

COMPOUNDS FOR THE TREATMENT OF KIDNEY DISEASE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/594,357, filed on October 30, 2023, the contents of which are incorporated by reference in its entirety.

[0002] Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder in which bilateral cysts develop in the kidneys. The cysts in polycystic kidney disease are noncancerous, fluid-filled sacs. The enlarging cysts can substantially increase kidney size and contribute to the compression, loss of surrounding renal tissue, and progressive decline of kidney function. The damage caused by the enlarging cysts and increase in kidney size ultimately lead to end-stage kidney disease (ESKD), kidney failure, and premature mortality. ADPKD is a heterogeneous renal disease with a high degree of symptom variability, including hypertension, nocturia, polyuria, hematuria, palpable kidneys, kidney stones, abdominal and flank pain, recurrent urinary tract infections, intracranial aneurysms, vascular dissections, valvular heart disease, hepatic and/or pancreatic cysts, diverticulosis, and abdominal wall hernias. ADPKD affects 1 in every 400 to 1,000 people and is the most common genetically linked kidney disorder. Approximately 50% of patients with ADPKD progress to end-stage renal disease (ESRD) at a median age of 58 years, making it the fourth leading cause of ESRD globally. However, cardio- and cerebro-vascular complications are the leading cause of death in patients with ADPKD. *Cornec-Le Gall et al., Autosomal dominant polycystic kidney disease. Lancet. 2019;393(10174):919-35.*

[0003] ADPKD is a Mendelian disease most commonly caused by germline loss of function mutations in one allele of the polycystin (PC) genes, PKD1, which encodes polycystin-1 (PC1) or PKD2, which encodes polycystin-2 (PC2). Mutations in either gene cause decreased expression of the PC1-PC2 complex at cell membranes. An analysis of over 1,100 ADPKD patients found that almost 80% of ADPKD patients have a germline mutation in PKD1 and that mutations in PKD1 typically cause more severe disease than PKD2 mutations. *Heyer et al., Predicted Mutation Strength of Nontruncating PKD1 Mutations Aids Genotype-Phenotype Correlations in Autosomal Dominant Polycystic Kidney Disease. 2016; J Am Soc Nephrol 27(9): 2872-2884.* Approximately one third of these patients have non-truncating PKD1 mutations, which typically results in ESKD at approximately 60-66 years of age. These non-truncating PKD1 mutations result in production of misfolded PC1 with reduced function.

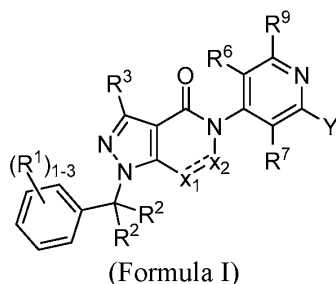
[0004] Mutations in *PKD1* or *PKD2* cause decreased expression of the PC1-PC2 complex at cell membranes. *Torres et al. Autosomal dominant polycystic kidney disease. Lancet. 2007;369(9569):1287-301; Rastogi et al., Autosomal dominant polycystic kidney disease: updated perspectives. Ther Clin Risk Manag. 2019;15(1041-52).* While the exact molecular function is unknown, reduced activity leads to kidney epithelial cell proliferation, cyst formation, and secretion of fluid into cysts. Renal survival data indicate that for germline, non-truncating mutations in *PKD1*, the low level of protein reaching the membrane retains some residual function. *Hopp et al., Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. J Clin Invest. 2012;122(11):4257-73.* This may also be the case in certain truncating mutations. Rare case studies of patients carrying hypomorphic *PKD1* mutations have helped inform a genetic dose-response model for ADPKD severity. *Id.* While cyst growth is dependent on PC1 dosage across a range of expression levels, available data suggest that a critical threshold of 20-30% of WT/WT cell surface PC1 expression is required to prevent cyst development. *Lanktree et al., Insights into Autosomal Dominant Polycystic Kidney Disease from Genetic Studies. Clinical Journal of the American Society of Nephrology. 2021;16(5):790-99; Gaimullin et al., Polycystin-1 maturation requires polycystin-2 in a dose-dependent manner. J Clin Invest. 2015;125(2):607-20; and Ong and Harris, A polycystin-centric view of cyst formation and disease: the polycystins revisited. Kidney Int. 2015;88(4):699-710.* Recently, two independent animal studies in adult-onset ADPKD mouse models demonstrated that genetic re-expression of *PKD1* has anticystic potential on a background of pre-existing cystogenesis. (*Torres, Rastogi*).

[0005] Current treatments for ADPKD include drugs aimed at slowing the rate of kidney cyst growth and thus kidney function decline, drugs aimed at controlling high blood pressure to delay the progression of the disease and slow kidney damage, drugs to treat/control the pain associated with polycystic kidney disease, drugs to treat bladder and kidney infections, dialysis, kidney transplant, and surgical or nonsurgical intervention for aneurysms. All of these treatments are symptomatic and do not address the underlying cause of the disease. Consequently, there is a great need to address the underlying cause of the disease, restore expression and translation of PC1, reduce the symptoms of ADPKD, and slow or halt decline in kidney function, cyst pain and adverse cerebro-/cardio-vascular events.

[0006] The compounds of this invention are useful as PC1 correctors that increase functional cell-surface PC1. These compounds may be administered to patients with non-

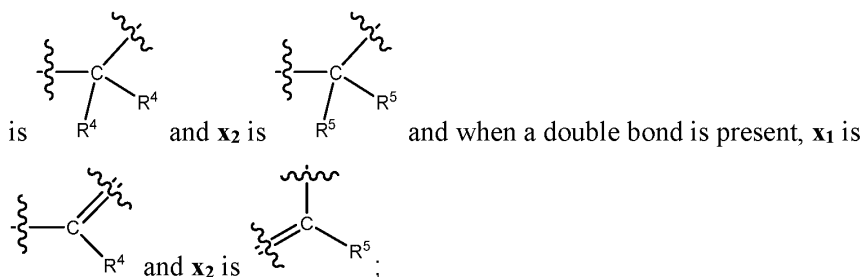
truncating mutations in the *PKD1* gene, and in some cases to patients with truncating mutations in the PKD1 gene to reduce the symptoms of ADPKD and to slow or halt decline in kidney function, cyst pain, and adverse cerebro-/cardio-vascular events.

[0007] The compounds of this invention include compounds of Formula I:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

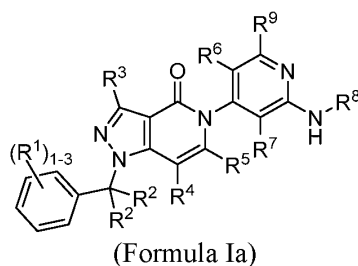
- $X_1 \text{---} X_2$ is a single bond or a double bond, wherein when a single bond is present, x_1



- each R^1 is independently selected from hydrogen, C₁-C₃ alkyl (substituted with 0-2 groups selected from oxo, hydroxyl, and amino), C₁-C₃ alkoxy, halogen, and cyano;
- each R^2 is independently selected from hydrogen and C₁-C₃ alkyl;
- R^3 is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- each R^4 and R^5 are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- R^6 and R^9 are independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- R^7 is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- R^8 is selected from:
 - o hydrogen,
 - o C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,

- halogen,
- C₁-C₃ alkoxy (substituted with 0-1 oxo group),
- C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
- 3- to 7-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
- 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
- C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
- 5- to 9-membered heterocyclyl substituted with 0-3 groups independently selected from:
 - oxo,
 - halogen
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group); and
- Y is selected from
 - OR⁸,
 - N(R⁸)₂, and
 - 3- to 10-membered heterocyclyl or 3- to 10-membered heteroaryl, each of which is substituted with 0-2 groups independently selected from:
 - N(R⁸)₂,
 - hydroxyl,
 - oxo,
 - C₁-C₃ alkoxy, and
 - C₁-C₃ alkyl (substituted with 0-2 groups selected from amino, hydroxyl, C₃-C₄ alkyl, oxo, and C₁-C₃ alkoxy).

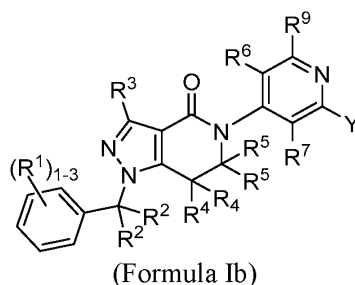
[0008] The compounds of this invention include compounds of Formula Ia:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- each **R²** is independently selected from hydrogen and C₁-C₃ alkyl;
- **R³** is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- **R⁴** and **R⁵** are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- **R⁶** and **R⁹** are independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group).

[0009] The compounds of this invention also include compounds of Formula Ib:

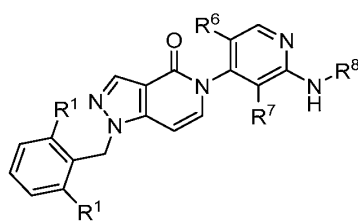


as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen, C₁-C₃ alkyl (substituted with 0-2 groups selected from oxo, hydroxyl, and amino), C₁-C₃ alkoxy, halogen, and cyano;
- each **R²** is independently selected from hydrogen and C₁-C₃ alkyl;
- **R³** is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- each **R⁴** and **R⁵** are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- **R⁶** and **R⁹** are independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and

- 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group);
- Y is selected from
 - N(R⁸)₂, and
 - 3- to 10-membered heterocyclyl or 3- to 10-membered heteroaryl, each of which is substituted with 0-2 groups independently selected from:
 - hydroxyl,
 - oxo,
 - C₁-C₃ alkoxy, and
 - C₁-C₃ alkyl (substituted with 0-2 groups selected from amino, hydroxyl, C₃-C₄ alkyl, oxo, and C₁-C₃ alkoxy).

[0010] The compounds disclosed herein also include compounds of Formula II:

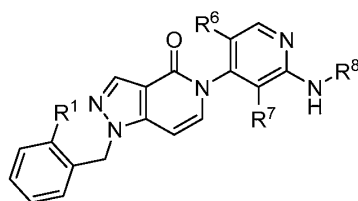


(Formula II),

as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein

- each **R¹** is independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁶** is selected from C₁-C₃ alkyl, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is as defined for Formula Ia.

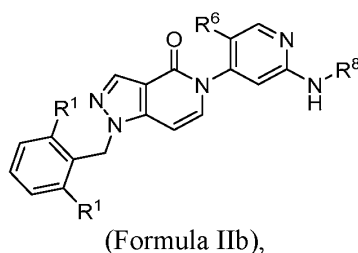
[0011] The compounds disclosed herein also include compounds of Formula IIa:



(Formula IIa),

as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein **R¹** is selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano; and all other variables are as defined above for Formula II.

[0012] The compounds disclosed herein also include compounds of Formula IIb:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen and halogen;
- **R⁶** is selected from halogen; and
- **R⁸** is selected from:
 - o C₁-C₅ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl, and
 - C₃-C₆ cycloalkyl;
 - o C₃-C₆ cycloalkyl, substituted with 0-2 groups selected from hydroxyl and halogen; and
 - o 5- to 6-membered heterocyclyl unsubstituted or substituted with C₁-C₃ alkyl, wherein the C₁-C₃ alkyl is substituted with 0-2 substituents selected from hydroxyl and halogen.

[0013] The compounds disclosed herein may be employed in pharmaceutical compositions, e.g., used in the manufacture of a medicament. The compounds and pharmaceutical compositions of the invention may be administered to treat ADPKD.

Definitions

[0014] As used herein, the term “alkyl” refers to a saturated or partially saturated, branched, or unbranched aliphatic hydrocarbon containing carbon atoms (such as, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms), which may contain a double (alkenyl) or triple (alkynyl) bond between one or more sets of adjacent carbon atoms. Alkyl groups may be substituted or unsubstituted. In some

embodiments, alkyl groups contain 1-10 alkyl carbon atoms. In other embodiments, alkyl groups contain 1-8 alkyl carbon atoms. In still other embodiments, alkyl groups contain 1-6 alkyl carbon atoms, and in yet other embodiments alkyl groups contain 1-4 alkyl carbon atoms or 1-3 alkyl carbon atoms.

[0015] The term “aliphatic” or “aliphatic group,” as used herein, means a straight-chain (i.e., unbranched) or branched, substituted, or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “cycloaliphatic,” “carbocycle,” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₈ hydrocarbon or bicyclic or tricyclic C₈-C₁₄ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said monocyclic, bicyclic, or tricyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, and (cycloalkyl)alkenyl. Suitable cycloaliphatic groups include cycloalkyl, bicyclic cycloalkyl (e.g., decalin), bridged bicycloalkyl such as norbornyl or [2.2.2]bicyclo-octyl, and bridged tricyclic such as adamantyl.

[0016] As used herein, the term “unsaturated” means that a moiety has one or more units of unsaturation.

[0017] As used herein, the term “pi bond” means a covalent bond formed by the p orbitals of adjacent atoms. Pi bonds exist where there is a multiple bond, i.e., a double or triple bond, between two atoms. For example, a carbon-carbon double bond consists of one pi bond, and a carbon-carbon triple bond consists of two pi bonds.

[0018] As used herein, the term “halogen” or “halo” means F, Cl, Br, or I.

[0019] As used herein, the term “haloalkyl group” refers to an alkyl group substituted with one or more halogen atoms, e.g., fluoroalkyl, which refers to an alkyl group substituted with one or more fluorine atoms. In some embodiments, a haloalkyl contains 1-5 halogen atoms. In some embodiments, a haloalkyl contains 1-3 halogen atoms. In some embodiments, a haloalkyl contains 3-5 halogen atoms. In some embodiments, one carbon atom of the alkyl group is substituted with one or more halogen atoms. In some embodiments, each carbon atom of the alkyl group is substituted with one or more halogen atoms. In some embodiments, one or more carbon atoms of the alkyl group is a perhalo carbon atom (i.e., all hydrogen atoms of the alkyl group are substituted by halogen atoms). In some embodiments, each carbon atom of the alkyl group is a perhalo carbon atom. Non-limiting examples of fluoroalkyl include —CHF_2 , $\text{—CH}_2\text{F}$, —CF_3 , $\text{—CF}_2\text{—}$, and perhaloalkyl, such as $\text{—CF}_2\text{CF}_3$.

[0020] As used herein, the terms “oxo” and “=O” refer to a substituent oxygen atom connected to another atom by a double bond.

[0021] The term “alkoxy,” as used herein, refers to an alkyl or cycloalkyl covalently bonded to an oxygen atom. Alkoxy groups may be substituted or unsubstituted.

[0022] As used herein, “cycloalkyl” refers to a monocyclic, bicyclic, tricyclic, or polycyclic non-aromatic hydrocarbon groups having 3 to 12 carbon atoms (such as, for example 3-10 carbons) and may include one or more unsaturated bonds. In some embodiments, cycloalkyl groups contain 3-12 carbon ring atoms. In other embodiments, cycloalkyl groups contain 3-10 carbon ring atoms. In still other embodiments, cycloalkyl groups contain 3-9 carbon ring atoms, and in yet other embodiments, cycloalkyl groups contain 3-8 carbon ring atoms, 3-7 carbon ring atoms, 3-6 carbon ring atoms, or 3-5 carbon ring atoms. “Cycloalkyl” groups encompass monocyclic, bicyclic, tricyclic, bridged, fused, and spiro rings, including mono spiro and dispiro rings. Cycloalkyl groups may be substituted or unsubstituted.

[0023] The term “aryl,” as used herein, is a functional group or substituent derived from an aromatic ring and encompasses monocyclic aromatic rings and bicyclic, tricyclic, and fused ring systems wherein at least one ring in the system is aromatic. An aryl group may be optionally substituted with one or more substituents.

[0024] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen; and a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or

NR⁺ (as in *N*-substituted pyrrolidiny)). In some embodiments, a heteroatom is selected from oxygen, sulfur, and nitrogen.

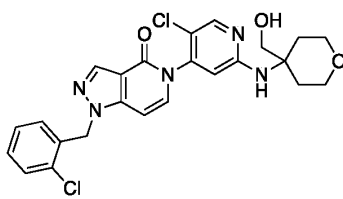
[0025] The term “heteroaliphatic,” as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced with one or more heteroatoms, for example, oxygen, sulfur, nitrogen, phosphorus, or silicon. In some embodiments, a heteroaliphatic group may be substituted with 1-5 heteroatoms. In some embodiments, a heteroaliphatic group may be substituted with 1-3 heteroatoms. In some embodiments, the heteroatoms are selected from oxygen, sulfur, and nitrogen. In some embodiments, a heteroaliphatic group may be substituted with 1-5 heteroatoms selected from oxygen, sulfur, and nitrogen. In some embodiments, a heteroaliphatic group may be substituted with 1-3 heteroatoms selected from oxygen, sulfur, and nitrogen. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include “heterocycle,” “heterocyclyl,” “heterocycloaliphatic,” and “heterocyclic” groups.

[0026] The term “heteroaryl ring,” as used herein, refers to an aromatic ring comprising at least one ring atom that is a heteroatom, such as O, N, S, P, or Si. In some embodiments, a heteroaryl ring comprises at least one ring atom that is a heteroatom selected from O, N, and S. Heteroaryl groups encompass monocyclic rings and bicyclic, tricyclic, bridged, fused, and spiro ring systems (including mono spiro and dispiro rings) having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains three to seven ring members. In some embodiments, a heteroaryl ring may be substituted with 1-5 heteroatoms. In some embodiments, a heteroaryl ring may be substituted with 1-3 heteroatoms. In some embodiments, the heteroatoms in a heteroaryl ring are selected from oxygen, sulfur, and nitrogen. In some embodiments, a heteroaryl ring may be substituted with 1-5 heteroatoms selected from oxygen, sulfur, and nitrogen. In some embodiments, a heteroaryl ring may be substituted with 1-3 heteroatoms selected from oxygen, sulfur, and nitrogen. A heteroaryl group may be optionally substituted with one or more substituents. In certain embodiments, the term “heteroaryl ring” encompasses heteroaryl rings with various oxidation states, such as heteroaryl rings containing *N*-oxides and sulfoxides.

[0027] As used herein, the term “heterocyclyl ring” refers to a non-aromatic hydrocarbon containing 3 to 12 atoms in a ring (such as, for example 3-10 atoms) comprising at least one ring atom that is a heteroatom, such as O, N, S, P, or Si, and may include one or more unsaturated bonds. “Heterocyclyl” rings encompass monocyclic, bicyclic, tricyclic,

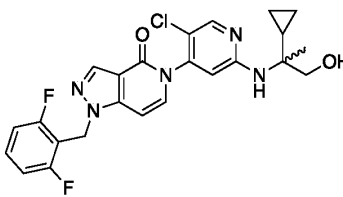
polycyclic, bridged, fused, and spiro rings, including mono spiro and dispiro rings. In some embodiments, a heterocyclyl ring has 1-5 heteroatoms. In some embodiments, a heterocyclyl ring has 1-3 heteroatoms. In some embodiments, the heteroatoms in a heterocyclyl ring are selected from oxygen, sulfur, and nitrogen. In some embodiments, a heterocyclyl ring may be substituted with 1-5 heteroatoms selected from oxygen, sulfur, and nitrogen. In some embodiments, a heterocyclyl ring may be substituted with 1-3 heteroatoms selected from oxygen, sulfur, and nitrogen.

[0028] As used herein, in any chemical structure or formula, a non-bold, straight bond, such as in Compound 34:



denotes that the configuration of the center is achiral.

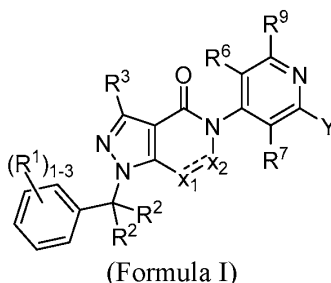
[0029] As used herein, in any chemical structure or formula, a non-bold, wavy bond (e.g., “”) at a stereocenter, such as in Compound 153:

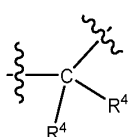
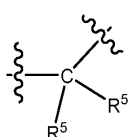


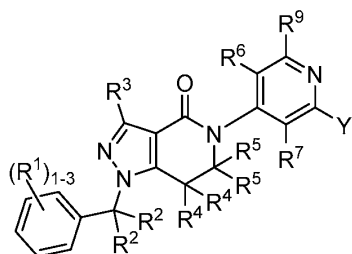
denotes that the compound was isolated as a mixture of stereoisomers (e.g., a mixture of syn and/or anti isomers or a racemic mixture).

[0030] As used herein, in any chemical structure or formula, a wavy line within a bond

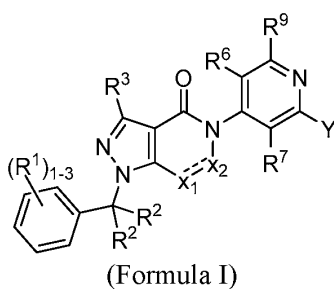
() indicates a point of attachment to the rest of a compound. For example, when $X_1 \text{---} X_2$ of Formula I:

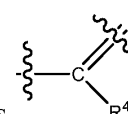
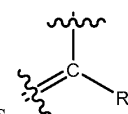


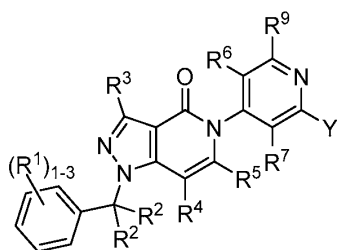
is a single bond, x_1 is  and x_2 is , which can be represented as



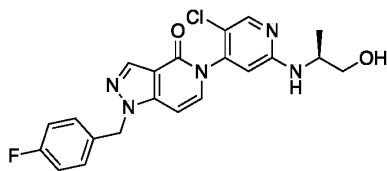
. For example, when $x_1 \text{---} x_2$ of Formula I:



is a double bond, x_1 is  and x_2 is , which can be represented as

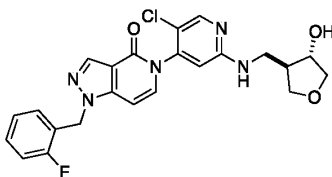


[0031] As used herein, in any chemical structure or formula, a bold or hashed wedge bond attached to a stereocenter of a compound, such as in Compound 60:



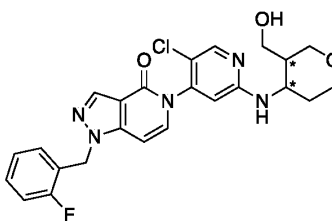
denotes the absolute stereochemistry of the stereocenter, as well as the relative stereochemistry of the stereocenter, relative to other stereocenter(s) to which bold or hashed wedge bonds are attached.

[0032] As used herein, in any chemical structure or formula, a bold or hashed straight bond attached to a stereocenter of a compound, such as in Compound 326:



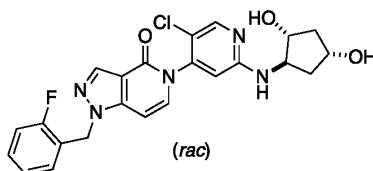
denotes the relative stereochemistry of the stereocenter, relative to other stereocenter(s) to which bold or hashed straight bonds are attached.

[0033] As used herein, in any chemical structure or formula, an asterisk adjacent to a stereocenter of a compound, such as in Compound 32:



denotes the presence of a stereocenter of unknown absolute configuration in the compound. Compound 32 is a single stereoisomer.

[0034] As used herein, the prefix “*rac*-,” when used in connection with a chiral compound, refers to a racemic mixture of the compound, such as in Compound 157:



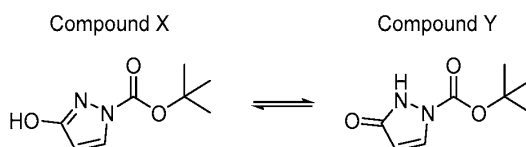
In a compound bearing the “*rac*-” prefix, the (*R*)- and (*S*)-designators in the chemical name reflect the relative stereochemistry of the compound.

[0035] As used herein, the prefix “*rel*-,” when used in connection with a chiral compound, refers to a single enantiomer of unknown absolute configuration. In a compound bearing the “*rel*-” prefix, the (*R*)- and (*S*)- designators in the chemical name reflect the relative stereochemistry of the compound, but do not necessarily reflect the absolute stereochemistry of the compound. Where the relative stereochemistry of a given stereocenter is unknown, no stereochemical designator is provided. In some instances, the absolute configuration of some stereocenters is known, while only the relative configuration of the other stereocenters is

known. In these instances, the stereochemical designators associated with the stereocenters of known absolute configuration are marked with an asterisk (*), e.g., (*R**)- and (*S**)-, while the stereochemical designators associated with stereocenters of unknown absolute configuration are not so marked. The unmarked stereochemical designators associated with the stereocenters of unknown absolute configuration reflect the relative stereochemistry of those stereocenters with respect to other stereocenters of unknown absolute configuration, but do not necessarily reflect the relative stereochemistry with respect to the stereocenters of known absolute configuration.

[0036] Certain compounds can exist as atropisomers. It will be appreciated that certain compounds of this disclosure may exist as separated atropisomers and/or mixtures of those atropisomers, i.e., a subclass of stereoisomers resulting from hindered rotation about single bonds or chirality axis and that can be isolated as separate chemical species.

[0037] Certain compounds disclosed herein may exist as tautomers and both tautomeric forms are intended, even though only a single tautomeric structure is depicted. For example, a description of Compound X is understood to include its tautomer Compound Y and vice versa, as well as mixtures thereof:



Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0038] “Tert” and “*t*-” are used interchangeably and mean tertiary.

[0039] Compounds described herein may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the disclosure. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted.”

“Substituted,” whether preceded by the term “optionally” or not, indicates that at least one hydrogen of the “substituted” group is replaced by a substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent chosen from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned by

this disclosure are preferably those that result in the formation of stable or chemically feasible compounds.

[0040] The term “compound,” when referring to a compound of this disclosure, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules.

[0041] The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein.

[0042] The term “stable compounds,” as used herein, refers to compounds which possess sufficient stability to allow for their manufacture and which maintain the integrity of the compounds for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediates, and/or treating a disease or condition responsive to therapeutic agents).

[0043] In the compounds of this disclosure, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen,” the position is understood to have hydrogen at its natural abundance isotopic composition.

[0044] As used herein, the term “derivative” refers to a collection of molecules having a chemical structure identical to a compound of this disclosure, except that one or more atoms of the molecule may have been substituted with another atom. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C or ^{14}C , are within the scope of this disclosure. Such compounds are useful as, for example, analytical tools, probes in biological assays, or compounds with improved therapeutic profiles.

[0045] As used herein, “deuterated derivative(s)” refers to a compound having the same chemical structure as a reference compound, with one or more hydrogen atoms replaced by a deuterium atom. In some embodiments, the one or more hydrogens replaced by deuterium are part of an alkyl group. In some embodiments, the one or more hydrogens replaced by deuterium are part of a methyl group. In some embodiments, the one or more hydrogens replaced by deuterium are part of an aryl group. In some embodiments, the one or more

hydrogens replaced by deuterium are part of a phenyl group. In chemical structures, deuterium may be represented as “D” or “²H.”

[0046] In compounds identified as a deuterated derivative, or containing a “D” or “²H” substitution, the deuterium atom is present in amounts exceeding its natural abundance; for example, the compound may have an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom). In some embodiments, if a substituent in a compound of the disclosure is denoted as deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0047] As used herein, the terms “about” and “approximately,” when used in connection with amounts, volumes, reaction times, reaction temperatures, etc. mean an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In some embodiments, the terms “about” and “approximately” mean within 1, 2, 3, or 4 standard deviations. In some embodiments, the terms “about” and “approximately” mean within 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, or 0.05% of a given value or range. In some embodiments, “about” and “approximately” mean within 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% of a given value or range. In certain embodiments, “about” and “approximately” mean within 15% of a given value or range. In some embodiments, “about” and “approximately” mean within 10% of a given value. In some embodiments, “about” and “approximately” mean within 5% of a given value.

[0048] As used herein, the symbol “~” appearing immediately before a numerical value has the same meaning as the terms “about” and “approximately.”

[0049] The term “at least one” refers to one or more.

[0050] The term “at least one compound selected from,” as used herein, refers to the selection of one or more of the compounds from a specified group. “Selected from” and “chosen from” may be used interchangeably herein.

[0051] As used herein, the term “ambient conditions” means room temperature, open air condition and uncontrolled humidity condition. As used herein, the term “room temperature” or “ambient temperature” means 15 °C to 30 °C.

[0052] As used herein, the term “active pharmaceutical ingredient” or “therapeutic agent” (“API”) refers to a biologically active compound.

[0053] The terms “patient” and “subject” are used interchangeably and refer to an animal, including a human.

[0054] The terms “effective dose” and “effective amount” are used interchangeably herein and refer to that amount of a compound that produces the desired effect for which it is administered (e.g., provision of more functional PC1 protein, improvement in ADPKD or a symptom of ADPKD, lessening the severity of ADPKD or a symptom of ADPKD, or slowing the progression of ADPKD or a symptom of ADPKD). The exact amount of an effective dose will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lloyd (1999) *The Art, Science and Technology of Pharmaceutical Compounding*).

[0055] As used herein, the terms “treatment,” “treating,” and the like generally mean restoring expression and translation of functional PC1 and improving one or more symptoms of ADPKD, delaying the onset of one or more symptoms of ADPKD, or lessening the severity of ADPKD or one or more symptoms of ADPKD in a subject. Thus, “treatment,” as used herein, includes, but is not limited to, slowing or halting decline in kidney function, generation of cysts, cyst growth, cyst pain, and reducing the frequency, severity, or delaying onset of adverse cerebro-/cardio-vascular events. In some embodiments, “treatment” means slowing or halting the generation of cysts. Improvements in, or lessening the severity of, any of the symptoms of ADPKD can be readily assessed according to standard methods and techniques known in the art.

[0056] As used herein, the term “in combination with,” when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to the patient prior to, concurrent with, or subsequent to each other.

[0057] The term “pharmaceutically acceptable,” as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response, and the like, and is commensurate with a reasonable benefit/risk ratio.

[0058] As used herein, the term “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. A “pharmaceutically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient. One of ordinary skill in the art would recognize that, when an amount of “a compound or a pharmaceutically acceptable salt thereof” is disclosed, the amount of the pharmaceutically acceptable salt form of the compound is the amount equivalent to the concentration of the free base of the compound.

[0059] A “free base” form of a compound does not contain an ionically bonded salt. It is noted that the disclosed amounts of the compounds or their pharmaceutically acceptable salts thereof herein are based upon their free base form. For example, “10 mg of at least one compound chosen from Compound **I** and pharmaceutically acceptable salts thereof” includes 10 mg of Compound **I** and a concentration of a pharmaceutically acceptable salt of Compound **I** equivalent to 10 mg of Compound **I**.

[0060] Suitable pharmaceutically acceptable salts are, for example, those disclosed in S. M. Berge et al. *J. Pharmaceutical Sciences*, 1977, 66, 1-19. For example, Table 1 of that article provides the following pharmaceutically acceptable salts:

Table 1 of Berge et al.:

Acetate	Iodide	Benzathine
Benzenesulfonate	Isethionate	Chloroprocaine
Benzoate	Lactate	Choline
Bicarbonate	Lactobionate	Diethanolamine
Bitartrate	Malate	Ethylenediamine
Bromide	Maleate	Meglumine
Calcium edetate	Mandelate	Procaine
Camsylate	Mesylate	Aluminum
Carbonate	Methylbromide	Calcium
Chloride	Methylnitrate	Lithium
Citrate	Methylsulfate	Magnesium
Dihydrochloride	Mucate	Potassium
Edetate	Napsylate	Sodium
Edisylate	Nitrate	Zinc
Estolate	Pamoate (Embonate)	Triethiodide
Esylate	Pantothenate	
Fumarate	Phosphate/diphosphate	
Glucaptate	Polygalacturonate	

Gluconate	Salicylate	
Glutamate	Stearate	
Glycolylarsanilate	Subacetate	
Hexylresorcinate	Succinate	
Hydrabamine	Sulfate	
Hydrobromide	Tannate	
Hydrochloride	Tartrate	
Hydroxynaphthoate	Teociate	

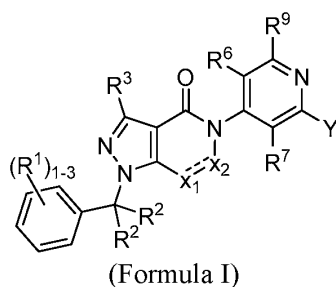
[0061] Non-limiting examples of pharmaceutically acceptable acid addition salts include: salts formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, or perchloric acid; salts formed with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid; and salts formed by using other methods used in the art, such as ion exchange. Non-limiting examples of pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, and valerate salts. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}alkyl)_4$ salts. This disclosure also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Suitable non-limiting examples of alkali and alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium. Further non-limiting examples of pharmaceutically acceptable salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Other suitable, non-limiting examples of pharmaceutically acceptable salts include besylate and glucosamine salts.

[0062] The term “prodrug,” as used herein, represents a compound that is transformed *in vivo* into a compound according to any one of the formulae listed herein. Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the

compounds of the invention may be, for example, amides. Amides that may be utilized as prodrugs in the present invention are phenyl amides, aliphatic (C₁-C₂₄) amides, acyloxymethyl amides, ureas, carbamates, and amino acid amides. For example, a compound of the invention that contains an NH group may be acylated at this position in its prodrug form. Other prodrug forms include esters, such as, for example phenyl esters, aliphatic (C₁-C₂₄) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and Judkins *et al.*, *Synthetic Communications* 26(23):4351-4367, 1996, each of which is incorporated in its entirety herein by reference. In some embodiments, the present invention features a prodrug of any one of the formulae or compounds listed herein.

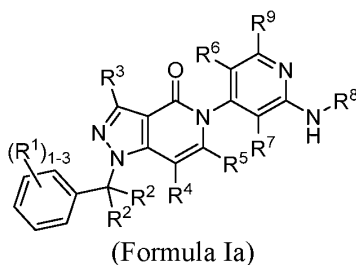
Compounds

[0063] In some embodiments, compounds of the invention are selected from compounds of Formula I:



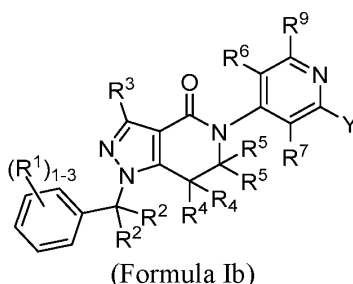
as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein the variables are as defined above for Formula I.

[0064] The compounds of Formula I include compounds of Formula Ia:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein the variables are as defined above for Formula Ia.

[0065] The compounds of Formula I also include compounds of Formula Ib:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein the variables are as defined above for Formula Ib.

[0066] In some embodiments of Formulae I, Ia, and Ib, each **R¹** is independently selected from hydrogen, methyl, methoxy, fluoro, chloro, and cyano. In some embodiments, **R¹** is fluoro. In some embodiments, there are two **R¹** and each is fluoro. In some embodiments, there are three **R¹** and each is fluoro. In some embodiments, **R¹** is chloro. In some embodiments, there are two **R¹** and each is chloro. In some embodiments, there are two **R¹** and one **R¹** is fluoro and one **R¹** is chloro. In some embodiments, there are two **R¹** and one **R¹** is fluoro and one **R¹** is methyl. In some embodiments, there are two **R¹** and one **R¹** is fluoro and one **R¹** is cyano.

[0067] In some embodiments of Formulae I, Ia, and Ib, at least one **R¹** is *ortho* to attachment point of the benzyl methylene. In some embodiments, there is only one **R¹** and it is *ortho* to the attachment point of the benzyl methylene. In some embodiments, there are two **R¹** and each is *ortho* to the attachment point of the benzyl methylene.

[0068] In some embodiments of Formulae I, Ia, and Ib, there is one **R¹** *ortho* to the attachment point of the benzyl methylene selected from fluoro, chloro, cyano, and methyl. In some embodiments, the one **R¹** is fluoro. In some embodiments, the one **R¹** is chloro. In some embodiments, the one **R¹** is cyano. In some embodiments, the one **R¹** is methyl.

[0069] In some embodiments of Formulae I, Ia, and Ib, there are two **R¹** and both are *ortho* to the attachment point of the benzyl methylene and each **R¹** is independently selected

from fluoro, chloro, cyano, and methyl. In some embodiments, each R^1 is fluoro. In some embodiments, each R^1 is selected from fluoro and chloro. In some embodiments, each R^1 is selected from fluoro and cyano. In some embodiments, each R^1 is selected from fluoro and methyl. In some embodiments, each R^1 is chloro.

[0070] In some embodiments of Formulae I, Ia, and Ib, at least one R^1 is *meta* to attachment point of the benzyl methylene. In some embodiments, there is one R^1 and it is *meta* to attachment point of the benzyl methylene. In some embodiments, the one R^1 is fluoro.

[0071] In some embodiments of Formulae I, Ia, and Ib, there is one R^1 and it is *para* to attachment point of the benzyl methylene. In some embodiments, the one R^1 is fluoro.

[0072] In some embodiments of Formulae I, Ia, and Ib, there are three R^1 and two R^1 are *ortho* to attachment point of the benzyl methylene and one R^1 is *meta* to attachment point of the benzyl methylene. In some embodiments, all three R^1 are fluoro.

[0073] In some embodiments of Formulae I, Ia, and Ib, there are three R^1 and two R^1 are *ortho* to attachment point of the benzyl methylene and one R^1 is *para* to attachment point of the benzyl methylene. In some embodiments, all three R^1 are fluoro.

[0074] In some embodiments of Formulae I, Ia, and Ib, each R^2 is independently selected from hydrogen and methyl. In some embodiments, each R^2 is hydrogen. In some embodiments, each R^2 is methyl. In some embodiments, one R^2 is hydrogen and one R^2 is methyl.

[0075] In some embodiments of Formulae I, Ia, and Ib, R^3 is selected from C₁-C₃ alkyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is cyano.

[0076] In some embodiments of Formulae I, Ia, and Ib, R^3 is hydrogen.

[0077] In some embodiments of Formulae I, Ia, and Ib, R^4 and R^5 are independently selected from hydrogen and methyl. In some embodiments, R^4 is methyl. In some embodiments, R^5 is methyl. In some embodiments, R^4 is methyl and R^5 is hydrogen. In some embodiments, R^4 is hydrogen and R^5 is methyl. In some embodiments, R^4 and R^5 are both hydrogen. In some embodiments of Formulae I, Ia, and Ib, R^6 is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano. In some embodiments, R^6 is selected from methyl, ethyl, fluoro, chloro, bromo, and cyano. In some embodiments, R^6 is methyl. In some embodiments, R^6 is fluoro. In some embodiments, R^6 is chloro. In some embodiments, R^6 is bromo. In some embodiments, R^6 is cyano.

[0078] In some embodiments of Formulae I, Ia, and Ib, R^7 is selected from hydrogen and methyl. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is methyl.

[0079] In some embodiments of Formulae I, Ia, and Ib, R^5 and R^7 are independently selected from hydrogen and C_1 - C_3 alkyl. In some embodiments, R^5 and R^7 are independently selected from hydrogen and methyl. In some embodiments, R^5 and R^7 are both hydrogen. In some embodiments, R^5 is hydrogen and R^7 is methyl. In some embodiments, R^5 is methyl and R^7 is hydrogen. In some embodiments, R^5 and R^7 are both methyl.

[0080] In some embodiments of Formulae I, Ia, and Ib, R^6 is methyl and R^7 is hydrogen. In some embodiments, R^6 is fluoro and R^7 is hydrogen. In some embodiments, R^6 is fluoro and R^7 is methyl. In some embodiments, R^6 is chloro and R^7 is hydrogen. In some embodiments, R^6 is chloro and R^7 is methyl. In some embodiments, R^6 is bromo and R^7 is hydrogen. In some embodiments, R^6 is cyano and R^7 is hydrogen.

[0081] In some embodiments of Formulae I, Ia, and Ib, R^5 is hydrogen, R^6 is halogen, and R^7 is hydrogen. In some embodiments, R^5 is hydrogen, R^6 is fluoro, and R^7 is hydrogen. In some embodiments, R^5 is hydrogen, R^6 is chloro, and R^7 is hydrogen. In some embodiments, R^5 is hydrogen, R^6 is bromo, and R^7 is hydrogen.

[0082] In some embodiments of Formulae I, Ia, and Ib, R^5 is hydrogen, R^6 is C_1 - C_3 alkyl, and R^7 is hydrogen. In some embodiments, R^5 is hydrogen, R^6 is methyl, and R^7 is hydrogen.

[0083] In some embodiments of Formulae I, Ia, and Ib, R^5 is hydrogen, R^6 is cyano, and R^7 is hydrogen.

[0084] In some embodiments of Formulae I, Ia, and Ib, R^5 is hydrogen, R^6 is halogen, and R^7 is methyl. In some embodiments, R^5 is hydrogen, R^6 is fluoro, and R^7 is methyl. In some embodiments, R^5 is hydrogen of Formulae I, Ia, and Ib, R^6 is chloro, and R^7 is methyl.

[0085] In some embodiments of Formulae I, Ia, and Ib, R^5 is methyl, R^6 is halogen, and R^7 is hydrogen. In some embodiments, R^5 is methyl, R^6 is chloro, and R^7 is hydrogen.

[0086] In some embodiments of Formulae I, Ia, and Ib, R^5 is methyl, R^6 is halogen, and R^7 is methyl. In some embodiments, R^5 is methyl, R^6 is chloro, and R^7 is methyl.

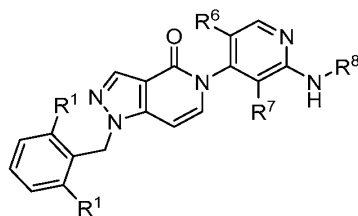
[0087] In some embodiments of Formulae I, Ia, and Ib, R^9 is selected from hydrogen, C_1 - C_3 alkyl, halogen, and cyano. In some embodiments, R^9 is hydrogen.

[0088] In some embodiments of Formulae I, Ia, and Ib, R^4 and R^5 are both hydrogen. In some embodiments, R^3 , R^4 , and R^5 are each hydrogen. In some embodiments, R^2 , R^3 , R^4 ,

and R^5 are each hydrogen. In some embodiments, R^2 , R^3 , R^4 , R^5 , and R^7 are each hydrogen.

In some embodiments, R^2 , R^3 , R^4 , R^5 , R^7 , and R^9 are each hydrogen.

[0089] In some embodiments, the compound of Formula I or Ia is a compound of Formula II:



(Formula II),

as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein each R^1 is independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;

R^6 is selected from C₁-C₃ alkyl, halogen, and cyano;

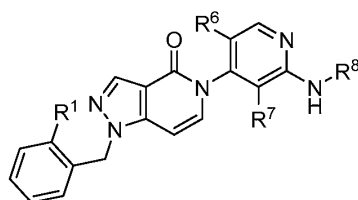
R^7 is selected from hydrogen, C₁-C₃ alkyl, and halogen; and

R^8 is selected from:

- hydrogen,
- C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
- C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
- 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,

- hydroxyl, and
- C₁-C₃ alkyl (substituted with 0-1 hydroxyl group).

[0090] In some embodiments, the compound of Formula I or Ia is a compound of Formula IIa:

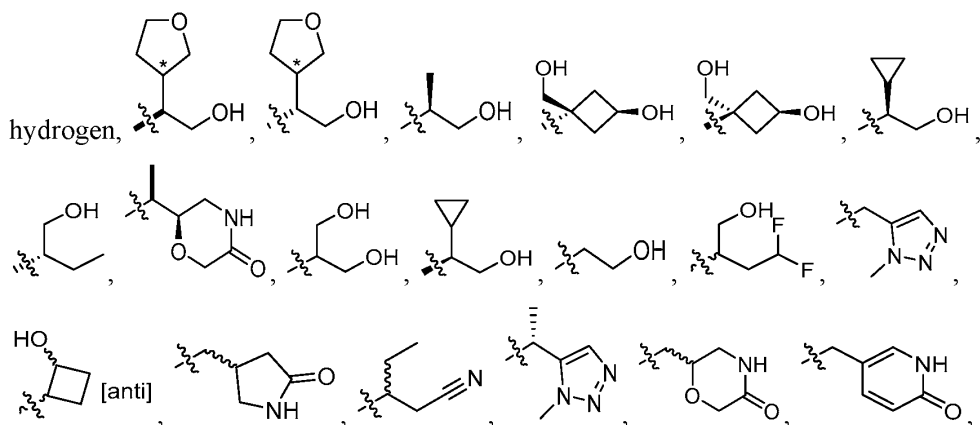


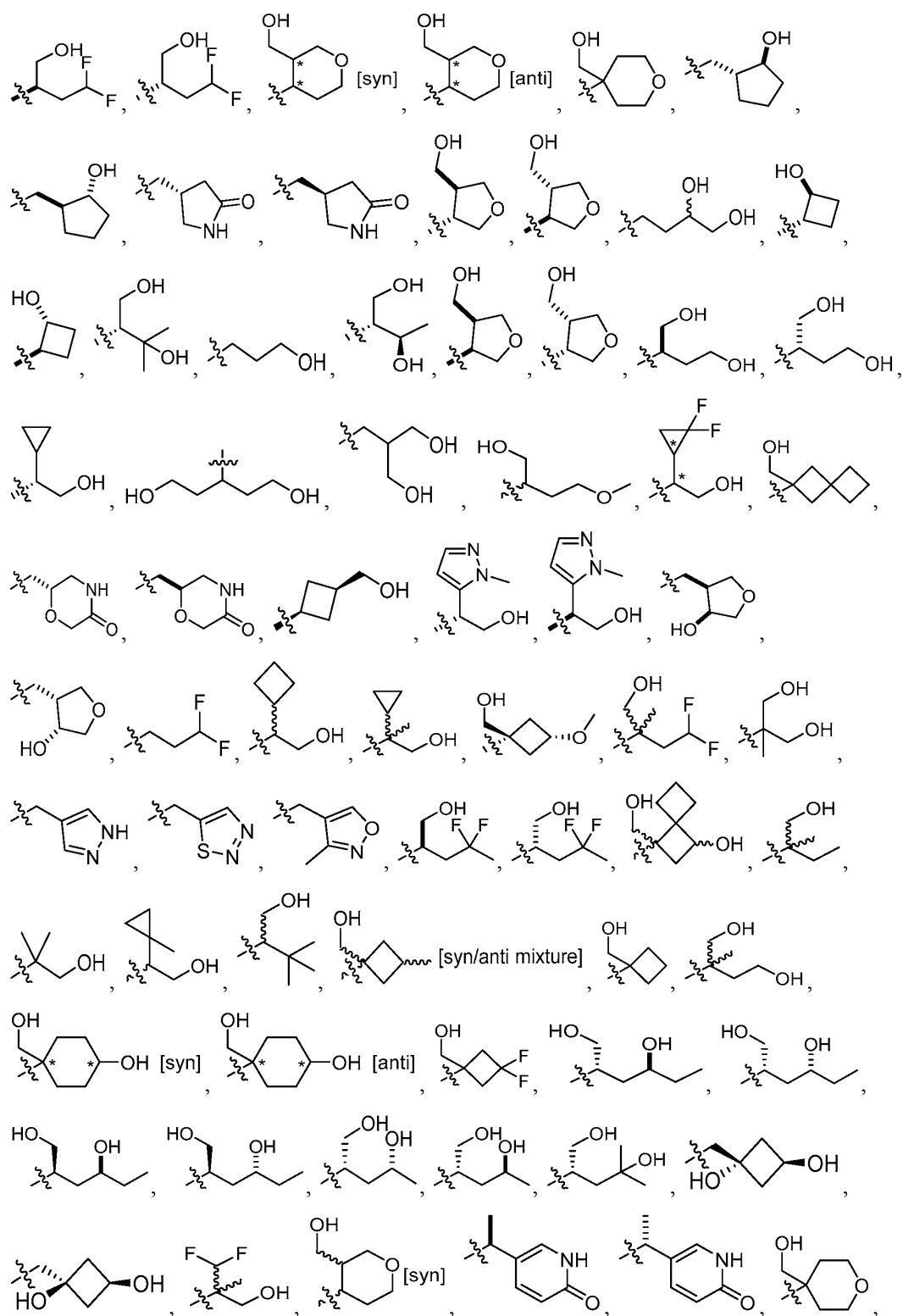
(Formula IIa),

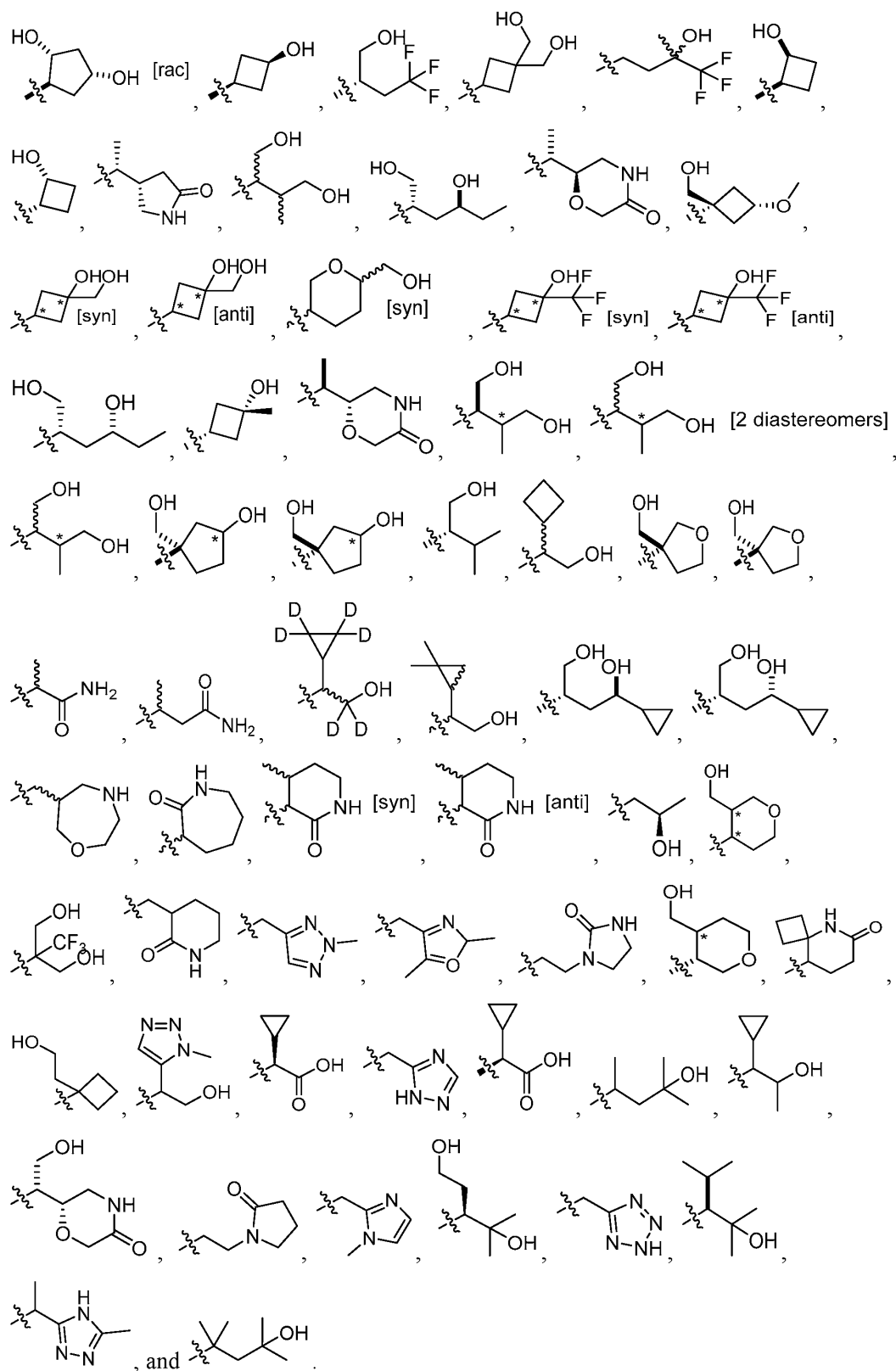
as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein **R¹** is selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano; and all other variables are as defined above for Formula II.

[0091] In some embodiments of Formulae II and IIa, each **R¹** is independently selected from hydrogen, fluoro, chloro, cyano, and methyl. In some embodiments of Formulae II and IIa, **R⁶** is selected from methyl, fluoro, chloro, bromo, and cyano. In some embodiments of Formulae II and IIa, **R⁷** is selected from hydrogen and methyl. In some embodiments of Formulae II and IIa, each **R¹** is independently selected from hydrogen, fluoro, chloro, cyano, and methyl; **R⁶** is selected from methyl, fluoro, chloro, and cyano; and **R⁷** is selected from hydrogen and methyl. In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from hydrogen, C₁-C₈ alkyl substituted with 0-5 groups, C₃-C₇ cycloalkyl substituted with 0-3 groups, and 5- to 9-membered heterocyclyl substituted with 0-2 groups.

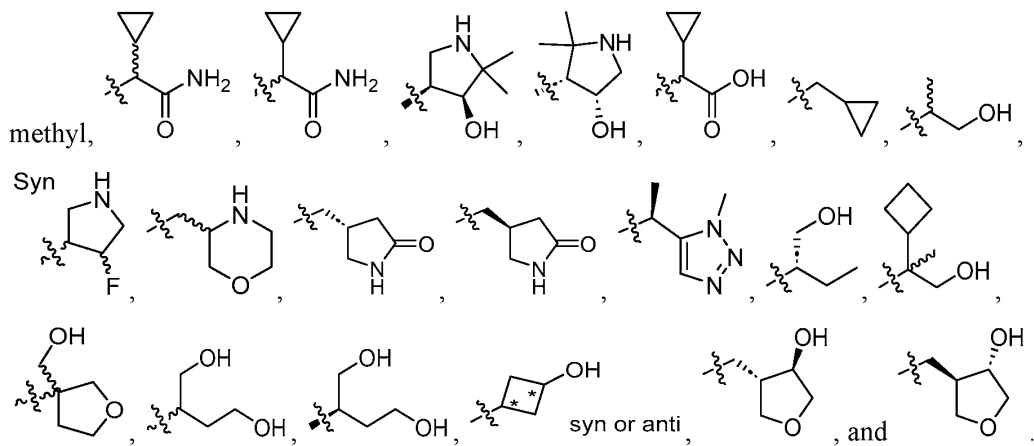
[0092] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from:





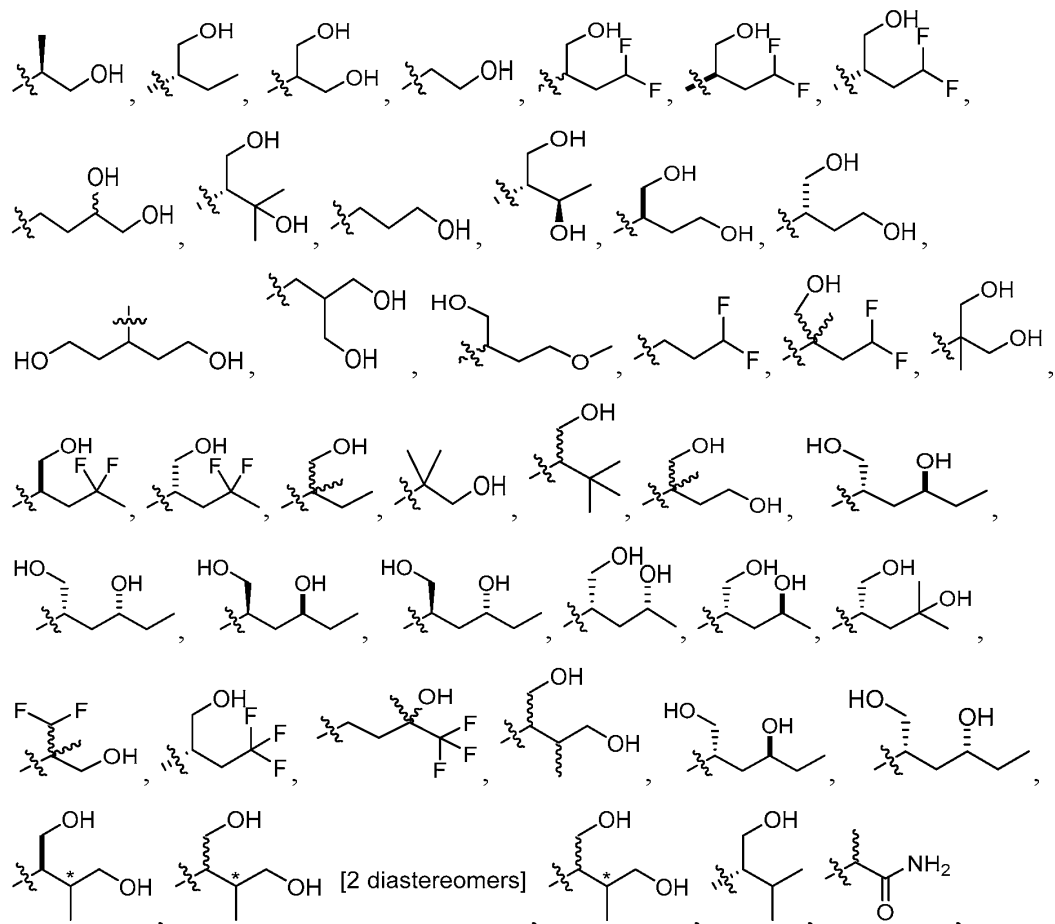


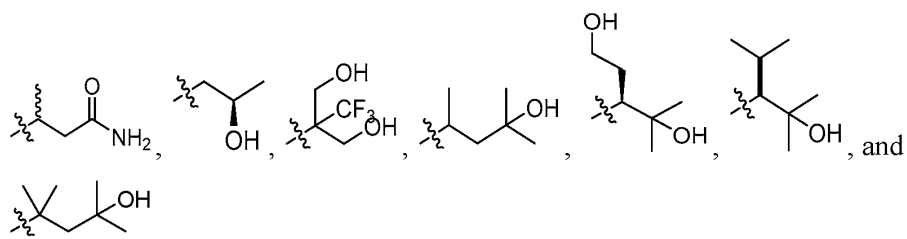
[0093] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from:



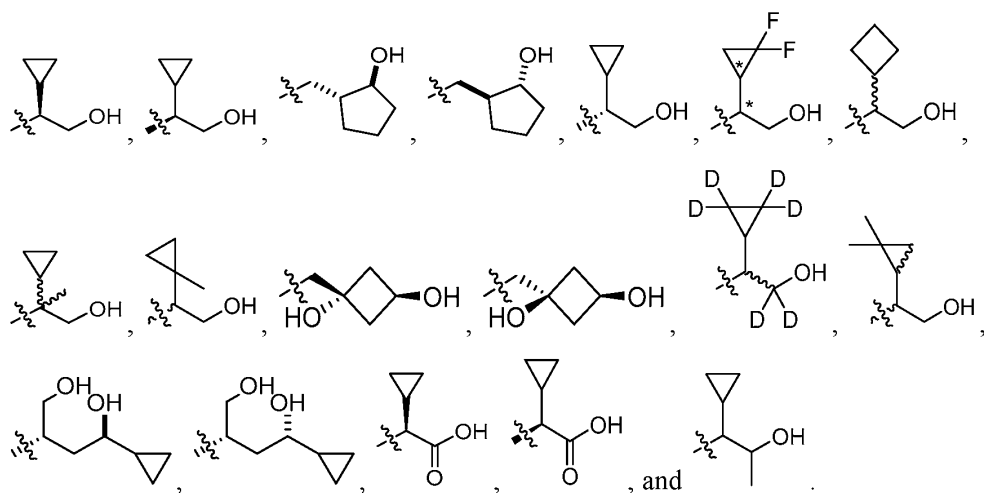
[0094] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from C₁-C₈ alkyl substituted with 0-5 groups.

[0095] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from:

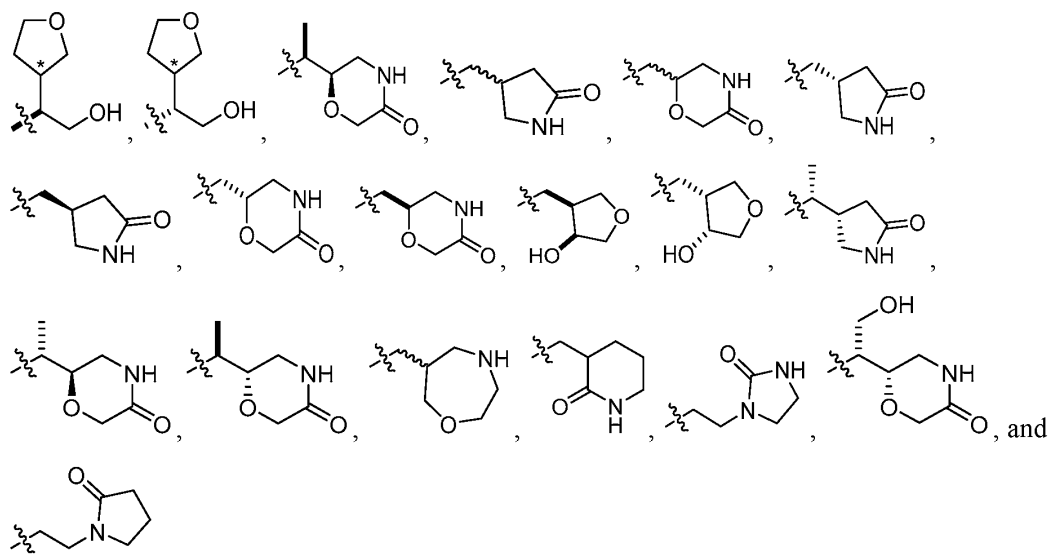


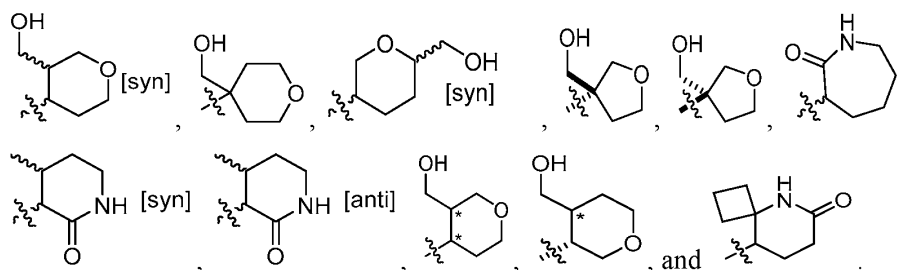


[0096] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from:

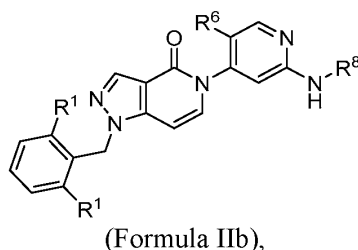


[0097] In some embodiments of Formulae I, Ia, Ib, II, and IIa, **R⁸** is selected from:





[00103] In some embodiments, the compound of Formula I or Ia is a compound of Formula IIb:



as well as tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen and halogen;
- **R⁶** is selected from halogen; and
- **R⁸** is selected from:
 - C₁-C₅ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl, and
 - C₃-C₆ cycloalkyl;
 - C₃-C₆ cycloalkyl, substituted with 0-2 groups selected from hydroxyl and halogen; and
 - 5- to 6-membered heterocyclyl unsubstituted or substituted with C₁-C₃ alkyl, wherein the C₁-C₃ alkyl is substituted with 0-2 substituents selected from hydroxyl and halogen.

[00104] In some embodiments of Formula IIb, each **R¹** is independently selected from hydrogen and fluoro. In some embodiments of Formula IIb, each **R¹** is hydrogen. In some embodiments of Formula IIb, one **R¹** is hydrogen and one **R¹** is fluoro. In some embodiments of Formula IIb, each **R¹** is fluoro.

[00105] In some embodiments of Formula IIb, **R⁶** is selected from fluoro and chloro. In some embodiments of Formula IIb, **R⁶** is fluoro. In some embodiments of Formula IIb, **R⁶** is chloro.

[00106] In some embodiments of Formula IIb, **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, **R⁸** is selected from C₁-C₃ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, **R⁸** is selected from C₁-C₃ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃ cycloalkyl. In some embodiments of Formula IIb, **R⁸** is selected from C₁-C₃ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₄ cycloalkyl. In some embodiments of Formula IIb, **R⁸** is selected from C₁-C₃ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₅ cycloalkyl.

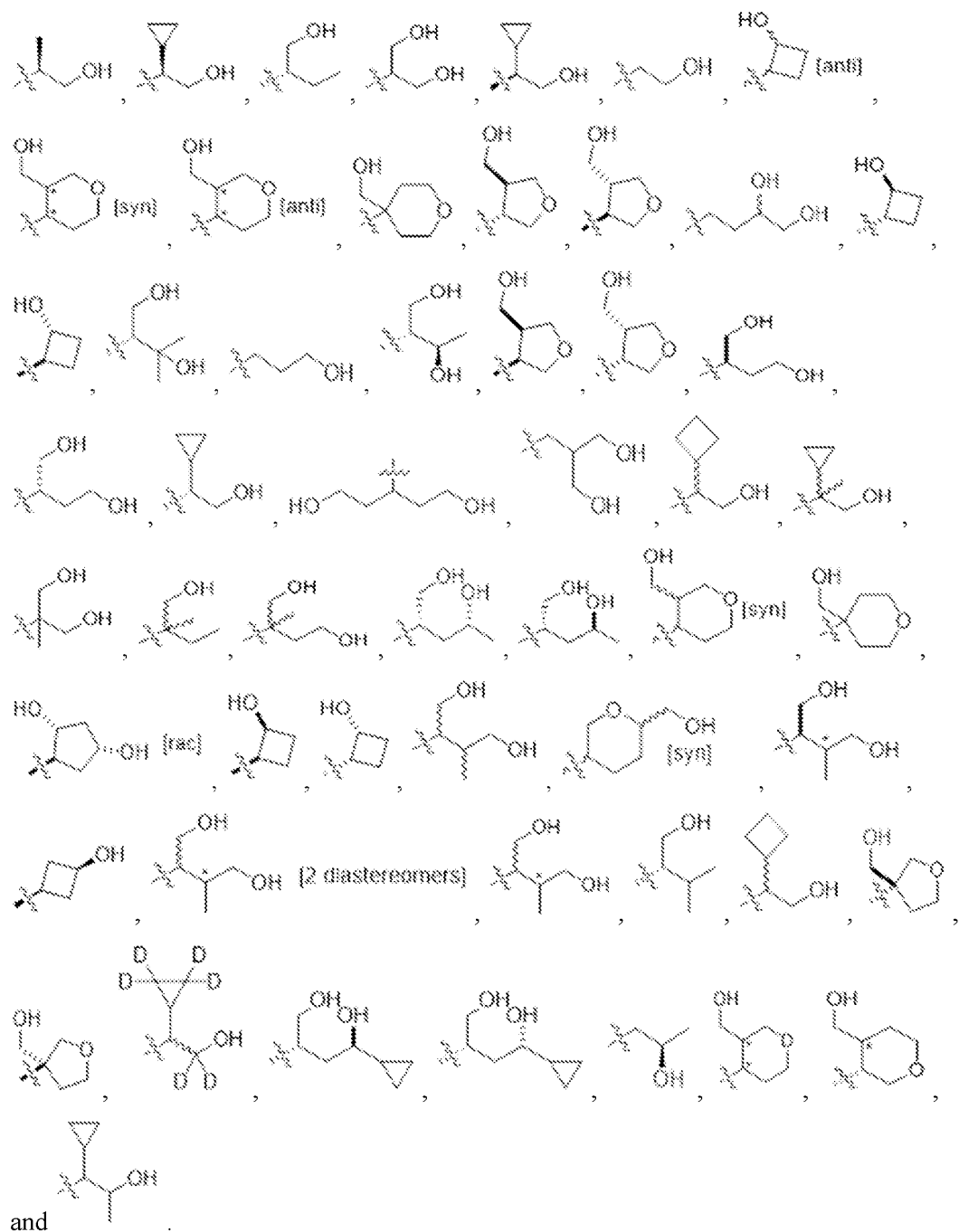
[00107] In some embodiments of Formula IIb, each **R¹** is independently selected from hydrogen and fluoro and **R⁶** is selected from fluoro and chloro. In some embodiments of Formula IIb, each **R¹** is independently selected from hydrogen and fluoro and **R⁶** is fluoro. In some embodiments of Formula IIb, each **R¹** is independently selected from hydrogen and fluoro and **R⁶** is chloro.

[00108] In some embodiments of Formula IIb, each **R¹** is fluoro and **R⁶** is selected from fluoro and chloro. In some embodiments of Formula IIb, each **R¹** is fluoro and **R⁶** is fluoro. In some embodiments of Formula IIb, each **R¹** is fluoro and **R⁶** is chloro.

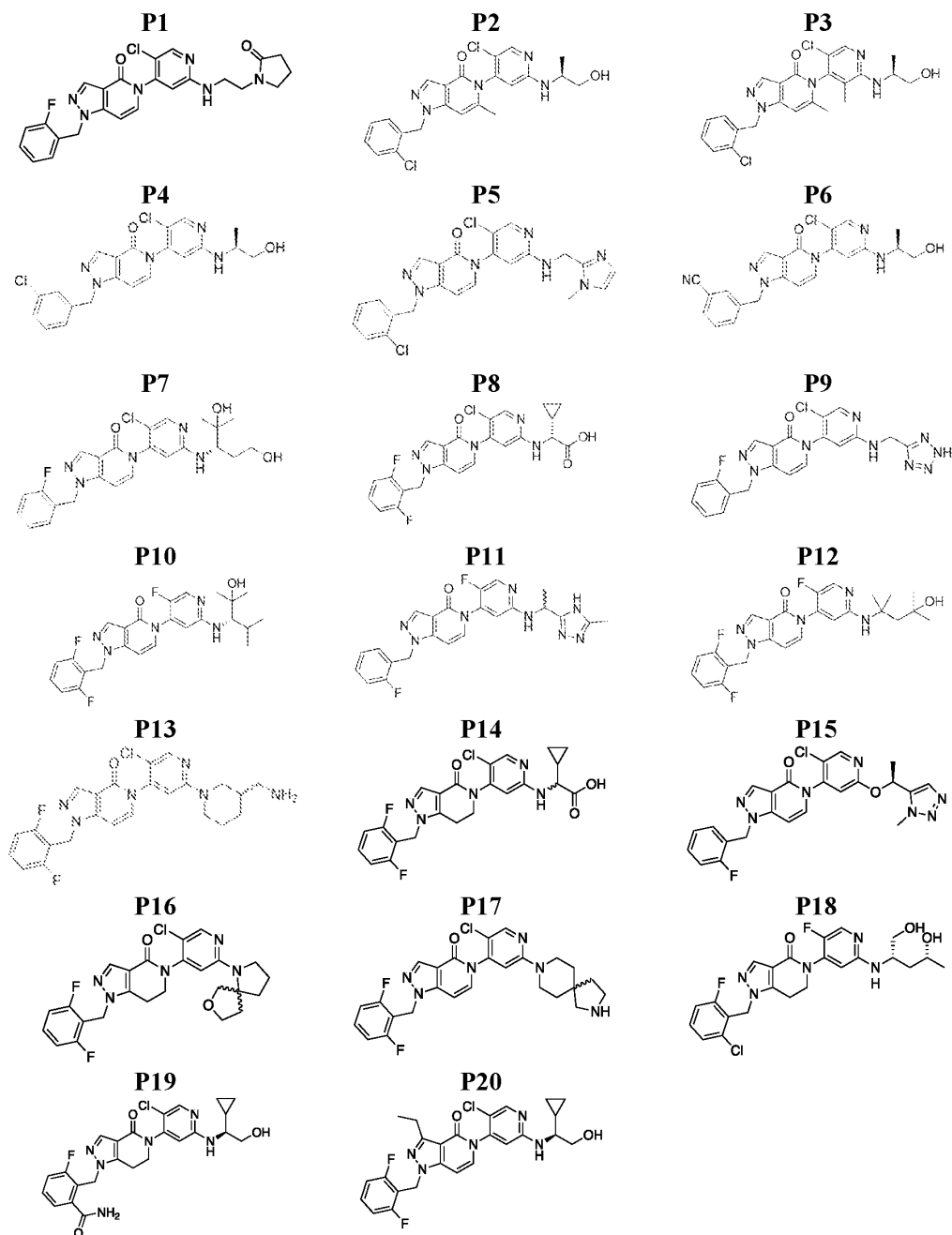
[00109] In some embodiments of Formula IIb, **R⁶** is selected from fluoro and chloro and **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, **R⁶** is fluoro and **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, **R⁶** is chloro and **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl.

[00110] In some embodiments of Formula IIb, each **R¹** is independently selected from hydrogen and fluoro, **R⁶** is selected from fluoro and chloro, and **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, each **R¹** is fluoro, **R⁶** is fluoro, and **R⁸** is selected from C₁-C₅ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl. In some embodiments of Formula IIb, each **R¹** is fluoro, **R⁶** is chloro, and **R⁸** is selected from C₁-C₃ alkyl substituted with 1-3 groups independently selected from hydroxyl and C₃-C₅ cycloalkyl.

[00111] In some embodiments of Formula IIb, $\mathbf{R}^8$ is selected from:



[00112] Compounds P1 – P20 did not demonstrate detectable activity in the assay described herein, therefore, in some embodiments, the compound of Formulae I, Ia, Ib, II, or IIa is not:

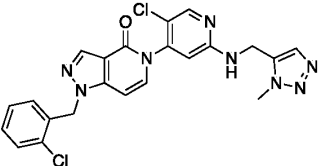
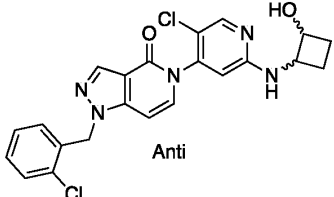
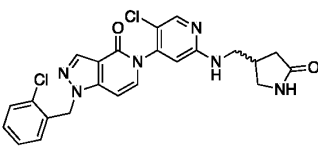
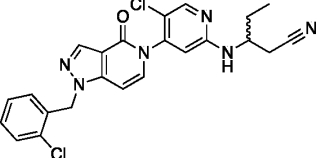
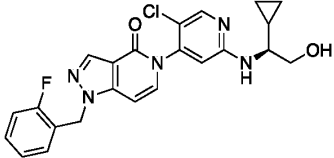
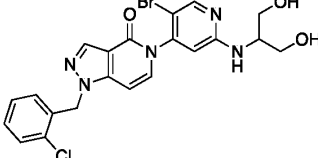
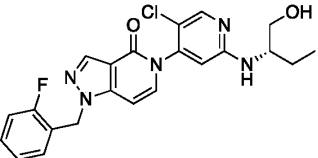
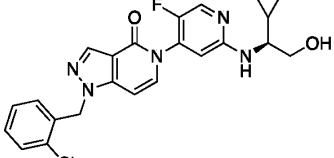
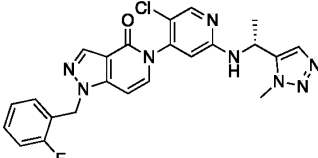
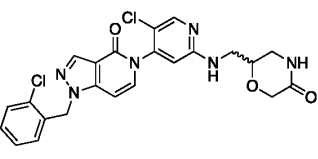
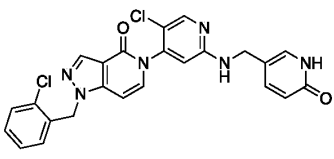
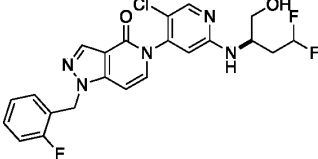
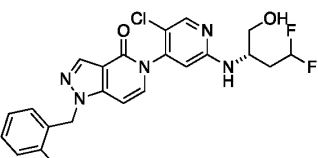
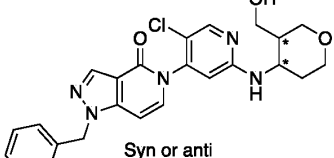
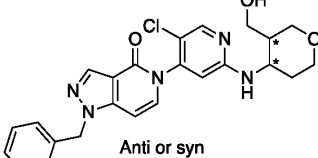
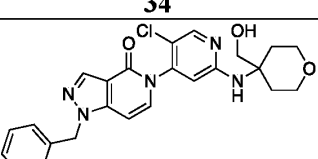
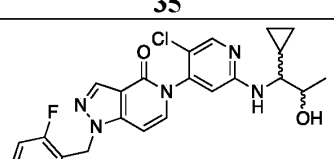
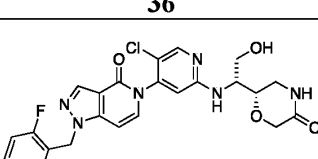
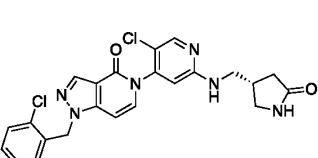
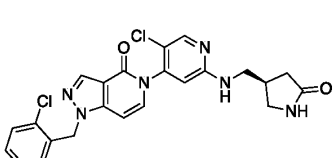
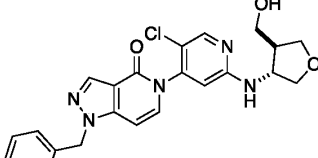


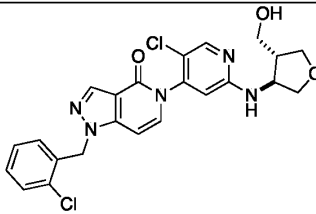
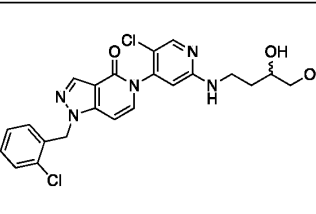
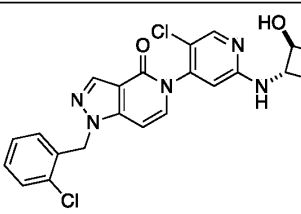
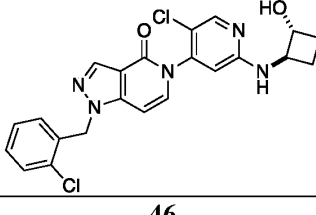
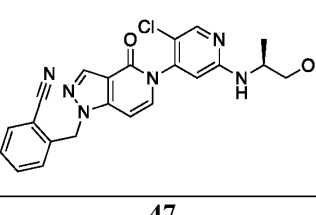
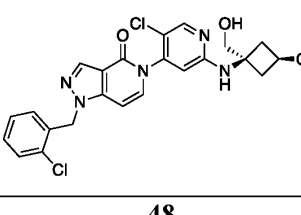
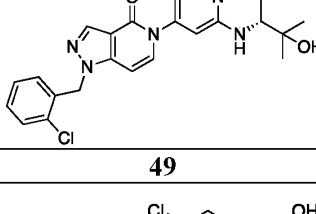
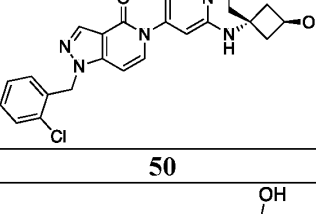
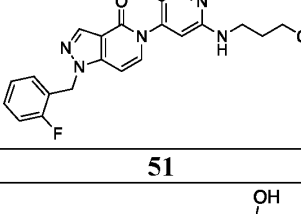
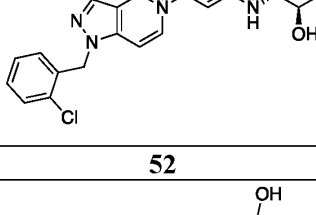
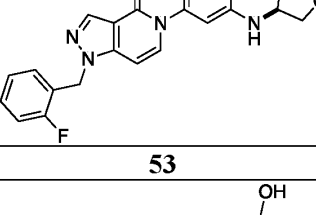
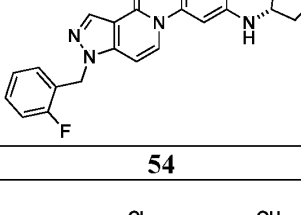
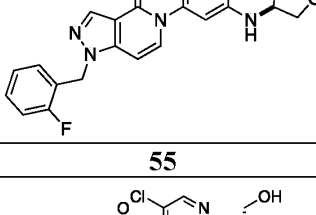
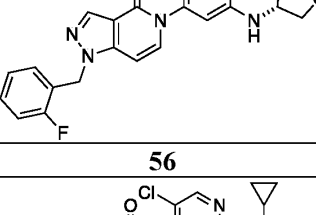
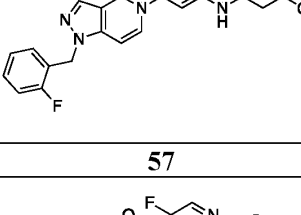
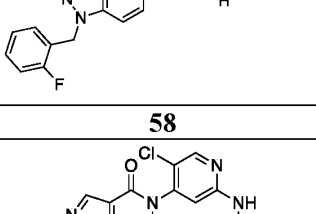
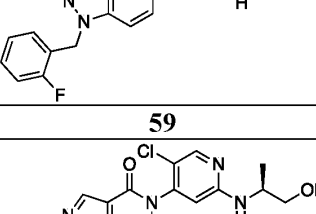
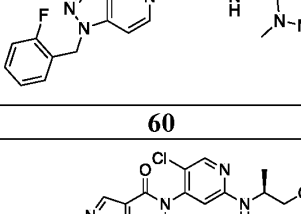
or a tautomer or atropisomer of the compound, deuterated derivative of the compound, tautomer, or atropisomer, or a pharmaceutically acceptable salt or prodrug of the compound, tautomer, atropisomer, or deuterated derivative.

