method S'	SFC: 1.79 min, 2.12 min, Column: Chiralpak IH-3, 100x4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: (0.2% ammonia gas in MeOH) in MeOH; Injected Volume: 2.20 µL; Run time: 4.0 min.
210	5-chloro-2-(2-(2-ethoxyphenyl)-7'-[(2R,4S)-4-hydroxypyrrolidin-2-yl]methyl)-7',8'-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl]nicotinonitrile	Ae	Int 140 and 2,5-dichloro-4-methoxy-pyridine	DIEA, i-PrOH, 110 °C, 12 h in the 1 st Step and TFA/DCM in 2 nd Step	Method M	¹ H NMR (400 MHz, CD ₃ OD) δ 8.37 (d, J = 2.6 Hz, 1H), 8.24 - 8.15 (m, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.83 (br d, J = 8.5 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.51 - 7.44 (m, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 4.62 - 4.57 (m, 1H), 4.41 - 4.31 (m, 2H), 4.31 - 4.20 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.06 - 3.97 (m, 1H), 3.97 - 3.87 (m, 1H), 3.45 - 3.40 (m, 2H), 3.38 (br d, J = 3.7 Hz, 2H), 3.29 - 3.22 (m, 2H), 2.93 - 2.84 (m, 3H), 2.32 - 2.15 (m, 3H), 2.07 - 1.94 (m, 2H), 1.85 (ddd, J = 4.1, 10.0, 13.8 Hz, 1H), 1.36 (t, J = 7.0 Hz, 3H)	TFA	LCMS: 2.23 min, 559.2 [M+H] ⁺ , Method S'	SFC: 1.25 min, 1.50 min, Column: Chiralpak AD-3, 50x4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: MeOH [0.2% ammonia (7 M in MeOH)]; Injected Volume:

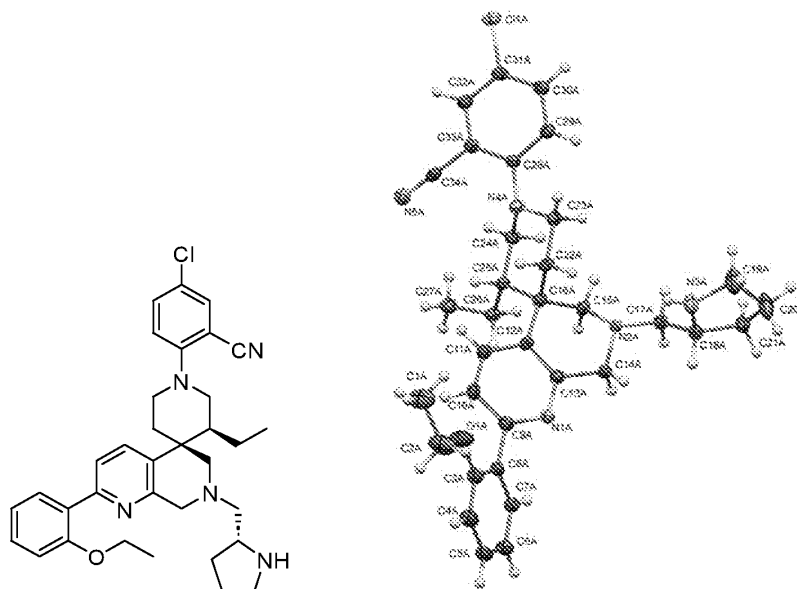
212	5-chloro-2-((3SR,4SR)-2-(2-(ethoxy-d5phenyl)-3-ethyl-7-((R)-pyrrolidin-2-yl)methyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)nicotinonitrile	Ae	Int 141 and 2,5-dichloronicotinonitrile	DIEA, t-PrOH, 110 °C, 12 h in the 1 st Step and TFA/DCM in 2 nd Step		Method L	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 8.37 (d, J = 2.6 Hz, 1H), 8.03 (t, J = 2.7 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 1.7, 7.5 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 4.59 - 4.44 (m, 1H), 4.39 - 4.25 (m, 1H), 4.09 (d, J = 15.3 Hz, 1H), 3.97 - 3.86 (m, 1H), 3.71 (d, J = 15.3 Hz, 1H), 3.50 - 3.43 (m, 1H), 3.42 - 3.34 (m, 1H), 3.30 - 3.18 (m, 2H), 3.10 - 2.96 (m, 1H), 2.83 - 2.79 (m, 1H), 2.76 - 2.67 (m, 1H), 2.58 (d, J = 12.3 Hz, 1H), 2.38 - 2.16 (m, 3H), 2.13 - 1.99 (m, 2H), 1.95 - 1.82 (m, 1H), 1.77 - 1.65 (m, 1H), 1.24 - 1.09 (m, 2H), 0.95 - 0.88 (m, 3H).	Formate	LCMS: 2.36 min, 576.1 [M+H] ⁺ , Method S ⁺	SFC: 1.35 min, 1.885 min, Column: Chiralpak AD-3, 50×4.6mm I.D., 3µm, Co-Solvent: 50%, Co-Solvent Name: isopropamide [(0.2% ammonia gas in MeOH) in MeOH], injected Volume: 6.00 µL, Run time: 3.0 min.
212-1	Enant12-5-chloro-2-[(3S,5S)-3'-ethyl-2-[2-(1,1,2,2-pentadeuterioethoxy)phenyl]-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-ylpyridine-3-carbonitrile		Ex. 212 SFC purification	SFC separation	chiral		¹ H NMR (400 MHz, CD ₃ OD) δ 8.36 (d, J = 2.6 Hz, 1H), 8.01 (d, J = 2.6 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.55 (dd, J = 1.7, 7.6 Hz, 1H), 7.37 (ddd, J = 1.7, 7.4, 8.3 Hz, 1H), 7.08 (dd, J = 0.8, 8.3 Hz, 1H), 7.04 (dt, J = 0.8, 7.5 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.30 (td, J = 2.0, 13.9 Hz, 1H), 3.89 (d, J = 15.6 Hz, 1H), 3.65 (d, J = 15.6 Hz, 1H), 3.57 - 3.45 (m, 1H), 3.41 - 3.33 (m, 1H), 3.29 - 3.23 (m, 1H), 3.10 - 2.98 (m, 2H), 2.92 (ddd, J = 6.4, 7.6, 10.4 Hz, 1H), 2.69 - 2.51 (m, 3H), 2.34 - 2.21 (m, 2H), 2.07 - 1.97 (m, 1H), 1.94 - 1.78 (m, 3H), 1.59 - 1.47 (m, 1H), 1.23 - 1.13 (m, 2H), 0.93 - 0.87 (m, 3H)		LCMS: 2.24 min, 576.3 [M+H] ⁺ , Method O	SFC: 1.39 min, 99.20% purity, Column Name: Chiralpak AD-3, 50×4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: isopropamide [(0.2% ammonia gas) 7M in MeOH], injected Volume: 3.00 µL, Run time: 3 min.
212-2	Enant12-5-chloro-2-[(3S,5S)-3'-ethyl-2-[2-(1,1,2,2-pentadeuterioethoxy)phenyl]-7-[(2R)-pyrrolidin-2-yl]methyl]spiro[6.8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-ylpyridine-3-carbonitrile		Ex. 212 SFC purification	SFC separation	chiral		¹ H NMR (400 MHz, CD ₃ OD) δ 8.36 (d, J = 2.6 Hz, 1H), 8.01 (d, J = 2.6 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 1.7, 7.6 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.04 (dt, J = 0.9, 7.5 Hz, 1H), 4.54 - 4.45 (m, 1H), 4.33 - 4.23 (m, 1H), 4.00 (d, J = 15.3 Hz, 1H), 3.54 - 3.46 (m, 1H), 3.51 (d, J = 15.3 Hz, 1H), 3.40 - 3.30 (m, 1H), 3.25 - 3.20 (m, 1H), 3.09 - 2.98 (m, 2H), 2.95 - 2.90 (m, 1H), 2.71 - 2.55 (m, 3H), 2.37 - 2.25 (m, 2H), 2.06 - 1.96 (m, 1H), 1.93 - 1.79 (m, 3H), 1.59 - 1.47 (m, 1H), 1.22 - 1.12 (m, 2H), 0.93 - 0.88 (m, 3H)		LCMS: 2.27 min, 576.3 [M+H] ⁺ , Method O	SFC: 1.93 min, 0.80% purity, Column Name: Chiralpak AD-3, 50×4.6 mm I.D., 3 µm, Co-Solvent: 50%, Co-Solvent Name: isopropamide [(0.2% ammonia gas) 7M in MeOH], injected Volume: 3.00 µL,

[illegible]

Table 33 – NMR and LCMS properties and the methods used to prepare and purify compounds represented by Examples

Ex. No.	Name	Route	Intermediate	Conditions	Purification Method	¹ H NMR	Salt Form	LCMS data
216	(R)-5-chloro-2-(2'-(2-ethoxyphenyl)-7-(pyrrolidin-2-ylmethyl)-7,8-dihydro-6H-spiro[piperidine-4,5'-[1,7]naphthyridin]-1-yl)benzoic acid	Af			Method AP	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.83 – 7.77 (m, 2H), 7.72 – 7.70 (m, 1H), 7.44 (bs, 1H), 7.38 – 7.34 (m, 3H), 7.12 – 7.10 (d, J = 8.0 Hz, 1H), 7.05 – 7.01 (t, J = 8.0 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.89 (s, 1H), 3.85 (s, 1H), 3.73 – 3.65 (m, 1H), 3.33– 3.15 (m, 6H), 2.88 – 2.79 (m, 3H), 2.70 – 2.67 (m, 1H), 2.16 – 2.06 (m, 3H), 1.92 – 1.80 (m, 4H), 1.59 – 1.52 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), exchangeable proton was not observed.	Formate	LCMS: 1.48 min, 561.2 [M+H] ⁺ , Method G

X-ray crystallographic analysis of 5-chloro-2-[(3'S,5S)-2-(2-ethoxyphenyl)-3'-ethyl-7-[[[(2R)-pyrrolidin-2-yl]methyl]spiro[6,8-dihydro-1,7-naphthyridine-5,4'-piperidine]-1'-yl]benzonitrile (Example 181-1)



- 5 **Crystal Data:** Empirical formula $3(C_{34}H_{40}ClN_5O)$, H_2O , $0.4(O)$ Formula weight 1734.89 Temperature 100(2) K Wavelength 0.71073 Å Crystal system Monoclinic Space group P21 Unit cell dimensions $a = 11.2353(9)$ Å $a = 90^\circ$. $b = 33.454(3)$ Å $b = 103.094(4)^\circ$. $c = 12.4819(10)$ Å $\beta = 90^\circ$. Volume 4569.6(6) Å³ Z 2 Density (calculated) 1.261 Mg/m³ Absorption coefficient 0.163 mm⁻¹ F (000) 1850 Crystal size 0.200 x 0.160 x 0.100 mm³ q range for data collection 1.861 to 30.891°. Index ranges $-15 \leq h \leq 15$, $-46 \leq k \leq 47$, $-17 \leq l \leq 16$ Reflections collected 87455 Independent reflections 25243 [R(int) = 0.0891] Completeness to $q = 25.242^\circ$ 99.9 % Absorption correction Semi-empirical from equivalents Max. and min. transmission 0.7461 and 0.6603. Refinement method Full-matrix least-squares on F² Data / restraints / parameters 25243 / 201 / 1203 Goodness-of-fit on F² 0.967 Final R indices [I > 2σ(I)] R1 = 0.0548, wR2 = 0.1056 R indices (all data) R1 = 0.1665, wR2 = 0.1377 Absolute structure parameter 0.01(2) Largest diff. peak and hole 0.401 and -0.358 e.Å⁻³ Measurement Bruker D8 QUEST PHOTON-III Detector Software Used SHELXTL-PLUS.

- Crystal growth:** Crystallization by slow evaporation of the solvent was adopted for growing crystals suitable for single-crystal X-ray diffraction studies. Crystals were obtained from Methyl tert-Butyl Ether (MTBE) solvent. About 20 mg of the compound (B.No. OMA-SYN-C37s-E1-R-004) was dissolved in Methyl tert-Butyl Ether (3ml) solvent under hot conditions and the solution was filtered into a clean beaker and kept for crystallization at room temperature. Crystals were obtained on the walls of the beaker after 10 days.

Refinement: X-ray data was collected at low temperature on a Bruker D8 QUEST instrument with an I μ S Mo microsource ($\lambda = 0.7107$ Å) and a PHOTON-III detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs (Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS, Inc., Madison, Wisconsin, USA). The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL (Sheldrick G. M. (2015). Acta Crystallogr C71: 3-8) program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. Atom C1 of molecule A was disordered over two positions and its site occupational factors were refined to 0.6(5) and 0.4(5) respectively. The atoms C17/C18/C19/C20/C21/N3 of molecule B were disordered over two positions and their site occupational factors were refined to 0.755(6) and 0.245(6) respectively. The N-H and O-H atoms were located in the difference Fourier map and their positions and isotropic displacement parameters were refined. Hydrogen atoms could not be located on the partial occupy water O2W. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(C)$ for other H atoms]. The absolute configuration has confirmed by unambiguous refinement of the absolute structure parameter (Flack, H. D. & Bernardinelli, G. (2000). J. Appl. Cryst. 33, 1143–1148).

BIOLOGICAL ACTIVITY

Terbium labelling and preparation of SNAP-tagged MC2 membranes

Cells were labelled with 100 nM of SNAP-Lumi4-Tb and incubated for 1 h at 37 °C under 5% CO₂ prior to harvesting, and pelleting by centrifugation at 3 min at 1200 rpm. Cell pellets were homogenized using an FastPrep-24 5G homogeniser (MP Biomedicals) and subsequently centrifuged and resuspended twice at 22,000×g at 4 °C (Eppendorf Centrifuge) for 30 min. The final pellet was resuspended in 10 mM HEPES and 0.1 mM EDTA, pH 7.4, at a concentration of 5–10 mg ml⁻¹ and stored at -20°C for later use.

Fluorescent Ligand Binding Assays

All fluorescent ligand binding experiments were performed with a Cy5-labelled small molecule MC2 antagonist in 384-well Optiplate plates in 1x Tag-lite buffer (PerkinElmer), with 2% DMSO, 0.04% pluronic acid and 100 µg/ml saponin. In all cases, non-specific binding was determined in the presence of 1 µM unlabelled MC2 antagonist. Signal detection was performed on a Pherastar FSX (BMG Labtech, Germany) using standard HTRF settings and

the HTRF ratios were calculated by dividing the acceptor signal (665nm) by the donor signal (620nm), and multiplying the value by 10,000.

TR-FRET Competitive Equilibrium Binding Assay

5 To determine the equilibrium dissociation constant (K_i) of competing test compounds, MC2 membranes (2µg per well) were incubated with a range of concentrations of test compounds in the presence of 100nM fluorescent tracer. HTRF ratios were obtained after overnight incubation at 25°C to ensure equilibrium had been reached.

10 **TR-FRET Competitive Binding Kinetic Assay**

To determine the association (k_{on}) and dissociation (k_{off}) rates of unlabelled compounds, a competitive kinetic binding assay was performed which involved the simultaneous addition of 100nM fluorescent tracer and increasing concentrations of competing ligand to MC2 membranes (2µg per well). The degree of bound fluorescent tracer at MC2 was determined at multiple timepoints by HTRF.

