Imidazole macrocycles for the treatment of autoimmune disease

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to antagonist of STING useful for treating autoimmune diseases.

FIELD OF THE INVENTION

Autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel diseases (IBD), refer to a spectrum of conditions where the immune system mistakenly attacks one's own body, leading to unresolved and inappropriately activated inflammation that become pathogenic. Many of the autoimmune diseases are poorly managed by existing treatments that provide only symptomatic relief. Steroid and broad immunosuppressant drugs (e.g. mycophenolate and cyclophosphamide) constitute the stand of care, but are associated with significant treatment-related toxicity. Pathway selective agents such as Adalizumab (anti-TNF antibody, for RA and IBD) occasionally resulting in infection or insufficient tumor surveillance. And Belimumab (anti-BAFF antibody, the only FDA-approved new drug for SLE) shows a slow onset of remission with modest efficacy in the clinic. In addition, the heterogeneity of many autoimmune diseases with no-existing treatment illustrates the difficulty in finding efficacy through the blockade of one immune pathway. Thus, currently available treatments fail to fulfill a greater unmet needs of autoimmune inflammatory diseases with limited remission, severe side effects, opportunistic infection, and poor quality of life with chronic inflammation.

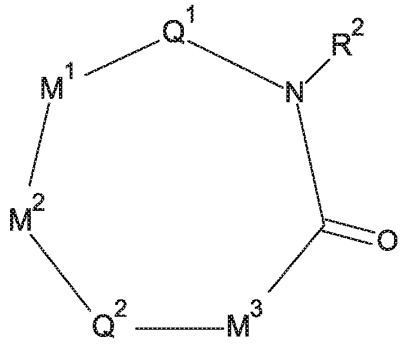
Stimulator of interferon genes (STING) is an endoplasmic reticulum (ER)-located transmembrane protein that is pivotal in mediating the host's innate sensing of pathogen-/damage-associated molecular patterns (PAMPs or DAMPs). In particular, the cyclic-GMP-AMP synthase (cGAS)-STING pathway has emerged as a critical mechanism for coupling cytosolic DNA recognition to the induction of type-I interferon (IFN) and broader immune defense programs. The binding of cGAS to double-stranded DNA (dsDNA) allosterically activates its catalytic site, leading to the production of 2'3'- cyclic GMP-AMP (cGAMP), a secondary messenger molecule that is agonistic to STING. Upon activation, STING translocates from ER to Golgi and recruits TANK-binding kinase 1 (TBK1), which phosphorylates interferon regulatory factor 3 (IRF3) and nuclear factor-kappa B (NF-κB) to initiate the expression of type-I IFN and a myriad of pro-inflammatory cytokines (e.g., IL-6 and TNFα), respectively. Besides 2'3'-cGAMP,

STING can be activated by other types of cyclic-di-nucleotides (CDNs), such as c-di-AMP, c-di-GMP, and 3',3'-cGAMP from bacteria. Following the signal transduction, STING is rapidly degraded to prevent it from constitutive signaling of the inflammatory responses.

While eliciting robust host defense responses, aberrant STING signaling fuels dysregulated immune responses associated with many pathologies. Gain-of-function (GoF) human STING mutations are the root cause of STING-associated vasculopathy with onset in infancy (SAVI), a monogenic disease characterized by the onset of auto-inflammation conditions called type I interferonopathies. Mechanistically, the disease-causing substitutions trigger ligand-independent, constitutive STING activation. Besides, STING is implicated in DNA-driven inflammations, such as Aicardi-Goutières Syndrome (AGS) and genetic forms of lupus. Unlike SAVI, the STING mediated continuous innate immune activation in AGS is caused by deficiencies in self-DNA clearance and metabolisms due to mutations in endonuclease gene TREX1 and/or DNASE2. Consistently, genetic and pharmacological inhibition of STING ameliorates systemic inflammation and morbidity in the Trex1-/- mouse model. Apart from genetic disorders, robust preclinical and clinical evidence supports a general pathogenic role of STING in a range of inflammation-associated disorders such as SLE and RA. A direct link between the cGAS-STING pathway and SLE was established by observing that PBMC from a subset of SLE patients has elevated cytosolic cGAMP than healthy controls. In addition, membrane vesicles from apoptotic cells in SLE sera have high ISGs-stimulating activities dependent on cGAS-STING. And that disrupting STING signaling ameliorated the development of lupus-like phenotypes in FcγrIIb-/- mice. Furthermore, multiple recent studies associate STING with distinct types of neurodegeneration. Taking Parkinson's disease as an example, missense mutations in PARKIN and PINK resulted in the accumulation of mitochondrial DNA that triggers neuronal inflammation in a cGAS-STING dependent manner. The absence of STING rescued the motor deficit and neuronal cell loss in the mouse disease model. Finally, STING also mediates tumorigenic DNA responses caused by chromosomal instability during cancer metastasis, and that STING-deficiency confers protection against colorectal and skin cancer in the mouse.