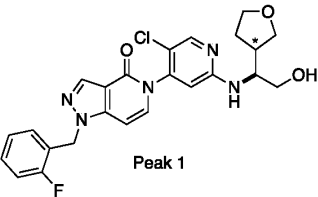
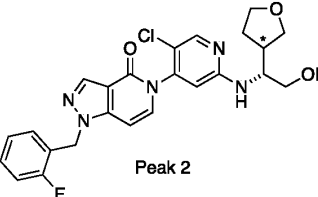
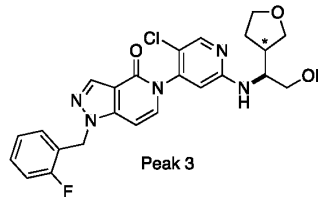
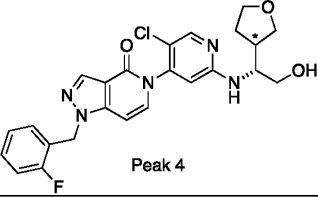
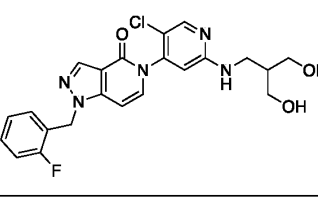
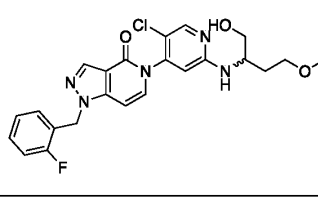
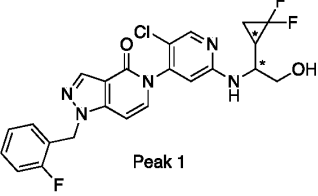
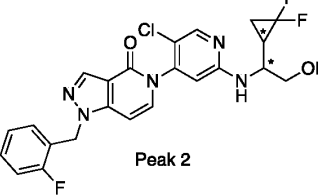
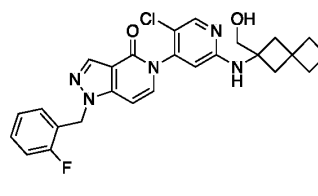
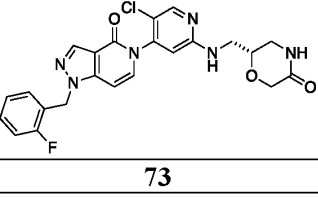
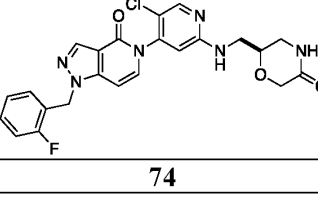
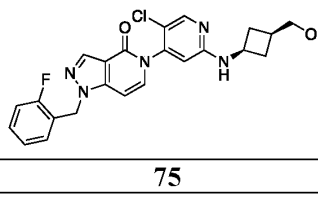
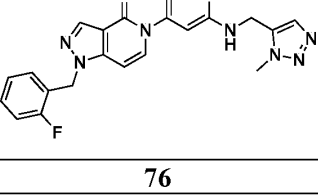
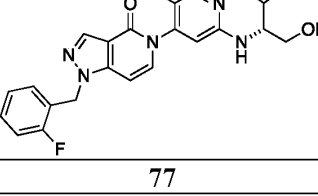
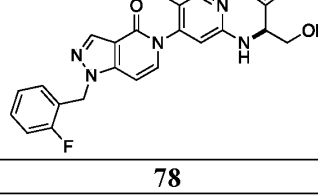
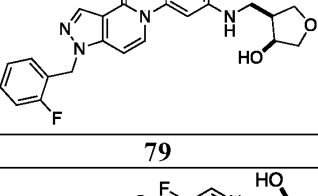
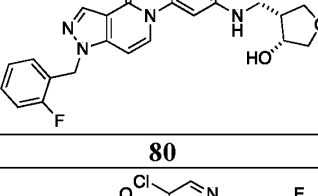
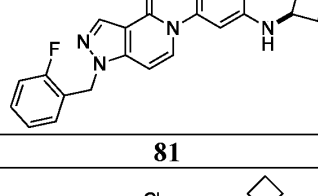
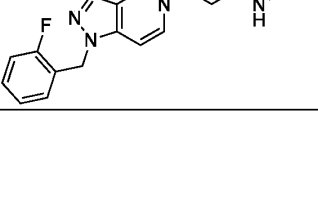
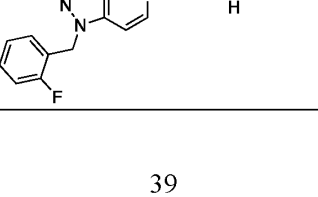
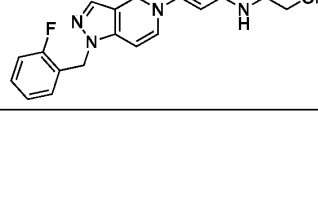
[00113] In one embodiment, the compounds of the invention are selected from Compounds 1 to 233 (Table 1), or tautomers or atropisomers thereof, or deuterated derivatives of the tautomers or atropisomers, or pharmaceutically acceptable salts or prodrugs of any of the foregoing.

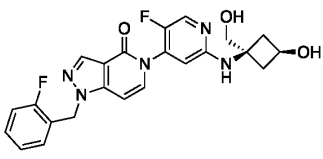
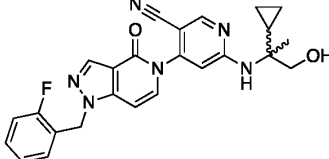
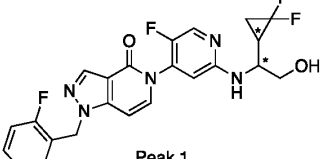
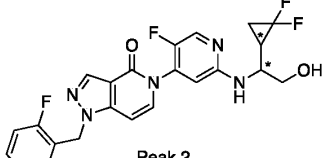
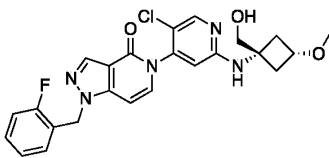
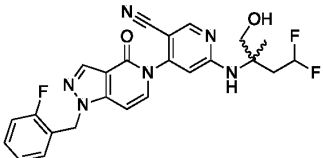
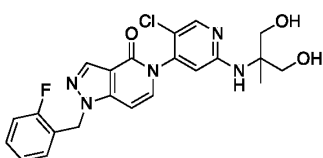
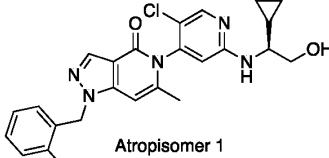
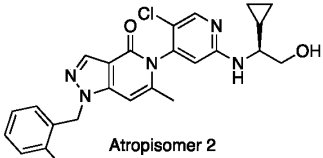
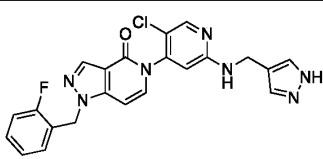
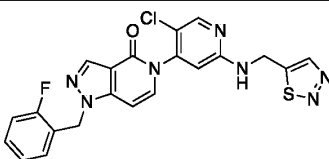
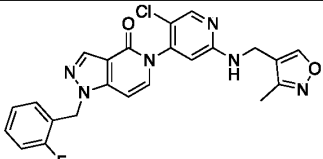
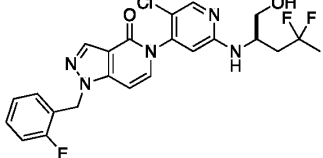
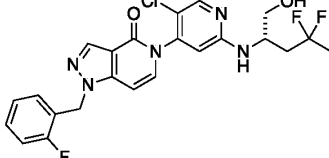
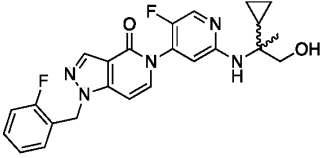
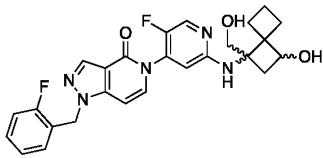
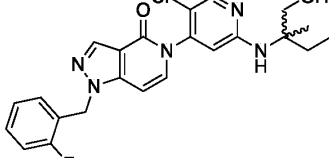
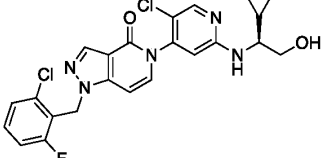
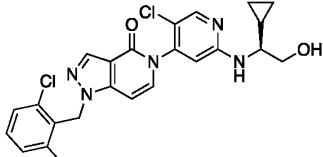
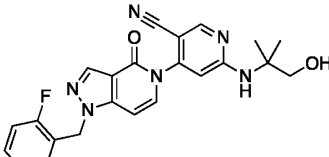
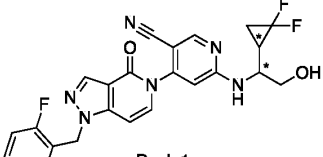
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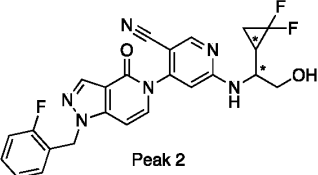
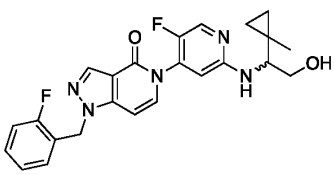
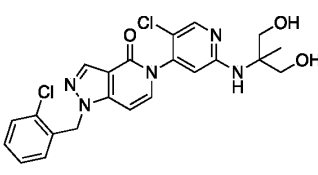
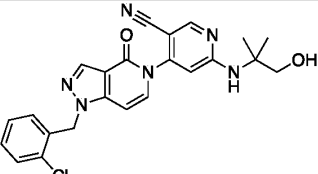
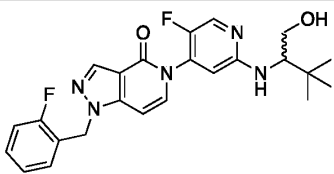
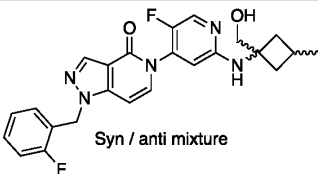
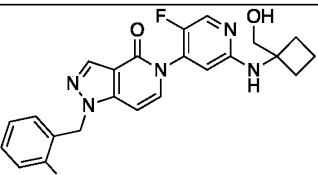
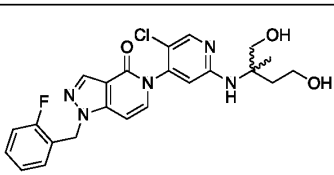
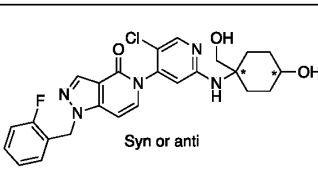
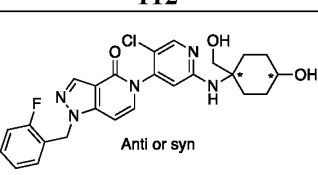
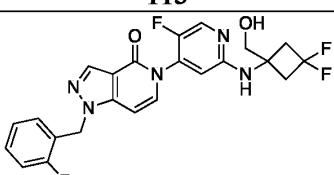
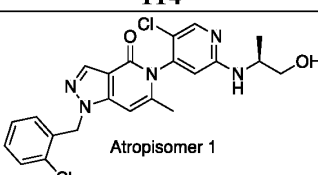
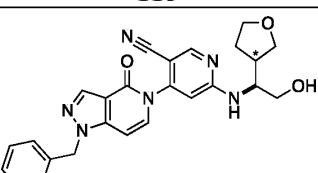
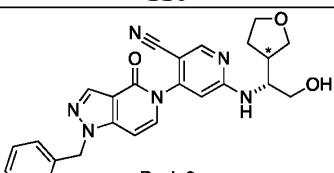
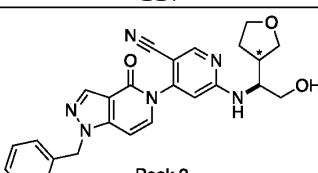
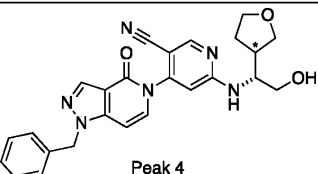
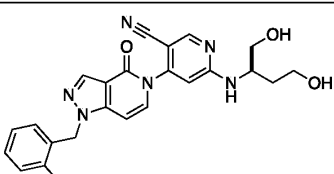
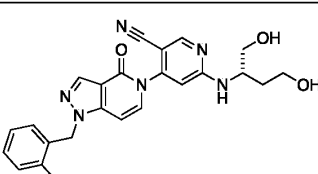
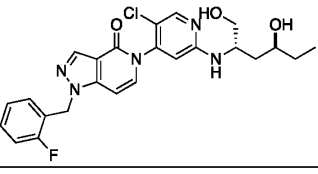
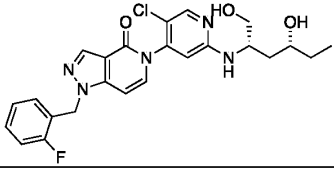
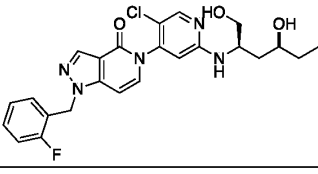
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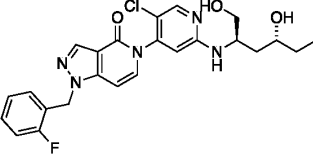
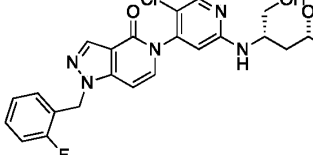
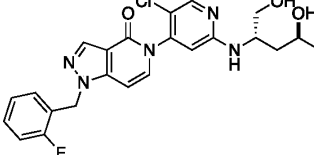
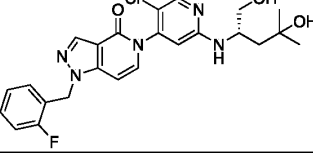
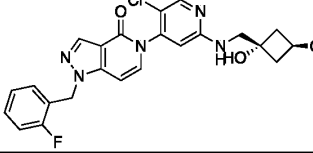
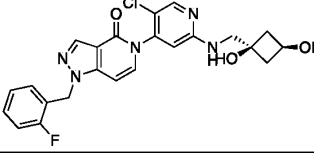
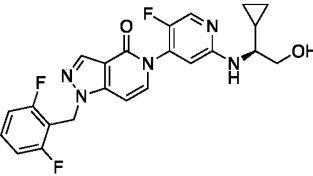
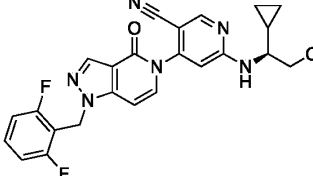
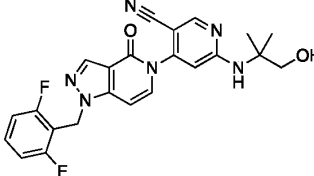
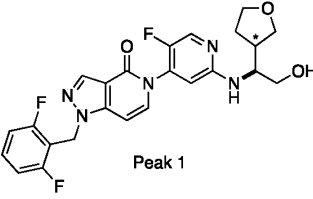
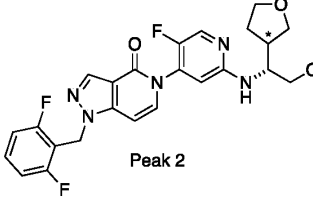
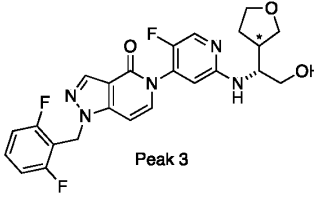
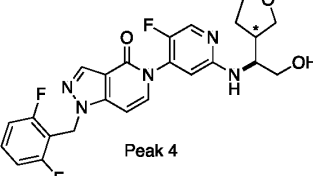
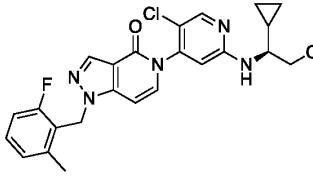
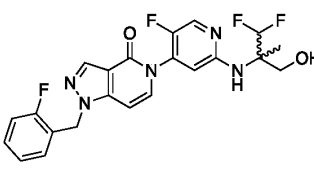
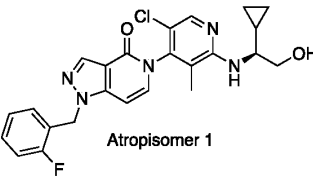
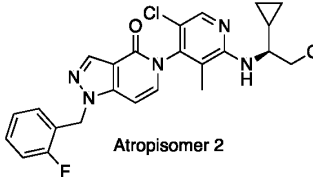
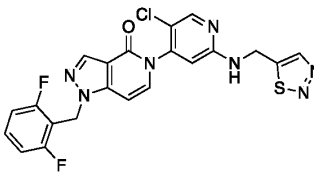
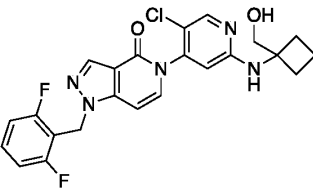
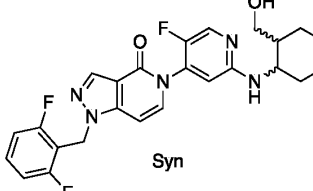
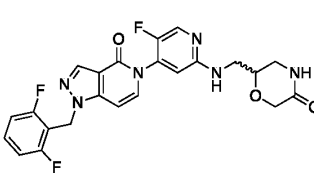
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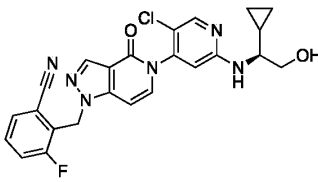
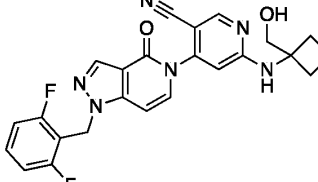
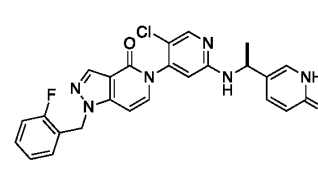
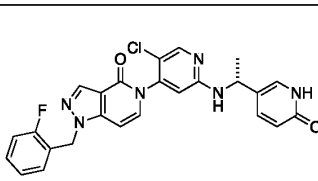
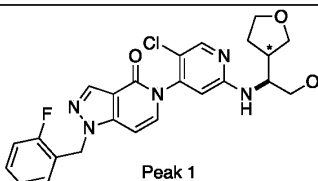
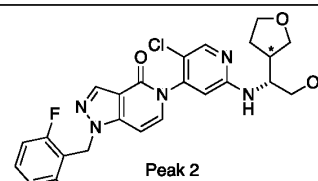
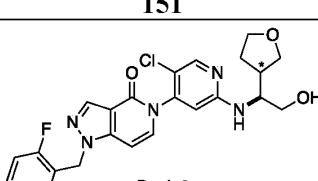
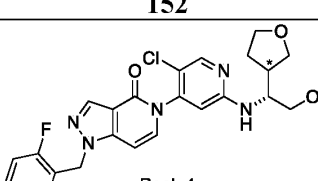
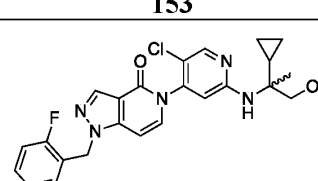
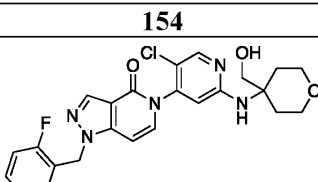
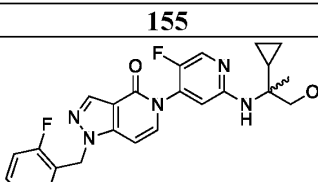
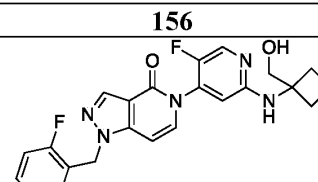
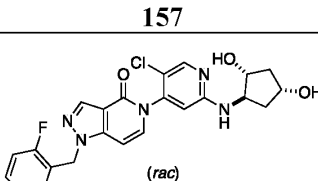
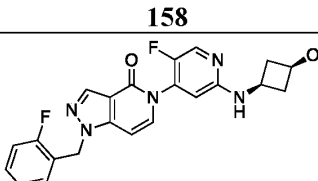
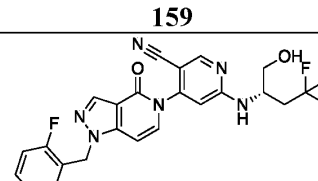
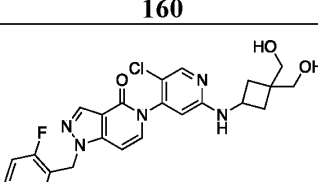
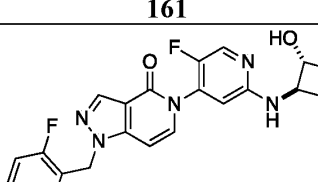
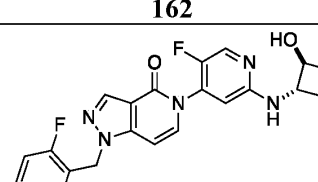
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61  Peak 1	62  Peak 2	63  Peak 3
64  Peak 4	65 	66 
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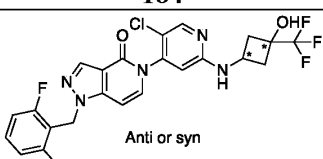
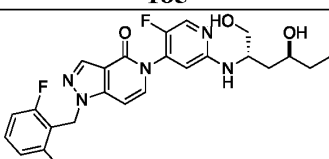
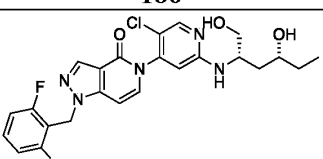
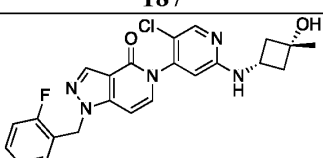
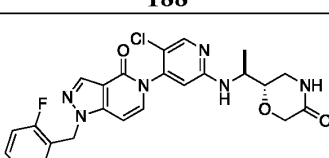
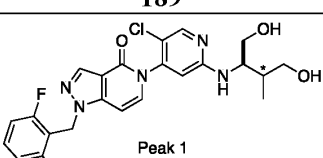
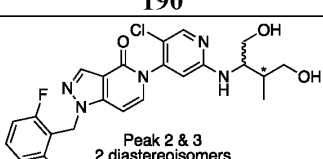
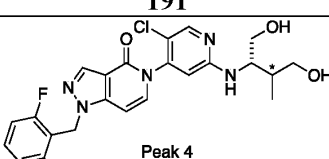
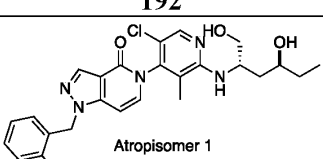
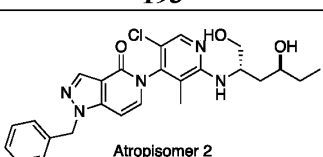
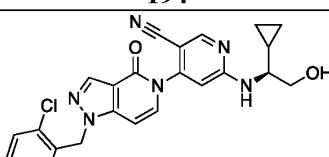
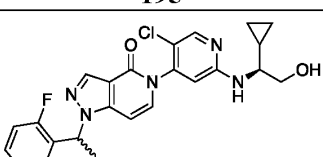
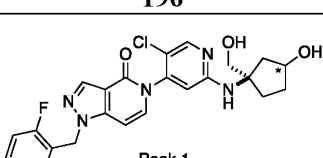
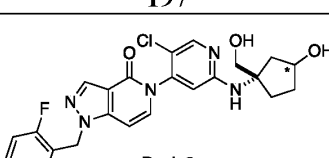
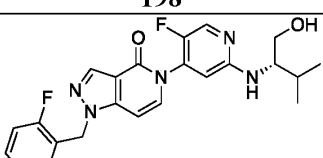
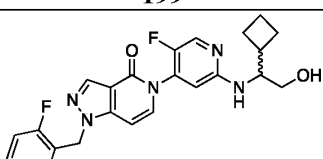
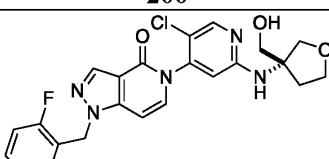
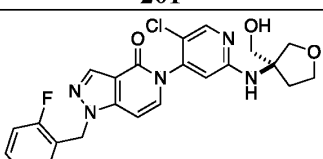
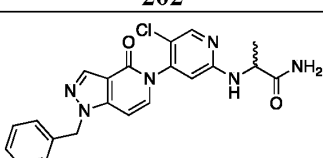
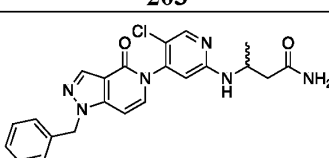
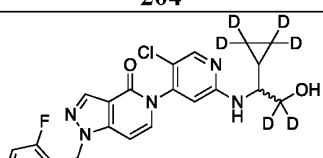
82 	83 	84  Peak 1
85  Peak 2	86 	87 
88 	89  Atropisomer 1	90  Atropisomer 2
91 	92 	93 
94 	95 	96 
97 	98 	99 
100 	101 	102  Peak 1

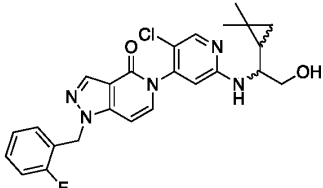
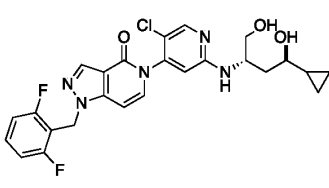
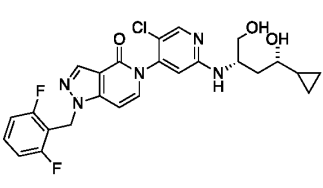
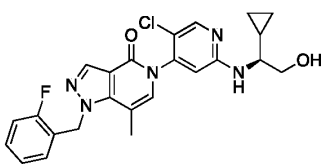
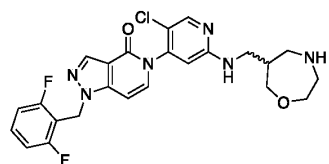
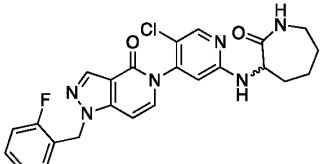
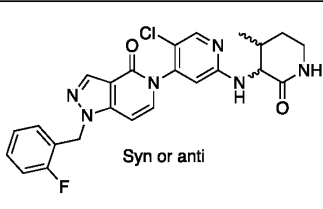
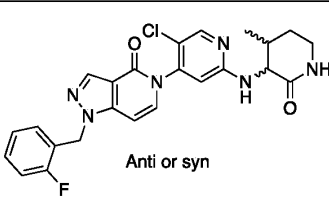
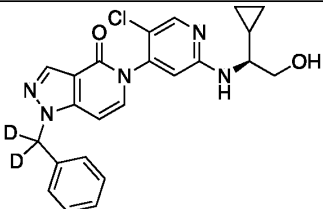
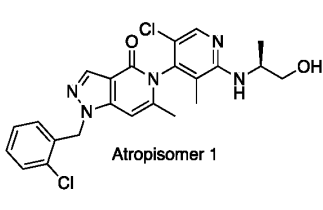
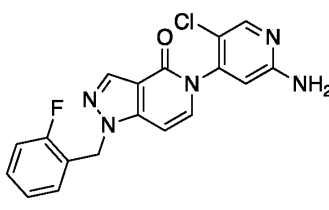
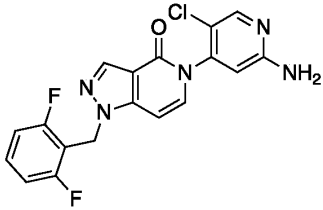
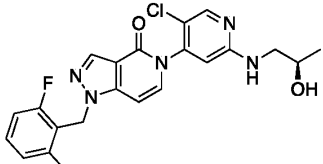
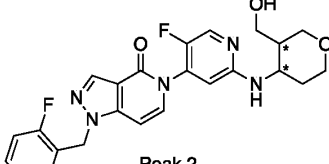
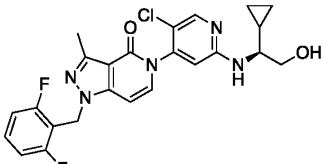
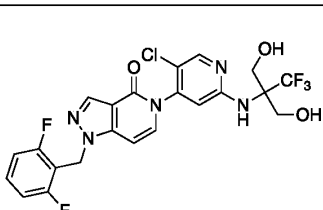
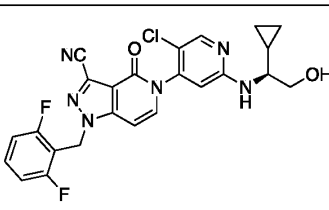
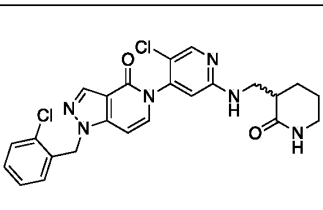
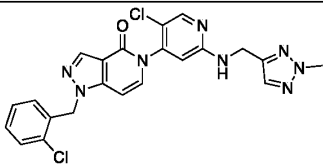
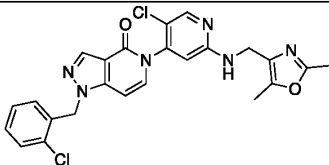
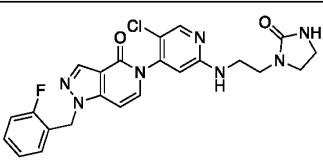
103  Peak 2	104 	105 
106 	107 	108  Syn / anti mixture
109 	110 	111  Syn or anti
112  Anti or syn	113 	114  Atropisomer 1
115  Peak 1	116  Peak 2	117  Peak 3
118  Peak 4	119 	120 
121 	122 	123 

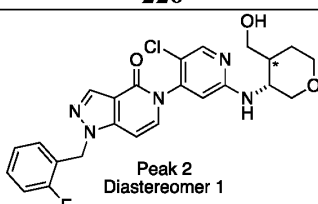
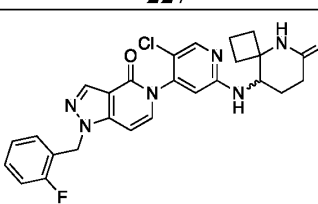
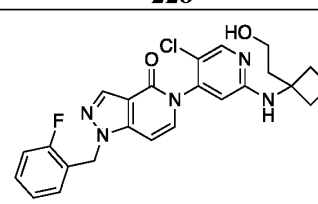
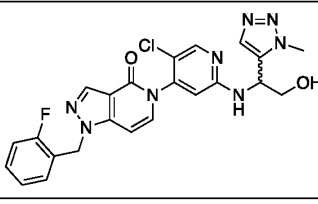
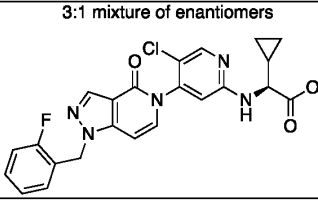
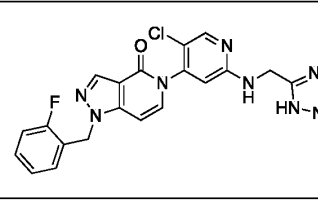
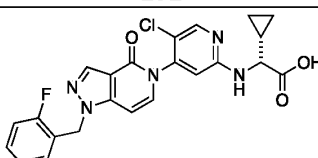
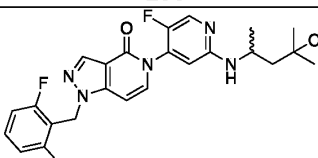
124 	125 	126 
127 	128 	129 
130 	131 	132 
133  Peak 1	134  Peak 2	135  Peak 3
136  Peak 4	137 	138 
139  Atropisomer 1	140  Atropisomer 2	141 
142 	143  Syn	144 

145 	146 	147 
148 	149  Peak 1	150  Peak 2
151  Peak 3	152  Peak 4	153 
154 	155 	156 
157  (rac)	158 	159 
160 	161 	162 

163	164	165
166	167	168
169	170	171
172	173	174
175	176	177
178	179	180 Syn or anti
181 Anti or syn	182 Syn	183 Syn or anti

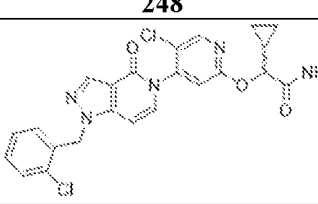
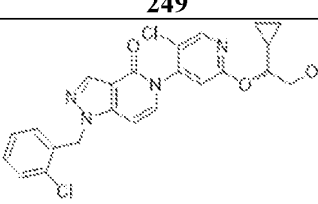
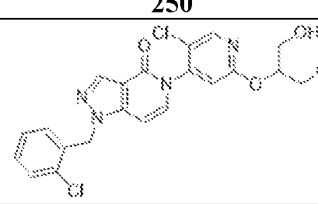
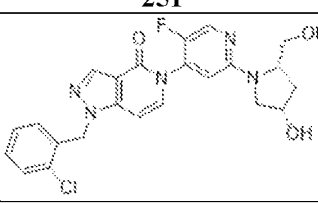
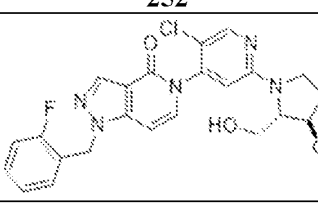
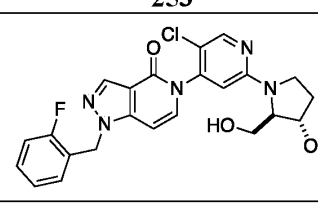
184  Anti or syn	185 	186 
187 	188 	189  Peak 1
190  Peak 2 & 3 2 diastereoisomers	191  Peak 4	192  Atropisomer 1
193  Atropisomer 2	194 	195 
196  Peak 1	197  Peak 2	198 
199 	200 	201 
202 	203 	204 

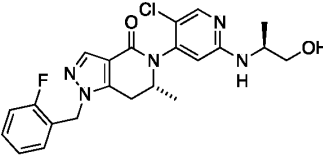
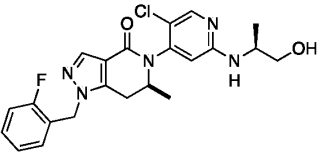
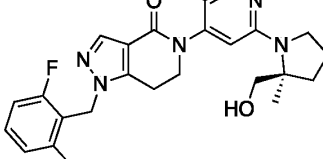
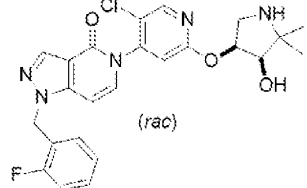
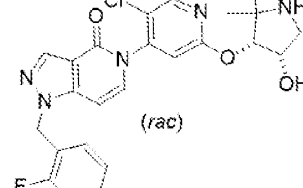
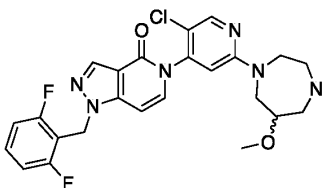
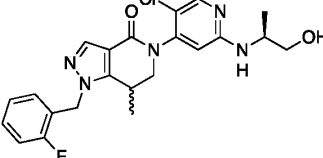
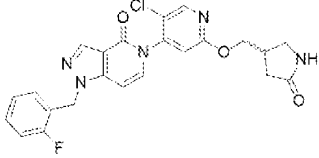
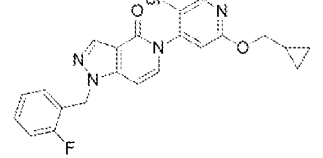
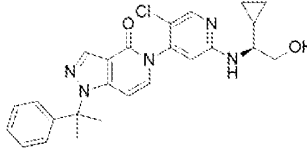
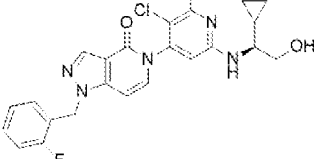
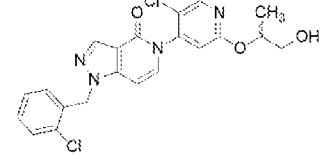
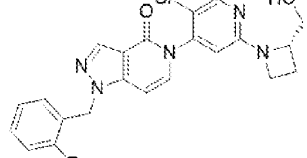
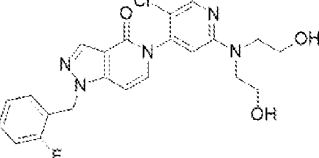
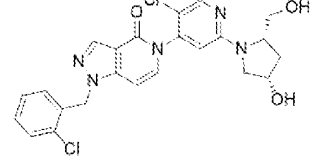
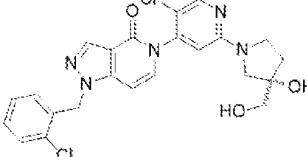
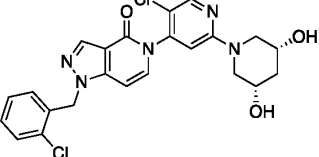
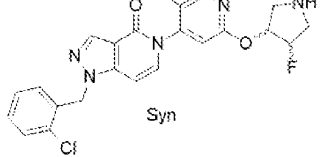
205 	206 	207 
208 	209 	210 
211  Syn or anti	212  Anti or syn	213 
214  Atropisomer 1	215 	216 
217 	218  Peak 2	219 
220 	221 	222 
223 	224 	225 

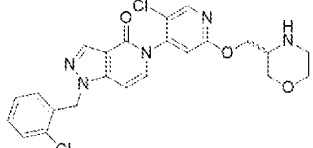
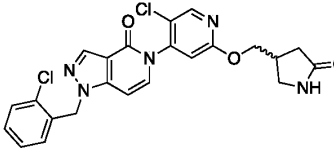
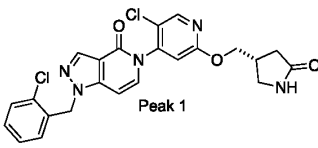
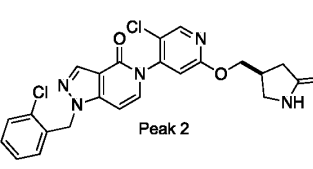
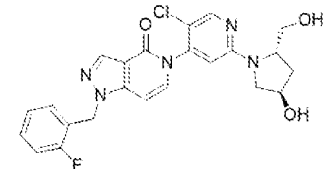
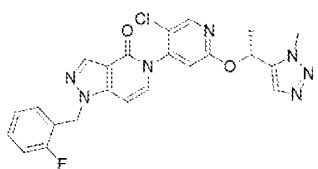
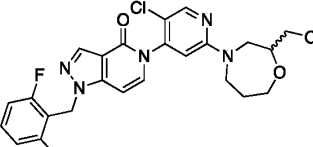
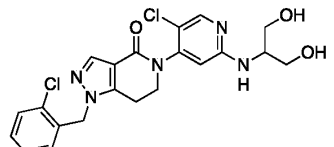
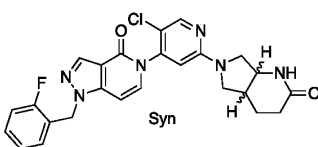
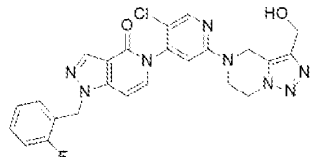
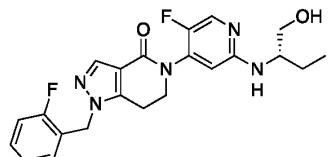
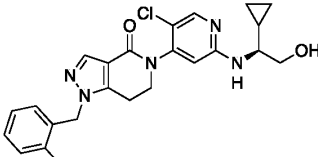
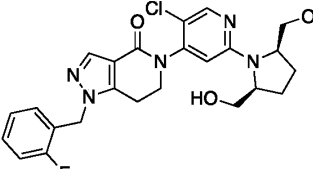
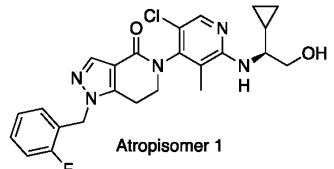
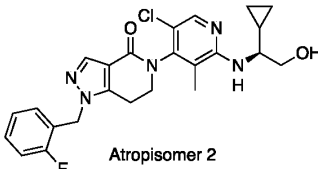
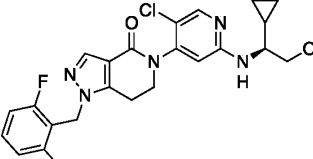
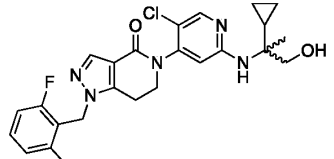
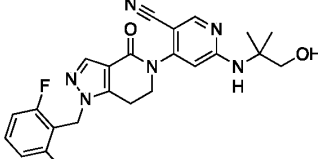
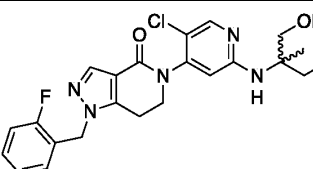
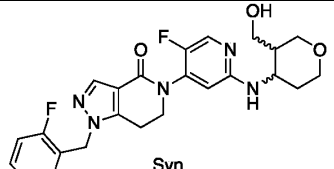
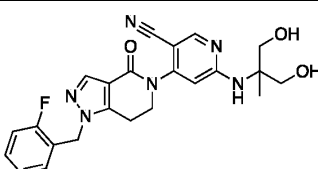
226 	227 	228 
229 	230 3:1 mixture of enantiomers 	231 
232 	233 	

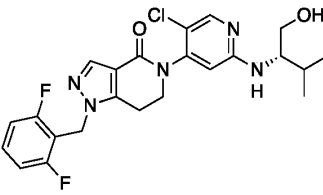
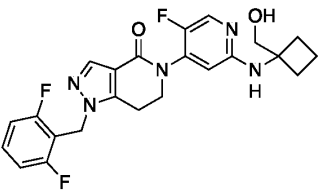
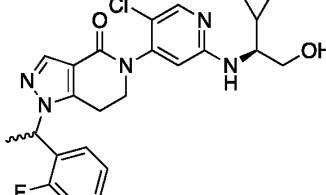
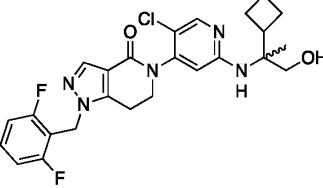
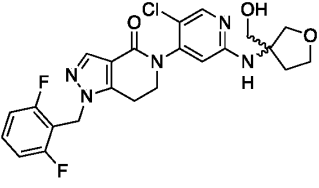
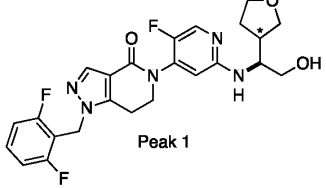
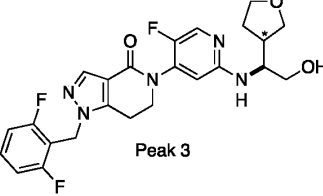
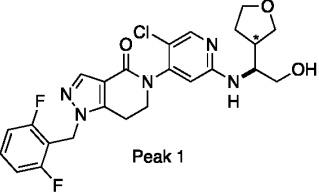
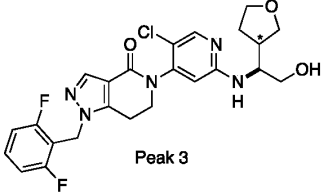
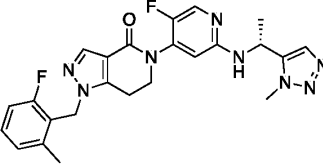
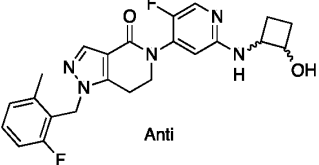
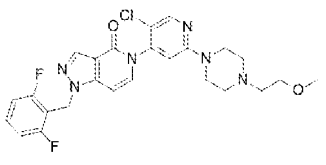
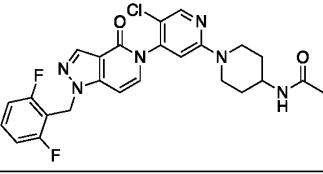
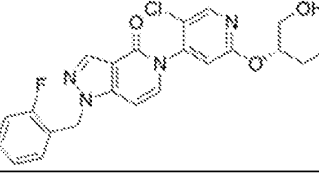
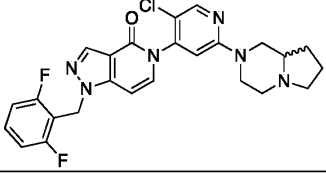
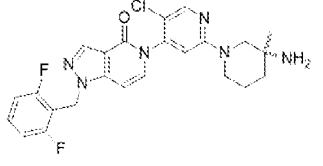
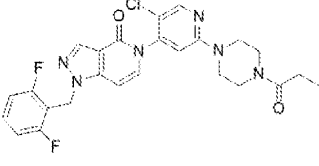
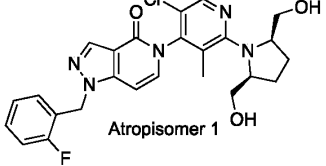
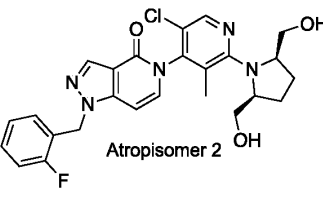
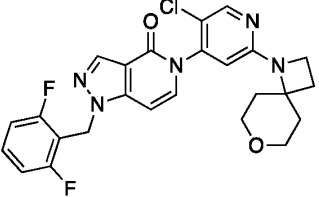
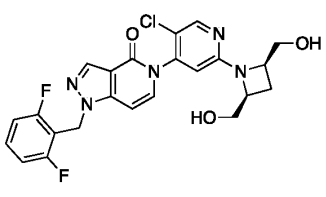
[00114] In some embodiments, the compounds of the invention are selected from Compounds 248 to 327 (Table 2), or tautomers or atropisomers thereof, or deuterated derivatives of the tautomers or atropisomers, or pharmaceutically acceptable salts or prodrugs of any of the foregoing.

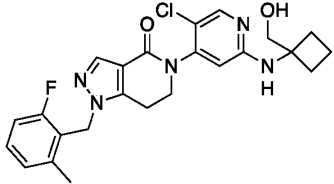
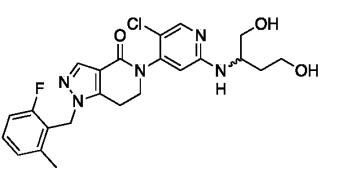
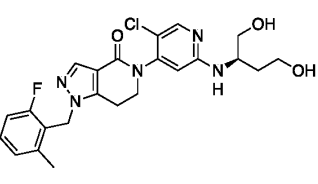
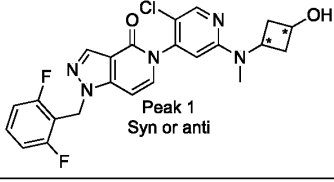
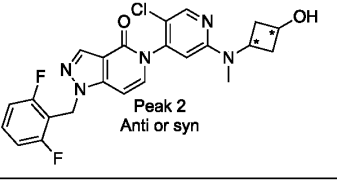
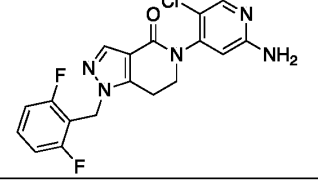
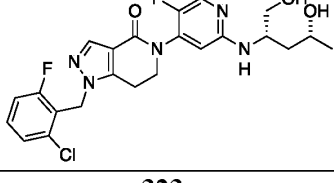
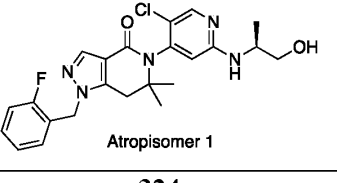
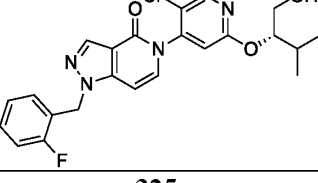
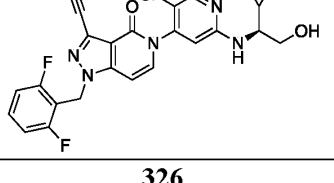
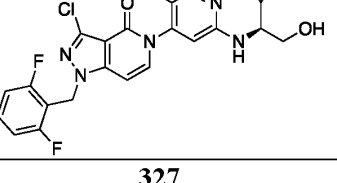
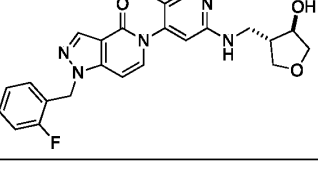
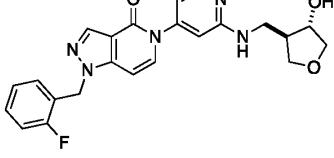
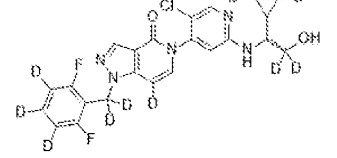
Table 2: Compounds 248 to 327

248 	249 	250 
251 	252 	253 

254 	255 	256 
257  (rac)	258  (rac)	259 
260 	261 	262 
263 	264 	265 
266 	267 	268 
269 	270 	271  Syn

272 	273 	274  Peak 1
275  Peak 2	276 	277 
278 	279 	280  Syn
281 	282 	283 
284 	285  Atropisomer 1	286  Atropisomer 2
287 	288 	289 
290 	291  Syn	292 

293 	294 	295 
296 	297 	298  Peak 1
299  Peak 3	300  Peak 1	301  Peak 3
302 	303  Anti	304 
305 	306 	307 
308 	309 	310  Atropisomer 1
311  Atropisomer 2	312 	313 

314 	315 	316 
317  Peak 1 Syn or anti	318  Peak 2 Anti or syn	319 
320 	321  Atropisomer 1	322 
323 	324 	325 
326 	327 	

[00115] It will also be appreciated that compounds of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, can exist in free form for treatment or, where appropriate, as pharmaceutically acceptable derivatives or prodrugs thereof. A pharmaceutically acceptable derivative or a prodrug includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need thereof is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof. Examples of prodrugs and their uses are well known in the art (*see, e.g.*, S. M. Berge et al. *J. Pharmaceutical Sciences*, 1977, 66, 1-19).

Pharmaceutical Compositions

[00116] In some embodiments, the disclosure provides pharmaceutical compositions comprising at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, and IIb, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing. In some embodiments, the pharmaceutical compositions may comprise a compound selected from Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing.

[00117] It will also be appreciated that a pharmaceutical composition of this disclosure can be employed in combination therapies; that is, the pharmaceutical compositions described herein further include at least one other active agent. Alternatively, a pharmaceutical composition comprising at least one compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing can be administered as a separate composition concurrently with, prior to, or subsequent to, a composition comprising at least one additional active agent.

[00118] In some embodiments, the compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, and the additional active agent are prepared for administration in the same pharmaceutical composition. In some embodiments, the compound and the additional active agent are prepared for administration in separate pharmaceutical compositions. In some embodiments, the compound and the additional active agent are prepared for simultaneous administration. In some embodiments, the compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing and the additional active agent are prepared for sequential administration.

[00119] In some embodiments, more than one compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, is provided for use in a method of treating ADPKD. In some embodiments, the more than one compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing is prepared for administration in the same pharmaceutical composition. In some embodiments, the more than one compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing is prepared for administration in separate pharmaceutical compositions.

[00120] In some embodiments, the additional active agent is a drug that acts to slow the rate of kidney cyst growth and/or kidney function decline. In some embodiments, the additional active agent is a drug that acts to control high blood pressure or other adverse cardiovascular events. In some embodiments, the additional active agent is an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB). In some embodiments, the additional active agent is a drug that helps slow the rate of kidney cyst growth. In some embodiments, the additional active agent is a vasopressin (V₂) receptor blocking agent such as tolvaptan. In some embodiments, the additional active agent is a drug that treats or controls pain associated with polycystic kidney disease. In some embodiments, the additional active agent is acetaminophen. In some embodiments, the additional active agent is a drug that treats bladder and kidney infections. In some embodiments, the additional active agent is an antibiotic.

[00121] As described above, pharmaceutical compositions disclosed herein may optionally further comprise at least one pharmaceutically acceptable carrier. The at least one pharmaceutically acceptable carrier may be chosen from adjuvants and vehicles. The at least one pharmaceutically acceptable carrier, as used herein, includes any and all solvents, diluents, other liquid vehicles, dispersion aids, suspension aids, surface active agents, isotonic agents, thickening agents, emulsifying agents, preservatives, solid binders, and lubricants, as suited to the particular dosage form desired. Remington: *The Science and Practice of*

Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier is incompatible with the compounds of this disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure. Non-limiting examples of suitable pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as phosphates, glycine, sorbic acid, and potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts, and electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars (such as lactose, glucose and sucrose), starches (such as corn starch and potato starch), cellulose and its derivatives (such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate), powdered tragacanth, malt, gelatin, talc, excipients (such as cocoa butter and suppository waxes), oils (such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil), glycols (such as propylene glycol and polyethylene glycol), esters (such as ethyl oleate and ethyl laurate), agar, buffering agents (such as magnesium hydroxide and aluminum hydroxide), alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, phosphate buffer solutions, non-toxic compatible lubricants (such as sodium lauryl sulfate and magnesium stearate), coloring agents, releasing agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservatives, and antioxidants).

[00122] In some embodiments, the compositions of the invention comprise a compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing. The compositions may further comprise at least one additional pharmaceutical ingredient and/or at least one carrier.

Methods of Treatment

[00123] In some embodiments, the disclosure provides methods of treating ADPKD comprising administering to a subject in need thereof at least one compounds selected from compounds of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing. In some embodiments, the subject in need thereof carries a mutation in the *PKDI* gene which encodes polycystin-1 (PC1). In some embodiments, the mutation in the *PKDI* gene of the subject in need is a non-truncating mutation. In some embodiments, the mutation in the *PKDI* gene of the subject in need results in a misfolded, non-functional PC1 protein.

[00124] In other embodiments, the disclosure provides methods of increasing polycystin-1 levels in a subject that carries a mutation in the *PKDI* gene which encodes polycystin-1 (PC1). In some embodiments, the mutation in the *PKDI* gene of the subject is a non-truncating mutation. In some embodiments, the mutation in the *PKDI* gene of the subject results in a misfolded, non-functional PC1 protein. In some embodiments, the mutation in the *PKDI* gene of the subject is a truncating mutation that results in a PC1 protein that benefits from correction with a PC1 corrector disclosed herein.

[00125] As discussed above, the disclosure also provides pharmaceutical compositions for use in treating ADPKD, wherein the pharmaceutical compositions comprise at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing.

[00126] In some embodiments of the method of treating ADPKD or method of increasing PC1 protein levels in a subject, the at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, or the pharmaceutical composition comprising the at least one compound, is administered once a day. In some embodiments of the method of treating ADPKD or the method of increasing PC1 protein levels in a subject, the at least one compound of Formula I or Formula II, including Compounds 1-233, tautomers and atropisomers of those compounds, deuterated

derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, or the pharmaceutical composition comprising the at least one compound, is administered twice a day. In some embodiments of the method of treating ADPKD or the method of increasing PC1 protein levels in a subject, the at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, or the pharmaceutical composition comprising the at least one compound, is administered multiple times in a day.

[00127] In some embodiments, the methods of the invention include administration of an additional active agent with a compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing to treat ADPKD. The method may comprise co-administering the additional active agent and a compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, in a single pharmaceutical composition or in separate pharmaceutical compositions. In some embodiments, the compound and the additional active agent are co-administered simultaneously. In some embodiments, the compound and the additional active agent are co-administered sequentially.

[00128] In some embodiments, the methods of treating ADPKD include administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, with an additional active agent that acts to slow the rate of kidney cyst growth and/or kidney function decline. In some embodiments, the additional active agent is a vasopressin (V₂) receptor blocking agent such as tolvaptan. In some embodiments, the methods of treating ADPKD include administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and

pharmaceutically acceptable salts and prodrugs of any of the foregoing, with an additional active agent that acts to control high blood pressure or other adverse cardiovascular events, such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB).

[00129] In some embodiments, the methods of treating ADPKD include administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, with an additional active agent that treats or controls pain associated with polycystic kidney disease. In some embodiments, the methods of treating ADPKD include administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, with an additional active agent that treats bladder and kidney infections. In some embodiments, the additional active agent is an antibiotic.

[00130] In some embodiments, the methods of treating ADPKD include enteral administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing. In some embodiments, the route of enteral administration is selected from oral and rectal. In some embodiments, the route of enteral administration is selected from nasogastric, nasoenteric, nasoduodenal, and nasojejunal.

[00131] In some embodiments, the methods of treating ADPKD include parenteral administration of at least one compound selected from compounds of Formulae I, Ia, Ib, II, IIa, IIb, Compounds 1-233, Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing. In some embodiments, the route of parenteral administration is selected from intravenous, intraperitoneal, epicutaneous, percutaneous, subcutaneous, intradermal, intramuscular, intranasal, intratracheal, intracranial, epidural, and intrathecal.

[00132] The disclosure also provides compounds of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing, for use in any of the methods described above.

[00133] In some embodiments, the method of treating, lessening the severity of, or symptomatically treating ADPKD in a patient comprises administering to the patient an effective amount of a compound of Formulae I, Ia, Ib, II, IIa, and IIb, including Compounds 1-233 and Compounds 248-327, tautomers and atropisomers of those compounds, deuterated derivatives of those compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing.

Synthesis of Compounds

[00134] All the specific and generic compounds, and the intermediates disclosed for making those compounds, are considered to be part of the disclosure.

[00135] One of ordinary skill in the art will appreciate that the methods described herein are generally applicable to other stereoisomers of the compounds described herein.

[00136] Should the name of a compound conflict with the structure of the compound anywhere in the present application, the structure supersedes the name and is intended to be controlling.

I. Abbreviations

[00137] Unless otherwise noted, or where the context dictates otherwise, the following abbreviations shall be understood to have the following meanings:

<u>Abbreviation</u>	<u>Meaning</u>
NMR	Nuclear magnetic resonance
ESI-MS	Electrospray mass spectrometry
LC/MS	Liquid chromatography-mass spectrometry
HPLC	High performance liquid chromatography
SFC	Supercritical fluid chromatography
ESI	Electrospray ionization
cm	Centimeters
g	Grams
mg	Milligrams
L	Liter(s)
mL	Milliliter(s)
μL	Microliter(s)
mmol	Millimole(s)

h	Hour(s)
min	Minute(s)
mm	Millimeter(s)
μm	Micrometer(s)
MHz	Megahertz
Hz	Hertz
N	Normal (concentration)
M	Molar (concentration)
mM	Millimolar (concentration)
ppm	Parts per million
% w/v	Weight-volume concentration
% w/w	Weight-weight concentration
B ₂ pin ₂	Bis(pinacolato)diboron
BTEAC	Benzyl triethylammonium chloride
^t Bu	<i>tert</i> -Butyl
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine
DIPA	<i>N,N</i> -Diisopropylamine
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	<i>N,N</i> -Dimethylpyridin-4-amine
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DPBS	Dulbecco's Phosphate Buffered Saline
EtOH	Ethanol
EtOAc	Ethyl acetate
FBS	Fetal Bovine Serum
G418	Geneticin™
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
HEK293	Human Embryonic Kidney 293 cell line
MeOH	Methanol
MeCN	Acetonitrile
2-MeTHF	2-Methyltetrahydrofuran
NEAA	Non-Essential Amino Acid
NMP	<i>N</i> -Methylpyrrolidone
PBS	Phosphate Buffered Saline
PPTS	Pyridinium <i>p</i> -toluenesulfonate
SCX	Strong Cation Exchange
SEM	2-(Trimethylsilyl)ethoxymethyl
SFC	Supercritical Fluid Chromatography
SPE	Solid Phase Extraction
STAB	Sodium triacetoxymethylborohydride
TBAF	Tetrabutylammonium fluoride
TBSCl	<i>tert</i> -Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMA	Trimethylaluminum
Tr	Trityl
TrypLE™	Reagent (catalog number 12604013)
RT	Ambient temperature

rt	Retention time
ca.	Circa (approximately)
μwave	Microwave

II. General Analytical Methods

NMR

[00138] NMR spectra were acquired on a Bruker Avance III 500 MHz NMR instrument equipped with a BBFO probe or on a Bruker Avance III HD 400 MHz NMR instrument equipped with a BBFO probe. NMR spectra were obtained as solutions in an appropriate deuterated solvent such as dimethyl sulfoxide-d₆ (DMSO-d₆).

Analytical SFC

[00139] Analytical supercritical fluid chromatography (SFC) separations of various isomeric mixtures were accomplished using a Waters Acquity UPC² instrument comprising a Convergence Manager, a Sample Manager, a Binary Solvent Manager, a Column Manager-30S, a PDA detector, an Isocratic Solvent Manager and a QDa detector.

Preparative SFC

[00140] Preparative SFC separations of various isomeric mixtures were accomplished using the following instruments:

- a) Waters Prep 100 SFC instrument comprising a Back Pressure Regulator, a 2767 Sample Manager, a 2545 Quaternary Gradient Module, a Back Pressure Regulator, a Column Oven, a 2998 PDA detector, an Isocratic Solvent Manager, a P200X pump, a SFC Flow Splitter-100, three SFC Heat Exchanger-1000, a Series III LC pump and a Qda detector.
- b) Berger Minigram SFC instrument equipped with a ALS-3100 autosampler, a Column Oven and a UV detector.
- c) Shimadzu Nexera UC Prep instrument comprising a CO₂ Cooling Unit, as LC-40P SF Solvent Delivery Module, a LC-40D Solvent Delivery Module, a LC-20AP Preparative Liquid Chromatograph, a LC-20AR Liquid Chromatograph, a CBM-40 System Controller, a SFC-40P Backpressure Regulator, a HEX-40 Heat Exchanger, a CTO-40C Column Oven, a SPD-M40 PDA detector, a FCV-20AH2 Valve Unit, a FRS-40 Sampler & Fraction Collector and a LCMS-2020 LC Mass Spectrometer.

UPLC

[00141] UPLC analysis was performed using a Waters Acquity UPLC-MS system comprising of a Binary Solvent Manager, a Column Manager, a 2777 Sample Manager,

PDA detector, a SQD Mass Spectrometer and an Evaporative Light Scattering Detector (ELSD).

Preparative HPLC

[00142] Preparative reverse-phase HPLC was carried out on a Waters AutoPurification HPLC-MS system equipped with a 2767 or 3767 Sample Manager, a 2545 Binary Gradient Module, a System Fluidics Organizer, two 515 HPLC pumps, a Flow Splitter, a 2998 PDA detector and a Qda detector.

III. General LC/MS Methods

[00143] The compounds were analyzed by LC/MS according to one of the following methods, as shown in Table 3.

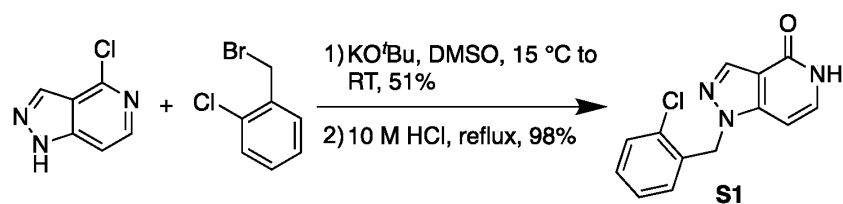
Table 3: LC/MS Methods

LC/MS Method	Method Description
A	Waters™ BEH C8 1.7 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (10 mM Ammonium Formate, pH 9), 45 °C, Flow rate 0.6 mL/min over 5.0 min
B	Waters™ BEH C18 2.5 μm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 1.4 min
C	Kinetex® EVO C18 2.6 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (10 mM Ammonium Formate, pH 9), 45 °C, Flow rate 1.0 mL/min over 1.5 min
D	Waters™ BEH C18 1.7 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% Formic Acid), 35 °C, Flow rate 1.3 mL/min over 4.0 min
E	Waters™ CSH C18 1.7 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% TFA, pH 2), 45 °C, Flow rate 0.6 mL/min over 5.0 min
F	Waters™ CSH C18 1.7 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% TFA), 45 °C, Flow rate 1.0 mL/min over 1.5 min
G	Waters™ BEH C18 2.5 μm 2.1 x 50 mm, 2 to 50% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
H	Waters™ BEH C18 2.5 μm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
I	Waters™ CSH C18 1.7 μm 2.1 x 50 mm, 2 to 95% MeCN in water (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 1.4 min
J	Kinetex® Polar C18 2.6 μm 3.0 x 50 mm, 5 to 95% MeCN in H ₂ O (0.1% Formic Acid), Flow rate 1.2 mL/min over 3 min

LC/MS Method	Method Description
K	Waters™ BEH C18 2.5 μm 2.1 x 50 mm, 2 to 20% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 2.0 min
L	Waters™ BEH C18 1.7 μm 2.1 x 50 mm, 50 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 1.4 min
M	Waters™ BEH C18 2.5 μm 2.1 x 50 mm, 20 to 70% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
N	Waters™ BEH C8 1.7 μm 2.1 x 50 mm, 50 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 1.4 min
O	Waters™ BEH C ₁₈ 1.7 μm 2.1 x 50 mm, 5 to 95% MeCN in water (5 mM Ammonium acetate), Flow rate 0.6 mL/min over 4 min
P	Waters™ BEH C ₁₈ 1.7 μm 2.1 x 100 mm, 10 to 90% MeCN in water (5 mM Ammonium acetate), Flow rate 0.3 mL/min over 10 min
Q	Waters™ Cortecs C ₁₈ 1.6 μm 3.0 x 30 mm, 3 to 98% MeCN in H ₂ O (0.05% Formic Acid), Flow rate 0.85 mL/min over 2 min
R	Waters™ CSH C18 1.7 μm 2.1 x 50 mm, 2 to 95% MeCN in water (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 1.4 min
S	Waters™ CSH C18 1.7 μm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 4.6 min

IV. Synthesis of Starting Materials

Starting Material 1: Synthesis of 1-(2-Chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (S1)



Step 1:

[00144] KO^tBu (160 g, 1.426 mol) was added portionwise to a cooled solution of 4-chloro-1H-pyrazolo[4,3-c]pyridine (170 g, 1.107 mol) in DMSO (1.7 L) under an argon atmosphere at such a rate to maintain the temperature between 15 and 25 °C. The resultant mixture was stirred at ambient temperature for a further 25 min. 1-(Bromomethyl)-2-chlorobenzene (292.86 g, 185 mL, 1.425 mol) was added dropwise, keeping the temperature between 15 and

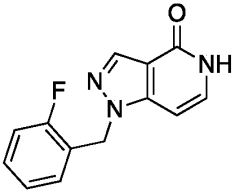
25 °C and the reaction was stirred at ambient temperature for 30 min. Water (2 L) was slowly added and the resulting slurry was stirred at ambient temperature for 1 h. The solid was filtered, washed with water (1 L) and heptane (2 L). Purification by flash chromatography (SiO₂, 100% DCM) gave a light yellow solid. The solid was heated at 80 °C in *i*PrOH (300 mL). The mixture was cooled down to ambient temperature. The slurry was filtered, washed with *i*PrOH (300 mL) and the solid was dried to give 4-chloro-1-(2-chlorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridine (S1, 160 g, 51%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.21 (s, 1H), 8.16 (d, *J* = 6.1 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.28 - 7.24 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 6.1 Hz, 1H), 5.69 (s, 2H) ppm. ESI-MS *m/z* calc. 277.017, found 278.0 (M+1)⁺.

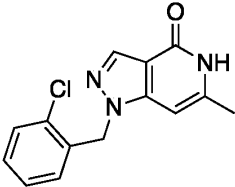
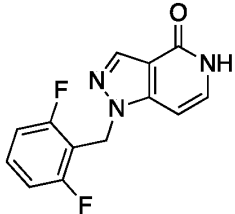
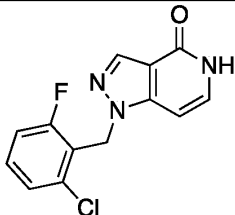
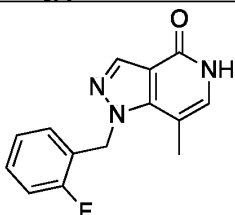
Step 2:

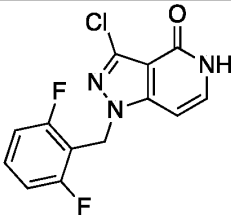
[00145] A solution of 4-chloro-1-(2-chlorobenzyl)-1*H*-pyrazolo[4,3-*c*]pyridine (200 g, 709.51 mmol) in HCl (1.4 L, 10 M aqueous solution, 14.0 mol) was heated under reflux for 20 h. The mixture was diluted with water (1.4 L) and cooled to ambient temperature. The solid was filtered, washed with water (500 mL) and dried in air to give 1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (S1, 182 g, 98%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 8.08 (s, 1H), 7.49 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.22 (m, 1H), 6.93 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.64 (d, *J* = 6.9 Hz, 1H), 5.61 (s, 2H) ppm. ESI-MS *m/z* calc. 259.051, found 260.0 (M+1)⁺.

[00146] The following Starting Materials were made using the method described in Starting Material 1, except that, in Step 1, different alkylating agents and/or 1*H*-pyrazolo[4,3-*c*]pyridines were respectively used in place of 1-(bromomethyl)-2-chlorobenzene and 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine. In the case of S18, Step 1 was carried out using the conditions described in the synthesis of Starting Material 3.

Table 4: Starting Materials Prepared Using the Method Described in Starting Material 1

Starting Material Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
S2		ESI-MS <i>m/z</i> calc. 243.081, found 244.1 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 8.05 (s, 1H), 7.41-7.33 (m, 1H), 7.24 - 7.11 (m, 4H), 6.67 (d, <i>J</i> = 6.9 Hz, 1H), 5.57 (s, 2H) ppm.

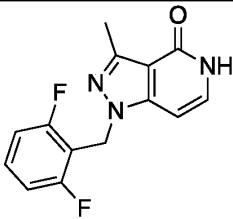
Starting Material Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
	1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		
S4	 1-(2-chlorobenzyl)-6-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 273.067, found 274.0 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (br s, 1H), 8.01 (s, 1H), 7.50 (dd, J = 7.9, 1.2 Hz, 1H), 7.34 (td, J = 7.6, 1.7 Hz, 1H), 7.30 - 7.26 (m, 1H), 6.83 (dd, J = 7.6, 1.6 Hz, 1H), 6.44 (s, 1H), 5.54 (s, 2H), 2.20 (s, 3H) ppm.
S7	 1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 261.071, found 262.0 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.05 (s, 1H), 7.99 (d, J = 0.8 Hz, 1H), 7.53 - 7.38 (m, 1H), 7.26 (dd, J = 7.3, 5.9 Hz, 1H), 7.20 - 7.06 (m, 2H), 6.71 (d, J = 7.2 Hz, 1H), 5.54 (s, 2H) ppm.
S9	 1-(2-chloro-6-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 277.042, found 279.9 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.05 (d, J = 5.8 Hz, 1H), 7.99 (d, J = 0.8 Hz, 1H), 7.46 (td, J = 8.2, 6.1 Hz, 1H), 7.38 (dt, J = 8.1, 1.1 Hz, 1H), 7.34 - 7.23 (m, 2H), 6.74 (d, J = 7.2 Hz, 1H), 5.60 (d, J = 1.7 Hz, 2H) ppm.
S12	 1-(2-fluorobenzyl)-7-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 257.096, found 258.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.20 (s, 1H), 7.38 - 7.29 (m, 1H), 7.15 (br d, J = 1.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 1.1 Hz, 1H), 6.70 (s, 1H), 5.82 (s, 2H), 2.30 (d, J = 1.1 Hz, 3H) ppm; exchangeable H not observed.

Starting Material Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
S18	 3-chloro-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS <i>m/z</i> calc. 295.032, found 296.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (d, <i>J</i> = 4 Hz, 1H), 7.56 - 7.43 (m, 1H), 7.22 (t, <i>J</i> = 6 Hz, 1H), 7.15 (t, <i>J</i> = 8 Hz, 2H), 6.72 (d, <i>J</i> = 7.2 Hz, 1H), 5.52 (s, 2H) ppm.

[00147] The following Starting Material was made using the method described in Starting material 1, except that, in Step 1, 2-(chloromethyl)-1,3-difluorobenzene and 4-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine were respectively used in place of 1-(bromomethyl)-2-chlorobenzene and 4-chloro-1H-pyrazolo[4,3-c]pyridine and the reaction was carried out using the conditions described below:

[00148] 2-(Chloromethyl)-1,3-difluorobenzene (1.116 g, 6.865 mmol) and K₂CO₃ (1.649 g, 11.931 mmol) were added to a stirred mixture of 4-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (1 g, 5.967 mmol) in DMF (10 mL) and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was poured into ice-water and the resulting solids were collected by filtration. Purification by reverse phase chromatography (80 g C₁₈ column, 50 to 80% MeCN in water with 0.1% NH₄OH) gave 4-chloro-1-(2,6-difluorobenzyl)-3-methyl-1H-pyrazolo[4,3-c]pyridine (1.045 g, 59%) as a colorless solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.08 (d, *J* = 6.0 Hz, 1H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.38 (tt, *J* = 8.4, 6.5 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 2H), 5.61 (s, 2H), 2.66 (s, 3H) ppm. ESI-MS *m/z* calc. 293.053, found 294.1 (M+1)⁺.

Table 5: Starting Material Prepared Using the Method Described in Starting Material 1

Starting Material Number	Structure	Name	LC/MS	NMR (shifts in ppm)
S14	 1-(2,6-difluorobenzyl)-3-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	1-(2,6-difluorobenzyl)-3-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS <i>m/z</i> calc. 243.081, found 244.1 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 8.05 (s, 1H), 7.41-7.33 (m, 1H), 7.24 - 7.11 (m, 4H), 6.67 (d, <i>J</i> = 6.9 Hz, 1H), 5.57 (s, 2H) ppm.

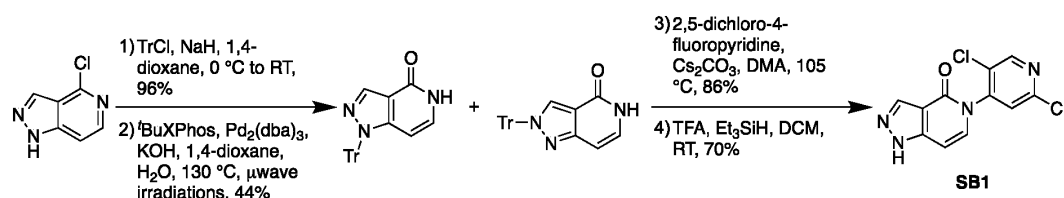
[00149] The following Starting Material was made using the method described in Starting material 1, except that, in Step 1, 2-(chloromethyl)-1,3-difluorobenzene and 4-chloro-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine were respectively used in place of 1-(bromomethyl)-2-chlorobenzene and 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine and the reaction was carried out using the conditions described for S14, using MeCN as the solvent in place of DMF. An additional cyanation step was introduced between Steps 1 and 2 as described below. In Step 2, the reaction was carried out using AcOH in place of 10 M HCl:

[00150] *Cyanation step:* CuCN (371 mg, 4.060 mmol) was added to a stirred solution of 4-chloro-1-(2,6-difluorobenzyl)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (1.3 g, 2.109 mmol) in NMP (20 mL) and the reaction mixture was heated at 120 °C for 12 h. The reaction was quenched by addition of ice-cold water and extracted with EtOAc (2 x 200 mL). The combined organic layers were concentrated *in vacuo*. Purification by flash chromatography (neutral alumina, 30 to 40% EtOAc in hexanes) gave 4-chloro-1-(2,6-difluorobenzyl)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (250 mg, 35%) as an off-white solid. ¹H NMR (400 MHz, Chloroform-*d*₃) δ 8.32 (d, *J* = 6.0 Hz, 1H), 7.51(d, *J* = 6.0 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.00 - 6.94 (m, 2H), 5.69 (m, 2H) ppm. ESI-MS *m/z* calc. 304.033, found 305.1 (M+1)⁺.