In parallel, the association (k_{on}) and dissociation (k_{off}) rates for the fluorescent tracer were determined through incubation of increasing concentrations of fluorescent tracer with MC2 membranes in the absence and presence of 1µM unlabelled MC2 antagonist. The degree of bound fluorescent tracer was calculated at multiple timepoints by HTRF detection and association kinetic curves were generated. The resulting data were globally fitted to the association kinetic model (Prism 8.0, GraphPad, San Diego, USA) to derive a best-fit estimate for k_{on} and k_{off} as described under data analysis. From these data an estimate for the equilibrium dissociation constant (K_d) could be calculated.

25 Competition kinetic data and fluorescent tracer kinetic parameters were fit globally to the equation first described by Motulsky and Mahan (*Mol. Pharmacol.*, 1984, 25, 1-9) to determine unlabelled compound k_{on} and k_{off} .

30 **EXAMPLE A**

pKi: Group A >9, Group B 7.5 to 9, Group C 6 to 7.5

Koff: Group A <0.02, Group B 0.02 to 0.07, Group C >0.07

Example	pKi	Koff (min-1)	pKi assay
1	C	C	pKd
2	C	B	pKd
3	C	B	pKd
4	C		pIC50

Example	pKi	Koff (min-1)	pKi assay
99-1	B		pKi_960
99-2	A	C	pKi_960
101-1	B	C	pKi_960
101-2	A	C	pKi_960

5	C	B	pKd
6	B	C	pKi_120
7	B	C	pKi_120
8	B	C	pKi_120
9	C		pKi_120
10	C	B	pKi_960
11	C		pKi_960
12	C		pKi_960
13	C		pKi_960
14	C		pKi_960
15	B	B	pKi_960
15-1	B	B	pKi_960
15-2	A	B	pKi_960
16	C		pKi_960
17	B	C	pKi_960
18	B	B	pKi_960
18-1	B	A	pKi_960
18-2	B	B	pKi_960
19	B	C	pKi_960
20	B	C	pKi_960
21	C	A	pKi_960
22	C		pKi_960
23	C	C	pKi_960
23-1	C		pKi_960
23-2	C		pKi_960
24	C		pKi_960
25	C	B	pKi_960
26	C		pKi_960
27	C		pKi_960
28	B	C	pKi_960
29	C		pKi_960
30	B	C	pKi_960
31	C		pKi_960
31-1	C	C	pKi_960
31-2	C		pKi_960
32	C	B	pKi_960
33	C		pKi_960
33-1	C		pKi_960
33-2	C		pKi_960
34	C		pKi_960
35	B	B	pKi_960
36	B	A	pKi_960
37	C		pKi_960
38	B	B	pKi_960
39	B	B	pKi_960
40	C		pKi_960

105	A		pKi_960
106	A	B	pKi_960
107	A		pKi_960
108	A		pKi_960
109	A		pKi_960
110	A	C	pKi_960
111	A	B	pKi_960
112	B	B	pKi_960
113	A	A	pKi_960
114	A	B	pKi_960
115	A	A	pKi_960
116	A	B	pKi_960
117	C	B	pKi_960
118	A	B	pKi_960
119	B	B	pKi_960
120	B	B	pKi_960
121	A	B	pKi_960
122	B	A	pKi_960
123	A	A	pKi_960
124	A	B	pKi_960
125	A	A	pKi_960
126	A	A	pKi_960
127	A	B	pKi_960
128	B	B	pKi_960
129	B	B	pKi_960
129-1	A	A	pKi_960
130	B	B	pKi_960
131	A	B	pKi_960
132	A	A	pKi_960
133	A	B	pKi_960
134	A	B	pKi_960
135	A	A	pKi_960
136	B	B	pKi_960
137	B	B	pKi_960
138	B	B	pKi_960
139	B	B	pKi_960
140	A	A	pKi_960
141	B	B	pKi_960
142	A	B	pKi_960
143	A	B	pKi_960
144	A	B	pKi_960
145	B	B	pKi_960
146	B	C	pKi_960
147	B	B	pKi_960
148	B	A	pKi_960
149	A	A	pKi_960

41	A		pKi_960
42	B	A	pKi_960
43	B	B	pKi_960
44	B	B	pKi_960
45	B	B	pKi_960
46-1	B		pKi_960
46-2	B		pKi_960
46	B	B	pKi_960
47	C	C	pKi_960
48	B	B	pKi_960
49	A	B	pKi_960
50	B	B	pKi_960
51-1	C		pKi_960
51-2	B		pKi_960
51	B	B	pKi_960
52	B	B	pKi_960
53	A	B	pKi_960
54	A	B	pKi_960
55	B	B	pKi_960
56	B	B	pKi_960
57	B		pKi_960
58	B		pKi_960
59	B	B	pKi_960
60	B	B	pKi_960
61	B		pKi_960
62	B	B	pKi_960
63	B		pKi_960
64	B	B	pKi_960
65	B		pKi_960
66	B	B	pKi_960
67	B	B	pKi_960
68	A		pKi_960
69	B	B	pKi_960
70	A	A	pKi_960
71	B		pKi_960
72	A	A	pKi_960
73	C		pKi_960
74	B		pKi_960
75	B	B	pKi_960
76	B		pKi_960
77	B	B	pKi_960
78	B	B	pKi_960
79	B		pKi_960
80	B		pKi_960
81	B		pKi_960
82	B	C	pKi_960

150	A	A	pKi_960
151	A	A	pKd
152	A	A	pKi_960
153	B	A	pKi_960
154	A	A	pKd
155	A	A	pKi_960
156	A	A	pKi_960
157	A	A	pKi_960
158	A	A	pKd
159	A	B	pKi_960
160	A	A	pKi_960
161	A		pKi_960
162	A	A	pKi_960
163	B	A	pKi_960
164	A	A	pKi_960
165	A	A	pKi_960
166	A	A	pKi_960
167	A	A	pKi_960
168	A	A	pKi_960
169	A	A	pKi_960
170	A	B	pKi_960
171	A	A	pKi_960
172	A	A	pKi_960
173	A	A	pKi_960
174	A	A	pKd
175	A	B	pKi_960
176	A	A	pKi_960
177	A	A	pKi_960
178	A	A	pKi_960
179	A	A	pKi_960
180	A	A	pKi_960
181	A	A	pKi_960
181-1	B	A	pKi_960
181-2	A	A	pKi_960
182	A	A	pKi_960
183	A	A	pKi_960
184	A	A	pKi_960
185	B	A	pKi_960
186	B	B	pKi_960
187	A	A	pKi_960
188	A	A	pKi_960
189	A	A	pKi_960
190	A	A	pKi_960
191	A	A	pKi_960
192	A	A	pKi_960
193	A	A	pKi_960

83	C	B	pKi_960
84	C		pKi_960
85	B	B	pKi_960
86	B	B	pKi_960
87	A	A	pKi_960
88	B		pKi_960
89	B	B	pKi_960
88-1	B	B	pKi_960
88-2	B		pKi_960
90	B	B	pKi_960
91	A	B	pKi_960
39-1	B	B	pKi_960
39-2	B		pKi_960
49-1	B	B	pKi_960
49-2	A	B	pKi_960
92	B	C	pKi_960
93	B	C	pKi_960
94	B	B	pKi_960
95	A	A	pKi_960
96	A	C	pKi_960
74-1	B		pKi_960
74-2	B	B	pKi_960
97	B	B	pKi_960
98	B		pKi_960
99	B	B	pKi_960
100	B	C	pKi_960
101	A	C	pKi_960
102-1	C	B	pKi_960
102-2	A	B	pKi_960
103	A	A	pKi_960
104	A	A	pKi_960

194	A	B	pKi_960
195	A	A	pKi_960
196	A	A	pKi_960
197	A	A	pKi_960
198	A	A	pKi_960
199	A	B	pKi_960
200	A	A	pKi_960
200-1	C	B	pKi_960
200-2	A	A	pKi_960
201	A	A	pKi_960
201-1	B	B	pKi_960
201-2	A	A	pKi_960
202	A	A	pKi_960
203	A	A	pKi_960
204	A	A	pKi_960
205	A	A	pKi_960
206	A	A	pKi_960
207	A	A	pKi_960
208	A	A	pKi_960
209	A	A	pKi_960
210	A	A	pKi_960
211	A	A	pKi_960
212	A	A	pKi_960
212-1	A	A	pKi_960
212-2	B	B	pKi_960
213	A	A	pKi_960
214	A	A	pKi_960
215	B	B	pKi_960
216	B	A	pKi_960
217	A	A	pKi_960
218	A	A	pKi_960

cAMP accumulation assay

Chinese hamster ovary (CHO) cells, stably expressing human or rat MC2 with MRAP, were maintained in DMEM/F12 cell culture medium supplemented with 10% fetal bovine serum and 1% l-glutamine. On the day of experimentation, cells were plated at 5000 cells/well in white low-volume 384-well plates in assay buffer (Hank's balanced salt solution (HBSS) containing 5 mM HEPES (pH 7.4) with 0.1% w/v BSA and 500 mM 3-isobutyl-1-methylxanthine) before being incubated with a range of concentrations of MC2 compounds for 2h at 37C, 5% CO₂. After 2h, increasing concentrations of ACTH1-24 were added to the cells for a set duration, before lysis and cAMP detection using the homogeneous time resolved fluorescence (HTRF) cAMP Gs HiRange kit (CisBio) according to the manufacturer's instructions. Fluorescence resonance energy transfer (FRET) levels were detected on a PHERAstar plate reader (BMG),

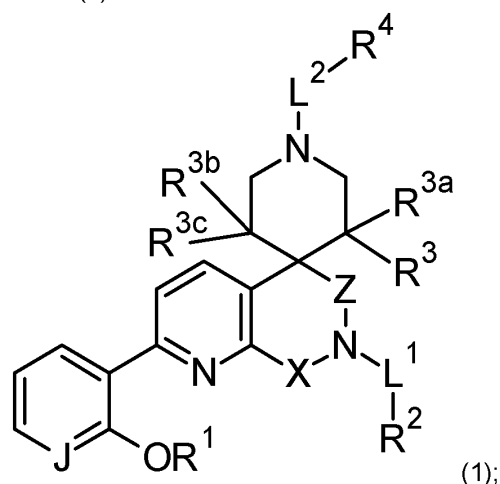
and data interpolated from a cAMP standard curve, and analysed using GraphPad Prism 8 (GraphPad). Results for the compounds Example 113, Example 134 and Example 135 are shown in Figure 1.

5 **Brief Description of the Figures**

Figure 1: Inhibition of ACTH1-24-mediated cAMP responses at human MC2 by the compounds Example 113, Example 134 and Example 135. MC2-expressing cells were incubated with compounds for 2h, before stimulation with ACTH1-24 for 15min, followed by lysis and cAMP detection. Slower dissociating compounds with lower K_{off} showed a greater
10 degree of insurmountability. Data represents n=1, in duplicates.

CLAIMS

1. A compound of formula (1):



or a salt thereof, wherein;

J is N or CH;

X is -CO-, -CH₂- or -CH₂CH₂-;

Z is a bond, -CH₂- or -CO-;

L¹ is $-(CH_2)_n-$, $-(CH_2)_nCONH-$, $-(CH_2)_nCOO-$, $-CO(CH_2)_nNH-$ or $-CO(CH_2)_n-$, where n is 0-5;

R¹ is C₁₋₄alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms:

R² is H, CO₂H, OH, NR^{2a}R^{2b}, CONR^{2a}R^{2b}, SO₂NR^{2a}R^{2b}, a 3-6 membered carbocyclic or heterocyclic ring which is optionally substituted with R¹⁰, R¹¹ and R¹², or a 7-10 membered bicyclic or heterobicyclic ring system which is optionally substituted with R¹⁰, R¹¹ and R¹².

R^{2a} and R^{2b} are independently H or C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms;

R³ is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R³ is joined to R^{3a} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

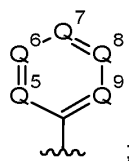
R^{3a} is H or is joined to R³ to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3b} is H, C₁₋₃alkyl optionally substituted with 1-3 fluorine atoms, C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms or CH₂C₃₋₄cycloalkyl optionally substituted with 1-3 fluorine atoms; or R^{3b} is joined to R^{3c} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms;

R^{3c} is H or is joined to R^{3b} to form a cyclopropyl or cyclobutyl ring either of which may be optionally substituted with 1-3 fluorine atoms:

wherein one or both of R^3 and R^{3b} is H;

L^2 is a bond or $-CO-$ and R^4 is a group:



wherein Q^5 is CR^5 or N; Q^6 is CR^6 or N; Q^7 is CR^7 or N; Q^8 is CR^8 or N; and Q^9 is CR^9 or N; where one, two or none of Q^5 , Q^6 , Q^7 , Q^8 and Q^9 is N;

or L^2 is $-CO-$ and R^4 is $-(CH_2)_qNH_2$, where q is 0-3;

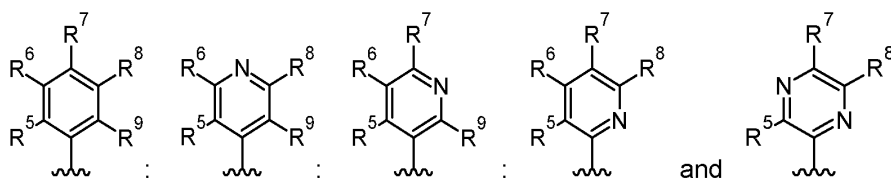
R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from H, halo, CN, $NR^{15}R^{16}$, C_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OC_{1-3} alkyl optionally substituted with 1-3 fluorine atoms, OCH_2 cyclopropyl optionally substituted with 1-3 fluorine atoms, OCH_2CN , CO_2H and SO_2Me ;

R^{10} , R^{11} and R^{12} are independently selected from H, OH, oxo, halo, C_{1-3} alkyl optionally substituted with OH or 1-3 fluorine atoms, SO_2NH_2 , OSO_2OH , OSO_2F , $B(OH)_2$, Bpin, $-(CH_2)_gNR^{13}R^{14}$, $-CH_2(CH_2)_g(OCH_2CH_2O)_yR^{13}$, $-(CH_2)_gCO_2R^{13}$ and $-(CH_2)_gCONR^{13}R^{14}$, where g is 0-3 and y is 1-3;

R^{13} and R^{14} are independently H or methyl; and

R^{15} and R^{16} are independently H or C_{1-3} alkyl.

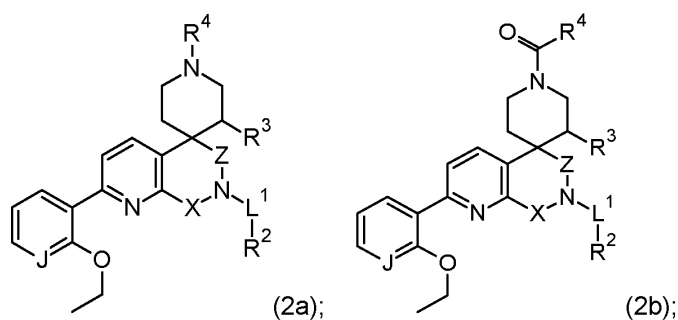
2. The compound according to claim 1, wherein R^4 is a group selected from:



3. The compound according to claim 1 or claim 2, wherein L^2 is a bond.

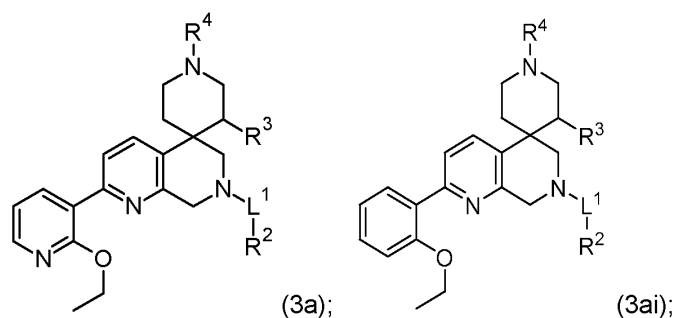
4. The compound according to any one of claims 1 to 3, wherein R^1 is ethyl or perdeuteroethyl.