Table 6: Starting Material Prepared Using the Method Described in Starting Material 1

Starting Material Number	Structure	Name	LC/MS	NMR (shifts in ppm)
S15		1-(2,6-difluorobenzyl)-4-oxo-4,5-dihydro-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine-3-carbonitrile	ESI-MS <i>m/z</i> calc. 286.067, found 287.3 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.59 (br s, 1H), 7.55 - 7.51 (m, 1H), 7.44 (d, <i>J</i> = 7.6 Hz, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.85 (d, <i>J</i> = 7.2 Hz, 1H), 5.70 (s, 2H) ppm.

Starting Material 2: Synthesis of 5-(2,5-Dichloropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (SB1)



Step 1:

[00151] Under a nitrogen atmosphere, NaH (1.84 g, 60 % dispersion in mineral oil, 46.0 mmol) was added portionwise to a solution of 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (6 g, 39.07 mmol) in 1,4-dioxane (60 mL) at 0 °C and the reaction mixture was stirred for 10 min at 0 °C. Trityl chloride (12.2 g, 43.76 mmol) was added in one portion and the cooling bath was removed. The reaction was stirred for 3 days at ambient temperature. The mixture was diluted with EtOAc and washed with 1 M NaOH. The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* to give a mixture of 4-chloro-1-trityl-1*H*-pyrazolo[4,3-*c*]pyridine (ESI-MS *m/z* calc. 395.119, found 396.0 (M+1)⁺) and 4-chloro-2-trityl-2*H*-pyrazolo[4,3-*c*]pyridine (ESI-MS *m/z* calc. 395.119, found 396.0 (M+1)⁺) (7.41 g, 96%), which was used without further purification in the next step.

Step 2:

[00152] In a microwave reactor vessel, KOH (6.2 g, 110.5 mmol) was added to a stirred mixture of 4-chloro-1-trityl-1*H*-pyrazolo[4,3-*c*]pyridine and 4-chloro-2-trityl-2*H*-pyrazolo[4,3-*c*]pyridine (5.54 g, 13.994 mmol) in 1,4-dioxane (15 mL) and water (5 mL) at ambient temperature and the mixture was degassed (vacuum nitrogen cycles x 3). Pd₂(dba)₃ (640 mg, 0.699 mmol) and ^tBuXPhos (590 mg, 1.389 mmol) were added and the mixture was degassed (vacuum nitrogen cycles x 3) and stirred under microwave irradiations at 130 °C for 90 min. After cooling to ambient temperature, the reaction was partitioned between EtOAc and water. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 100% EtOAc in heptane) gave a mixture of 1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (ESI-MS *m/z* calc. 377.153, found 376.0 (M-1)⁻) and 2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (ESI-MS *m/z* calc. 377.1528, found 376.0 (M-1)⁻) (2.29 g, 44%) as a yellow solid, which was used without further purification in the next step.

Step 3:

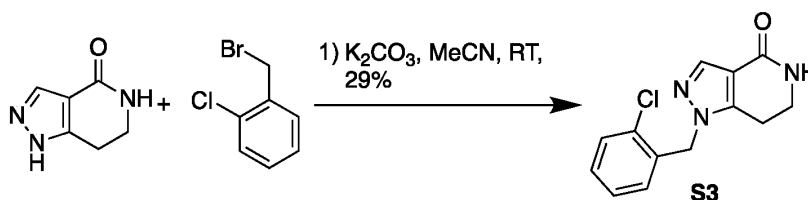
[00153] Cs₂CO₃ (4.9 g, 15.04 mmol) was added to a stirred mixture of 1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (2.84 g, 7.524 mmol), and 2,5-dichloro-4-fluoro-pyridine (1.6 g, 9.640 mmol) in DMA (20 mL) under nitrogen and the reaction was heated at 105 °C for 90 min. After cooling to ambient temperature, the mixture was partitioned between EtOAc and water and stirred vigorously for 30 min. The resulting suspension was filtered and washed with EtOAc to give

1.04 g of a pale yellow solid. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 50% EtOAc in heptane) gave a pale yellow solid, which was combined with the original precipitate to give a mixture of 5-(2,5-dichloropyridin-4-yl)-1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (¹H NMR (500 MHz, DMSO-*d*₆) δ 8.75 (s, 1H), 8.30 (d, *J* = 0.8 Hz, 1H), 7.98 (s, 1H), 7.43 - 7.32 (m, 10H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.16 - 7.10 (m, 5H), 5.34 (dd, *J* = 7.9, 0.8 Hz, 1H) ppm. ESI-MS *m/z* calc. 522.101, found 521.0 (M-1)⁻) and 5-(2,5-dichloropyridin-4-yl)-2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (ESI-MS *m/z* calc. 522.101, found 521.0 (M-1)⁻) (3.4g, 86%) as a pale yellow solid, which was used without further purification in the next step.

Step 4:

[00154] Et₃SiH (2.6 mL, 16.28 mmol) and TFA (2.5 mL, 32.45 mmol) were successively added to a stirred mixture of 5-(2,5-dichloropyridin-4-yl)-1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(2,5-dichloropyridin-4-yl)-2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (3.4 g, 6.496 mmol) in DCM (20 mL) under nitrogen and the mixture was stirred for 30 min at ambient temperature. The reaction was concentrated *in vacuo* and the residue azeotroped with DCM (x 2) then partitioned between EtOAc and a saturated NaHCO₃ solution. A precipitate was collected by filtration, washing with EtOAc. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 100% EtOAc in heptane) gave after combining with the original precipitate 5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (SB1, 1.27 g, 70%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.65 (s, 1H), 8.78 (s, 1H), 8.26 (s, 1H), 7.99 (s, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 6.74 (dd, *J* = 7.4, 0.9 Hz, 1H) ppm. ESI-MS *m/z* calc. 279.992, found 281.0 (M+1)⁺.

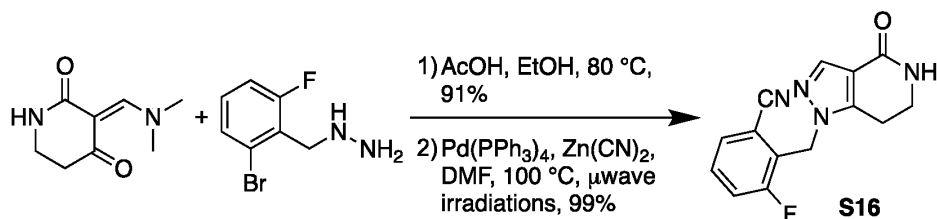
Starting Material 3: Synthesis of 1-(2-chlorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (S3)



Step 1:

[00155] 1-(Bromomethyl)-2-chlorobenzene (316.60 mg, 0.2 mL, 1.541 mmol) was added to a suspension of 1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (200 mg, 1.444 mmol) and K₂CO₃ (600 mg, 4.341 mmol) in MeCN (2 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was partitioned between water and EtOAc. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by recrystallisation from hot *i*PrOH gave 1-(2-chlorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S3**, 120 mg, 29%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 - 7.21 (m, 2H), 6.93 - 6.90 (m, 1H), 5.40 (s, 3H), 3.58 (td, *J* = 6.9, 2.7 Hz, 2H), 2.90 (dt, *J* = 29.3, 6.9 Hz, 2H) ppm. ESI-MS *m/z* calc. 261.067, found 262.0 (M+1)⁺.

Starting Material 4: Synthesis of 3-fluoro-2-((4-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)methyl)benzonitrile (S16**)**

**Step 1:**

[00156] AcOH (52.8 mg, 50 μL, 0.879 mmol) was added to a solution of 3-((dimethylamino)methylene)piperidine-2,4-dione (715 mg, 4.144 mmol) and (2-bromo-6-fluorobenzyl)hydrazine hydrochloride (2.219 g, 3.232 mmol) in EtOH (40 mL) and the reaction mixture was heated to 80 °C overnight. The mixture was cooled to ambient temperature then, in an ice bath. The solid was collected by filtration to give 1-(2-bromo-6-fluorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (948 mg, 91%) as a cream solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 - 7.89 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.28 - 7.20 (m, 1H, overlapped with solvent), 7.14 - 7.06 (m, 1H), 5.52 - 5.43 (m, 1H), 5.40 (d, *J* = 1.8 Hz, 2H), 3.66 - 3.57 (m, 2H), 3.02 (t, *J* = 6.9 Hz, 2H) ppm. ESI-MS *m/z* calc. 323.007, found 324.1 (M+1)⁺.

Step 2:

[00157] A mixture of 1-(2-bromo-6-fluorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (8.5 g, 26.223 mmol), Zn(CN)₂ (6.16 g, 52.463 mmol) and Pd(PPh₃)₄ (4.55 g,

3.938 mmol) was suspended in degassed DMF (80 mL) and the reaction mixture was stirred under microwave irradiations at 100 °C for 30 min. Water was added and the resulting solid was collected by filtration. The solid was heated in a mixture of DCM and MeOH and filtered. The mother liquors were concentrated *in vacuo* to give 3-fluoro-2-((4-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)methyl)benzonitrile (**S16**, 8.81 g, 99%) as a dark brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 (br d, *J* = 6.1 Hz, 1H), 7.70 - 7.49 (m, 3H), 7.30 (br s, 1H), 5.45 (s, 2H), 3.50 - 3.37 (m, 2H), 3.03 (br t, *J* = 6.6 Hz, 2H) ppm. ESI-MS *m/z* calc. 270.092, found 271.1 (M+1)⁺.

[00158] The following Starting Materials were made using the method described in Starting Material 4, except that Step 2 was omitted. In Step 1, different hydrazines and/or piperidine-2,4-diones were used in place of (2-bromo-6-fluorobenzyl)hydrazine hydrochloride and 3-((dimethylamino)methylene)piperidine-2,4-dione respectively.

Table 7: Starting Materials Prepared Using the Method Described in Starting Material 4

Starting Material Number	Structure	Name	LC/MS	NMR (shifts in ppm)
S5		1-(2-fluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	ESI-MS <i>m/z</i> calc. 245.096, found 246.1 (M+1) ⁺	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.93 (s, 1H), 7.34 - 7.28 (m, 1H), 7.19 - 7.06 (m, 3H), 5.66 (s, 1H), 5.32 (s, 2H), 3.59 (td, <i>J</i> = 6.9, 2.3 Hz, 2H), 2.91 (t, <i>J</i> = 6.9 Hz, 2H) ppm.
S6		<i>rac</i> -1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	ESI-MS <i>m/z</i> calc. 259.112, found 260.1 (M+1) ⁺	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.69 (s, 1H), 7.42 - 7.32 (m, 1H), 7.30 - 7.10 (m, 4H), 5.40 - 5.24 (m, 2H), 3.82 - 3.70 (m, 1H), 3.09 (dd, <i>J</i> = 16.0, 5.0 Hz, 1H), 2.57 (dd, <i>J</i> = 16.0, 10.1 Hz, 1H), 1.21 (d, <i>J</i> = 6.4 Hz, 3H) ppm.
S8		1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	ESI-MS <i>m/z</i> calc. 263.087, found 264.1 (M+1) ⁺	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.61 (s, 1H), 7.49 - 7.38 (m, 1H), 7.24 (br s, 1H), 7.11 (t, <i>J</i> = 8.2 Hz, 2H), 5.30 (s, 2H), 3.39 (td, <i>J</i> = 6.9, 2.7 Hz, 2H), 2.93 (t, <i>J</i> = 6.9 Hz, 2H) ppm.

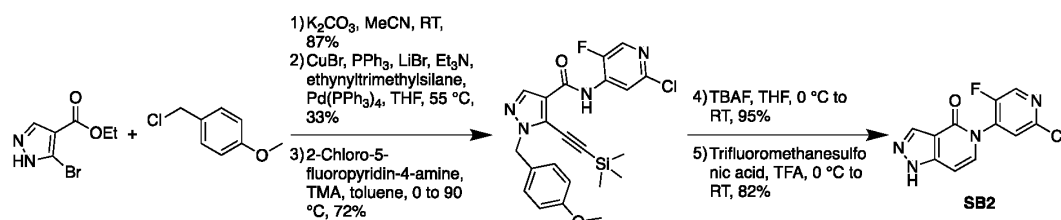
Starting Material Number	Structure	Name	LC/MS	NMR (shifts in ppm)
S10		1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 259.112, found 260.1 (M+1) ⁺ .	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.86 (s, 1H), 7.23 - 7.19 (m, 1H), 7.02 - 6.99 (m, 1H), 6.92 (t, J = 9.2 Hz, 1H), 5.62 (br s, 1H), 5.32 (d, J = 1.8 Hz, 2H), 3.56 (t, J = 6.9 Hz, 2H), 2.87 (t, J = 6.9 Hz, 2H), 2.44 (s, 3H) ppm.
S11		1-(2-chloro-6-fluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 279.058, found 280.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.63 (s, 1H), 7.48 - 7.42 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 - 7.26 (m, 2H), 5.37 (s, 2H), 3.44 - 3.40 (m, 2H), 3.00 (t, J = 7.2 Hz, 2H) ppm.
S17		<i>rac</i> -1-(1-(2-fluorophenyl)ethyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 259.112, found 260.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 (s, 1H), 7.40 - 7.32 (m, 1H), 7.30 - 7.16 (m, 4H), 5.88 (q, J = 6.8 Hz, 1H), 3.4 - 3.33 (m, 2H), 3.06 - 2.96 (m, 1H), 2.69 - 2.59 (m, 1H), 1.81 (d, J = 7.0 Hz, 3H) ppm.
SB3		5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-6,6-dimethyl-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS m/z calc. 418.076, found 419.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.51 (s, 1H), 7.96 (s, 1H), 7.38 - 7.31 (m, 1H), 7.29 - 7.22 (m, 2H), 7.19 - 7.13 (m, 1H), 7.10 (t, J = 9.2 Hz, 1H), 5.38 - 5.29 (m, 2H), 3.18 (d, J = 16.0 Hz, 1H), 2.94 (d, J = 16.0 Hz, 1H), 1.42 (s, 3H), 1.24 (s, 3H) ppm.

[00159] The following Starting Material was made using the method described in Starting Material 4, except that Step 2 was omitted. In Step 1, different hydrazine and piperidine-2,4-dione were used in place of (2-bromo-6-fluorobenzyl)hydrazine hydrochloride and 3-((dimethylamino)methylene)piperidine-2,4-dione respectively. A final Boc deprotection step was carried out at ambient temperature using an excess of TFA in DCM, conditions well known in the art.

Table 8: Starting Material Prepared Using the Method Described in Starting Material 4

Starting Material Number	Structure	Name	LC/MS	NMR (shifts in ppm)
S13		<i>rac</i> -1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	ESI-MS <i>m/z</i> calc. 259.112, found 260.1 (M+1) ⁺ .	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.92 (s, 1H), 7.33 - 7.27 (m, 1H), 7.15 - 7.05 (m, 3H), 5.69 (s, 1H), 5.33 (s, 2H), 3.74 (dd, <i>J</i> = 12.4, 5.0 Hz, 1H), 3.27 (d, <i>J</i> = 11.9 Hz, 1H), 3.17 - 3.09 (m, 1H), 1.22 (d, <i>J</i> = 6.9 Hz, 3H) ppm.

Starting Material 5: Synthesis of 5-(2-chloro-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (SB2)



Step 1:

[00160] K₂CO₃ (13 g, 89.359 mmol) and 1-(chloromethyl)-4-methoxybenzene (7.581 g, 7 mL, 45.987 mmol) were added to a stirred solution of ethyl 5-bromo-1H-pyrazole-4-carboxylate (10 g, 43.372 mmol) in MeCN (100 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was filtered through a pad of Celite[®], washing with EtOAc (500 mL). The mother liquors were concentrated *in vacuo* to give ethyl 5-bromo-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (14 g, 87%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (s, 1H), 7.30 - 7.26 (m, 2H), 6.94 - 6.90 (m, 2H), 5.25 (s, 2H), 4.25 - 4.18 (m, 2H), 3.73 (s, 3H), 1.28 - 1.24 (m, 3H) ppm.

Step 2:

[00161] CuBr (648 mg, 4.291 mmol), triphenylphosphine (592 mg, 2.144 mmol), LiBr (1.17 g, 12.799 mmol) and Et₃N (110.35 g, 160 mL, 1.036 mol) were successively added to a stirred solution of ethyl 5-bromo-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (16 g, 42.893 mmol) in THF (160 mL) at ambient temperature and the mixture was degassed by bubbling nitrogen through the solution for 10 min. Ethynyltrimethylsilane (23.574 g, 35 mL, 228.02 mmol) and Pd(PPh₃)₄ (5.21 g, 4.283 mmol) were successively added and the reaction

was stirred at 55 °C for 72 h. The mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (300 g SiO₂, 40 to 50 % DCM in hexanes) gave ethyl 1-(4-methoxybenzyl)-5-((trimethylsilyl)ethynyl)-1*H*-pyrazole-4-carboxylate (9 g, 33%) as brown solid. ESI-MS *m/z* calc. 356.156, found 357.3 (M+1)⁺.

Step 3:

[00162] 2-Chloro-5-fluoropyridin-4-amine (181 mg, 1.173 mmol) and TMA (1.2 mL, 2 M solution in toluene, 2.4 mmol) were added to a stirred solution of ethyl 1-(4-methoxybenzyl)-5-((trimethylsilyl)ethynyl)-1*H*-pyrazole-4-carboxylate (500 mg, 0.783 mmol) in toluene (5 mL) at 0 °C and the reaction mixture was stirred at 90 °C for 16 h. The reaction was quenched by addition of a saturated brine solution (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *N*-(2-chloro-5-fluoropyridin-4-yl)-1-(4-methoxybenzyl)-5-((trimethylsilyl)ethynyl)-1*H*-pyrazole-4-carboxamide (700 mg, 72%) as an off-white solid. ESI-MS *m/z* calc. 456.119, found 457.2 (M+1)⁺.

Step 4:

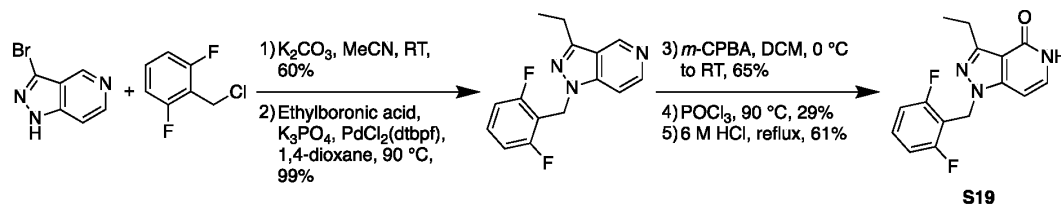
[00163] TBAF (10.7 mL, 1 M solution in THF, 10.700 mmol) was added to a stirred solution of *N*-(2-chloro-5-fluoropyridin-4-yl)-1-(4-methoxybenzyl)-5-((trimethylsilyl)ethynyl)-1*H*-pyrazole-4-carboxamide (1.9 g, 2.136 mmol) in THF (19 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO₂, 30 % EtOAc in hexanes) gave 5-(2-chloro-5-fluoropyridin-4-yl)-1-(4-methoxybenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (850 mg, 95%) as white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 1.6 Hz, 1H), 8.12 (s, 1H), 7.43 (q, *J* = 1.6 Hz, 1H), 7.29 - 7.26 (m, 2H), 6.95 - 6.87 (m, 3H), 6.67 (d, *J* = 0.8 Hz, 1H), 5.39 (s, 2H), 3.81 (s, 3H) ppm. ESI-MS *m/z* calc. 384.079, found 385.4 (M+1)⁺.

Step 5:

[00164] Trifluoromethanesulfonic acid (850 mg, 0.5 mL, 5.551 mmol) was added to a stirred solution of 5-(2-chloro-5-fluoropyridin-4-yl)-1-(4-methoxybenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1.1 g, 2.621 mmol) in TFA (11 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The mixture was concentrated *in vacuo* to give 5-(2-chloro-5-fluoropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**SB2**,

900 mg, 82%) as brown gummy solid, which was used without further purification in the next step. ESI-MS m/z calc. 264.021, found 265.2 ($M+1$)⁺.

Starting Material 6: Synthesis of 1-(2,6-difluorobenzyl)-3-ethyl-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (S19)



Step 1:

[00165] K_2CO_3 (1.2 g, 8.509 mmol) was added to a stirred solution of 3-bromo-1H-pyrazolo[4,3-*c*]pyridine (840 mg, 4.157 mmol) and 2-(chloromethyl)-1,3-difluorobenzene (1.1 g, 6.631 mmol) in MeCN (13 mL) and the reaction mixture was stirred at ambient temperature for 12 h. The reaction was quenched by addition of water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO_2 , 0 to 90% EtOAc in hexanes) gave 3-bromo-1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridine (860 mg, 60%) as a pale yellow solid. 1H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.49 (d, $J = 6.0$ Hz, 1H), 7.42 (d, $J = 6.0$ Hz, 1H), 7.34 - 7.26 (m, 1H), 6.95 - 6.91 (m, 2H), 5.59 (s, 2H) ppm. ESI-MS m/z calc. 322.987, found 324.0 ($M+1$)⁺.

Step 2:

[00166] K_3PO_4 (1.2 g, 5.540 mmol) was added to a stirred solution of 3-bromo-1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-*c*]pyridine (720 mg, 2.086 mmol) and ethylboronic acid (1.1 g, 14.590 mmol) in 1,4-dioxane (10.8 mL) and the reaction mixture was degassed by passing nitrogen gas through the mixture for 15 min. $PdCl_2(dtbpf)$ (40 mg, 0.332 mmol) was added and the reaction was stirred at 90 °C for 12 h. The reaction was cooled to ambient temperature, quenched by addition of water (150 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO_2 , 0 to 50% EtOAc in hexanes) gave 1-(2,6-difluorobenzyl)-3-ethyl-1H-pyrazolo[4,3-*c*]pyridine (590 mg, 99%) as a brown sticky solid. 1H NMR (400 MHz, Chloroform-*d*) δ 9.07 (s, 1H), 8.44 (d, $J = 6.4$ Hz, 1H), 7.42 (d, $J = 6.0$ Hz, 1H), 7.32 - 7.26 (m, 1H), 6.94 - 6.92 (m, 2H), 5.57 (s, 2H), 3.03 (q, $J = 6.4$ Hz, 2H), 1.40 (t, $J = 7.6$ Hz, 3H) ppm. ESI-MS m/z calc. 273.108, found 274.2 ($M+1$)⁺.

Step 3:

[00167] *m*-CPBA (760 mg, 70 % w/w, 3.083 mmol) was added to a stirred solution of 1-(2,6-difluorobenzyl)-3-ethyl-1*H*-pyrazolo[4,3-*c*]pyridine (560 mg, 1.955 mmol) in DCM (8.4 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 12 h. The reaction was quenched by addition of water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with a NaHCO₃ solution (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 1-(2,6-difluorobenzyl)-3-ethyl-1*H*-pyrazolo[4,3-*c*]pyridine 5-oxide (460 mg, 65%) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.16 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.35 - 7.31 (m, 1H), 6.97 - 6.93 (m, 2H), 5.54 (s, 2H), 2.92 (q, *J* = 8.0 Hz, 2H), 1.35 (t, *J* = 7.6 Hz, 3H) ppm. ESI-MS *m/z* calc. 289.103, found 290.2 (M+1)⁺.

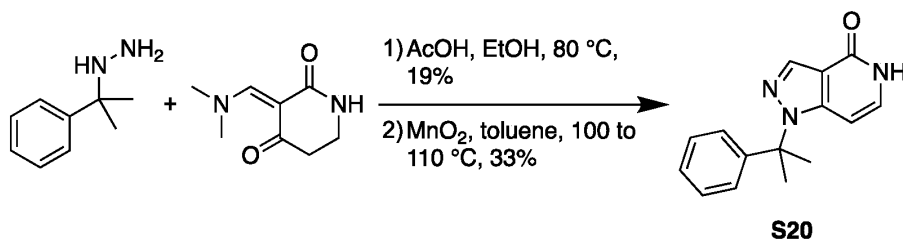
Step 4:

[00168] A solution of 1-(2,6-difluorobenzyl)-3-ethyl-1*H*-pyrazolo[4,3-*c*]pyridine 5-oxide (440 mg, 1.521 mmol) in POCl₃ (13.160 g, 8 mL, 85.827 mmol) was stirred at 90 °C for 12 h. The reaction was quenched by addition of water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a NaHCO₃ solution (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 20% EtOAc in hexanes) gave 4-chloro-1-(2,6-difluorobenzyl)-3-ethyl-1*H*-pyrazolo[4,3-*c*]pyridine (200 mg, 29%) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.2 Hz, 1H), 7.36 - 7.36 (m, 2H), 6.94 - 6.90 (m, 2H), 5.54 (s, 2H), 3.18 - 3.12 (m, 2H), 1.40 - 1.36 (m, 3H) ppm. ESI-MS *m/z* calc. 307.069, found 308.2 (M+1)⁺.

[00169] Step 5:

[00170] A solution of 4-chloro-1-(2,6-difluorobenzyl)-3-ethyl-1*H*-pyrazolo[4,3-*c*]pyridine (190 mg, 0.413 mmol) in HCl (1.9 mL, 6 M solution in water) was stirred at 100 °C for 12 h. The reaction was cooled to ambient temperature, diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with a NaHCO₃ solution (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (Inertsil® ODS-3 C₁₈ column, 20 to 99% MeCN in water with 0.1 % formic acid) gave 1-(2,6-difluorobenzyl)-3-ethyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S19**, 74 mg, 61%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.93 (s, 1H), 7.49 - 7.41 (m, 1H), 7.21 - 7.18 (m, 1H), 7.16 - 7.09 (m, 2H), 6.60 (d, *J* = 7.2 Hz, 1H), 5.45 (s, 2H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 2.8 Hz, 3H) ppm. ESI-MS *m/z* calc. 289.103, found 290.3 (M+1)⁺.

Starting Material 7: Synthesis of 1-(2-phenylpropan-2-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (S20)



Step 1:

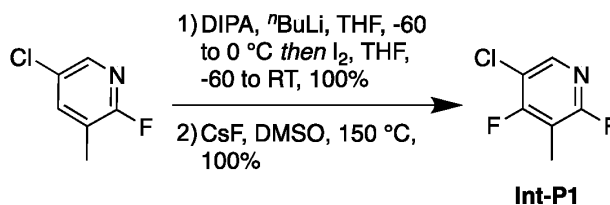
[00171] (*E*)-3-((dimethylamino)methylene)piperidine-2,4-dione (1.78 g, 10.054 mmol) and AcOH (300.96 mg, 285 μ L, 5.012 mmol) were successively added to a solution of (2-phenylpropan-2-yl)hydrazine dihydrochloride (2.23 g, 9.994 mmol) in EtOH (30 mL) and the reaction mixture was heated to 80 °C for 16 h. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was partitioned between water and EtOAc. The aqueous phase was separated and extracted with EtOAc (2 x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 10% MeOH in DCM) gave 1-(2-phenylpropan-2-yl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one (521 mg, 19%) as a pale yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.30 - 7.39 (m, 3H), 7.12 - 7.17 (m, 2H), 5.37 (br s, 1H), 3.26 (td, *J* = 6.8, 2.5 Hz, 2H), 2.26 (t, *J* = 6.8 Hz, 2H), 1.97 - 1.98 (m, 6H) ppm. ESI-MS *m/z* calc. 255.137, found 256.1 (M+1)⁺.

Step 2:

[00172] Activated MnO₂ (1.18 g, 13.573 mmol) was added to a solution of 1-(2-phenylpropan-2-yl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one (200 mg, 0.682 mmol) in toluene (10 mL) and the reaction mixture was stirred at 100 °C for 48 h. Additional activated MnO₂ (592 mg, 6.810 mmol) was added and the reaction was stirred at 110 °C for 24 h. The mixture was cooled to ambient temperature, filtered over a pad of Celite[®] and the filtered cake was washed with DCM (2 x 20 mL) and MeOH (1 x 20 mL). The filtrates were collected and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 20 to 50% EtOAc in heptane) gave 1-(2-phenylpropan-2-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (**S20**, 73 mg, 33%) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.22 (s, 1H), 7.32 - 7.35 (m, 3H), 7.19 (br d, *J* = 7.1 Hz, 2H), 6.75 (br d, *J* = 4.8 Hz, 1H), 5.55 (br d, *J* = 6.8 Hz, 1H), 2.01 (s, 6H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 253.122, found 254.1 (M+1)⁺.

V. Synthesis of Intermediates

Intermediate 1: Synthesis of 5-chloro-2,4-difluoro-3-methylpyridine (Int-P1)



Step 1:

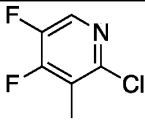
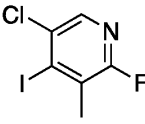
[00173] Under argon, n BuLi (300 mL, 2.5 M solution in hexanes, 750.0 mmol) was added to a stirred solution of DIPA (75.810 g, 105 mL, 749.18 mmol) in THF (1 L) over 15 min, keeping the internal temperature below $0\text{ }^\circ\text{C}$ and the reaction was cooled to $-60\text{ }^\circ\text{C}$. A solution of 5-chloro-2-fluoro-3-methylpyridine (100 g, 686.99 mmol) in THF (200 mL) was added dropwise keeping the internal temperature below $-60\text{ }^\circ\text{C}$ and the mixture was stirred at $-60\text{ }^\circ\text{C}$ for 2 h. A solution of iodine (200 g, 787.99 mmol) in THF (200 mL) was added keeping the internal temperature below $-60\text{ }^\circ\text{C}$ and the resulting mixture was slowly warmed up to ambient temperature overnight keeping the cooling bath in place. The reaction mixture was diluted with EtOAc (500 mL) and quenched by addition of a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (1 L). The organic layer was separated, washed with water (300 mL) and concentrated *in vacuo*. The solid was slurried in MeOH (250 mL) and stirred at ambient temperature for 3 h. The solid was filtered, washed with ice-cold MeOH (200 mL) and dried to give 5-chloro-2-fluoro-4-iodo-3-methylpyridine (116 g, 61%) as an off-white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 2.47 (s, 3H) ppm.

Step 2:

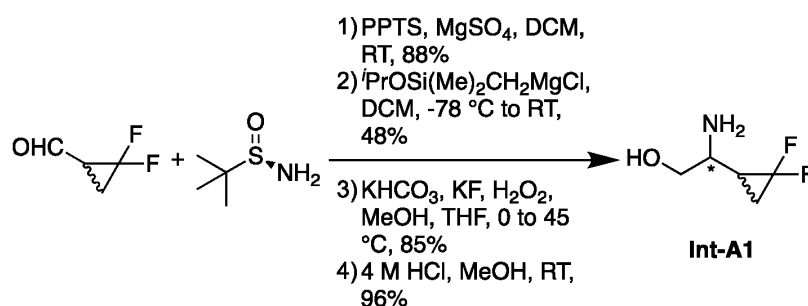
[00174] CsF (350 mg, 2.304 mmol) was added to a stirred solution of 5-chloro-2-fluoro-4-iodo-3-methylpyridine (150 mg, 0.553 mmol) in DMSO (0.8 mL) and the reaction was heated at $150\text{ }^\circ\text{C}$ for 48 h. The reaction was cooled to ambient temperature to give a solution of 5-chloro-2,4-difluoro-3-methylpyridine (**Int-P1**), which was used without further purification in the next step, assuming 100% yield.

[00175] The following Intermediates were made using the method described in Intermediate 1, except that, in Step 1, different pyridines and/or electrophiles were used in place of 5-chloro-2-fluoro-3-methylpyridine and iodine respectively. Step 2 was omitted.

Table 9: Intermediates Prepared Using the Method Described in Intermediate 1

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
Int-P2	 2-chloro-4,5-difluoro-3-methylpyridine	No ionization observed in ES+/-	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.18 (d, <i>J</i> = 8.7 Hz, 1H), 2.34 (s, 3H) ppm.
Int-P3	 5-chloro-2-fluoro-4-iodo-3-methylpyridine	No ionization observed in ES+/-	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.20 (dt, <i>J</i> = 1.4, 0.7 Hz, 1H), 3.31 (s, 3H) ppm.

Intermediate 2: Synthesis of 2-amino-2-(2,2-difluorocyclopropyl)ethan-1-ol as a mixture of 2 diastereomers (Int-A1)



Step 1:

[00176] (*R*)-2-methylpropane-2-sulfonamide (525 mg, 4.332 mmol), PPTS (55 mg, 0.219 mmol) and MgSO₄ (2.60 g, 21.6 mmol) were successively added to a stirred solution of *rac*-2,2-difluorocyclopropane-1-carbaldehyde (31.4 g, 1.6 % w/w solution in DCM, 4.737 mmol) and the reaction mixture was stirred at ambient temperature for 90 h. The mixture was filtered and an additional amount of MgSO₄ (2.6 g, 21.6 mmol) was added. The reaction was stirred at ambient temperature for 16 h. The mixture was filtered. The filtrates were washed successively with water (10 mL), with a saturated aqueous NH₄Cl solution (10 mL) and with a saturated aqueous NaHCO₃ solution (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give (*R*)-*N*-((*E*)-(2,2-difluorocyclopropyl)methylene)-2-methylpropane-2-sulfonamide (929 mg, 88%) as a mixture of 2 diastereomers and as a dark orange oil. ESI-MS *m/z* calc. 209.069, found 210.1 (M+1)⁺.

Step 2:

[00177] ((Isopropoxydimethylsilyl)methyl)magnesium chloride (220 mL, 0.58 M solution in THF, 127.60 mmol) was slowly added over 30 min to a solution of the 2 diastereomers of (*R*)-*N*-((*E*)-(2,2-difluorocyclopropyl)methylene)-2-methylpropane-2-sulfinamide (14 g, 63.558 mmol) in DCM (500 mL) at -78 °C and the reaction was stirred at -78 °C for 1 h. The mixture was warmed to ambient temperature over 2 h. The reaction was partitioned with water. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give (*R*)-*N*-(1-(2,2-difluorocyclopropyl)-2-(isopropoxydimethylsilyl)ethyl)-2-methylpropane-2-sulfinamide (21 g, 48%) as a mixture of 2 diastereomers and as a brown oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.05 - 3.99 (m, 1H), 3.35 - 3.18 (m, 1H), 1.59 - 1.28 (m, 3H), 1.26 - 1.14 (m, 16H), 0.20 - 0.06 (m, 8H) ppm.

Step 3:

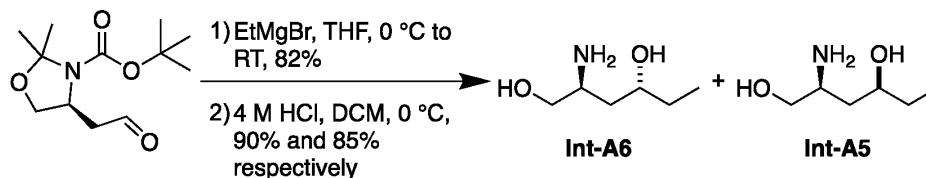
[00178] KF (180 mg, 3.098 mmol) and H₂O₂ (499.5 mg, 1.5 mL, 30 % w/w solution in water, 4.405 mmol) were successively added to a solution of a mixture of 2 diastereomers of (*R*)-*N*-(1-(2,2-difluorocyclopropyl)-2-(isopropoxydimethylsilyl)ethyl)-2-methylpropane-2-sulfinamide (1 g, 1.464 mmol) and KHCO₃ (150 mg, 1.498 mmol) in a mixture of MeOH (4 mL) and THF (4 mL) at 0 °C and the reaction mixture was stirred at 45 °C for 2 h. The reaction was cooled to ambient temperature and poured over water. The mixture was extracted with EtOAc. The organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 75% EtOAc in heptane) gave (*R*)-*N*-(1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)-2-methylpropane-2-sulfinamide (0.5 g, 85%) as a mixture of 2 diastereomers. ¹H NMR (400 MHz, Methanol-*d*₄) δ 3.67 - 3.63 (m, 1H), 3.59 (dd, *J* = 6.0, 1.8 Hz, 1H), 3.01 - 2.93 (m, 1H), 1.87-1.77 (m, 1H), 1.54 (qt, *J* = 12.0, 4.0 Hz, 1H), 1.39 - 1.30 (m, 1H), 1.26 - 1.22 (m, 9H) ppm; exchangeable H not observed.

Step 4:

[00179] HCl (4 mL, 4 M solution in 1,4-dioxane, 16.0 mmol) was added to a stirred solution of a mixture of 2 diastereomers of (*R*)-*N*-(1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)-2-methylpropane-2-sulfinamide (1.038 g, 3.630 mmol) in methanol (10 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction was concentrated *in vacuo*. Purification by trituration from a 1:5 mixture of EtOAc and Et₂O gave 2-amino-2-(2,2-difluorocyclopropyl)ethan-1-ol hydrochloride (**Int-A1**, 860 mg, 96%) as a mixture of 2 diastereomers. ¹H NMR (400 MHz, Methanol-*d*₄) δ 3.79 (dd, *J* = 11.4, 3.7 Hz,

1H), 3.64 (q, $J = 6.0$ Hz, 1H), 3.03 (t, $J = 5.3$ Hz, 1H), 1.96 - 1.87 (m, 1H), 1.78 - 1.69 (m, 1H), 1.55 - 1.46 (m, 1H) ppm; exchangeable H not observed.

Intermediate 3: Synthesis of *rel*-(2*S*^{*},4*R*)-2-aminohexane-1,4-diol (Int-A6) and *rel*-(2*S*^{*},4*S*)-2-aminohexane-1,4-diol (Int-A5)



Step 1:

[00180] EtMgBr (1.2 mL, 3 M solution in Et₂O, 3.6 mmol) was added to a stirred solution of *tert*-butyl (*S*)-2,2-dimethyl-4-(2-oxoethyl)oxazolidine-3-carboxylate (400 mg, 1.303 mmol) in THF (10 mL) at -10 °C and the reaction mixture was stirred at 0 °C to ambient temperature for 4 h. The reaction was quenched by addition of a NH₄Cl solution (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (alumina, 0 to 40% EtOAc in hexanes) gave:

[00181] **First Eluting Isomer:** *tert*-butyl *rel*-(*S*^{*})-4-((*R*)-2-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (150 mg, 38%) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.40 (d, $J = 5.2$ Hz, 1H), 3.85 (t, $J = 12$ Hz, 2H), 3.32 (s, 1H), 1.70 (s, 1H), 1.45 - 1.40 (m, 19H), 0.85 (t, $J = 7.2$ Hz, 3H) ppm.

[00182] **Second Eluting Isomer:** *tert*-butyl *rel*-(*S*^{*})-4-((*S*)-2-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (180 mg, 44%) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm = 4.40 - 4.37 (m, 1H), 4.01 - 3.98 (m, 1H), 3.88 - 3.78 (m, 2H), 1.70 (s, 1H), 1.46 - 1.23 (m, 19H), 0.85 (t, $J = 7.2$ Hz, 3H) ppm.

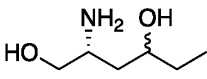
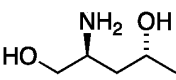
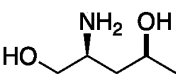
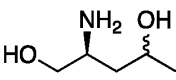
Step 2:

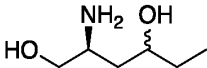
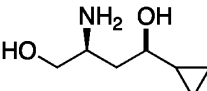
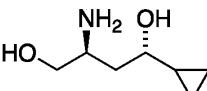
[00183] HCl (1 mL, 4 M solution in 1,4-dioxane, 4.0 mmol) was added to a stirred solution of *tert*-butyl *rel*-(*S*^{*})-4-((*R*)-2-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (150 mg, 0.497 mmol) in DCM (5 mL) at 0 °C and the reaction mixture was stirred for 3 h. The mixture was concentrated *in vacuo*. Purification by trituration from Et₂O gave *rel*-(2*S*^{*},4*R*)-2-aminohexane-1,4-diol hydrochloride (**Int-A6**, 80 mg, 90%) as a brown gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (s, 3H), 5.30 (br s, 1H), 4.70 (br s, 1H), 3.61 - 3.52 (m, 2H), 3.44 - 3.39 (m, 1H), 3.23 (d, $J = 5.2$ Hz, 1H), 1.59 - 1.56 (m, 1H), 1.49 - 1.33 (m, 3H), 0.85 (t, $J = 7.2$ Hz, 3H) ppm.

[00184] *tert*-Butyl *rel*-(*S*^{*})-4-((*S*)-2-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (180 mg, 0.577 mmol) (Second Eluting Isomer) was treated in the same way as *tert*-butyl *rel*-(*S*^{*})-4-((*R*)-2-hydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (First Eluting Isomer) to give *rel*-(2*S*^{*},4*S*)-2-aminoheptane-1,4-diol hydrochloride (**Int-A5**, 91 mg, 85%) as a brown gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 (br s, 3H), 5.26 (br s, 1H), 4.95 (br s, 1H), 3.60 (t, *J* = 11.2Hz, 1H), 3.47 (d, *J* = 4.4Hz, 2H), 3.23 (br s, 1H), 1.63 - 1.60 (m, 1H), 1.49 - 1.34 (m, 3H), 0.87 - 0.83 (m, 3H) ppm.

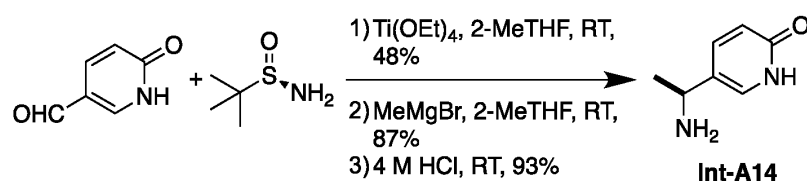
[00185] The following Intermediates were made using the method described in Intermediate 3, except that, in Step 1, different starting materials and/or Grignard reagents were respectively used in place of *tert*-butyl (*S*)-2,2-dimethyl-4-(2-oxoethyl)oxazolidine-3-carboxylate and EtMgBr.

Table 10: Intermediates Prepared Using the Method Described in Intermediate 3

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
Int-A7	 (2 <i>R</i>)-2-aminoheptane-1,4-diol as a mixture of 2 diastereomers	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.74 (s, 3H), 5.25 (d, <i>J</i> = 5.2 Hz, 1H), 4.88 (d, <i>J</i> = 4.4 Hz, 1H), 3.62 - 3.58 (m, 1H), 3.48 - 3.43 (m, 2H), 3.22 (br s, 1H), 1.62 - 1.59 (m, 1H), 1.47 - 1.41 (m, 3H), 0.87 - 0.83 (m, 3H) ppm.
Int-A8	 <i>rel</i> -(2 <i>S</i> [*] ,4 <i>R</i>)-2-aminopentane-1,4-diol	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.95 (br s, 3H), 5.45 (br s, 1H), 4.85 (br s, 1H), 3.83 - 3.80 (m, 1H), 3.79 - 3.60 (m, 1H), 3.58 - 3.38 (m, 1H), 3.20 - 3.16 (m, 1H), 1.60 - 1.46 (m, 2H), 1.07 (d, <i>J</i> = 6.4Hz, 3H) ppm.
Int-A9	 <i>rel</i> -(2 <i>S</i> [*] ,4 <i>S</i>)-2-aminopentane-1,4-diol	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.79 (br s, 3H), 5.25 (t, <i>J</i> = 4.8 Hz, 1H), 4.93 (d, <i>J</i> = 3.2Hz, 1H), 3.75 (d, <i>J</i> = 2.8Hz, 1H), 3.61 - 3.57 (m, 1H), 3.47 - 3.44 (m, 1H), 3.20 (s, 1H), 1.59 - 1.57 (m, 1H), 1.51 - 1.47 (m, 1H), 1.07 (d, <i>J</i> = 6.4Hz, 3H) ppm.
Int-A11	 <i>rel</i> -(2 <i>S</i> [*] ,4 <i>S</i>)-2-aminopentane-1,4-diol	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.91 (br s, 3H), 5.27 (d, <i>J</i> = 4 Hz, 1H), 4.93 (br s, 1H), 3.95 - 3.75 (m, 1H), 3.58 - 3.43 (m,

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
	(2 <i>S</i>)-2-aminopentane-1,4-diol as a mixture of 2 diastereomers		2H), 3.20 (s, 1H), 1.60 - 1.47 (m, 2H), 1.08 - 1.06 (m, 3H) ppm.
Int-A19	 (2 <i>S</i>)-2-amino-4-hydroxyhexane as a mixture of 2 diastereomers	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.78 (br s, 3H), 5.25 (s, 1H), 4.88 (d, <i>J</i> = 4.8 Hz, 1H), 3.88 - 3.84 (m, 2H), 3.49 - 3.45 (m, 2H), 1.76 - 1.73 (m, 2H), 1.38 - 1.33 (m, 2H), 0.88 - 0.83 (m, 3H) ppm.
Int-A23	 <i>rel</i> -(1 <i>R</i> ,3 <i>S</i>)-3-amino-1-cyclopropylbutane-1,4-diol	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 3.42 - 3.39 (m, 1H), 3.27 - 3.24 (m, 1H), 3.07 - 3.04 (m, 2H), 1.51 - 1.46 (m, 2H), 0.81 - 0.72 (m, 1H), 0.36 - 0.32 (m, 2H), 0.23 - 0.22 (m, 2H) ppm; exchangeable H not observed.
Int-A24	 <i>rel</i> -(1 <i>S</i> ,3 <i>S</i>)-3-amino-1-cyclopropylbutane-1,4-diol	No chromophore in molecule	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 4.51 (s, 1H), 3.38 - 3.32 (m, 1H), 3.27 - 3.22 (m, 1H), 3.07 - 3.02 (m, 1H), 2.92 - 2.90 (m, 1H), 1.42 - 1.36 (m, 2H), 0.76 - 0.74 (m, 1H), 0.34 - 0.31 (m, 2H), 0.23 - 0.14 (m, 2H); exchangeable H not observed ppm.

Intermediate 4: Synthesis of *rel*-(*S*)-5-(1-aminoethyl)pyridin-2(1*H*)-one (Int-A14)



Step 1:

[00186] (*R*)-2-Methylpropane-2-sulfonamide (4.5 g, 37.128 mmol) and Ti(OEt)₄ (19.584 g, 18 mL, 85.854 mmol) were successively added to a solution of 6-oxo-1,6-dihydropyridine-3-carbaldehyde (4.15 g, 33.710 mmol) in 2-MeTHF (50 mL) and the reaction mixture was stirred at ambient temperature overnight. The reaction was quenched by addition of methanol (30 mL) and a saturated aqueous NaHCO₃ solution (30 mL), and the mixture was stirred for a 30 min at ambient temperature. The solid was filtered and washed with methanol (2 x 30 mL). The filtrates were partitioned between DCM and water and the resulting suspension was filtered. The filtrates were concentrated *in vacuo* to remove DCM. The formed suspension

was filtered. The solid was washed with water (2 x 20 mL) then dried *in vacuo* to give (*R,E*)-2-methyl-*N*-((6-oxo-1,6-dihydropyridin-3-yl)methylene)propane-2-sulfinamide (4.1 g, 48%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 13.04 (br s, 1H), 8.38 (s, 1H), 8.10 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 9.6 Hz, 1H), 1.26 (s, 9H) ppm. ESI-MS *m/z* calc. 226.078, found 227.1 (M+1)⁺.

Step 2:

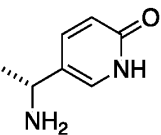
[00187] MeMgBr (18 mL, 3 M solution in Et₂O, 54.0 mmol) was added slowly to a stirred solution of (*R,E*)-2-methyl-*N*-((6-oxo-1,6-dihydropyridin-3-yl)methylene)propane-2-sulfinamide (4.1 g, 17.919 mmol) in 2-MeTHF (30 mL) under argon and the reaction mixture was stirred at ambient temperature for 5 days. The reaction was quenched by addition of water and concentrated *in vacuo*. Purification by reverse phase chromatography (120 g C₁₈ column, 0 to 50% MeOH in water with 0.1% ammonium hydroxide then, 120 g C₁₈ column, 0 to 40% MeCN in water with 0.1% formic acid) gave *rel*-(*R*^{*})-2-methyl-*N*-((*S*)-1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)propane-2-sulfinamide (3.780 g, 87%) as a pale yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.67 (dd, *J* = 9.4, 4.0 Hz, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 6.58 (d, *J* = 9.5 Hz, 1H), 4.36 (q, *J* = 6.7 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.23 (s, 9H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 242.109, found 243.0 (M+1)⁺.

Step 3:

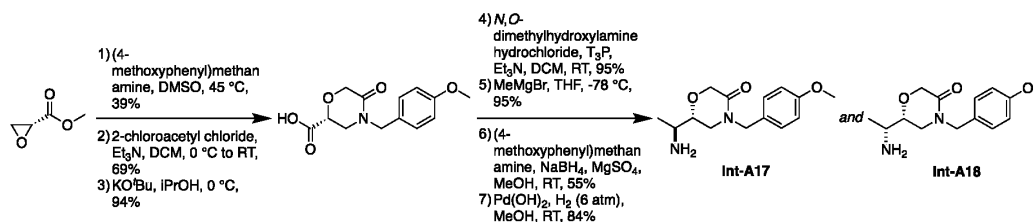
[00188] A stirred solution of *rel*-(*R*^{*})-2-methyl-*N*-((*S*)-1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)propane-2-sulfinamide (660 mg, 2.685 mmol) in HCl (6.71 mL, 4 M solution in 1,4-dioxane, 26.840 mmol) was stirred at ambient temperature for 3 h. Et₂O was added and the solid was filtered to give *rel*-(*S*)-5-(1-aminoethyl)pyridin-2(1*H*)-one hydrochloride (**Int-A14**, 447 mg, 93%) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (s, 3H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.49 (s, 1H), 6.36 (d, *J* = 9.6 Hz, 1H), 4.19 (t, *J* = 6.0 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 138.079, found 139.0 (M+1)⁺.

[00189] The following Intermediate was made using the method described in Intermediate 4, except that, in Step 1, (*S*)-2-methylpropane-2-sulfinamide was used in place of (*R*)-2-Methylpropane-2-sulfinamide.

Table 11: Intermediate Prepared Using the Method Described in Intermediate 4

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
Int-A15	 <i>rel-(R)</i> -5-(1-aminoethyl)pyridin-2(1 <i>H</i>)-one	ESI-MS <i>m/z</i> calc. 138.079, found 139.0 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.02 (dd, <i>J</i> = 9.2, 2.7 Hz, 1H), 7.90 (d, <i>J</i> = 2.3 Hz, 1H), 6.91 (d, <i>J</i> = 9.2 Hz, 1H), 4.47 (q, <i>J</i> = 6.9 Hz, 1H), 1.62 (d, <i>J</i> = 6.9 Hz, 3H) ppm; exchangeable H not observed.

Intermediate 5: Synthesis of *rel-(R*)*-6-((*S*)-1-aminoethyl)-4-(4-methoxybenzyl)morpholin-3-one (Int-A17) and *rel-(R*)*-6-((*R*)-1-aminoethyl)-4-(4-methoxybenzyl)morpholin-3-one (Int-A18)



Step 1:

[00190] (4-methoxyphenyl)methanamine (31 g, 225.98 mmol) was added to a solution of methyl (*R*)-oxirane-2-carboxylate (23 g, 225.29 mmol) in DMSO (180 mL) and the reaction mixture was stirred at 45 °C for 6 h. The reaction was cooled to ambient temperature and water was added, causing a precipitate to crash out of solution. The solid was filtered and the mother liquors were extracted with EtOAc (2 x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 7 to 93% MeOH in DCM) gave methyl (*R*)-2-hydroxy-3-((4-methoxybenzyl)amino)propanoate (24.9 g, 39%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.22 - 7.17 (m, 2H), 6.85 (dt, *J* = 9.2, 2.4 Hz, 2H), 4.27 (dd, *J* = 5.7, 3.9 Hz, 1H), 3.81 - 3.79 (m, 3H), 3.77 (s, 3H), 3.75 - 3.68 (m, 2H), 2.99 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.86 (q, *J* = 6.1 Hz, 1H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 239.116, found 240.12 (M+1)⁺.

Step 2:

[00191] 2-Chloroacetyl chloride (7.941 g, 5.6 mL, 70.308 mmol) was added dropwise to a solution of methyl (*R*)-2-hydroxy-3-((4-methoxybenzyl)amino)propanoate (15.68 g, 54.085 mmol) and triethylamine (10.890 g, 15 mL, 107.62 mmol) in DCM (400 mL) at 0 °C and the

mixture was stirred at 0 °C for 15 min and to ambient temperature for 1 h. The reaction was quenched by addition of a saturated NaHCO₃ solution and extracted with DCM (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 30 to 100% EtOAc in heptane) gave methyl (*R*)-3-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-2-hydroxypropanoate (12.47 g, 69%) as a yellow oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.12 - 7.29 (m, 2 H), 6.75 - 7.03 (m, 2 H), 4.66 - 4.82 (m, 1 H), 4.47 - 4.61 (m, 1 H), 4.22 - 4.46 (m, 2 H), 4.08 - 4.16 (m, 1 H), 3.77 - 3.84 (m, 3H), 3.72 - 3.77 (m, 3 H), 3.38 - 3.71 (m, 2 H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 315.087, found 316.1 (M+1)⁺.

Step 3:

[00192] A solution of KO^tBu (8.36 g, 74.502 mmol) in ⁱPrOH (80 mL) was added dropwise to a stirred solution of methyl (*R*)-3-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-2-hydroxypropanoate (12.47 g, 37.282 mmol) in ⁱPrOH (170 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 4.5 h. The reaction was quenched at 0 °C by addition of HCl (500 mL, 1 M aqueous solution) and the reaction was extracted with DCM (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give (*R*)-4-(4-methoxybenzyl)-5-oxomorpholine-2-carboxylic acid (9.5 g, 94%) as a pale yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.22 - 7.19 (m, 2H), 6.90 - 6.88 (m, 2H), 4.54 (s, 2H), 4.51 - 4.46 (dd, *J* = 8.2, 4.6 Hz, 1H), 4.40 (d, *J* = 16.9 Hz, 1H), 4.25 (d, *J* = 16.9 Hz, 1H), 3.76 (s, 3H), 3.58 - 3.42 (m, 2H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 265.095, found 264.1 (M-1)⁻.

Step 4:

[00193] Triethylamine (6.534 g, 9 mL, 64.572 mmol) was added to a stirred solution of (*R*)-4-(4-methoxybenzyl)-5-oxomorpholine-2-carboxylic acid (6.22 g, 19.392 mmol), *N,O*-dimethylhydroxylamine hydrochloride (2.2 g, 22.554 mmol) and T3P (15 mL, 50 % w/v solution in EtOAc, 23.571 mmol) in DCM (150 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction was partitioned between DCM and water. The organic layer was separated, dried (Na₂SO₄), filtrated and concentrated *in vacuo* to give (*R*)-*N*-methoxy-4-(4-methoxybenzyl)-*N*-methyl-5-oxomorpholine-2-carboxamide (6.3 g, 95%) as a yellow oil which solidified on standing. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.20 (dt, *J* = 9.2, 2.4 Hz, 2H), 6.85 (dt, *J* = 9.2, 2.4 Hz, 2H), 4.66 - 4.60 (m, 2H), 4.48 (dd, *J* = 15.3, 8.5 Hz, 2H), 4.26 (d, *J* = 16.5 Hz, 1H), 3.78 (d, *J* = 6.0 Hz, 3H), 3.68 (s, 3H), 3.61 - 3.52 (m, 1H), 3.28 - 3.23 (m, 1H), 3.16 (s, 3H) ppm. ESI-MS *m/z* calc. 308.137, found 309.0 (M+1)⁺.

Step 5:

[00194] MeMgBr (6 mL, 3 M solution in Et₂O, 18.0 mmol) was added to a solution of (*R*)-*N*-methoxy-4-(4-methoxybenzyl)-*N*-methyl-5-oxomorpholine-2-carboxamide (2.75 g, 8.027 mmol) in THF (50 mL) at -78 °C and the reaction mixture was stirred under argon for 1 h. The reaction was quenched by addition of water, warmed to ambient temperature and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give (*R*)-6-acetyl-4-(4-methoxybenzyl)morpholin-3-one (2.35 g, 95%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dt, *J* = 9.3, 2.5 Hz, 2H), 6.86 (dt, *J* = 9.2, 2.4 Hz, 2H), 4.61 (d, *J* = 14.7 Hz, 1H), 4.49 - 4.40 (m, 2H), 4.28 (d, *J* = 16.5 Hz, 1H), 4.14 - 4.08 (m, 1H), 3.79 (s, 3H), 3.36 (dd, *J* = 12.6, 3.4 Hz, 1H), 3.27 (dd, *J* = 12.5, 10.4 Hz, 1H), 2.23 (s, 3H) ppm. ESI-MS *m/z* calc. 263.116, found 264.1 (M+1)⁺.

Step 6:

[00195] (4-Methoxyphenyl)methanamine (2.5 g, 18.224 mmol) was added to a suspension of (*R*)-6-acetyl-4-(4-methoxybenzyl)morpholin-3-one (2.4 g, 7.748 mmol) and MgSO₄ (1 g, 8.308 mmol) in MeOH (30 mL) and the reaction mixture was stirred at ambient temperature for 4 h. NaBH₄ (0.7 g, 18.503 mmol) was added portionwise and the reaction mixture was stirred at ambient temperature for 17 h. The reaction was quenched by addition of water and extracted with EtOAc (2 x). The organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 5% MeOH in DCM) followed by reverse phase chromatography (80 g C₁₈ column, 20 to 80% MeCN in water with 0.1% ammonium hydroxide) of each of the diastereoisomers gave:

[00196] First Eluting Isomer: *rel*-(*R*^{*})-4-(4-methoxybenzyl)-6-((*S*)-1-((4-methoxybenzyl)amino)ethyl)morpholin-3-one (1.01 g, 33%) as a colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.21 - 7.18 (m, 2H), 7.15 (dd, *J* = 6.6, 2.1 Hz, 2H), 6.90 - 6.85 (m, 2H), 6.82 (td, *J* = 5.7, 3.2 Hz, 2H), 4.51 (dd, *J* = 33.7, 14.4 Hz, 2H), 4.19 (dd, *J* = 39.6, 16.7 Hz, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.65 (dt, *J* = 10.2, 4.4 Hz, 1H), 3.58 - 3.55 (m, 1H), 3.25 - 3.17 (m, 2H), 2.74 - 2.68 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 384.205, found 385.3 (M+1)⁺.

[00197] Second Eluting Isomer: *rel*-(*R*^{*})-4-(4-methoxybenzyl)-6-((*R*)-1-((4-methoxybenzyl)amino)ethyl)morpholin-3-one (0.7 g, 22%) as a colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.19 (td, *J* = 6.0, 2.9 Hz, 4H), 6.90 - 6.83 (m, 4H), 4.51 (q, *J* = 14.2 Hz, 2H), 4.26 - 4.16 (m, 2H), 3.76 (m, 7H), 3.58 - 3.52 (m, 2H), 3.23 - 3.18 (m, 2H), 2.70 (dt,

$J = 13.9, 6.5$ Hz, 1H), 0.98 (d, $J = 6.4$ Hz, 3H) ppm; exchangeable H not observed. ESI-MS m/z calc. 384.205, found 385.3 (M+1)⁺.

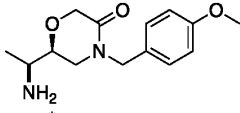
Step 7:

[00198] In an autoclave, Pd(OH)₂ (300 mg, 20 % w/w on carbon, 0.427 mmol) was added to a stirred solution of *rel*-(*R*^{*})-4-(4-methoxybenzyl)-6-((*S*)-1-((4-methoxybenzyl)amino)ethyl)morpholin-3-one (1.01 g, 2.550 mmol) (First Eluting Isomer) in methanol (30 mL) and the reaction mixture was stirred under hydrogen (6 atm) for 18 h at ambient temperature. The reaction mixture was filtered through a pad of Celite[®] and the filtrate was concentrated *in vacuo*. Purification by reverse phase chromatography (C₁₈ column, 10 to 50% MeCN in water with 0.1% ammonium hydroxide) gave *rel*-(*R*^{*})-6-((*S*)-1-aminoethyl)-4-(4-methoxybenzyl)morpholin-3-one (**Int-A17**, 325 mg, 48%) as a colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.21 (dt, $J = 9.2, 2.4$ Hz, 2H), 6.88 (dt, $J = 9.3, 2.5$ Hz, 2H), 4.62 (d, $J = 14.7$ Hz, 1H), 4.44 (d, $J = 14.2$ Hz, 1H), 4.29 - 4.25 (m, 1H), 4.17 (d, $J = 16.5$ Hz, 1H), 3.76 (s, 3H), 3.55 - 3.50 (m, 1H), 3.26 - 3.20 (m, 2H), 2.94 - 2.88 (m, 1H), 1.06 (d, $J = 6.4$ Hz, 3H) ppm; exchangeable H not observed. ESI-MS m/z calc. 264.147, found 265.1 (M+1)⁺.

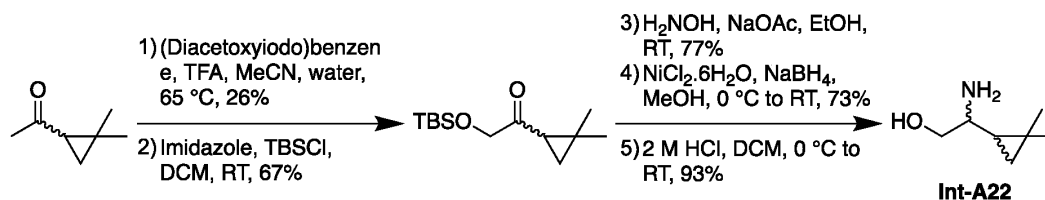
[00199] *rel*-(*R*^{*})-4-(4-Methoxybenzyl)-6-((*R*)-1-((4-methoxybenzyl)amino)ethyl)morpholin-3-one (0.7 g, 1.741 mmol) (Second Eluting Isomer) was treated in the same way as *rel*-(*R*^{*})-4-(4-methoxybenzyl)-6-((*S*)-1-((4-methoxybenzyl)amino)ethyl)morpholin-3-one (First Eluting Isomer) to give *rel*-(*R*^{*})-6-((*R*)-1-aminoethyl)-4-(4-methoxybenzyl)morpholin-3-one (**Int-A18**, 170 mg, 36%) as a colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.22 - 7.19 (m, 2H), 6.88 (dt, $J = 9.3, 2.5$ Hz, 2H), 4.57 (d, $J = 14.2$ Hz, 1H), 4.49 (d, $J = 14.2$ Hz, 1H), 4.28 (d, $J = 16.5$ Hz, 1H), 4.16 (d, $J = 16.5$ Hz, 1H), 3.76 (s, 3H), 3.41 (q, $J = 7.0$ Hz, 1H), 3.19 (d, $J = 7.3$ Hz, 2H), 2.85 - 2.78 (m, 1H), 0.99 (d, $J = 6.4$ Hz, 3H) ppm; exchangeable H not observed. ESI-MS m/z calc. 264.147, found 265.1 (M+1)⁺.

[00200] The following Intermediate was made using the method described in Intermediate 5, except that, in Step 1, methyl (*S*)-oxirane-2-carboxylate was used in place of methyl (*R*)-oxirane-2-carboxylate.

Table 12: Intermediate Prepared Using the Method Described in Intermediate 5

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
Int-A20	 $rel-(S^*)-6-((S)-1-$ $aminoethyl)-4-(4-$ $methoxybenzyl)morphol$ $in-3-one$	ESI-MS m/z calc. 264.147, found 265.1 ($M+1$) ⁺ .	¹ H NMR (400 MHz, Methanol- d_4) δ 7.23 - 7.20 (m, 2H), 6.88 (dt, J = 9.3, 2.5 Hz, 2H), 4.62 (d, J = 14.2 Hz, 1H), 4.44 (d, J = 14.2 Hz, 1H), 4.22 (dd, J = 38.5, 16.5 Hz, 2H), 3.78 (d, J = 14.2 Hz, 3H), 3.58 - 3.50 (m, 1H), 3.33 - 3.21 (m, 2H), 2.91 (dt, J = 12.7, 6.1 Hz, 1H), 1.06 (d, J = 6.4 Hz, 3H ppm; exchangeable H not observed.

Intermediate 6: Synthesis of *rac*-2-amino-2-(2,2-dimethylcyclopropyl)ethan-1-ol (Int-A22)



Step 1:

[00201] TFA (725.2 mg, 0.5 mL, 6.233 mmol) and (diacetoxyiodo)benzene (2 g, 6.085 mmol) were successively added to a stirred solution of *rac*-1-(2,2-dimethylcyclopropyl)ethan-1-one (500 mg, 3.119 mmol) in a mixture of MeCN (12 mL) and water (3 mL) at 0 °C and the reaction mixture was stirred at 65 °C for 3 h. The reaction was quenched by addition of water and extracted into EtOAc (2 x 30 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO_2 , 0 to 20% EtOAc in hexanes) gave *rac*-1-(2,2-dimethylcyclopropyl)-2-hydroxyethan-1-one (150 mg, 26%) as a pale yellow oil. ¹H NMR (400 MHz, DMSO- d_6) δ 5.07 (t, J = 6.0 Hz, 1H), 4.18 - 4.04 (m, 2H), 2.04 - 2.01 (m, 1H), 1.31 (s, 3H), 1.08 - 1.06 (m, 1H), 1.01 (s, 3H), 0.88 - 0.86 (m, 1H) ppm.

Step 2:

[00202] Imidazole (75 mg, 1.080 mmol) and TBSCl (100 mg, 0.6502 mmol) were successively added to a stirred solution of *rac*-1-(2,2-dimethylcyclopropyl)-2-hydroxyethan-1-one (100 mg, 0.546 mmol) in DCM (3 mL) and the reaction mixture was stirred at ambient

temperature for 16 h. The reaction was diluted with water (20 mL) and extracted with DCM (2 x 30 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-one (100 mg, 67%) as a pale yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.21 (dd, *J* = 20.4, 17.2 Hz, 2H), 2.15 (t, *J* = 5.6 Hz, 1H), 1.31 (q, *J* = 5.2 Hz, 1H), 1.21 (s, 3H), 1.09 (s, 3H), 0.93 (s, 9H), 0.88 (q, *J* = 3.6 Hz, 1H), 0.09 (s, 6H) ppm.

Step 3:

[00203] Sodium acetate (185 mg, 2.2101 mmol) and hydroxylamine (290 mg, 1.766 mmol) were successively added to a stirred solution of *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-one (400 mg, 1.485 mmol) in EtOH (10 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of water and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-one oxime (300 mg, 77%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.51 (s, 1H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.30 (d, *J* = 15.6 Hz, 1H), 1.53 - 1.50 (m, 1H), 1.13 (s, 3H), 0.93 - 0.82 (m, 12H), 0.53 - 0.50 (m, 1H), 0.19 (s, 6H) ppm, 0.05 (m, 1H) ppm.

Step 4:

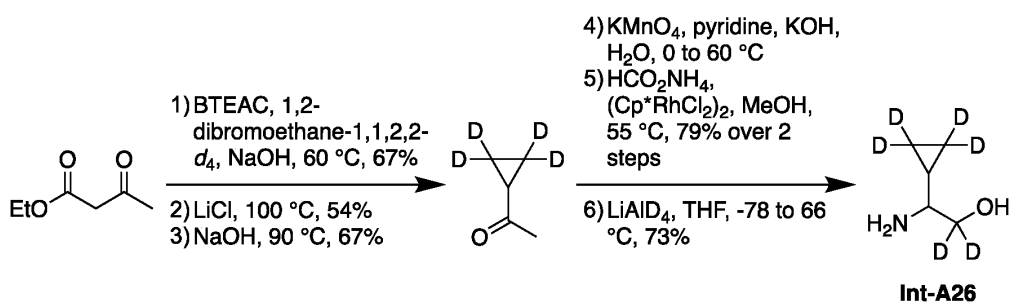
[00204] NiCl₂·6H₂O (200 mg, 0.799 mmol) and NaBH₄ (165 mg, 4.274 mmol) were successively added to a stirred solution of *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-one oxime (220 mg, 0.839 mmol) in MeOH (5 mL) at 0 °C and the reaction mixture was stirred at ambient temperature overnight. The mixture was diluted with EtOAc (40 mL) and filtered through a pad of Celite®. The filtrates were collected, washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-amine (175 mg, 73%) as a pale yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.58 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.39 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.33 - 2.31 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.85 - 0.83 (m, 1H), 0.40 - 0.38 (m, 1H), 0.33 - 0.28 (m, 1H), 0.04 (s, 6H) ppm; exchangeable H not observed.

Step 5:

[00205] HCl (2 mL, 2 M solution in Et₂O, 4.0 mmol) was added to a stirred solution of *rac*-2-((*tert*-butyldimethylsilyl)oxy)-1-(2,2-dimethylcyclopropyl)ethan-1-amine (160 mg, 0.559

mmol) in DCM (3 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was concentrated *in vacuo*. Purification by trituration from Et₂O gave *rac*-2-amino-2-(2,2-dimethylcyclopropyl)ethan-1-ol hydrochloride (**Int-A22**, 90 mg, 93%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (br s, 3H), 5.30 (t, *J* = 4.8 Hz, 1H), 3.64 - 3.59 (m, 1H), 3.52 - 3.46 (m, 1H), 2.67 (t, *J* = 1.6 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H), 0.71 - 0.67 (m, 1H), 0.50 - 0.47 (m, 1H), 0.19 (t, *J* = 4.8 Hz, 1H) ppm.

Intermediate 7: Synthesis of 2-amino-2-(cyclopropyl-2,2,3,3-*d*₄)ethan-1,1-*d*₂-1-ol (Int-A26)



Step 1:

[00206] BTEAC (30.9 g, 136 mmol) was added with stirring to NaOH (436 g, 50 wt.% aqueous solution, 5.45 mol) at 60 °C. A mixture of ethyl acetoacetate (35.3 g, 271 mmol) and 1,2-dibromoethane-1,1,2,2-*d*₄ (52.5 g, 326 mmol) were added at once and the resultant suspension was vigorously stirred at 60 °C for 2 h. The reaction was cooled to ambient temperature. The mixture was diluted with deionized water (350 mL) and cooled to an internal temperature of 0 °C. Concentrated aqueous HCl (500 mL) was added dropwise while keeping the internal temperature below 20 °C. The acidic mixture (pH 2 - 3) was extracted with Et₂O (3 x 400 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10 to 50% EtOAc in hexanes) gave 1-acetylcyclopropane-1-carboxylic-2,2,3,3-*d*₄ acid (30.1 g, 67%) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 2.20 (s, 3H) ppm; exchangeable H not observed.

Step 2:

[00207] Anhydrous LiCl (14.5 g, 0.342 mol) was added to 1-acetylcyclopropane-1-carboxylic-2,2,3,3-*d*₄ acid (30.1 g, 228 mmol) and the neat reaction mixture was stirred at 100 °C for 2 h. The mixture was cooled to ambient temperature, diluted with Et₂O (100 mL), filtered, and the filter cake was rinsed with Et₂O (2 x 50 mL). The mother liquors were collected and concentrated under reduced pressure below 15 °C to give 5-chloropentan-2-

one-4,4,5,5-*d*₄ (10.62 g, 42% yield) as a pale yellow oil. The remaining filter cake was dissolved in HCl (100 mL, 1 M aqueous solution) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give additional amounts of 5-chloropentan-2-one-4,4,5,5-*d*₄ (16.1 g, 12%) as a pale yellow semi-solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 2.17 (s, 3H), 2.62 (s, 2H) ppm.

Step 3:

[00208] NaOH (20.43 g, 25 wt.% aqueous solution, 127.9 mmol) was added to 5-chloropentan-2-one-4,4,5,5-*d*₄ (10.6 g, 85.2 mmol) and the reaction mixture was stirred at 90 °C for 2 h. The reaction was cooled to ambient temperature and saturated with NaCl. The mixture was extracted with Et₂O (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and the volatiles were removed by fractional distillation below 70 °C under atmospheric pressure to give 1-(cyclopropyl-2,2,3,3-*d*₄)ethan-1-one (5.58 g, 67.0%) as a pale yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 1.90 (s, 1H), 2.23 (s, 3H) ppm.

Step 4:

[00209] KMnO₄ (25.1 g, 158.8 mmol) was added over 10 min to a mixture of 1-(cyclopropyl-2,2,3,3-*d*₄)ethan-1-one (7.00 g, 79.4 mmol), pyridine (18.84 g, 238.2 mmol) and KOH (5.35 g, 95.3 mmol) in deionized water (238 mL) at 0 °C and the reaction mixture was stirred at 60 °C for 3 h. The resultant suspension was filtered, and the filter cake was rinsed with warm (50 °C) deionized water (3 x 50 mL). The combined mother liquors were concentrated *in vacuo* to give a pale-yellow solid (20.9 g) consisting of a mixture of potassium 2-(cyclopropyl-2,2,3,3-*d*₄)-2-oxoacetate (ca. 6.65 g, 54 wt. %) and KOH (14.26 g, ~ 3.2 equivalents), which was used without further purification in the next step. ¹H NMR (400 MHz, D₂O) δ 12.28 (s, 1H) ppm; exchangeable H not observed.

Step 5:

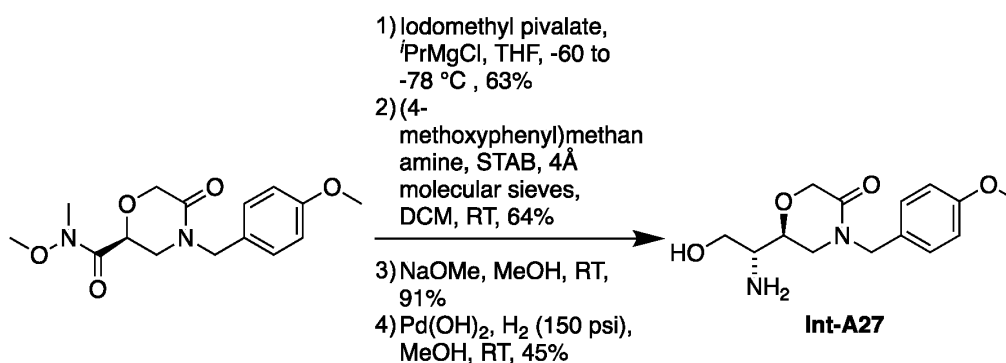
[00210] Ammonium formate (6.00 g, 96.0 mmol) was added to a stirred solution of 2-(cyclopropyl-2,2,3,3-*d*₄)-2-oxoacetic acid (ca. 3.00 g, 19.2 mmol) in MeOH (48 mL) at ambient temperature and the solution was degassed (vacuum nitrogen cycles x 5). (Cp^{*}RhCl₂)₂ (29.7 mg, 48 μmol) was added and the mixture was degassed again (vacuum nitrogen cycles x 5). The reaction was stirred and heated under a N₂ atmosphere at 55 °C for 22 h. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude yellow solid was triturated from Et₂O (30 mL) to remove the catalyst and dissolved in deionized water (30 mL). Purification by ion exchange resin (15 g DOWEX 50WX8, 5% NH₄OH in deionized water) gave 2-amino-2-(cyclopropyl-2,2,3,3-*d*₄)acetic acid (1.82 g, 79%

over 2 steps) as an off-white solid. ^1H NMR (400 MHz, D_2O) δ 3.07 (d, J = 9.6 Hz, 1H), 1.08 (d, J = 9.6 Hz, 1H) ppm; exchangeable H not observed.

Step 6:

[00211] LiAlD_4 (5.41 g, 129.0 mmol) was added over 5 min to a -78°C mixture of 2-amino-2-(cyclopropyl-2,2,3,3- d_4)acetic acid (5.12 g, 43.0 mmol) in anhydrous THF (210 mL) under a N_2 atmosphere and the mixture was stirred at -78°C for 30 min, at ambient temperature for 1 h and at reflux for 17 h. The reaction was cooled to -78°C and NaOH (20 mL, 5 wt.% aqueous solution) was slowly added over 10 min. The cold bath was removed, the resulting suspension was stirred at ambient temperature for 1 h, filtered and the filter cake was rinsed with Et_2O (5 x 60 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 2-amino-2-(cyclopropyl-2,2,3,3- d_4)ethan-1,1- d_2 -1-ol (**Int-A26**, 3.35 g, 73%) as a light yellow oil. ^1H NMR (400 MHz, Chloroform- d) δ 1.90 - 2.50 (br s, 3H), 2.06 (d, J = 9.2 Hz, 1H), 0.67 (d, J = 8.8 Hz, 1H) ppm.

Intermediate 8: Synthesis of *rel*-(S^*)-6-((*R*)-1-amino-2-hydroxyethyl)-4-(4-methoxybenzyl)morpholin-3-one (**Int-A27**)



Step 1:

[00212] $t\text{PrMgCl}$ (11.2 mL, 2 M solution in THF, 22.4 mmol) was slowly added to a solution of iodomethyl pivalate (4.519 g, 2.8 mL, 18.670 mmol) in THF (30 mL) at -60°C and the reaction mixture was stirred at -60°C for 1 h. The resulting solution was added dropwise to a solution of (*S*)-*N*-methoxy-4-(4-methoxybenzyl)-*N*-methyl-5-oxomorpholine-2-carboxamide (2.5 g, 7.482 mmol) in THF (30 mL) at -78°C . The reaction mixture was stirred for 1 h at -78°C and quenched by addition of a saturated aqueous NH_4Cl solution. The mixture was warmed to ambient temperature and partitioned between EtOAc and water. The organic layer was separated, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 20 to 100% EtOAc in heptane) gave (*S*)-2-(4-(4-

methoxybenzyl)-5-oxomorpholin-2-yl)-2-oxoethyl pivalate (1.793 g, 63%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.90 - 6.83 (m, 2H), 4.97 - 4.87 (m, 2H), 4.69 (d, *J* = 14.2 Hz, 1H), 4.47 - 4.39 (m, 2H), 4.37 - 4.24 (m, 2H), 3.81 (s, 3H), 3.38 (s, 1H), 3.37 (d, *J* = 2.3 Hz, 1H), 1.25 (s, 9H) ppm. ESI-MS *m/z* calc. 363.168, found 364.2 (M+1)⁺.

Step 2:

[00213] A mixture of (*S*)-2-(4-(4-methoxybenzyl)-5-oxomorpholin-2-yl)-2-oxoethyl pivalate (1.65 g, 4.313 mmol), (4-methoxyphenyl)methanamine (1.187 g, 1.13 mL, 8.649 mmol) and 4Å molecular sieves in DCM (25 mL) was stirred at ambient temperature for 16 h. STAB (1.83 g, 8.634 mmol) was added and the reaction mixture was stirred for a further 4 h. The mixture was partitioned with a saturated aqueous NaHCO₃ solution. The aqueous phase was separated and extracted with DCM. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10 to 100% EtOAc in heptane) gave:

[00214] First Eluting Isomer: *rel*-(*S*)-2-((*S*^{*})-4-(4-methoxybenzyl)-5-oxomorpholin-2-yl)-2-((4-methoxybenzyl)amino)ethyl pivalate (1.135 g, 52%) as a pale yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.16 (dd, *J* = 26.1, 8.2 Hz, 4H), 6.89 - 6.80 (m, 4H), 4.52 (s, 2H), 4.31 - 4.25 (m, 2H), 4.15 - 4.09 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 (s, 1H), 3.67 - 3.58 (m, 2H), 3.32 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.19 (t, *J* = 11.2 Hz, 1H), 2.81 - 2.77 (m, 1H), 1.16 (d, *J* = 8.7 Hz, 9H) ppm. ESI-MS *m/z* calc. 484.257, found 485.3 (M+1)⁺.

[00215] Second Eluting Isomer: *rel*-(*R*)-2-((*S*^{*})-4-(4-methoxybenzyl)-5-oxomorpholin-2-yl)-2-((4-methoxybenzyl)amino)ethyl pivalate (314 mg, 12%) as a pale yellow oil, which solidified on standing. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.19 - 7.15 (m, 4H), 6.87 - 6.82 (m, 4H), 4.53 (dd, *J* = 54.5, 14.7 Hz, 2H), 4.37 - 4.29 (m, 1H), 4.18 - 4.05 (m, 4H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 - 3.69 (m, 1H), 3.64 (d, *J* = 13.3 Hz, 1H), 3.46 (t, *J* = 11.4 Hz, 1H), 2.97 (dd, *J* = 11.9, 3.2 Hz, 1H), 2.79 (q, *J* = 5.2 Hz, 1H), 1.16 - 1.11 (m, 9H) ppm. ESI-MS *m/z* calc. 484.257, found 485.3 (M+1)⁺.

Step 3:

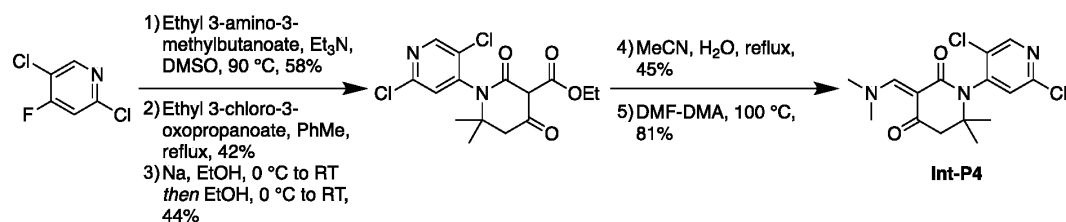
[00216] NaOMe (0.25 mL, 25 % w/v solution in MeOH, 1.157 mmol) was added to a solution of *rel*-(*R*)-2-((*S*^{*})-4-(4-methoxybenzyl)-5-oxomorpholin-2-yl)-2-((4-methoxybenzyl)amino)ethyl pivalate (Second Eluting Isomer, 315 mg, 0.534 mmol) in MeOH (3 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The mixture was poured onto ice/water and extracted with EtOAc (x 2). The combined organic

phases were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give *rel*-(*S*^{*})-6-((*R*)-2-hydroxy-1-((4-methoxybenzyl)amino)ethyl)-4-(4-methoxybenzyl)morpholin-3-one (286 mg, 91%) as a pale yellow oil, which solidified on standing. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.25 - 7.16 (m, 4H), 6.94 - 6.87 (m, 2H), 6.87 - 6.81 (m, 2H), 4.53 (q, *J* = 14.7 Hz, 2H), 4.33 - 4.12 (m, 2H), 3.85 - 3.75 (m, 8H), 3.69 - 3.49 (m, 3H), 3.40 - 3.33 (m, 1H), 3.14 (dd, *J* = 12.4, 2.7 Hz, 1H), 2.66 - 2.60 (m, 1H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 400.200, found 399.2 (M-1)⁺.

Step 4:

[00217] Pd(OH)₂ (80 mg, 20 % w/w, 0.114 mmol) was added to a solution of *rel*-(*S*^{*})-6-((*R*)-2-hydroxy-1-((4-methoxybenzyl)amino)ethyl)-4-(4-methoxybenzyl)morpholin-3-one (286 mg, 0.487 mmol) in MeOH (20 mL) and the reaction mixture was stirred under a pressure of 150 psi of hydrogen for 16 h. The reaction was filtered through a pad of Celite[®] and the filtrates were concentrated *in vacuo*. Purification by reverse phase chromatography (12 g C₁₈ column, 0 to 50% MeCN in water with 0.1% ammonium hydroxide) followed by purification by flash chromatography (SiO₂, 0 to 10% MeOH in DCM) gave *rel*-(*S*^{*})-6-((*R*)-1-amino-2-hydroxyethyl)-4-(4-methoxybenzyl)morpholin-3-one (**Int-A27**, 63 mg, 45%) as a colorless oil, which solidified on standing. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.22 - 7.20 (m, 2H), 6.90 - 6.87 (m, 2H), 4.53 (dd, *J* = 35.9, 14.4 Hz, 2H), 4.23 (dd, *J* = 41.7, 16.5 Hz, 2H), 3.76-3.70 (m, 4H), 3.51 (q, *J* = 5.6 Hz, 1H), 3.46 - 3.33 (m, 2H), 3.20 (dd, *J* = 12.1, 3.0 Hz, 1H), 2.75 (q, *J* = 5.6 Hz, 1H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 280.142, found 281.1 (M+1)⁺.

Intermediate 9: Synthesis of (*E*)-1-(2,5-dichloropyridin-4-yl)-3-((dimethylamino)methylene)-6,6-dimethylpiperidine-2,4-dione (**Int-P4**)



Step 1:

[00218] Et₃N (3.340 g, 4.6 mL, 33.003 mmol) was added to a solution of 2,5-dichloro-4-fluoropyridine (2.5 g, 15.062 mmol) and ethyl 3-amino-3-methylbutanoate hydrochloride (3.28 g, 18.056 mmol) in DMSO (50 mL) and the reaction mixture heated at 90 °C for 20 h. The reaction was cooled to ambient temperature and quenched by addition of water. The

mixture was extracted with EtOAc (3 x). The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 50% EtOAc in heptane) gave ethyl 3-((2,5-dichloropyridin-4-yl)amino)-3-methylbutanoate (2.57 g, 58%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 6.71 (s, 1H), 5.71 (br s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.68 (s, 2H), 1.53 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 290.059, found 291.0 (M+1)⁺.

Step 2:

[00219] Ethyl 3-chloro-3-oxopropanoate (2.623 g, 2.23 mL, 17.418 mmol) was added dropwise to a solution of ethyl 3-((2,5-dichloropyridin-4-yl)amino)-3-methylbutanoate (2.56 g, 8.698 mmol) in toluene (50 mL) and the reaction mixture was stirred at reflux for 20 h. The reaction was cooled to ambient temperature, quenched by addition of a saturated aqueous NaHCO₃ solution and extracted with DCM (3 x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 50% EtOAc in heptane) gave ethyl 3-(*N*-(2,5-dichloropyridin-4-yl)-3-ethoxy-3-oxopropanamido)-3-methylbutanoate (1.58 g, 42%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.74 (s, 1H), 4.23 - 4.11 (m, 4H), 3.86 (d, *J* = 15.5 Hz, 1H), 3.04 (d, *J* = 15.7 Hz, 1H), 2.93 (d, *J* = 15.5 Hz, 1H), 2.67 (d, *J* = 15.5 Hz, 1H), 1.68 (s, 3H), 1.33 - 1.23 (m, 6H), 1.19 (s, 3H) ppm. ESI-MS *m/z* calc. 404.091, found 405.2 (M+1)⁺.

Step 3:

[00220] Sodium (81 mg, 3.523 mmol) was added portionwise to EtOH (4 mL) at 0 °C under argon and the resulting mixture was stirred until the sodium was completely dissolved. The mixture was warmed to ambient temperature, then added dropwise to a stirred solution of ethyl 3-(*N*-(2,5-dichloropyridin-4-yl)-3-ethoxy-3-oxopropanamido)-3-methylbutanoate (1.28 g, 2.948 mmol) in EtOH (25 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 20 h. The reaction was quenched by addition of water and extracted with EtOAc. The EtOAc layer was separated and discarded. The aqueous layer was acidified to pH ~2 by addition of a 2 M aqueous HCl solution. The solid was filtered to give ethyl 1-(2,5-dichloropyridin-4-yl)-6,6-dimethyl-2,4-dioxopiperidine-3-carboxylate (447 mg, 40%) as a white solid. The aqueous layer was further extracted with EtOAc (3 x) and the combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give additional ethyl 1-(2,5-dichloropyridin-4-yl)-6,6-dimethyl-2,4-dioxopiperidine-3-

carboxylate (48 mg, 4%) as a beige solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 14.33 (s, 1H), 8.48 (s, 1H), 7.28 (s, 1H, overlapped with solvent), 4.30 - 4.42 (m, 2H), 3.11 (d, J = 16.8 Hz, 1H), 2.55 (d, J = 17.6 Hz, 1H), 1.53 (s, 3H), 1.37 (t, J = 7.25 Hz, 3H), 1.14 (s, 3H) ppm. ESI-MS m/z calc. 358.049, found 359.1 ($\text{M}+1$) $^+$.

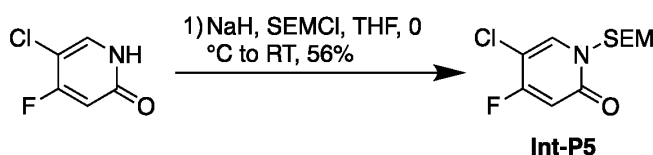
Step 4:

[00221] A solution of ethyl 1-(2,5-dichloropyridin-4-yl)-6,6-dimethyl-2,4-dioxopiperidine-3-carboxylate (80 mg, 0.212 mmol) in acetonitrile (3.6 mL) and water (36 μL) was stirred at reflux for 2 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 75% EtOAc in heptane) gave 1-(2,5-dichloropyridin-4-yl)-6,6-dimethylpiperidine-2,4-dione (29 mg, 45%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.28 (s, 1H, overlapped with solvent), 3.42 - 3.62 (m, 2H), 2.96 (d, J = 15.3 Hz, 1H), 2.73 (d, J = 16.0 Hz, 1H), 1.49 (m, 3H), 1.23 (s, 3H) ppm. ESI-MS m/z calc. 286.028, found 287.0 ($\text{M}+1$) $^+$.

Step 5:

[00222] A mixture of 1-(2,5-dichloropyridin-4-yl)-6,6-dimethylpiperidine-2,4-dione (37 mg, 0.128 mmol) in DMF-DMA (179.4 mg, 0.2 mL, 1.506 mmol) was heated at 100 $^\circ\text{C}$ for 1 h then cooled to ambient temperature. The solvent was decanted and the resulting solid triturated with Et₂O (2 x) then dried under vacuum to give (*E*)-1-(2,5-dichloropyridin-4-yl)-3-((dimethylamino)methylene)-6,6-dimethylpiperidine-2,4-dione (**Int-P4**, 37 mg, 81%) as a pale yellow solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 7.99 (s, 1H), 7.24 (s, 1H), 3.34 (s, 3H), 3.21 (s, 3H), 2.93 (d, J = 15.6 Hz, 1H), 2.49 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.13 (s, 3H) ppm. ESI-MS m/z calc. 341.070, found 342.1 ($\text{M}+1$) $^+$.

Intermediate 10: Synthesis of 5-chloro-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)pyridin-2(1H)-one (Int-P5)

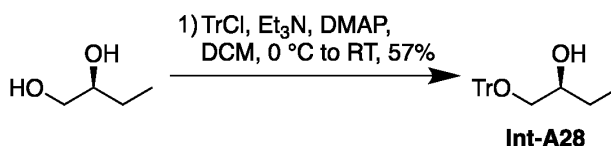


Step 1:

[00223] NaH (1.65 g, 60 % dispersion in mineral oil, 41.254 mmol) was added to a stirred solution of 5-chloro-4-fluoropyridin-2(1H)-one (2 g, 13.556 mmol) in THF (30 mL) at 0 $^\circ\text{C}$ and the reaction mixture was stirred for 15 min at 0 $^\circ\text{C}$. SEMCl (3.391 g, 3.6 mL, 20.341 mmol) was added and the mixture was stirred at ambient temperature for 2 h. The reaction

was quenched by addition of ice cold water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 40 to 50% EtOAc in heptane) gave 5-chloro-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)pyridin-2(1*H*)-one (**Int-P5**, 2.3 g, 56%) as brown oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.26 (d, *J* = 9.6 Hz, 1H), 6.52 (d, *J* = 11.6 Hz, 1H), 5.23 (s, 2H), 3.58 (t, *J* = 8.4 Hz, 2H), 0.86 (t, *J* = 8.0 Hz, 2H), -0.03 (s, 9H) ppm. ESI-MS *m/z* calc. 277.070, found 278.0 (M+1)⁺.

Intermediate 11: Synthesis of (*S*)-1-(trityloxy)butan-2-ol (**Int-A28**)



Step 1:

[00224] Et₃N (726 mg, 1 mL, 7.175 mmol) and DMAP (43 mg, 0.352 mmol) were successively added to a solution of (*S*)-butane-1,2-diol (320 mg, 3.551 mmol) and TrCl (990 mg, 3.551 mmol) in DCM (10 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 20 h. The mixture was diluted with HCl (1% aqueous solution) and extracted with DCM (3 x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 25% EtOAc in heptane) gave (*S*)-1-(trityloxy)butan-2-ol (**Int-A28**, 680 mg, 57%) as a colourless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.38 - 7.43 (m, 6H), 7.33 (t, *J* = 7.6 Hz, 6H), 7.22 - 7.28 (m, 3H), 4.64 (d, *J* = 5.4 Hz, 1H), 3.54 (dt, *J* = 7.5, 5.0 Hz, 1H), 2.93 (dd, *J* = 8.9, 5.6 Hz, 1H), 2.78 (dd, *J* = 8.9, 5.6 Hz, 1H), 1.47 - 1.60 (m, 1H), 1.28 - 1.37 (m, 1H), 0.79 (t, *J* = 7.4 Hz, 3H) ppm. ESI-MS *m/z* calc. 332.178, found 331.4 (M-1)⁻.

[00225] The following Intermediate was made using the method described in Intermediate 11, except that, in Step 1, (*S*)-3-methylbutane-1,2-diol was used in place of (*S*)-butane-1,2-diol.

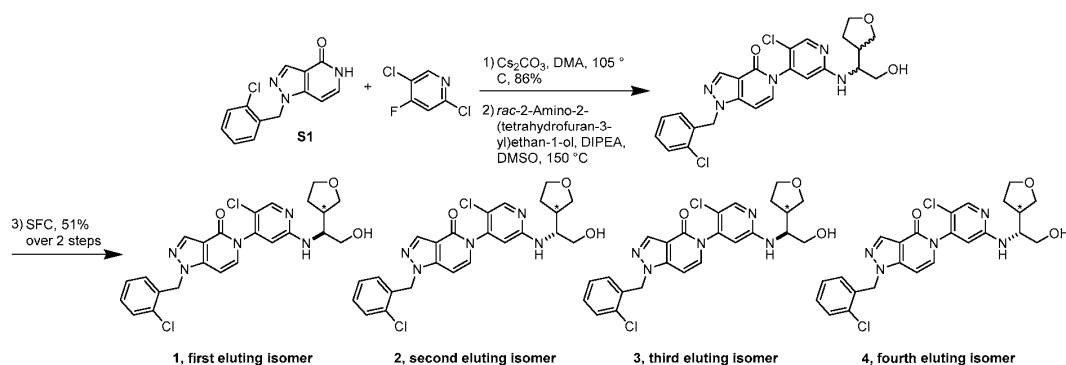
Table 13: Intermediate Prepared Using the Method Described in Intermediate 11

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
Int-A29		No chromophore in molecule	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.39 - 7.34 (m, 6H), 7.27 - 7.15 (m, 9H), 3.42 - 3.36 (br m, 1H),

Intermediate Number	Compound Structure/ Compound Name	LC/MS	NMR (shifts in ppm)
	(<i>S</i>)-3-methyl-1-(trityloxy)butan-2-ol		3.18 (dd, $J = 9.4, 3.3$ Hz, 1H), 3.00 (dd, $J = 9.4, 7.6$ Hz, 1H), 2.21 (br s, 1H), 1.67 - 1.57 (m, 1H), 0.84 - 0.78 (d, $J = 4.0$ Hz, 3H), 0.69 (d, $J = 6.8$ Hz, 3H) ppm.

VI. Synthesis of Compounds

Example 1: Synthesis of *rel*-5-(5-Chloro-2-(((1*S*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 1), *rel*-5-(5-chloro-2-(((1*R*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 2), *rel*-5-(5-chloro-2-(((1*S*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 3) and *rel*-5-(5-chloro-2-(((1*R*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 4)



Step 1:

[00226] Cs_2CO_3 (18.3 g, 56.17 mmol) was added to a solution of 2,5-dichloro-4-fluoropyridine (4.604 g, 27.74 mmol) and 1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S1**, 7.30 g, 28.11 mmol) in DMA (80 mL) and the reaction mixture was heated to 105 °C for 1 h. The reaction was diluted with water (300 mL). The solid was filtered, washed with heptane (100 mL) and dried at 40 °C under vacuum to give 1-(2-chlorobenzyl)-5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (9.622 g, 86%) as an off-white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.78 (s, 1H), 8.23 (d, $J = 0.8$ Hz, 1H), 8.02 (s, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.53 - 7.50 (m, 1H), 7.42 - 7.31 (m, 2H), 7.12 - 7.05 (m, 1H), 7.00 (dd, $J = 7.6, 0.9$ Hz, 1H), 5.75 - 5.63 (m, 2H) ppm. ESI-MS m/z calc. 404.000, found 405.2 ($\text{M}+1$) $^+$.

Step 2:

[00227] DIPEA (159.4 mg, 214.8 μ L, 1.233 mmol) was added to a stirred solution of 1-(2-chlorobenzyl)-5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, 0.123 mmol) and *rac*-2-amino-2-(tetrahydrofuran-3-yl)ethan-1-ol (80.87 mg, 0.617 mmol) in DMSO (300 μ L) and the reaction mixture was stirred at 150 °C for 20 h. The mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 30 to 45% MeCN in water with 1% NH₄OH) gave *rac*-5-(5-chloro-2-((2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one.

Step 3:

[00228] The isomers of *rac*-5-(5-chloro-2-((2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one were separated by chiral SFC using a Chiralpak[®] IB-3 column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO₂; Flow rate 100 mL/min) to give:

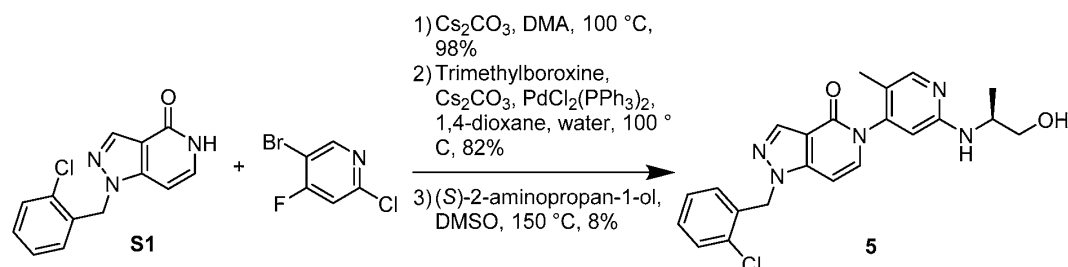
[00229] **First Eluting Isomer (rt = 7.62 minutes):** *rel*-5-(5-chloro-2-(((1*S*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 1, 2.6 mg, 19%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 7.54 - 7.42 (m, 2H), 7.41 - 7.31 (m, 2H), 7.09 (dd, *J* = 7.4, 2.0 Hz, 1H), 6.95 (t, *J* = 8.7 Hz, 1H), 6.90 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 5.67 (d, *J* = 4.5 Hz, 2H), 4.77 - 4.74 (m, 1H), 4.01 - 3.98 (m, 1H), 3.84 - 3.76 (m, 1H), 3.75 - 3.66 (m, 1H), 3.63 - 3.55 (m, 1H), 3.50 - 3.36 (m, 3H), 2.49 - 2.42 (m, 1H), 1.96 - 1.92 (m, 1H), 1.72 - 1.59 (m, 1H) ppm. ESI-MS *m/z* calc. 499.118, found 500.4 (M+1)⁺.

[00230] **Second Eluting Isomer (rt = 10.16 minutes):** *rel*-5-(5-chloro-2-(((1*R*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 2, 1.6 mg, 11%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.19 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 7.54 - 7.42 (m, 2H), 7.40 - 7.32 (m, 2H), 7.09 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.96 - 6.87 (m, 2H), 6.64 (s, 1H), 5.67 (d, *J* = 4.5 Hz, 2H), 4.76 - 4.72 (m, 1H), 4.00 - 3.96 (m, 1H), 3.82 - 3.70 (m, 2H), 3.68 - 3.51 (m, 2H), 3.50 - 3.40 (m, 2H), 2.00 - 1.94 (m, 1H), 1.69 - 1.58 (m, 1H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 499.118, found 500.4 (M+1)⁺.

[00231] Third Eluting Isomer (rt = 12.52 minutes): *rel*-5-(5-chloro-2-(((1*S*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **3**, 1.5 mg, 11%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.19 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 7.54 - 7.41 (m, 2H), 7.41 - 7.30 (m, 2H), 7.09 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.96 - 6.87 (m, 2H), 6.64 (s, 1H), 5.67 (d, *J* = 4.7 Hz, 2H), 4.76 - 4.72 (m, 1H), 3.98 (s, 1H), 3.76 (dtd, *J* = 18.6, 8.1, 3.8 Hz, 2H), 3.62 (td, *J* = 8.2, 7.0 Hz, 1H), 3.57 - 3.39 (m, 3H), 2.09 - 1.82 (m, 1H), 1.69 - 1.57 (m, 1H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 499.118, found 500.4 (M+1)⁺.

[00232] Fourth Eluting Isomer (rt = 15.09 minutes): *rel*-5-(5-chloro-2-(((1*R*)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **4**, 1.4 mg, 10%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.20 (d, *J* = 0.8 Hz, 1H), 8.12 (s, 1H), 7.54 - 7.42 (m, 2H), 7.36 (dtd, *J* = 17.9, 7.4, 1.7 Hz, 2H), 7.09 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.95 (t, *J* = 8.7 Hz, 1H), 6.90 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 5.67 (d, *J* = 4.5 Hz, 2H), 4.78 - 4.74 (m, 1H), 4.01 - 3.97 (m, 1H), 3.84 - 3.76 (m, 1H), 3.75 - 3.66 (m, 1H), 3.64 - 3.55 (m, 1H), 3.48 - 3.39 (m, 3H), 2.51 - 2.42 (m, 1H), 1.96 - 1.92 (m, 1H), 1.72 - 1.59 (m, 1H) ppm. ESI-MS *m/z* calc. 499.118, found 500.4 (M+1)⁺.

Example 2: Synthesis of (*S*)-1-(2-Chlorobenzyl)-5-(2-((1-hydroxypropan-2-yl)amino)-5-methylpyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **5)**



Step 1:

[00233] Cs₂CO₃ (990 mg, 3.038 mmol) was added to a stirred solution of 1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S1**, 393 mg, 1.513 mmol) and 5-bromo-2-chloro-4-fluoropyridine (320 mg, 1.521 mmol) in DMA (6 mL) and the reaction mixture was stirred at 100 °C for 30 min. The mixture was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give 5-(5-bromo-2-chloropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-

c]pyridin-4-one (665 mg, 98%), which was used without further purification in the next step.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 8.23 (d, *J* = 0.8 Hz, 1H), 7.99 (s, 1H), 7.55 - 7.49 (m, 2H), 7.42 - 7.31 (m, 2H), 7.13 - 7.07 (m, 1H), 7.00 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.77 - 5.63 (m, 2H) ppm. ESI-MS *m/z* calc. 447.949, found 451.0 (M+1)⁺.

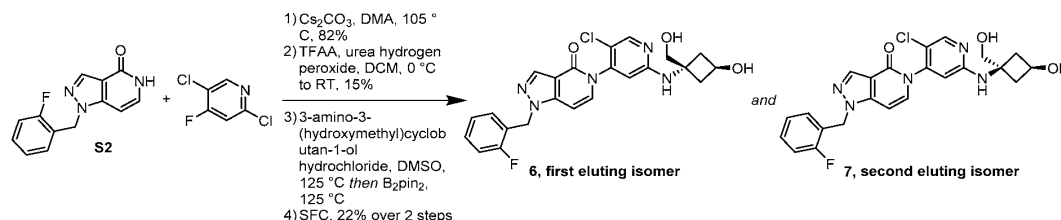
Step 2:

[00234] PdCl₂(PPh₃)₂ (7.9 mg, 0.011 mmol) was added to a stirred suspension of 5-(5-bromo-2-chloropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, 0.111 mmol), Cs₂CO₃ (73 mg, 0.224 mmol) and trimethyl boroxine (80 μL, 50 % w/v solution in THF, 0.319 mmol) in a mixture of 1,4-dioxane (500 μL) and water (50 μL). The mixture was degassed by bubbling nitrogen gas through and the reaction was heated to 100 °C for 2 h. The mixture was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 50% EtOAc in heptane) gave 5-(2-chloro-5-methylpyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (35 mg, 82%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 0.7 Hz, 1H), 8.22 (d, *J* = 0.8 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.55 - 7.49 (m, 2H), 7.41 - 7.30 (m, 2H), 7.11 - 7.06 (m, 1H), 6.96 (dd, *J* = 7.5, 0.9 Hz, 1H), 5.74 - 5.63 (m, 2H), 2.06 (s, 3H) ppm. ESI-MS *m/z* calc. 384.055, found 385.1 (M+1)⁺.

Step 3:

[00235] A solution of 5-(2-chloro-5-methylpyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (35 mg, 0.091 mmol) and (*S*)-2-aminopropan-1-ol (71 mg, 0.945 mmol) in DMSO (0.5 mL) was heated to 150 °C and stirred for 22 h. Purification by reverse phase HPLC (C₁₈ X-bridge column, 30 to 45% MeCN in water with 1% NH₄OH) gave (*S*)-1-(2-chlorobenzyl)-5-(2-((1-hydroxypropan-2-yl)amino)-5-methylpyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **5**, 3.1 mg, 8%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 0.9 Hz, 1H), 7.94 (s, 1H), 7.51 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.44 - 7.30 (m, 4H), 7.08 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.86 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.39 (s, 1H), 6.30 (t, *J* = 7.4 Hz, 1H), 5.67 (d, *J* = 5.3 Hz, 2H), 4.72 - 4.68 (m, 1H), 3.95 - 3.89 (m, 1H), 3.50 - 3.46 (m, 1H), 1.83 (s, 3H), 1.12 (dd, *J* = 6.6, 5.0 Hz, 3H) ppm. ESI-MS *m/z* calc. 423.146, found 424.4 (M+1)⁺.

Example 3: Synthesis of 5-(5-Chloro-2-(((1*r*,3*r*)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 6) and 5-(5-chloro-2-(((1*s*,3*s*)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 7)



Step 1:

[00236] Cs_2CO_3 (17.6 g, 54.02 mmol) was added to a solution of 2,5-dichloro-4-fluoropyridine (4.444 g, 26.77 mmol) and 1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S2**, 6.500 g, 26.72 mmol) in DMA (80 mL) and the reaction mixture was heated to 105 °C for 1 h. The reaction mixture was diluted with water (300 mL) causing a precipitate to crash out of solution. The solid was collected by filtration, washed with heptane (100 mL) and dried at 40 °C under vacuum to give 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (8.51 g, 82%) as an off-white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.78 (s, 1H), 8.20 (d, $J = 0.8$ Hz, 1H), 8.01 (s, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.44 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 7.02 (dt, $J = 7.6, 0.8$ Hz, 1H), 5.71 - 5.60 (m, 2H) ppm. ESI-MS m/z calc. 388.029, found 389.0 ($\text{M}+1$)⁺.

Step 2:

[00237] TFAA (3.5 mL, 25.18 mmol) was added to a solution of urea hydrogen peroxide (2.4 g, 25.51 mmol) in DCM (20 mL) at 0 °C and the mixture was stirred for 15 min. A solution of 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1 g, 2.569 mmol) in DCM (20 mL) was added and the reaction was stirred at ambient temperature for 2 h. The mixture was diluted with DCM (15 mL) and neutralised by addition of a NaHCO_3 solution. The aqueous layer was separated and extracted with DCM (2 x 10 mL). The combined organic extracts were passed through a phase separator and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO_2 , 0 to 100% EtOAc in heptane, then 0 to 20% MeOH in EtOAc) gave 2,5-dichloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridine 1-oxide (159 mg, 15%) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.07 (s, 1H), 8.31 (s, 1H), 8.20 (d, $J = 0.8$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.44 - 7.32 (m, 1H), 7.30 - 7.14 (m, 3H), 7.06 - 6.78 (m, 1H), 5.67 (d, $J = 15.5$ Hz, 1H), 5.62 (d, $J = 15.5$ Hz, 1H) ppm. ESI-MS m/z calc. 404.024, found 405.2 ($\text{M}+1$)⁺.

Step 3:

[00238] A solution of 3-amino-3-(hydroxymethyl)cyclobutan-1-ol hydrochloride (330 mg, as a 1:1 mixture of diastereomers, 2.148 mmol) in MeOH (1 mL) was deposited on an SCX-cartridge preliminary washed with MeOH (10 mL). The amine was released by eluting the cartridge with a 2 N methanolic ammonia solution and the resulting filtrates were concentrated *in vacuo*. The residue was dissolved in DMSO (2 mL), added to 2,5-dichloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridine 1-oxide (150 mg, 0.370 mmol) and the reaction mixture was heated and stirred at 125 °C for 16 h. B₂pin₂ (150 mg, 0.591 mmol) was added and the mixture was stirred at 125 °C for 1 h. The reaction was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 23 to 38% MeCN in water with 1% ammonium hydroxide) gave 5-(5-chloro-2-((3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one as a mixture of 2 diastereomers.

Step 4:

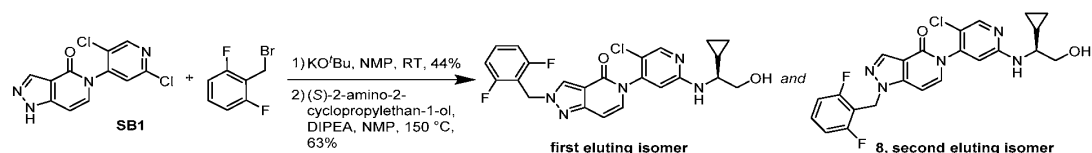
[00239] The diastereomers of 5-(5-chloro-2-((3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one were separated by chiral SFC using a Chiralpak® IG column, 5 µm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 50 to 60% MeOH (supplemented with 20 mM ammonia), 60 to 50% CO₂; Flow rate 100 mL/min) to give:

[00240] First Eluting Isomer (rt = 2.63 minutes): 5-(5-chloro-2-(((1*r*,3*r*)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (Compound 6, 14.2 mg, 8% over 2 steps) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (d, *J* = 0.9 Hz, 1H), 8.12 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.31 - 7.16 (m, 3H), 7.04 (s, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.56 (s, 1H), 5.68 - 5.56 (m, 2H), 4.95 (br s, 1H), 4.81 (br s, 1H), 4.24 - 4.11 (m, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 3.56 (d, *J* = 10.7 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.03 - 1.93 (m, 2H) ppm. ESI-MS *m/z* calc. 469.132, found 468.1 (M-1)⁺.

[00241] Second Eluting Isomer (rt = 3.50 minutes): 5-(5-chloro-2-(((1*s*,3*s*)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (Compound 7, 25.2 mg, 14% over 2 steps) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.16 (d, *J* = 0.8 Hz, 1H), 8.10 (s, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.30 - 7.14 (m, 4H), 6.91 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.51 (s, 1H), 5.70 - 5.55 (m, 2H), 4.96 (d, *J* = 6.4 Hz, 1H), 4.84 (t, *J* = 5.7 Hz, 1H), 4.15 - 3.86 (m, 1H),

3.58 (dd, $J = 10.9, 5.6$ Hz, 1H), 3.50 (dd, $J = 10.8, 5.6$ Hz, 1H), 2.67 - 2.55 (m, 2H), 1.90 (dd, $J = 12.3, 7.0$ Hz, 2H) ppm. ESI-MS m/z calc. 469.132, found 468.2 ($M-1$)⁺.

Example 4: Synthesis of (S)-5-(5-Chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (Compound 8)



Step 1:

[00242] Under nitrogen, KO^tBu (40 mg, 0.357 mmol) was added in one portion to a solution of 5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (**SB1**, 50 mg, 0.178 mmol) and 2-(bromomethyl)-1,3-difluorobenzene (70 mg, 0.338 mmol) in NMP (1 mL) and the reaction mixture was stirred at ambient temperature for 3 h. The reaction was quenched by addition of water and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 38 to 53% MeCN in water with 0.1% ammonium hydroxide) gave a ~ 1:1 mixture of 5-(2,5-dichloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (ESI-MS m/z calc. 406.020, found 407.0 ($M+1$)⁺) and 5-(2,5-dichloropyridin-4-yl)-2-(2,6-difluorobenzyl)-2,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (ESI-MS m/z calc. 406.020, found 407.0 ($M+1$)⁺) (32 mg, 44%) as an off-white solid, which was used without further purification in the next step.

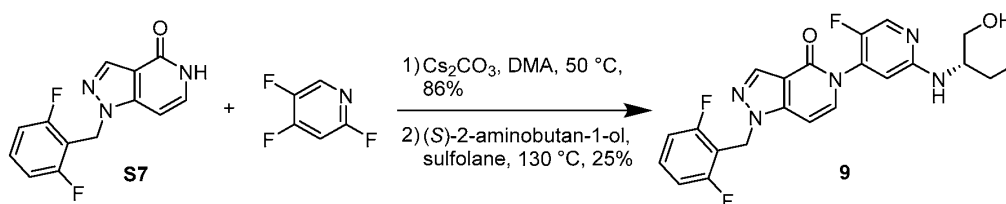
Step 2:

[00243] (S)-2-amino-2-cyclopropylethan-1-ol (50 mg, 0.494 mmol) and DIPEA (70 μ L, 0.402 mmol) were successively added to a ~ 1:1 mixture of 5-(2,5-dichloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one and 5-(2,5-dichloropyridin-4-yl)-2-(2,6-difluorobenzyl)-2,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (36 mg, 0.088 mmol) in NMP (1 mL) and the reaction mixture was stirred at 150 °C overnight. The reaction was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 30 to 45% MeCN in water with 0.1% ammonium hydroxide) gave a pale brown solid. The regioisomers were separated by SFC using a DEAP column, 5 μ m particle size, 25 cm x 10 mm from Princeton Chromatography, Inc. (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO₂; Flow rate 10 mL/min) to give:

[00244] First Eluting Isomer (rt = 2.50 minutes): (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-2-(2,6-difluorobenzyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (6.2 mg, 30%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 4.3 Hz, 1H), 7.83 (s, 1H), 7.27 (tt, *J* = 8.4, 6.6 Hz, 1H), 6.98 - 6.89 (m, 3H), 6.63 (t, *J* = 6.8 Hz, 1H), 6.35 (d, *J* = 0.9 Hz, 1H), 6.32 (ddd, *J* = 7.5, 3.7, 0.8 Hz, 1H), 5.38 (s, 2H), 4.46 (d, *J* = 17.9 Hz, 1H), 3.33 - 3.24 (m, 3H), 0.76 (tq, *J* = 8.1, 4.8, 4.0 Hz, 1H), 0.26 - 0.03 (m, 3H), -0.00 (tt, *J* = 9.2, 4.3 Hz, 1H) ppm. ESI-MS *m/z* calc. 471.127, found 472.0 (M+1)⁺.

[00245] Second Eluting Isomer (rt = 3.35 minutes): (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **8**, 7.02 mg, 33%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.13 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.10 (s, 1H), 7.53 - 7.46 (m, 2H), 7.21 - 7.14 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 1.1 Hz, 1H), 5.63 (s, 2H), 4.71 (dt, *J* = 17.9, 5.3 Hz, 1H), 3.59 - 3.49 (m, 3H), 1.16 - 0.95 (m, 1H), 0.55 - 0.29 (m, 3H), 0.25 (ddd, *J* = 8.7, 6.4, 4.6 Hz, 1H) ppm. ESI-MS *m/z* calc. 471.127, found 472.0 (M+1)⁺.

Example 5: Synthesis of (*S*)-1-(2,6-Difluorobenzyl)-5-(5-fluoro-2-((1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **9)**



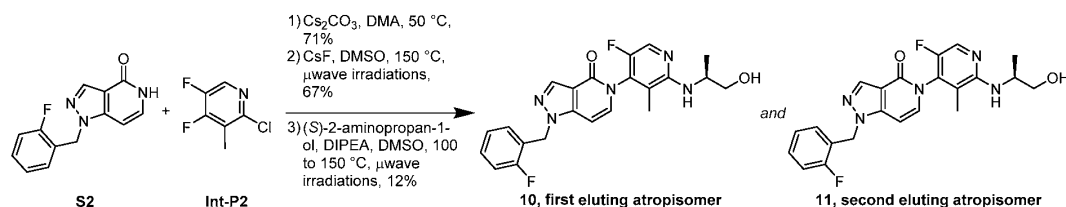
Step 1:

[00246] Cs₂CO₃ (11.7 g, 35.91 mmol) was added to a stirred solution of 1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S7**, 5.01 g, 18.60 mmol) and 2,4,5-trifluoropyridine (2.39 g, 17.96 mmol) in DMA (50 mL) and the reaction was stirred at 50 °C for 23 h. The mixture was cooled to ambient temperature, quenched by addition of water (200 mL) and stirred for 2 h. The resulting solid was filtered and washed with water and heptane. Purification by trituration from hot MeOH gave 1-(2,6-difluorobenzyl)-5-(2,4,5-trifluoropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (5.99 g, 86%) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (t, *J* = 1.4 Hz, 1H), 8.18 (d, *J* = 0.8 Hz, 1H), 7.75 - 7.65 (m, 2H), 7.50 (tt, *J* = 8.5, 6.7 Hz, 1H), 7.23 - 7.12 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 5.65 (s, 2H) ppm. ESI-MS *m/z* calc. 374.079, found 375.0 (M+1)⁺.

Step 2:

[00247] A 4 mL screw-top vial, containing a solution of 1-(2,6-difluorobenzyl)-5-(2,5-difluoropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (70 mg, 0.187 mmol) and (*S*)-2-aminobutan-1-ol (51 mg, 0.572 mmol) in sulfolane (0.7 mL) was sealed and the mixture was stirred at 130 °C for 2.5 days. The mixture was cooled to ambient temperature, diluted with EtOAc (7 mL) and washed with a half-saturated brine solution (2 x 3 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ Sunfire column, 23% to 38% MeCN in water with 0.1 % formic acid) gave (*S*)-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 9, 21.2 mg, 25%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 0.8 Hz, 1H), 8.08 (d, *J* = 1.9 Hz, 1H), 7.61 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.50 (ddd, *J* = 15.1, 8.5, 6.7 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 5.0 Hz, 1H), 6.50 (d, *J* = 8.1 Hz, 1H), 5.63 (s, 2H), 4.64 (t, *J* = 5.5 Hz, 1H), 3.78 (d, *J* = 5.6 Hz, 1H), 3.50 (dt, *J* = 10.0, 4.9 Hz, 1H), 3.40 - 3.33 (m, 1H), 1.68 (dq, *J* = 13.9, 6.6 Hz, 1H), 1.45 (dq, *J* = 14.3, 7.6 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm. ESI-MS *m/z* calc. 443.157, found 444.5 (M+1)⁺.

Example 6: Synthesis of 5-(5-Fluoro-2-(((*S*)-1-hydroxypropan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 10) and 5-(5-fluoro-2-(((*S*)-1-hydroxypropan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 11)

**Step 1:**

[00248] Cs₂CO₃ (4 g, 12.277 mmol) was added to a stirred mixture of 2-chloro-4,5-difluoro-3-methylpyridine (**Int-P2**, 1.689 mg, 6.764 mmol) and 1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S2**, 1.75 g, 7.195 mmol) in DMA (25 mL) and the reaction mixture was heated at 50 °C for 1 h. The reaction was partitioned between water and EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 100% EtOAc in heptane) followed by reverse phase chromatography (12 g C₁₈ column, 20 to 80% MeCN in water with 0.1%

ammonium hydroxide) gave 5-(2-chloro-5-fluoro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1.871 g, 71%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 8.24 (d, *J* = 0.9 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.17 - 7.09 (m, 2H), 6.89 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.52 (s, 2H), 2.22 (s, 3H) ppm. ESI-MS *m/z* calc. 386.075, found 387.1 (M+1)⁺.

Step 2:

[00249] A stirred suspension of 5-(2-chloro-5-fluoro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (150 mg, 0.385 mmol) and CsF (351 mg, 2.311 mmol) in DMSO (3.5 mL) was heated to 150 °C under microwave irradiations for 4 h. The reaction was poured over a saturated NaHCO₃ solution and extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (12 g C₁₈ column, 50 to 100% MeCN in water with 0.1% formic acid) gave 5-(2,5-difluoro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (127 mg, 67%) as a pale brown oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 8.07 (s, 1H), 7.37 - 7.28 (m, 2H), 7.17 - 7.09 (m, 2H), 6.93 - 6.90 (m, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.52 (s, 2H), 2.12 (s, 3H) ppm. ESI-MS *m/z* calc. 370.104, found 371.1 (M+1)⁺.

Step 3:

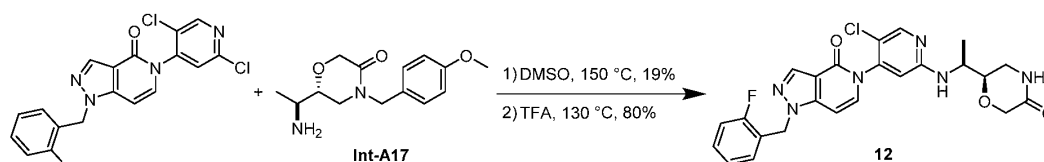
[00250] DIPEA (200.34 mg, 0.27 mL, 1.550 mmol) was added to a stirred solution of 5-(2,5-difluoro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (127 mg, 0.260 mmol) and (*S*)-2-aminopropan-1-ol (115.80 mg, 0.12 mL, 1.542 mmol) in DMSO (1.2 mL) and the reaction mixture was successively heated for 1h each at 100 °C, at 120 °C and at 130 °C. The mixture was further heated under microwave irradiations at 150 °C for 5 h. The reaction was quenched by addition of water and extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (25 g C₁₈ column, 20 to 60% MeCN in water with 0.1% formic acid) gave:

[00251] First Eluting Atropisomer (rt = 1.7 minutes): further purified by reverse phase chromatography (12 g C₁₈ column, 20 to 37% MeCN in water with 0.1% formic acid), gave 5-(5-fluoro-2-(((*S*)-1-hydroxypropan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **10**, 6 mg, 5%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.97 (s, 1H), 7.35 - 7.27 (m, 2H), 7.16 - 7.09 (m, 2H), 6.93 - 6.91 (m, 1H), 6.54 (d, *J* = 7.3 Hz, 1H), 5.51 (s, 2H), 4.23 (s, 2H), 3.81 (dd, *J*

= 10.5, 2.3 Hz, 1H), 3.59 (dd, J = 10.5, 6.9 Hz, 1H), 1.89 (s, 3H), 1.27 (d, J = 6.0 Hz, 3H) ppm; exchangeable H not observed. ESI-MS m/z calc. 425.166, found 426.2 (M+1)⁺.

[00252] Second Eluting Atropisomer (rt = 1.8 minutes): further purified by flash chromatography (SiO₂, 20 to 100% EtOAc in heptane), gave 5-(5-fluoro-2-(((S)-1-hydroxypropan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (Compound **11**, 8 mg, 7%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, J = 0.9 Hz, 1H), 7.98 (s, 1H), 7.36-7.27 (m, 2H), 7.16-7.08 (m, 2H), 6.92 (dd, J = 7.6, 1.1 Hz, 1H), 6.53 (d, J = 7.3 Hz, 1H), 5.51 (s, 2H), 4.29 (d, J = 6.4 Hz, 1H), 4.20 (qd, J = 6.5, 3.0 Hz, 1H), 3.79 (d, J = 10.1 Hz, 1H), 3.68-3.61 (m, 2H), 1.89 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H) ppm. ESI-MS m/z calc. 425.166, found 426.2 (M+1)⁺.

Example 7: Synthesis of *rel*-(*R*^{*})-6-(((S)-1-((5-Chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)ethyl)morpholin-3-one (Compound **12)**



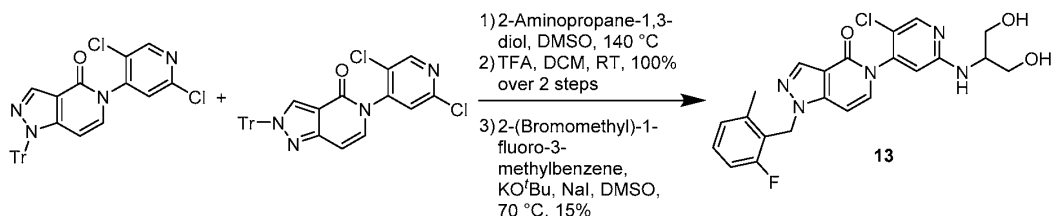
Step 1:

[00253] A 4 mL screw-top vial, containing a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (70 mg, prepared using the method described in Example 3 Step 1, 0.180 mmol) and *rel*-(*R*^{*})-6-(((S)-1-aminoethyl)-4-(4-methoxybenzyl)morpholin-3-one (**Int-A17**, 95 mg, 0.359 mmol) in DMSO (0.7 mL), was sealed and the reaction mixture was stirred at 150 °C for 48 h. The reaction was cooled to ambient temperature, diluted with EtOAc (10 mL) and washed with a half-saturated brine solution (2 x 5 mL). The organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 5% MeOH in EtOAc) gave *rel*-(*R*^{*})-6-(((S)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)ethyl)-4-(4-methoxybenzyl)morpholin-3-one (22 mg, 19%) as a yellow glassy solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (t, J = 0.8 Hz, 1H), 8.14 (d, J = 1.1 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.31 - 7.16 (m, 5H), 7.02 (dd, J = 14.5, 8.7 Hz, 1H), 6.95 - 6.87 (m, 3H), 6.60 (d, J = 3.1 Hz, 1H), 5.64 (s, 2H), 4.53 - 4.39 (m, 2H), 4.27 - 4.08 (m, 3H), 3.77 (dd, J = 13.7, 7.3 Hz, 4H), 3.28 - 3.23 (m, 2H), 1.17 - 1.13 (m, 3H) ppm. ESI-MS m/z calc. 616.200, found 617.2 (M+1)⁺.

Step 2:

[00254] A 4 mL screw-top vial, containing a stirred solution of *rel*-(*R*^{*})-6-((*S*)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)ethyl)-4-(4-methoxybenzyl)morpholin-3-one (21 mg, 0.033 mmol) in TFA (500 μ L, 6.490 mmol), was sealed and the reaction mixture was stirred at 120 °C for 70 min then, at 130 °C for 110 min. The reaction was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 23 to 38% MeCN in water with 0.1% ammonium hydroxide) gave *rel*-(*R*^{*})-6-((*S*)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)ethyl)morpholin-3-one (Compound **12**, 13 mg, 80%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (s, 2H), 7.97 (dd, *J* = 15.4, 3.8 Hz, 1H), 7.48 (dd, *J* = 7.5, 6.2 Hz, 1H), 7.40 (dddd, *J* = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.31 - 7.19 (m, 3H), 7.08 - 7.01 (m, 1H), 6.93 (dt, *J* = 7.6, 0.7 Hz, 1H), 6.63 (d, *J* = 1.2 Hz, 1H), 5.64 (d, *J* = 3.3 Hz, 2H), 4.15 (s, 1H), 4.13 - 3.99 (m, 2H), 3.66 (dddd, *J* = 13.1, 9.9, 6.3, 3.7 Hz, 1H), 3.27 - 3.16 (m, 2H), 1.19 (t, *J* = 6.8 Hz, 3H) ppm. ESI-MS *m/z* calc. 496.143, found 497.3 (M+1)⁺.

Example 8: Synthesis of 5-(5-Chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **13)**

**Step 1:**

[00255] 2-Aminopropane-1,3-diol (746.8 mg, 8.197 mmol) was added to a stirred mixture of 5-(2,5-dichloropyridin-4-yl)-1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(2,5-dichloropyridin-4-yl)-2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1.344 g, prepared using the method described in Starting material 2 Step 1 to 3, 2.567 mmol) in DMSO (1 mL) and the reaction mixture was heated at 140 °C for 2 h. The reaction was cooled to ambient temperature and partitioned between EtOAc and a saturated NaHCO₃ solution. The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* to give a mixture of 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(5-chloro-2-((1,3-dihydroxypropan-2-

yl)amino)pyridin-4-yl)-2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one, which was used without further purification in the next step.

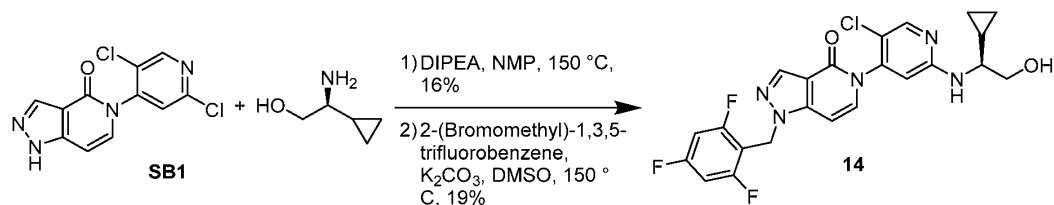
Step 2:

[00256] TFA (2.8 mL, 36.34 mmol) was added to a stirred mixture of 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-trityl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-2-trityl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one in DCM (10 mL) and the reaction mixture was stirred at ambient temperature for 20 h. The reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc and a saturated NaHCO₃ solution. The organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (24g column, 0 to 100% 3:1 EtOAc:EtOH in heptane gave 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1.15 g, 100% over 2 steps). ESI-MS *m/z* calc. 335.079, found 336.1 (M+1)⁺.

Step 3:

[00257] NaI (5.3 mg, 0.035 mmol) and KO^tBu (27.5 mg, 0.245 mmol) were successively added to a stirred mixture of 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, 0.111 mmol) and 2-(bromomethyl)-1-fluoro-3-methylbenzene (27.4 mg, 0.135 mmol) in DMSO (0.5 mL) and the reaction mixture was heated at 70 °C for 20 min. Purification by reverse phase HPLC (C₁₈ Sunfire column, 30 to 45% MeCN in water with 0.1% TFA then C₁₈ X-bridge column, 23 to 38% MeCN in water with 0.1% ammonium hydroxide) gave 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **13**, 7.8 mg, 15%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.13 (s, 1H), 8.11 (d, *J* = 0.8 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.30 (td, *J* = 8.0, 6.0 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 6.92 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.68 (s, 1H), 5.58 (t, *J* = 1.7 Hz, 2H), 4.67 (dt, *J* = 11.0, 5.4 Hz, 2H), 3.91 (s, 1H), 3.59 - 3.46 (m, 4H), 2.43 (s, 3H) ppm. ESI-MS *m/z* calc. 457.132, found 458.3 (M+1)⁺.

Example 9: Synthesis of (*S*)-5-(5-Chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,4,6-trifluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 14)



Step 1:

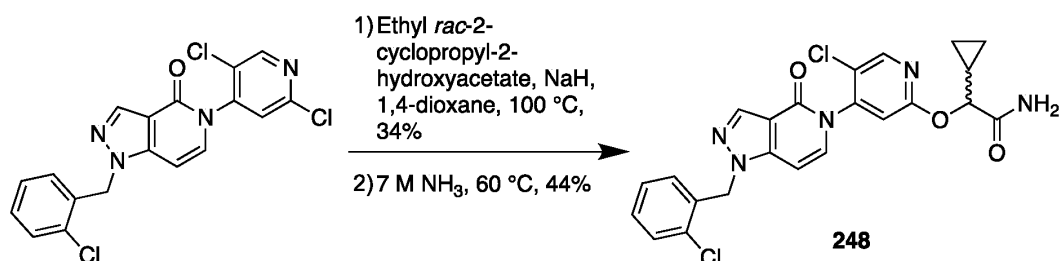
[00258] DIPEA (200 μ L, 1.148 mmol) was added to a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**SB1**, 127 mg, 0.452 mmol) and (2*S*)-2-amino-2-cyclopropyl-ethanol (200 mg, 1.977 mmol) in NMP (2 mL) and the reaction mixture was heated at 150 °C for 16 h. The mixture was cooled to ambient temperature. Purification by reverse phase HPLC (C₁₈ X-bridge column, 16 to 31% MeCN in water with 0.1% ammonium hydroxide, then C₁₈ X-bridge column, 0 to 23% MeCN in water with 0.05% TFA) gave after passing the collected fraction through SPE bicarbonate cartridges, eluting with 3:1 MeCN/water and after lyophilization (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (25.54 mg, 16%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.33 (s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.06 (dd, *J* = 19.7, 7.4 Hz, 1H), 6.66 - 6.60 (m, 1H), 6.42 - 6.35 (m, 2H), 4.46 (d, *J* = 19.3 Hz, 1H), 3.28 (dtq, *J* = 12.3, 8.0, 4.4, 3.3 Hz, 3H), 0.76 (qt, *J* = 8.1, 5.0 Hz, 1H), 0.24 - 0.04 (m, 3H), 0.04 - -0.07 (m, 1H) ppm. ESI-MS *m/z* calc. 345.099, found 346.0 (M+1)⁺.

Step 2:

[00259] K₂CO₃ (41.2 mg, 0.298 mmol) was added to a stirred solution of 2-(bromomethyl)-1,3,5-trifluorobenzene (26.3 mg, 0.117 mmol) and (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (40 mg, 0.116 mmol) in DMSO (400 μ L) and the reaction mixture was heated at 150 °C for 5 h. The mixture was cooled to ambient temperature. Purification by reverse phase HPLC (C₁₈ Sunfire column, 31 to 45% MeCN in water with 0.1% trifluoroacetic acid) gave (*S*)-5-(5-Chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,4,6-trifluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **14**, 11.2 mg, 19%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.16 - 8.13 (m, 1H), 8.10 (s, 1H), 7.50 (dd, *J* = 17.9, 7.5 Hz, 1H), 7.32 - 7.24 (m, 2H), 7.13 - 7.07 (m, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 5.59 (s, 2H),

3.90 (s, 1H), 3.61 - 3.45 (m, 3H), 1.01 (qt, $J = 8.2, 5.0$ Hz, 1H), 0.43 (dddd, $J = 14.7, 9.5, 5.5, 3.3$ Hz, 1H), 0.40 - 0.30 (m, 2H), 0.23 (td, $J = 5.9, 3.6$ Hz, 1H) ppm. ESI-MS m/z calc. 489.118, found 490.2 (M+1)⁺.

Example 10: Synthesis of *rac*-2-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)oxy)-2-cyclopropylacetamide (Compound 248)



Step 1:

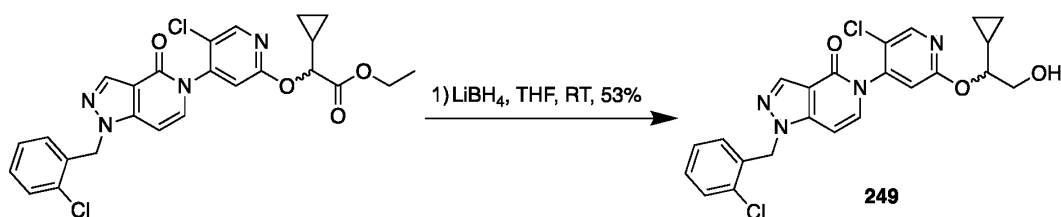
[00260] In a screw-top vial, NaH (14.79 mg, 60 % dispersion in mineral oil, 0.370 mmol) was added to a stirred solution of ethyl *rac*-2-cyclopropyl-2-hydroxyacetate (53.33 mg, 0.370 mmol) in 1,4-dioxane (0.7 mL) and the mixture was stirred at ambient temperature for 10 min. 1-(2-Chlorobenzyl)-5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, prepared using the method described in Example 1 Step 1, 0.123 mmol) was added to the reaction mixture, the vial was sealed and the mixture was stirred at 100 °C for 90 min. The reaction was cooled to ambient temperature and poured onto a half-saturated NH₄Cl solution (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The organic extracts were washed with a saturated brine solution, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography gave ethyl *rac*-2-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)oxy)-2-cyclopropylacetate (28 mg, 34%). ESI-MS m/z calc. 512.102, found 513.2 (M+1)⁺.

Step 2:

[00261] In a screw-top vial, ethyl *rac*-2-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)oxy)-2-cyclopropylacetate (12 mg, 0.023 mmol) was dissolved in methanolic ammonia (1 mL, 7 M solution in MeOH, 7.0 mmol). The vial was sealed and the reaction mixture was stirred at 60 °C for 16 h. The mixture was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC gave *rac*-2-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)oxy)-2-cyclopropylacetamide (Compound **248**, 5

mg, 44%) as a white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.36 (d, J = 7.7 Hz, 1H), 8.23 (dd, J = 4.7, 0.8 Hz, 1H), 7.54 - 7.51 (m, 1H), 7.51 - 7.44 (m, 2H), 7.41 - 7.33 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.17 - 7.09 (m, 2H), 6.95 (td, J = 7.4, 0.9 Hz, 1H), 5.69 (d, J = 3.5 Hz, 2H), 4.55 (t, J = 9.1 Hz, 1H), 1.27 (qt, J = 8.5, 4.8 Hz, 1H), 0.73 - 0.66 (m, 1H), 0.60 (ddd, J = 8.3, 3.5, 1.7 Hz, 2H), 0.49 - 0.38 (m, 1H) ppm. ESI-MS m/z calc. 483.086, found 484.2 ($M+1$) $^+$.

Example 11: Synthesis of *rac*-5-(5-chloro-2-(1-cyclopropyl-2-hydroxyethoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 249)

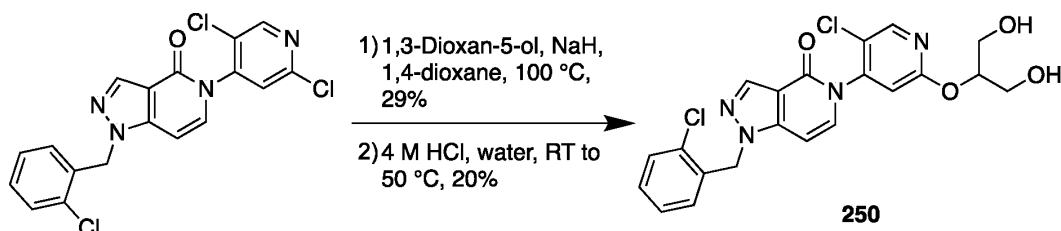


Step 1:

[00262] LiBH₄ (63 μL , 2 M solution in THF, 0.126 mmol) was added to a solution of ethyl *rac*-2-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)oxy)-2-cyclopropylacetate (28 mg, prepared using the method described in Example 10 Step 1 starting with ethyl *rac*-2-cyclopropyl-2-hydroxyacetate, 0.042 mmol) in THF (1 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of a half-saturated NH₄Cl solution (5 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The organic extracts were washed with a saturated brine solution, dried (MgSO₄), filtered and concentrated *in vacuo*.

Purification by reverse phase HPLC gave *rac*-5-(5-Chloro-2-(1-cyclopropyl-2-hydroxyethoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **249**, 10.6 mg, 53%) as a white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.37 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 1.1 Hz, 1H), 7.55 - 7.46 (m, 2H), 7.41 - 7.33 (m, 2H), 7.13 - 7.08 (m, 2H), 6.94 (ddd, J = 7.6, 1.9, 0.9 Hz, 1H), 5.69 (d, J = 4.1 Hz, 2H), 4.84 (dt, J = 21.4, 5.6 Hz, 1H), 4.69 (p, J = 5.2, 4.7 Hz, 1H), 3.68 (tp, J = 11.7, 6.5, 5.8 Hz, 2H), 1.19 - 1.10 (m, 1H), 0.58 - 0.33 (m, 4H) ppm. ESI-MS m/z calc. 470.091, found 471.2 ($M+1$) $^+$.

Example 12: Synthesis of 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)oxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (Compound 250)



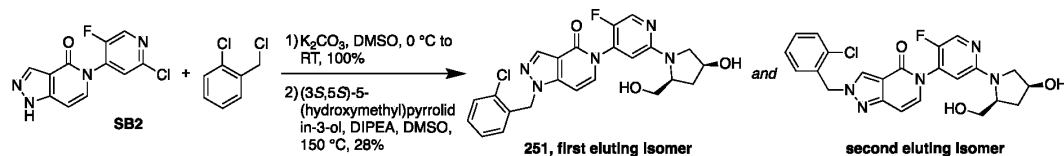
Step 1:

[00263] NaH (15 mg, 60 % dispersion in mineral oil, 0.375 mmol) was added to a solution of 1,3-dioxan-5-ol (39 mg, 0.375 mmol) in 1,4-dioxane (0.7 mL) and the mixture was stirred at ambient temperature for 10 min. 1-(2-Chlorobenzyl)-5-(2,5-dichloropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (50 mg, prepared using the method described in Example 1 Step 1, 0.123 mmol) was added and the reaction mixture was stirred at 100 °C for 8 h. The mixture was cooled to ambient temperature and partitioned between EtOAc (10 mL) and a half-saturated brine solution (5 mL). The organic extracts were separated, dried (MgSO₄), filtered and concentrated *in vacuo* to give 5-(2-((1,3-dioxan-5-yl)oxy))-5-chloropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (50 mg, 29%) as a yellow oil. ESI-MS *m/z* calc. 472.071, found 473.1 (M+1)⁺.

Step 2:

[00264] A solution of 5-(2-((1,3-dioxan-5-yl)oxy))-5-chloropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (50 mg, 0.036 mmol) in HCl (1 mL, 4 M solution in 1,4-dioxane, 4.0 mmol) and water (22 µL, 1.221 mmol) was stirred at ambient temperature for 16 h then, at 50 °C for a further 75 min. The reaction was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC gave 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)oxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (Compound **250**, 12 mg, 20%) as a pale-yellow solid. ¹H NMR (500 MHz, Methanol-*d*₄) δ 8.39 - 8.34 (m, 1H), 8.24 (d, *J* = 0.8 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.38 - 7.29 (m, 3H), 7.09 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.06 - 7.02 (m, 1H), 6.86 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.72 (d, *J* = 2.3 Hz, 2H), 4.47 (ddd, *J* = 11.0, 9.1, 4.3 Hz, 1H), 4.38 (ddd, *J* = 13.0, 11.1, 6.2 Hz, 1H), 4.05 - 3.96 (m, 1H), 3.72 - 3.60 (m, 2H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 460.071, found 461.3 (M+1)⁺.

Example 13: Synthesis of 1-(2-chlorobenzyl)-5-(5-fluoro-2-((2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 251)



Step 1:

[00265] K_2CO_3 (1.6 g, 10.998 mmol) and 1-chloro-2-(chloromethyl)benzene (393.30 mg, 0.3 mL, 2.320 mmol) were successively added to a stirred solution of 5-(2-chloro-5-fluoropyridin-4-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**SB2**, 900 mg, 2.142 mmol) in DMSO (9 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The mixture was diluted with ice cold water (50 mL). The aqueous phase was separated and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with ice cold water (2 x 100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO_2 , 30% EtOAc in hexanes) gave a mixture of 5-(2-chloro-5-fluoropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(2-chloro-5-fluoropyridin-4-yl)-2-(2-chlorobenzyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (844.2 mg, 100%) as an off-white solid. ESI-MS *m/z* calc. 388.029, found 389.2 ($M+1$)⁺.

Step 2:

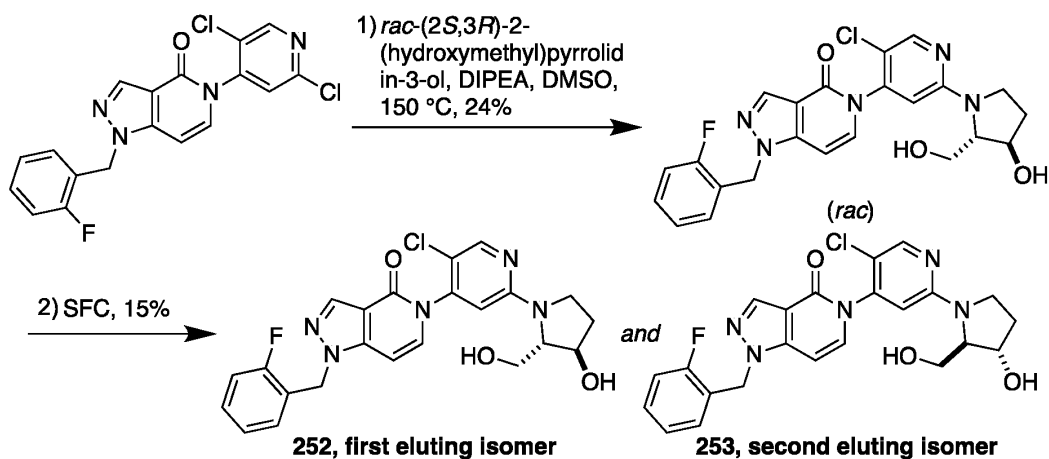
[00266] DIPEA (360 μ L, 2.067 mmol) and (3*S*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-ol hydrochloride (136 mg, 0.885 mmol) were successively added to a stirred suspension of a mixture of 5-(2-chloro-5-fluoropyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one and 5-(2-chloro-5-fluoropyridin-4-yl)-2-(2-chlorobenzyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (98 mg, 0.252 mmol) in DMSO (300 μ L) and the reaction mixture was stirred at 150 °C for 16 h. The reaction was cooled to ambient temperature, diluted with DMSO (2 mL) and MeOH (2 mL), filtered and purified by reverse phase HPLC (C_{18} X-bridge column, 30% to 45% MeCN in water with 1% TFA). The regioisomers were then separated by chiral SFC using a Chiralcel® OJ-H column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 15% MeOH (supplemented with 20 mM ammonia), 85% CO_2 ; Flow rate 100 mL/min) to give:

[00267] **First Eluting Isomer (rt = 5.10 minutes):** 1-(2-chlorobenzyl)-5-(5-fluoro-2-((2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1,5-dihydro-4*H*-

pyrazolo[4,3-*c*]pyridin-4-one (Compound **251**, 16 mg, 13%) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.22 (d, *J* = 1.7 Hz, 1H), 8.21 (d, *J* = 0.8 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.41 - 7.29 (m, 3H), 7.05 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.93 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.68 (d, *J* = 4.8 Hz, 1H), 5.68 (s, 2H), 5.20 (s, 1H), 4.99 (s, 1H), 4.35 (d, *J* = 5.3 Hz, 1H), 4.04 (s, 1H), 3.70 - 3.62 (m, 2H), 3.46 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.35 (d, *J* = 11.4 Hz, 1H), 2.19 - 2.08 (m, 1H), 2.00 - 1.93 (m, 1H) ppm. ESI-MS *m/z* calc. 469.132, found 470.3 (M+1)⁺.

[00268] Second Eluting Isomer (rt = 6.93 minutes): 2-(2-chlorobenzyl)-5-(5-fluoro-2-((2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (18 mg, 15%) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77 (d, *J* = 0.8 Hz, 1H), 8.21 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.65 - 6.60 (m, 2H), 5.66 (s, 2H), 5.20 (s, 1H), 4.99 (s, 1H), 4.35 (d, *J* = 5.3 Hz, 1H), 4.03 (s, 1H), 3.71 - 3.60 (m, 2H), 3.46 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.37 - 3.32 (m, 1H), 2.15 (ddd, *J* = 13.8, 9.0, 5.3 Hz, 1H), 1.96 (dq, *J* = 13.4, 1.7 Hz, 1H) ppm. ESI-MS *m/z* calc. 469.132, found 470.3 (M+1)⁺.

Example 14: Synthesis of *rel*-5-(5-chloro-2-((2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **252) and *rel*-5-(5-chloro-2-((2*R*,3*S*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **253**)**



Step 1:

[00269] DIPEA (500 μL, 2.870 mmol) was added to a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (103

mg, prepared using the method described in Example 3 Step 1, 0.265 mmol) and *rac*-(2*S*,3*R*)-2-(hydroxymethyl)pyrrolidin-3-ol hydrochloride (219 mg, 1.426 mmol) in DMSO (0.5 mL) and the reaction mixture was stirred at 150 °C for 20 h. The mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 24 to 38% MeCN in water with 1% NH₄OH) gave *rac*-5-(5-chloro-2-((2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (30 mg, 24%). ESI-MS *m/z* calc. 469.132, found 470.0 (M+1)⁺.

Step 2:

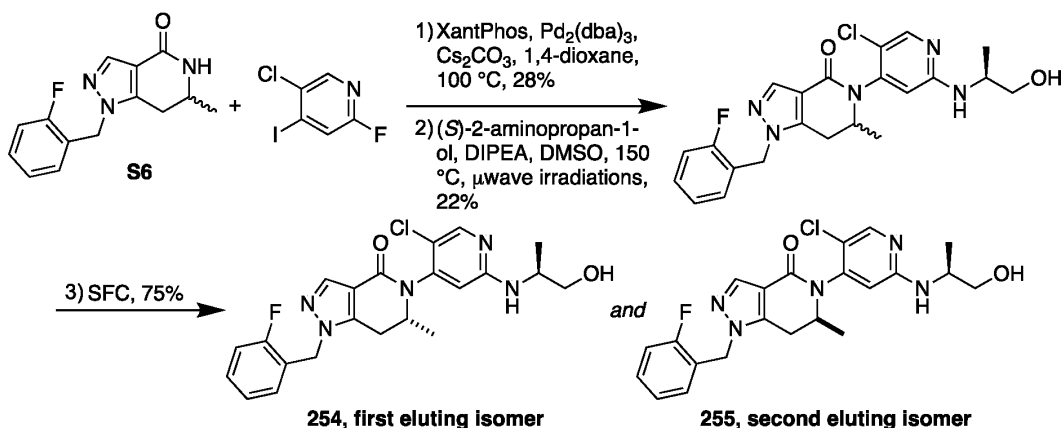
[00270] The enantiomers of *rac*-5-(5-chloro-2-((2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one were separated by chiral SFC using a Chiralcel® OJ-H column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 23% 1:1 MeOH:MeCN (supplemented with 0.2% DMIPA), 77% CO₂; Flow rate 10 mL/min) and further purified by reverse phase HPLC (C₁₈ X-bridge column, 24 to 38% MeCN in water with 1% NH₄OH) to give:

[00271] First Eluting Isomer (rt = 3.77 minutes): *rel*-5-(5-chloro-2-((2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **252**, 10.6 mg, 8%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 1.5 Hz, 1H), 8.17 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.30 - 7.16 (m, 3H), 6.92 (dd, *J* = 7.6, 4.1 Hz, 1H), 6.69 (s, 1H), 5.64 (q, *J* = 15.5 Hz, 2H), 4.94 - 4.88 (m, 1H), 4.81 (t, *J* = 5.7 Hz, 1H), 4.28 (t, *J* = 3.6 Hz, 1H), 3.92 - 3.71 (m, 1H), 3.60 - 3.56 (m, 1H), 3.45 - 3.41 (m, 1H), 3.38 - 3.34 (m, 1H), 3.26 - 3.14 (m, 1H), 2.17 - 2.10 (m, 1H), 1.84 (dd, *J* = 13.0, 6.5 Hz, 1H) ppm. ESI-MS *m/z* calc. 469.132, found 470.2 (M+1)⁺.

[00272] Second Eluting Isomer (rt = 4.61 minutes): *rel*-5-(5-chloro-2-((2*R*,3*S*)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **253**, 9.0 mg, 7%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 1.5 Hz, 1H), 8.17 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.29 - 7.17 (m, 3H), 6.92 (dd, *J* = 7.6, 4.1 Hz, 1H), 6.69 (s, 1H), 5.64 (q, *J* = 15.4 Hz, 2H), 4.94 - 4.88 (m, 1H), 4.81 (t, *J* = 5.8 Hz, 1H), 4.28 (t, *J* = 3.5 Hz, 1H), 3.86 - 3.82 (m, 1H), 3.64 - 3.51 (m, 1H), 3.44 - 3.40 (m, 1H), 3.36 (s, 1H), 3.25 - 3.13 (m, 1H), 2.17

- 2.08 (m, 1H), 1.84 (dd, $J = 12.8, 6.7$ Hz, 1H) ppm. ESI-MS m/z calc. 469.132, found 470.2 (M+1)⁺.

Example 15: Synthesis of *rel*-(*R*)-5-(5-chloro-2-(((*S)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 254) and *rel*-(*S*)-5-(5-chloro-2-(((*S**)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound 255)**



Step 1:

[00273] A stirred mixture of *rac*-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S6**, 50 mg, 0.191 mmol), 5-chloro-2-fluoro-4-iodopyridine (58 mg, 0.225 mmol), XantPhos (12 mg, 0.021 mmol) and Cs₂CO₃ (140 mg, 0.430 mmol) in 1,4-dioxane (1 mL) was degassed with argon gas for 10 min. Pd₂(dba)₃ (11 mg, 0.012 mmol) was added and the reaction mixture was heated at 100 °C overnight. The reaction was cooled to ambient temperature and concentrated *in vacuo*. The residue was diluted with EtOAc, washed with water (2 x), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (25 g C₁₈ column, 10 to 80% MeCN in water with 0.1% ammonium hydroxide) gave *rac*-5-(5-chloro-2-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (21.077 mg, 28%) as a pale yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.87 (s, 1H), 7.25 - 7.20 (m, 1H), 7.15 - 7.11 (m, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 7.03 - 6.96 (m, 1H), 6.91 (s, 1H), 5.23 (s, 2H), 4.18 - 4.10 (m, 1H), 3.29 (dd, $J = 16.2, 7.3$ Hz, 1H), 2.79 (dd, $J = 16.2, 6.7$ Hz, 1H), 1.12 (d, $J = 6.6$ Hz, 3H) ppm. ESI-MS m/z calc. 388.090, found 389.0 (M+1)⁺.

Step 2:

[00274] (S)-2-Aminopropan-1-ol (50 mg, 0.448 mmol) and DIPEA (96.460 mg, 0.13 mL, 0.746 mmol) were successively added to a stirred solution of *rac*-5-(5-chloro-2-

fluoropyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (51 mg, 0.122 mmol) in DMSO (1.5 mL) and the reaction mixture was heated under microwave irradiations at 150 °C for 2 h. The reaction was diluted in EtOAc and washed with water (x 2), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (25 g C₁₈ column, 0 to 50% MeCN in water with 0.1% formic acid, then 12 g C₁₈ column, 0 to 30% MeCN in water with 0.1% formic acid) gave 5-(5-chloro-2-(((*S*)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (11.9 mg, 22%) as a mixture of diastereomers and as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.07 (s, 1H), 7.90 (s, 1H), 7.43 - 7.37 (m, 1H), 7.28 - 7.15 (m, 3H), 6.58 (d, *J* = 0.8 Hz, 1H), 5.46 (d, *J* = 2.6 Hz, 2H), 4.23 (br, s, 1H), 4.03 - 3.97 (m, 1H), 3.62 - 3.53 (m, 2H), 3.46 (dd, *J* = 16.3, 7.2 Hz, 1H), 3.06 (dd, *J* = 16.4, 7.0 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 443.152, found 444.2 (M+1)⁺.

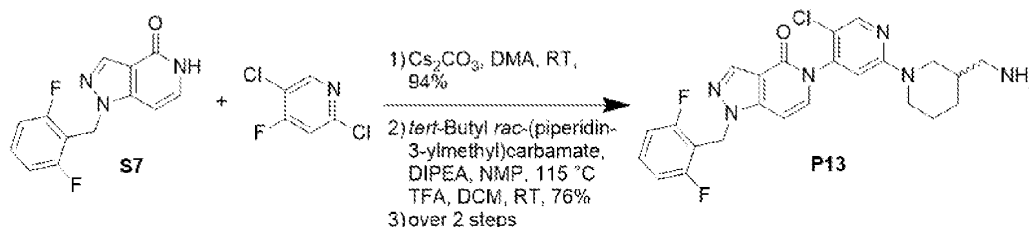
Step 3:

[00275] The diastereomers of 5-(5-chloro-2-(((*S*)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (15 mg, 0.034 mmol) were separated by chiral SFC using a Chiralpak® IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 22% MeOH (supplemented with 20 mM ammonia), 78% CO₂; Flow rate 100 mL/min) to give:

[00276] First Eluting Isomer (rt = 3.78 minutes): *rel*-(*R*)-5-(5-chloro-2-(((*S*^{*})-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **254**, 3.3 mg, 44%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 1H), 7.84 (s, 1H), 7.44 - 7.37 (m, 1H), 7.29 - 7.19 (m, 3H), 6.62 (s, 1H), 6.55 (s, 1H), 5.43 (s, 2H), 4.72 (t, *J* = 5.5 Hz, 1H), 4.11 (s, 1H), 3.91 (s, 1H), 3.48 (dt, *J* = 10.2, 5.0 Hz, 1H), 3.42 - 3.33 (m, 1H), 3.06 (d, *J* = 16.9 Hz, 1H), 1.15 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 443.152, found 444.2 (M+1)⁺.