5. The compound according to claim 1 or claim 2, which is a compound of Formula (2a) or (2b):



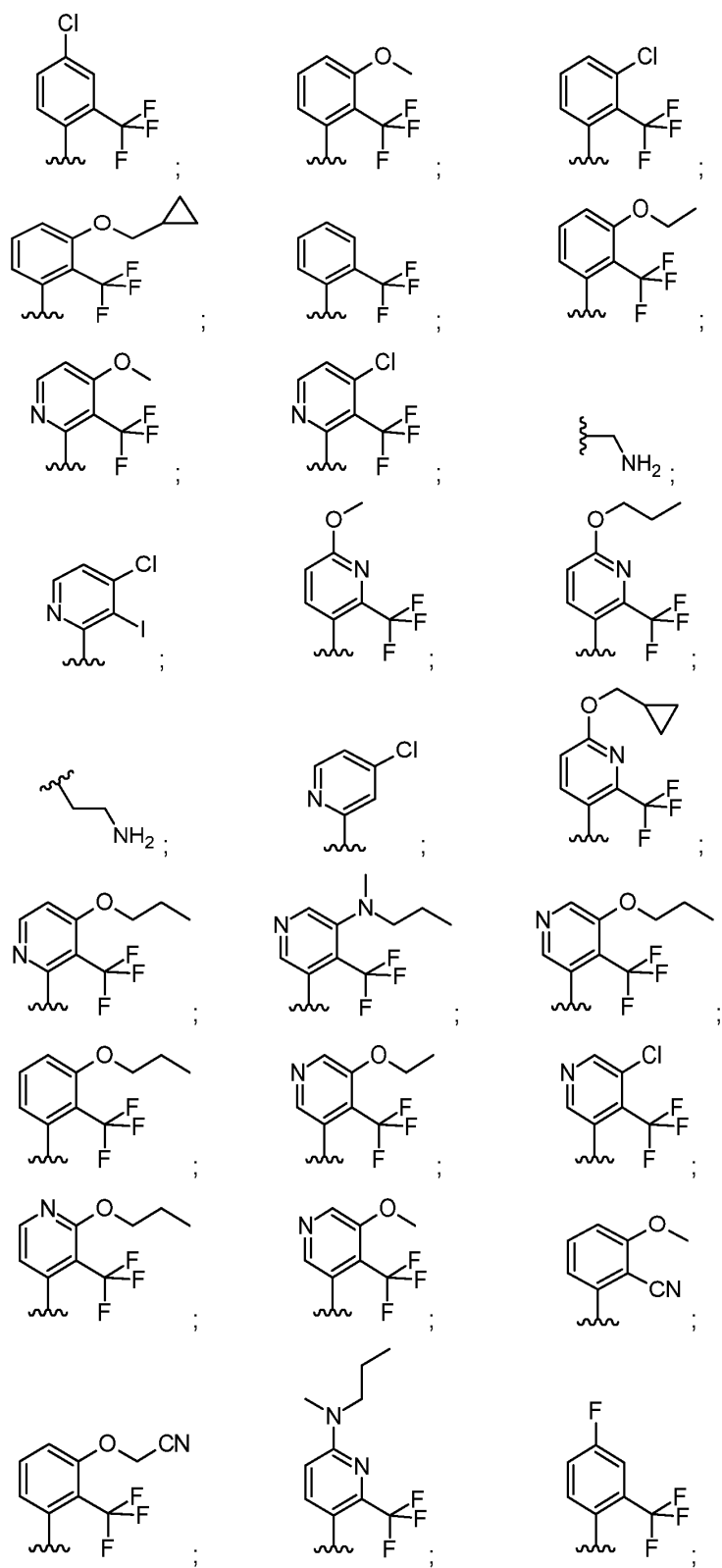
or a salt thereof.

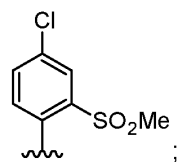
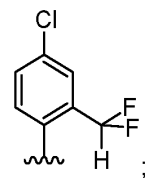
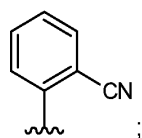
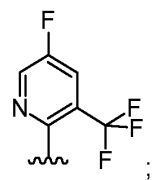
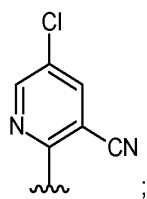
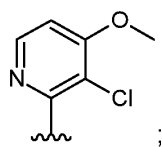
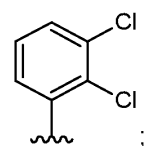
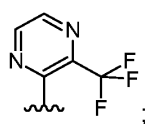
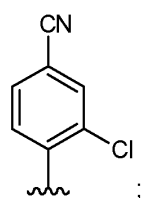
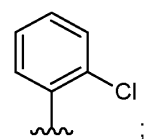
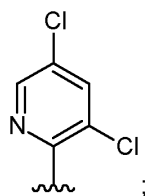
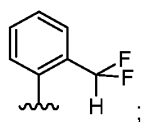
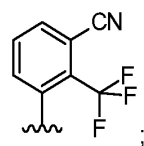
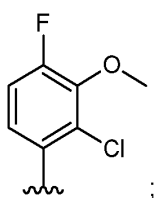
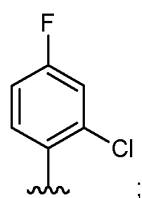
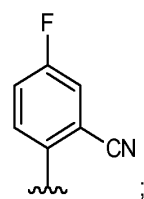
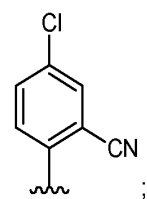
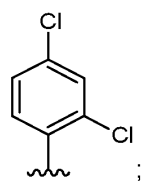
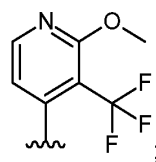
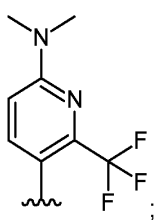
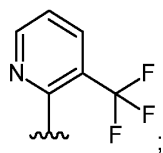
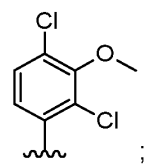
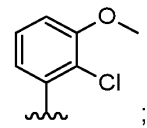
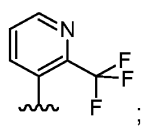
6. The compound according to any one of claims 1 to 5, wherein J is N.
7. The compound according to any one of claims 1 to 5, wherein J is CH.
8. The compound according to claim 1 or claim 2, which is a compound of Formula (3a) or (3ai):

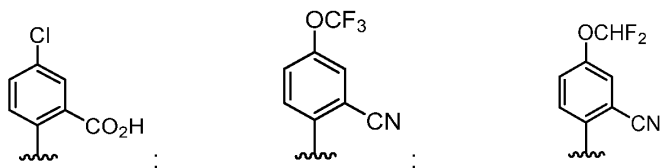


or a salt thereof.

9. The compound according to any one of claims 1 to 8, wherein R³ is H, methyl or ethyl.
10. The compound according to any one of claims 1 to 9, wherein R³ is ethyl.
11. The compound according to any one of claims 1 to 10, wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from H, Cl, F, I, CN, CF₃, CF₂H, -OMe, -OEt, -OⁱPr, -N(CH₃)(CH₂CH₂CH₃), -N(CH₃)₂, -OCH₂CN, -OCH₂cyclopropyl, -CO₂H and -SO₂Me.
12. The compound according to any one of claims 1 to 11, wherein R⁴ is selected from:

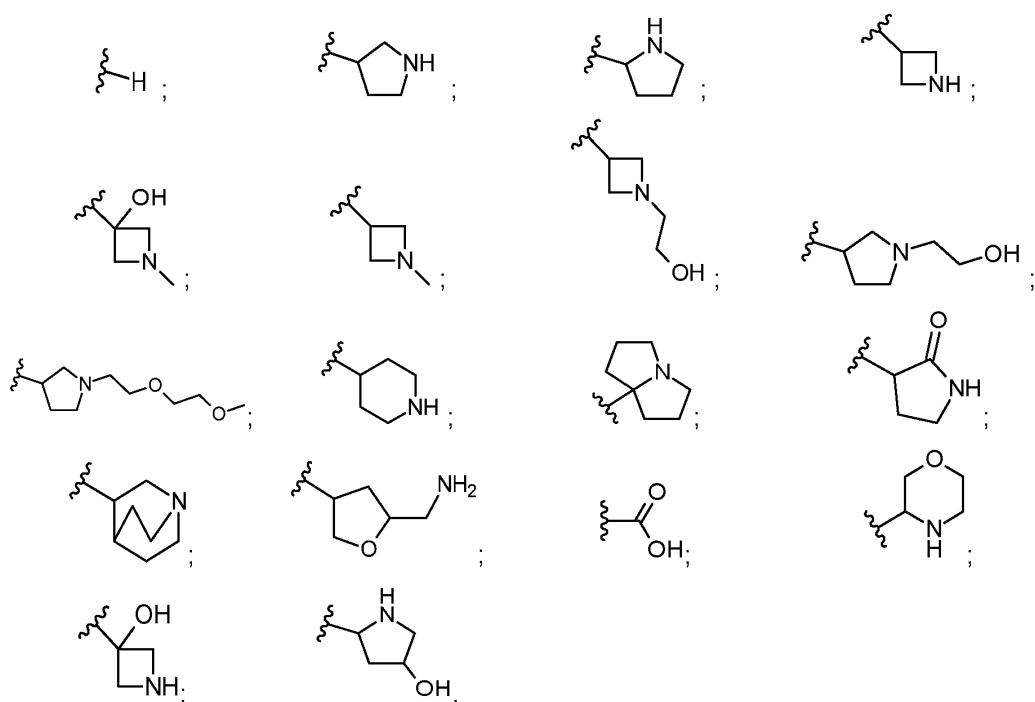






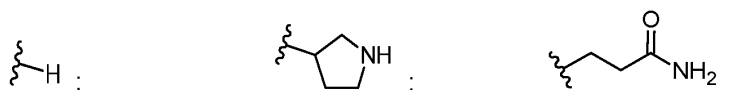
13. The compound according to any one of claims 1 to 12, wherein L^1 is a bond, - CH_2CH_2CONH- , - $COO-$, - CH_2CH_2COO- , - CH_2CH_2CO- , - $COCH_2NH-$, - $COCH_2CH_2NH-$, - $CO-$, - CH_2CH_2- or - CH_2- .

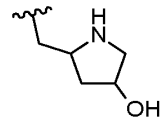
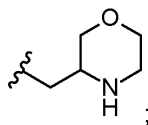
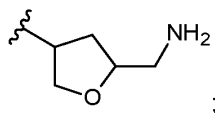
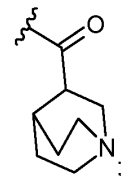
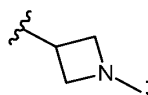
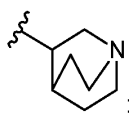
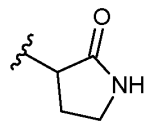
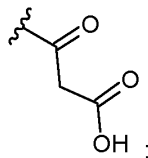
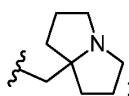
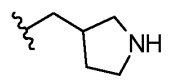
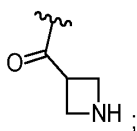
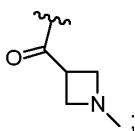
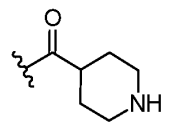
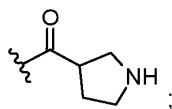
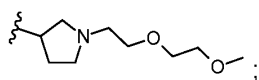
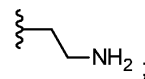
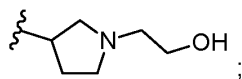
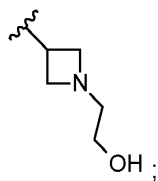
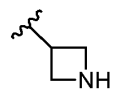
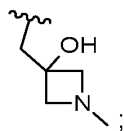
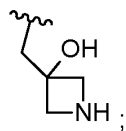
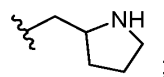
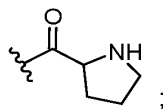
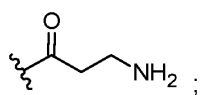
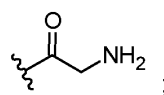
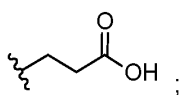
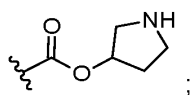
14. The compound according to any one of claims 1 to 13, wherein R^2 is selected from:



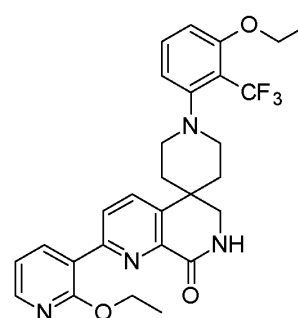
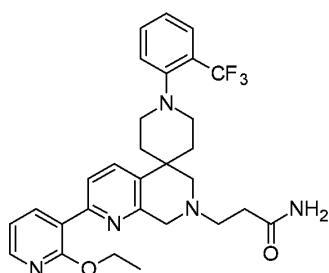
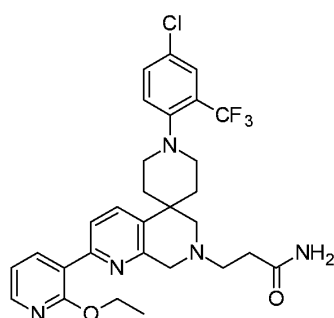
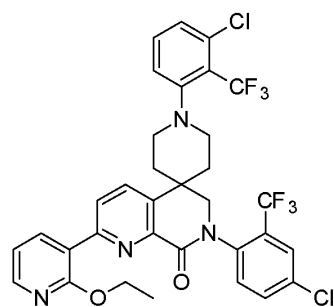
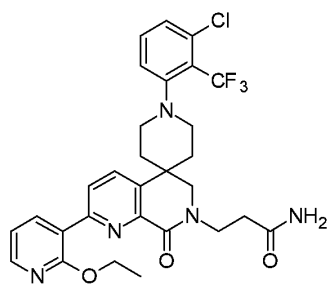
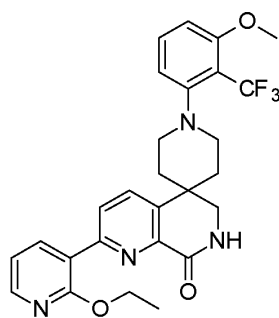
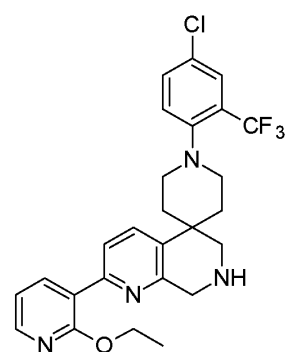
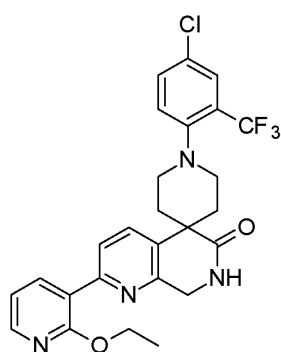
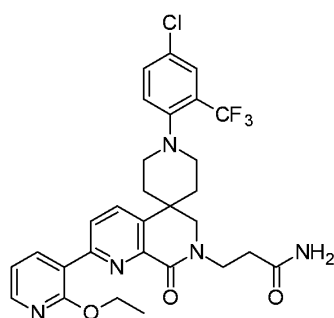
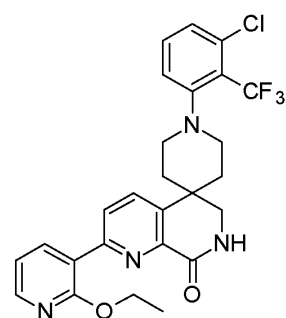
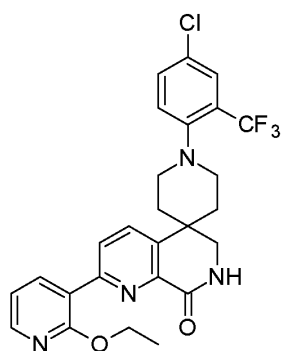
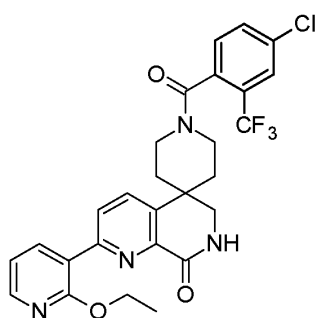
15. The compound according to any one of claims 1 to 13, wherein R^2 is H.