[00277] Second Eluting Isomer (rt = 3.50 minutes): *rel*-(*S*)-5-(5-chloro-2-(((*S*^{*})-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **255**, 2.3 mg, 31%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.45 - 7.36 (m, 1H), 7.29 - 7.19 (m, 3H), 6.62 (s, 1H), 6.54 (s, 1H), 5.43 (s, 2H), 4.70 (t, *J* = 5.6 Hz, 1H), 4.11 (s, 1H), 3.91 (s, 1H), 3.47 (dt, *J* = 10.4, 5.2 Hz, 1H), 3.42 - 3.33 (m, 1H), 3.06 (d, *J* = 16.7 Hz, 1H), 1.15 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 443.152, found 444.2 (M+1)⁺.

Example 16: Synthesis of *rac*-5-(2-(3-(aminomethyl)piperidin-1-yl)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound P13)



Step 1:

[00278] Cs_2CO_3 (28.2 g, 86.551 mmol) was added to a stirred mixture of 1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S7**, 11.3 g, 40.753 mmol) and 2,5-dichloro-4-fluoropyridine (7.25 g, 43.680 mmol) in DMA (170 mL) and the reaction mixture was stirred at ambient temperature for 22 h. The reaction was poured over water (300 mL) to give a slurry. The solid was filtered, recrystallised from hot MeOH (1 L) and dried under vacuum at 40 °C to give 5-(2,5-dichloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (16.2 g, 94%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.15 (s, 1H), 7.36 (s, 1H), 7.33 - 7.24 (m, 1H), 6.96 - 6.87 (m, 3H), 6.62 (d, J = 7.6 Hz, 1H), 5.46 (s, 2H) ppm. ESI-MS m/z calc. 406.020, found 407.1 ($\text{M}+1$) $^+$.

Step 2:

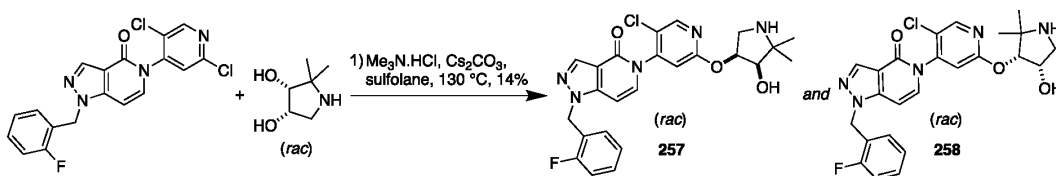
[00279] DIPEA (30 μL , 0.172 mmol) was added to a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (12 mg, 0.029 mmol) and *tert*-butyl *rac*-(piperidin-3-ylmethyl)carbamate (21.43 mg, 0.1 mmol) in NMP (1 mL) and the reaction mixture was stirred overnight at 115 °C. The reaction was cooled to ambient temperature and concentrated *in vacuo*. Purification by reverse phase HPLC (C_{18} X-bridge column, MeCN in water with 0.1% ammonium hydroxide) gave *tert*-butyl *rac*-((1-(5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)piperidin-3-yl)methyl)carbamate, which was used without further purification in the next step.

Step 3:

[00280] TFA (1 mL) was added to a stirred solution of *tert*-butyl *rac*-((1-(5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)piperidin-3-yl)methyl)carbamate in DCM (1 mL) and the reaction mixture was stirred at

ambient temperature for 1 h. The reaction was concentrated *in vacuo*. The residue was taken up in a mixture of MeCN and water and passed through a SPE bicarbonate cartridge. The filtrate was collected and lyophilised overnight to give *rac*-5-(2-(3-(aminomethyl)piperidin-1-yl)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **P13**, 13.27 mg, 76% over 2 steps) as a solid. ESI-MS *m/z* calc. 484.159, found 485.0 (M+1)⁺.

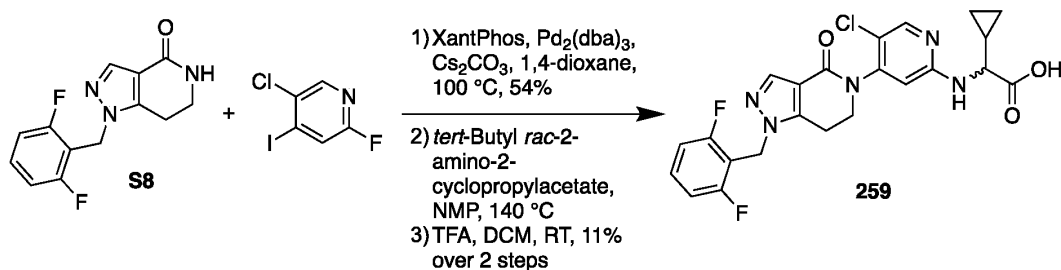
Example 17: Synthesis of *rac*-5-(5-chloro-2-(((3*S*,4*R*)-4-hydroxy-5,5-dimethylpyrrolidin-3-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **257) and *rac*-5-(5-chloro-2-(((3*R*,4*S*)-4-hydroxy-2,2-dimethylpyrrolidin-3-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **258**)**



Step 1:

[00281] Me₃N.HCl (15 mg, 0.157 mmol) and Cs₂CO₃ (200 mg, 0.614 mmol) were successively added to a stirred mixture of *rac*-(3*R*,4*S*)-2,2-dimethylpyrrolidine-3,4-diol hydrochloride (50 mg, 0.298 mmol) and 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, prepared using the method described in Example 3 Step 1, 0.129 mmol) in sulfolane (400 μL) and the reaction mixture was stirred at 130 °C for 24 h. Purification by reverse phase HPLC (C₁₈ X-bridge column, 0 to 100% MeCN in water with 0.1% NH₄OH) gave, after lyophilisation, *rac*-5-(5-chloro-2-(((3*S*,4*R*)-4-hydroxy-5,5-dimethylpyrrolidin-3-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **257**, 8.7 mg, 10%) (ESI-MS *m/z* calc. 483.147, found 484.3 (M+1)⁺) and *rac*-5-(5-chloro-2-(((3*R*,4*S*)-4-hydroxy-2,2-dimethylpyrrolidin-3-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **258**, 3.2 mg, 4%) (ESI-MS *m/z* calc. 483.147, found 482.2 (M-1)⁻).

Example 18: Synthesis of *rac*-2-((5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetic acid (Compound P14)



Step 1:

[00282] 1-(2,6-Difluorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S8**, 5 g, 18.99 mmol) and 5-chloro-2-fluoro-4-iodopyridine (5.52 g, 21.44 mmol) were treated via the method described in Example 15 Step 1 to give, after purification by flash chromatography (80 g SiO₂, 0 to 100% 3:1 EtOAc/EtOH in heptane), 5-(5-chloro-2-fluoropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (5.120 g, 54%) as a brown solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.44 (s, 1H), 7.85 (s, 1H), 7.60 - 7.37 (m, 2H), 7.32 - 6.95 (m, 2H), 5.42 (s, 2H), 4.19 - 3.91 (m, 2H), 3.26 (t, *J* = 6.6 Hz, 2H) ppm. ESI-MS *m/z* calc. 392.065, found 393.1 (M+1)⁺.

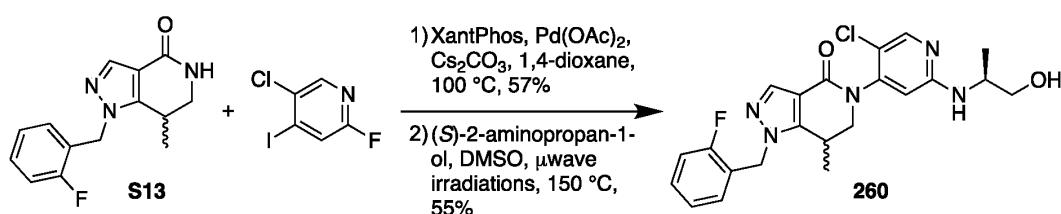
Step 2 and 3:

[00283] A stirred solution of 5-(5-chloro-2-fluoropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (1.97 g, 3.912 mmol) and *tert*-butyl *rac*-2-amino-2-cyclopropylacetate (2.58 g, 15.07 mmol) in NMP (11 mL) was heated to 140 °C for 22 h. The reaction mixture was partitioned between EtOAc (100 mL) and water (100 mL). The aqueous layer was separated and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 47 to 95% MeCN in water with 1% ammonium hydroxide) gave *tert*-butyl *rac*-2-((5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetate which was used without further purification in the next step.

[00284] TFA (438 μL, 5.685 mmol) was added to a solution of *tert*-butyl *rac*-2-((5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetate in DCM (900 μL) and the reaction mixture was stirred at ambient temperature for 5 h. The mixture was concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ X-bridge column, 0 to 23% MeCN in water with 1% ammonium

hydroxide) gave *rac*-2-((5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetic acid (Compound **P14**, 202 mg, 11% over 2 steps). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.00 (s, 1H), 7.80 (s, 1H), 7.50 (tt, *J* = 8.4, 6.6 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 6.67 (s, 1H), 5.40 (s, 2H), 3.89 (s, 2H), 3.77 (t, *J* = 7.4 Hz, 2H), 3.21 (s, 1H), 1.15 (qt, *J* = 8.1, 4.9 Hz, 1H), 0.61 - 0.20 (m, 4H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 487.122, found 488.3 (M+1)⁺.

Example 19: Synthesis of a mixture of diastereomers of 5-(5-chloro-2-(((*S*)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **260)**



Step 1:

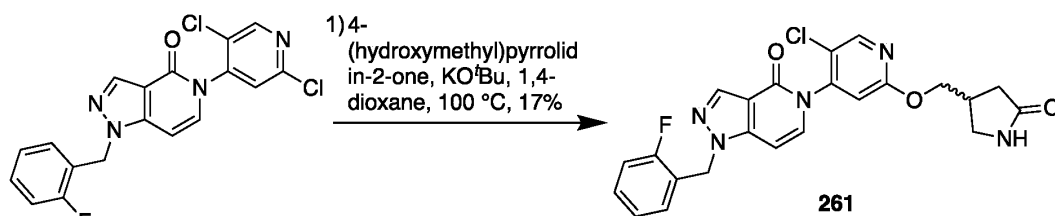
[00285] A stirred solution of 5-chloro-2-fluoro-4-iodopyridine (287 mg, 1.115 mmol), *rac*-5-(5-chloro-2-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S13**, 238 mg, 0.900 mmol), XantPhos (160 mg, 0.277 mmol) and Cs₂CO₃ (440 mg, 1.350 mmol) in 1,4-dioxane (15 mL) was degassed with argon gas for 20 min. Pd(OAc)₂ (18 mg, 0.080 mmol) was added and the reaction mixture was heated at 100 °C for 16 h. The reaction was cooled to ambient temperature and partitioned between water (25 mL) and EtOAc (20 mL). The aqueous phase was separated and extracted with EtOAc (20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (12 g C₁₈ column, 20 to 80% MeCN in water with 0.1% ammonium hydroxide) gave *rac*-5-(5-chloro-2-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (200 mg, 57%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.34 (s, 1H), 7.92 (s, 1H), 7.42 - 7.35 (m, 1H), 7.25 (d, *J* = 1.8 Hz, 1H), 7.22 - 7.14 (m, 3H), 5.50 - 5.46 (m, 2H), 4.47 - 4.38 (m, 1H), 3.66 - 3.58 (m, 1H), 3.51 - 3.42 (m, 1H), 1.36 (d, *J* = 7.0 Hz, 3H) ppm. ESI-MS *m/z* calc. 388.090, found 389.2 (M+1)⁺.

Step 2:

[00286] (*S*)-2-aminopropan-1-ol (394.4 mg, 0.4 mL, 5.251 mmol) and *rac*-5-(5-chloro-2-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (200 mg, 0.514 mmol) were treated via the method described in Example 1

Step 2 except that DIPEA was not required. Purification by reverse phase chromatography (12 g C₁₈ column, 20 to 80% MeCN in water with 0.1% ammonium hydroxide) gave 5-(5-chloro-2-(((*S*)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5,6,7-tetrahydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **260**, 130 mg, 55%) as a mixture of diastereomers and as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.03 - 7.99 (m, 1H), 7.89 (s, 1H), 7.42 - 7.34 (m, 1H), 7.23 - 7.13 (m, 3H), 6.53 (s, 1H), 5.47 (s, 2H), 4.33 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.03 - 3.94 (m, 1H), 3.62 - 3.47 (m, 3H), 3.47 - 3.39 (m, 1H), 1.35 (br d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 443.152, found 444.2 (M+1)⁺.

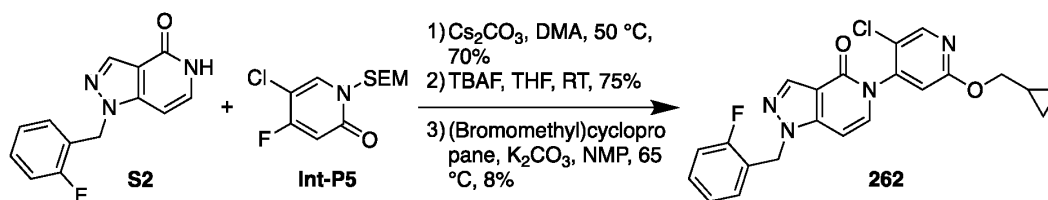
Example 20: Synthesis of *rac*-5-(5-chloro-2-((5-oxopyrrolidin-3-yl)methoxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **261)**



Step 1:

[00287] KO^tBu (29 mg, 0.258 mmol) was added to a stirred solution of 4-(hydroxymethyl)pyrrolidin-2-one (29 mg, 0.252 mmol) in 1,4-dioxane (1 mL) and the reaction mixture was stirred at ambient temperature for 5 min. A solution of 5-(2,5-dichloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (50 mg, prepared using the method described in Example 3 Step 1, 0.127 mmol) in 1,4-dioxane (0.5 mL) was added dropwise and the mixture was heated at 100 °C for 20 h. The reaction was cooled to ambient temperature, quenched by addition of water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (12 g C₁₈ column, 2 to 100% MeCN in water with 0.1% NH₄OH) gave *rac*-5-(5-chloro-2-((5-oxopyrrolidin-3-yl)methoxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **261**, 10 mg, 17%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (s, 1H), 8.19 (s, 1H), 7.59 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.31 - 7.19 (m, 4H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.65 (d, *J* = 3.2 Hz, 2H), 4.37 - 4.25 (m, 2H), 3.44 - 3.38 (m, 1H), 3.10 (dd, *J* = 9.8, 5.5 Hz, 1H), 2.93 - 2.83 (m, 1H), 2.33 (dd, *J* = 16.6, 9.0 Hz, 1H), 2.09 - 2.02 (m, 1H) ppm. ESI-MS *m/z* calc. 467.116, found 468.2 (M+1)⁺.

Example 21: Synthesis of 5-(5-chloro-2-(cyclopropylmethoxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (Compound 262)



Step 1:

[00288] Cs₂CO₃ (2.15 g, 6.599 mmol) was added to a stirred solution of 1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (**S2**, 0.8 g, 3.289 mmol) and 5-chloro-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)pyridin-2(1H)-one (**Int-P5**, 1 g, 3.291 mmol) in DMA (5 mL) and the reaction mixture was stirred at 50 °C for 1 h. The reaction was diluted with ice cold water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 40 to 50% EtOAc in heptane) gave 5-(5-chloro-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (1.4 g, 70%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (d, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.18 (m, 3H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.78 (s, 1H), 5.70-5.58 (m, 2H), 5.34 - 5.28 (m, 2H), 3.65 (t, *J* = 8.0 Hz, 2H), 0.92 (t, *J* = 8.0 Hz, 2H), 0.009 (s, 9H) ppm. ESI-MS *m/z* calc. 500.145, found 501.1 (M+1)⁺.

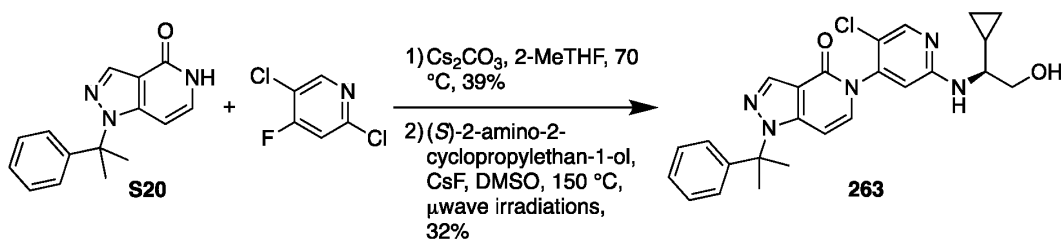
Step 2:

[00289] TBAF (10 mL, 1 M solution in THF, 10 mmol) was added to a stirred solution of 5-(5-chloro-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (1.4 g, 2.295 mmol) in THF (5 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of a saturated NH₄Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 15 to 20% MeOH in DCM) gave 5-(5-chloro-2-oxo-1,2-dihydropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (645 mg, 75%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.90 - 11.40 (br, s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.43 - 7.35 (m, 1H), 7.29 - 7.16 (m, 3H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.67 (s, 1H), 5.67 - 6.59 (m, 2H) ppm. ESI-MS *m/z* calc. 370.063, found 371.2 (M+1)⁺.

Step 3:

[00290] K_2CO_3 (38 mg, 0.275 mmol) was added to a stirred mixture of, 5-(5-chloro-2-oxo-1,2-dihydropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (63 mg, 0.170 mmol) and (bromomethyl)cyclopropane (25 μL , 0.258 mmol) in NMP (0.5 mL) and the reaction mixture was stirred at 65 °C for 24 h. Purification by reverse phase HPLC (C_{18} X-bridge column, 0 to 100% MeCN in water with 0.1% NH_4OH) gave, after lyophilisation, 5-(5-chloro-2-(cyclopropylmethoxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **262**, 5.7 mg, 8%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.40 (d, 1H), 8.17 (d, 1H), 7.50 - 7.48 (d, 1H), 7.39 - 7.36 (m, 1H), 7.30 - 7.17 (m, 4H), 6.95 - 6.93 (m, 1H), 5.64 (m, 2H), 4.16 - 4.13 (d, 2H), 1.28 - 1.24 (m, 1H), 0.57 - 0.54 (m, 2H), 0.36 - 0.33 (m, 2H) ppm. ESI-MS m/z calc. 424.110, found 425.4 ($\text{M}+1$)⁺.

Example 22: Synthesis of (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-phenylpropan-2-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **263)**

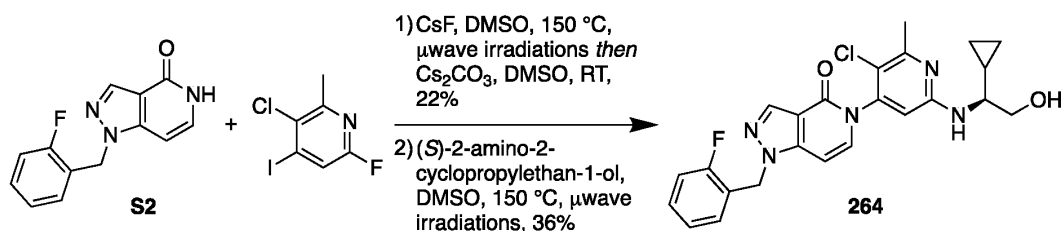
**Step 1:**

[00291] 2,5-Dichloro-4-fluoropyridine (38 mg, 0.229 mmol) was added to a stirred mixture of 1-(2-phenylpropan-2-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (**S20**, 73 mg, 0.225 mmol) and Cs_2CO_3 (154 mg, 0.473 mmol) in 2-MeTHF (3 mL) and the reaction mixture was heated at 70 °C for 3.5 h. The reaction was cooled to ambient temperature and concentrated *in vacuo*. The residue was partitioned between DCM and water. The aqueous phase was separated and extracted with DCM (2 x). The combined organic phases were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (10 to 50% EtOAc in heptane) gave 5-(2,5-dichloropyridin-4-yl)-1-(2-phenylpropan-2-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (37 mg, 39%) as a white solid. ^1H NMR (400 MHz, $\text{Chloroform}-d$) δ 8.54 (s, 1H), 8.27 (s, 1H), 7.33 - 7.43 (m, 5H), 7.24 - 7.26 (m, 1H), 6.59 (d, $J = 7.7$ Hz, 1H), 5.63 (d, $J = 7.6$ Hz, 1H), 2.05 (s, 6H) ppm. ESI-MS m/z calc. 398.070, found 399.1 ($\text{M}+1$)⁺.

Step 2:

[00292] CsF (20 mg, 0.132 mmol) was added to a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1-(2-phenylpropan-2-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (37 mg, 0.088 mmol) and (*S*)-2-amino-2-cyclopropylethan-1-ol (45 mg, 0.445 mmol) in DMSO (1 mL) and the reaction mixture was heated at 150 °C under microwave irradiations for 3 h. Additional CsF (20 mg, 0.132 mmol) was added and the reaction was heated at 150 °C under microwave irradiations for a further 1 h. The mixture was partitioned between water and EtOAc and extracted with EtOAc (2 x). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (C₁₈ CSH column, 20 to 60% MeCN in water with 0.1% formic acid) gave (*S*)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-phenylpropan-2-yl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **263**, 13 mg, 32%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.20 (s, 1H), 8.03 (s, 1H), 7.36 - 7.42 (m, 2H), 7.30 - 7.35 (m, 1H), 7.27 (d, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 0.9 Hz, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 3.70 - 3.78 (m, 1H), 3.60 - 3.68 (m, 1H), 3.34 - 3.44 (m, 1H), 2.04 (d, *J* = 3.2 Hz, 6H), 0.97 - 1.08 (m, 1H), 0.41 - 0.58 (m, 2H), 0.26 - 0.38 (m, 2H) ppm; exchangeable H not observed. ESI-MS *m/z* calc. 463.178, found 464.3 (M+1)⁺.

Example 23: Synthesis of (*S*)-5-(3-chloro-6-((1-cyclopropyl-2-hydroxyethyl)amino)-2-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **264)**



Step 1:

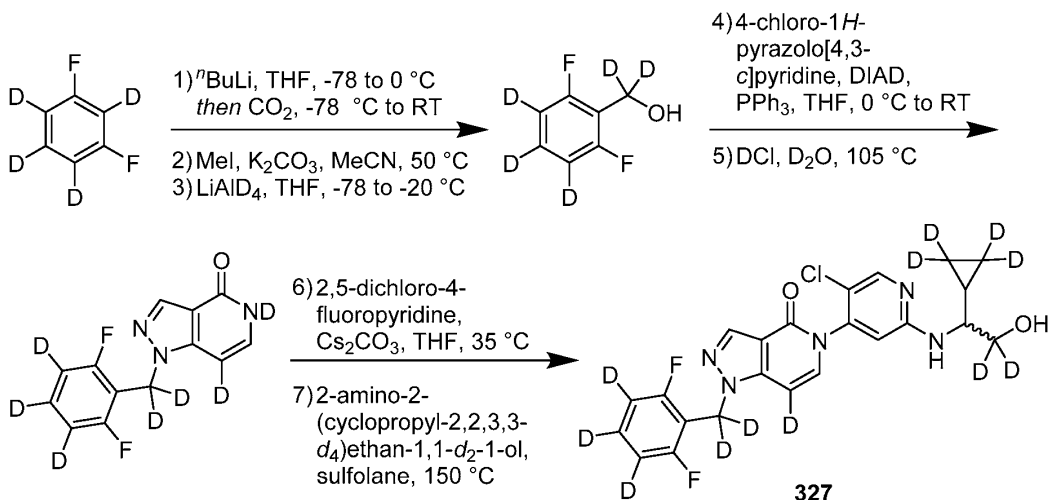
[00293] A mixture of 3-chloro-6-fluoro-4-iodo-2-methylpyridine (212.04 mg, 0.781 mmol) and CsF (356 mg, 2.344 mmol) in DMSO (2 mL) was stirred at 150 °C under microwave irradiations for 1 h. 1-(2-Fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (200 mg, 0.781 mmol), Cs₂CO₃ (763 mg, 2.342 mmol) and DMSO (4 mL) were added and the reaction mixture was stirred at ambient temperature for 3 h. The mixture was diluted with water (25 mL) and extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10 to 80% EtOAc in heptane) gave 5-(3-chloro-6-fluoro-2-

methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (67 mg, 22%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 (s, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.36 - 7.43 (m, 1H), 7.17 - 7.30 (m, 3H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.65 (d, *J* = 7.0 Hz, 2H), 2.59 (s, 3H) ppm. ESI-MS *m/z* calc. 386.075, found 387.1 (M+1)⁺.

Step 2:

[00294] A solution of 5-(3-chloro-6-fluoro-2-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (67 mg, 0.173 mmol) and (*S*)-2-amino-2-cyclopropylethan-1-ol (88 mg, 0.870 mmol) in DMSO (1 mL) was heated at 150 °C under microwave irradiations for 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (25 g C₁₈ column, 10 to 50% MeCN in water with 0.1% formic acid then, 12 g C₁₈ column, 10 to 50% MeCN in water with 0.1% NH₄OH) followed by flash chromatography (SiO₂, 20 to 100% EtOAc in DCM) gave (*S*)-5-(3-chloro-6-((1-cyclopropyl-2-hydroxyethyl)amino)-2-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (Compound **264**, 29 mg, 36%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (s, 1H), 7.41 - 7.46 (m, 1H), 7.36 - 7.41 (m, 1H), 7.23 - 7.30 (m, 2H), 7.21 (d, *J* = 6.5 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.74 (br dd, *J* = 7.8, 4.2 Hz, 1H), 6.46 (s, 1H), 5.63 (d, *J* = 3.4 Hz, 2H), 4.65 - 4.74 (m, 1H), 3.48 - 3.58 (m, 2H), 2.38 (s, 3H), 1.23 (br s, 1H), 0.93 - 1.04 (m, 1H), 0.28 - 0.47 (m, 3H), 0.15 - 0.27 (m, 1H) ppm. ESI-MS *m/z* calc. 467.152, found 468.3 (M+1)⁺.

Example 24: Synthesis of *rac*-5-(5-chloro-2-((1-(cyclopropyl-2,2,3,3-*d*₄)-2-hydroxyethyl-2,2-*d*₂)amino)pyridin-4-yl)-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-7-*d* (Compound 327)



Step 1:

[00295] Under a nitrogen atmosphere, ⁿBuLi (2.5 M in hexanes, 1.15 eq) is added dropwise over 12 min to a stirred mixture of 1,3-difluorobenzene-2,4,5,6-*d*₄ (1.00 eq) in THF (39 vol) at -78 °C and the solution is stirred and warmed over 1.25 h to 0 °C. The reaction is cooled to -78 °C and the nitrogen inlet is switched to the CO₂ inlet. A stainless-steel pressure chamber is charged with CO₂ (80 psi, 2.57 eq) and the CO₂ is slowly passed through the mixture over 7 min. The reaction is gradually warmed over 5 h to ambient temperature. The mixture is cooled to -20 °C, quenched by slow addition of an aqueous 1 M aqueous HCl solution (39 vol) to pH 1 over 35 min and warmed to 0 °C. The reaction mixture is extracted with Et₂O (3 x 41 vol). The combined organic phases are washed with an aqueous saturated NaCl solution (41 vol), dried (Na₂SO₄), and concentrated *in vacuo*. Purification by trituration from hexanes (20 vol) at ambient temperature overnight gives after filtration 2,6-difluorobenzoic-3,4,5-*d*₃ acid as an off-white solid.

[00296] Step 2:

[00297] In a sealed flask, K₂CO₃ (1.30 eq) and MeI (4.00 eq) are added to a stirred solution of 2,6-difluorobenzoic-3,4,5-*d*₃ acid (1.00 eq) in dry MeCN (36 vol). The flask is sealed and the reaction mixture is stirred at 50 °C for 48 h. The mixture is partitioned with deionized water (38 vol) and extracted with Et₂O (3 x 38 vol). The combined organic phases are washed with a saturated aqueous NaCl solution (38 vol), dried (Na₂SO₄), filtered and concentrated *in*

vacuo. Purification by flash chromatography (SiO₂, 100% Et₂O) gives methyl 2,6-difluorobenzoate-3,4,5-*d*₃ as an oil.

[00298] Step 3:

[00299] Under a nitrogen atmosphere, LiAD₄ (1.00 eq) is added slowly to a stirred solution of methyl-2,6-difluorobenzoate-3,4,5-*d*₃ (1.00 eq) in dry THF (100 vol) at -78 °C and the suspension is stirred at -78 °C for 1 h and at -20 °C for 18 h. The solution is cooled to -78 °C and quenched by addition of DCl (1 M solution in D₂O, 2.8 vol). The reaction is warmed to 0 °C and stirred for 20 min. The mixture is diluted with D₂O (31 vol) and extracted with Et₂O (3 x 78 vol). The combined organic phases are dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10% EtOAc in hexanes) gives (2,6-difluorophenyl-3,4,5-*d*₃)methan-*d*₂-ol as an oil.

[00300] Step 4:

[00301] Under a nitrogen atmosphere, a solution of DIAD (1.20 eq) in THF (17 vol) is added dropwise to a stirred solution of (2,6-difluorophenyl-3,4,5-*d*₃)methan-*d*₂-ol (1.20 eq), 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (1.20 eq) and PPh₃ (1.20 eq) in THF (34 vol) at 0 °C. The cooling bath is removed and the reaction mixture is stirred at 21 °C for 18 h. The mixture is concentrated *in vacuo* at 30 °C. Purification by flash chromatography (SiO₂, 15:15:70 mixture of EtOAc, DCM and hexanes) gives 4-chloro-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1*H*-pyrazolo[4,3-*c*]pyridine as a white solid.

[00302] Step 5:

[00303] Concentrated DCl (35 wt % solution in D₂O, 17.5 eq) is added to a stirred solution of 4-chloro-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1*H*-pyrazolo[4,3-*c*]pyridine (1.00 eq) in D₂O (10 vol) at 21 °C and the reaction mixture is heated at 105 °C for 27 h. The cloudy suspension is filtered, washing the filter cake with D₂O (2 x 5 vol). The solid is dried *in vacuo* to give 1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-5,7-*d*₂ as an off-white solid.

[00304] Step 6:

[00305] Cs₂CO₃ (2.00 eq) is added to a stirred solution of 1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-5,7-*d*₂ (1.00 eq) and 2,5-dichloro-4-fluoropyridine (1.20 eq) in THF (59 vol) and the suspension is stirred at 35 °C for 24 h. Purification by flash chromatography (SiO₂, 50% EtOAc in hexanes then 20% EtOAc in DCM) followed by trituration from ⁿhexane gives 5-(2,5-dichloropyridin-4-yl)-1-((2,6-

difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-7-*d* as a white solid.

[00306] Step 7:

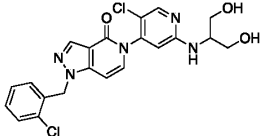
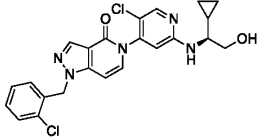
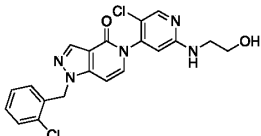
[00307] In a vial, a stirred solution of 5-(2,5-dichloropyridin-4-yl)-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-7-*d* (1 eq) and 2-amino-2-(cyclopropyl-2,2,3,3-*d*₄)ethan-1,1-*d*₂-1-ol (**Int-A26**, 4 eq) in sulfolane (3 vol) is flushed with nitrogen gas. The vial is sealed and heated at 150 °C for 72 h. The reaction mixture is cooled to ambient temperature. The mixture is diluted with 2 M HCl (5 vol) and extracted with EtOAc (6 vol). The combined organic phases are washed with 2 M HCl (3 vol). The combined aqueous layers are basified with 2 N NaOH (9 vol). EtOH (3 vol) is added and the mixture is stirred at ambient temperature overnight. The formed precipitate is filtered, washed with a 4:1 mixture of water and EtOH (3 x 2 vol) and dried under vacuum at 50 °C overnight. The filtrate is transferred to an addition funnel and extracted with EtOAc (3 x 8 vol). The combined organic extracts are washed with water (8 vol) and brine (8 vol), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (60g C₁₈ Sfar Duo column, 10 to 100% MeCN in water) gives a second crop of solid. The solids from both crops are combined, recrystallized from EtOH (14 vol) and heptane (28 vol) and dried under vacuum at 50 °C over the weekend to give *rac*-5-(5-chloro-2-((1-(cyclopropyl-2,2,3,3-*d*₄)-2-hydroxyethyl-2,2-*d*₂)amino)pyridin-4-yl)-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-7-*d* (Compound **327**).

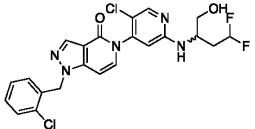
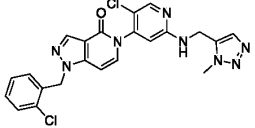
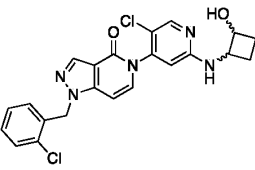
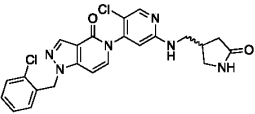
[00308] The enantiomers of *rac*-5-(5-chloro-2-((1-(cyclopropyl-2,2,3,3-*d*₄)-2-hydroxyethyl-2,2-*d*₂)amino)pyridin-4-yl)-1-((2,6-difluorophenyl-3,4,5-*d*₃)methyl-*d*₂)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one-7-*d* (Compound **327**) can be separated by chiral SFC, using analogous methods to those disclosed in the specification.

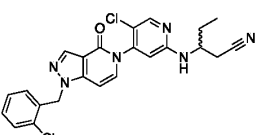
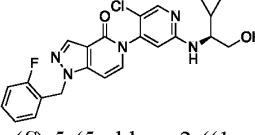
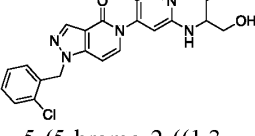
[00309] In Step 1, CO₂ can be substituted for ¹³CO₂ or ¹⁴CO₂.

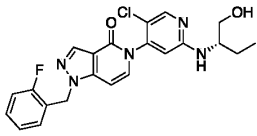
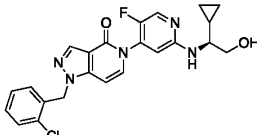
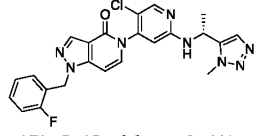
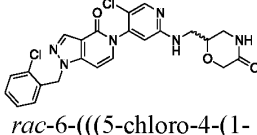
[00310] The following compounds were made using methods analogous to those disclosed in the specification.

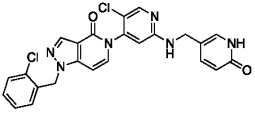
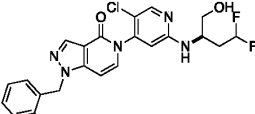
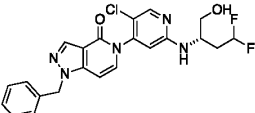
Table 14: Compounds Prepared Using Analogous Methods

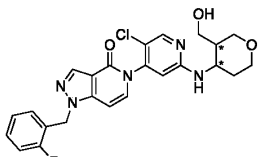
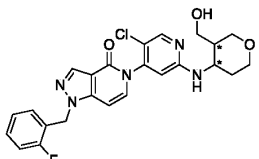
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
15	 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 459.086, found 460.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.14 (s, 1H), 7.54 - 7.49 (m, 1H), 7.44 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.12 - 7.06 (m, 1H), 6.90 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.75 (d, <i>J</i> = 7.9 Hz, 1H), 6.69 (s, 1H), 5.73 - 5.61 (m, 2H), 4.71 - 4.62 (m, 2H), 3.93 - 3.89 (m, 1H), 3.58 - 3.44 (m, 4H) ppm.
16	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 469.107, found 470.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (dd, <i>J</i> = 1.9, 0.8 Hz, 1H), 8.10 (s, 1H), 7.55 - 7.42 (m, 2H), 7.42 - 7.31 (m, 2H), 7.10 (dd, <i>J</i> = 7.5, 2.0 Hz, 1H), 6.93 - 6.86 (m, 2H), 6.63 (d, <i>J</i> = 1.2 Hz, 1H), 5.68 (d, <i>J</i> = 5.1 Hz, 2H), 4.70 (dt, <i>J</i> = 19.2, 5.4 Hz, 1H), 3.60 - 3.47 (m, 2H), 1.06 - 0.96 (m, 1H), 0.52 - 0.07 (m, 4H) ppm; exchangeable H not observed.
17	 5-(5-chloro-2-((2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 429.076, found 430.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.15 (s, 1H), 7.54 - 7.49 (m, 1H), 7.44 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.11 - 7.05 (m, 1H), 7.03 (t, <i>J</i> = 5.7 Hz, 1H), 6.89 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.63 (s, 1H), 5.73 - 5.61 (m, 2H), 4.72 (t, <i>J</i> = 5.4 Hz, 1H), 3.57 - 3.48 (m, 2H), 3.40 - 3.31 (m, 2H) ppm.

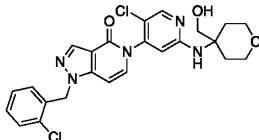
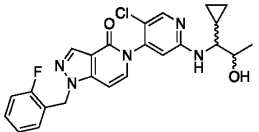
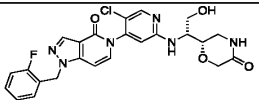
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
18	 <i>rac</i>-5-(5-chloro-2-((4,4-difluoro-1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 493.088, found 494.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.23 - 8.15 (m, 2H), 7.55 - 7.49 (m, 1H), 7.45 (dd, <i>J</i> = 7.5, 0.6 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 (dd, <i>J</i> = 7.4, 1.9 Hz, 1H), 7.01 (t, <i>J</i> = 8.1 Hz, 1H), 6.90 (ddd, <i>J</i> = 7.6, 3.8, 0.9 Hz, 1H), 6.62 (d, <i>J</i> = 5.8 Hz, 1H), 6.30 - 5.92 (m, 1H), 5.67 (d, <i>J</i> = 4.7 Hz, 2H), 4.98 - 4.89 (m, 1H), 4.16 - 4.12 (m, 1H), 3.56 - 3.49 (m, 1H), 3.45 - 3.31 (m, 1H), 2.26 - 2.00 (m, 2H) ppm.
19	 5-(5-chloro-2-(((1-methyl-1H-1,2,3-triazol-5-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 480.098, found 481.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.23 (s, 1H), 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 7.59 (s, 1H), 7.57 - 7.48 (m, 2H), 7.46 (d, <i>J</i> = 7.6 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.11 - 7.05 (m, 1H), 6.91 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.70 (s, 1H), 5.67 (d, <i>J</i> = 6.3 Hz, 2H), 4.61 (qd, <i>J</i> = 15.8, 5.7 Hz, 2H), 4.03 (s, 3H) ppm.
20	Anti  <i>rac</i>-5-(5-chloro-2-(((1<i>S</i>,2<i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 455.092, found 456.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.15 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.44 (dd, <i>J</i> = 7.5, 3.7 Hz, 1H), 7.40 - 7.31 (m, 3H), 7.11 - 7.06 (m, 1H), 6.90 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.58 (s, 1H), 5.73 - 5.61 (m, 2H), 5.28 (dd, <i>J</i> = 12.7, 7.1 Hz, 1H), 4.01 - 3.97 (m, 1H), 3.87 (p, <i>J</i> = 7.6 Hz, 1H), 2.04 - 1.92 (m, 2H), 1.42 (p, <i>J</i> = 10.0 Hz, 1H), 1.25 - 1.16 (m, 1H) ppm.
21		S1		ESI-MS <i>m/z</i> calc. 482.102, found	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.17 (s, 1H), 7.54 - 7.48 (m, 2H), 7.46

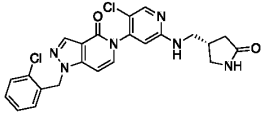
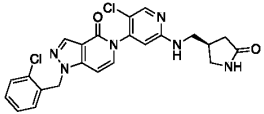
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rac</i> -5-(5-chloro-2-(((5-oxopyrrolidin-3-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one			483.2 (M+1) ⁺ .	(d, <i>J</i> = 7.4 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.25 - 7.19 (m, 1H), 7.11 - 7.06 (m, 1H), 6.90 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.61 (s, 1H), 5.73 - 5.61 (m, 2H), 3.37 - 3.23 (m, 3H), 3.04 - 2.97 (m, 1H), 2.69 - 2.64 (m, 1H), 2.31 - 2.22 (m, 1H), 1.95 (ddd, <i>J</i> = 16.7, 6.1, 1.7 Hz, 1H) ppm.
22	 <i>rac</i> -3-((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)pyridin-2-yl)amino)pentanenitrile	S1		ESI-MS <i>m/z</i> calc. 466.108, found 467.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.21 - 8.19 (m, 1H), 7.55 - 7.45 (m, 2H), 7.41 - 7.30 (m, 2H), 7.26 - 7.20 (m, 1H), 7.10 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.91 (dt, <i>J</i> = 7.5, 1.1 Hz, 1H), 6.69 (s, 1H), 6.61 (s, 1H), 5.73 - 5.62 (m, 2H), 4.10 - 3.94 (m, 1H), 2.93 - 2.82 (m, 1H), 2.80 - 2.70 (m, 1H), 1.71 - 1.59 (m, 2H), 0.98 - 0.91 (m, 3H) ppm.
23	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 453.137, found 454.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (dd, <i>J</i> = 2.0, 0.8 Hz, 1H), 8.08 (s, 1H), 7.51 - 7.35 (m, 2H), 7.31 - 7.17 (m, 3H), 6.94 - 6.85 (m, 2H), 6.62 (d, <i>J</i> = 1.0 Hz, 1H), 5.63 (d, <i>J</i> = 3.8 Hz, 2H), 4.69 (dt, <i>J</i> = 18.4, 5.3 Hz, 1H), 3.57 - 3.45 (m, 2H), 1.00 (s, 1H), 0.52 - 0.11 (m, 4H) ppm.
24	 5-(5-bromo-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 503.036, found 506.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.21 (s, 1H), 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.49 (m, 1H), 7.44 - 7.30 (m, 3H), 7.13 - 7.07 (m, 1H), 6.89 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.77 (d, <i>J</i> = 7.9 Hz, 1H), 6.69 (s, 1H), 5.73 - 5.61 (m, 2H), 4.67 (dt, <i>J</i> = 13.1, 5.5 Hz, 2H), 3.93 - 3.89

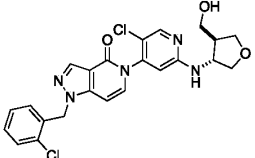
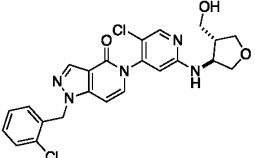
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					(m, 1H), 3.58 - 3.44 (m, 4H) ppm.
25	 (S)-5-(5-chloro-2-((1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 441.137, found 442.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.47 (t, <i>J</i> = 7.6 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 6.91 (d, <i>J</i> = 7.6 Hz, 1H), 6.77 (t, <i>J</i> = 7.4 Hz, 1H), 6.61 (d, <i>J</i> = 1.1 Hz, 1H), 5.64 (s, 1H), 5.63 (s, 1H), 4.66 (dt, <i>J</i> = 13.8, 5.5 Hz, 1H), 3.83 - 3.79 (m, 1H), 3.52 - 3.44 (m, 1H), 3.42 - 3.31 (m, 1H), 1.74 - 1.61 (m, 1H), 1.50 - 1.37 (m, 1H), 0.90 (td, <i>J</i> = 7.4, 3.1 Hz, 3H) ppm.
26	 (S)-1-(2-chlorobenzyl)-5-(2-((1-cyclopropyl-2-hydroxyethyl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 453.137, found 454.4 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.97 (s, 1H), 7.81 (d, <i>J</i> = 1.8 Hz, 1H), 7.38 - 7.22 (m, 2H), 7.12 (dtd, <i>J</i> = 19.7, 7.4, 1.6 Hz, 2H), 6.83 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.68 (d, <i>J</i> = 7.6 Hz, 1H), 6.43 - 6.29 (m, 2H), 5.44 (s, 2H), 4.44 (d, <i>J</i> = 8.9 Hz, 1H), 3.39 - 3.17 (m, 3H), 0.29 - 0.10 (m, 5H) ppm.
27	 (R)-5-(5-chloro-2-((1-(1-methyl-1H-1,2,3-triazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 478.143, found 479.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.21 (d, <i>J</i> = 1.2 Hz, 1H), 8.16 (dd, <i>J</i> = 1.8, 0.8 Hz, 1H), 7.66 (d, <i>J</i> = 4.8 Hz, 1H), 7.54 - 7.36 (m, 3H), 7.31 - 7.15 (m, 3H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.63 (d, <i>J</i> = 1.2 Hz, 1H), 5.63 (s, 2H), 5.33 (q, <i>J</i> = 6.7 Hz, 1H), 4.01 (s, 3H), 1.52 (dd, <i>J</i> = 6.8, 5.0 Hz, 3H) ppm.
28	 <i>rac</i>-6-(((5-chloro-4-(1-(2-chlorobenzyl)-4-oxo-	S1		ESI-MS <i>m/z</i> calc. 498.097, found 499.3 (M+1) ⁺ .	

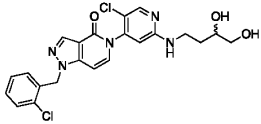
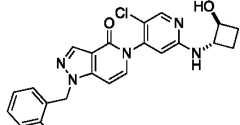
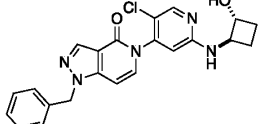
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)methyl)morpholin-3-one				
29	 5-(5-chloro-2-(((6-oxo-1,6-dihydropyridin-3-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 492.087, found 493.3 (M+1) ⁺ .	
30	Peak 1  <i>rel</i>-(R)-5-(5-chloro-2-(((4,4-difluoro-1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralcel [®] OD-H column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 45% MeOH (supplemented with 20 mM ammonia), 55% CO ₂ ; Flow rate 10 mL/min); rt = 3.84 min	ESI-MS <i>m/z</i> calc. 477.118, found 478.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.14 (m, 2H), 7.46 (dd, <i>J</i> = 7.6, 0.8 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 7.02 (t, <i>J</i> = 8.2 Hz, 1H), 6.92 (dd, <i>J</i> = 7.6, 3.1 Hz, 1H), 6.62 (s, 1H), 6.29 - 5.92 (m, 1H), 5.63 (d, <i>J</i> = 3.5 Hz, 2H), 4.93 (dt, <i>J</i> = 14.9, 5.5 Hz, 1H), 4.16 - 4.12 (m, 1H), 3.56 - 3.49 (m, 1H), 3.45 - 3.33 (m, 1H), 2.25 - 2.16 (m, 1H), 2.11 - 1.95 (m, 1H) ppm.
31	Peak 2  <i>rel</i>-(S)-5-(5-chloro-2-(((4,4-difluoro-1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralcel [®] OD-H column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 45% MeOH	ESI-MS <i>m/z</i> calc. 477.118, found 478.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.15 (m, 2H), 7.46 (dd, <i>J</i> = 7.5, 0.8 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 7.01 (t, <i>J</i> = 8.3 Hz, 1H), 6.92 (dd, <i>J</i> = 7.6, 3.1 Hz, 1H), 6.62 (s, 1H), 6.27 - 5.97 (m, 1H), 5.63 (d, <i>J</i> = 3.5 Hz, 2H), 4.93 (dt, <i>J</i> = 14.8, 5.5 Hz, 1H), 4.16 - 4.12 (m, 1H),

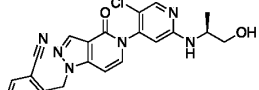
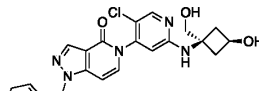
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one		(supplemented with 20 mM ammonia), 55% CO ₂ ; Flow rate 10 mL/min; rt = 4.88 min		3.55 - 3.49 (m, 1H), 3.45 - 3.33 (m, 1H), 2.25 - 2.14 (m, 1H), 2.10 - 1.94 (m, 1H) ppm.
32	Peak 1 Syn or anti  <i>rel</i> -5-(5-chloro-2-((3-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 5.64 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 2H), 7.48 (dd, <i>J</i> = 8.9, 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.30 - 7.18 (m, 3H), 7.03 (dd, <i>J</i> = 7.7, 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.69 (s, 1H), 5.64 (d, <i>J</i> = 2.6 Hz, 2H), 4.52 - 4.46 (m, 1H), 4.22 - 4.18 (m, 1H), 3.82 - 3.71 (m, 2H), 3.54 - 3.46 (m, 4H), 2.03 - 1.99 (m, 1H), 1.65 - 1.61 (m, 2H) ppm.
33	Peak 2 Anti or syn  <i>rel</i> -5-(5-chloro-2-((3-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 5.64 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.9 Hz, 2H), 7.48 (dd, <i>J</i> = 8.9, 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.17 (m, 3H), 7.03 (dd, <i>J</i> = 7.8, 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.69 (s, 1H), 5.64 (d, <i>J</i> = 2.5 Hz, 2H), 4.51 - 4.47 (m, 1H), 4.22 - 4.18 (m, 1H), 3.82 - 3.75 (m, 2H), 3.54 - 3.46 (m, 4H), 2.04 - 1.98 (m, 1H), 1.66 - 1.60 (m, 2H) ppm.

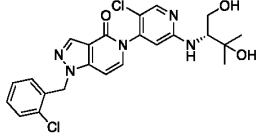
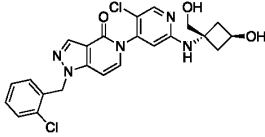
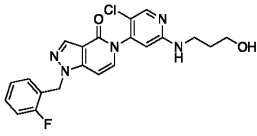
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			mL/min); rt = 8.73 min		
34	 5-(5-chloro-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS m/z calc. 499.118, found 500.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.10 (s, 1H), 7.52 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 - 7.31 (m, 2H), 7.09 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.91 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 5.67 (d, <i>J</i> = 2.2 Hz, 2H), 4.80 (t, <i>J</i> = 5.6 Hz, 1H), 3.74 (dd, <i>J</i> = 10.7, 5.5 Hz, 1H), 3.67 - 3.61 (m, 3H), 3.60 - 3.52 (m, 2H), 2.19 (d, <i>J</i> = 13.8 Hz, 1H), 2.10 (d, <i>J</i> = 13.9 Hz, 1H), 1.71 - 1.65 (m, 2H) ppm.
35	 <i>rac</i>-5-(5-chloro-2-((1-cyclopropyl-2-hydroxypropyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS m/z calc. 467.152, found 468.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (dd, <i>J</i> = 3.0, 0.8 Hz, 1H), 8.07 (d, <i>J</i> = 7.5 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.19 (m, 3H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.85 (t, <i>J</i> = 7.8 Hz, 0.8H), 6.75 (d, <i>J</i> = 9.0 Hz, 0.2H), 6.70 (d, <i>J</i> = 1.8 Hz, 0.2H), 6.66 (d, <i>J</i> = 2.2 Hz, 0.8H), 5.64 (d, <i>J</i> = 3.0 Hz, 2H), 4.73 - 4.63 (m, 1H), 3.80 (ddt, <i>J</i> = 16.2, 10.9, 5.7 Hz, 1H), 3.45 (s, 1H), 1.22 - 1.00 (m, 4H), 0.54 - 0.40 (m, 1H), 0.37 - 0.30 (m, 1H), 0.29 - 0.18 (m, 2H) ppm.
36	 <i>rel</i>-(<i>S</i>[*])-6-((<i>R</i>)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-	S2		ESI-MS m/z calc. 512.138, found 513.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (dd, <i>J</i> = 7.3, 6.4 Hz, 2H), 8.09 (d, <i>J</i> = 4.1 Hz, 0.2H), 8.00 - 7.92 (m, 0.8H), 7.52 - 7.45 (m, 1H), 7.40 (tdd, <i>J</i> = 7.5, 5.4, 1.9 Hz, 1H), 7.32 - 7.18 (m, 3H), 7.13 - 7.07 (m, 0.2H), 7.00 (t, <i>J</i> = 7.4 Hz, 0.8H),

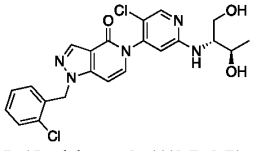
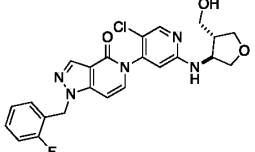
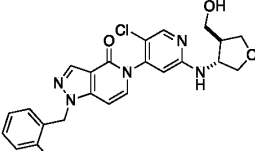
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	yl)amino)-2-hydroxyethyl)morpholin-3-one				6.93 (d, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 1.3$ Hz, 0.7H), 6.68 (d, $J = 1.7$ Hz, 0.3H), 5.64 (d, $J = 3.4$ Hz, 2H), 4.91 - 4.78 (m, 1H), 4.17 (s, 1H), 4.12 - 3.93 (m, 2H), 3.87 - 3.77 (m, 1H), 3.64 (d, $J = 9.0$ Hz, 1H), 3.60 - 3.51 (m, 1H), 3.47 - 3.34 (m, 1H), 3.29 - 3.18 (m, 1H) ppm.
37	 (S)-5-(5-chloro-2-(((5-oxopyrrolidin-3-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS m/z calc. 482.102, found 483.2 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.23 (d, $J = 0.9$ Hz, 1H), 8.16 (s, 1H), 7.49 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.38 - 7.29 (m, 3H), 7.08 (dd, $J = 7.6, 1.8$ Hz, 1H), 6.83 (dd, $J = 7.5, 0.9$ Hz, 1H), 6.64 (s, 1H), 5.71 (d, $J = 3.7$ Hz, 2H), 3.54 (dd, $J = 10.1, 7.8$ Hz, 1H), 3.48 - 3.43 (m, 2H), 3.22 (dd, $J = 10.2, 5.3$ Hz, 1H), 2.86 (dp, $J = 14.3, 7.3$ Hz, 1H), 2.49 (ddd, $J = 17.1, 8.9, 2.5$ Hz, 1H), 2.19 (dd, $J = 17.1, 6.3$ Hz, 1H) ppm; exchangeable H not observed.
38	 (R)-5-(5-chloro-2-(((5-oxopyrrolidin-3-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS m/z calc. 482.102, found 483.2 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.23 (d, $J = 0.8$ Hz, 1H), 8.16 (s, 1H), 7.49 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.38 - 7.28 (m, 3H), 7.08 (dd, $J = 7.6, 1.8$ Hz, 1H), 6.83 (dd, $J = 7.5, 0.9$ Hz, 1H), 6.64 (d, $J = 0.5$ Hz, 1H), 5.71 (d, $J = 3.7$ Hz, 2H), 3.54 (dd, $J = 10.1, 7.9$ Hz, 1H), 3.48 - 3.42 (m, 2H), 3.22 (dd, $J = 10.2, 5.3$ Hz, 1H), 2.92 - 2.81 (m, $J = 7.1$ Hz, 1H), 2.49 (ddd, $J = 17.0, 8.8, 2.5$ Hz, 1H), 2.18 (dd, $J = 17.1, 6.3$ Hz, 1H) ppm;

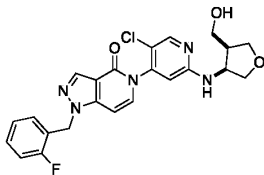
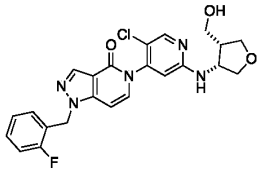
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					exchangeable H not observed.
39	Peak 1  <i>rel</i> -5-(5-chloro-2-(((3 <i>R</i> ,4 <i>S</i>)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S1	Chiralcel® OJ column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 33% 1:1 MeOH: ^{<i>i</i>} Pr OH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 10 mL/min); rt = 4.08 min	ESI-MS <i>m/z</i> calc. 485.102, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.22 - 8.15 (m, 2H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.46 (dd, <i>J</i> = 7.5, 1.3 Hz, 1H), 7.41 - 7.28 (m, 3H), 7.09 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.90 (dt, <i>J</i> = 7.6, 1.0 Hz, 1H), 6.62 (d, <i>J</i> = 1.1 Hz, 1H), 5.73 - 5.62 (m, 2H), 4.80 - 4.77 (m, 1H), 4.13 - 4.09 (m, 1H), 3.97 - 3.90 (m, 2H), 3.58 - 3.45 (m, 2H), 3.44 - 3.39 (m, 1H), 2.33 - 2.22 (m, 1H) ppm; exchangeable H not observed.
40	Peak 2  <i>rel</i> -5-(5-chloro-2-(((3 <i>S</i> ,4 <i>R</i>)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S1	Chiralcel® OJ column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 33% 1:1 MeOH: ^{<i>i</i>} Pr OH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 10 mL/min); rt = 4.82 min	ESI-MS <i>m/z</i> calc. 485.102, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.18 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.46 (dd, <i>J</i> = 7.5, 1.3 Hz, 1H), 7.41 - 7.28 (m, 3H), 7.09 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.90 (dt, <i>J</i> = 7.5, 1.0 Hz, 1H), 6.62 (d, <i>J</i> = 1.1 Hz, 1H), 5.73 - 5.62 (m, 2H), 4.80 - 4.77 (m, 1H), 4.13 - 4.08 (m, 1H), 3.97 - 3.90 (m, 2H), 3.58 - 3.45 (m, 2H), 3.44 - 3.37 (m, 1H), 2.31 - 2.23 (m, 1H) ppm; exchangeable H not observed.

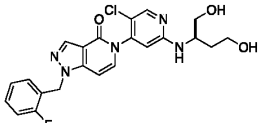
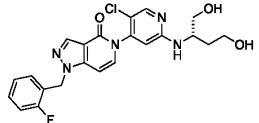
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
41	 <i>rac</i>-5-(5-chloro-2-((3,4-dihydroxybutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 473.102, found 474.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.9 Hz, 1H), 8.15 (s, 1H), 7.51 (dd, <i>J</i> = 7.8, 1.4 Hz, 1H), 7.45 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.08 (dd, <i>J</i> = 7.6, 1.9 Hz, 1H), 6.98 (t, <i>J</i> = 5.5 Hz, 1H), 6.92 - 6.87 (m, 1H), 6.58 (s, 1H), 5.73 - 5.61 (m, 2H), 4.55 - 4.46 (m, 2H), 3.55 - 3.49 (m, 1H), 3.39 - 3.35 (m, 1H), 3.29 - 3.22 (m, 1H), 1.78 - 1.71 (m, 1H), 1.50 - 1.42 (m, 1H) ppm; exchangeable H not observed.
42	Peak 1  <i>rel</i>-5-(5-chloro-2-(((1<i>S</i>,2<i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 40% 1:1 MeOH:Pr OH (supplemented with 20 mM ammonia), 60% CO ₂ ; Flow rate 100 mL/min); rt = 4.91 min	ESI-MS <i>m/z</i> calc. 455.092, found 456.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.15 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.44 (dd, <i>J</i> = 7.5, 3.7 Hz, 1H), 7.40 - 7.30 (m, 3H), 7.08 (dd, <i>J</i> = 7.3, 1.9 Hz, 1H), 6.90 (dd, <i>J</i> = 7.5, 0.8 Hz, 1H), 6.58 (s, 1H), 5.73 - 5.61 (m, 2H), 5.30 - 5.26 (m, 1H), 4.01 - 3.97 (m, 1H), 3.91 - 3.82 (m, 1H), 2.04 - 1.92 (m, 2H), 1.48 - 1.36 (m, 1H), 1.27 - 1.10 (m, 1H) ppm.
43	Peak 2  <i>rel</i>-5-(5-chloro-2-(((1<i>R</i>,2<i>R</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc.	ESI-MS <i>m/z</i> calc. 455.092, found 456.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.15 (s, 1H), 7.52 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.44 (dd, <i>J</i> = 7.5, 3.6 Hz, 1H), 7.40 - 7.30 (m, 3H), 7.08 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.90 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.58 (s,

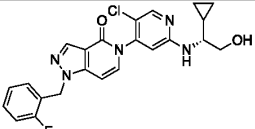
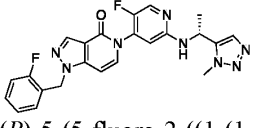
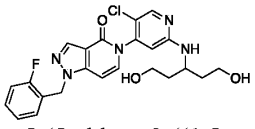
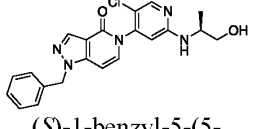
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		(Mobile phase: 40% 1:1 MeOH: ⁱ Pr OH (supplemented with 20 mM ammonia), 60% CO ₂ ; Flow rate 100 mL/min); rt = 5.87 min		¹ H), 5.73 - 5.61 (m, 2H), 4.01 - 3.97 (m, 1H), 3.87 (q, <i>J</i> = 7.8 Hz, 1H), 2.03 - 1.94 (m, 2H), 1.48 - 1.36 (m, 1H), 1.23 - 1.19 (m, 1H) ppm; exchangeable H not observed.
44	 (<i>S</i>)-2-((5-(5-chloro-2-((1-hydroxypropan-2-yl)amino)pyridin-4-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)benzonitrile	SB1		ESI-MS <i>m/z</i> calc. 434.126, found 435.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 8.14 (s, 1H), 7.88 (dd, <i>J</i> = 7.8, 1.3 Hz, 1H), 7.71 (td, <i>J</i> = 7.7, 1.4 Hz, 1H), 7.59 - 7.50 (m, 1H), 7.40 (d, <i>J</i> = 7.5 Hz, 1H), 7.33 (d, <i>J</i> = 7.9 Hz, 1H), 6.89 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.63 (s, 1H), 6.52 (d, <i>J</i> = 7.8 Hz, 1H), 5.76 (s, 2H), 4.47 (s, 1H), 3.96 (hept, <i>J</i> = 6.3 Hz, 1H), 3.56 - 3.47 (m, 1H), 3.42 - 3.36 (m, 1H), 1.17 (d, <i>J</i> = 6.5 Hz, 3H) ppm.
45	 5-(5-chloro-2-(((1<i>s</i>,3<i>s</i>)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 8.10 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.44 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 - 7.29 (m, 2H), 7.17 (s, 1H), 7.09 (dd, <i>J</i> = 7.4, 1.9 Hz, 1H), 6.89 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.52 (s, 1H), 5.69 (d, <i>J</i> = 15.8 Hz, 1H), 5.65 (d, <i>J</i> = 15.8 Hz, 1H), 4.97 (s, 1H), 4.84 (s, 1H), 4.00 - 3.91 (m, 1H), 3.58 (d, <i>J</i> = 10.8 Hz, 1H), 3.51 (d, <i>J</i> = 10.8 Hz, 1H), 2.65 - 2.56 (m, 2H), 1.94 - 1.86 (m, 2H) ppm.

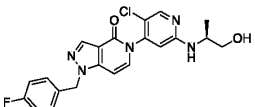
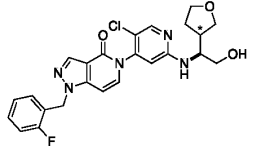
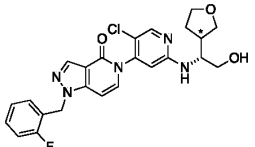
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
46	 (<i>R</i>)-5-(5-chloro-2-((1,3-dihydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 487.118, found 488.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (s, 1H), 8.10 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.45 (dd, <i>J</i> = 16.5, 7.5 Hz, 1H), 7.42 - 7.29 (m, 2H), 7.11 - 7.06 (m, 1H), 6.90 (d, <i>J</i> = 7.5 Hz, 1H), 6.75 (s, 1H), 6.71 - 6.61 (m, 1H), 5.77 - 5.60 (m, 2H), 4.60 (d, <i>J</i> = 32.6 Hz, 1H), 4.51 (d, <i>J</i> = 15.3 Hz, 1H), 3.98 (s, 1H), 3.83 - 3.67 (m, 1H), 3.62 - 3.46 (m, 1H), 1.17 (d, <i>J</i> = 5.1 Hz, 3H), 1.11 (d, <i>J</i> = 5.9 Hz, 3H) ppm.
47	 5-(5-chloro-2-(((1<i>r</i>,3<i>r</i>)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.13 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.38 (td, <i>J</i> = 7.6, 2.0 Hz, 1H), 7.35 - 7.30 (m, 1H), 7.09 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 7.04 (s, 1H), 6.89 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.56 (s, 1H), 5.72 - 5.66 (m, 1H), 5.69 - 5.62 (m, 1H), 4.94 (d, <i>J</i> = 5.9 Hz, 1H), 4.80 (t, <i>J</i> = 5.7 Hz, 1H), 4.20 - 4.14 (m, 1H), 3.63 (dd, <i>J</i> = 10.7, 5.6 Hz, 1H), 3.56 (dd, <i>J</i> = 10.7, 5.6 Hz, 1H), 2.42 - 2.34 (m, 2H), 2.04 - 1.95 (m, 2H) ppm.
48	 5-(5-chloro-2-((3-hydroxypropyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 427.121, found 426.1 (M-1) ⁻ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.12 (m, 2H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.43 - 7.35 (m, 1H), 7.30 - 7.16 (m, 4H), 7.00 (t, <i>J</i> = 5.6 Hz, 1H), 6.91 (dt, <i>J</i> = 7.6, 0.6 Hz, 1H), 6.57 (s, 1H), 5.63 (d, <i>J</i> = 5.2 Hz, 2H), 4.46 (t, <i>J</i> = 5.2 Hz, 1H), 3.52 - 3.44 (m, 2H), 3.30 - 3.27 (m, 1H), 1.73 - 1.64 (m, 2H) ppm.

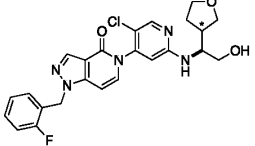
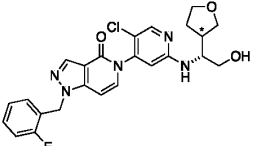
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
49	 5-(5-chloro-2-(((2R,3R)-1,3-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 473.102, found 474.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.11 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.46 (dd, <i>J</i> = 10.9, 7.5 Hz, 1H), 7.36 (dtd, <i>J</i> = 17.5, 7.5, 1.7 Hz, 2H), 7.12 - 7.06 (m, 1H), 6.89 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.76 (d, <i>J</i> = 1.2 Hz, 1H), 6.59 (d, <i>J</i> = 8.3 Hz, 1H), 5.73 - 5.62 (m, 2H), 4.68 (dd, <i>J</i> = 7.2, 4.6 Hz, 1H), 4.65 - 4.58 (m, 1H), 4.03 - 3.99 (m, 1H), 3.94 - 3.78 (m, 1H), 3.57 - 3.39 (m, 2H), 1.08 (t, <i>J</i> = 6.1 Hz, 3H) ppm.
50	Peak 1  <i>rel</i>-5-(5-chloro-2-(((3S,4R)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralcel [®] OJ column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 17% MeOH (supplemented with 20 mM ammonia), 83% CO ₂ ; Flow rate 100 mL/min); rt = 5.30 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.14 (m, 2H), 7.47 (dd, <i>J</i> = 7.5, 1.3 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.33 - 7.17 (m, 4H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.61 (d, <i>J</i> = 1.1 Hz, 1H), 5.63 (d, <i>J</i> = 3.7 Hz, 2H), 4.80 - 4.76 (m, 1H), 4.13 - 4.09 (m, 1H), 3.97 - 3.89 (m, 2H), 3.61 - 3.45 (m, 3H), 3.44 - 3.37 (m, 1H), 2.33 - 2.22 (m, 1H) ppm.
51	Peak 2  <i>rel</i>-5-(5-chloro-2-(((3R,4S)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralpak [®] OJ column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 17% MeOH (supplemented with 20 mM ammonia), 83% CO ₂ ; Flow rate 100 mL/min); rt = 5.30 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.14 (m, 2H), 7.47 (dd, <i>J</i> = 7.5, 1.3 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.33 - 7.17 (m, 4H), 6.92 (d, <i>J</i> = 7.4 Hz, 1H), 6.61 (d, <i>J</i> = 1.0 Hz, 1H), 5.63 (d, <i>J</i> = 3.7 Hz, 2H), 4.80 - 4.76 (m, 1H), 4.13 - 4.09 (m, 1H), 3.97 - 3.89 (m, 2H), 3.58

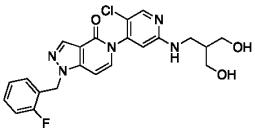
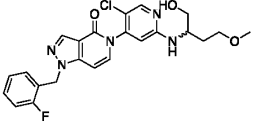
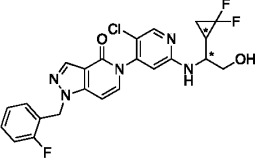
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	drofuran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		MeOH (supplemented with 20 mM ammonia), 83% CO ₂ ; Flow rate 100 mL/min); rt = 6.59 min		- 3.45 (m, 3H), 3.41 (s, 1H), 2.33 - 2.22 (m, 1H) ppm.
52	Peak 1  <i>rel</i> -5-(5-chloro-2-(((3 <i>S</i> ,4 <i>S</i>)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 32% MeOH (supplemented with 20 mM ammonia), 68% CO ₂ ; Flow rate 100 mL/min); rt = 5.63 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 1.7 Hz, 1H), 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 7.47 (dd, <i>J</i> = 12.1, 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.18 (m, 3H), 7.10 (d, <i>J</i> = 7.8 Hz, 1H), 6.92 (dt, <i>J</i> = 7.6, 0.7 Hz, 1H), 6.68 (d, <i>J</i> = 1.1 Hz, 1H), 5.64 (d, <i>J</i> = 2.8 Hz, 2H), 4.63 - 4.47 (m, 2H), 3.96 - 3.85 (m, 2H), 3.67 (dd, <i>J</i> = 8.4, 7.6 Hz, 1H), 3.63 - 3.50 (m, 2H), 3.44 - 3.35 (m, 1H), 2.59 - 2.51 (m, 1H) ppm.
53	Peak 2  <i>rel</i> -5-(5-chloro-2-(((3 <i>R</i> ,4 <i>R</i>)-4-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 32% MeOH (supplemented with 20 mM ammonia), 68% CO ₂ ; Flow rate 100 mL/min)	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 1.7 Hz, 1H), 8.17 (d, <i>J</i> = 0.9 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.15 (m, 3H), 7.10 (d, <i>J</i> = 7.8 Hz, 1H), 6.95 - 6.90 (m, 1H), 6.68 (d, <i>J</i> = 1.1 Hz, 1H), 5.64 (d, <i>J</i> = 2.8 Hz, 2H), 4.65 - 4.46 (m, 2H), 3.96 - 3.85 (m, 2H), 3.67 (dd, <i>J</i> = 8.5, 7.6 Hz, 1H), 3.63 - 3.49 (m, 2H), 3.40 (t, <i>J</i> = 9.6 Hz, 1H), 2.59 - 2.50 (m, 1H) ppm.

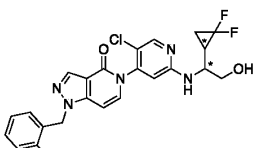
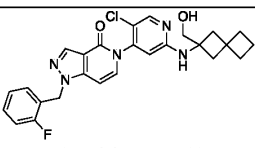
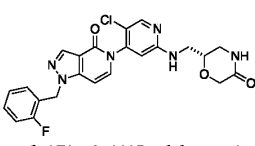
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			mL/min); rt = 7.55 min		
54	Peak 1  <i>rel</i>-(<i>R</i>)-5-(5-chloro-2-((1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Chiral Art Amylose-SA column, 5 μm particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 40% 1:1 <i>i</i>PrOH:MeCN (supplemented with 20 mM ammonia), 60% CO₂; Flow rate 100 mL/min); rt = 3.72 min	ESI-MS <i>m/z</i> calc. 457.132, found 458.3 (M+1)⁺.	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.50 - 7.34 (m, 2H), 7.32 - 7.15 (m, 3H), 6.91 (d, <i>J</i> = 7.5 Hz, 1H), 6.80 (t, <i>J</i> = 7.4 Hz, 1H), 6.61 (s, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 2H), 4.75 - 4.64 (m, 1H), 4.49 - 4.39 (m, 1H), 4.00 - 3.95 (m, 1H), 3.53 - 3.33 (m, 2H), 1.81 (s, 1H), 1.65 - 1.54 (m, 1H) ppm; exchangeable H not observed.
55	Peak 2  <i>rel</i>-(<i>S</i>)-5-(5-chloro-2-((1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Chiral Art Amylose-SA column, 5 μm particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 40% 1:1 <i>i</i>PrOH:MeCN (supplemented with 20 mM ammonia), 60% CO₂; Flow rate 100 mL/min); rt = 3.72 min	ESI-MS <i>m/z</i> calc. 457.132, found 458.3 (M+1)⁺.	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.50 - 7.34 (m, 2H), 7.32 - 7.15 (m, 3H), 6.91 (d, <i>J</i> = 7.5 Hz, 1H), 6.80 (t, <i>J</i> = 7.3 Hz, 1H), 6.61 (s, 1H), 5.66 - 5.60 (m, 2H), 4.75 - 4.66 (m, 1H), 4.49 - 4.39 (m, 1H), 4.07 - 3.89 (m, 1H), 3.56 - 3.34 (m, 3H), 1.85 - 1.76 (m, 1H), 1.65 - 1.52 (m, 1H) ppm; exchangeable H not observed.

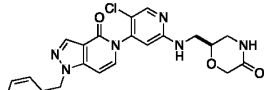
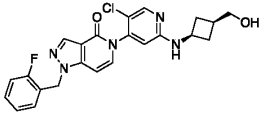
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
56	 (R)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 453.137, found 454.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (dd, <i>J</i> = 2.0, 0.8 Hz, 1H), 8.08 (s, 1H), 7.51 - 7.35 (m, 3H), 7.31 - 7.17 (m, 4H), 6.98 - 6.85 (m, 2H), 6.62 (d, <i>J</i> = 1.1 Hz, 1H), 5.63 (d, <i>J</i> = 3.9 Hz, 2H), 4.69 (dt, <i>J</i> = 18.8, 5.3 Hz, 1H), 3.60 - 3.45 (m, 2H), 1.00 (m, 1H), 0.50 - 0.19 (m, 4H) ppm.
57	 (R)-5-(5-fluoro-2-((1-(1-methyl-1H-1,2,3-triazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 462.173, found 463.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.15 (d, <i>J</i> = 1.9 Hz, 1H), 7.64 (d, <i>J</i> = 0.6 Hz, 1H), 7.57 (dd, <i>J</i> = 7.6, 0.6 Hz, 1H), 7.39 (dddd, <i>J</i> = 8.3, 7.2, 5.4, 2.0 Hz, 1H), 7.27 - 7.17 (m, 4H), 6.95 (dt, <i>J</i> = 7.7, 0.6 Hz, 1H), 6.60 (d, <i>J</i> = 5.0 Hz, 1H), 5.64 (s, 2H), 5.28 (p, <i>J</i> = 7.0 Hz, 1H), 4.01 (s, 3H), 1.51 (d, <i>J</i> = 6.9 Hz, 3H) ppm.
58	 5-(5-chloro-2-((1,5-dihydroxypentan-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 471.147, found 472.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.30 - 7.16 (m, 3H), 6.94 - 6.88 (m, 1H), 6.82 (d, <i>J</i> = 8.4 Hz, 1H), 6.57 (s, 1H), 5.63 (d, <i>J</i> = 2.8 Hz, 2H), 4.40 (dt, <i>J</i> = 10.1, 5.1 Hz, 2H), 4.07 - 4.03 (m, 1H), 3.46 (q, <i>J</i> = 5.8 Hz, 4H), 1.71 - 1.61 (m, 4H) ppm.
59	 (S)-1-benzyl-5-(5-chloro-2-((1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 409.131, found 410.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.14 (s, 1H), 7.44 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.33 - 7.28 (m, 3H), 6.93 (dd, <i>J</i> = 7.6, 0.8 Hz, 1H), 6.81 (t, <i>J</i> = 7.8 Hz, 1H), 6.59 (s, 1H), 5.62 (d, <i>J</i> = 15.5 Hz, 1H), 5.57 (d, <i>J</i> = 15.5

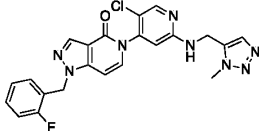
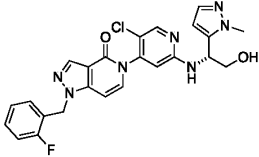
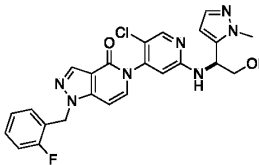
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				Hz, 1H), 4.73 (dt, <i>J</i> = 11.0, 5.5 Hz, 1H), 3.94 (d, <i>J</i> = 9.7 Hz, 1H), 3.58 - 3.41 (m, 1H), 1.14 (t, <i>J</i> = 6.4 Hz, 3H) ppm; exchangeable H not observed.
60	 (<i>S</i>)-5-(5-chloro-2-((1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(4-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 427.121, found 428.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.14 (s, 1H), 7.45 (d, <i>J</i> = 7.4 Hz, 1H), 7.42 - 7.30 (m, 2H), 7.25 - 7.14 (m, 2H), 7.07 - 6.92 (m, 1H), 6.82 (t, <i>J</i> = 7.8 Hz, 1H), 6.59 (s, 1H), 5.61 (d, <i>J</i> = 15.8 Hz, 1H), 5.56 (d, <i>J</i> = 15.8 Hz, 1H), 4.73 (dt, <i>J</i> = 11.0, 5.5 Hz, 1H), 4.00 - 3.84 (m, 1H), 3.48 (dt, <i>J</i> = 10.3, 5.2 Hz, 1H), 1.14 (t, <i>J</i> = 6.4 Hz, 3H) ppm.
61	Peak 1  <i>rel</i>-5-(5-chloro-2-(((1<i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB-3 column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 5.16 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.9 Hz, 1H), 8.12 (s, 1H), 7.47 (dd, <i>J</i> = 15.5, 7.5 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 6.99 - 6.89 (m, 2H), 6.64 (d, <i>J</i> = 1.3 Hz, 1H), 5.63 (d, <i>J</i> = 2.9 Hz, 2H), 4.80 - 4.65 (m, 1H), 4.06 - 3.92 (m, 1H), 3.84 - 3.76 (m, 1H), 3.75 - 3.66 (m, 1H), 3.64 - 3.55 (m, 1H), 3.47 - 3.36 (m, 3H), 2.51 - 2.42 (m, 1H), 2.00 - 1.88 (m, 1H), 1.72 - 1.59 (m, 1H) ppm.
62	Peak 2 	S2	Chiralpak [®] IB-3 column, 5 μm particle size, 25 cm x 20 mm from	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 8.12 (s, 1H), 7.47 (dd, <i>J</i> = 18.3, 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.16 (m, 3H), 6.96 - 6.89 (m, 2H), 6.63 (s, 1H),

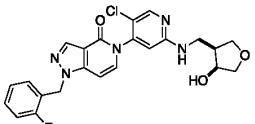
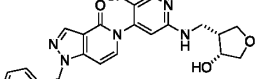
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rel</i> -5-(5-chloro-2-(((1 <i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 6.71 min		5.63 (d, <i>J</i> = 2.9 Hz, 2H), 4.76 - 4.72 (m, 1H), 4.00 - 3.96 (m, 1H), 3.82 - 3.70 (m, 2H), 3.67 - 3.58 (m, 1H), 3.56 - 3.40 (m, 3H), 2.02 - 1.92 (m, 1H), 1.69 - 1.57 (m, 1H) ppm; exchangeable H not observed.
63	Peak 3  <i>rel</i> -5-(5-chloro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB-3 column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 8.29 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 8.12 (s, 1H), 7.47 (dd, <i>J</i> = 18.2, 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.17 (m, 3H), 6.96 - 6.88 (m, 2H), 6.63 (s, 1H), 5.63 (d, <i>J</i> = 2.9 Hz, 2H), 4.77 - 4.73 (m, 1H), 4.00 - 3.96 (m, 1H), 3.82 - 3.70 (m, 2H), 3.67 - 3.58 (m, 1H), 3.58 - 3.39 (m, 3H), 2.02 - 1.92 (m, 1H), 1.69 - 1.57 (m, 1H) ppm; exchangeable H not observed.
64	Peak 4  <i>rel</i> -5-(5-chloro-2-(((1 <i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB-3 column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25% MeOH (supplemented with 20 mM ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 8.29 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.47 (dd, <i>J</i> = 15.5, 7.5 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.17 (m, 3H), 6.96 (t, <i>J</i> = 8.7 Hz, 1H), 6.93 - 6.89 (m, 1H), 6.64 (d, <i>J</i> = 1.3 Hz, 1H), 5.63 (d, <i>J</i> = 2.9 Hz, 2H), 4.78 - 4.74 (m, 1H), 4.04 - 3.92 (m, 1H), 3.84 - 3.74 (m, 1H), 3.75 - 3.66 (m, 1H), 3.64 - 3.55 (m, 1H), 3.50 - 3.35 (m, 3H), 2.51

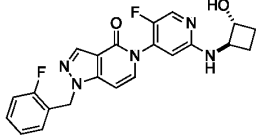
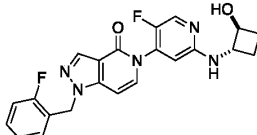
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one		ammonia), 75% CO ₂ ; Flow rate 100 mL/min); rt = 9.59 min		- 2.42 (m, 1H), 2.00 - 1.88 (m, 1H), 1.72 - 1.59 (m, 1H) ppm.
65	 5-(5-chloro-2-((3-hydroxymethyl)propyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 457.132, found 458.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.14 (s, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.16 (m, 3H), 6.98 (t, <i>J</i> = 5.8 Hz, 1H), 6.91 (dt, <i>J</i> = 7.6, 0.7 Hz, 1H), 6.61 (s, 1H), 5.63 (d, <i>J</i> = 3.1 Hz, 2H), 4.45 (td, <i>J</i> = 5.3, 1.2 Hz, 2H), 3.52 - 3.38 (m, 4H), 3.26 (t, <i>J</i> = 6.2 Hz, 2H), 1.85 - 1.75 (m, 1H) ppm.
66	 <i>rac</i>-5-(5-chloro-2-((1-hydroxy-4-methoxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 471.147, found 470.2 (M-1) ⁻ .	
67	Peak 1  <i>rel</i>-5-(5-chloro-2-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Chiralcel® OD-H column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 65% MeOH (supplemented with 20 mM ammonia), 35% CO ₂ ; Flow rate	ESI-MS <i>m/z</i> calc. 489.118, found 490.3 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.17 (s, 1H), 8.13 (s, 1H), 7.51 - 7.35 (m, 2H), 7.29 - 7.08 (m, 4H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.66 (d, <i>J</i> = 1.5 Hz, 1H), 5.63 (d, <i>J</i> = 2.7 Hz, 2H), 5.02 - 4.97 (m, 1H), 3.97 - 3.92 (m, 1H), 3.57 - 3.52 (m, 2H), 2.00 - 1.84 (m, 1H), 1.59 (s, 1H), 1.41 - 1.36 (m, 1H) ppm.

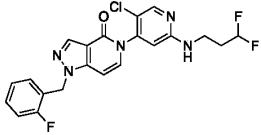
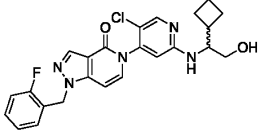
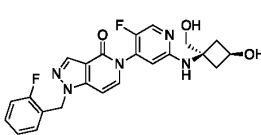
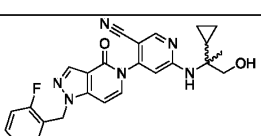
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			10 mL/min); rt = 2.75 min		
68	Peak 2  <i>rel</i> -5-(5-chloro-2-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralcel® OD-H column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 65% MeOH (supplemented with 20 mM ammonia), 35% CO ₂ ; Flow rate 10 mL/min); rt = 3.89 min	ESI-MS <i>m/z</i> calc. 489.118, found 490.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.14 (s, 1H), 7.47 (dd, <i>J</i> = 12.3, 7.5 Hz, 1H), 7.45 - 7.35 (m, 1H), 7.32 - 7.14 (m, 4H), 6.93 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 (d, <i>J</i> = 1.9 Hz, 1H), 5.64 (d, <i>J</i> = 4.1 Hz, 2H), 5.03 - 4.99 (m, 1H), 3.97 - 3.93 (m, 1H), 3.57 - 3.50 (m, 2H), 2.00 - 1.87 (m, 1H), 1.65 - 1.54 (m, 1H), 1.47 - 1.32 (m, 1H) ppm.
69	 5-(5-chloro-2-((2-(hydroxymethyl)spiro[3.3]heptan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 493.168, found 494.3 (M+1) ⁺ .	
70	Peak 1  <i>rel</i> -(<i>R</i>)-6-(((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)methyl)morpholin-3-one	S2	Chiralcel® OJ column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 40% 1:1 MeOH:Me	ESI-MS <i>m/z</i> calc. 482.127, found 483.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.18 (s, 1H), 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 7.98 (s, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.0 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.31 - 7.25 (m, 1H), 7.22 (td, <i>J</i> = 7.4, 6.2 Hz, 2H), 6.93 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 (s, 1H), 5.64 (d, <i>J</i> = 3.4 Hz, 2H), 4.11 - 3.97 (m, 2H), 3.86 (s, 1H), 3.49 (s, 1H), 3.44 (s, 1H), 3.25 (d, <i>J</i> = 13.7

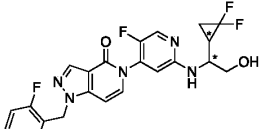
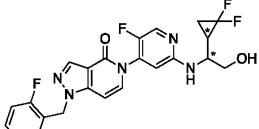
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			CN (supplemented with 0.2% DMIPA), 60% CO ₂ ; Flow rate 10 mL/min; rt = 3.43 min		Hz, 1H), 3.13 (t, <i>J</i> = 10.4 Hz, 1H) ppm; exchangeable H not observed.
71	Peak 2  <i>rel</i> -(<i>S</i>)-6-(((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)methyl)morpholin-3-one	S2	Chiralcel® OJ column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation (Mobile phase: 40% 1:1 MeOH:MeCN (supplemented with 0.2% DMIPA), 60% CO ₂ ; Flow rate 10 mL/min); rt = 4.32 min	ESI-MS <i>m/z</i> calc. 482.127, found 483.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.18 (s, 1H), 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 7.98 (s, 1H), 7.47 (dd, <i>J</i> = 7.6, 1.0 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.31 - 7.25 (m, 1H), 7.25 - 7.18 (m, 2H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 6.67 (s, 1H), 5.69 - 5.59 (m, 2H), 4.10 - 3.98 (m, 2H), 3.85 (d, <i>J</i> = 5.4 Hz, 1H), 3.46 (d, <i>J</i> = 23.4 Hz, 2H), 3.25 (d, <i>J</i> = 12.6 Hz, 1H), 3.13 (t, <i>J</i> = 11.3 Hz, 1H) ppm.
72	 5-(5-chloro-2-(((1 <i>s</i> ,3 <i>s</i>)-3-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 453.137, found 454.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.20 (d, <i>J</i> = 0.9 Hz, 1H), 8.12 (s, 1H), 7.39 (tdd, <i>J</i> = 7.5, 5.3, 1.8 Hz, 1H), 7.33 (d, <i>J</i> = 7.5 Hz, 1H), 7.27 (td, <i>J</i> = 7.6, 1.8 Hz, 1H), 7.22 - 7.13 (m, 2H), 6.88 (dt, <i>J</i> = 7.5, 0.8 Hz, 1H), 6.56 (s, 1H), 5.65 (d, <i>J</i> = 3.2 Hz, 2H), 4.19 (p, <i>J</i> = 8.1 Hz, 1H), 3.54 (d, <i>J</i> = 6.1 Hz, 2H), 2.52 (dddd, <i>J</i> = 11.6, 9.1, 7.3, 5.4, 2.7 Hz, 2H), 2.29 - 2.18 (m, 1H), 1.69 (q, <i>J</i> = 9.6 Hz, 2H)

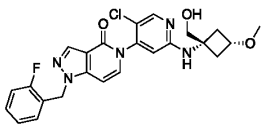
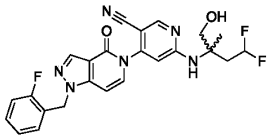
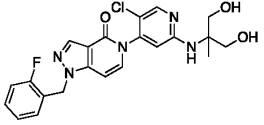
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					ppm; exchangeable H not observed.
73	 5-(5-chloro-2-(((1-methyl-1H-1,2,3-triazol-5-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 464.128, found 465.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.23 (s, 1H), 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 7.59 (s, 1H), 7.55 (t, <i>J</i> = 5.8 Hz, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.16 (m, 3H), 6.95 - 6.90 (m, 1H), 6.69 (s, 1H), 5.69 - 5.58 (m, 2H), 4.71 - 4.51 (m, 2H), 4.03 (s, 3H) ppm.
74	Peak 1  <i>rel</i>-(<i>R</i>)-5-(5-chloro-2-((2-hydroxy-1-(1-methyl-1H-pyrazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 32% MeOH (supplemented with 20 mM ammonia), 68% CO ₂ ; Flow rate 100 mL/min; rt = 4.97 min	ESI-MS <i>m/z</i> calc. 493.143, found 494.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 1.2 Hz, 1H), 8.16 (dd, <i>J</i> = 4.3, 0.8 Hz, 1H), 7.46 (dd, <i>J</i> = 7.5, 2.6 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.32 - 7.16 (m, 4H), 6.92 (dd, <i>J</i> = 7.6, 4.0 Hz, 1H), 6.68 (d, <i>J</i> = 0.9 Hz, 1H), 6.23 (d, <i>J</i> = 1.9 Hz, 1H), 5.63 (d, <i>J</i> = 2.9 Hz, 2H), 5.36 - 5.20 (m, 1H), 5.09 - 5.05 (m, 1H), 3.83 (d, <i>J</i> = 2.3 Hz, 3H), 3.78 - 3.62 (m, 2H) ppm.
75	Peak 2  <i>rel</i>-(<i>S</i>)-5-(5-chloro-2-((2-hydroxy-1-(1-methyl-1H-pyrazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	(<i>R,R</i>)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 32% MeOH (supplemen	ESI-MS <i>m/z</i> calc. 493.143, found 494.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (d, <i>J</i> = 1.2 Hz, 1H), 8.16 (dd, <i>J</i> = 4.3, 0.8 Hz, 1H), 7.46 (dd, <i>J</i> = 7.5, 2.6 Hz, 1H), 7.42 - 7.34 (m, 2H), 7.32 - 7.16 (m, 4H), 6.92 (dd, <i>J</i> = 7.6, 4.0 Hz, 1H), 6.68 (d, <i>J</i> = 1.0 Hz, 1H), 6.23 (d, <i>J</i> = 1.9 Hz, 1H), 5.63 (d, <i>J</i> = 3.0 Hz, 2H), 5.31 - 5.20 (m, 1H), 5.09 - 5.05 (m, 1H), 3.83 (d, <i>J</i> =

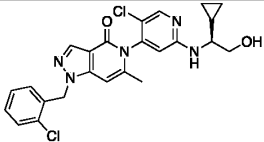
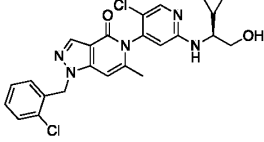
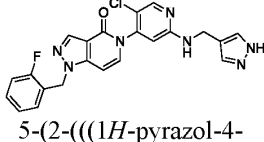
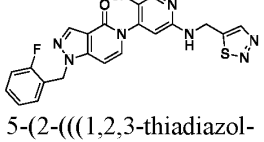
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		ted with 20 mM ammonia), 68% CO ₂ ; Flow rate 100 mL/min); rt = 6.50 min		2.4 Hz, 3H), 3.75 - 3.71 (m, 1H), 3.70 - 3.62 (m, 1H) ppm.
76	Peak 1  <i>rel</i> -5-(5-chloro-2-(((3 <i>S</i> ,4 <i>S</i>)-4-hydroxytetrahydrofuran-3-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Lux TM Cellulose-3 column, 5 µm particle size, 25 cm x 10 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 10 mL/min); rt = 3.68 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (s, 1H), 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.6 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.24 (m, 2H), 7.24 - 7.19 (m, 1H), 7.03 (d, <i>J</i> = 6.3 Hz, 1H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.62 (s, 1H), 5.68 - 5.60 (m, 2H), 5.00 (t, <i>J</i> = 4.7 Hz, 1H), 4.23 (s, 1H), 3.86 - 3.78 (m, 2H), 3.60 (dd, <i>J</i> = 9.3, 1.5 Hz, 1H), 3.51 - 3.41 (m, 2H), 3.37 - 3.32 (m, 1H), 2.41 - 2.34 (m, 1H) ppm.
77	Peak 2  <i>rel</i> -5-(5-chloro-2-(((3 <i>R</i> ,4 <i>R</i>)-4-hydroxytetrahydrofuran-3-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Lux TM Cellulose-3 column, 5 µm particle size, 25 cm x 10 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 10 mL/min); rt = 4.56 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (s, 1H), 8.17 (d, <i>J</i> = 0.9 Hz, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.6 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.3, 5.4, 1.9 Hz, 1H), 7.31 - 7.18 (m, 3H), 7.06 - 7.01 (m, 1H), 6.95 - 6.90 (m, 1H), 6.62 (s, 1H), 5.70 - 5.59 (m, 2H), 5.00 (t, <i>J</i> = 4.7 Hz, 1H), 4.23 (s, 1H), 3.86 - 3.78 (m, 2H), 3.60 (dd, <i>J</i> = 9.3, 1.5 Hz, 1H), 3.51 - 3.41 (m, 2H), 3.34 (d, <i>J</i> = 5.1 Hz, 1H), 2.40 - 2.33 (m, 1H) ppm.

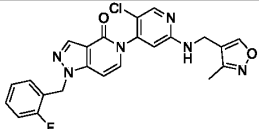
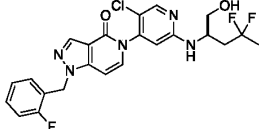
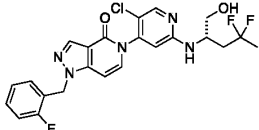
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
78	Peak 1  <i>rel</i> -5-(5-fluoro-2-(((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IG column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 0.2% DMIPA), 70% CO ₂ ; Flow rate 100 mL/min); rt = 5.82 min	ESI-MS <i>m/z</i> calc. 423.151, found 424.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.10 (d, <i>J</i> = 1.8 Hz, 1H), 7.55 (d, <i>J</i> = 7.5 Hz, 1H), 7.39 (tdd, <i>J</i> = 7.4, 5.3, 2.0 Hz, 1H), 7.28 - 7.17 (m, 3H), 7.05 (d, <i>J</i> = 7.4 Hz, 1H), 6.94 (d, <i>J</i> = 7.5 Hz, 1H), 6.54 (d, <i>J</i> = 5.0 Hz, 1H), 5.64 (s, 2H), 3.99 - 3.90 (m, 1H), 3.85 (q, <i>J</i> = 7.8 Hz, 1H), 2.03 - 1.94 (m, 2H), 1.80 - 1.74 (m, 1H), 1.41 (tt, <i>J</i> = 10.5, 8.9 Hz, 1H), 1.25 - 1.15 (m, 1H) ppm.
79	Peak 2  <i>rel</i> -5-(5-fluoro-2-(((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IG column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 0.2% DMIPA), 70% CO ₂ ; Flow rate 100 mL/min); rt = 7.26 min	ESI-MS <i>m/z</i> calc. 423.151, found 424.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.11 (d, <i>J</i> = 1.8 Hz, 1H), 7.56 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.28 - 7.18 (m, 3H), 7.06 (d, <i>J</i> = 7.4 Hz, 1H), 6.95 (d, <i>J</i> = 7.6 Hz, 1H), 6.55 (d, <i>J</i> = 5.0 Hz, 1H), 5.65 (s, 2H), 3.95 (t, <i>J</i> = 8.0 Hz, 1H), 3.86 (q, <i>J</i> = 7.8 Hz, 1H), 2.03 - 1.94 (m, 2H), 1.78 - 1.74 (m, 1H), 1.42 (tt, <i>J</i> = 10.5, 9.0 Hz, 1H), 1.25 - 1.17 (m, 1H) ppm.

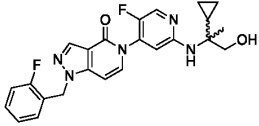
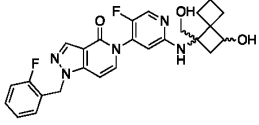
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
80	 5-(5-chloro-2-((3,3-difluoropropyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 447.107, found 448.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (s, 1H), 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.31 - 7.12 (m, 4H), 6.95 - 6.89 (m, 1H), 6.61 (s, 1H), 6.16 (tt, <i>J</i> = 56.6, 4.5 Hz, 1H), 5.69 - 5.58 (m, 2H), 3.46 - 3.38 (m, 2H), 2.19 - 2.04 (m, 2H) ppm.
81	 <i>rac</i>-5-(5-chloro-2-((1-cyclobutyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 467.152, found 468.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.47 (dd, <i>J</i> = 18.2, 7.5 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.18 (m, 3H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.73 (t, <i>J</i> = 8.8 Hz, 1H), 6.65 (d, <i>J</i> = 1.9 Hz, 1H), 5.64 (d, <i>J</i> = 3.1 Hz, 2H), 4.56 (dt, <i>J</i> = 21.3, 5.4 Hz, 1H), 3.98 (s, 1H), 3.45 - 3.36 (m, 2H), 2.57 (q, <i>J</i> = 8.2 Hz, 1H), 1.94 (q, <i>J</i> = 7.5 Hz, 2H), 1.85 - 1.71 (m, 4H) ppm.
82	 5-(5-fluoro-2-(((1s,3s)-3-hydroxy-1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 453.161, found 454.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.06 (d, <i>J</i> = 1.9 Hz, 1H), 7.55 (dd, <i>J</i> = 7.6, 0.6 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.4, 5.4, 1.9 Hz, 1H), 7.28 - 7.23 (m, 2H), 7.23 - 7.17 (m, 1H), 6.96 - 6.92 (m, 1H), 6.89 (s, 1H), 6.50 (d, <i>J</i> = 5.1 Hz, 1H), 5.64 (s, 2H), 4.96 (d, <i>J</i> = 6.3 Hz, 1H), 4.84 (t, <i>J</i> = 5.6 Hz, 1H), 3.97 (h, <i>J</i> = 7.1 Hz, 1H), 3.54 (d, <i>J</i> = 5.5 Hz, 2H), 2.60 (ddd, <i>J</i> = 9.9, 7.2, 2.8 Hz, 2H), 1.94 - 1.84 (m, 2H) ppm.
83		S2		ESI-MS <i>m/z</i> calc. 458.187, found	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.49 (s, 1H), 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H),

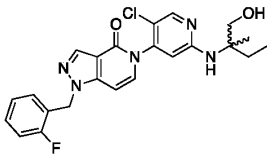
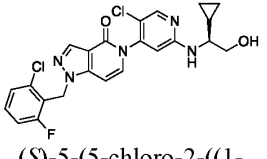
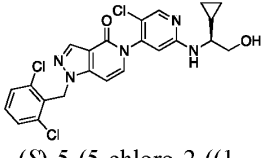
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rac</i> -6-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)nicotinonitrile			459.2 (M+1) ⁺ .	7.44 - 7.35 (m, 1H), 7.33 - 7.17 (m, 4H), 6.97 (dt, <i>J</i> = 7.7, 0.6 Hz, 1H), 6.73 (s, 1H), 5.65 (s, 2H), 4.91 (t, <i>J</i> = 5.7 Hz, 1H), 3.80 - 3.76 (m, 1H), 3.69 - 3.65 (m, 1H), 1.51 (p, <i>J</i> = 7.6 Hz, 1H), 1.04 (s, 3H), 0.47 - 0.31 (m, 4H) ppm.
84	Peak 1  <i>rel</i> -5-(2-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)-5-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 23% MeOH (supplemented with 20 mM ammonia), 77% CO ₂ ; Flow rate 2 mL/min); rt = 4.82 min	ESI-MS <i>m/z</i> calc. 473.147, found 474.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.9 Hz, 1H), 8.08 (d, <i>J</i> = 1.9 Hz, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.25 (tdd, <i>J</i> = 9.6, 7.6, 1.5 Hz, 2H), 7.20 (td, <i>J</i> = 7.4, 1.2 Hz, 1H), 6.95 (d, <i>J</i> = 7.6 Hz, 1H), 6.90 (d, <i>J</i> = 8.4 Hz, 1H), 6.63 (d, <i>J</i> = 5.0 Hz, 1H), 5.65 (s, 2H), 4.97 (s, 1H), 3.91 (s, 1H), 3.54 (t, <i>J</i> = 4.0 Hz, 2H), 1.92 (dtd, <i>J</i> = 14.6, 10.9, 7.8 Hz, 1H), 1.58 (dh, <i>J</i> = 11.9, 3.8 Hz, 1H), 1.45 - 1.33 (m, 1H) ppm.
85	Peak 2  <i>rel</i> -5-(2-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)-5-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 23% MeOH (supplemented with 20 mM ammonia), 77% CO ₂ ; Flow rate 2 mL/min); rt = 8.09 min	ESI-MS <i>m/z</i> calc. 473.147, found 474.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.40 (tdd, <i>J</i> = 7.6, 5.4, 1.9 Hz, 1H), 7.28 - 7.22 (m, 2H), 7.20 (td, <i>J</i> = 7.4, 1.2 Hz, 1H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.91 (d, <i>J</i> = 8.5 Hz, 1H), 6.64 (d, <i>J</i> = 5.0 Hz, 1H), 5.65 (s, 2H), 4.99 (s, 1H), 3.91 (s, 1H), 3.54 (dd, <i>J</i> = 5.0, 2.9 Hz, 2H), 1.97 - 1.87 (m, 1H), 1.57 (dq, <i>J</i> = 12.2, 4.8 Hz, 1H), 1.43 - 1.35 (m, 1H) ppm.

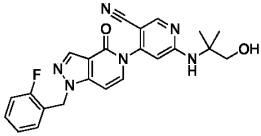
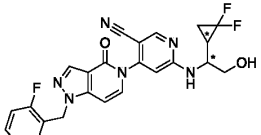
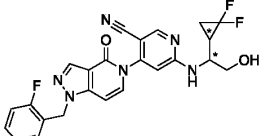
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
86	 5-(5-chloro-2-(((1s,3s)-1-(hydroxymethyl)-3-methoxycyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 483.147, found 484.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.9 Hz, 1H), 8.12 (s, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.24 (m, 2H), 7.24 - 7.18 (m, 2H), 6.95 - 6.90 (m, 1H), 6.53 (s, 1H), 5.64 (d, <i>J</i> = 3.8 Hz, 2H), 4.92 (t, <i>J</i> = 5.6 Hz, 1H), 3.74 (p, <i>J</i> = 6.8 Hz, 1H), 3.62 (dd, <i>J</i> = 10.8, 5.2 Hz, 1H), 3.54 (dd, <i>J</i> = 10.8, 5.2 Hz, 1H), 3.12 (s, 3H), 2.66 - 2.57 (m, 2H), 1.97 - 1.90 (m, 2H) ppm.
87	 <i>rac</i>-6-((4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)amino)-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)nicotinonitrile	S2		ESI-MS <i>m/z</i> calc. 482.168, found 483.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.54 (s, 1H), 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 7.55 (d, <i>J</i> = 7.6 Hz, 1H), 7.46 (s, 1H), 7.44 - 7.35 (m, 1H), 7.32 - 7.16 (m, 3H), 6.99 (dt, <i>J</i> = 7.6, 0.7 Hz, 1H), 6.72 (d, <i>J</i> = 0.5 Hz, 1H), 6.11 (tt, <i>J</i> = 56.1, 4.8 Hz, 1H), 5.64 (s, 2H), 5.10 (t, <i>J</i> = 5.6 Hz, 1H), 3.74 - 3.58 (m, 2H), 2.69 (d, <i>J</i> = 17.8 Hz, 1H), 2.44 - 2.24 (m, 1H), 1.39 (s, 3H) ppm.
88	 5-(5-chloro-2-((1,3-dihydroxy-2-methylpropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 457.132 found 458.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.45 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 9.1, 7.3, 5.4, 1.9 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.26 - 7.17 (m, 2H), 6.92 (d, <i>J</i> = 7.5 Hz, 1H), 6.76 (s, 1H), 6.45 (s, 1H), 5.64 (d, <i>J</i> = 1.7 Hz, 2H), 4.89 (dt, <i>J</i> = 8.8, 5.7 Hz, 2H), 3.71 - 3.53 (m, 4H), 1.28 (s, 3H) ppm.
89	Atropisomer 1	S4		ESI-MS <i>m/z</i> calc. 483.123, found	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.17 (d, 1H), 8.12 (d, 1H), 7.50-7.48 (dd, 1H), 7.35-7.30

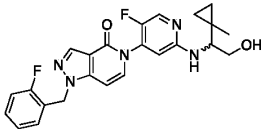
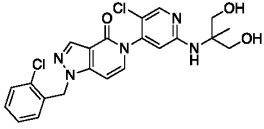
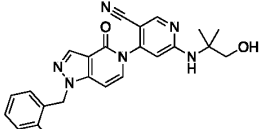
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-6-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one			484.3 (M+1) ⁺ .	(m, 2H), 7.00-6.98 (dd, 1H), 6.74 (d, 1H), 6.60 (d, 1H), 5.67 (m, 2H), 3.81-3.79 (m, 1H), 3.70-67 (m, 1H), 3.47-3.45 (m, 1H), 2.12 (d, 3H), 1.09-1.01 (m, 1H), 0.60-0.51 (m, 2H), 0.43-0.32 (m, 2H) ppm; exchangeable H not observed.
90	Atropisomer 2  (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-6-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S4		ESI-MS m/z calc. 483.123, found 484.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol-d ₄) δ 8.17 (d, 1H), 8.12 (d, 1H), 7.50-7.48 (dd, 1H), 7.35-7.30 (m, 2H), 7.00-6.98 (dd, 1H), 6.74 (d, 1H), 6.60 (d, 1H), 5.67 (m, 2H), 3.81-3.79 (m, 1H), 3.70-67 (m, 1H), 3.42-3.38 (m, 1H), 2.12 (d, 3H), 1.09-1.01 (m, 1H), 0.58-0.48 (m, 2H), 0.39-0.32 (m, 2H) ppm; exchangeable H not observed.
91	 5-(2-(((1H-pyrazol-4-yl)methyl)amino)-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS m/z calc. 449.117, found 450.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO-d ₆) δ 12.62 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.57 (s, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.30 - 7.16 (m, 4H), 6.91 (d, J = 7.6 Hz, 1H), 6.62 (s, 1H), 5.69 - 5.58 (m, 2H), 4.33 (d, J = 5.6 Hz, 2H) ppm.
92	 5-(2-(((1,2,3-thiadiazol-5-yl)methyl)amino)-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS m/z calc. 467.073, found 468.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.91 (s, 1H), 8.30 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.84 (t, J = 6.0 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.30 - 7.16 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 5.69 - 5.58 (m, 2H), 4.97 - 4.85 (m, 2H) ppm.

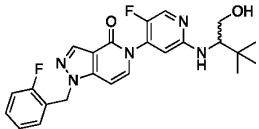
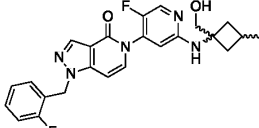
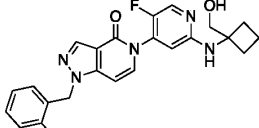
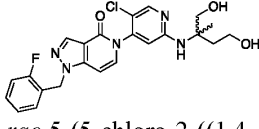
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
93	 5-(5-chloro-2-(((3-methylisoxazol-4-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 464.116, found 465.1 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 8.22 (s, 1H), 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.45 - 7.32 (m, 2H), 7.32 - 7.15 (m, 3H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.65 (s, 1H), 5.63 (d, <i>J</i> = 3.1 Hz, 2H), 4.30 (t, <i>J</i> = 5.3 Hz, 2H), 2.26 (s, 3H) ppm.
94	Peak 1  <i>rel</i>-(<i>R</i>)-5-(5-chloro-2-((4,4-difluoro-1-hydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 26% MeOH (supplemented with 20 mM ammonia), 74% CO ₂ ; Flow rate 100 mL/min); rt = 3.68 min	ESI-MS <i>m/z</i> calc. 491.134, found 492.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 7.47 (dd, <i>J</i> = 7.5, 5.9 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.16 (m, 3H), 7.00 - 6.89 (m, 2H), 6.60 (s, 1H), 5.63 (d, <i>J</i> = 3.4 Hz, 2H), 4.94 - 4.90 (m, 1H), 4.24 - 4.20 (m, 1H), 3.50 - 3.46 (m, 1H), 3.37 - 3.26 (m, 1H), 2.29 (s, 1H), 2.15 - 1.91 (m, 1H), 1.62 (td, <i>J</i> = 19.2, 2.9 Hz, 3H) ppm; exchangeable H not observed.
95	Peak 2  <i>rel</i>-(<i>S</i>)-5-(5-chloro-2-((4,4-difluoro-1-hydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 26% MeOH (supplemented with 20 mM ammonia),	ESI-MS <i>m/z</i> calc. 491.134, found 492.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 1.5 Hz, 2H), 7.47 (dd, <i>J</i> = 7.5, 5.9 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.17 (m, 3H), 6.96 (t, <i>J</i> = 9.1 Hz, 1H), 6.91 (d, <i>J</i> = 7.5 Hz, 1H), 6.60 (s, 1H), 5.63 (d, <i>J</i> = 3.4 Hz, 2H), 4.93 - 4.89 (m, 1H), 4.24 - 4.21 (m, 1H), 3.49 - 3.46 (m, 1H), 3.30 - 3.27 (m, 1H), 2.36 - 2.23 (m, 1H), 2.16 - 1.93 (m, 1H), 1.68 - 1.56 (m, 3H) ppm.

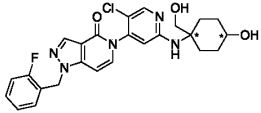
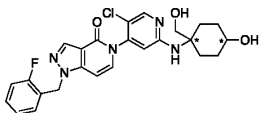
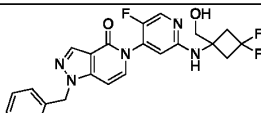
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			74% CO ₂ ; Flow rate 100 mL/min; rt = 6.22 min		
96	 <i>rac</i>-5-(2-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)-5-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 451.182, found 452.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.06 (d, <i>J</i> = 1.9 Hz, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (tdd, <i>J</i> = 7.7, 5.4, 2.0 Hz, 1H), 7.25 (tdd, <i>J</i> = 9.5, 7.4, 1.5 Hz, 2H), 7.20 (td, <i>J</i> = 7.4, 1.2 Hz, 1H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.73 (d, <i>J</i> = 5.1 Hz, 1H), 6.23 (s, 1H), 5.65 (s, 2H), 5.09 (t, <i>J</i> = 5.7 Hz, 1H), 3.71 (dd, <i>J</i> = 10.7, 5.7 Hz, 1H), 3.61 (dd, <i>J</i> = 10.7, 5.8 Hz, 1H), 1.41 (tt, <i>J</i> = 8.1, 5.8 Hz, 1H), 1.01 (s, 3H), 0.45 - 0.40 (m, 1H), 0.39 - 0.31 (m, 3H) ppm.
97	 <i>rac</i>-5-(5-fluoro-2-((3-hydroxy-1-(hydroxymethyl)spiro[3.3]heptan-1-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 493.193, found 494.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (t, <i>J</i> = 1.8 Hz, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (tdd, <i>J</i> = 7.5, 5.3, 2.0 Hz, 1H), 7.28 - 7.23 (m, 2H), 7.23 - 7.18 (m, 1H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.73 (d, <i>J</i> = 5.1 Hz, 0.5H), 6.62 - 6.57 (m, 1H), 6.19 (s, 0.5H), 5.65 (s, 2H), 5.01 (dd, <i>J</i> = 14.4, 6.0 Hz, 1H), 4.65 (t, <i>J</i> = 5.0 Hz, 0.5H), 4.55 (t, <i>J</i> = 5.4 Hz, 0.5H), 4.02 - 3.95 (m, 1H), 3.87 - 3.77 (m, 1H), 3.67 (dd, <i>J</i> = 10.7, 5.1 Hz, 0.5H), 3.37 - 3.33 (m, 0.5H), 2.62 (d, <i>J</i> = 9.2 Hz, 0.5H), 2.39 (d, <i>J</i> = 7.6 Hz, 0.5H), 2.27 (q, <i>J</i> = 9.6 Hz, 0.5H), 2.22 - 2.13 (m, 0.5H), 2.11 - 2.04 (m, 0.5H), 1.85 (q, <i>J</i> = 9.2 Hz, 0.5H), 1.73

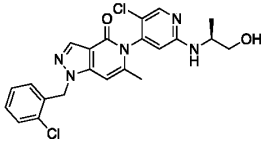
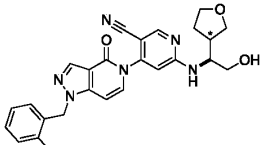
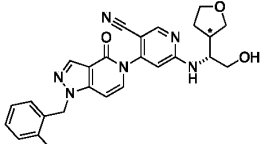
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					(dd, $J = 12.0, 5.5$ Hz, 1H), 1.66 (dt, $J = 8.6, 4.6$ Hz, 1.5H), 1.51 (dd, $J = 11.2, 8.2$ Hz, 0.5H) ppm; exchangeable H not observed.
98	 <i>rac</i>-5-(5-chloro-2-((1-hydroxy-2-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 455.152, found 456.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, $J = 0.8$ Hz, 1H), 8.10 (s, 1H), 7.46 (dd, $J = 7.5, 3.5$ Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.16 (m, 3H), 6.91 (d, $J = 7.5$ Hz, 1H), 6.69 (d, $J = 1.2$ Hz, 1H), 6.44 (s, 1H), 5.63 (s, 2H), 4.92 (t, $J = 5.7$ Hz, 1H), 3.70 - 3.39 (m, 2H), 1.99 - 1.84 (m, 1H), 1.73 - 1.60 (m, 1H), 1.25 (d, $J = 4.6$ Hz, 3H), 0.80 (td, $J = 7.5, 3.2$ Hz, 3H) ppm.
99	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-chloro-6-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB1		ESI-MS m/z calc. 487.098, found 488.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.12 (dd, $J = 1.9, 0.8$ Hz, 1H), 8.10 (s, 1H), 7.55 - 7.45 (m, 2H), 7.41 (dt, $J = 8.2, 1.0$ Hz, 1H), 7.32 (ddd, $J = 9.6, 8.3, 1.2$ Hz, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.63 (d, $J = 1.0$ Hz, 1H), 5.67 (d, $J = 1.5$ Hz, 2H), 4.71 (dt, $J = 18.2, 5.3$ Hz, 1H), 3.66 - 3.44 (m, 3H), 1.01 (dtd, $J = 13.0, 8.0, 4.9$ Hz, 1H), 0.47 - 0.28 (m, 3H), 0.28 - 0.21 (m, 1H) ppm.
100	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-dichlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB1		ESI-MS m/z calc. 503.068, found 504.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.23 - 8.03 (m, 2H), 7.57 (d, $J = 0.8$ Hz, 1H), 7.56 (s, 1H), 7.54 - 7.43 (m, 2H), 6.98 (dd, $J = 7.5, 0.9$ Hz, 1H), 6.89 (t, $J = 7.4$ Hz, 1H), 6.64 (d, $J = 0.9$ Hz, 1H), 5.75 (s, 2H), 4.71 (dt, $J = 18.2, 5.3$ Hz, 1H), 3.63 - 3.44 (m, 3H), 1.06 - 0.96 (m, 1H), 0.49 - 0.28 (m, 1H).

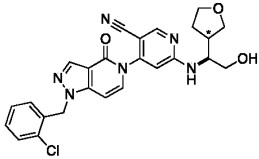
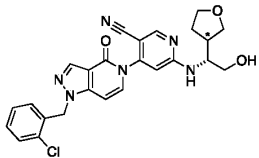
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				3H), 0.24 (td, <i>J</i> = 5.4, 3.4 Hz, 1H) ppm.
101	 4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)-6-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile	S2		ESI-MS <i>m/z</i> calc. 432.171, found 432.9 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.50 (s, 1H), 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 7.56 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.35 (m, 2H), 7.32 - 7.16 (m, 3H), 7.00 - 6.94 (m, 1H), 6.69 - 6.65 (m, 1H), 5.64 (s, 2H), 4.93 (t, <i>J</i> = 5.7 Hz, 1H), 3.58 (d, <i>J</i> = 5.7 Hz, 2H), 1.35 (s, 6H) ppm.
102	Peak 1  <i>rel</i>-6-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)nicotinonitrile	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25 to 35% MeOH (supplemented with 20 mM ammonia), 75 to 65% CO ₂ ; Flow rate 100 mL/min); rt = 3.96 min	ESI-MS <i>m/z</i> calc. 480.152, found 481.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.20 (d, <i>J</i> = 0.9 Hz, 1H), 8.06 (s, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.40 (s, 1H), 7.32 - 7.17 (m, 3H), 7.01 - 6.95 (m, 1H), 6.68 - 6.64 (m, 1H), 5.65 (s, 2H), 5.12 - 5.08 (m, 1H), 4.13 - 4.09 (m, 1H), 3.56 (d, <i>J</i> = 4.8 Hz, 2H), 2.03 - 1.90 (m, 1H), 1.67 - 1.56 (m, 1H), 1.42 - 1.35 (m, 1H) ppm.
103	Peak 2  <i>rel</i>-6-((1-(2,2-difluorocyclopropyl)-2-hydroxyethyl)amino)-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)nicotinonitrile	S2	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 25 to 35% MeOH (supplemented with 20	ESI-MS <i>m/z</i> calc. 480.152, found 481.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.10 (s, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.32 - 7.17 (m, 3H), 7.00 - 6.93 (m, 1H), 6.66 (s, 1H), 5.65 (s, 2H), 5.20 - 5.16 (m, 1H), 4.13 - 4.09 (m, 1H), 3.56 (d, <i>J</i> = 4.9 Hz, 2H), 2.03 - 1.90 (m, 1H), 1.67 - 1.56 (m, 1H), 1.41 - 1.37 (m, 1H) ppm.

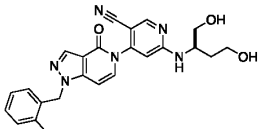
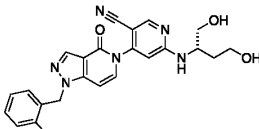
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			mM ammonia), 75 to 65% CO ₂ ; Flow rate 100 mL/min); rt = 7.05 min		
104	 <i>rac</i>-5-(5-fluoro-2-((2-hydroxy-1-(1-methylcyclopropyl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 451.182, found 453.2 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.95 (d, 1H), 7.75 (d, 1H), 7.20 - 7.19 (d, 1H), 7.15 - 7.13 (m, 1H), 7.01 - 6.99 (m, 1H), 6.95 - 6.90 (m, 2H), 6.64 - 6.63 (d, 1H), 6.42 - 6.41 (d, 1H), 5.40 (s, 2H), 3.56 - 3.53 (m, 1H), 3.44 - 3.40 (m, 1H), 3.32 - 3.30 (m, 1H), 0.87 (s, 3H), 0.38 - 0.36 (m, 1H), 0.31 - 0.29 (m, 1H), 0.12 - 0.08 (m, 1H), 0.02 - 0.00 (m, 1H) ppm; exchangeable H not observed.
105	 5-(5-chloro-2-((1,3-dihydroxy-2-methylpropan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 473.102, found 474.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.21 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (s, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.6 Hz, 1H), 7.45 (d, <i>J</i> = 7.5 Hz, 1H), 7.36 (dtd, <i>J</i> = 17.5, 7.4, 1.7 Hz, 2H), 7.10 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.90 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.77 (s, 1H), 6.45 (s, 1H), 5.68 (d, <i>J</i> = 3.0 Hz, 2H), 4.89 (d, <i>J</i> = 7.5 Hz, 2H), 3.69 - 3.55 (m, 4H), 1.28 (s, 3H) ppm.
106	 4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile	S1		ESI-MS <i>m/z</i> calc. 448.141, found 448.9 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.55 (d, <i>J</i> = 7.5 Hz, 1H), 7.51 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.41 - 7.30 (m, 3H), 7.10 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.96 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.68 (s, 1H), 5.68 (s, 2H), 4.94 (t, <i>J</i> = 5.6 Hz, 1H), 3.60 - 3.56

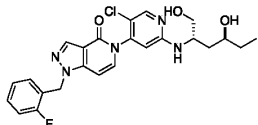
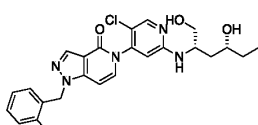
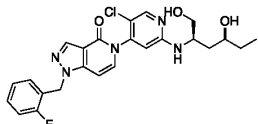
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					(m, 2H), 1.35 (s, 6H) ppm.
107	 <i>rac</i>-5-(5-fluoro-2-((1-hydroxy-3,3-dimethylbutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 453.198, found 454.4 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.20 (d, 1H), 7.99 (d, 1H), 7.45 - 7.43 (dd, 1H), 7.39 - 7.38 (m, 1H), 7.27 - 7.24 (m, 1H), 7.20 - 7.14 (m, 2H), 6.89 - 6.87 (d, 1H), 6.68 - 6.67 (d, 1H), 5.64 (s, 2H), 3.94 - 3.92 (m, 1H), 3.89 - 3.86 (dd, 1H), 3.57 - 3.54 (m, 1H), 1.02 (s, 9H) ppm; exchangeable H not observed.
108	Mixture of syn and anti  5-(5-fluoro-2-((1-(hydroxymethyl)-3-methylcyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 451.182, found 452.3 (M+1) ⁺ .	
109	 5-(5-fluoro-2-((1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 437.166, found 438.3 (M+1) ⁺ .	
110	 <i>rac</i>-5-(5-chloro-2-((1,4-dihydroxy-2-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 471.147, found 472.2 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.39 (tdd, <i>J</i> = 7.4, 5.2, 1.7 Hz, 1H), 7.33 (dd, <i>J</i> = 7.6, 2.2 Hz, 1H), 7.27 (td, <i>J</i> = 7.5, 1.8 Hz, 1H), 7.23 - 7.14 (m, 2H), 6.88 (d, <i>J</i> =

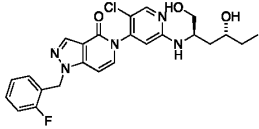
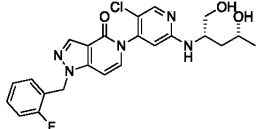
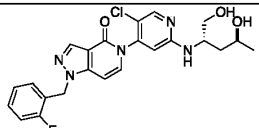
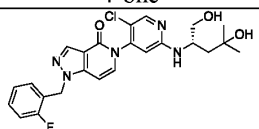
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				7.5 Hz, 1H), 6.67 (s, 1H), 5.65 (d, <i>J</i> = 3.1 Hz, 2H), 3.90 - 3.55 (m, 4H), 2.29 - 2.15 (m, 1H), 2.10 - 1.96 (m, 1H), 1.38 (s, 3H) ppm; exchangeable H not observed.
111	Peak 1 Syn or anti  5-(5-chloro-2-((4-hydroxymethyl)cyclohexyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 497.163, found 498.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.2, 5.4, 1.9 Hz, 1H), 7.30 - 7.17 (m, 4H), 6.96 - 6.88 (m, 1H), 6.76 (s, 1H), 5.63 (s, 2H), 4.74 (t, <i>J</i> = 5.6 Hz, 1H), 4.45 (d, <i>J</i> = 4.4 Hz, 1H), 3.67 (dd, <i>J</i> = 10.6, 5.7 Hz, 1H), 3.57 (dd, <i>J</i> = 10.5, 5.6 Hz, 1H), 3.37 (dt, <i>J</i> = 10.2, 5.3 Hz, 1H), 2.32 (d, <i>J</i> = 11.9 Hz, 1H), 2.24 (d, <i>J</i> = 11.8 Hz, 1H), 1.58 (d, <i>J</i> = 12.1 Hz, 3H), 1.46 - 1.30 (m, 3H) ppm.
112	Peak 2 Anti or syn  5-(5-chloro-2-((4-hydroxymethyl)cyclohexyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 497.163, found 498.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (s, 1H), 7.45 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.7, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.14 (m, 4H), 6.91 (d, <i>J</i> = 7.6 Hz, 1H), 6.72 (s, 1H), 5.63 (s, 2H), 4.80 (t, <i>J</i> = 5.7 Hz, 1H), 4.33 (d, <i>J</i> = 3.5 Hz, 1H), 3.76 - 3.68 (m, 1H), 3.67 (q, <i>J</i> = 2.9 Hz, 1H), 3.65 - 3.59 (m, 1H), 1.90 - 1.84 (m, 4H), 1.63 (s, 2H), 1.44 - 1.34 (m, 2H) ppm.
113	 5-(2-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-5-fluoropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 473.147, found 474.3 (M+1) ⁺ .	

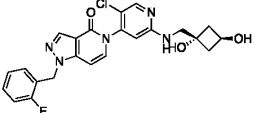
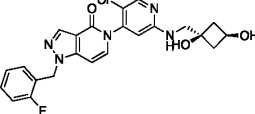
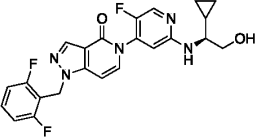
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	fluoropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one				
114	Atropisomer 1  5-(5-chloro-2-(((S)-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-6-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S4		ESI-MS <i>m/z</i> calc. 457.107, found 458.2 (M+1) ⁺ .	
115	Peak 1  <i>rel</i> -4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-(((1S)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotino nitrile	S1	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 5.37 min	ESI-MS <i>m/z</i> calc. 490.152, found 491.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.50 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.86 (d, <i>J</i> = 8.6 Hz, 1H), 7.58 (d, <i>J</i> = 7.5 Hz, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.12 - 7.07 (m, 1H), 6.96 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.63 (s, 1H), 5.68 (s, 2H), 4.85 - 4.82 (m, 1H), 4.22 - 4.18 (m, 1H), 3.80 (t, <i>J</i> = 8.0 Hz, 1H), 3.74 - 3.67 (m, 1H), 3.60 (q, <i>J</i> = 7.8 Hz, 1H), 3.49 - 3.37 (m, 4H), 1.99 - 1.89 (m, 1H), 1.68 - 1.57 (m, 1H) ppm.
116	Peak 2  <i>rel</i> -4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-(((1S)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotino nitrile	S1	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel	ESI-MS <i>m/z</i> calc. 490.152, found 491.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.50 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.84 (d, <i>J</i> = 8.5 Hz, 1H), 7.57 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 - 7.49 (m, 1H), 7.41 - 7.30 (m, 2H), 7.10 (d, <i>J</i> = 7.5 Hz, 1H), 6.96 (dd, <i>J</i>

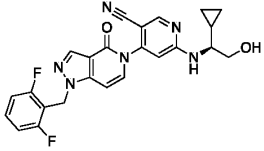
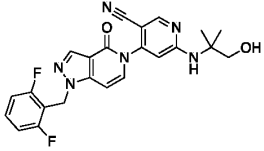
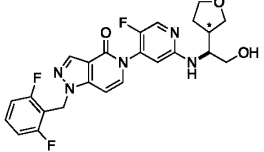
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rel</i> -4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-(((1 <i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotino nitrile		Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 7.92 min		= 7.6, 0.9 Hz, 1H), 6.62 (s, 1H), 5.68 (s, 2H), 4.85 - 4.81 (m, 1H), 4.21 - 4.18 (m, 1H), 3.80 - 3.71 (m, 2H), 3.63 (q, <i>J</i> = 7.8 Hz, 1H), 3.59 - 3.45 (m, 3H), 3.41 (t, <i>J</i> = 8.0 Hz, 1H), 2.00 - 1.96 (m, 1H), 1.67 - 1.59 (m, 1H) ppm.
117	Peak 3  <i>rel</i> -4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotino nitrile	S1	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 9.32 min	ESI-MS <i>m/z</i> calc. 490.152, found 491.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.50 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.84 (d, <i>J</i> = 8.6 Hz, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.52 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.10 (d, <i>J</i> = 7.4 Hz, 1H), 6.96 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.62 (s, 1H), 5.68 (s, 2H), 4.85 - 4.81 (m, 1H), 4.21 - 4.18 (m, 1H), 3.80 - 3.71 (m, 2H), 3.63 (q, <i>J</i> = 7.9 Hz, 1H), 3.58 - 3.46 (m, 3H), 3.42 (t, <i>J</i> = 8.1 Hz, 1H), 2.01 - 1.96 (m, 1H), 1.65 - 1.61 (m, 1H) ppm.
118	Peak 4  <i>rel</i> -4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-(((1 <i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotino nitrile	S1	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 9.32 min	ESI-MS <i>m/z</i> calc. 490.152, found 491.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.23 (d, <i>J</i> = 0.9 Hz, 1H), 7.88 - 7.84 (m, 1H), 7.58 (d, <i>J</i> = 7.5 Hz, 1H), 7.52 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.41 - 7.31 (m, 2H), 7.10 (d, <i>J</i> = 7.4 Hz, 1H), 6.96 (dd, <i>J</i> = 7.6 Hz, 1H), 6.63 (s, 1H), 5.68 (s, 2H), 4.84 (m, 1H), 4.20 (m, 1H), 3.80 (t, <i>J</i> = 8.1 Hz, 1H),

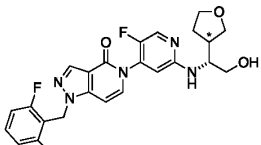
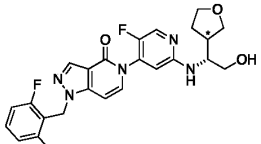
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)nicotinonitrile		MeOH:Me CN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 11.33 min		3.74 - 3.67 (m, 1H), 3.60 (q, <i>J</i> = 7.8 Hz, 1H), 3.53 - 3.37 (m, 4H), 2.01 - 1.88 (m, 1H), 1.68 - 1.57 (m, 1H) ppm.
119	Peak 1  <i>rel-(R)-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-((1,4-dihydroxybutan-2-yl)amino)nicotinonitrile</i>	S1	Lux TM Cellulose-2 column, 5 µm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 12.42 min	ESI-MS <i>m/z</i> calc. 464.136, found 465.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.51 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.73 (s, 1H), 7.56 (d, <i>J</i> = 7.5 Hz, 1H), 7.52 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 (d, <i>J</i> = 7.4 Hz, 1H), 6.96 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 6.61 (s, 1H), 5.68 (s, 2H), 4.81 - 4.78 (m, 1H), 4.48 - 4.45 (m, 1H), 4.25 - 4.21 (m, 1H), 3.50 - 3.43 (m, 4H), 1.83 - 1.80 (m, 1H), 1.66 - 1.60 (m, 1H) ppm.
120	Peak 2  <i>rel-(S)-4-(1-(2-chlorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-((1,4-dihydroxybutan-2-yl)amino)nicotinonitrile</i>	S1	Lux TM Cellulose-2 column, 5 µm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 12.42 min	ESI-MS <i>m/z</i> calc. 464.136, found 465.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.50 (s, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.73 (s, 1H), 7.56 (d, <i>J</i> = 7.6 Hz, 1H), 7.52 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 (d, <i>J</i> = 7.6 Hz, 1H), 6.96 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.61 (s, 1H), 5.68 (s, 2H), 4.81 - 4.78 (m, 1H), 4.48 - 4.45 (m, 1H), 4.25 - 4.21 (m, 1H), 3.51 - 3.44 (m, 4H), 1.83 - 1.80 (m, 1H), 1.66 - 1.59 (m, 1H) ppm.

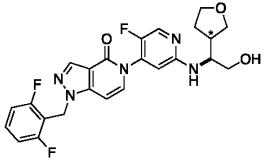
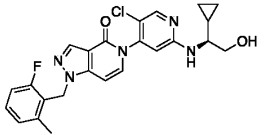
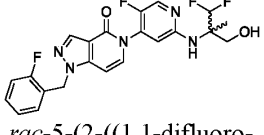
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			70% CO ₂ ; Flow rate 100 mL/min); rt = 14.86 min		
121	 <i>rel</i>-5-(5-chloro-2-(((2<i>S</i>[*],4<i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 485.163, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 1.0 Hz, 1H), 8.13 (d, <i>J</i> = 1.3 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 7.31 - 7.18 (m, 3H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.81 (t, <i>J</i> = 7.9 Hz, 1H), 6.61 (s, 1H), 5.64 (d, <i>J</i> = 3.9 Hz, 2H), 4.68 (dt, <i>J</i> = 13.9, 5.4 Hz, 1H), 4.39 (dd, <i>J</i> = 10.7, 5.5 Hz, 1H), 4.04 (s, 1H), 3.55 - 3.37 (m, 3H), 1.77 - 1.69 (m, 1H), 1.60 - 1.41 (m, 2H), 1.36 - 1.28 (m, 1H), 0.86 (tt, <i>J</i> = 7.5, 2.1 Hz, 3H) ppm.
122	 <i>rel</i>-5-(5-chloro-2-(((2<i>S</i>[*],4<i>R</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 485.163, found 486.3 (M+1) ⁺ .	
123	 <i>rel</i>-5-(5-chloro-2-(((2<i>R</i>[*],4<i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 485.163, found 486.2 (M+1) ⁺ .	

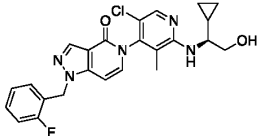
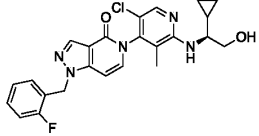
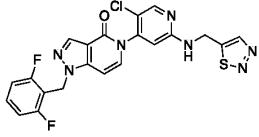
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
124	 <i>rel</i> -5-(5-chloro-2-(((2 <i>R</i> *,4 <i>R</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 485.163, found 486.3 (<i>M</i> +1) ⁺ .	
125	 <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> *,4 <i>R</i>)-1,4-dihydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 471.147, found 472.2 (<i>M</i> +1) ⁺ .	
126	 <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> *,4 <i>S</i>)-1,4-dihydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 471.147, found 472.3 (<i>M</i> +1) ⁺ .	
127	 (<i>S</i>)-5-(5-chloro-2-((1,4-dihydroxy-4-methylpentan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-	S2		ESI-MS <i>m/z</i> calc. 485.163, found 486.3 (<i>M</i> +1) ⁺ .	

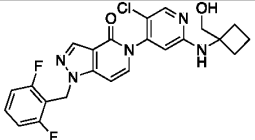
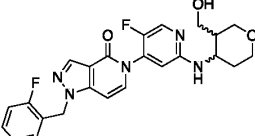
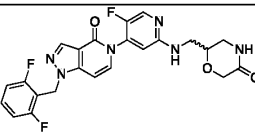
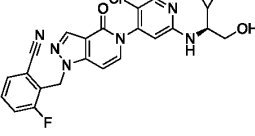
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
128	Peak 1  5-(5-chloro-2-((((1 <i>r</i> ,3 <i>r</i>)-1,3-dihydroxycyclobutyl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 469.132, found 470.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.9 Hz, 1H), 8.14 (s, 1H), 7.46 (d, <i>J</i> = 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.32 - 7.17 (m, 3H), 6.95 - 6.91 (m, 1H), 6.87 (t, <i>J</i> = 5.8 Hz, 1H), 6.72 (s, 1H), 5.69 - 5.58 (m, 2H), 4.98 (s, 1H), 4.87 (d, <i>J</i> = 5.4 Hz, 1H), 4.28 (ddt, <i>J</i> = 13.1, 7.3, 5.9 Hz, 1H), 3.40 (t, <i>J</i> = 4.5 Hz, 2H), 2.18 - 2.11 (m, 2H), 1.90 (ddd, <i>J</i> = 12.8, 6.0, 1.8 Hz, 2H) ppm.
129	Peak 2  5-(5-chloro-2-((((1 <i>s</i> ,3 <i>s</i>)-1,3-dihydroxycyclobutyl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.20 (d, <i>J</i> = 0.8 Hz, 1H), 8.13 (d, <i>J</i> = 0.5 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.35 (s, 1H), 7.27 (td, <i>J</i> = 7.6, 1.8 Hz, 1H), 7.22 - 7.14 (m, 2H), 6.88 (dt, <i>J</i> = 7.6, 0.8 Hz, 1H), 6.71 (d, <i>J</i> = 0.5 Hz, 1H), 5.65 (d, <i>J</i> = 3.4 Hz, 2H), 3.94 (p, <i>J</i> = 7.2 Hz, 1H), 3.43 (s, 2H), 2.60 - 2.54 (m, 2H), 1.99 (dd, <i>J</i> = 12.3, 7.2 Hz, 2H) ppm; exchangeable H not observed.
130	 (S)-5-(2-((1-cyclopropyl-2-hydroxyethyl)amino)-5-fluoropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 455.157, found 456.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.89 (d, <i>J</i> = 0.8 Hz, 1H), 7.80 (d, <i>J</i> = 1.8 Hz, 1H), 7.36 (d, <i>J</i> = 7.7 Hz, 1H), 7.25 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 6.97 - 6.87 (m, 2H), 6.76 - 6.71 (m, 1H), 6.38 - 6.30 (m, 2H), 5.39 (s, 2H), 4.43 (t, <i>J</i> = 5.4 Hz, 1H), 3.35 - 3.25 (m, <i>J</i> = 5.2 Hz, 2H), 3.22 (tt, <i>J</i> = 8.2, 5.0 Hz, 1H), 0.76 (qt, <i>J</i> = 8.2, 5.0 Hz, 1H), 0.24 - 0.04 (m,

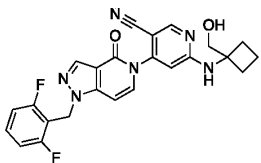
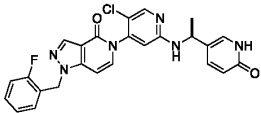
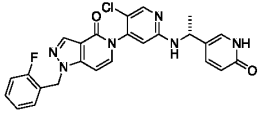
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					3H), -0.01 (dtd, $J = 9.1$, 5.3, 3.8 Hz, 1H) ppm.
131	 (S)-6-((1-cyclopropyl-2-hydroxyethyl)amino)-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)nicotinonitrile	S7		ESI-MS m/z calc. 462.162, found 463.4 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.15 (d, $J = 0.8$ Hz, 1H), 7.85 (s, 1H), 7.60 (d, $J = 7.5$ Hz, 1H), 7.55 - 7.43 (m, 1H), 7.21 - 7.11 (m, 2H), 7.00 (d, $J = 7.6$ Hz, 1H), 6.62 (s, 1H), 5.63 (s, 2H), 4.80 (s, 1H), 3.71 - 3.50 (m, 3H), 1.06 - 1.00 (m, 1H), 0.50 - 0.37 (m, 2H), 0.36 - 0.18 (m, 2H) ppm.
132	 4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile	S7		ESI-MS m/z calc. 450.162, found 451.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.51 (s, 1H), 8.15 (d, $J = 0.8$ Hz, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.54 - 7.44 (m, 1H), 7.40 (s, 1H), 7.20 - 7.12 (m, 2H), 7.00 (dd, $J = 7.5$, 0.8 Hz, 1H), 6.68 (d, $J = 0.5$ Hz, 1H), 5.63 (s, 2H), 4.93 (t, $J = 5.6$ Hz, 1H), 3.58 (s, 2H), 1.35 (s, 6H) ppm.
133	Peak 1  rel-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1S)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μ m particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 35 to 50% 1: ⁱ PrOH:MeCN (supplemented with 0.2% DMIPA), 65 to 50% CO ₂ ; Flow rate 100	ESI-MS m/z calc. 485.167, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.13 (d, $J = 0.8$ Hz, 1H), 8.08 (d, $J = 1.8$ Hz, 1H), 7.61 (dd, $J = 7.6$, 0.6 Hz, 1H), 7.49 (tt, $J = 8.5$, 6.7 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.67 (d, $J = 8.8$ Hz, 1H), 6.62 (d, $J = 5.0$ Hz, 1H), 5.63 (s, 2H), 4.70 (t, $J = 5.4$ Hz, 1H), 4.01 - 3.90 (m, 1H), 3.81 (t, $J = 8.0$ Hz, 1H), 3.71 (td, $J = 8.2$, 4.3 Hz, 1H), 3.60 (td, $J = 8.1$, 7.1 Hz, 1H), 3.46 - 3.39 (m, 3H), 1.99 - 1.90 (m, 1H), 1.67 (dq, $J = 12.3$, 8.2 Hz, 1H) ppm; exchangeable H not observed.

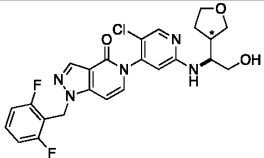
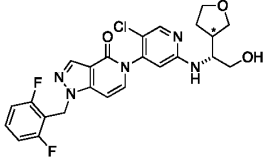
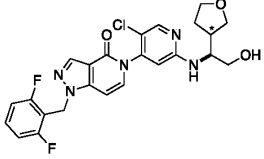
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			mL/min); rt = 4.38 min		
134	Peak 2  <i>rel</i>-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1<i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μ m particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 35 to 50% 1: ^{<i>i</i>} PrOH:Me CN (supplemented with 0.2% DMIPA), 65 to 50% CO ₂ ; Flow rate 100 mL/min); rt = 5.07 min	ESI-MS <i>m/z</i> calc. 485.167, found 487.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (d, <i>J</i> = 7.7 Hz, 1H), 7.49 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 (s, 1H), 6.63 (d, <i>J</i> = 5.0 Hz, 1H), 5.63 (s, 2H), 3.94 (s, 2H), 3.82 - 3.71 (m, 2H), 3.63 (td, <i>J</i> = 8.2, 7.0 Hz, 1H), 3.56 - 3.40 (m, 3H), 2.03 - 1.93 (m, 1H), 1.64 (dq, <i>J</i> = 12.1, 8.3 Hz, 1H) ppm; exchangeable H not observed.
135	Peak 3  <i>rel</i>-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1<i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μ m particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 35 to 50% 1: ^{<i>i</i>} PrOH:Me CN (supplemented with 0.2% DMIPA), 65 to 50% CO ₂ ; Flow rate 100 mL/min); rt = 5.61 min	ESI-MS <i>m/z</i> calc. 485.167, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (dd, <i>J</i> = 7.6, 0.6 Hz, 1H), 7.49 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 (d, <i>J</i> = 8.8 Hz, 1H), 6.62 (d, <i>J</i> = 5.0 Hz, 1H), 5.63 (s, 2H), 4.71 (t, <i>J</i> = 5.4 Hz, 1H), 3.96 (s, 1H), 3.81 (t, <i>J</i> = 8.0 Hz, 1H), 3.71 (td, <i>J</i> = 8.2, 4.3 Hz, 1H), 3.60 (td, <i>J</i> = 8.1, 7.0 Hz, 1H), 3.42 (dt, <i>J</i> = 10.8, 7.5 Hz, 3H), 2.50 - 2.43 (m, 1H), 2.00 - 1.90 (m, 1H), 1.67 (dq, <i>J</i> = 12.1, 8.2 Hz, 1H) ppm.

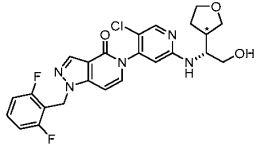
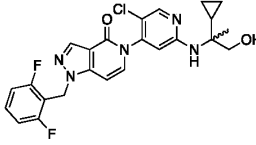
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
136	Peak 4  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μ m particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 35 to 50% 1: <i>i</i> PrOH:MeCN (supplemented with 0.2% DMIPA), 65 to 50% CO ₂ ; Flow rate 100 mL/min); rt = 8.39 min	ESI-MS <i>m/z</i> calc. 485.167, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (dd, <i>J</i> = 7.6, 0.6 Hz, 1H), 7.49 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 - 6.59 (m, 2H), 5.63 (s, 2H), 4.69 (t, <i>J</i> = 5.3 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.79 (t, <i>J</i> = 8.1 Hz, 1H), 3.75 (dt, <i>J</i> = 8.2, 4.1 Hz, 1H), 3.63 (td, <i>J</i> = 8.2, 7.1 Hz, 1H), 3.56 - 3.41 (m, 3H), 1.97 (dtd, <i>J</i> = 12.1, 7.7, 4.1 Hz, 1H), 1.64 (dq, <i>J</i> = 12.2, 8.3 Hz, 1H), 1.04 (d, <i>J</i> = 6.1 Hz, 1H) ppm.
137	 <i>(S)</i> -5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 467.152, found 468.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.12 - 8.10 (m, 1H), 8.10 (s, 1H), 7.47 (dd, <i>J</i> = 18.0, 7.5 Hz, 1H), 7.30 (td, <i>J</i> = 7.9, 6.0 Hz, 1H), 7.13 - 7.02 (m, 2H), 6.93 (d, <i>J</i> = 7.5 Hz, 2H), 6.65 (d, <i>J</i> = 1.5 Hz, 1H), 5.63 - 5.53 (m, 2H), 3.60 - 3.41 (m, 3H), 2.43 (s, 3H), 1.00 (qt, <i>J</i> = 8.2, 5.0 Hz, 1H), 0.44 (qd, <i>J</i> = 5.5, 2.7 Hz, 1H), 0.41 - 0.26 (m, 2H), 0.26 - 0.18 (m, 1H) ppm; exchangeable H not observed.
138	 <i>rac</i> -5-(2-((1,1-difluoro-3-hydroxy-2-methylpropan-2-yl)amino)-5-fluoropyridin-4-yl)-1-(2-	S2		ESI-MS <i>m/z</i> calc. 461.147, found 462.2 (M+1) ⁺ .	

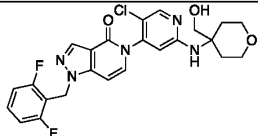
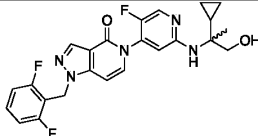
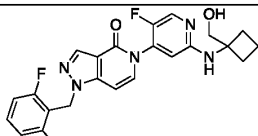
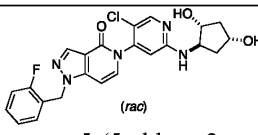
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
139	Atropisomer 1  5-(5-chloro-2-(((<i>S</i>)-1-cyclopropyl-2-hydroxyethyl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 467.152, found 468.1 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.18 (s, 1H), 7.99 (s, 1H), 7.38-7.33 (m, 1H), 7.28-7.25 (m, 1H), 7.21-7.11 (m, 3H), 6.90 (d, <i>J</i> = 7.8 Hz, 1H), 5.69 (d, <i>J</i> = 7.3 Hz, 1H), 5.63 (s, 2H), 3.80-3.70 (m, 2H), 3.66-3.60 (m, 1H), 1.87 (s, 3H), 1.14-1.05 (m, 1H), 0.58-0.28 (m, 4H) ppm; exchangeable H not observed.
140	Atropisomer 2  5-(5-chloro-2-(((<i>S</i>)-1-cyclopropyl-2-hydroxyethyl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 467.152, found 468.1 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.18 (d, <i>J</i> = 0.9 Hz, 1H), 7.99 (s, 1H), 7.39-7.33 (m, 1H), 7.29-7.23 (m, 2H), 7.18-7.12 (m, 2H), 6.90 (d, <i>J</i> = 7.3 Hz, 1H), 5.69 (d, <i>J</i> = 7.8 Hz, 0.5H), 5.63 (s, 2H), 3.78 (dd, <i>J</i> = 11.0, 4.6 Hz, 1H), 3.72 (dd, <i>J</i> = 10.8, 4.8 Hz, 1H), 3.65-3.58 (m, 1H), 1.88 (s, 3H), 1.15-1.06 (m, 1H), 0.58-0.27 (m, 4H) ppm; exchangeable H not observed.
141	 5-(2-(((1,2,3-thiadiazol-5-yl)methyl)amino)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 485.064, found 486.0 (M+1) ⁺ .	

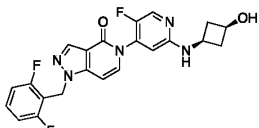
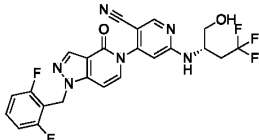
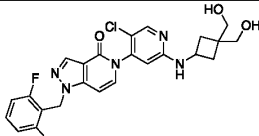
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
142	 5-(5-chloro-2-((1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 471.127, found 472.0 (M+1) ⁺ .	
143	Syn  <i>rac</i>-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((3<i>S</i>,4<i>R</i>)-3-(hydroxymethyl)tetrahydro-2<i>H</i>-pyran-4-yl)amino)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 485.167, found 486.3 (M+1) ⁺ .	
144	 <i>rac</i>-6-(((4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)-5-fluoropyridin-2-yl)amino)methyl)morpholin-3-one	S7		ESI-MS <i>m/z</i> calc. 484.147, found 485.3 (M+1) ⁺ .	
145	 (<i>S</i>)-2-((5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-<i>c</i>]pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 478.132, found 479.32 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.86 - 7.78 (m, 1H), 7.66 (dd, <i>J</i> = 8.2, 4.0 Hz, 2H), 7.52 (dd, <i>J</i> = 14.6, 7.5 Hz, 1H), 7.00 (d, <i>J</i> = 7.6 Hz, 1H), 6.90 (t, <i>J</i> = 6.5 Hz, 1H), 6.63 (s, 1H), 5.74 (s, 2H), 4.72 (s, 1H), 3.51 (d,

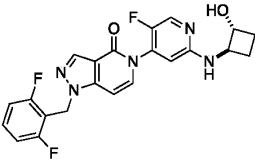
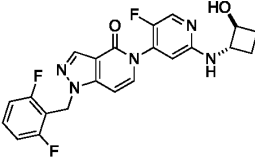
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-1-yl)methyl)-3-fluorobenzonitrile				$J = 11.6$ Hz, 3H), 1.01 (d, $J = 9.4$ Hz, 1H), 0.48 - 0.27 (m, 3H), 0.24 (s, 1H) ppm.
146	 4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)-6-((1-(hydroxymethyl)cyclobutyl)amino)nicotinonitrile	S7		ESI-MS m/z calc. 462.162, found 463.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.48 (d, $J = 0.4$ Hz, 1H), 8.15 (d, $J = 0.8$ Hz, 1H), 7.99 (s, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.54 - 7.44 (m, 1H), 7.21 - 7.12 (m, 2H), 7.00 (dd, $J = 7.6, 0.9$ Hz, 1H), 6.56 (s, 1H), 5.63 (s, 2H), 4.91 (t, $J = 5.5$ Hz, 1H), 3.70 (s, 2H), 2.25 - 2.10 (m, 4H), 1.91 - 1.71 (m, 2H) ppm.
147	Peak 1  <i>rel</i>-(<i>S</i>)-5-(5-chloro-2-((1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 490.132, found 491.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.40 (s, 1H), 8.17 (t, $J = 1.2$ Hz, 2H), 7.50 (dt, $J = 9.5, 2.9$ Hz, 1H), 7.46 (dd, $J = 12.4, 7.5$ Hz, 1H), 7.44 - 7.38 (m, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.31 - 7.18 (m, 4H), 6.92 (d, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 4.3$ Hz, 1H), 6.32 (d, $J = 9.5$ Hz, 1H), 5.64 (d, $J = 3.9$ Hz, 2H), 4.83 (d, $J = 9.7$ Hz, 1H), 1.39 (dd, $J = 6.9, 4.6$ Hz, 3H) ppm.
148	Peak 2  <i>rel</i>-(<i>R</i>)-5-(5-chloro-2-((1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 490.132, found 491.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.40 (s, 1H), 8.17 (t, $J = 1.2$ Hz, 2H), 7.50 (dt, $J = 9.5, 2.9$ Hz, 1H), 7.46 (dd, $J = 12.4, 7.5$ Hz, 1H), 7.40 (tdd, $J = 7.5, 5.2, 1.8$ Hz, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.31 - 7.18 (m, 4H), 6.92 (d, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 4.3$ Hz, 1H), 6.32 (d, $J = 9.4$ Hz, 1H), 5.64 (d, $J = 3.8$ Hz, 2H), 4.83 (s, 1H), 1.39 (dd, $J = 6.9, 4.6$ Hz, 3H) ppm.
149	Peak 1	S7	Chiralpak [®] IB column, 5 μ m	ESI-MS m/z calc. 501.138,	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, $J = 1.6$ Hz, 2H), 7.55 - 7.45

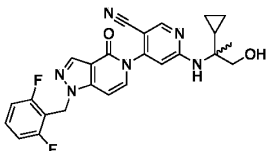
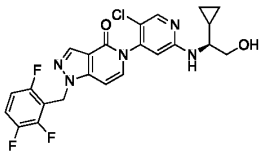
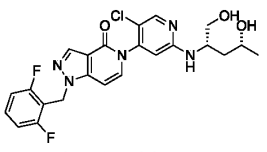
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rel</i>-5-(5-chloro-2-(((1<i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one		particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:PrOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 5.78 min	found 502.3 (M+1) ⁺ .	(m, 2H), 7.21 - 7.13 (m, 2H), 6.96 (d, <i>J</i> = 7.6 Hz, 2H), 6.65 (d, <i>J</i> = 1.4 Hz, 1H), 5.63 (s, 2H), 4.74 (dt, <i>J</i> = 20.9, 5.4 Hz, 1H), 4.01 (s, 1H), 3.81 (td, <i>J</i> = 8.3, 1.9 Hz, 1H), 3.71 (ddt, <i>J</i> = 8.1, 4.3, 1.9 Hz, 1H), 3.64 - 3.56 (m, 1H), 3.51 - 3.37 (m, 3H), 2.47 (d, <i>J</i> = 8.0 Hz, 1H), 1.95 (dt, <i>J</i> = 12.0, 8.1, 4.1 Hz, 1H), 1.65 (dq, <i>J</i> = 12.3, 7.9 Hz, 1H) ppm.
150	Peak 2  <i>rel</i>-5-(5-chloro-2-(((1<i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:PrOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 7.95 min	ESI-MS <i>m/z</i> calc. 501.138, found 502.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.14 (d, <i>J</i> = 0.8 Hz, 1H), 8.13 (s, 1H), 7.45 (tt, <i>J</i> = 8.5, 6.5 Hz, 1H), 7.37 (dd, <i>J</i> = 14.2, 7.5 Hz, 1H), 7.10 - 7.02 (m, 2H), 6.97 (d, <i>J</i> = 7.5 Hz, 1H), 6.66 (d, <i>J</i> = 1.9 Hz, 1H), 5.66 (s, 2H), 4.07 (s, 1H), 3.96 - 3.88 (m, 2H), 3.82 - 3.71 (m, 2H), 3.68 - 3.58 (m, 2H), 2.67 - 2.57 (m, 1H), 2.12 (dd, <i>J</i> = 7.2, 2.8 Hz, 1H), 1.83 - 1.72 (m, 1H) ppm; exchangeable H not observed.
151	Peak 3 	S7	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel	ESI-MS <i>m/z</i> calc. 501.138, found 502.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.14 (s, 1H), 8.13 (s, 1H), 7.45 (tt, <i>J</i> = 8.4, 6.5 Hz, 1H), 7.37 (dd, <i>J</i> = 14.3, 7.5 Hz, 1H), 7.10 - 7.02 (m, 2H), 6.97 (d, <i>J</i> = 7.5 Hz, 1H), 6.66 (d, <i>J</i> = 1.9 Hz, 1H),

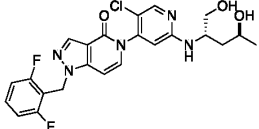
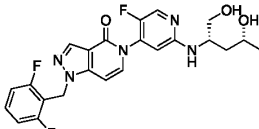
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rel</i> -5-(5-chloro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		Corporation (Mobile phase: 30% 1:1 MeOH: ⁱ PrOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 10.06 min		5.66 (s, 2H), 4.07 (s, 1H), 3.96 - 3.88 (m, 2H), 3.82 - 3.71 (m, 2H), 3.68 - 3.58 (m, 2H), 2.62 (qd, <i>J</i> = 8.1, 4.4 Hz, 1H), 2.13 (ddt, <i>J</i> = 12.0, 7.8, 4.0 Hz, 1H), 1.83 - 1.72 (m, 1H) ppm; exchangeable H not observed.
152	Peak 4  <i>rel</i> -5-(5-chloro-2-(((1 <i>R</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH: ⁱ PrOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 12.67 min	ESI-MS <i>m/z</i> calc. 501.138, found 502.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 1.3 Hz, 2H), 7.55 - 7.45 (m, 2H), 7.21 - 7.13 (m, 2H), 6.96 (t, <i>J</i> = 8.8 Hz, 2H), 6.65 (d, <i>J</i> = 1.4 Hz, 1H), 5.63 (s, 2H), 4.74 (d, <i>J</i> = 20.4 Hz, 1H), 4.01 (s, 1H), 3.81 (td, <i>J</i> = 8.0, 1.9 Hz, 1H), 3.75 - 3.67 (m, 1H), 3.64 - 3.56 (m, 1H), 3.50 - 3.37 (m, 3H), 2.47 (d, <i>J</i> = 8.1 Hz, 1H), 1.94 (ddd, <i>J</i> = 12.1, 8.5, 4.8 Hz, 1H), 1.72 - 1.60 (m, 1H) ppm.
153	 <i>rac</i> -5-(5-chloro-2-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 485.143, found 486.0 (M+1) ⁺ .	