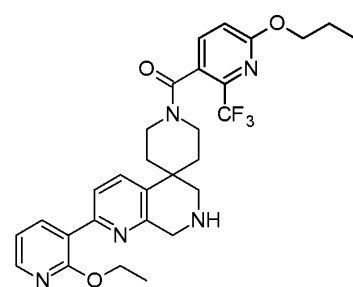
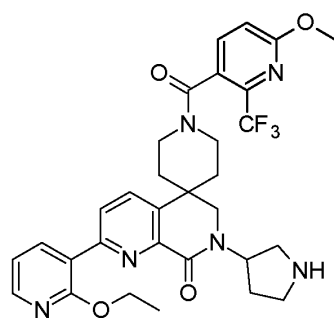
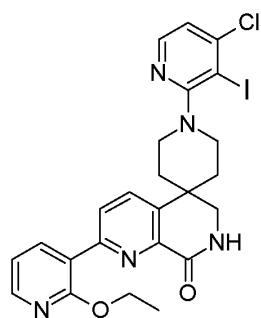
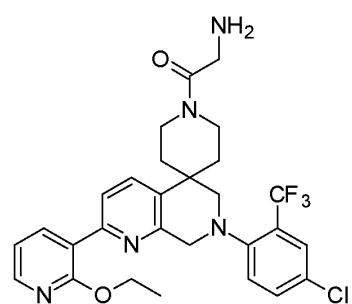
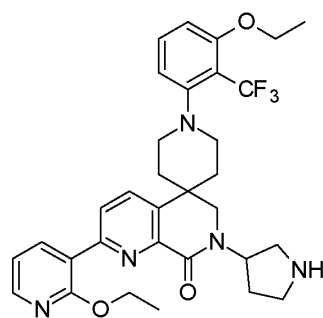
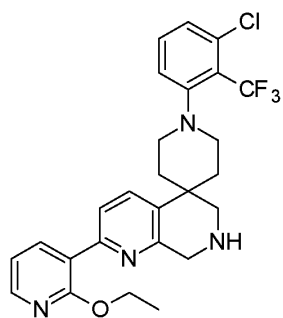
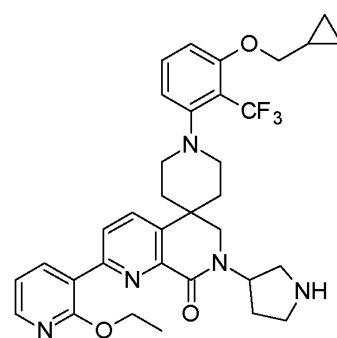
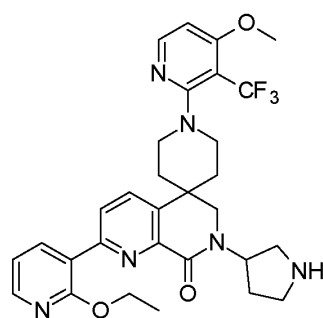
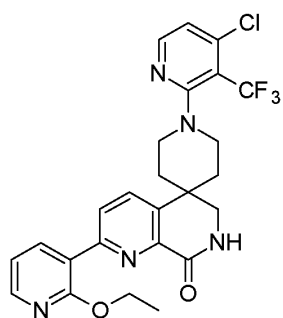
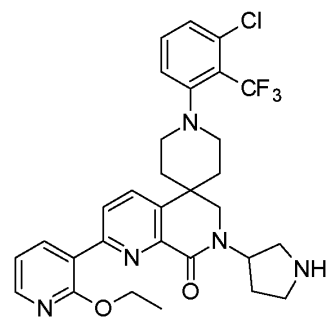
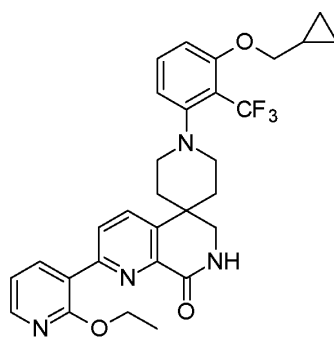
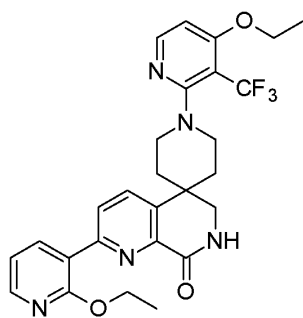
16. The compound according to any one of claims 1 to 12, wherein the moiety $-L^1-R^2$ is selected from:

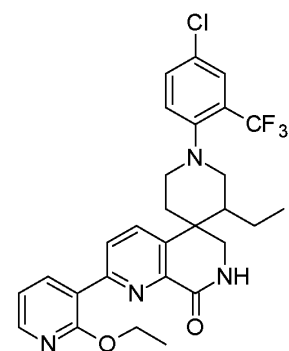
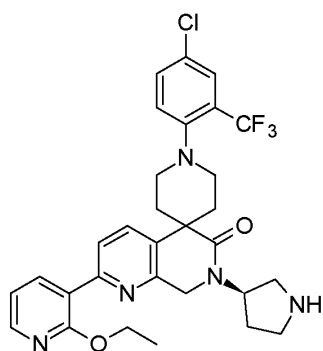
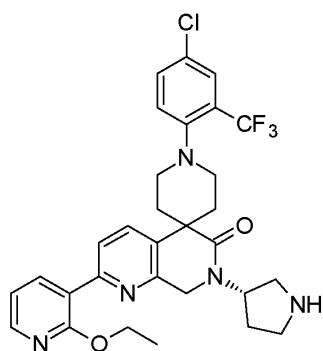
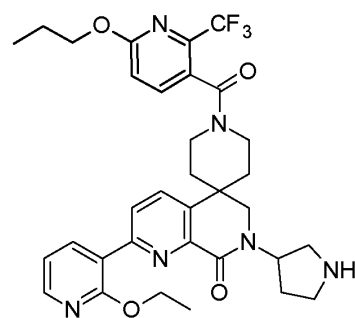
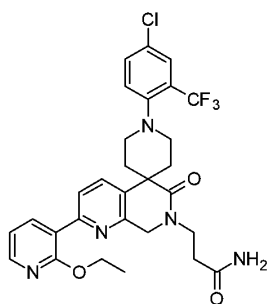
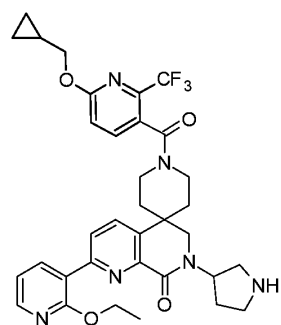
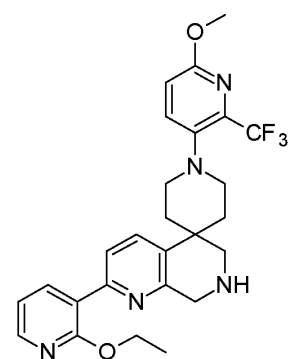
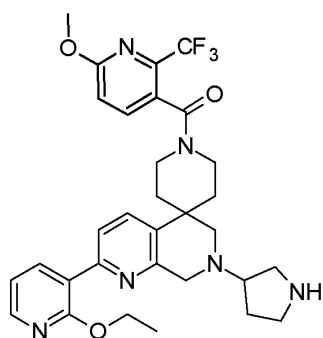
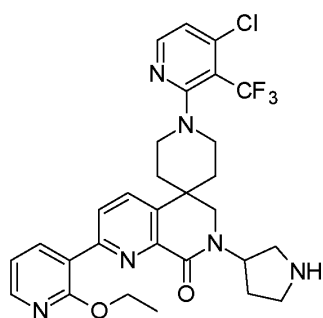
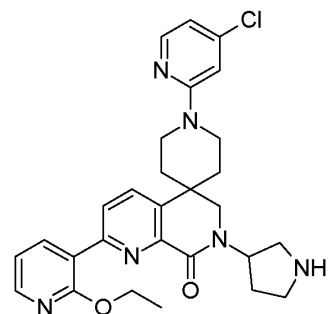
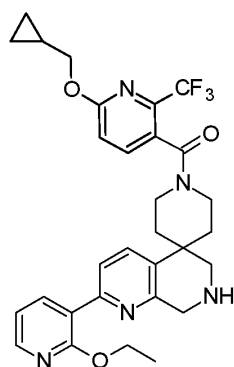
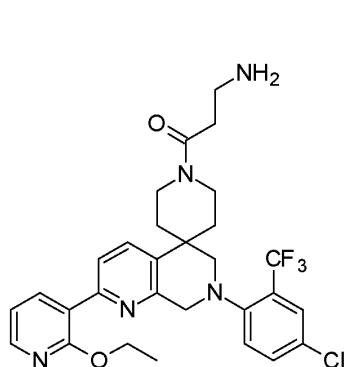


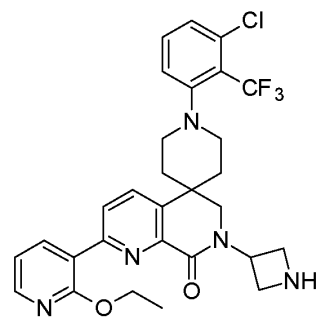
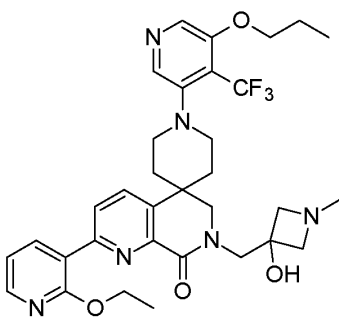
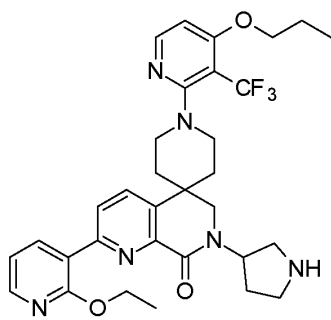
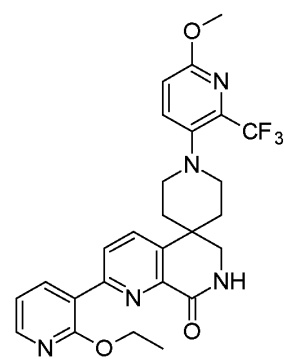
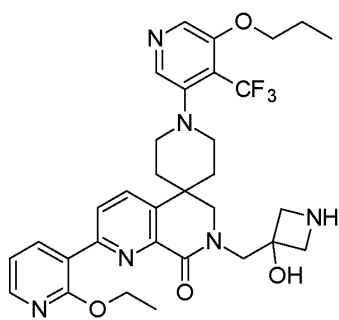
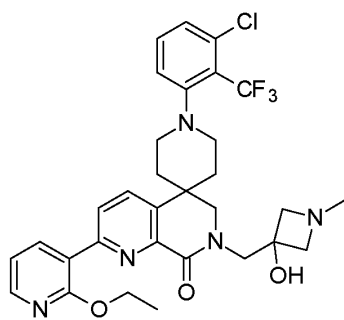
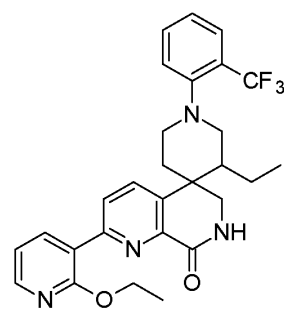
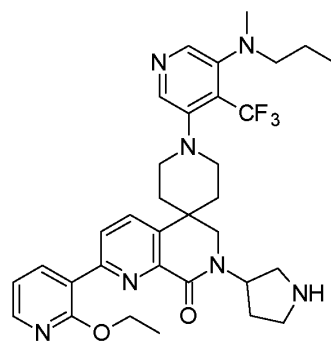
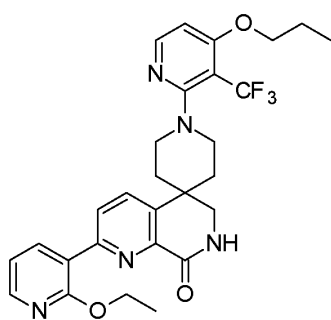
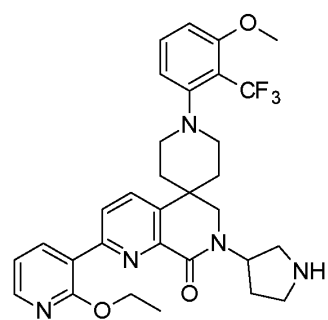
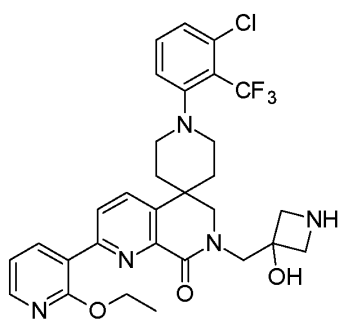
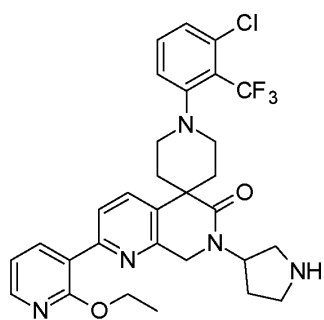