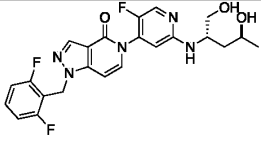
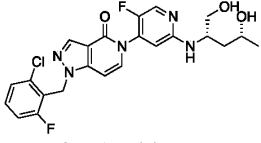
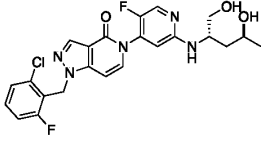
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
154	 5-(5-chloro-2-((4-(hydroxymethyl)tetrahydro-2<i>H</i>-pyran-4-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 501.138, found 502.4 (M+1) ⁺ .	
155	 <i>rac</i>-5-(2-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)-5-fluoropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 469.173, found 470.0 (M+1) ⁺ .	
156	 1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 455.157, found 456.3 (M+1) ⁺ .	
157	 <i>rac</i>-5-(5-chloro-2-(((1<i>R</i>,2<i>R</i>,4<i>R</i>)-2,4-dihydroxycyclopentyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 - 8.15 (m, 2H), 7.47 (dd, <i>J</i> = 7.5, 4.1 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.32 - 7.17 (m, 3H), 7.02 (d, <i>J</i> = 6.6 Hz, 1H), 6.93 (d, <i>J</i> = 7.5 Hz, 1H), 6.60 (d, <i>J</i> = 2.1 Hz, 1H), 5.70 - 5.59 (m,

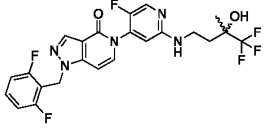
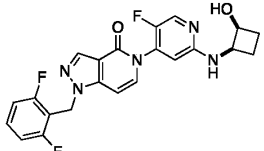
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				2H), 4.95 (dd, $J = 9.5$, 4.9 Hz, 1H), 4.62 (dd, $J = 4.5$, 2.6 Hz, 1H), 4.12 (s, 1H), 4.02 (s, 1H), 3.83 (q, $J = 5.0$ Hz, 1H), 2.25 (dt, $J = 13.8$, 7.1 Hz, 1H), 1.99 (tdd, $J = 12.0$, 7.5, 4.0 Hz, 1H), 1.63 (dq, $J = 13.8$, 7.0 Hz, 1H), 1.43 (dt, $J = 12.9$, 6.2 Hz, 1H) ppm.
158	 1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>S</i> ,3 <i>S</i>)-3-hydroxycyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 441.141, found 443.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.12 (d, $J = 0.8$ Hz, 1H), 8.09 (d, $J = 1.8$ Hz, 1H), 7.59 (dd, $J = 7.6$, 0.6 Hz, 1H), 7.49 (tt, $J = 8.4$, 6.6 Hz, 1H), 7.20 - 7.11 (m, 2H), 7.00 - 6.93 (m, 2H), 6.48 (d, $J = 5.0$ Hz, 1H), 5.62 (s, 2H), 5.04 (d, $J = 6.0$ Hz, 1H), 3.89 - 3.78 (m, 1H), 3.75 - 3.64 (m, 1H), 2.67 - 2.58 (m, 2H), 1.76 - 1.65 (m, 2H) ppm.
159	 (S)-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-((4,4,4-trifluoro-1-hydroxybutan-2-yl)amino)nicotinonitrile	S7		ESI-MS m/z calc. 504.133, found 505.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.56 (s, 1H), 8.15 (d, $J = 0.8$ Hz, 1H), 7.96 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.5$ Hz, 1H), 7.54 - 7.44 (m, 1H), 7.21 - 7.12 (m, 2H), 7.01 (dd, $J = 7.5$, 0.8 Hz, 1H), 6.63 (s, 1H), 5.63 (s, 2H), 5.14 (s, 1H), 4.54 (s, 1H), 3.54 (s, 1H), 3.46 - 3.37 (m, 1H), 2.72 - 2.64 (m, 1H) ppm; exchangeable H not observed.
160	 5-(2-((3,3-bis(hydroxymethyl)cyclobutyl)amino)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 501.138, found 502.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.14 (s, 1H), 8.12 (d, $J = 0.8$ Hz, 1H), 7.54 - 7.44 (m, 2H), 7.21 (d, $J = 7.0$ Hz, 1H), 7.21 - 7.12 (m, 2H), 6.94 (dd, $J = 7.6$, 0.8 Hz, 1H), 6.52 (s, 1H), 5.62 (s, 2H), 4.54 (t, $J = 5.5$ Hz, 1H), 4.49 (t, $J = 5.3$ Hz, 1H), 4.19 (s, 1H), 3.43 (d, $J = 5.5$

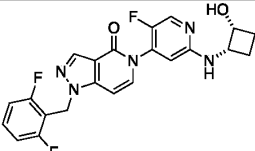
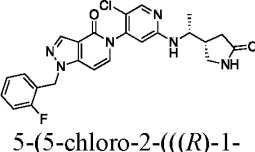
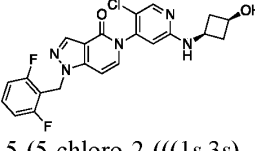
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				Hz, 2H), 3.32 (d, J = 5.3 Hz, 2H), 2.15 - 2.05 (m, 2H), 1.76 - 1.68 (m, 2H) ppm.
161	Peak 1  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiralpak [®] IC column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 5.00 min	ESI-MS m/z calc. 441.141, found 442.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.11 (dd, J = 10.9, 1.3 Hz, 2H), 7.59 (dd, J = 7.6, 0.6 Hz, 1H), 7.53 - 7.44 (m, 1H), 7.20 - 7.11 (m, 2H), 7.05 (d, J = 7.5 Hz, 1H), 7.00 - 6.95 (m, 1H), 6.55 (d, J = 4.9 Hz, 1H), 5.62 (s, 2H), 5.28 (s, 1H), 3.94 (q, J = 8.0 Hz, 1H), 3.85 (q, J = 7.7 Hz, 1H), 2.04 - 1.92 (m, 2H), 1.47 - 1.36 (m, 1H), 1.23 - 1.14 (m, 1H) ppm.
162	Peak 2  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiralpak [®] IC column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 6.02 min	ESI-MS m/z calc. 441.141, found 442.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.12 (d, J = 0.8 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.59 (dd, J = 7.6, 0.6 Hz, 1H), 7.53 - 7.44 (m, 1H), 7.20 - 7.11 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 7.00 - 6.95 (m, 1H), 6.55 (d, J = 4.9 Hz, 1H), 5.62 (s, 2H), 5.27 (s, 1H), 3.98 - 3.90 (m, 1H), 3.89 - 3.81 (m, 1H), 2.03 - 1.92 (m, 2H), 1.47 - 1.36 (m, 1H), 1.27 - 1.14 (m, 1H) ppm.

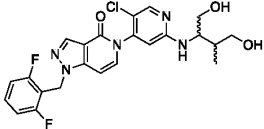
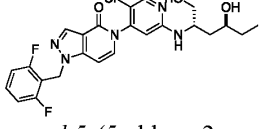
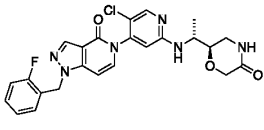
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
163	 <i>rac</i>-6-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)nicotinonitrile	S7		ESI-MS <i>m/z</i> calc. 476.177, found 477.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.49 (s, 1H), 8.16 (d, <i>J</i> = 0.8 Hz, 1H), 7.60 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.32 (s, 1H), 7.21 - 7.12 (m, 2H), 7.03 - 6.98 (m, 1H), 6.74 (s, 1H), 5.63 (s, 2H), 4.91 (s, 1H), 3.80 - 3.76 (m, 1H), 3.69 - 3.66 (m, 1H), 1.54 - 1.48 (m, 1H), 1.04 (s, 3H), 0.47 - 0.38 (m, 1H), 0.41 - 0.32 (m, 3H) ppm.
164	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,3,6-trifluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 489.118, found 490.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 (dd, <i>J</i> = 2.0, 0.8 Hz, 1H), 8.09 (s, 1H), 7.56 (dd, <i>J</i> = 9.6, 5.1 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.22 (dddt, <i>J</i> = 9.3, 5.7, 3.6, 2.0 Hz, 1H), 6.96 (d, <i>J</i> = 7.6 Hz, 1H), 6.91 (dd, <i>J</i> = 8.2, 5.2 Hz, 1H), 6.62 (d, <i>J</i> = 1.2 Hz, 1H), 5.69 - 5.63 (m, 2H), 4.73 (s, 1H), 3.59 - 3.46 (m, 3H), 1.00 (qt, <i>J</i> = 8.1, 5.0 Hz, 1H), 0.43 (dtt, <i>J</i> = 9.2, 7.0, 2.9 Hz, 1H), 0.40 - 0.27 (m, 2H), 0.23 (dtdd, <i>J</i> = 9.0, 7.0, 4.8, 2.1 Hz, 1H) ppm.
165	Peak 1  <i>rel</i>-5-(5-chloro-2-(((2<i>S</i>[*],4<i>R</i>)-1,4-dihydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate	ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 - 8.12 (m, 2H), 7.54 - 7.45 (m, 2H), 7.21 - 7.13 (m, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.80 (t, <i>J</i> = 8.8 Hz, 1H), 6.62 (d, <i>J</i> = 1.0 Hz, 1H), 5.63 (s, 2H), 4.70 (d, <i>J</i> = 12.9 Hz, 1H), 4.54 - 4.46 (m, 1H), 4.04 (s, 1H), 3.72 (s, 1H), 3.50 - 3.44 (m, 1H), 3.43 - 3.33 (m, 1H), 1.68 - 1.58 (m, 1H), 1.48 (ddd, <i>J</i> = 13.5, 9.8, 3.3 Hz, 1H), 1.09 (d, <i>J</i> = 6.2 Hz, 3H) ppm.

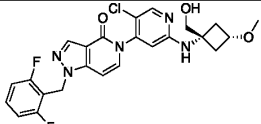
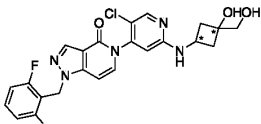
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			100 mL/min); rt = 5.27 min		
166	Peak 2  <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> [*] ,4 <i>S</i>)-1,4-dihydroxypentan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 7.42 min	ESI-MS <i>m/z</i> calc. 489.138, found 490.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 1.2 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.21 - 7.13 (m, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.81 (t, <i>J</i> = 7.7 Hz, 1H), 6.62 (s, 1H), 5.63 (s, 2H), 4.70 (d, <i>J</i> = 12.6 Hz, 1H), 4.45 (dd, <i>J</i> = 10.4, 4.8 Hz, 1H), 4.02 (s, 1H), 3.74 (d, <i>J</i> = 9.3 Hz, 1H), 3.50 (d, <i>J</i> = 10.5 Hz, 1H), 3.45 - 3.34 (m, 1H), 1.71 - 1.53 (m, 2H), 1.08 (dd, <i>J</i> = 6.1, 4.0 Hz, 3H) ppm.
167	Peak 1  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(2-(((2 <i>S</i> [*] ,4 <i>R</i>)-1,4-dihydroxypentan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 4.69 min	ESI-MS <i>m/z</i> calc. 473.167, found 474.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.9 Hz, 1H), 7.60 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 5.0 Hz, 1H), 6.52 (d, <i>J</i> = 8.0 Hz, 1H), 5.63 (s, 2H), 4.67 (t, <i>J</i> = 5.4 Hz, 1H), 4.52 (d, <i>J</i> = 4.8 Hz, 1H), 3.99 (s, 1H), 3.80 - 3.66 (m, 1H), 3.47 (dt, <i>J</i> = 9.9, 4.7 Hz, 1H), 3.38 (dt, <i>J</i> = 10.9, 5.7 Hz, 1H), 1.62 (ddd, <i>J</i> = 13.5, 9.4, 3.8 Hz, 1H), 1.46 (ddd, <i>J</i> = 13.5, 9.7, 3.2 Hz, 1H), 1.09 (d, <i>J</i> = 6.2 Hz, 3H) ppm.
168	Peak 2	S7	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm	ESI-MS <i>m/z</i> calc. 473.167, found	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.9 Hz, 1H), 8.08 (d, <i>J</i> = 1.9 Hz, 1H), 7.60 (d, <i>J</i> = 7.5 Hz, 1H), 7.49 (tt, <i>J</i> =

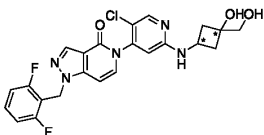
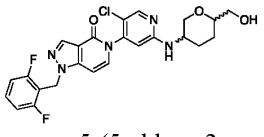
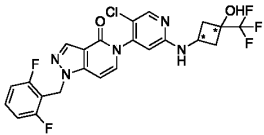
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rel</i>-1-(2,6-difluorobenzyl)-5-(2-(((2S*,4S)-1,4-dihydroxypentan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		x 30 mm from Phenomene x Inc. (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 5.84 min	474.2 (M+1) ⁺ .	8.4, 6.6 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 5.0 Hz, 1H), 6.52 (d, <i>J</i> = 8.2 Hz, 1H), 5.63 (s, 2H), 4.67 (t, <i>J</i> = 5.5 Hz, 1H), 4.44 (d, <i>J</i> = 4.8 Hz, 1H), 3.97 (d, <i>J</i> = 7.7 Hz, 1H), 3.75 (dt, <i>J</i> = 12.0, 6.1 Hz, 1H), 3.50 (dt, <i>J</i> = 9.8, 4.7 Hz, 1H), 3.39 (dt, <i>J</i> = 10.7, 5.5 Hz, 1H), 1.66 (dt, <i>J</i> = 12.7, 6.2 Hz, 1H), 1.57 (dt, <i>J</i> = 13.5, 7.4 Hz, 1H), 1.08 (d, <i>J</i> = 6.1 Hz, 3H) ppm.
169	Peak 1  <i>rel</i>-1-(2-chloro-6-fluorobenzyl)-5-(2-(((2S*,4R)-1,4-dihydroxypentan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S9	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 6.16 min	ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.12 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.9 Hz, 1H), 7.59 (dd, <i>J</i> = 7.5, 0.6 Hz, 1H), 7.49 (td, <i>J</i> = 8.2, 6.1 Hz, 1H), 7.41 (dt, <i>J</i> = 8.0, 1.0 Hz, 1H), 7.31 (ddd, <i>J</i> = 9.5, 8.3, 1.2 Hz, 1H), 7.01 (dd, <i>J</i> = 7.6, 0.8 Hz, 1H), 6.60 (d, <i>J</i> = 5.0 Hz, 1H), 6.51 (d, <i>J</i> = 8.1 Hz, 1H), 5.67 (d, <i>J</i> = 1.5 Hz, 2H), 4.67 (t, <i>J</i> = 5.5 Hz, 1H), 4.52 (d, <i>J</i> = 4.7 Hz, 1H), 3.99 (s, 1H), 3.77 - 3.68 (m, 1H), 3.47 (dt, <i>J</i> = 10.1, 4.9 Hz, 1H), 3.38 (dt, <i>J</i> = 10.5, 5.9 Hz, 1H), 1.62 (ddd, <i>J</i> = 13.5, 9.4, 3.8 Hz, 1H), 1.46 (ddd, <i>J</i> = 13.4, 9.7, 3.2 Hz, 1H), 1.09 (d, <i>J</i> = 6.2 Hz, 3H) ppm.
170	Peak 2  <i>rel</i>-1-(2-chloro-6-fluorobenzyl)-5-(2-(((2S*,4S)-1,4-dihydroxypentan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S9	Lux TM Cellulose-2 column, 5 μm particle size, 15 cm x 30 mm from Phenomene x Inc. (Mobile phase: 33%	ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.12 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.9 Hz, 1H), 7.60 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (td, <i>J</i> = 8.2, 6.1 Hz, 1H), 7.41 (dt, <i>J</i> = 8.0, 1.0 Hz, 1H), 7.31 (ddd, <i>J</i> = 9.6, 8.3, 1.2 Hz, 1H), 7.01 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 5.0 Hz, 1H), 6.51 (d, <i>J</i> = 8.2 Hz,

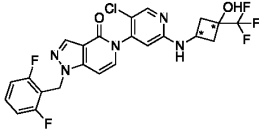
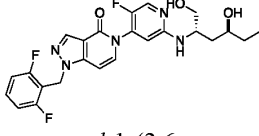
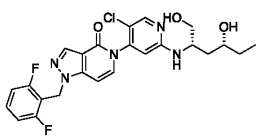
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min; rt = 7.83 min		¹ H, 5.67 (d, <i>J</i> = 1.6 Hz, 2H), 4.67 (t, <i>J</i> = 5.5 Hz, 1H), 4.44 (d, <i>J</i> = 4.9 Hz, 1H), 3.96 (d, <i>J</i> = 9.5 Hz, 1H), 3.75 (dt, <i>J</i> = 11.9, 6.1 Hz, 1H), 3.54 - 3.46 (m, 1H), 3.39 (dt, <i>J</i> = 10.9, 5.6 Hz, 1H), 1.66 (dt, <i>J</i> = 13.6, 6.2 Hz, 1H), 1.57 (dt, <i>J</i> = 13.6, 7.4 Hz, 1H), 1.08 (d, <i>J</i> = 6.1 Hz, 3H) ppm.
171	 <i>rac</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((4,4,4-trifluoro-3-hydroxy-3-methylbutyl)amino)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 511.144, found 512.3 (M+1) ⁺ .	
172	Peak 1  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7	Chiralpak [®] IG column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH:MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min; rt = 9.65 min	ESI-MS <i>m/z</i> calc. 441.141, found 442.3 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.09 (d, <i>J</i> = 1.9 Hz, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.53 - 7.43 (m, 1H), 7.21 - 7.10 (m, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.68 (d, <i>J</i> = 5.0 Hz, 1H), 6.62 (d, <i>J</i> = 6.9 Hz, 1H), 5.63 (s, 2H), 5.19 - 5.14 (m, 1H), 4.36 - 4.32 (m, 1H), 4.27 - 4.23 (m, 1H), 2.09 - 2.00 (m, 2H), 1.90 - 1.73 (m, 2H) ppm.
173	Peak 2	S7	Chiralpak [®] IG column, 5 μm	ESI-MS <i>m/z</i> calc. 441.141,	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.10 (d, <i>J</i> =

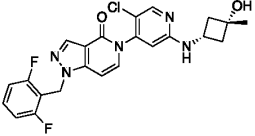
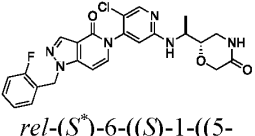
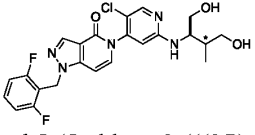
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rel</i>-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1<i>S</i>,2<i>R</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one		particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% 1:1 MeOH: MeCN (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 13.22 min	found 442.3 (M+1) ⁺ .	1.9 Hz, 1H), 7.61 - 7.55 (m, 1H), 7.55 - 7.43 (m, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.69 (d, <i>J</i> = 5.0 Hz, 1H), 6.63 (d, <i>J</i> = 6.9 Hz, 1H), 5.63 (s, 2H), 5.16 (d, <i>J</i> = 4.7 Hz, 1H), 4.37 - 4.33 (m, 1H), 4.28 - 4.24 (m, 1H), 2.10 - 1.99 (m, 2H), 1.91 - 1.73 (m, 2H) ppm.
174	 5-(5-chloro-2-(((<i>R</i>)-1-((<i>R</i>)-5-oxopyrrolidin-3-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 480.148, found 481.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.16 (s, 1H), 7.54 - 7.46 (m, 2H), 7.40 (dddd, <i>J</i> = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.24 - 7.18 (m, 1H), 7.01 (d, <i>J</i> = 8.4 Hz, 1H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 1.5 Hz, 1H), 5.64 (d, <i>J</i> = 2.6 Hz, 2H), 4.05 (s, 1H), 3.33 - 3.26 (m, 1H), 3.03 (dt, <i>J</i> = 9.7, 6.3 Hz, 1H), 2.58 (dt, <i>J</i> = 14.9, 7.7 Hz, 1H), 2.21 (ddd, <i>J</i> = 16.9, 9.1, 7.9 Hz, 1H), 2.04 (dd, <i>J</i> = 16.7, 8.3 Hz, 1H), 1.10 (dd, <i>J</i> = 9.6, 6.5 Hz, 3H) ppm.
175	 5-(5-chloro-2-(((1<i>s</i>,3<i>s</i>)-3-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 457.112, found 458.0 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.14 (s, 1H), 8.12 (d, <i>J</i> = 0.8 Hz, 1H), 7.49 (dd, <i>J</i> = 7.1, 5.6 Hz, 2H), 7.24 (d, <i>J</i> = 7.0 Hz, 1H), 7.20 - 7.12 (m, 2H), 6.94 (d, <i>J</i> = 7.5 Hz, 1H), 6.51 (s, 1H), 5.62 (s, 2H), 5.06 (d, <i>J</i> = 6.0 Hz, 1H), 3.91 - 3.64 (m, 2H), 2.66

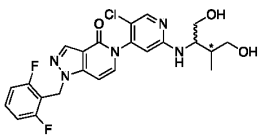
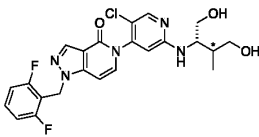
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				- 2.59 (m, 2H), 1.73 (s, 2H) ppm.
176	 <i>rac</i>-5-(5-chloro-2-((1,4-dihydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 489.138, found 490.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 - 8.11 (m, 2H), 7.54 - 7.46 (m, 2H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.96 (d, <i>J</i> = 7.5 Hz, 1H), 6.73 (t, <i>J</i> = 10.1 Hz, 1H), 6.69 (d, <i>J</i> = 1.1 Hz, 1H), 5.63 (s, 2H), 4.74 - 4.64 (m, 1H), 4.57 (dt, <i>J</i> = 9.3, 5.5 Hz, 1H), 4.08 (s, 1H), 3.52 (tt, <i>J</i> = 10.7, 5.6 Hz, 1H), 3.45 (td, <i>J</i> = 11.0, 5.7 Hz, 0.5H), 3.37 (dq, <i>J</i> = 10.4, 5.4 Hz, 0.5H), 1.94 (dt, <i>J</i> = 12.2, 6.2 Hz, 1H), 0.94 (d, <i>J</i> = 7.3 Hz, 1H), 0.87 (dd, <i>J</i> = 6.9, 1.2 Hz, 2H) ppm; exchangeable H not observed.
177	Peak 1  <i>rel</i>-5-(5-chloro-2-(((2<i>S</i>[*],4<i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μm particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 100 mL/min); rt = 6.31 min	ESI-MS <i>m/z</i> calc. 503.154, found 504.2 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.13 (q, <i>J</i> = 1.0 Hz, 2H), 7.56 - 7.44 (m, 2H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.81 (t, <i>J</i> = 7.7 Hz, 1H), 6.62 (s, 1H), 5.63 (s, 2H), 4.68 (dt, <i>J</i> = 10.8, 5.4 Hz, 1H), 4.39 (dd, <i>J</i> = 8.2, 5.5 Hz, 1H), 4.04 (s, 1H), 3.56 - 3.38 (m, 3H), 1.78 - 1.70 (m, 1H), 1.56 - 1.39 (m, 2H), 1.31 (dt, <i>J</i> = 13.7, 7.1 Hz, 1H), 0.86 (t, <i>J</i> = 7.3 Hz, 3H) ppm.
178		S2		ESI-MS <i>m/z</i> calc. 496.143, found	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 - 8.16 (m, 1H), 8.15 (d, <i>J</i> = 2.1 Hz, 1H), 7.96 (d, <i>J</i> = 2.9 Hz, 1H), 7.49 (dd, <i>J</i> =

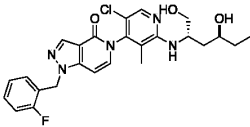
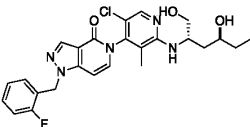
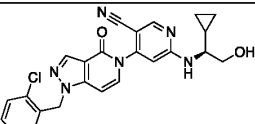
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rel</i> -(<i>R</i> [*])-6-((<i>R</i>)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)pyridin-2-yl)amino)ethyl)morpholin-3-one			497.3 (M+1) ⁺ .	14.4, 7.5 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.31 - 7.18 (m, 3H), 7.01 - 6.97 (m, 1H), 6.93 (d, <i>J</i> = 7.4 Hz, 1H), 6.66 (d, <i>J</i> = 3.6 Hz, 1H), 5.64 (d, <i>J</i> = 2.7 Hz, 2H), 4.28 (s, 1H), 4.10 (dd, <i>J</i> = 16.4, 2.0 Hz, 1H), 4.02 (d, <i>J</i> = 16.4 Hz, 1H), 3.76 (dq, <i>J</i> = 9.1, 4.5 Hz, 1H), 3.23 - 3.15 (m, 2H), 1.18 (dd, <i>J</i> = 9.5, 6.8 Hz, 3H) ppm.
179	 5-(5-chloro-2-(((1 <i>s</i> ,3 <i>s</i>)-1-(hydroxymethyl)-3-methoxycyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 501.138, found 502.1 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.14 - 8.09 (m, 2H), 7.55 - 7.43 (m, 2H), 7.17 (dd, <i>J</i> = 16.2, 8.2 Hz, 3H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.53 (s, 1H), 5.62 (s, 2H), 4.91 (t, <i>J</i> = 5.6 Hz, 1H), 3.77 - 3.69 (m, 1H), 3.64 - 3.49 (m, 2H), 3.12 (s, 3H), 2.66 - 2.57 (m, 2H), 1.97 - 1.88 (m, 2H) ppm.
180	Peak 1 Syn or anti  5-(5-chloro-2-((3-hydroxy-3-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiralpak [®] ID column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 7.42 min	ESI-MS <i>m/z</i> calc. 487.122, found 488.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 8.11 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.21 (d, <i>J</i> = 6.5 Hz, 1H), 7.21 - 7.12 (m, 2H), 6.97 - 6.92 (m, 1H), 6.52 (s, 1H), 5.62 (s, 2H), 4.80 (s, 1H), 4.68 - 4.64 (m, 1H), 4.36 - 4.32 (m, 1H), 3.26 (s, 2H), 2.20 - 2.11 (m, 2H), 2.07 - 1.98 (m, 2H) ppm.
181	Peak 2 Anti or syn	S7	Chiralpak [®] ID column,	ESI-MS <i>m/z</i> calc.	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.12 (dd,

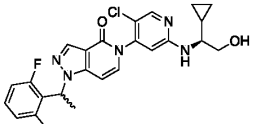
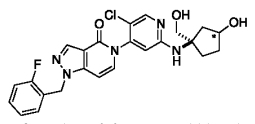
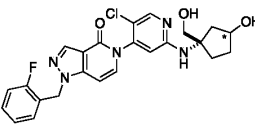
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 5-(5-chloro-2-((3-hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% MeOH (supplemented with 20 mM ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 9.06 min	487.122, found 488.2 (M+1) ⁺ .	J = 3.1, 0.6 Hz, 2H), 7.48 - 7.39 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.95 (dd, J = 7.6, 0.8 Hz, 1H), 6.56 (d, J = 0.5 Hz, 1H), 5.64 (s, 2H), 3.91 - 3.81 (m, 1H), 3.52 (s, 2H), 2.71 - 2.61 (m, 2H), 1.97 - 1.89 (m, 2H) ppm; exchangeable H not observed.
182	Syn  <i>rac</i>-5-(5-chloro-2-(((3<i>S</i>,6<i>S</i>)-6-(hydroxymethyl)tetrahydro-2<i>H</i>-pyran-3-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 501.138, found 502.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.15 (s, 1H), 8.12 (d, J = 0.7 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.21 - 7.12 (m, 2H), 7.08 (d, J = 7.3 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 5.62 (s, 2H), 4.57 (q, J = 5.4 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.91 - 3.83 (m, 1H), 3.61 - 3.54 (m, 1H), 3.46 - 3.39 (m, 1H), 3.38 - 3.27 (m, 2H), 1.94 - 1.84 (m, 1H), 1.81 - 1.70 (m, 1H), 1.59 - 1.44 (m, 2H) ppm.
183	Peak 1 Syn or anti  5-(5-chloro-2-((3-(trifluoromethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 525.099, found 526.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (s, 1H), 8.12 (d, J = 0.8 Hz, 1H), 7.54 - 7.43 (m, 3H), 7.21 - 7.12 (m, 2H), 6.95 (d, J = 7.5 Hz, 1H), 6.56 (s, 1H), 6.47 (s, 1H), 5.62 (s, 2H), 4.54 (q, J = 7.8 Hz, 1H), 2.47 - 2.38 (m, 2H), 2.28 - 2.19 (m, 2H) ppm.

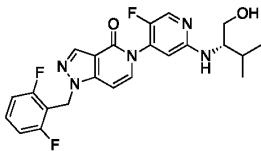
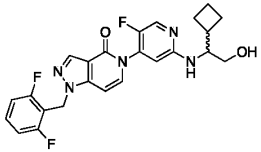
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
184	Peak 2 Anti or syn  5-(5-chloro-2-((3-hydroxy-3-(trifluoromethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 525.099, found 526.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.54 - 7.44 (m, 3H), 7.20 - 7.12 (m, 2H), 6.95 (d, <i>J</i> = 7.6 Hz, 1H), 6.62 (s, 1H), 6.58 (s, 1H), 5.62 (d, <i>J</i> = 1.9 Hz, 2H), 4.04 - 3.98 (m, 1H), 2.90 - 2.80 (m, 2H), 2.20 - 2.11 (m, 2H) ppm.
185	Peak 1  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(2-(((2 <i>S</i> [*] ,4 <i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5-dihydro-4H-pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiralcel® OJ column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 10% MeOH (supplemented with 20 mM ammonia), 90% CO ₂ ; Flow rate 100 mL/min); rt = 5.53 min	ESI-MS <i>m/z</i> calc. 487.183, found 488.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.59 (d, <i>J</i> = 7.5 Hz, 1H), 7.49 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.16 (t, <i>J</i> = 8.0 Hz, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 5.0 Hz, 1H), 6.51 (d, <i>J</i> = 8.1 Hz, 1H), 5.63 (s, 2H), 4.66 (t, <i>J</i> = 5.4 Hz, 1H), 4.39 (d, <i>J</i> = 5.4 Hz, 1H), 3.98 (s, 1H), 3.51 (dt, <i>J</i> = 10.3, 4.8 Hz, 2H), 3.42 (dt, <i>J</i> = 10.6, 5.4 Hz, 1H), 1.74 (dt, <i>J</i> = 13.7, 6.0 Hz, 1H), 1.54 - 1.39 (m, 2H), 1.32 (dq, <i>J</i> = 13.9, 7.3 Hz, 1H), 0.86 (t, <i>J</i> = 7.4 Hz, 3H) ppm.
186	Peak 2  <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> [*] ,4 <i>R</i>)-1,4-dihydroxyhexan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7	Chiral Art Amylose-SA column, 5 μm particle size, 25 cm x 20 mm from YMC Europe GmbH (Mobile	ESI-MS <i>m/z</i> calc. 503.154, found 504.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.13 (q, <i>J</i> = 1.2 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.81 (t, <i>J</i> = 8.1 Hz, 1H), 6.62 (s, 1H), 5.63 (s, 2H), 4.70 (s, 1H), 4.39 (s, 1H), 4.04 (s, 1H), 3.50 (s, 3H), 1.79 - 1.70 (m, 1H), 1.55 - 1.39 (m, 2H), 1.32 (dt, <i>J</i> = 14.0,

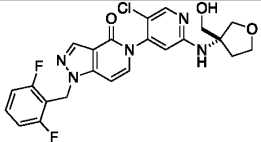
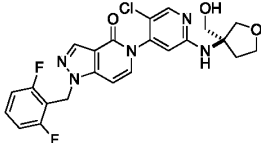
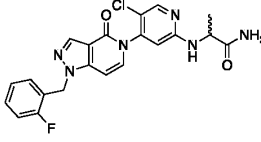
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 100 mL/min; rt = 9.71 min		7.2 Hz, 1H), 0.86 (t, <i>J</i> = 7.3 Hz, 3H) ppm.
187	 5-(5-chloro-2-(((1 <i>S</i> ,3 <i>S</i>)-3-hydroxy-3-methylcyclobutyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 471.127, found 472.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.15 (s, 1H), 8.12 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.23 (d, <i>J</i> = 6.7 Hz, 1H), 7.20 - 7.12 (m, 2H), 6.94 (d, <i>J</i> = 7.5 Hz, 1H), 6.54 (s, 1H), 5.62 (d, <i>J</i> = 2.5 Hz, 2H), 4.96 (s, 1H), 3.80 (m, 1H), 2.42 - 2.32 (m, 2H), 1.96 - 1.88 (m, 2H), 1.25 (s, 3H) ppm.
188	 <i>rel</i> -(<i>S</i> [*])-6-((<i>S</i>)-1-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)pyridin-2-yl)amino)ethyl)morpholin-3-one	S2		ESI-MS <i>m/z</i> calc. 496.143, found 497.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (s, 2H), 7.97 (dd, <i>J</i> = 15.4, 3.8 Hz, 1H), 7.48 (dd, <i>J</i> = 7.5, 6.2 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.30 - 7.19 (m, 3H), 7.05 (t, <i>J</i> = 7.6 Hz, 1H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 6.63 (d, <i>J</i> = 1.2 Hz, 1H), 5.64 (d, <i>J</i> = 3.2 Hz, 2H), 4.15 (s, 1H), 4.13 - 4.00 (m, 2H), 3.66 (dddd, <i>J</i> = 13.2, 9.9, 6.3, 3.7 Hz, 1H), 3.27 - 3.16 (m, 2H), 1.19 (t, <i>J</i> = 6.8 Hz, 3H) ppm.
189	Peak 1  <i>rel</i> -5-(5-chloro-2-(((2 <i>R</i>)-1,4-dihydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-	S7	Chiralpak® IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile	ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.15 - 8.11 (m, 2H), 7.55 - 7.45 (m, 2H), 7.21 - 7.13 (m, 2H), 6.96 (d, <i>J</i> = 7.6 Hz, 1H), 6.73 (t, <i>J</i> = 10.0 Hz, 1H), 6.69 (d, <i>J</i> = 1.1 Hz, 1H), 5.63 (s, 2H), 4.68 (dt, <i>J</i> = 16.4, 5.4 Hz, 1H), 4.57 (ddd, <i>J</i> = 9.2, 6.0, 5.0 Hz,

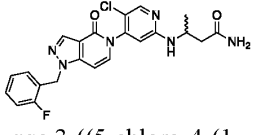
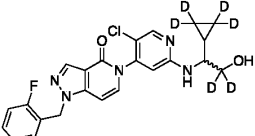
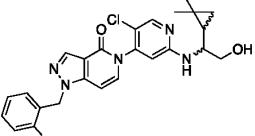
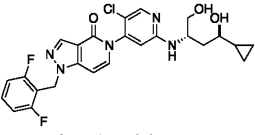
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one		phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 100 mL/min; rt = 7.13 min		¹ H, 4.07 (s, 1H), 3.51 - 3.48 (m, 2H), 3.36 (td, <i>J</i> = 10.8, 4.8 Hz, 1H), 3.30 - 3.26 (m, 1H), 1.95 (dq, <i>J</i> = 13.0, 6.7 Hz, 1H), 0.87 (dd, <i>J</i> = 6.9, 1.2 Hz, 3H) ppm.
190	Peak 2 & 3  <i>rac</i> -5-(5-chloro-2-((1,4-dihydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 100 mL/min; rt = 10.12 min	ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	
191	Peak 4  <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i>)-1,4-dihydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7	Chiralpak [®] IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ;	ESI-MS <i>m/z</i> calc. 489.138, found 490.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.15 - 8.09 (m, 2H), 7.55 - 7.45 (m, 2H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.96 (d, <i>J</i> = 7.5 Hz, 1H), 6.74 (t, <i>J</i> = 9.4 Hz, 1H), 6.69 (d, <i>J</i> = 1.1 Hz, 1H), 5.63 (s, 2H), 4.69 (s, 1H), 4.58 (s, 1H), 4.07 (s, 1H), 3.55 - 3.42 (m, 2H), 3.36 (dt, <i>J</i> = 10.8, 5.6 Hz, 1H), 1.94 (dt, <i>J</i> = 13.0, 6.5 Hz, 1H), 0.87 (dd, <i>J</i> = 6.9, 1.2 Hz, 3H) ppm; exchangeable H not observed.

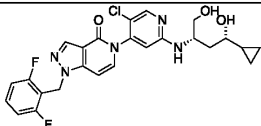
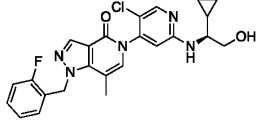
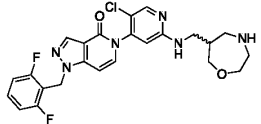
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			Flow rate 100 mL/min); rt = 12.01 min		
192	Atropisomer 1  <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> [*] ,4 <i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 499.179, found 500.2 (<i>M</i> +1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.07 (d, <i>J</i> = 0.7 Hz, 1H), 7.44 - 7.35 (m, 2H), 7.33 - 7.18 (m, 3H), 6.98 - 6.93 (m, 1H), 5.97 (d, <i>J</i> = 7.2 Hz, 1H), 5.69 - 5.59 (m, 2H), 4.64 (t, <i>J</i> = 5.7 Hz, 1H), 4.50 (d, <i>J</i> = 5.3 Hz, 1H), 4.25 - 4.15 (m, 1H), 3.63 - 3.55 (m, 1H), 3.55 - 3.46 (m, 1H), 3.44 - 3.36 (m, 1H), 1.86 - 1.76 (m, 4H), 1.64 - 1.55 (m, 1H), 1.51 - 1.40 (m, 1H), 1.40 - 1.28 (m, 1H), 0.86 (t, <i>J</i> = 7.4 Hz, 3H) ppm.
193	Atropisomer 2  <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> [*] ,4 <i>S</i>)-1,4-dihydroxyhexan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 499.179, found 500.2 (<i>M</i> +1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.07 (d, <i>J</i> = 0.7 Hz, 1H), 7.44 - 7.36 (m, 2H), 7.33 - 7.17 (m, 3H), 6.98 - 6.93 (m, 1H), 5.94 (d, <i>J</i> = 7.5 Hz, 1H), 5.64 (s, 2H), 4.68 (t, <i>J</i> = 5.7 Hz, 1H), 4.44 (d, <i>J</i> = 5.3 Hz, 1H), 4.26 - 4.16 (m, 1H), 3.61 - 3.51 (m, 1H), 3.54 - 3.39 (m, 2H), 1.85 - 1.76 (m, 4H), 1.63 - 1.53 (m, 1H), 1.50 - 1.39 (m, 1H), 1.39 - 1.27 (m, 1H), 0.86 (t, <i>J</i> = 7.4 Hz, 3H) ppm.
194	 (<i>S</i>)-4-(1-(2-chloro-6-fluorobenzyl)-4-oxo-1,4-dihydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-((1-cyclopropyl-1-hydroxyethyl)amino)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S9		ESI-MS <i>m/z</i> calc. 478.132, found 479.2 (<i>M</i> +1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.47 (s, 1H), 8.14 (d, <i>J</i> = 0.8 Hz, 1H), 7.85 (s, 1H), 7.60 (d, <i>J</i> = 7.6 Hz, 1H), 7.52 - 7.44 (m, 1H), 7.43 - 7.38 (m, 1H), 7.35 - 7.27 (m, 1H), 7.03 (d, <i>J</i> = 7.6 Hz, 1H), 6.63 (s, 1H), 5.68 (s, 2H), 4.81 - 4.78 (m, 1H), 3.73

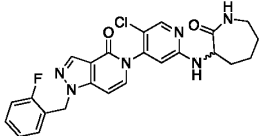
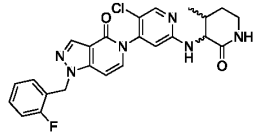
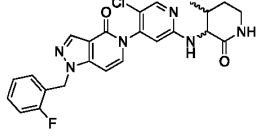
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	2-hydroxyethyl)amino)nicotinonitrile				- 3.51 (m, 3H), 1.06 - 1.01 (m, 1H), 0.52 - 0.36 (m, 2H), 0.35 - 0.13 (m, 2H) ppm.
195	 <i>rac</i>-5-(5-chloro-2-(((<i>S</i>)-1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(1-(2,6-difluorophenyl)ethyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB1		ESI-MS <i>m/z</i> calc. 485.143, found 486.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, <i>J</i> = 2.1 Hz, 1H), 8.08 (d, <i>J</i> = 4.7 Hz, 1H), 7.50 - 7.38 (m, 2H), 7.13 (td, <i>J</i> = 8.6, 1.9 Hz, 2H), 6.95 (s, 1H), 6.77 - 6.68 (m, 1H), 6.62 (q, <i>J</i> = 2.2 Hz, 1H), 6.29 (q, <i>J</i> = 7.0 Hz, 1H), 3.53 - 3.46 (m, 3H), 2.00 (t, <i>J</i> = 5.9 Hz, 3H), 0.99 (qt, <i>J</i> = 8.9, 4.3 Hz, 1H), 0.44 (dt, <i>J</i> = 9.3, 3.9 Hz, 1H), 0.41 - 0.29 (m, 2H), 0.22 (dq, <i>J</i> = 9.5, 3.8 Hz, 1H) ppm; exchangeable H not observed.
196	Peak 1  <i>rel</i>-5-(5-chloro-2-(((1<i>R</i>)-3-hydroxy-1-(hydroxymethyl)cyclopentyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Lux TM i-Amilose-1 column, 5 μm particle size, 25 cm x 21.2 mm from Phenomenex Inc. (Mobile phase: 35% MeOH (supplemented with 0.2% ammonia), 65% CO ₂ ; Flow rate 50 mL/min); rt = 7.30 min	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.11 (s, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.4 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.32 - 7.17 (m, 3H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.84 (s, 1H), 6.69 (d, <i>J</i> = 2.7 Hz, 1H), 5.64 (d, <i>J</i> = 1.8 Hz, 2H), 4.91 (td, <i>J</i> = 5.6, 2.5 Hz, 1H), 4.80 (d, <i>J</i> = 4.9 Hz, 1H), 4.09 (q, <i>J</i> = 5.5 Hz, 1H), 3.63 - 3.44 (m, 2H), 2.10 (dt, <i>J</i> = 13.6, 6.6 Hz, 1H), 2.06 - 1.94 (m, 1H), 1.79 (d, <i>J</i> = 14.0 Hz, 2H), 1.72 (dt, <i>J</i> = 12.4, 6.0 Hz, 1H), 1.61 (dt, <i>J</i> = 12.7, 6.3 Hz, 1H) ppm.
197	Peak 2 	S2	Lux TM i-Amilose-1 column, 5 μm particle size, 25 cm x 21.2 mm	ESI-MS <i>m/z</i> calc. 483.147, found 484.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 8.11 (s, 1H), 7.47 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 7.40 (dddd, <i>J</i> = 9.1, 7.3, 5.4, 1.9 Hz, 1H), 7.32 - 7.19 (m, 3H), 6.92 (d, <i>J</i>

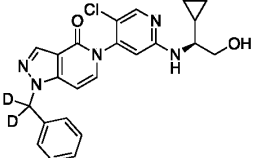
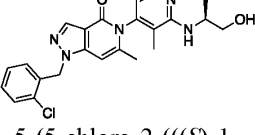
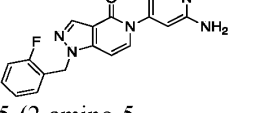
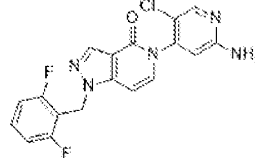
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rel</i> -5-(5-chloro-2-(((1 <i>S</i>)-3-hydroxy-1-(hydroxymethyl)cyclopentyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		from Phenomene x Inc. (Mobile phase: 35% MeOH (supplemented with 0.2% ammonia), 65% CO ₂ ; Flow rate 50 mL/min); rt = 8.70 min		= 7.6 Hz, 1H), 6.84 (d, <i>J</i> = 2.0 Hz, 1H), 6.69 (d, <i>J</i> = 2.7 Hz, 1H), 5.64 (d, <i>J</i> = 1.9 Hz, 2H), 4.91 (td, <i>J</i> = 5.6, 2.5 Hz, 1H), 4.80 (d, <i>J</i> = 4.8 Hz, 1H), 4.09 (q, <i>J</i> = 5.4 Hz, 1H), 3.64 - 3.45 (m, 2H), 2.10 (dt, <i>J</i> = 13.6, 6.6 Hz, 1H), 2.00 (td, <i>J</i> = 12.7, 6.3 Hz, 1H), 1.85 - 1.76 (m, 2H), 1.72 (dq, <i>J</i> = 13.3, 6.6 Hz, 1H), 1.61 (dt, <i>J</i> = 12.7, 6.4 Hz, 1H) ppm.
198	 (<i>S</i>)-1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((1-hydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 457.173, found 458.5 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 (d, <i>J</i> = 0.8 Hz, 1H), 8.07 (d, <i>J</i> = 1.9 Hz, 1H), 7.61 (d, <i>J</i> = 7.6 Hz, 1H), 7.50 (tt, <i>J</i> = 8.4, 6.7 Hz, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.65 (d, <i>J</i> = 5.0 Hz, 1H), 6.45 (d, <i>J</i> = 8.7 Hz, 1H), 5.63 (s, 2H), 4.57 (t, <i>J</i> = 5.3 Hz, 1H), 3.80 (dd, <i>J</i> = 8.7, 5.7 Hz, 1H), 3.55 - 3.40 (m, <i>J</i> = 5.2 Hz, 2H), 1.98 (dq, <i>J</i> = 13.6, 6.9 Hz, 1H), 0.93 (dd, <i>J</i> = 6.8, 1.9 Hz, 6H) ppm.
199	 <i>rac</i> -5-(2-((1-cyclobutyl-2-hydroxyethyl)amino)-5-fluoropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 469.173, found 470.5 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.14 (d, <i>J</i> = 0.8 Hz, 1H), 8.07 (d, <i>J</i> = 1.9 Hz, 1H), 7.65 - 7.58 (m, 1H), 7.50 (tt, <i>J</i> = 8.5, 6.7 Hz, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 6.98 (d, <i>J</i> = 7.6 Hz, 1H), 6.63 (d, <i>J</i> = 5.1 Hz, 1H), 6.44 (d, <i>J</i> = 8.6 Hz, 1H), 5.63 (s, 2H), 4.54 (t, <i>J</i> = 5.4 Hz, 1H), 3.94 (dt, <i>J</i> = 8.6, 4.1 Hz, 1H), 3.38 (q, <i>J</i> = 4.1 Hz, 2H), 2.57 (q, <i>J</i> = 8.4 Hz, 1H), 1.98 - 1.90 (m, 2H), 1.89 - 1.70 (m, 4H) ppm.
200	Peak 1	S7	Lux™ Cellulose-4	ESI-MS <i>m/z</i> calc.	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 (d, <i>J</i> =

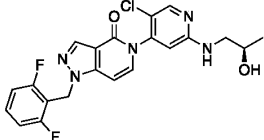
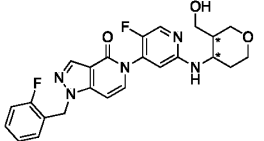
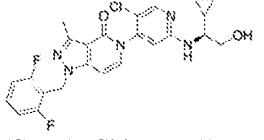
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rel-(R)-5-(5-chloro-2-((3-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one</i>		column, 5 μ m particle size, 25 cm x 21.2 mm from Phenomene x Inc. (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 7.40 min	487.122, found 488.2 (M+1) ⁺ .	2.9 Hz, 1H), 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 7.49 (ddd, <i>J</i> = 9.4, 7.9, 6.1 Hz, 2H), 7.21 - 7.11 (m, 3H), 6.96 (d, <i>J</i> = 7.6 Hz, 1H), 6.66 (s, 1H), 5.63 (s, 2H), 4.99 (s, 1H), 3.91 - 3.63 (m, 6H), 2.18 - 2.05 (m, 2H) ppm.
201	Peak 2  <i>rel-(S)-5-(5-chloro-2-((3-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one</i>	S7	Lux TM Cellulose-4 column, 5 μ m particle size, 25 cm x 21.2 mm from Phenomene x Inc. (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 8.73 min	ESI-MS <i>m/z</i> calc. 487.122, found 488.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 (d, <i>J</i> = 2.9 Hz, 1H), 8.13 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.45 (m, 2H), 7.21 - 7.11 (m, 3H), 6.96 (d, <i>J</i> = 7.6 Hz, 1H), 6.66 (s, 1H), 5.63 (s, 2H), 5.00 (s, 1H), 3.90 - 3.63 (m, 6H), 2.19 - 2.04 (m, 2H) ppm.
202	 <i>rac-2-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-4-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one</i>	S2		ESI-MS <i>m/z</i> calc. 440.116, found 441.3 (M+1) ⁺ .	

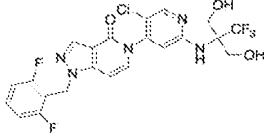
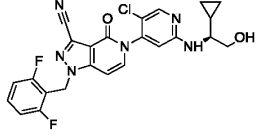
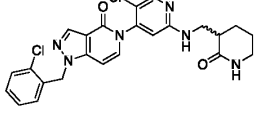
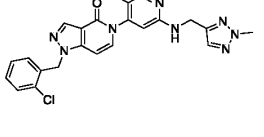
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	5-yl)pyridin-2-yl)amino)propanamide				
203	 <i>rac</i> -3-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)butanamide	S2		ESI-MS <i>m/z</i> calc. 454.132, found 455.3 (M+1) ⁺ .	
204	 <i>rac</i> -5-(5-chloro-2-((1-(cyclopropyl-2,2,3,3- <i>d</i> ₄)-2-hydroxyethyl-2,2- <i>d</i> ₂)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 459.174, found 460.2 (M+1) ⁺ .	
205	 <i>rac</i> -5-(5-chloro-2-((1-(2,2-dimethylcyclopropyl)-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 481.168, found 482.3 (M+1) ⁺ .	
206	 <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> [*] ,4 <i>R</i>)-4-cyclopropyl-1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 515.154, found 516.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12 (dd, <i>J</i> = 2.8, 0.8 Hz, 2H), 7.54 - 7.45 (m, 2H), 7.21 - 7.13 (m, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.77 (t, <i>J</i> = 8.8 Hz, 1H), 6.61 (s, 1H), 5.63 (s, 2H), 4.68 (s, 1H), 4.54 - 4.45 (m, 1H), 4.07 (s, 1H), 3.51 - 3.36 (m, 2H), 2.99 (d, <i>J</i> = 12.6 Hz,

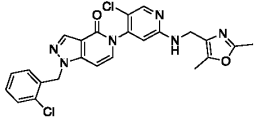
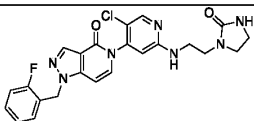
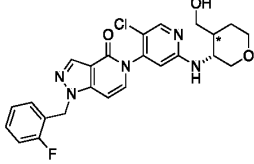
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				1H), 1.73 (ddt, $J = 13.9$, 9.4, 4.1 Hz, 1H), 1.65 (td, $J = 10.3$, 3.2 Hz, 1H), 0.81 (p, $J = 5.1$ Hz, 1H), 0.34 (ddt, $J = 8.8$, 6.2, 3.6 Hz, 2H), 0.25 (t, $J = 4.9$ Hz, 1H), 0.20 - 0.14 (m, 1H) ppm.
207	 <i>rel</i> -5-(5-chloro-2-(((2 <i>S</i> *,4 <i>S</i>)-4-cyclopropyl-1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 515.154, found 516.4 (M+1) ⁺ .	
208	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-7-methyl-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S12		ESI-MS m/z calc. 467.152, found 468.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.26 (s, 1H), 8.08 (s, 1H), 7.41 - 7.34 (m, 1H), 7.23 - 7.07 (m, 3H), 6.85 - 6.79 (m, 1H), 6.64 (s, 1H), 5.87 (d, $J = 5.4$ Hz, 2H), 3.77 (s, 1H), 3.71 - 3.65 (m, 1H), 3.49 - 3.39 (m, 1H), 2.38 - 2.34 (m, 3H), 1.05 (br d, $J = 4.6$ Hz, 1H), 0.56 (br d, $J = 3.8$ Hz, 1H), 0.49 (br d, $J = 4.4$ Hz, 1H), 0.43 - 0.29 (m, 2H) ppm; exchangeable H not observed.
209	 <i>rac</i> -5-(2-(((1,4-oxazepan-6-yl)methyl)amino)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S7		ESI-MS m/z calc. 500.154, found 501.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, $J = 1.1$ Hz, 1H), 8.12 (d, $J = 0.8$ Hz, 1H), 7.54 - 7.45 (m, 2H), 7.27 - 7.07 (m, 3H), 6.95 (d, $J = 7.6$ Hz, 1H), 6.60 (s, 1H), 5.63 (s, 2H), 3.80 (dd, $J = 12.3$, 5.0 Hz, 1H), 3.60 (d, $J = 5.0$ Hz, 2H), 3.52 (ddd, $J = 12.3$, 6.8, 3.0 Hz, 1H), 3.16 (t, $J = 6.3$ Hz, 2H), 3.05 - 2.95 (m, 1H), 2.89

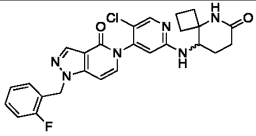
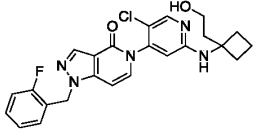
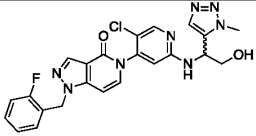
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					- 2.75 (m, 2H), 2.64 (p, J = 1.9 Hz, 1H), 2.15 (d, J = 6.5 Hz, 1H) ppm; exchangeable H not observed.
210	 <i>rac</i> -5-(5-chloro-2-((2-oxoazepan-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 480.148, found 481.3 (M+1) ⁺ .	
211	Peak 1 Syn or anti  <i>rac</i> -5-(5-chloro-2-((4-methyl-2-oxopiperidin-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 480.148, found 481.3 (M+1) ⁺ .	
212	Peak 2 Anti or syn  <i>rac</i> -5-(5-chloro-2-((4-methyl-2-oxopiperidin-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 480.148, found 481.3 (M+1) ⁺ .	

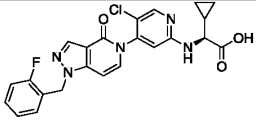
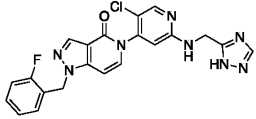
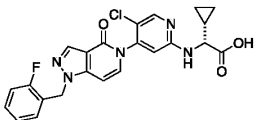
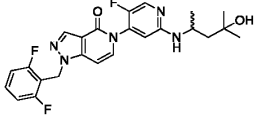
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
213	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(phenylmethyl-d_2)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	SB1		ESI-MS m/z calc. 437.159, found 438.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- d_4) δ 8.20 (s, 1H), 8.12 (s, 1H), 7.41 - 7.25 (m, 6H), 7.02 (d, J = 3.6 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 3.85 (dd, J = 11.2, 3.8 Hz, 1H), 3.69 (ddd, J = 11.1, 6.7, 2.1 Hz, 1H), 3.33 (d, J = 8.7 Hz, 1H), 1.11 - 1.00 (m, 1H), 0.66 - 0.60 (m, 1H), 0.57 (qd, J = 9.4, 5.2 Hz, 1H), 0.38 (dq, J = 9.0, 5.7 Hz, 2H) ppm; exchangeable H not observed.
214	Atropisomer 1  5-(5-chloro-2-(((S)-1-hydroxypropan-2-yl)amino)-3-methylpyridin-4-yl)-1-(2-chlorobenzyl)-6-methyl-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S4		ESI-MS m/z calc. 471.123, found 472.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- d_4) δ 8.17 (d, J = 0.6 Hz, 1H), 8.08 (s, 1H), 7.49 - 7.45 (m, 1H), 7.36 - 7.26 (m, 2H), 7.02 - 6.98 (m, 1H), 6.78 (s, 1H), 5.66 (s, 2H), 4.34 - 4.25 (m, 1H), 3.64 (s, 2H), 2.05 - 2.01 (m, 3H), 1.86 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H) ppm; exchangeable H not observed.
215	 5-(2-amino-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS m/z calc. 369.079, found 370.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.17 (d, J = 0.8 Hz, 1H), 8.10 (s, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.40 (dddd, J = 8.3, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.18 (m, 3H), 6.95 - 6.90 (m, 1H), 6.53 (s, 1H), 6.45 (s, 2H), 5.64 (d, J = 3.2 Hz, 2H) ppm.
216	 5-(2-amino-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS m/z calc. 387.070, found 387.9 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- d_6) δ 8.12 (d, J = 0.8 Hz, 1H), 8.10 (s, 1H), 7.54 - 7.44 (m, 2H), 7.21 - 7.12 (m, 2H), 6.95 (d, J = 7.4 Hz, 1H), 6.53 (s, 1H), 6.45 (s, 2H), 5.62 (s, 2H) ppm.

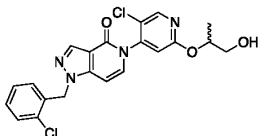
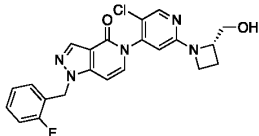
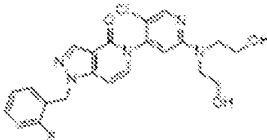
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
217	 (<i>R</i>)-5-(5-chloro-2-((2-hydroxypropyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 455.112, found 446.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.14 (s, 1H), 8.12 (d, <i>J</i> = 0.8 Hz, 1H), 7.53 - 7.45 (m, 2H), 7.16 (t, <i>J</i> = 8.0 Hz, 2H), 7.03 - 6.97 (m, 1H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.66 (s, 1H), 5.62 (s, 2H), 4.73 (dd, <i>J</i> = 13.0, 4.7 Hz, 1H), 3.79 (dtd, <i>J</i> = 6.3, 3.3, 1.7 Hz, 1H), 3.26 (ddd, <i>J</i> = 13.3, 7.6, 5.7 Hz, 1H), 3.21 - 3.10 (m, 1H), 1.09 (dd, <i>J</i> = 6.3, 1.2 Hz, 3H) ppm.
218	Peak 2  <i>rel</i>-5-(5-fluoro-2-((3-(hydroxymethyl)tetrahydro-2<i>H</i>-pyran-4-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2	Chiralcel® OJ column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 18% MeOH (supplemented with 20 mM ammonia), 82% CO ₂ ; Flow rate 100 mL/min); rt = 4.92 min	ESI-MS <i>m/z</i> calc. 467.177, found 468.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 8.12 (d, <i>J</i> = 1.9 Hz, 1H), 7.59 (dd, <i>J</i> = 7.6, 0.6 Hz, 1H), 7.40 (dddd, <i>J</i> = 8.2, 7.2, 5.4, 2.0 Hz, 1H), 7.29 - 7.17 (m, 3H), 6.95 (dt, <i>J</i> = 7.7, 0.6 Hz, 1H), 6.79 (d, <i>J</i> = 7.7 Hz, 1H), 6.66 (d, <i>J</i> = 5.0 Hz, 1H), 5.65 (s, 2H), 4.49 (t, <i>J</i> = 5.1 Hz, 1H), 4.18 (p, <i>J</i> = 6.5 Hz, 1H), 3.79 (dt, <i>J</i> = 11.5, 5.8 Hz, 2H), 3.54 - 3.46 (m, 4H), 2.01 (q, <i>J</i> = 7.9 Hz, 1H), 1.63 (q, <i>J</i> = 6.0 Hz, 2H) ppm.
219	 (<i>S</i>)-5-(5-Chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-3-methyl-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S14		ESI-MS <i>m/z</i> calc. 485.143, found 486.26 (M+1) ⁺ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.05 (s, 1H), 7.51 - 7.33 (m, 2H), 7.12 (t, <i>J</i> = 8.0 Hz, 2H), 6.88 - 6.78 (m, 2H), 6.57 (d, <i>J</i> = 0.9 Hz, 1H), 5.48 (s, 2H), 4.70 (br s, 1H), 3.48 (br s, 3H), 2.36 (s, 3H), 1.03 - 0.90 (m, 1H), 0.46 - 0.14 (m, 4H) ppm.

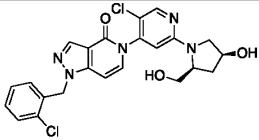
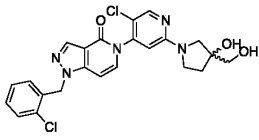
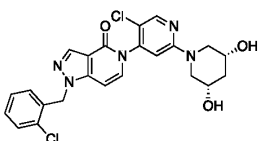
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
220	 5-(5-Chloro-2-((1,1,1-trifluoro-3-hydroxy-2-(hydroxymethyl)propan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 529.094, found 530.4 (M+1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.24 (s, 1H), 8.14 (d, <i>J</i> = 0.9 Hz, 1H), 7.54 (d, <i>J</i> = 7.5 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 2H), 7.01 - 6.96 (m, 1H), 6.86 (s, 1H), 6.54 (s, 1H), 5.63 (s, 2H), 5.48 (q, <i>J</i> = 6.0 Hz, 2H), 4.02 (dd, <i>J</i> = 11.7, 6.3 Hz, 1H), 3.96 (dd, <i>J</i> = 11.6, 6.1 Hz, 1H), 3.91 (s, 2H) ppm.
221	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-<i>c</i>]pyridine-3-carbonitrile	S15		ESI-MS <i>m/z</i> calc. 496.123, found 497.4 (M+1)⁺.	
222	 <i>rac</i>-5-(5-chloro-2-(((2-oxopiperidin-3-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 496.118, found 497.3 (M+1)⁺.	
223		S1		ESI-MS <i>m/z</i> calc. 480.098, found 481.1 (M+1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.20 (s, 1H), 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 7.62 (s, 1H), 7.51 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.49 (t, <i>J</i> = 5.8 Hz, 1H), 7.45

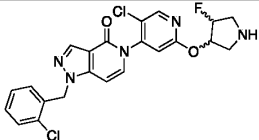
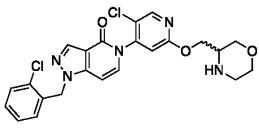
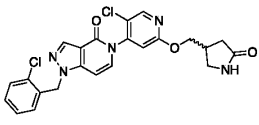
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	5-(5-chloro-2-(((2-methyl-2 <i>H</i> -1,2,3-triazol-4-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				(d, $J = 7.5$ Hz, 1H), 7.41 - 7.30 (m, 2H), 7.08 (dd, $J = 7.5, 1.9$ Hz, 1H), 6.90 (dd, $J = 7.6, 0.9$ Hz, 1H), 6.66 (s, 1H), 6.02 - 5.33 (m, 2H), 4.53 (d, $J = 5.8$ Hz, 2H), 4.10 (s, 3H) ppm.
224	 5-(5-chloro-2-(((2,5-dimethyloxazol-4-yl)methyl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S1		ESI-MS m/z calc. 494.102, found 495.5 (M+1) ⁺ .	
225	 5-(5-chloro-2-((2-(2-oxoimidazolidin-1-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS m/z calc. 481.143, found 482.2 (M+1) ⁺ .	
226	Diastereomer 1 Peak 2  <i>rel</i> -5-(5-chloro-2-(((3 <i>R</i>)-4-(hydroxymethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IB column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 30% MeOH (supplemented with 20 mM	ESI-MS m/z calc. 483.147, found 484.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.16 (d, $J = 0.9$ Hz, 1H), 8.15 (d, $J = 0.9$ Hz, 1H), 7.47 (dd, $J = 7.5, 3.2$ Hz, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.16 (m, 3H), 6.96 - 6.88 (m, 2H), 6.59 (s, 1H), 5.63 (d, $J = 3.2$ Hz, 2H), 4.49 (d, $J = 20.6$ Hz, 1H), 3.97 - 3.83 (m, 2H), 3.79 - 3.75 (m, 1H), 3.57 - 3.51 (m, 1H), 3.41 - 3.32 (m, 1H), 3.34 - 3.30 (m, 1H), 2.98 - 2.89 (m, 1H), 1.82 -

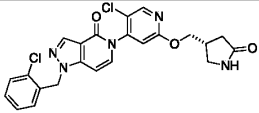
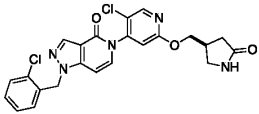
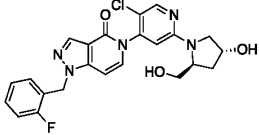
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one		ammonia), 70% CO ₂ ; Flow rate 100 mL/min); rt = 6.88 min		1.76 (m, 1H), 1.65 - 1.61 (m, 1H), 1.53 - 1.39 (m, 1H) ppm.
227	 <i>rac</i> -5-(5-chloro-2-((6-oxo-5-azaspiro[3.5]nonan-9-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 506.163, found 507.3 (M+1) ⁺ .	
228	 5-(5-chloro-2-((1-(2-hydroxyethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 467.152, found 468.3 (M+1) ⁺ .	
229	 <i>rac</i> -5-(5-chloro-2-((2-hydroxy-1-(1-methyl-1 <i>H</i> -1,2,3-triazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 494.138, found 495.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.44 (s, 1H), 8.17 (d, <i>J</i> = 0.8 Hz, 1H), 7.66 (d, <i>J</i> = 4.3 Hz, 1H), 7.48 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.30 - 7.17 (m, 4H), 6.96 (dd, <i>J</i> = 7.7, 2.3 Hz, 1H), 5.70 - 5.58 (m, 2H), 4.52 - 4.36 (m, 3H), 4.05 (s, 3H) ppm; exchangeable H not observed.
230	3:1 mixture of enantiomers	S2		ESI-MS <i>m/z</i> calc. 467.116,	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (dd, <i>J</i> = 3.5, 0.8 Hz, 1H), 8.12

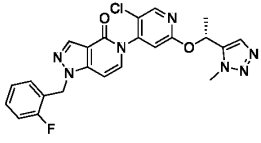
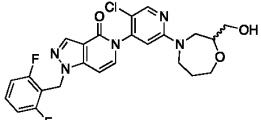
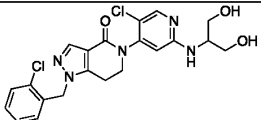
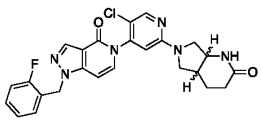
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 (S)-2-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetic acid			found 468.2 (M+1) ⁺ .	(d, <i>J</i> = 1.3 Hz, 1H), 7.48 (dd, <i>J</i> = 7.5, 0.8 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.31 - 7.18 (m, 3H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 6.72 (s, 1H), 5.64 (d, <i>J</i> = 3.3 Hz, 2H), 3.79 (q, <i>J</i> = 8.5 Hz, 1H), 1.16 (dt, <i>J</i> = 8.0, 5.7, 2.8 Hz, 1H), 0.56 - 0.33 (m, 5H) ppm; exchangeable H not observed.
231	 5-(2-(((1H-1,2,4-triazol-5-yl)methyl)amino)-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 450.112, found 451.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 13.82 (s, 1H), 8.17 (s, 1H), 8.17 (d, <i>J</i> = 0.9 Hz, 1H), 7.53 (s, 1H), 7.47 - 7.35 (m, 2H), 7.30 - 7.17 (m, 3H), 6.92 (d, <i>J</i> = 7.6 Hz, 1H), 6.72 (s, 1H), 5.69 - 5.58 (m, 2H), 4.59 - 4.55 (m, 2H) ppm; exchangeable H not observed.
232	Peak 1  <i>rel</i>-(R)-2-((5-chloro-4-(1-(2-fluorobenzyl)-4-oxo-1,4-dihydro-5H-pyrazolo[4,3-c]pyridin-5-yl)pyridin-2-yl)amino)-2-cyclopropylacetic acid	S2	(R,R)-Whelk-O [®] 1 column, 5 μm particle size, 25 cm x 21.1 mm from Regis Technologies, Inc. (Mobile phase: 32% MeOH (supplemented with 20 mM ammonia), 68% CO ₂ ; Flow rate 100 mL/min); rt = 4.00 min	ESI-MS <i>m/z</i> calc. 467.116, found 468.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (dd, <i>J</i> = 3.5, 0.8 Hz, 1H), 8.12 (d, <i>J</i> = 1.7 Hz, 1H), 7.48 (dd, <i>J</i> = 7.5, 1.4 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.25 (m, 2H), 7.25 - 7.18 (m, 1H), 6.93 (d, <i>J</i> = 7.5 Hz), 0.58 - 0.31 (m, 4H) ppm; exchangeable H not observed.
233		S7		ESI-MS <i>m/z</i> calc. 471.188, found	

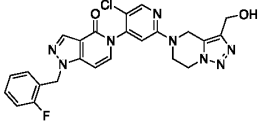
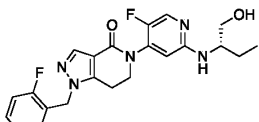
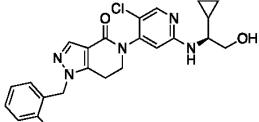
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rac</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((4-hydroxy-4-methylpentan-2-yl)amino)pyridin-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one			472.2 (M+1) ⁺ .	
265	 <i>rac</i> -5-(5-chloro-2-((1-hydroxypropan-2-yl)oxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 444.076, found 445.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.42 (s, 1H), 8.22 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.41 - 7.32 (m, 2H), 7.13 - 7.08 (m, 2H), 6.94 (dq, <i>J</i> = 7.5, 0.9 Hz, 1H), 5.69 (d, <i>J</i> = 4.5 Hz, 2H), 5.17 (ddd, <i>J</i> = 10.9, 6.2, 4.8 Hz, 1H), 4.88 (dt, <i>J</i> = 11.5, 5.7 Hz, 1H), 3.60 (dt, <i>J</i> = 11.4, 5.7 Hz, 1H), 3.53 (tt, <i>J</i> = 10.9, 5.2 Hz, 1H), 1.28 (t, <i>J</i> = 6.5 Hz, 3H) ppm.
266	 (S)-5-(5-chloro-2-(2-(hydroxymethyl)azetidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 439.121, found 440.5 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.25 (d, <i>J</i> = 1.4 Hz, 1H), 8.16 (s, 1H), 7.46 - 7.35 (m, 2H), 7.29 - 7.16 (m, 3H), 6.92 (dd, <i>J</i> = 7.5, 2.2 Hz, 1H), 6.75 (d, <i>J</i> = 3.5 Hz, 1H), 5.70 - 5.54 (m, 2H), 4.95 (q, <i>J</i> = 5.0 Hz, 1H), 4.29 - 4.25 (m, 1H), 3.92 - 3.76 (m, 2H), 3.74 - 3.61 (m, 2H), 2.32 - 2.28 (m, 1H), 2.22 - 2.15 (m, 1H) ppm.
267	 5-(2-(bis(2-hydroxyethyl)amino)-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 457.132, found 458.5 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.22 (s, 1H), 8.18 - 8.13 (m, 1H), 7.48 - 7.43 (m, 1H), 7.42 - 7.36 (m, 1H), 7.30 - 7.16 (m, 3H), 6.91 (dd, <i>J</i> = 7.6, 0.7 Hz, 1H), 6.85 (s, 1H), 5.71 - 5.57 (m, 2H), 4.75 - 4.68 (m, 2H), 3.62 - 3.49 (m, 8H) ppm.

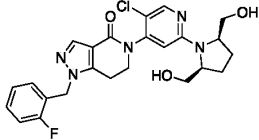
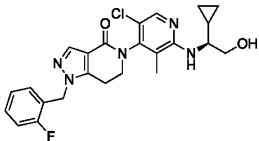
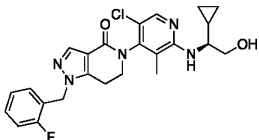
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
268	 5-(5-chloro-2-((2<i>S</i>,4<i>S</i>)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.1 (M+1) ⁺ .	
269	 <i>rac</i>-5-(5-chloro-2-(3-hydroxy-3-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.1 (M+1) ⁺ .	¹ H NMR (500 MHz, Acetonitrile- <i>d</i> ₃) δ 8.21 (s, 1H), 8.11 (d, <i>J</i> = 0.8 Hz, 1H), 7.48 (dd, <i>J</i> = 7.9, 1.4 Hz, 1H), 7.32 (s, 2H), 7.19 (d, <i>J</i> = 7.5 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.65 (dd, <i>J</i> = 7.5, 0.9 Hz, 1H), 6.51 (d, <i>J</i> = 3.0 Hz, 1H), 5.61 (s, 2H), 3.57 - 3.50 (m, 3H), 3.49 - 3.42 (m, 1H), 3.40 - 3.36 (m, 1H), 3.17 - 3.13 (m, 1H), 3.06 - 3.02 (m, 1H), 2.10 - 2.01 (m, 1H), 1.93 - 1.87 (m, 1H) ppm; exchangeable H not observed.
270	 5-(5-chloro-2-((3<i>R</i>,5<i>S</i>)-3,5-dihydropiperidin-1-yl)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.26 (s, 1H), 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 7.52 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.45 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 - 7.30 (m, 2H), 7.09 - 7.03 (m, 2H), 6.90 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 5.68 (q, <i>J</i> = 15.9 Hz, 2H), 4.94 (d, <i>J</i> = 5.0 Hz, 2H), 4.29 (t, <i>J</i> = 11.7 Hz, 2H), 3.50 - 3.40 (m, 2H), 2.58 - 2.50 (m, 2H), 2.21 - 2.15 (m, 1H), 1.28 (q, <i>J</i> = 11.0 Hz, 1H) ppm.
271	Syn	S1		ESI-MS <i>m/z</i> calc. 473.082,	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.47 (d, <i>J</i> = 2.4 Hz, 1H), 8.24 - 8.19

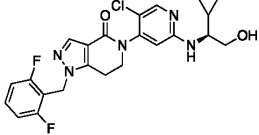
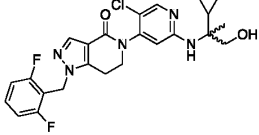
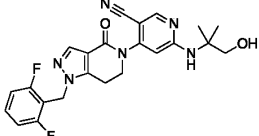
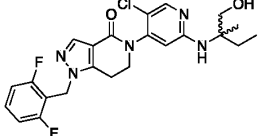
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rac</i>-5-(5-chloro-2-(((3<i>S</i>,4<i>R</i>)-4-fluoropyrrolidin-3-yl)oxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one			found 474.1 (M+1) ⁺ .	(m, 1H), 7.56 - 7.47 (m, 2H), 7.42 - 7.31 (m, 2H), 7.26 (d, <i>J</i> = 1.3 Hz, 1H), 7.11 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.95 (dd, <i>J</i> = 7.6, 1.1 Hz, 1H), 5.69 (d, <i>J</i> = 4.7 Hz, 2H), 5.36 - 5.14 (m, 2H), 3.30 - 3.21 (m, 2H, overlapped with water), 3.03 - 2.90 (m, 1H), 2.87 - 2.78 (m, 1H), 2.60 - 2.40 (m, 1H, overlapped with solvent) ppm.
272	 <i>rac</i>-5-(5-chloro-2-(morpholin-3-ylmethoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 485.102, found 486.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.44 (d, <i>J</i> = 0.3 Hz, 1H), 8.22 (d, <i>J</i> = 0.8 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.41 - 7.33 (m, 2H), 7.19 (s, 1H), 7.12 - 7.07 (m, 1H), 6.95 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 5.74 - 5.63 (m, 2H), 4.25 - 4.13 (m, 2H), 3.80 (dd, <i>J</i> = 10.8, 3.0 Hz, 1H), 3.66 (dt, <i>J</i> = 10.9, 2.8 Hz, 1H), 3.43 - 3.36 (m, 1H), 3.23 (dd, <i>J</i> = 10.8, 9.3 Hz, 1H), 3.07 (d, <i>J</i> = 8.2 Hz, 1H), 2.76 (dt, <i>J</i> = 22.2, 12.0 Hz, 2H) ppm; exchangeable H not observed.
273	 <i>rac</i>-5-(5-chloro-2-((5-oxopyrrolidin-3-yl)methoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S1		ESI-MS <i>m/z</i> calc. 483.086, found 484.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.45 (s, 1H), 8.22 (d, <i>J</i> = 0.8 Hz, 1H), 7.58 (s, 1H), 7.54 - 7.51 (m, 1H), 7.50 (d, <i>J</i> = 7.6 Hz, 1H), 7.41 - 7.33 (m, 2H), 7.21 (s, 1H), 7.12 - 7.08 (m, 1H), 6.95 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 5.73 - 5.64 (m, 2H), 4.36 - 4.26 (m, 2H), 3.41 (m, 1H), 3.11 (m, 1H), 2.88 (m, 1H), 2.33 (dd, <i>J</i> = 16.7, 9.1 Hz, 1H), 2.05 (dd, <i>J</i> = 16.7, 6.7 Hz, 1H) ppm
274	Peak 1	S1	Chiralcel® OJ-H	ESI-MS <i>m/z</i> calc.	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.45 (s, 1H),

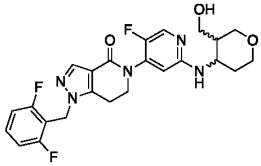
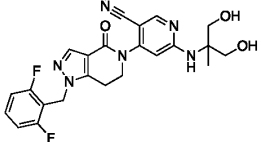
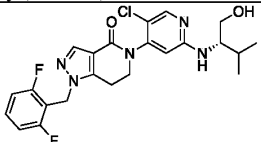
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	 <i>rel-(R)-5-(5-chloro-2-((5-oxopyrrolidin-3-yl)methoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one</i>		column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 2 mL/min); rt = 5.32 min	483.086, found 484.2 (M+1) ⁺ .	8.22 (d, <i>J</i> = 0.8 Hz, 1H), 7.58 (s, 1H), 7.53 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.50 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 - 7.33 (m, 2H), 7.21 (s, 1H), 7.12 - 7.08 (m, 1H), 6.95 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 5.73 - 5.64 (m, 2H), 4.35 - 4.27 (m, 2H), 3.41 (ddd, <i>J</i> = 9.7, 7.9, 0.9 Hz, 1H), 3.11 (dd, <i>J</i> = 9.7, 5.6 Hz, 1H), 2.88 (p, <i>J</i> = 7.3 Hz, 1H), 2.33 (dd, <i>J</i> = 16.7, 9.0 Hz, 1H), 2.09 - 2.02 (m, 1H) ppm.
275	Peak 2  <i>rel-(S)-5-(5-chloro-2-((5-oxopyrrolidin-3-yl)methoxy)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one</i>	S1	Chiralcel [®] OJ-H column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 20% MeOH (supplemented with 20 mM ammonia), 80% CO ₂ ; Flow rate 2 mL/min); rt = 6.14 min	ESI-MS <i>m/z</i> calc. 483.086, found 484.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.45 (s, 1H), 8.22 (d, <i>J</i> = 0.8 Hz, 1H), 7.58 (s, 1H), 7.53 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.50 (d, <i>J</i> = 7.5 Hz, 1H), 7.37 (dtd, <i>J</i> = 18.6, 7.4, 1.7 Hz, 2H), 7.21 (s, 1H), 7.10 (dd, <i>J</i> = 7.5, 1.9 Hz, 1H), 6.95 (dd, <i>J</i> = 7.6, 0.9 Hz, 1H), 5.74 - 5.64 (m, 2H), 4.35 - 4.26 (m, 2H), 3.41 (dd, <i>J</i> = 9.7, 8.1 Hz, 1H), 3.11 (dd, <i>J</i> = 9.8, 5.6 Hz, 1H), 2.88 (p, <i>J</i> = 7.3 Hz, 1H), 2.33 (dd, <i>J</i> = 16.7, 9.0 Hz, 1H), 2.09 - 2.01 (m, 1H) ppm.
276	 5-(5-chloro-2-((2<i>S</i>,4<i>R</i>)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	

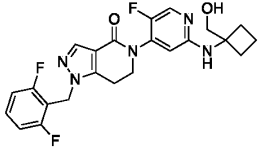
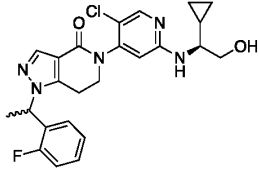
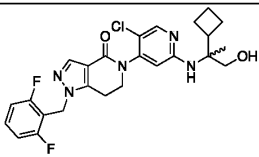
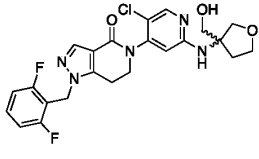
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
277	 (<i>R</i>)-5-(5-chloro-2-(1-(1-methyl-1<i>H</i>-1,2,3-triazol-5-yl)ethoxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 479.127, found 480.2 (<i>M</i>+1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.48 (d, <i>J</i> = 2.4 Hz, 1H), 8.18 (dd, <i>J</i> = 4.0, 0.8 Hz, 1H), 7.85 (d, <i>J</i> = 5.1 Hz, 1H), 7.51 (dd, <i>J</i> = 7.5, 4.7 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.31 - 7.18 (m, 4H), 6.97 (dd, <i>J</i> = 7.6, 4.0 Hz, 1H), 6.39 (p, <i>J</i> = 6.4 Hz, 1H), 5.70 - 5.58 (m, 2H), 4.08 (d, <i>J</i> = 3.7 Hz, 3H), 1.72 (dd, <i>J</i> = 6.6, 4.3 Hz, 3H) ppm.
278	 <i>rac</i>-5-(5-chloro-2-(2-(hydroxymethyl)-1,4-oxazepan-4-yl)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 501.138, found 502.0 (<i>M</i>+1)⁺.	
279	 5-(5-chloro-2-((1,3-dihydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-chlorobenzyl)-1,5,6,7-tetrahydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S3		ESI-MS <i>m/z</i> calc. 461.102, found 462.2 (<i>M</i>+1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.03 (s, 1H), 7.86 (s, 1H), 7.54 - 7.48 (m, 1H), 7.42 - 7.32 (m, 2H), 7.14 - 7.08 (m, 1H), 6.62 (s, 1H), 6.52 (d, <i>J</i> = 7.9 Hz, 1H), 5.45 (s, 2H), 4.63 (t, <i>J</i> = 5.5 Hz, 2H), 3.94 - 3.75 (m, 3H), 3.55 - 3.43 (m, 4H), 3.14 (t, <i>J</i> = 6.7 Hz, 2H) ppm.
280	Syn  <i>rac</i>-5-(5-chloro-2-((4<i>aR</i>,7<i>aR</i>)-2-oxooctahydro-6<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 492.148, found 493.3 (<i>M</i>+1)⁺.	

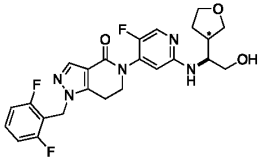
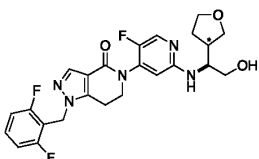
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrrolo[3,4- <i>b</i>]pyridin-6-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
281	 5-(5-chloro-2-(3-(hydroxymethyl)-6,7-dihydro-[1,2,3]triazolo[1,5-<i>a</i>]pyrazin-5(4<i>H</i>)-yl)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 506.138, found 507.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.41 (s, 1H), 8.19 (d, <i>J</i> = 0.8 Hz, 1H), 7.51 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 (dddd, <i>J</i> = 8.2, 7.2, 5.5, 2.0 Hz, 1H), 7.35 (s, 1H), 7.29 - 7.16 (m, 3H), 6.96 (dt, <i>J</i> = 7.6, 0.7 Hz, 1H), 5.70 (d, <i>J</i> = 15.5 Hz, 1H), 5.63 (d, <i>J</i> = 15.5 Hz, 1H), 5.14 (t, <i>J</i> = 5.7 Hz, 1H), 4.95 (d, <i>J</i> = 16.8 Hz, 1H), 4.87 (d, <i>J</i> = 16.8 Hz, 1H), 4.57 (d, <i>J</i> = 5.5 Hz, 2H), 4.47 - 4.42 (m, 2H), 4.14 (t, <i>J</i> = 5.5 Hz, 2H) ppm.
282	 (<i>S</i>)-5-(5-fluoro-2-((1-hydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5,6,7-tetrahydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S5		ESI-MS <i>m/z</i> calc. 427.182, found 428.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.94 (d, <i>J</i> = 2.7 Hz, 1H), 7.86 (s, 1H), 7.41 (dddd, <i>J</i> = 8.2, 7.3, 5.4, 2.0 Hz, 1H), 7.35 - 7.15 (m, 3H), 6.56 (d, <i>J</i> = 5.2 Hz, 1H), 5.43 (s, 2H), 3.97 (t, <i>J</i> = 6.6 Hz, 2H), 3.73 (d, <i>J</i> = 8.1 Hz, 1H), 3.46 (dd, <i>J</i> = 10.6, 4.8 Hz, 1H), 3.35 (dd, <i>J</i> = 10.6, 5.9 Hz, 2H), 3.16 (d, <i>J</i> = 13.2 Hz, 3H), 1.74 - 1.59 (m, 1H), 1.41 (dq, <i>J</i> = 13.6, 7.5 Hz, 1H), 0.89 (t, <i>J</i> = 7.4 Hz, 3H) ppm.
283	 (<i>S</i>)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2-	S5		ESI-MS <i>m/z</i> calc. 455.152, found 456.1 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.97 (s, 1H), 7.83 (s, 1H), 7.45 - 7.36 (m, 1H), 7.31 - 7.18 (m, 3H), 6.65 (d, <i>J</i> = 8.0 Hz, 1H), 6.55 (s, 1H), 5.42 (s, 2H), 4.65 (t, <i>J</i> = 5.4 Hz, 1H), 3.96 - 3.79 (m, 2H), 3.57 - 3.41 (m, 3H), 3.19 - 3.13 (m, 2H), 1.03 -

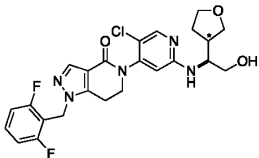
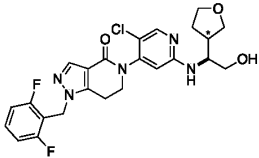
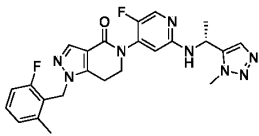
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	fluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one				0.93 (m, 1H), 0.46 - 0.25 (m, 3H), 0.23 - 0.10 (m, 1H) ppm.
284	 5-(2-((2R,5S)-2,5-bis(hydroxymethyl)pyrrolidin-1-yl)-5-chloropyridin-4-yl)-1-(2-fluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S5		ESI-MS <i>m/z</i> calc. 485.163, found 486.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.15 (s, 1H), 7.84 (s, 1H), 7.45 - 7.36 (m, 1H), 7.30 - 7.18 (m, 3H), 6.72 (s, 1H), 5.43 (s, 2H), 4.82 - 4.75 (m, 2H), 4.02 - 3.79 (m, 4H), 3.58 - 3.50 (m, 2H), 3.42 - 3.34 (m, 2H), 3.20 - 3.15 (m, 2H), 1.98 - 1.86 (m, 4H) ppm.
285	Atropisomer 1  (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S5		ESI-MS <i>m/z</i> calc. 469.168, found 469.9 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.93 (d, <i>J</i> = 0.7 Hz, 1H), 7.83 (s, 1H), 7.45 - 7.36 (m, 1H), 7.33 - 7.21 (m, 3H), 5.78 (d, <i>J</i> = 8.1 Hz, 1H), 5.42 (s, 2H), 4.59 (t, <i>J</i> = 5.7 Hz, 1H), 3.84 - 3.67 (m, 2H), 3.68 - 3.59 (m, 1H), 3.56 (t, <i>J</i> = 5.6 Hz, 2H), 3.20 (t, <i>J</i> = 6.8 Hz, 2H), 1.96 (s, 3H), 1.10 - 0.99 (m, 1H), 0.43 (s, 1H), 0.39 - 0.32 (m, 2H), 0.27 - 0.18 (m, 1H) ppm.
286	Atropisomer 2  (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S5		ESI-MS <i>m/z</i> calc. 469.168, found 470.0 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.93 (d, <i>J</i> = 0.7 Hz, 1H), 7.83 (s, 1H), 7.45 - 7.36 (m, 1H), 7.33 - 7.18 (m, 3H), 5.76 (d, <i>J</i> = 8.1 Hz, 1H), 5.42 (s, 2H), 4.64 (t, <i>J</i> = 5.7 Hz, 1H), 3.86 - 3.69 (m, 2H), 3.68 - 3.59 (m, 1H), 3.57 (t, <i>J</i> = 5.6 Hz, 2H), 3.20 (t, <i>J</i> = 6.8 Hz, 2H), 1.96 (d, <i>J</i> = 0.6 Hz, 3H), 1.10 - 1.00 (m, 1H), 0.47 - 0.38 (m, 1H), 0.36 - 0.28 (m, 2H), 0.26 - 0.18 (m, 1H) ppm.

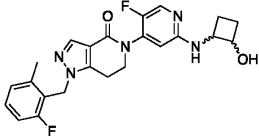
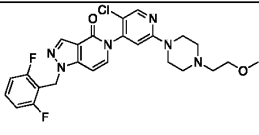
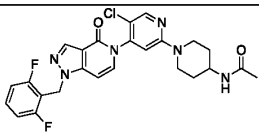
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
287	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 473.143, found 474.3 (M+1) ⁺ .	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 8.00 (s, 1H), 7.84 (s, 1H), 7.46 (tt, <i>J</i> = 8.4, 6.5 Hz, 1H), 7.15 - 6.92 (m, 2H), 6.61 (s, 1H), 5.46 (d, <i>J</i> = 0.9 Hz, 2H), 3.99 (t, <i>J</i> = 6.7 Hz, 2H), 3.79 - 3.64 (m, 2H), 3.41 - 3.37 (m, 1H), 3.30 (t, <i>J</i> = 6.7 Hz, 2H), 1.04 (qt, <i>J</i> = 8.2, 5.0 Hz, 1H), 0.59 - 0.45 (m, 2H), 0.41 - 0.29 (m, 2H) ppm; exchangeable H not observed.
288	 rac-5-(5-chloro-2-((2-cyclopropyl-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 487.159, found 488.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.01 (s, 1H), 7.80 (s, 1H), 7.50 (tt, <i>J</i> = 8.4, 6.6 Hz, 1H), 7.30 - 7.11 (m, 2H), 6.71 (s, 1H), 6.29 (s, 1H), 5.40 (s, 2H), 5.12 (t, <i>J</i> = 5.8 Hz, 1H), 4.09 (q, <i>J</i> = 5.3 Hz, 2H), 3.89 (s, 2H), 3.70 (dd, <i>J</i> = 10.7, 5.7 Hz, 1H), 3.59 (dd, <i>J</i> = 10.7, 5.8 Hz, 1H), 1.40 (ddd, <i>J</i> = 14.0, 8.1, 6.0 Hz, 1H), 0.99 (s, 3H), 0.50 - 0.12 (m, 4H) ppm.
289	 4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)-6-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile	S8		ESI-MS <i>m/z</i> calc. 452.177, found 451.1 (M-1) ⁻ .	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (s, 1H), 7.82 (s, 1H), 7.55 - 7.43 (m, 1H), 7.22 - 7.11 (m, 3H), 6.61 - 6.57 (m, 1H), 5.40 (s, 2H), 4.93 (t, <i>J</i> = 5.7 Hz, 1H), 3.98 (t, <i>J</i> = 6.6 Hz, 2H), 3.55 (d, <i>J</i> = 5.7 Hz, 2H), 3.22 (t, <i>J</i> = 6.5 Hz, 2H), 1.32 (s, 6H) ppm.
290		S8		ESI-MS <i>m/z</i> calc. 475.159, found 476.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.00 (s, 1H), 7.79 (s, 1H), 7.50 (tt, <i>J</i> = 8.5, 6.7 Hz, 1H), 7.25 - 7.10 (m, 2H), 6.65 (s, 1H), 6.26 (s, 1H), 5.40 (s, 2H), 4.99 (t, <i>J</i> = 5.7 Hz,

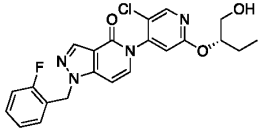
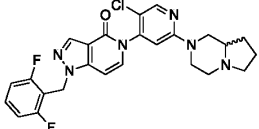
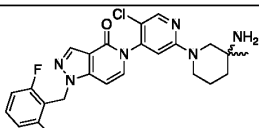
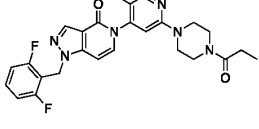
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rac</i> -5-(5-chloro-2-((1-hydroxy-2-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				1H), 4.09 (q, <i>J</i> = 5.3 Hz, 1H), 3.88 (s, 2H), 3.67 - 3.46 (m, 2H), 3.27 - 3.12 (m, 3H), 1.90 (dq, <i>J</i> = 14.7, 7.4 Hz, 2H), 1.75 - 1.52 (m, 1H), 0.79 (t, <i>J</i> = 7.4 Hz, 3H) ppm.
291	Syn  <i>rac</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((3 <i>R</i> ,4 <i>S</i>)-3-(hydroxymethyl)tetrahydro-2 <i>H</i> -pyran-4-yl)amino)pyridin-4-yl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 487.183, found 489.5 (<i>M</i> +1) ⁺ .	
292	 4-(1-(2,6-difluorobenzyl)-4-oxo-1,4,6,7-tetrahydro-5 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-5-yl)-6-(((1,3-dihydroxy-2-methylpropan-2-yl)amino)nicotinonitrile	S8		ESI-MS <i>m/z</i> calc. 468.172, found 469.4 (<i>M</i> +1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.33 (s, 1H), 7.83 (s, 1H), 7.54 - 7.44 (m, 1H), 7.21 - 7.12 (m, 2H), 6.97 (s, 1H), 6.67 (d, <i>J</i> = 0.5 Hz, 1H), 5.40 (s, 2H), 4.85 (t, <i>J</i> = 5.7 Hz, 2H), 3.98 (t, <i>J</i> = 6.5 Hz, 2H), 3.64 (dd, <i>J</i> = 10.7, 5.7 Hz, 2H), 3.58 (dd, <i>J</i> = 10.7, 5.8 Hz, 2H), 3.22 (t, <i>J</i> = 6.6 Hz, 2H), 1.27 (s, 3H) ppm.
293	 (<i>S</i>)-5-(5-chloro-2-((1-hydroxy-3-methylbutan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 475.159, found 474.1 (<i>M</i> -1) ⁻ .	

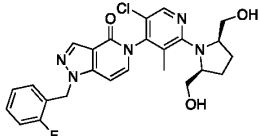
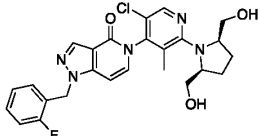
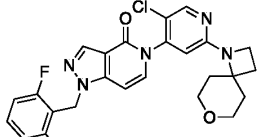
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	pyrazolo[4,3- <i>c</i>]pyridin-4-one				
294	 1-(2,6-difluorobenzyl)-5-(5-fluoro-2-((1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 457.173, found 458.3 (M+1) ⁺ .	
295	 <i>rac</i>-5-(5-chloro-2-(((<i>S</i>)-1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(1-(2-fluorophenyl)ethyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S17		ESI-MS <i>m/z</i> calc. 469.168, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.97 (s, 1H), 7.87 (s, 1H), 7.38 (q, <i>J</i> = 6.9 Hz, 2H), 7.22 (dd, <i>J</i> = 12.0, 7.8 Hz, 2H), 6.65 (d, <i>J</i> = 7.9 Hz, 1H), 6.54 (s, 1H), 5.94 (q, <i>J</i> = 6.9 Hz, 1H), 4.66 (s, 1H), 3.97 - 3.63 (m, 2H), 3.60 - 3.42 (m, 3H), 3.26 (dt, <i>J</i> = 16.8, 6.3 Hz, 1H), 2.90 (dt, <i>J</i> = 15.7, 7.3 Hz, 1H), 1.85 (d, <i>J</i> = 6.9 Hz, 3H), 1.06 - 0.84 (m, 1H), 0.51 - 0.10 (m, 4H) ppm.
296	 <i>rac</i>-5-(5-chloro-2-((2-cyclobutyl-1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 501.174, found 502.2 (M+1) ⁺ .	
297		S8		ESI-MS <i>m/z</i> calc. 489.138, found 490.2 (M+1) ⁺ .	

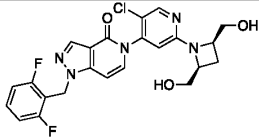
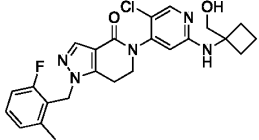
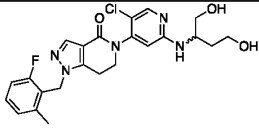
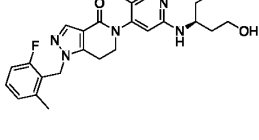
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	<i>rac</i> -5-(5-chloro-2-((3-(hydroxymethyl)tetrahydrofuran-3-yl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
298	Peak 1  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8	Chiralpak [®] IB column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 35% ⁱ PrOH (supplemented with 20 mM ammonia), 65% CO ₂ ; Flow rate 100 mL/min); rt = 7.34 min	ESI-MS <i>m/z</i> calc. 487.183, found 488.3 (M+1) ⁺ .	
299	Peak 3  <i>rel</i> -1-(2,6-difluorobenzyl)-5-(5-fluoro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8	Chiralpak [®] IB column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 35% ⁱ PrOH (supplemented with 20 mM ammonia), 65% CO ₂ ; Flow rate 100 mL/min); rt	ESI-MS <i>m/z</i> calc. 487.183, found 488.3 (M+1) ⁺ .	

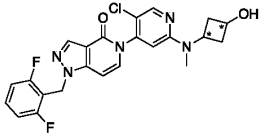
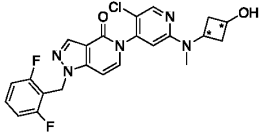
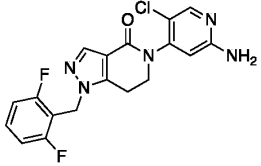
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
			= 13.07 min		
300	Peak 1  <i>rel</i> -5-(5-chloro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8	Chiralpak® IB column, 5 µm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 4.84 min	ESI-MS <i>m/z</i> calc. 503.154, found 504.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.02 (s, 1H), 7.79 (s, 1H), 7.50 (tt, <i>J</i> = 8.4, 6.7 Hz, 1H), 7.22 - 7.13 (m, 2H), 6.75 (d, <i>J</i> = 8.8 Hz, 1H), 6.59 (s, 1H), 5.40 (s, 2H), 4.71 (s, 1H), 3.96 (s, 2H), 3.90 (s, 1H), 3.80 (t, <i>J</i> = 8.0 Hz, 1H), 3.70 (td, <i>J</i> = 8.2, 4.3 Hz, 1H), 3.59 (td, <i>J</i> = 8.1, 7.0 Hz, 1H), 3.46 - 3.36 (m, 3H), 3.22 (s, 1H), 2.46 (p, <i>J</i> = 8.1 Hz, 2H), 1.98 - 1.88 (m, 1H), 1.65 (dq, <i>J</i> = 12.2, 8.2 Hz, 1H) ppm; exchangeable H not observed.
301	Peak 3  <i>rel</i> -5-(5-chloro-2-(((1 <i>S</i>)-2-hydroxy-1-(tetrahydrofuran-3-yl)ethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S8	Chiralpak® IB column, 5 µm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 33% MeOH (supplemented with 20 mM ammonia), 67% CO ₂ ; Flow rate 100 mL/min); rt = 9.06 min	ESI-MS <i>m/z</i> calc. 503.154, found 504.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.02 (s, 1H), 7.79 (s, 1H), 7.50 (tt, <i>J</i> = 8.5, 6.7 Hz, 1H), 7.22 - 7.13 (m, 2H), 6.71 (d, <i>J</i> = 8.9 Hz, 1H), 6.59 (s, 1H), 5.40 (s, 2H), 4.70 (s, 1H), 3.95 (s, 1H), 3.89 (s, 1H), 3.81 - 3.70 (m, 3H), 3.62 (td, <i>J</i> = 8.2, 7.0 Hz, 1H), 3.53 - 3.40 (m, 2H), 3.22 (s, 1H), 2.48 (d, <i>J</i> = 8.2 Hz, 1H), 2.01 - 1.92 (m, 2H), 1.63 (dq, <i>J</i> = 12.2, 8.3 Hz, 2H) ppm.
302		S10		ESI-MS <i>m/z</i> calc. 478.204, found 479.3 (M+1) ⁺ .	

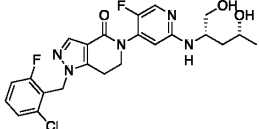
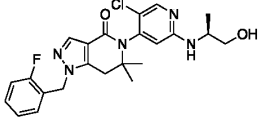
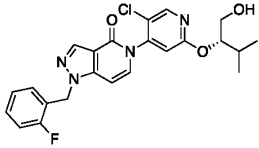
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	(R)-5-(5-fluoro-2-((1-(1-methyl-1H-1,2,3-triazol-5-yl)ethyl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one				
303	Anti  <i>rac</i>-5-(5-fluoro-2-(((1<i>S</i>,2<i>S</i>)-2-hydroxycyclobutyl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S10		ESI-MS <i>m/z</i> calc. 439.182, found 440.3 (<i>M</i> +1) ⁺ .	
304	 5-(5-chloro-2-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 514.170, found 515.0 (<i>M</i> +1) ⁺ .	
305	 <i>N</i>-(1-(5-chloro-4-(1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydro-5<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-5-yl)piperidin-4-yl)acetamide	S7		ESI-MS <i>m/z</i> calc. 512.154, found 513.3 (<i>M</i> +1) ⁺ .	

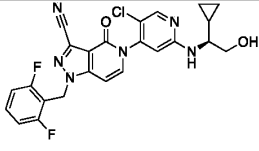
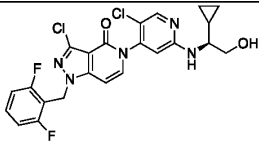
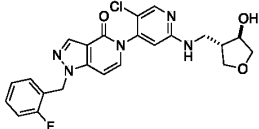
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
306	 (S)-5-(5-chloro-2-((1-hydroxybutan-2-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 442.121, found 441.1 (M-1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.30 (s, 1H), 8.17 (s, 1H), 7.38 - 7.32 (m, 2H), 7.26 - 7.22 (m, 1H), 7.17 - 7.10 (m, 2H), 6.96 (d, <i>J</i> = 4.6 Hz, 1H), 6.88-6.86 (m, 1H), 5.62 (s, 2H), 5.16 (s, <i>J</i> = 5.6 Hz, 1H), 3.78 - 3.65 (m, 2H), 1.78-1.69 (m, 2H), 0.97 (td, <i>J</i> = 7.4, 2.1 Hz, 3H) ppm; exchangeable H not observed.
307	 <i>rac</i>-5-(5-chloro-2-(hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1H)-yl)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 496.159, found 497.0 (M+1) ⁺ .	
308	 <i>rac</i>-5-(2-(3-amino-3-methylpiperidin-1-yl)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 484.159, found 485.0 (M+1) ⁺ .	
309	 5-(5-chloro-2-(4-propionylpiperazin-1-yl)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 512.154, found 513.2 (M+1) ⁺ .	

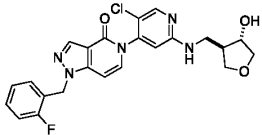
Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one				
310	Atropisomer 1  5-(2-((2<i>R</i>,5<i>S</i>)-2,5-bis(hydroxymethyl)pyrrolidin-1-yl)-5-chloro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 497.163, found 496.1 (<i>M</i>-1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.27 (d, <i>J</i> = 0.7 Hz, 1H), 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.33 - 7.18 (m, 3H), 7.00 (d, <i>J</i> = 7.6 Hz, 1H), 5.65 (s, 2H), 4.69 - 4.65 (m, 2H), 4.20 - 4.11 (m, 1H), 4.06 - 3.98 (m, 1H), 3.59 - 3.48 (m, 2H), 3.28 (m, 2H), 2.02 (s, 3H), 1.92 - 1.73 (m, 4H) ppm.
311	Atropisomer 2  5-(2-((2<i>R</i>,5<i>S</i>)-2,5-bis(hydroxymethyl)pyrrolidin-1-yl)-5-chloro-3-methylpyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 497.163, found 496.2 (<i>M</i>-1)⁺.	¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 8.27 (d, <i>J</i> = 0.7 Hz, 1H), 8.18 (d, <i>J</i> = 0.8 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.33 - 7.18 (m, 3H), 7.00 (d, <i>J</i> = 7.5 Hz, 1H), 5.65 (s, 2H), 4.70 - 4.64 (m, 2H), 4.20 - 4.11 (m, 1H), 4.06 - 3.98 (m, 1H), 3.58 - 3.48 (m, 2H), 3.30 - 3.16 (m, 2H), 2.02 (s, 3H), 1.92 - 1.85 (m, 3H), 1.87 - 1.77 (m, 1H) ppm.
312	 5-(5-chloro-2-(7-oxa-1-azaspiro[3.5]nonan-1-yl)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 497.143, found 498.0 (<i>M</i>+1)⁺.	

Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
313	 5-(2-((2R,4S)-2,4-bis(hydroxymethyl)azetidin-1-yl)-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 487.122, found 488.0 (M+1) ⁺ .	
314	 5-(5-chloro-2-((1-(hydroxymethyl)cyclobutyl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S10		ESI-MS <i>m/z</i> calc. 469.168, found 470.3 (M+1) ⁺ .	
315	 <i>rac</i>-5-(5-chloro-2-((1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S10		ESI-MS <i>m/z</i> calc. 473.163, found 474.3 (M+1) ⁺ .	
316	 (<i>R</i>)-5-(5-chloro-2-((1,4-dihydroxybutan-2-yl)amino)pyridin-4-yl)-1-(2-fluoro-6-methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S10		ESI-MS <i>m/z</i> calc. 473.163, found 474.3 (M+1) ⁺ .	

Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
	methylbenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one				
317	Peak 1 Syn or anti  5-(5-chloro-2-((3-hydroxycyclobutyl)(methyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 471.127, found 472.2 (M+1) ⁺ .	¹ H NMR (500 MHz, Acetonitrile- <i>d</i> ₃) δ 8.22 (s, 1H), 8.03 (d, <i>J</i> = 0.9 Hz, 1H), 7.48 - 7.38 (m, 1H), 7.21 (d, <i>J</i> = 7.6 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.79 - 6.74 (m, 1H), 6.67 (s, 1H), 5.54 (d, <i>J</i> = 1.2 Hz, 2H), 4.26 - 4.16 (m, 1H), 3.97 - 3.87 (m, 1H), 3.14 (d, <i>J</i> = 6.5 Hz, 1H), 2.99 (s, 3H), 2.66 - 2.55 (m, 2H), 2.05 - 1.97 (m, 2H) ppm.
318	Peak 2 Anti or syn  5-(5-chloro-2-((3-hydroxycyclobutyl)(methyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one	S7		ESI-MS <i>m/z</i> calc. 471.127, found 472.4 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.27 (s, 1H), 8.11 (d, <i>J</i> = 0.8 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.21 - 7.12 (m, 2H), 6.95 (d, <i>J</i> = 7.5 Hz, 1H), 6.81 (s, 1H), 5.68 - 5.57 (m, 2H), 5.16 - 5.06 (m, 1H), 5.03 - 5.00 (m, 1H), 4.26 - 4.20 (m, 1H), 2.96 (s, 3H), 2.43 - 2.32 (m, 2H), 2.16 - 2.05 (m, 2H) ppm.
319	 5-(2-amino-5-chloropyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one	S8		ESI-MS <i>m/z</i> calc. 389.085, found 390.2 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.99 (s, 1H), 7.79 (s, 1H), 7.50 (tt, <i>J</i> = 8.4, 6.7 Hz, 1H), 7.25 - 7.08 (m, 2H), 6.49 (s, 1H), 6.24 (s, 2H), 5.40 (s, 2H), 3.89 (s, 2H), 3.27 - 3.14 (m, 2H) ppm.

Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
320	 <i>rel</i>-1-(2-chloro-6-fluorobenzyl)-5-(2-(((2<i>S</i>[*],4<i>R</i>)-1,4-dihydroxypentan-2-yl)amino)-5-fluoropyridin-4-yl)-1,5,6,7-tetrahydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S11		ESI-MS <i>m/z</i> calc. 491.154, found 492.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.91 (d, <i>J</i> = 2.6 Hz, 1H), 7.79 (s, 1H), 7.48 (td, <i>J</i> = 8.2, 6.1 Hz, 1H), 7.40 (dt, <i>J</i> = 8.0, 1.0 Hz, 2H), 7.31 (ddd, <i>J</i> = 9.5, 8.3, 1.2 Hz, 2H), 6.52 (d, <i>J</i> = 5.2 Hz, 1H), 6.27 (d, <i>J</i> = 8.0 Hz, 1H), 5.44 (d, <i>J</i> = 1.4 Hz, 2H), 4.65 (t, <i>J</i> = 5.5 Hz, 1H), 4.58 (d, <i>J</i> = 4.6 Hz, 1H), 3.98 (t, <i>J</i> = 6.6 Hz, 2H), 3.71 (d, <i>J</i> = 4.7 Hz, 1H), 3.45 (dt, <i>J</i> = 10.2, 5.0 Hz, 1H), 3.24 (t, <i>J</i> = 6.6 Hz, 2H), 1.60 (ddd, <i>J</i> = 13.4, 9.4, 3.7 Hz, 1H), 1.43 (ddd, <i>J</i> = 13.3, 9.7, 3.2 Hz, 1H), 1.08 (d, <i>J</i> = 6.2 Hz, 3H) ppm.
321	Atropisomer 1  (<i>S</i>)-5-(5-chloro-2-((1-hydroxypropan-2-yl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-6,6-dimethyl-1,5,6,7-tetrahydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	SB3		ESI-MS <i>m/z</i> calc. 457.168, found 458.3 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.03 (s, 1H), 7.85 (s, 1H), 7.39 - 7.34 (m, 1H), 7.23 - 7.11 (m, 3H), 6.54 (s, 1H), 5.47 - 5.38 (m, 2H), 4.03 - 3.95 (m, 1H), 3.60 - 3.51 (m, 2H), 3.18 (s, 2H), 1.41 (s, 3H), 1.27 (s, 3H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H) ppm; exchangeable H not observed.
322	 (<i>S</i>)-5-(5-chloro-2-((1-hydroxy-3-methylbutan-2-yl)oxy)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4<i>H</i>-pyrazolo[4,3-<i>c</i>]pyridin-4-one	S2		ESI-MS <i>m/z</i> calc. 456.136, found 457.2 (M+1) ⁺ .	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.29 (d, <i>J</i> = 1.4 Hz, 1H), 8.17 (s, 1H), 7.39 - 7.30 (m, 2H), 7.27 - 7.21 (m, 1H), 7.17 - 7.10 (m, 2H), 6.97 (d, <i>J</i> = 6.0 Hz, 1H), 6.87 (dd, <i>J</i> = 7.8, 2.3 Hz, 1H), 5.62 (s, 2H), 5.13 - 5.07 (m, 1H), 3.80 - 3.71 (m, 2H), 2.17 - 2.08 (m, 1H), 1.00 - 0.97 (m, 6H) ppm; exchangeable H not observed.

Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
323	 (S)-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine-3-carbonitrile	S15		ESI-MS <i>m/z</i> calc. 496.123, found 497.4 (M+1) ⁺ .	
324	 (S)-3-chloro-5-(5-chloro-2-((1-cyclopropyl-2-hydroxyethyl)amino)pyridin-4-yl)-1-(2,6-difluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridine-4-one	S18		ESI-MS <i>m/z</i> calc. 505.088, found 506.1 (M+1) ⁺ .	
325	Peak 1  <i>rel</i>-5-(5-chloro-2-(((3<i>S</i>,4<i>R</i>)-4-hydroxytetrahydrofuran-3-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridine-4-one	S2	Chiralpak [®] IC column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 40% MeOH (supplemented with 20 mM ammonia), 60% CO ₂ ; Flow rate 100 mL/min); rt = 5.08 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (d, <i>J</i> = 2.8 Hz, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.4 Hz, 1H), 7.40 (tdd, <i>J</i> = 7.5, 5.4, 1.9 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.24 - 7.17 (m, 2H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 6.60 (s, 1H), 5.69 - 5.60 (m, 2H), 5.00 (s, 1H), 4.06 (dq, <i>J</i> = 5.1, 2.5 Hz, 1H), 3.87 (ddd, <i>J</i> = 8.3, 6.4, 1.6 Hz, 1H), 3.83 (dd, <i>J</i> = 9.3, 4.9 Hz, 1H), 3.51 (dd, <i>J</i> = 8.6, 3.9 Hz, 1H), 3.48 (dd, <i>J</i> = 9.3, 2.7 Hz, 1H), 3.26 (q, <i>J</i> = 7.1 Hz, 1H), 3.16 (tt, <i>J</i> = 13.4, 6.1 Hz, 1H), 2.32 (d, <i>J</i> = 8.1 Hz, 1H) ppm;

Cmpd No.	Compound Structure/ Compound Name	Starting Material	SFC Conditions if applicable	LC/MS	NMR (shifts in ppm)
					exchangeable H not observed.
326	Peak 2  <i>rel</i> -5-(5-chloro-2-(((3 <i>R</i> ,4 <i>S</i>)-4-hydroxytetrahydrofuran-3-yl)methyl)amino)pyridin-4-yl)-1-(2-fluorobenzyl)-1,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-one	S2	Chiralpak [®] IC column, 5 μ m particle size, 25 cm x 20 mm from Daicel Corporation (Mobile phase: 40% MeOH (supplemented with 20 mM ammonia), 60% CO ₂ ; Flow rate 100 mL/min); rt = 6.59 min	ESI-MS <i>m/z</i> calc. 469.132, found 470.3 (M+1) ⁺ .	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 - 8.16 (m, 1H), 7.47 (dd, <i>J</i> = 7.5, 1.4 Hz, 1H), 7.40 (dddd, <i>J</i> = 9.0, 7.3, 5.4, 1.9 Hz, 1H), 7.30 - 7.24 (m, 2H), 7.24 - 7.15 (m, 2H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 6.60 (s, 1H), 5.69 - 5.58 (m, 2H), 5.00 (s, 1H), 4.06 (dq, <i>J</i> = 5.2, 2.6 Hz, 1H), 3.87 (ddd, <i>J</i> = 8.3, 6.4, 1.6 Hz, 1H), 3.83 (dd, <i>J</i> = 9.2, 4.9 Hz, 1H), 3.54 - 3.49 (m, 1H), 3.48 (dd, <i>J</i> = 9.2, 2.7 Hz, 1H), 3.26 (q, <i>J</i> = 7.1 Hz, 1H), 3.15 (dq, <i>J</i> = 13.4, 6.2 Hz, 1H), 2.36 - 2.28 (m, 1H) ppm; exchangeable H not observed.

Biological Activity Data

[00311] The compounds of Formulae I, Ia, Ib, II, IIa, and IIb, having activity as detected in the assay described below using the combined EC₅₀/E_{max} evaluation described below, are useful as PC1 correctors that increase functional cell-surface PC1. A compound of Formulae I, Ia, Ib, II, IIa, or IIb that demonstrates detectable activity exhibits an E_{max} value ≥ 3.0 . E_{max} can be calculated by any method known in the art.

[00312] In some embodiments, the compounds of Formulae I, Ia, Ib, II, IIa, and IIb are compounds having an activity as detected in the assay described below, such compounds having an EC₅₀ which is ≤ 1.0 μ M or having a detectable activity based on an EC₅₀ value > 1.0 μ M combined with an E_{max} score of ≥ 3.0 . In some embodiments, the compounds of Formulae I, Ia, Ib, II, IIa, and IIb are compounds having an EC₅₀ value which is ≤ 0.05 μ M, > 0.05 μ M but ≤ 0.2 μ M, > 0.2 μ M but ≤ 1.0 μ M, or having a detectable activity based on an EC₅₀ value > 1.0 μ M combined with an E_{max} score of ≥ 3.0 , as detected in the assay described below. In some embodiments, the compounds of Formulae I, Ia, Ib, II, IIa, and IIb are compounds having an EC₅₀ value which is ≤ 1.0 μ M as detected in the assay described below. In some embodiments, the compounds of Formulae I, Ia, Ib, II, IIa, and IIb that do not have

activity in the assay described below using the combined EC_{50}/E_{max} evaluation described above are excluded from the invention.

I. Assay

Measurement of cell surface PC1 in HEK293 cell lines overexpressing mutant PC1

Assay overview

[00313] For routine assessment of compound impact on trafficking of mutant PC1, an assay was developed based on whole-well luminescence from HEK293 cells. A cell line was established with stable overexpression of L2816P PKD modified at the N-terminus with the 11-amino acid HiBiT™ epitope tag and overexpression of WT PKD2 from a random genomic locus via lentiviral integration. Expression of both polycystins were verified via western blots and cell surface assays. At baseline, L2816P is predominantly misfolded and not trafficked to the cell surface, resulting in a low luminescence signal from cells probed with the Nano-Glo HiBiT extracellular detection system. Acute incubation at reduced temperatures results in elevated cell-surface PC1 levels as revealed by an increase in luminescence.

Reagents

[00314] DMEM, HEPES, NEAA, G418, Puromycin, Blasticidin, TrypLE, PBS and Doxycycline were obtained from Thermo Fisher (Loughborough, UK). FBS was obtained from Life Technologies (Paisley, UK). Nano-Glo® HiBiT assay kits (N2422, lot 0000523864) were obtained from Promega (Southampton, UK). Jump-In™ T-Rex™ HEK293 kit (A15008) was obtained from Thermo Fisher (Loughborough, UK). BioTek washer/dispenser (EL406) was obtained from Agilent (Wokingham, UK). PHERAstar reader was obtained from BMG LABTECH (Aylesbury, UK).

Assay protocol

[00315] HEK293 cells expressing HiBiT-tagged L2816P PKD1 were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1X Non-Essential Amino Acid (NEAA), 1X (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), 500µg/mL G418, 10µg/mL puromycin, 5µg/mL blasticidin and 1µg/mL doxycycline. 24 hours prior to running the assay, cells were dissociated with TrypLE solution after 1X Dulbecco's Phosphate Buffered Saline (DPBS) wash. The cells were harvested and seeded at a density of 5000 cells / well in 25µL volume into Corning 384 well plates containing 125nL of pre-dispensed compound. Concentration

response data was generated in duplicate over 10 points at final assay concentrations from 0.00320 μ M to 50.0 μ M. Assay plates were incubated at 37°C/5% CO₂ for 24 hours then washed 7x with DPBS before the addition of detection reagent. The LgBiT™ peptide contained within the detection reagent binds with high affinity to any HiBiT tagged PC1 L2816P at the cell surface, generating a luminescent signal. After addition of detection reagent, plates were read on a luminescence reader. Raw data were converted to fold difference over baseline by dividing the signal by the mean of the neutral control ($E_{\max}$, DMSO-treated cells). Normalized data were fitted with a 3-parameter Hill model (EC_{50} , Hill slope, Sinf). Modifications and variations of the embodiments described herein may be made without departing from the scope, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only.

II. Activity Data

[00316] The following table represents ADPKD/PC1 activity for representative compounds of the invention generated using the assay disclosed above, wherein “++++” indicates that EC_{50} value is $\leq 0.05 \mu$ M; “+++” indicates that EC_{50} value is $> 0.05 \mu$ M but $\leq 0.2 \mu$ M; “++” indicates that EC_{50} value is $> 0.2 \mu$ M but $\leq 1.0 \mu$ M; and “+” indicates that the compound demonstrates detectable activity based on an EC_{50} value $> 1.0 \mu$ M combined with an $E_{\max}$ score of ≥ 3.0 . “ND” indicates that Compound 327 was not tested for ADPKD/PC1 activity as of the filing date of this application but is expected to have detectable activity in the assay described above.

Table 15. Biological Activity Data for Compounds 1 to 233 and 248 to 327

Compound No.	Detectable Activity	Compound No.	Detectable Activity
1	++++	50	++
2	++	51	++
3	+++	52	++
4	++	53	++
5	+	54	+++
6	+++	55	++
7	++++	56	+++
8	++++	57	++
9	++++	58	++
10	++	59	+++
11	+	60	++
12	+++	61	+++
13	++	62	++
14	+++	63	+++
15	+++	64	++
16	++++	65	++
17	++	66	++
18	+++	67	++++
19	++	68	+++
20	+++	69	+
21	++	70	++
22	+	71	++
23	+++	72	++
24	++	73	++
25	+++	74	+
26	+++	75	+++
27	+++	76	++
28	++	77	++
29	++	78	++
30	+++	79	++
31	++	80	++
32	+++	81	++
33	++	82	+++
34	++	83	+++
35	+	84	++++
36	+	85	+++
37	++	86	+++
38	++	87	++
39	++	88	+++
40	++	89	++
41	++	90	+
42	++	91	++
43	++	92	+++
44	++	93	++
45	++++	94	+++
46	++	95	++
47	+++	96	+++
48	++	97	++
49	++	98	+++

Compound No.	Detectable Activity	Compound No.	Detectable Activity
99	++++	150	++
100	++++	151	+++
101	++	152	++
102	+++	153	++++
103	+	154	+++
104	++	155	+++
105	+++	156	++++
106	+++	157	+
107	++	158	+++
108	+++	159	++
109	+++	160	+++
110	+++	161	+++
111	++	162	++
112	++	163	++++
113	++	164	+++
114	++	165	+++
115	++	166	++++
116	+	167	+++
117	+	168	+++
118	++	169	+++
119	++	170	+++
120	+	171	+++
121	+++	172	+++
122	++	173	+
123	++	174	++
124	+	175	+++
125	++	176	+++
126	+++	177	++++
127	+++	178	++
128	++	179	+++
129	++	180	++
130	++++	181	+++
131	++++	182	++
132	+++	183	++
133	+++	184	++++
134	++	185	+++
135	++	186	++
136	+++	187	++++
137	++++	188	++
138	++	189	+++
139	++++	190	+++
140	+	191	++
141	+++	192	++++
142	++++	193	+
143	+++	194	+++
144	++	195	+++
145	++	196	+++
146	++++	197	+++
147	++	198	+++
148	++	199	++
149	++++	200	++++

Compound No.	Detectable Activity	Compound No.	Detectable Activity
201	++	266	+
202	+++	267	++
203	++	268	+++
204	++++	269	++
205	+++	270	+
206	+++	271	+
207	++++	272	+
208	+	273	+
209	+++	274	+
210	++	275	+
211	+++	276	++
212	+++	277	++
213	++	278	++
214	++++	279	++
215	+++	280	+
216	+++	281	+
217	++++	282	++
218	+++	283	++
219	+++	284	++++
220	+++	285	++++
221	+++	286	+
222	+++	287	+++
223	+++	288	++++
224	+	289	++
225	++	290	+++
226	+++	291	+++
227	+++	292	++
228	++++	293	+++
229	++	294	++
230	+++	295	+
231	++	296	++++
232	+++	297	++++
233	++	298	+++
248	+	299	+++
249	+	300	+++
250	+	301	+++
251	+++	302	+
252	++	303	++
253	+	304	+
254	+	305	++
255	++	306	++
256	++	307	++
257	++	308	++
258	++	309	++
259	++	310	++
260	++	311	+
261	+	312	++
262	++	313	++
263	++	314	+++
264	+	315	+++
265	+	316	++

Compound No.	Detectable Activity	Compound No.	Detectable Activity
317	++	323	++
318	++	324	+
319	++	325	++
320	++	326	+++
321	+	327	ND
322	++		

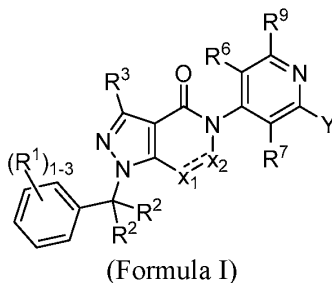
Other Embodiments

[00317] All publications and patents referred to in this disclosure are incorporated herein by reference in their entirety to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference in their entirety. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms defined in this disclosure is intended to be controlling.

[00318] The foregoing discussion discloses and describes merely exemplary embodiments of this disclosure. One skilled in the art will readily recognize, from such discussion and from the accompanying claims, that various changes, modifications, and variations can be made therein without departing from the spirit and scope of this disclosure as defined in the following claims.

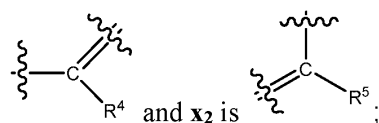
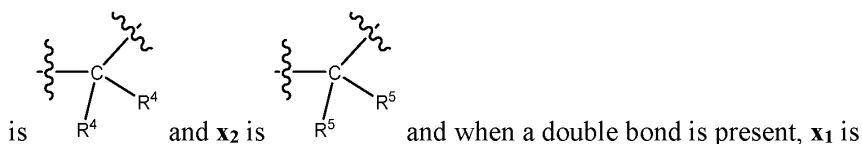
CLAIMS

1. A compound of Formula I:



a tautomer or atropisomer thereof, a deuterated derivative of the compound, tautomer, or atropisomer, or pharmaceutically acceptable salt or prodrug of the compound, tautomer, atropisomer, or deuterated derivative, wherein:

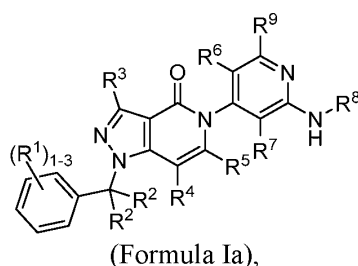
- $X_1 \text{---} X_2$ is a single bond or a double bond, wherein when a single bond is present, x_1



- each R^1 is independently selected from hydrogen, C₁-C₃ alkyl (substituted with 0-2 groups selected from oxo, hydroxyl, and amino), C₁-C₃ alkoxy, halogen, and cyano;
- each R^2 is independently selected from hydrogen and C₁-C₃ alkyl;
- R^3 is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- each R^4 and R^5 are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- R^6 and R^9 are independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- R^7 is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- R^8 is selected from:
 - o hydrogen,
 - o C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),

- C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 7-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-3 groups independently selected from:
 - oxo,
 - halogen
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group); and
- Y is selected from
 - OR⁸,
 - N(R⁸)₂, and
 - 3- to 10-membered heterocyclyl or 3- to 10-membered heteroaryl, each of which is substituted with 0-2 groups independently selected from:
 - N(R⁸)₂,
 - hydroxyl,
 - oxo,
 - C₁-C₃ alkoxy, and
 - C₁-C₃ alkyl (substituted with 0-2 groups selected from amino, hydroxyl, C₃-C₄ alkyl, oxo, and C₁-C₃ alkoxy).

2. A compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt according to claim 1, selected from a compound of Formula Ia:

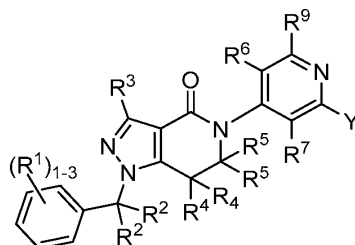


or a tautomer or atropisomer thereof, a deuterated derivative of the tautomer or atropisomer, or a pharmaceutically acceptable salt or prodrug of any of the foregoing, wherein:

- each R¹ is independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;

- each **R**² is independently selected from hydrogen and C₁-C₃ alkyl;
- **R**³ is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- **R**⁴ and **R**⁵ are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- **R**⁶ and **R**⁹ are independently selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- **R**⁷ is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R**⁸ is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group).

3. A compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt according to claim 1, selected from a compound of Formula Ib:



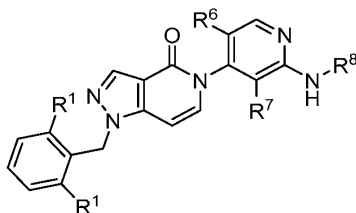
(Formula Ib)

a tautomer or atropisomer thereof, a deuterated derivative of the compound, tautomer, or atropisomer, or pharmaceutically acceptable salt or prodrug of the compound, tautomer, atropisomer, or deuterated derivative, wherein:

- each **R¹** is independently selected from hydrogen, C₁-C₃ alkyl (substituted with 0-2 groups selected from oxo, hydroxyl, and amino), C₁-C₃ alkoxy, halogen, and cyano;
- each **R²** is independently selected from hydrogen and C₁-C₃ alkyl;
- **R³** is selected from hydrogen, C₁-C₃ alkyl, halogen, and cyano;
- each **R⁴** and **R⁵** are independently selected from hydrogen, C₁-C₃ alkyl, and halogen;
- **R⁶** and **R⁹** are independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,

- C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group); and
 - Y is selected from
 - N(R⁸)₂, and
 - 3- to 10-membered heterocyclyl or 3- to 10-membered heteroaryl, each of which is substituted with 0-2 groups independently selected from:
 - hydroxyl,
 - oxo,
 - C₁-C₃ alkoxy, and
 - C₁-C₃ alkyl (substituted with 0-2 groups selected from amino, hydroxyl, C₃-C₄ alkyl, oxo, and C₁-C₃ alkoxy).
4. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 3, wherein each **R¹** is independently selected from hydrogen, methyl, methoxy, fluoro, chloro, and cyano.
5. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 4, wherein **R²** is independently selected from hydrogen and methyl.
6. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 5, wherein **R³** is selected from hydrogen, methyl, and cyano.
7. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 6, wherein **R⁴** and **R⁵** are independently selected from hydrogen and methyl.
8. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 7, wherein **R⁶** is selected from hydrogen, methyl, ethyl, fluoro, chloro, bromo, and cyano.
9. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 8, wherein **R⁷** is selected from hydrogen and fluoro.

10. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 1, selected from compounds of Formula II:

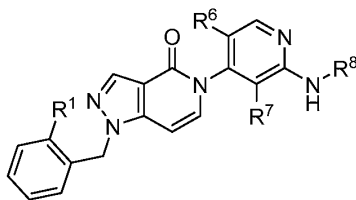


(Formula II),

tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁶** is selected from C₁-C₃ alkyl, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group).

11. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 1, selected from compounds of Formula IIa:

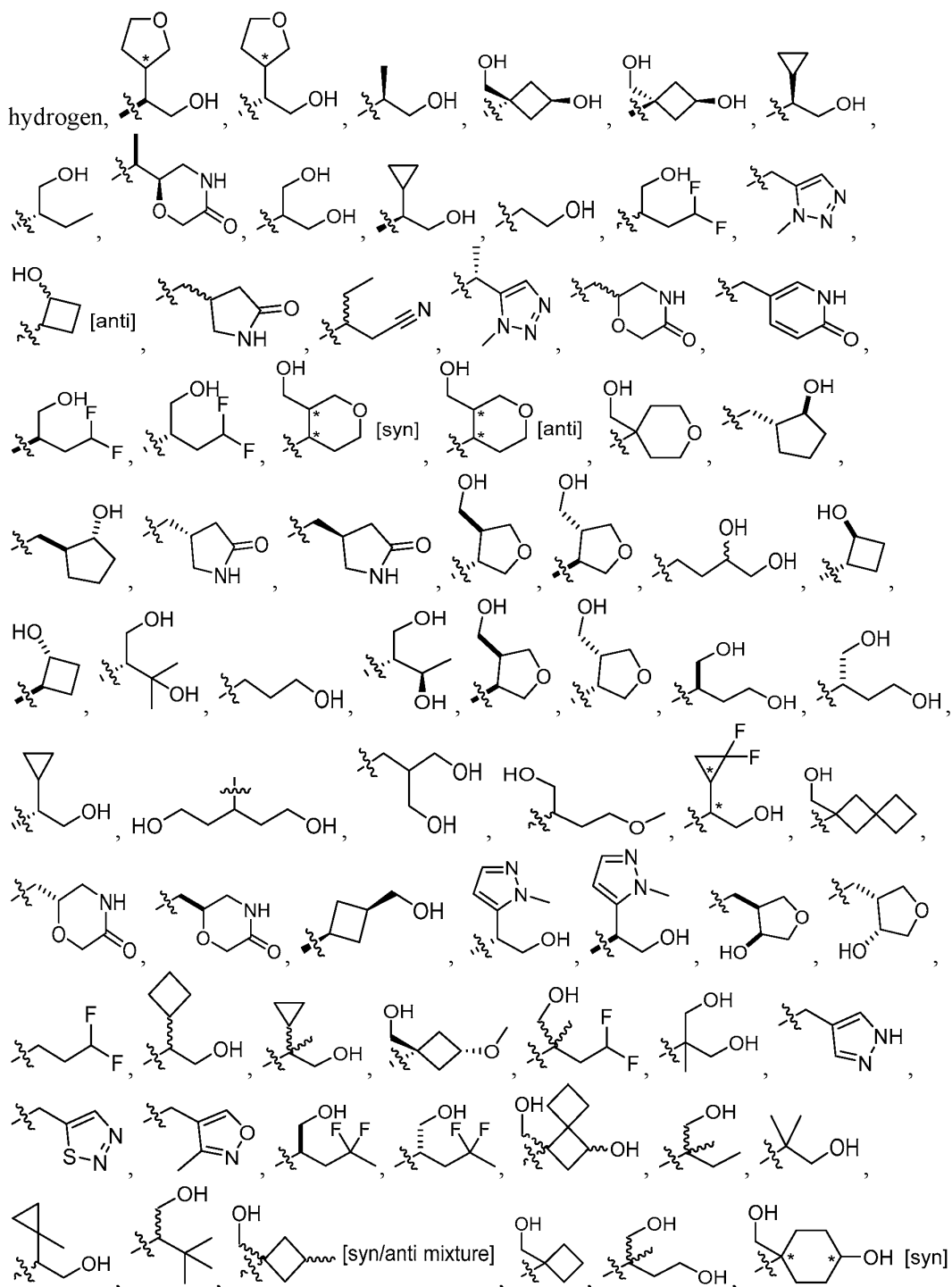


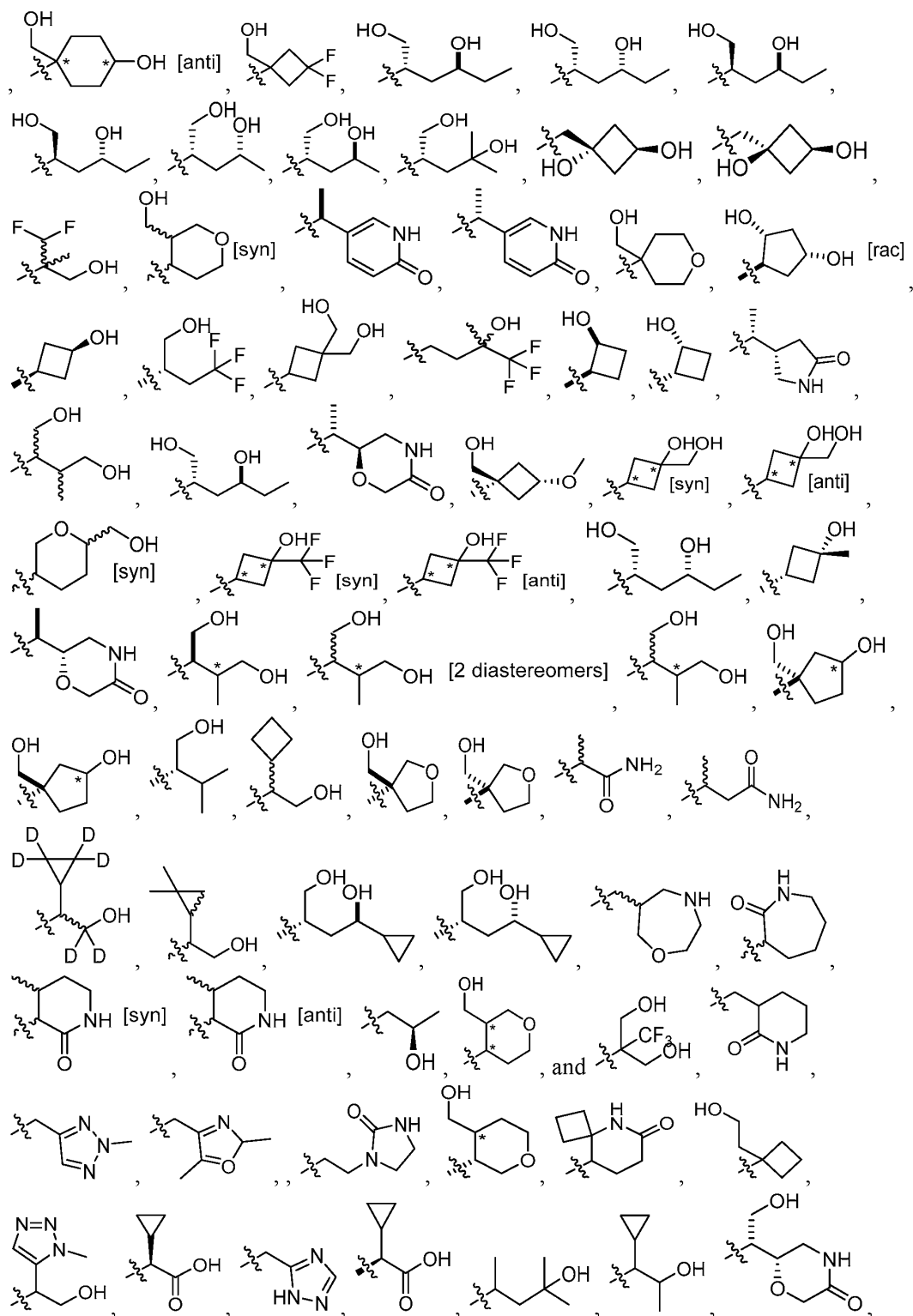
(Formula IIa),

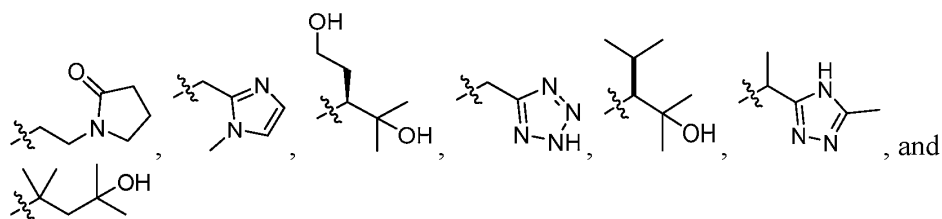
tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- **R¹** is selected from hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, and cyano;
- **R⁶** is selected from C₁-C₃ alkyl, halogen, and cyano;
- **R⁷** is selected from hydrogen, C₁-C₃ alkyl, and halogen; and
- **R⁸** is selected from:
 - hydrogen,
 - C₁-C₈ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl,
 - oxo,
 - amino,
 - cyano,
 - halogen,
 - C₁-C₃ alkoxy (substituted with 0-1 oxo group),
 - C₃-C₆ cycloalkyl (substituted with 0-2 groups independently selected from hydroxyl, halogen, C₁-C₃ alkyl),
 - 3- to 6-membered heterocyclyl (substituted with 0-3 groups independently selected from halogen, hydroxyl, oxo, and C₁-C₃ alkyl (substituted with 0-1 hydroxyl group)), and
 - 5- to 6-membered heteroaryl (substituted with 0-3 groups independently selected from oxo, C₁-C₃ alkyl, and C₃-C₆ cycloalkyl);
 - C₃-C₇ cycloalkyl substituted with 0-3 groups independently selected from:
 - hydroxyl,
 - halogen,
 - C₁-C₃ alkyl (substituted with 0-3 groups independently selected from hydroxyl and halogen), and
 - C₁-C₃ alkoxy; and
 - 5- to 9-membered heterocyclyl substituted with 0-2 groups independently selected from:
 - oxo,
 - hydroxyl, and
 - C₁-C₃ alkyl (substituted with 0-1 hydroxyl group).

12. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 11, wherein **R⁸** is selected from:

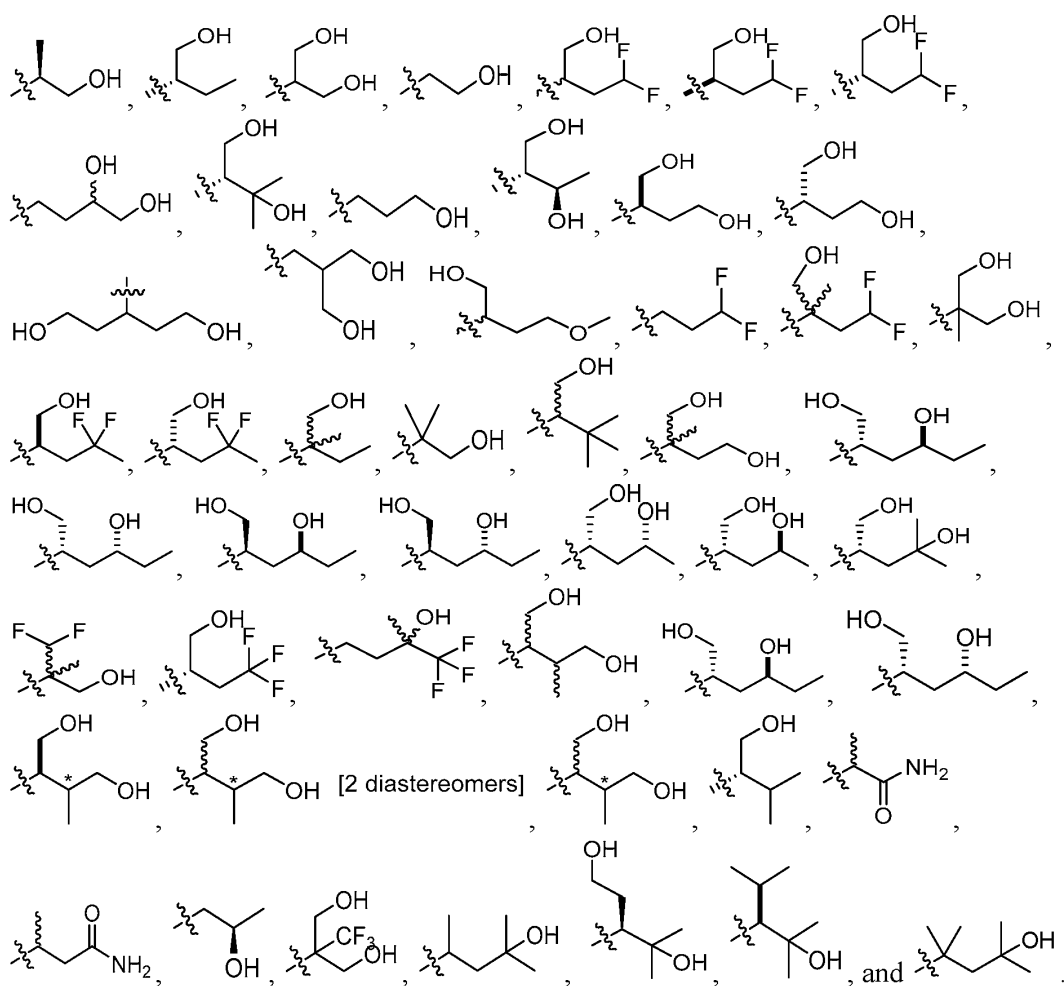




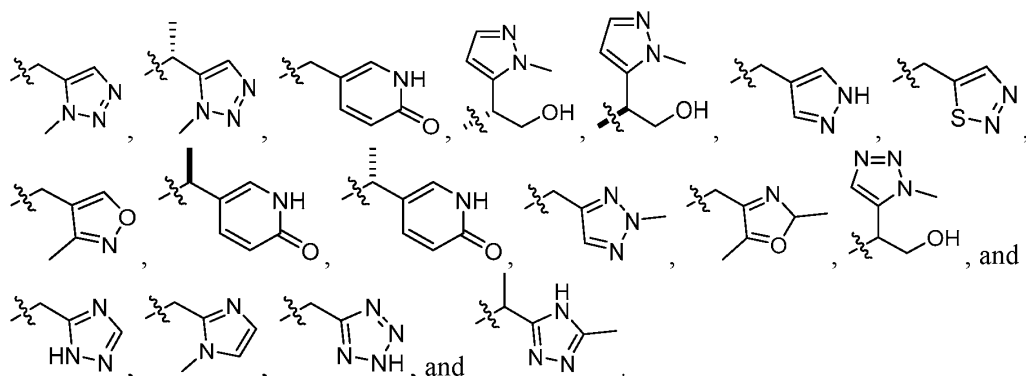


13. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 12, wherein **R**⁸ is selected from C₁-C₈ alkyl substituted with 0-5 groups.

14. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 13, wherein **R**⁸ is selected from:

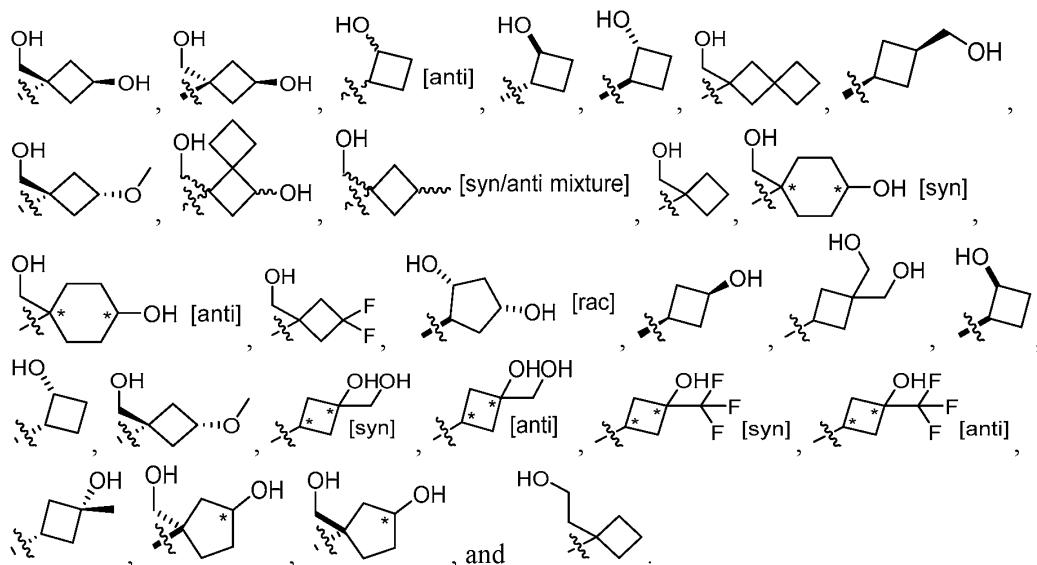


17. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 13, wherein **R⁸** is selected from:



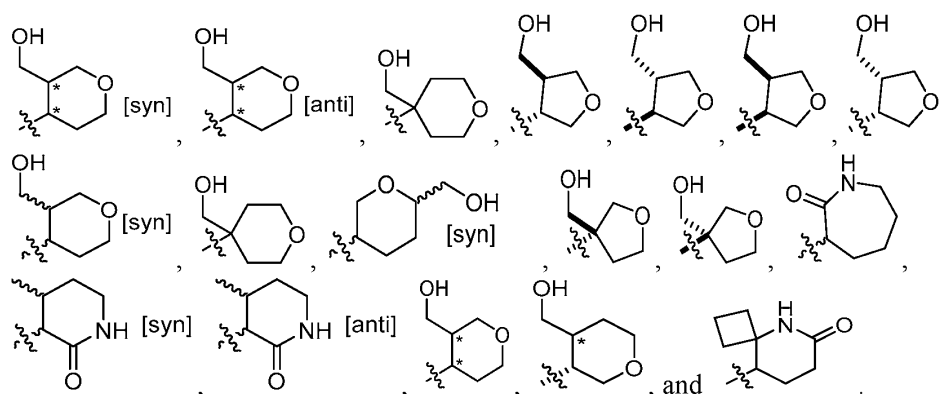
18. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 12, wherein **R⁸** is selected from C₃-C₇ cycloalkyl substituted with 0-3 groups.

19. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 18, wherein **R**⁸ is selected from:



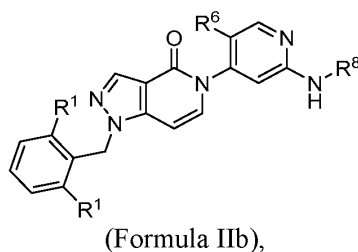
20. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of any one of claims 1 to 12, wherein **R⁸** is selected from 5- to 9-membered heterocyclyl substituted with 0-2 groups.

21. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 20, wherein **R⁸** is selected from:



22. A compound selected from Compounds 1-233 of Table 1 and Compounds 248-327 of Table 2, tautomers or atropisomers thereof, deuterated derivatives of the tautomers or atropisomers, and pharmaceutically acceptable salts and prodrugs of any of the foregoing.

23. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 1, selected from compound of Formula IIb:

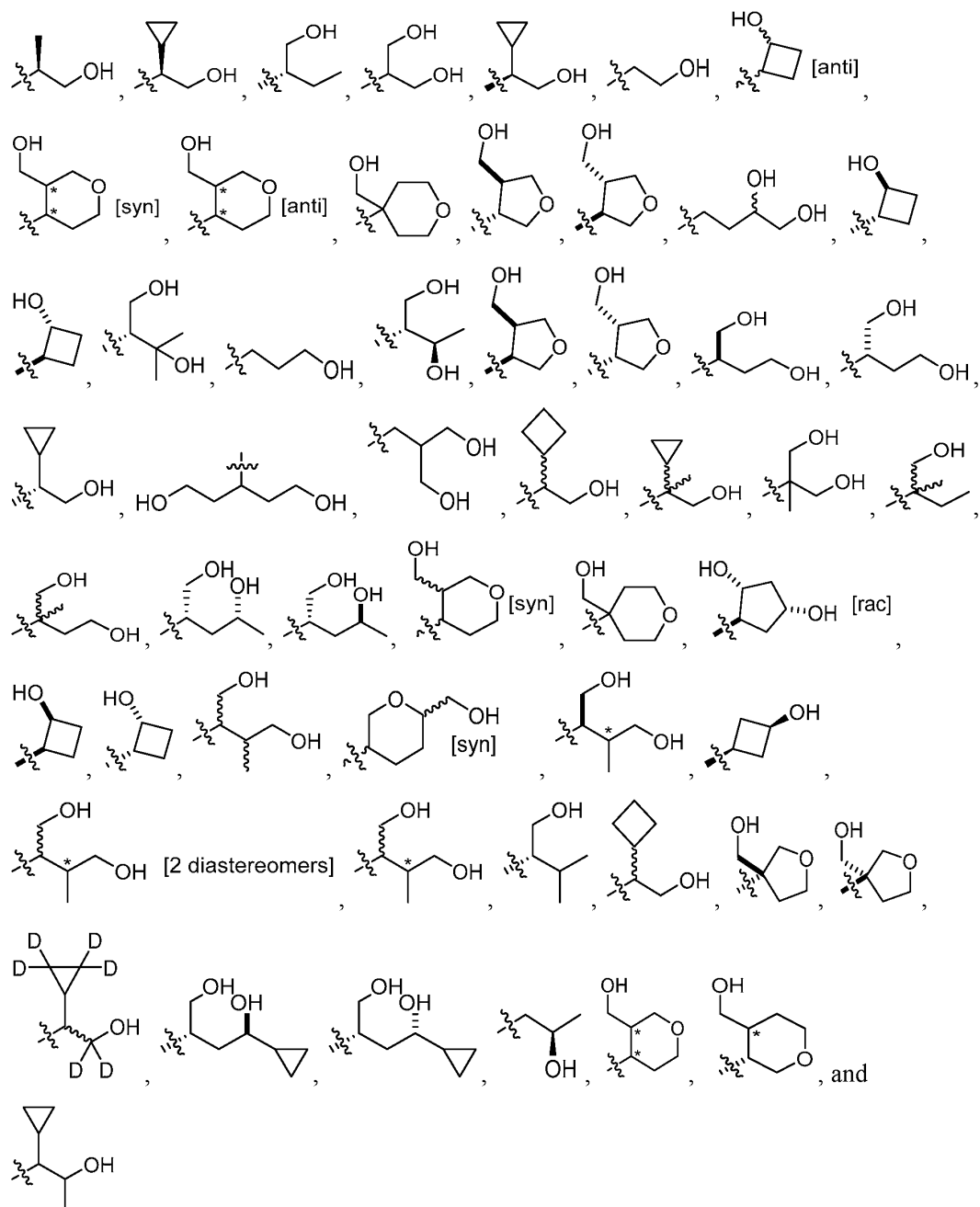


tautomers or atropisomers of those compounds, deuterated derivatives of the compounds, tautomers, and atropisomers, and pharmaceutically acceptable salts and prodrugs of those compounds, tautomers, atropisomers, and deuterated derivatives, wherein:

- each **R¹** is independently selected from hydrogen and halogen;
- **R⁶** is selected from halogen; and
- **R⁸** is selected from:
 - o C₁-C₅ alkyl substituted with 0-5 groups independently selected from:
 - hydroxyl, and
 - C₃-C₆ cycloalkyl;

- C₃-C₆ cycloalkyl, substituted with 0-2 groups selected from hydroxyl and halogen; and
- 5- to 6-membered heterocyclyl unsubstituted or substituted with C₁-C₃ alkyl, wherein the C₁-C₃ alkyl is substituted with 0-2 substituents selected from hydroxyl and halogen.

24. The compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug of claim 23, wherein **R⁸** is selected from:

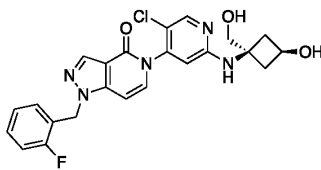


25. A compound selected from:

Compound 7	Compound 8	Compound 23
Compound 27	Compound 30	Compound 99
Compound 130	Compound 146	Compound 149
Compound 163	Compound 192	Compound 201
Compound 213	Compound 217	Compound 218
Compound 220	Compound 327	

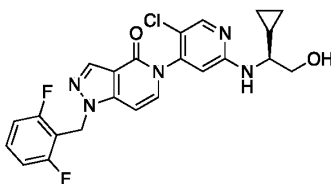
or a tautomer or atropisomer thereof, or a deuterated derivative of the tautomer or atropisomer, or a pharmaceutically acceptable salt or prodrug of any of the foregoing.

26. A compound having the following formula:



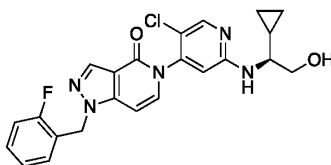
(Compound 7).

27. A compound having the following formula:



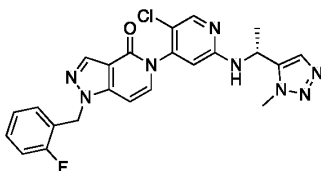
(Compound 8).

28. A compound having the following formula:



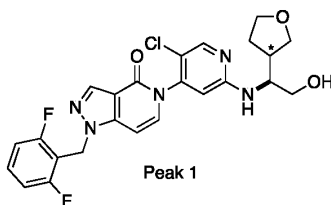
(Compound 23).

29. A compound having the following formula:



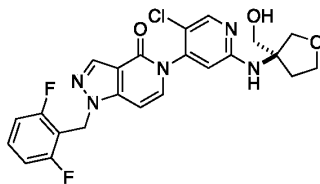
(Compound 27).

30. A compound having the following formula:



(Compound 149).

31. A compound having the following formula:



(Compound 201).

32. A pharmaceutical composition comprising a compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug according to any one of claims 1 to 31 and a pharmaceutical carrier.

33. A method of treating autosomal dominant polycystic kidney disease (ADPKD) in a patient using a compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug according to any one of claims 1 to 31 or a pharmaceutical composition according to claim 32.

34. Use of a compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug according to any one of claims 1 to 31 in the manufacture of a medicament for treating autosomal dominant polycystic kidney disease (ADPKD) in a patient in need thereof.

35. A compound, tautomer, atropisomer, deuterated derivative, or pharmaceutically acceptable salt or prodrug according to any one of claims 1 to 31 or a pharmaceutical composition according to claim 32 for use in treating autosomal dominant polycystic kidney disease (ADPKD) in a patient in need thereof.