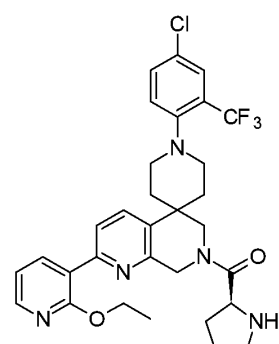
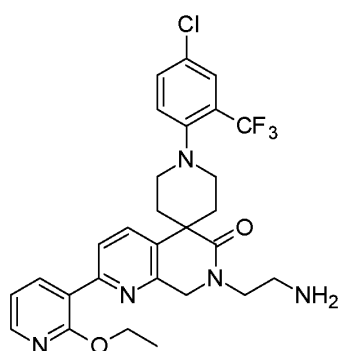
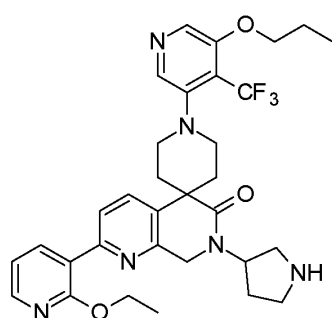
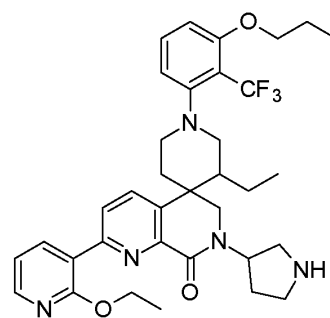
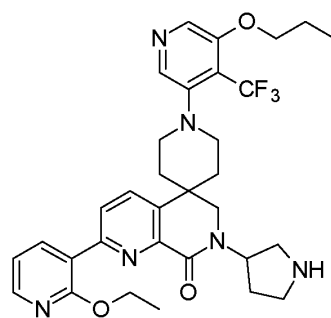
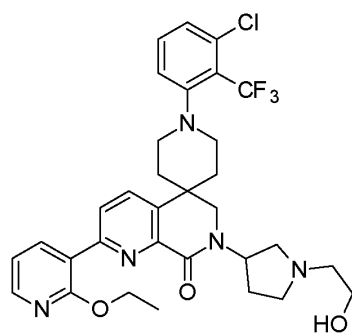
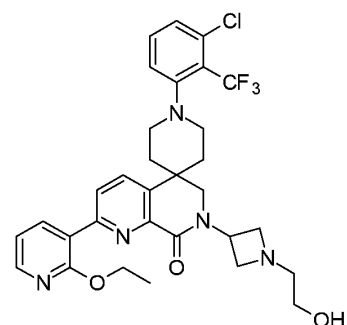
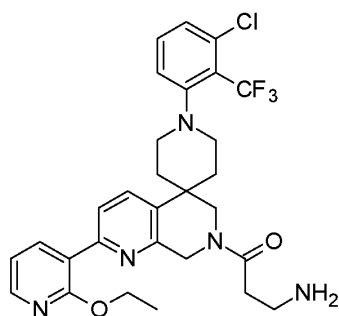
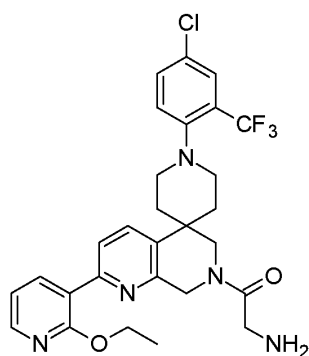
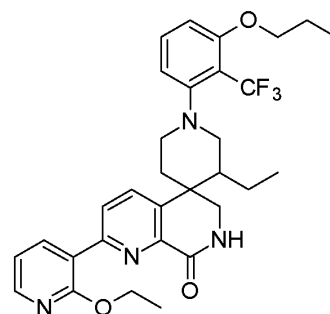
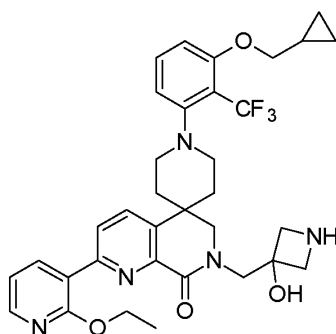
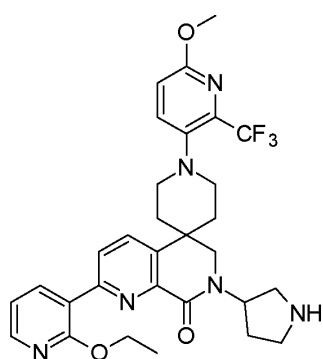
17. The compound according to claim 1, which is selected from:

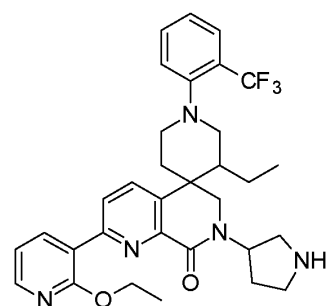
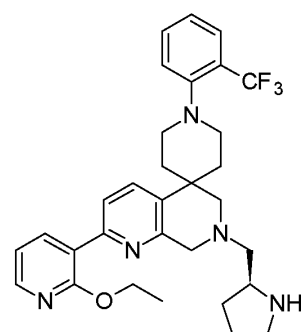
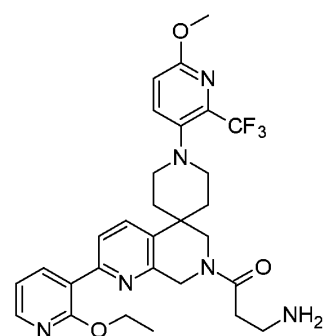
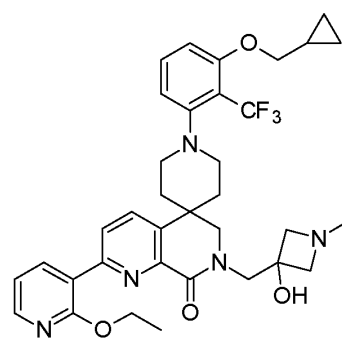


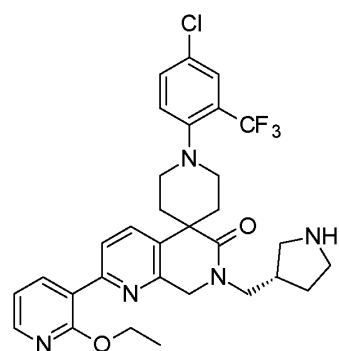
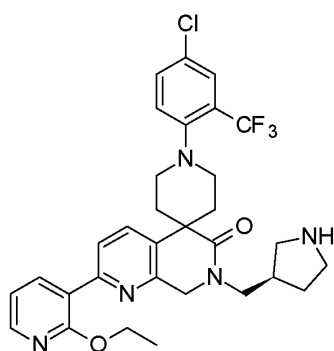
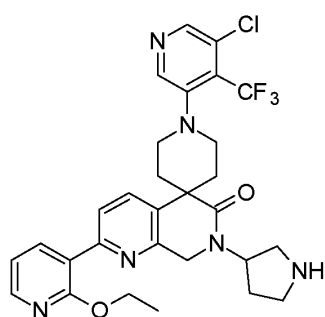
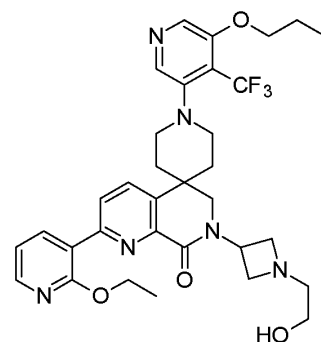
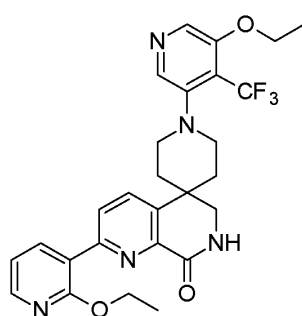
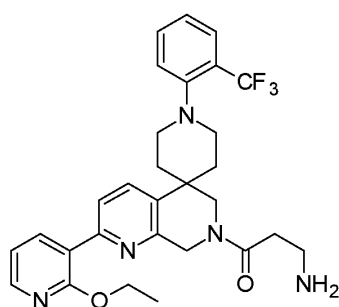
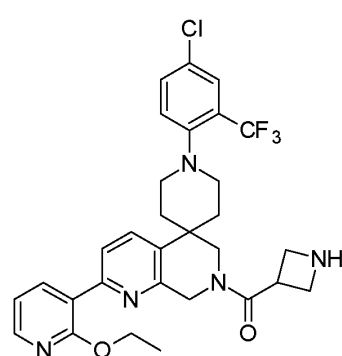
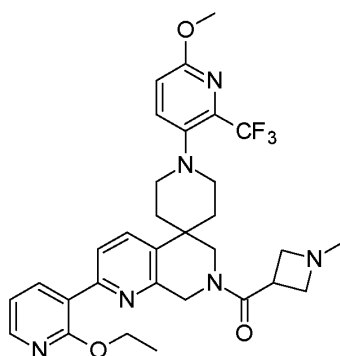
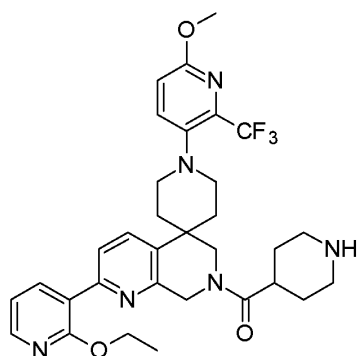
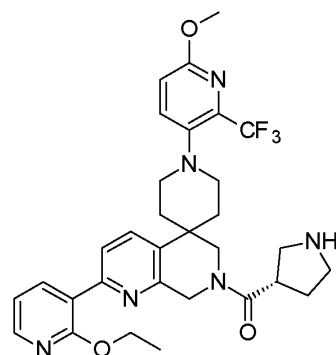
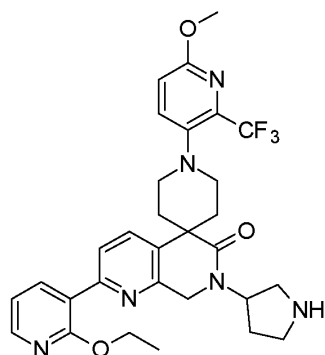
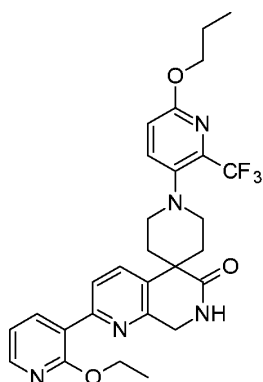


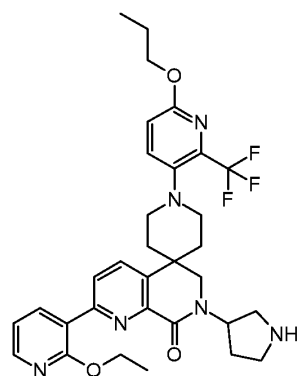
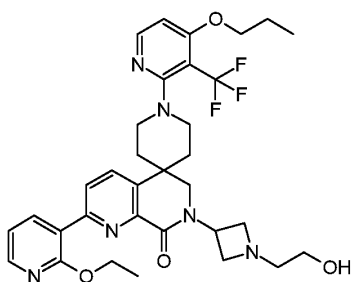
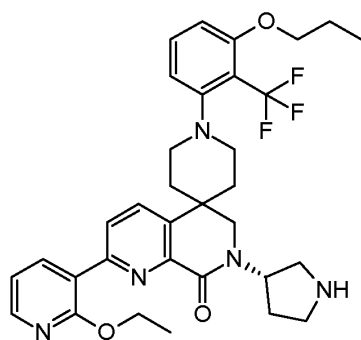
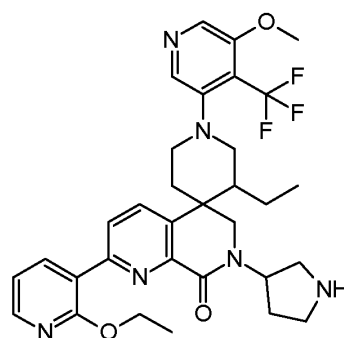
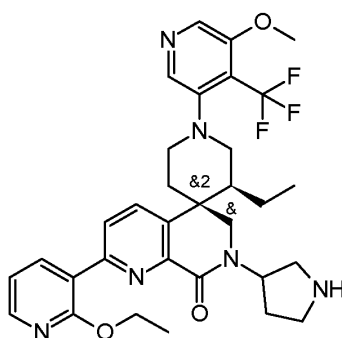
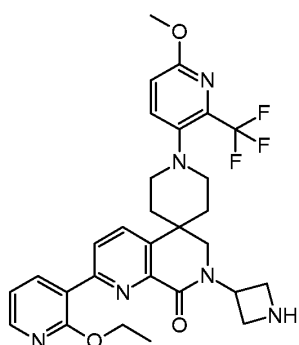
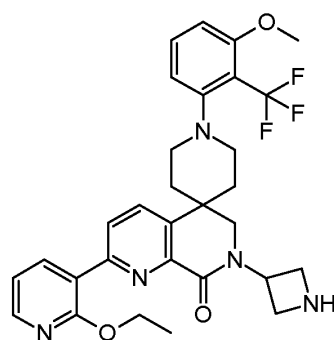
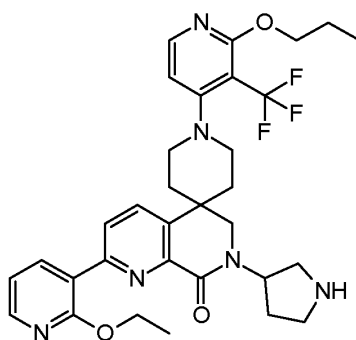
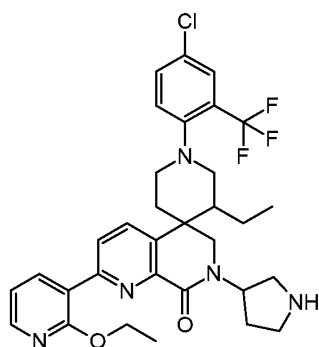
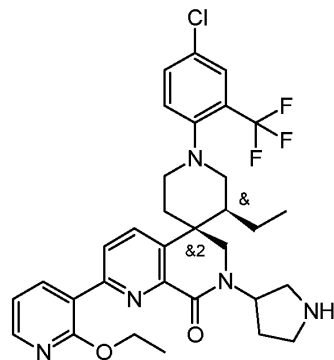
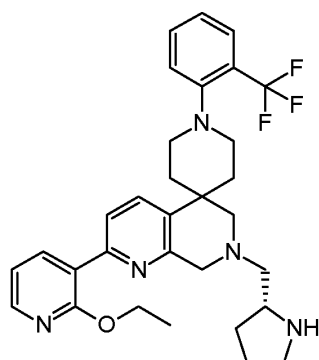
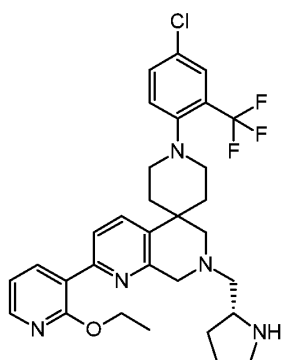


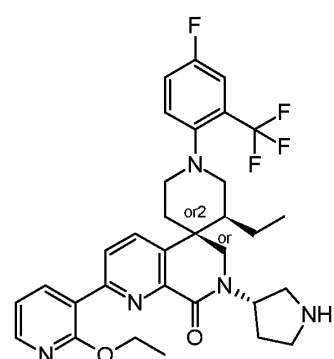
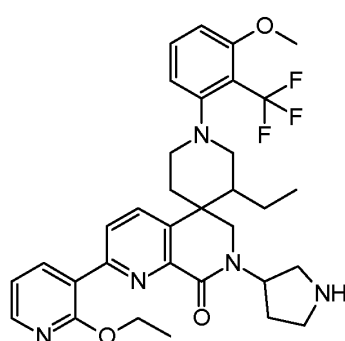
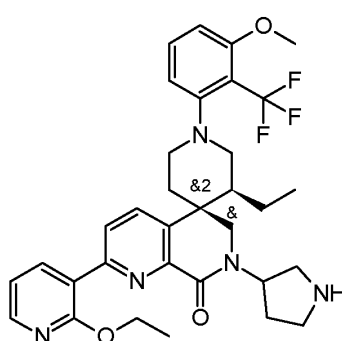
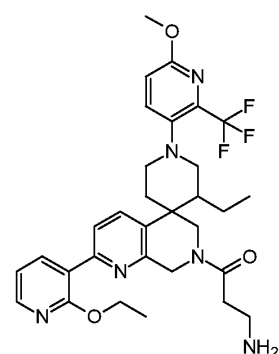
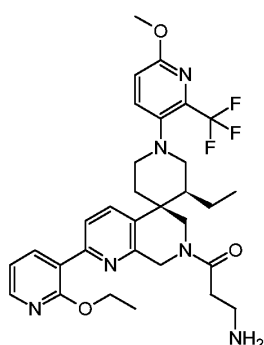
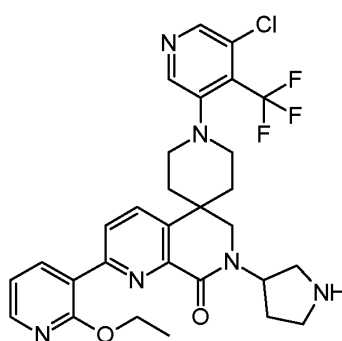
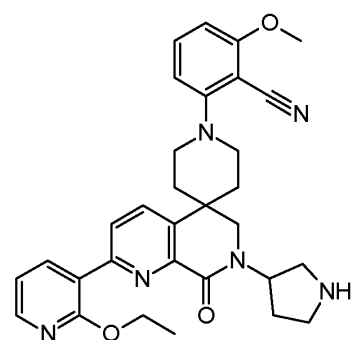
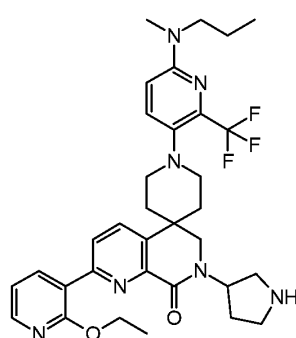
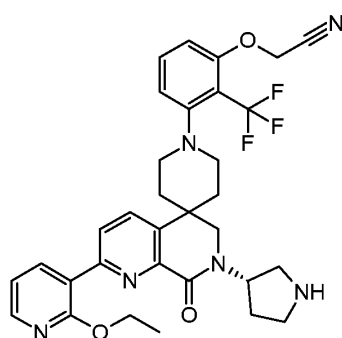
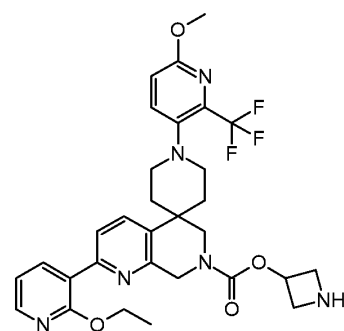
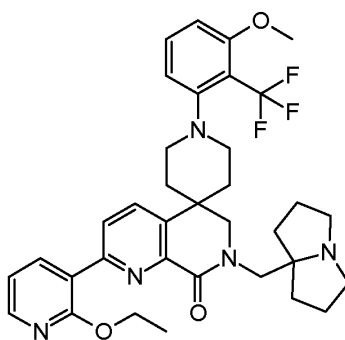
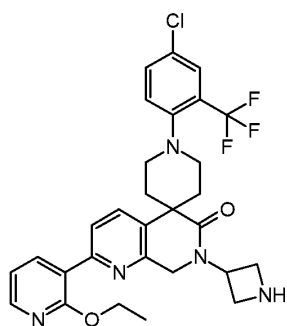


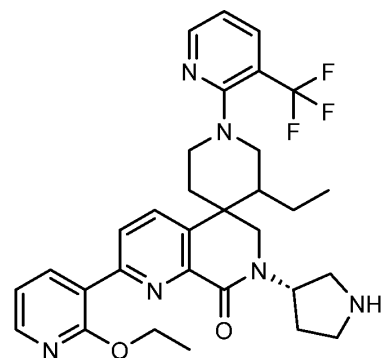
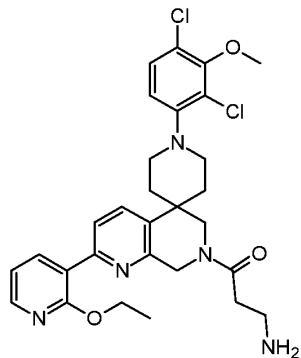
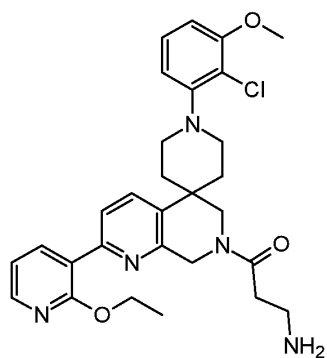
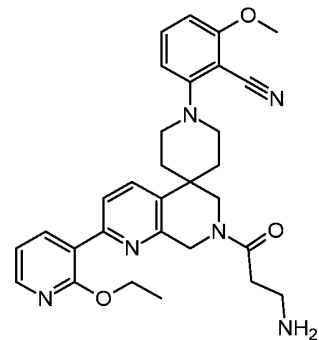
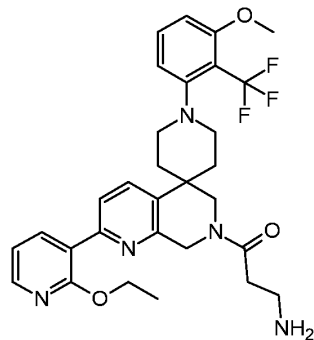
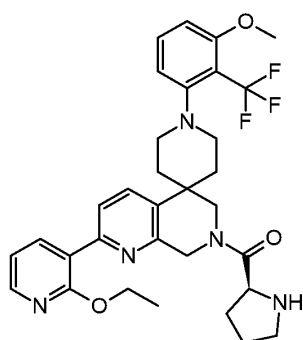
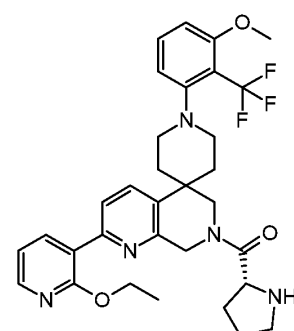
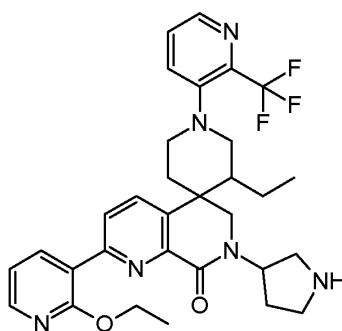
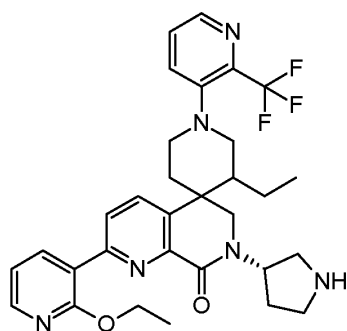
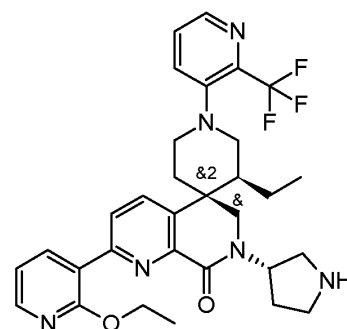
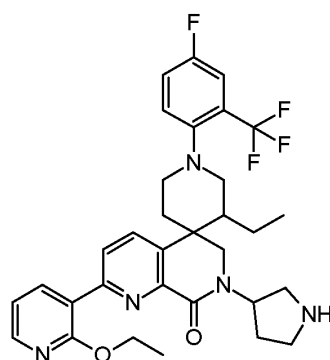
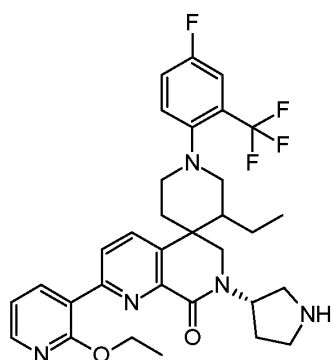


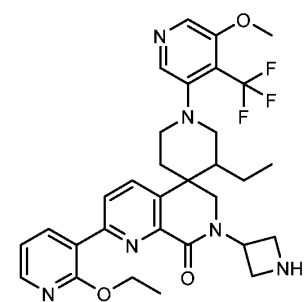
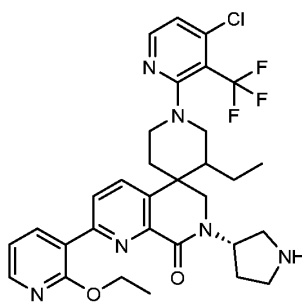
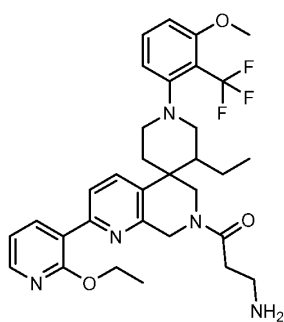
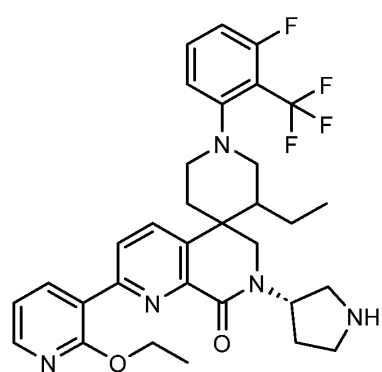
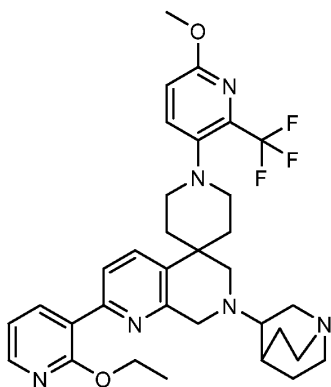
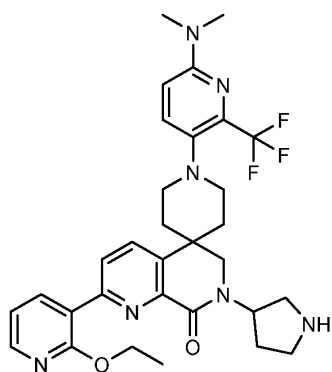
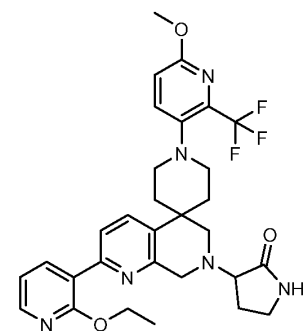
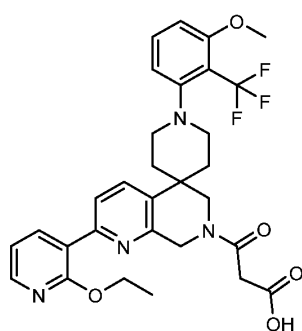
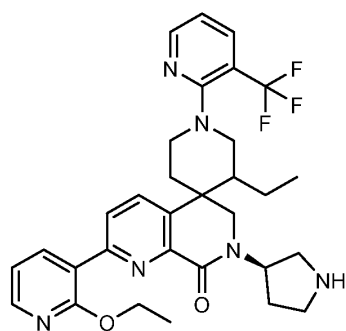
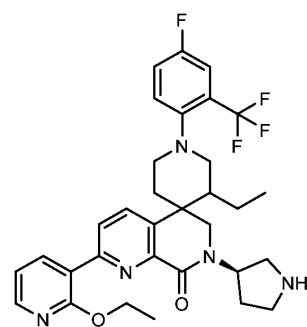
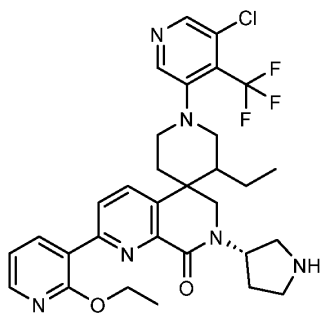
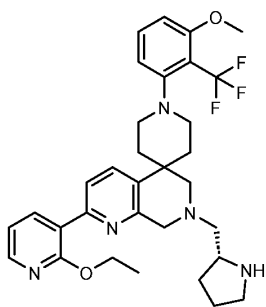


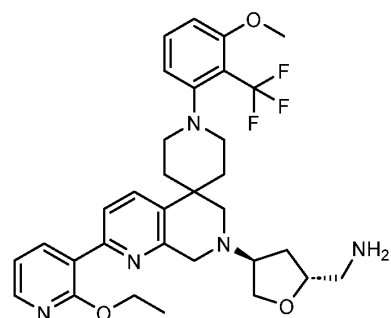
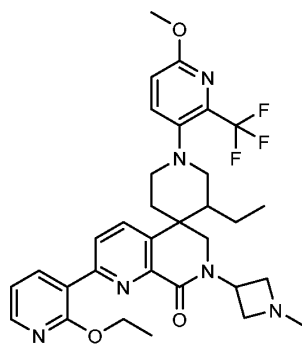
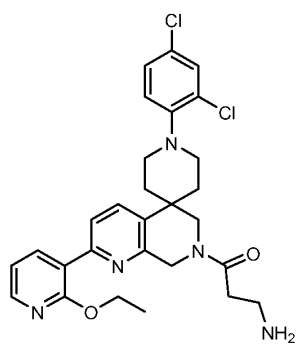
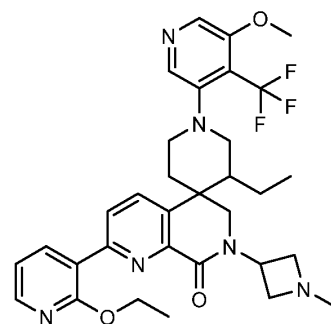
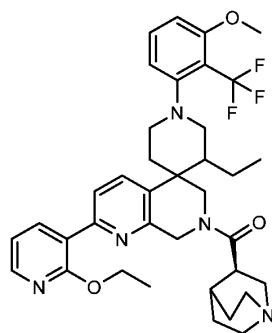
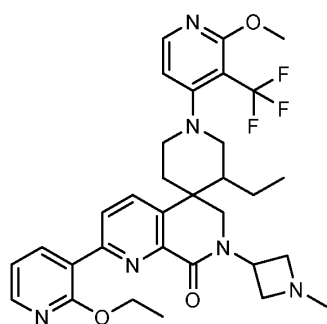
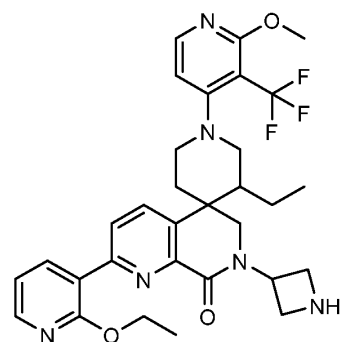
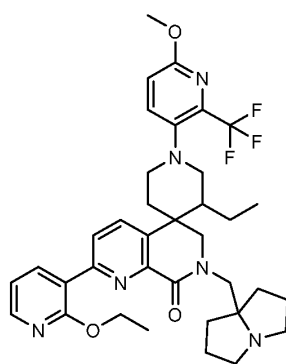
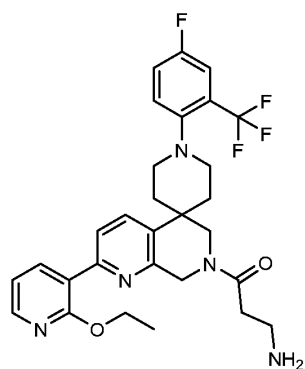
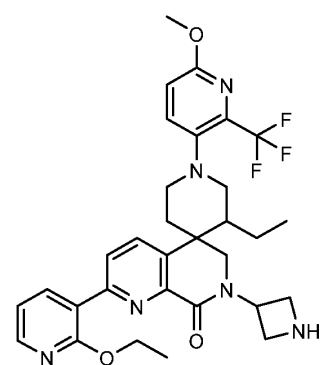
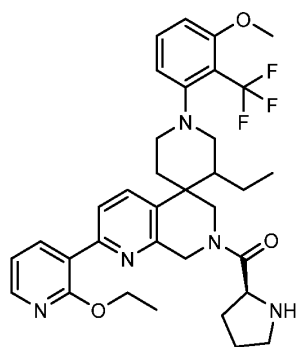
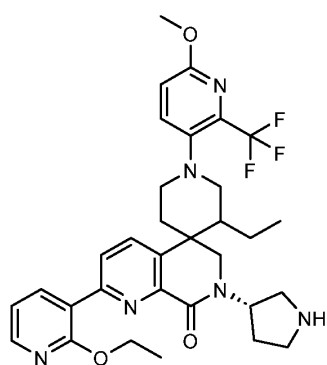


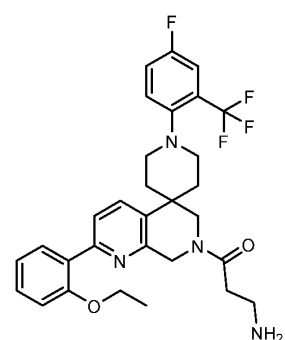
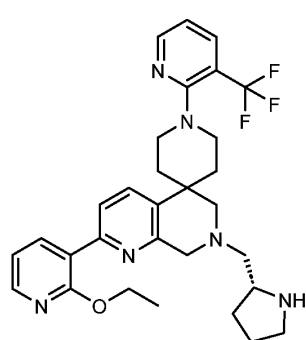
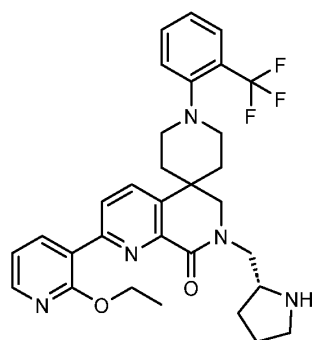
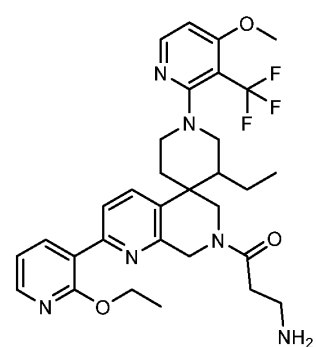
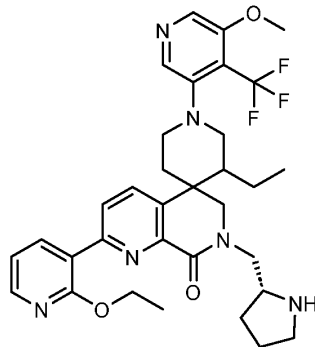
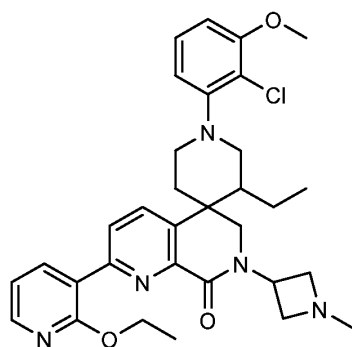
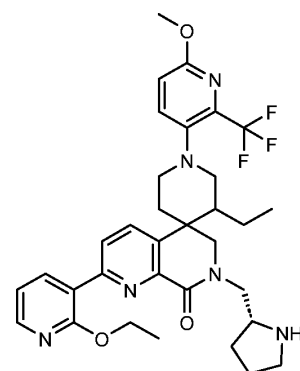
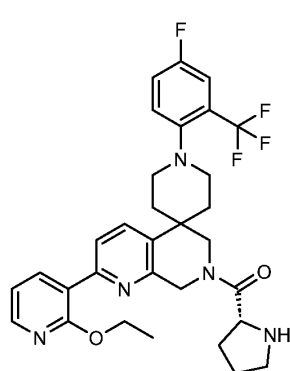
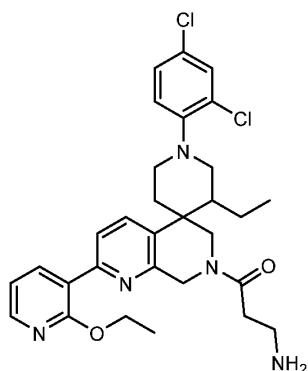
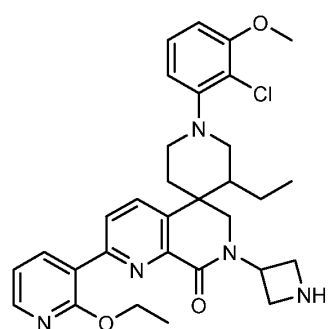
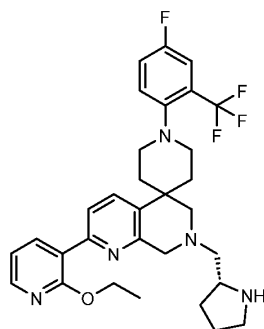
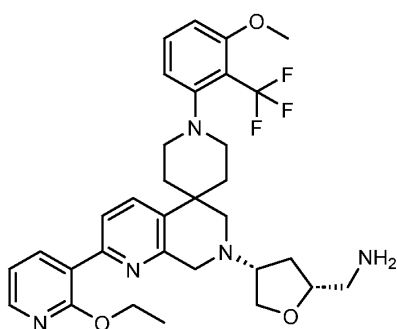


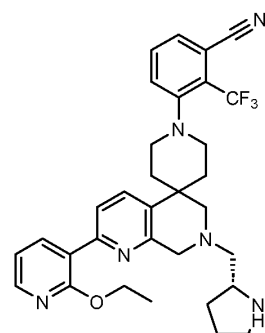
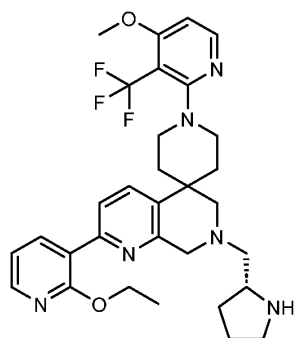
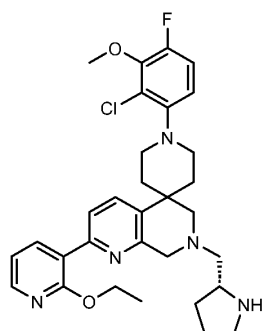
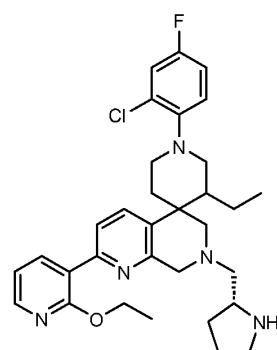
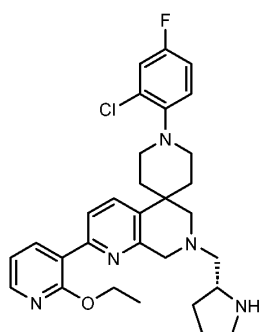
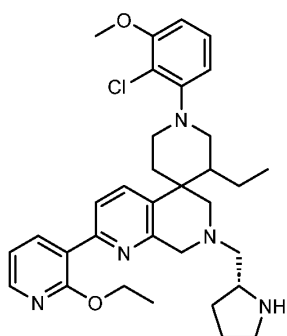
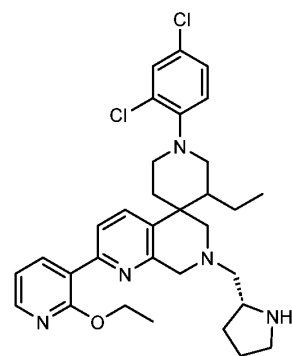
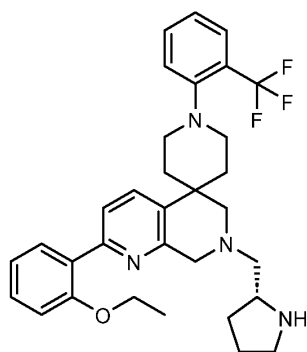
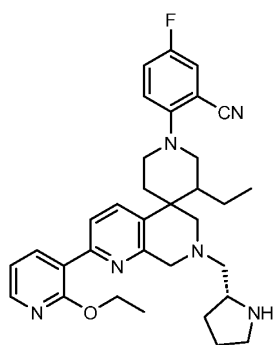
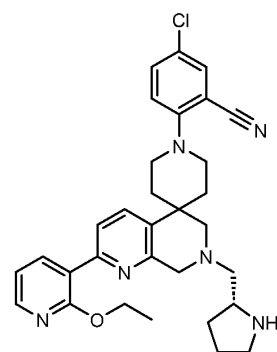
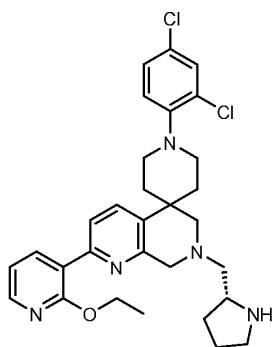
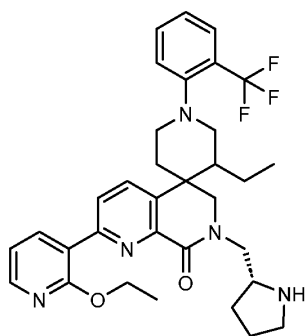


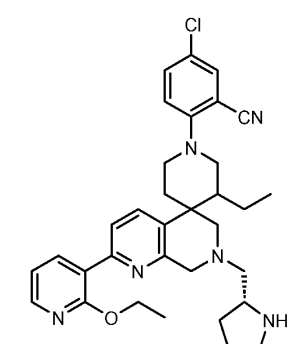
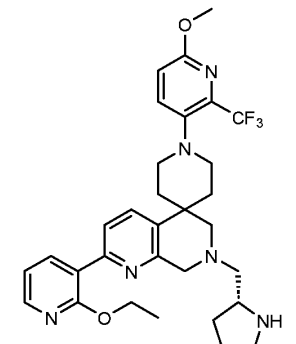
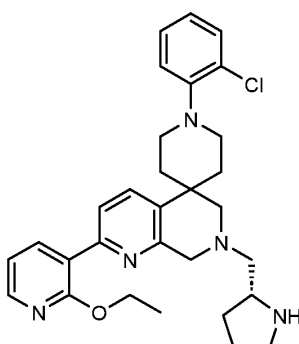
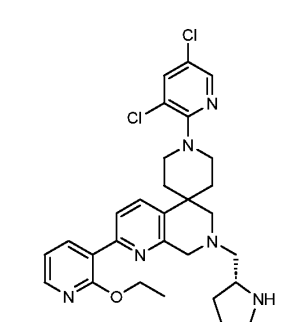
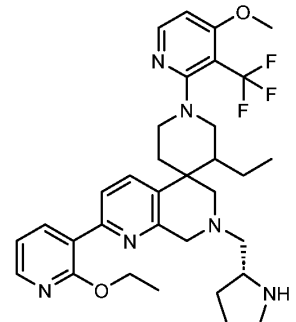
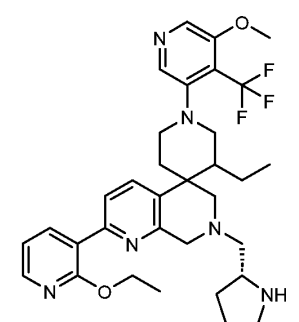
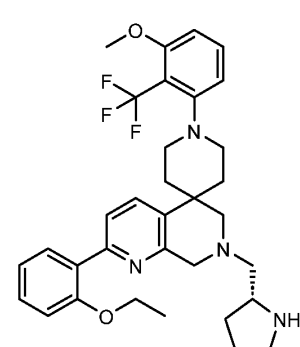
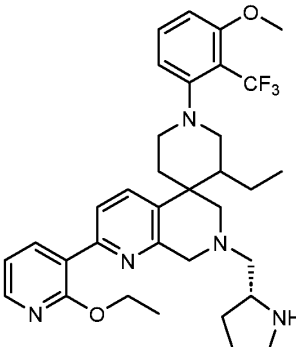
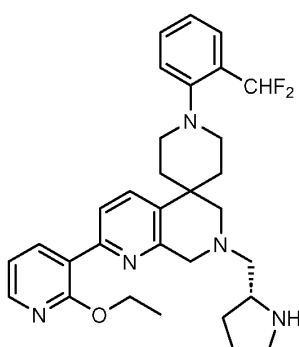
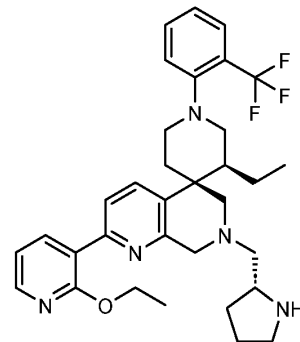
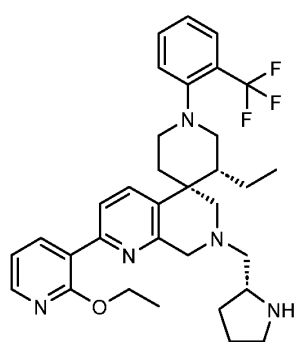
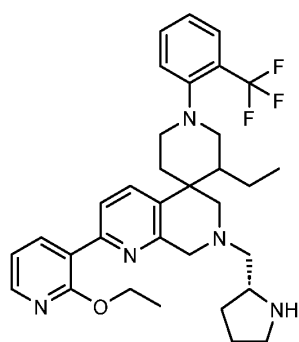


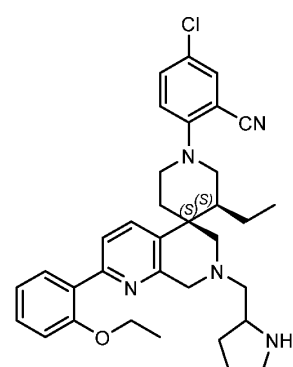
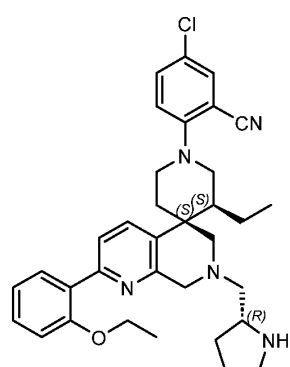
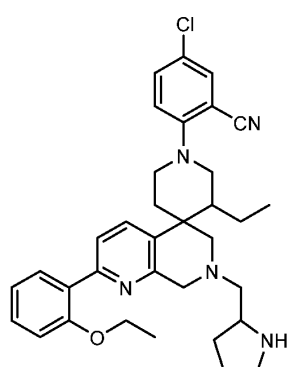
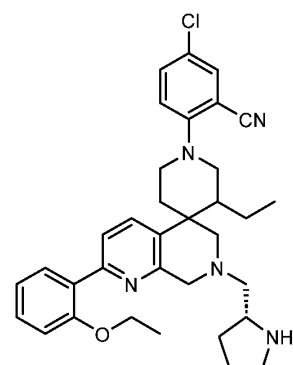
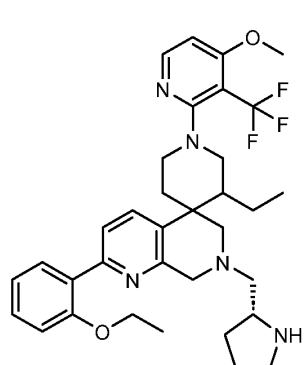
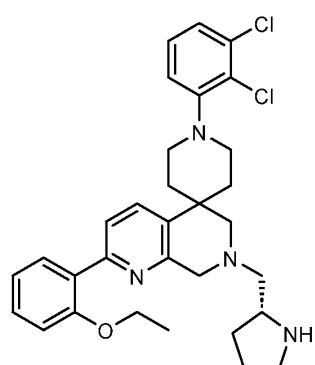
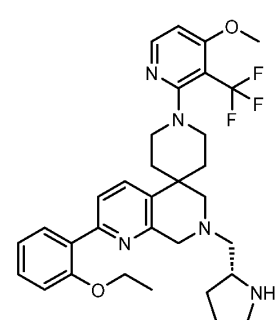
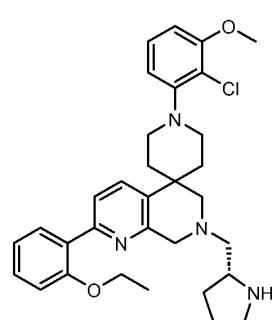
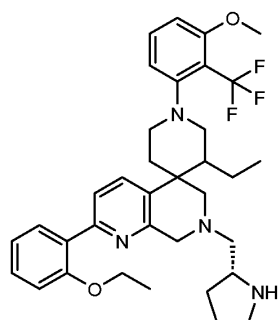
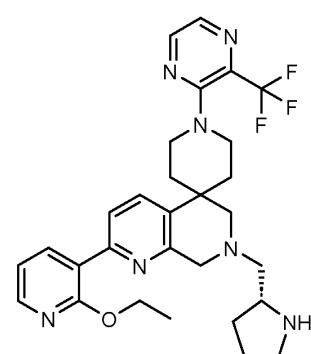
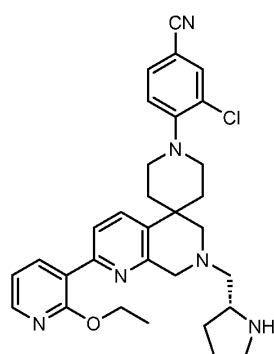
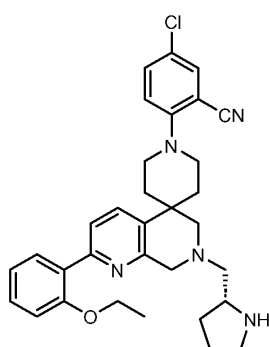


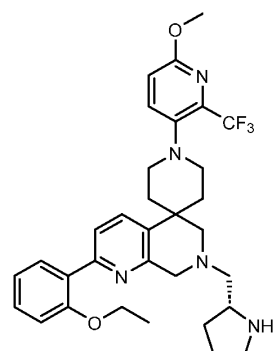
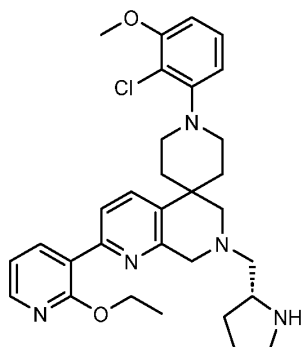
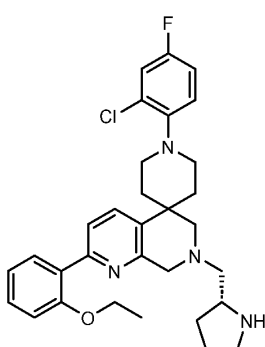
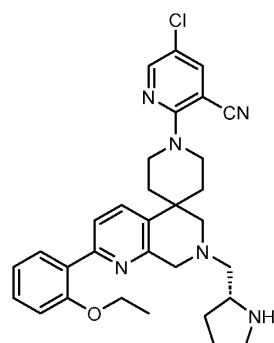
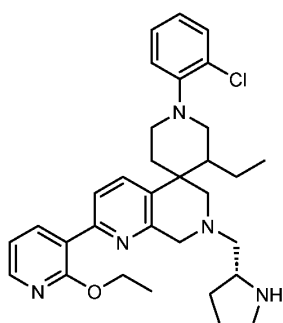
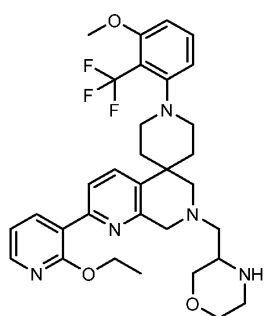
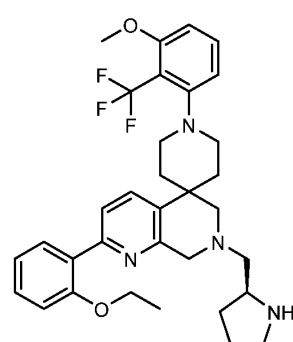
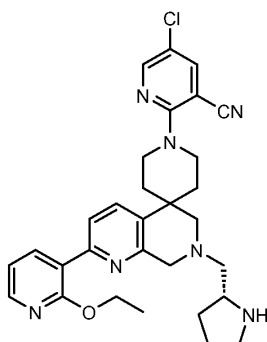
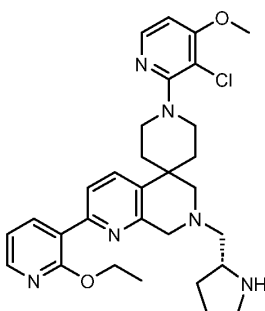
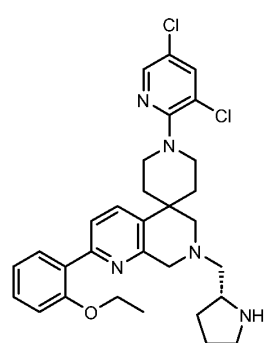
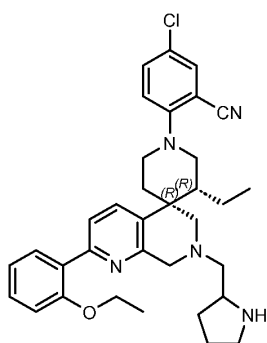
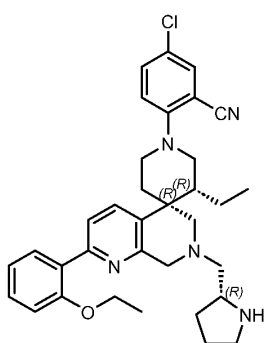


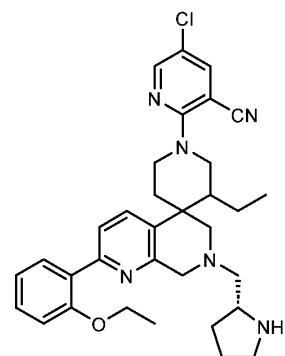
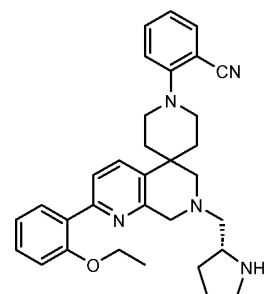
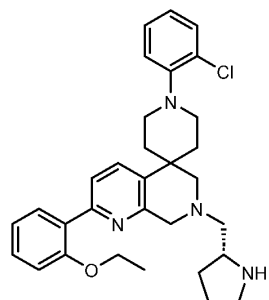
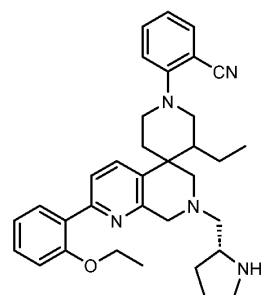
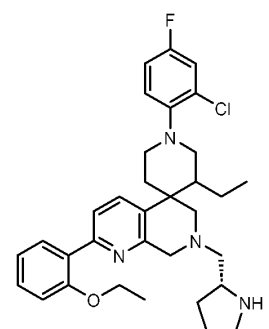
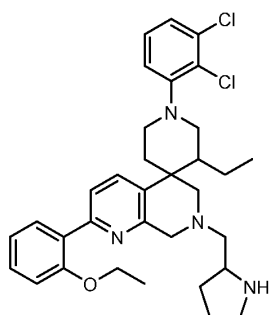
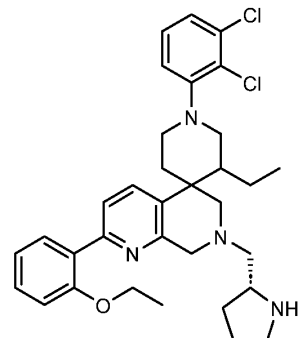
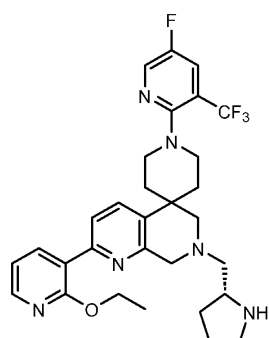
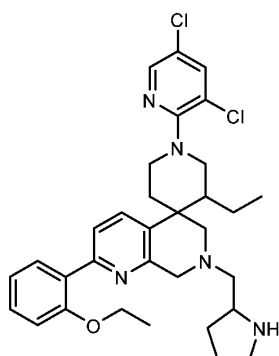
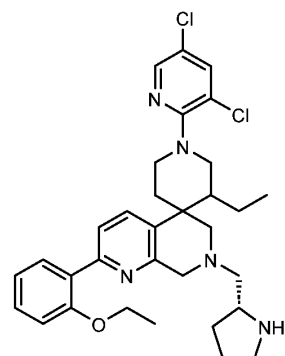
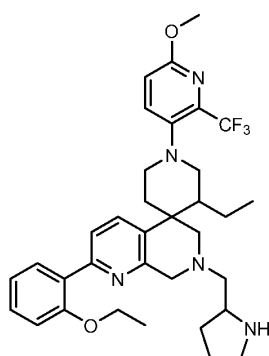
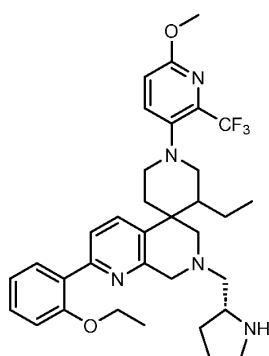


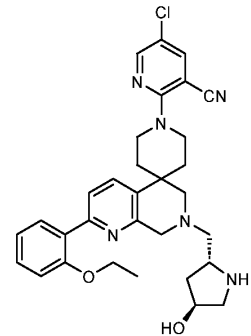
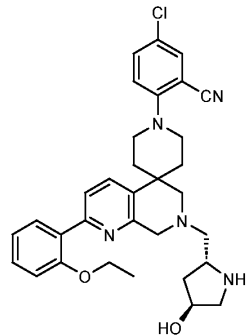
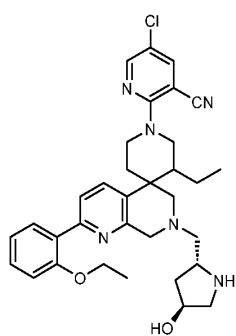
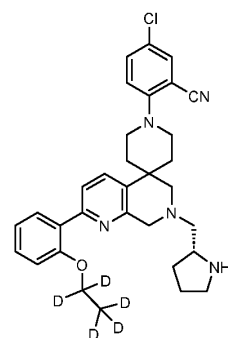
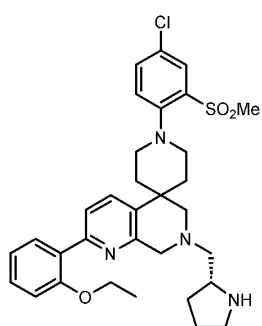
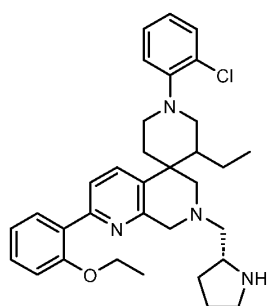
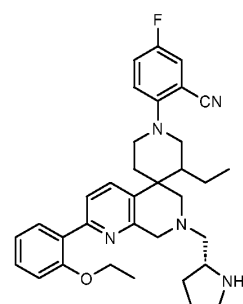
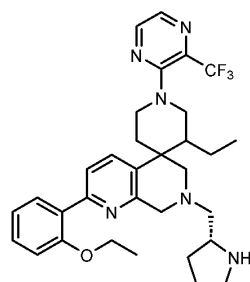
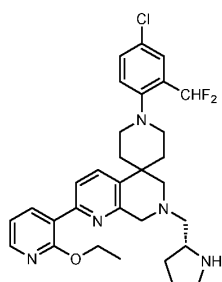
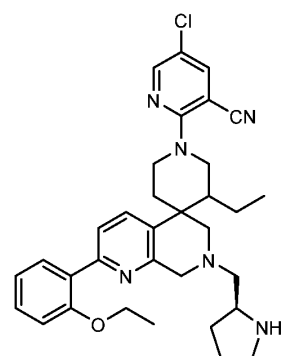
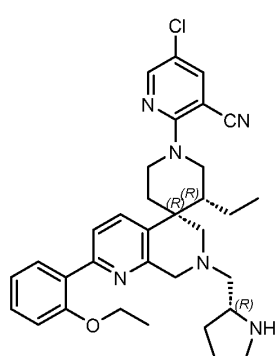
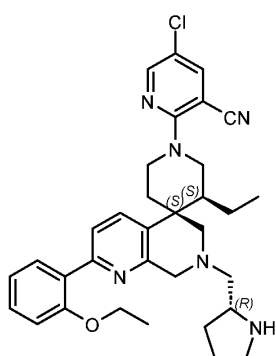


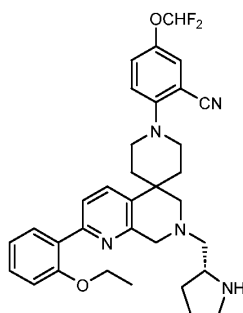
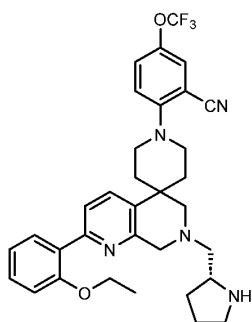
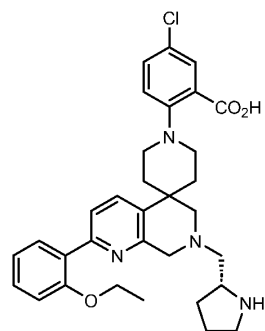
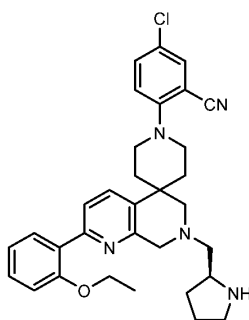
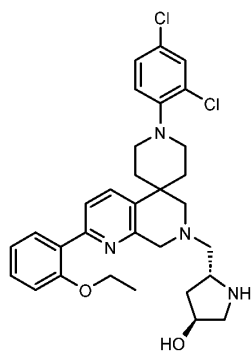
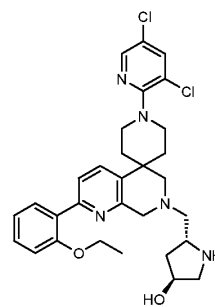
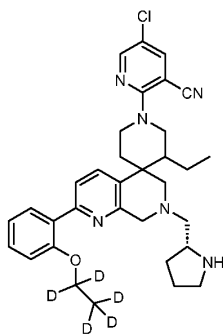
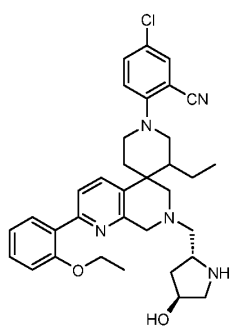












or a salt thereof.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 and a pharmaceutically acceptable excipient.

19. A combination comprising a compound according to any one of claims 1 to 17 and a CRF₁ antagonist.

20. A combination comprising a compound according to any one of claims 1 to 17 and an ACTH antibody.

21. The compound, composition or combination according to any one of claims 1 to 20 for use in medicine.
22. The compound, composition or combination according to any one of claims 1 to 20 for use in the treatment of a disorder associated with MC2R or that would benefit from the modulation of MC2R activity.
23. The compound, composition or combination according to any one of claims 1 to 20 for use in the treatment of congenital adrenal hyperplasia (CAH), Cushing's disease, ectopic ACTH syndrome, polycystic ovary syndrome (PCOS), depressive illness, septic shock, or disorders or symptoms related thereto.