SUMMARY OF THE INVENTION

The present invention relates to novel compounds of formula (Ia),



(Ia),

wherein

M^1 is heteroarylene optionally substituted by R^1; wherein

R^1 is deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, $(R)_2N$, RCO, RSO_2, $RNHSO_2$, R_2NSO_2, RSO(NR), R_3Si, $ROC_{1-6}alkyl$, $RSC_{1-6}alkyl$, $RNHC_{1-6}alkyl$, $(R)_2NC_{1-6}alkyl$, $RSO_2C_{1-6}alkyl$, $RNHSO_2C_{1-6}alkyl$, $R_2NSO_2C_{1-6}alkyl$, $RSO(NR)C_{1-6}alkyl$ or $R_3SiC_{1-6}alkyl$; wherein R is H, R^a, R^b or R^c;

R^a is $C_{1-6}alkyl$ optionally substituted by R^b or R^c;

R^b is $C_{3-7}cycloalkyl$, heterocyclyl, heteroaryl or aryl, said $C_{3-7}cycloalkyl$, heterocyclyl, heteroaryl and aryl being unsubstituted or optionally substituted by deuterio, halogen or R^c;

R^c is selected from deuterio, $C_{1-6}alkyl$, $(C_{1-6}alkyl)_3Si$, $haloC_{1-6}alkyl$, $deuterioC_{1-6}alkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, $deuterioC_{1-6}alkoxy$, $C_{2-6}alkenyl$, $haloC_{2-6}alkenyl$, $deuterioC_{2-6}alkenyl$, $C_{2-6}alkynyl$, $haloC_{2-6}alkynyl$, $deuterioC_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $haloC_{3-7}cycloalkyl$, $deuterioC_{3-7}cycloalkyl$, amino, $C_{1-6}alkylamino$, $(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylcarbonylamino$, $haloC_{1-6}alkylamino$, $haloC_{1-6}alkylcarbonylamino$, $(haloC_{1-6}alkyl)_2amino$, $C_{3-7}cycloalkylamino$, $C_{3-7}cycloalkylcarbonylamino$, $(C_{3-7}cycloalkyl)_2amino$, $haloC_{3-7}cycloalkylamino$, $(haloC_{3-7}cycloalkyl)_2amino$, $C_{3-7}cycloalkyl(C_{1-6}alkyl)amino$, $haloC_{3-7}cycloalkyl(C_{1-6}alkyl)amino$, $C_{1-6}alkylsulfonylamino$, $haloC_{1-6}alkylsulfonylamino$, $C_{1-6}alkoxyC_{1-6}alkyl$, $(haloC_{1-6}alkoxy)C_{1-6}alkyl$, $C_{1-6}alkoxy(halo)C_{1-6}alkyl$, $C_{3-7}cycloalkylC_{1-6}alkyl$, $C_{3-7}cycloalkylhaloC_{1-6}alkyl$, $C_{1-6}alkylcarbonyl$, $haloC_{1-6}alkylcarbonyl$, $C_{3-7}cycloalkylcarbonyl$, $haloC_{3-7}cycloalkylcarbonyl$, $C_{1-6}alkoxycarbonyl$, $haloC_{1-6}alkoxycarbonyl$, $C_{3-7}cycloalkoxycarbonyl$, $haloC_{3-7}cycloalkoxycarbonyl$, $C_{1-6}alkylaminocarbonyl$, $(C_{1-6}alkyl)_2aminocarbonyl$, $C_{3-7}cycloalkylaminocarbonyl$, ($C_{3-}$

$_{7}$cycloalkyl)$_2$aminocarbonyl, C_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, haloC_{1-6}alkylaminocarbonyl, halo(C_{1-6}alkyl)$_2$aminocarbonyl, haloC_{3-7}cycloalkylaminocarbonyl, halo(C_{3-7}cycloalkyl)$_2$aminocarbonyl, haloC_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, C_{1-6}alkylhaloC_{3-7}cycloalkylaminocarbonyl, (C_{1-6}alkyl)$_3$ammonio, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfanyl, C_{3-7}cycloalkylsulfinyl, C_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkylsulfanyl, haloC_{1-6}alkylsulfinyl, haloC_{1-6}alkylsulfonyl, haloC_{3-7}cycloalkylsulfanyl, haloC_{3-7}cycloalkylsulfinyl, haloC_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, (haloC_{1-6}alkylamino)sulfonyl, (C_{1-6}alkyl)$_2$aminosulfonyl, (haloC_{1-6}alkyl)$_2$aminosulfonyl, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkoxy)$_2$phosphoryl, hydroxy(C_{1-6}alkoxy)phosphoryl, C_{1-6}alkoxyphosphoryl, hydroxy, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, hydroxylhaloC_{1-6}alkoxy, hydroxyC_{3-7}cycloalkyl, hydroxyhaloC_{3-7}cycloalkyl and sulfonimidoyl optionally substituted by H, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, heteroaryl and heterocyclyl;

M^2 is arylene, heterocyclylene or heteroarylene, said arylene, heterocyclylene or heteroarylene being optionally substituted by R^1;

M^3 is heterocyclylene which is unsubstituted or optionally substituted by R^3;

R^2 is deuterio, R, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RSO_2C_{1-6}alkyl, RNHC_{1-6}alkyl or (R)$_2$NC_{1-6}alkyl;

R^3 is heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl or arylcarbonyl, said heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl and arylcarbonyl being unsubstituted or optionally substituted by R^1;

Q^1 is -M-, -M-O-M-, -M-S-M-, -M-SO_2-M-, -M-SO(NH)-M-, -M-SO(NR)-M-, -M-SiR_2-M- or -M-N(R)-M-; wherein M is C_{1-6}alkylene unsubstituted or optionally substituted by the substituents independently selected from deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, R_2N, RSO_2, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RNHC_{1-6}alkyl, (R)$_2$NC_{1-6}alkyl and RSO_2C_{1-6}alkyl;

Q^2 is NH, O, S, SO, SO_2, P(O)R, PO(NR), Se, N(R), SiR_2, heterocyclyl, heteroaryl or aryl;

or a pharmaceutically acceptable salt thereof.

Another object of the present invention is related to novel compounds of formula (I) or (Ia). Their manufacture, medicaments based on a compound in accordance with the invention

and their production as well as the use of compounds of formula (I) or (Ia) as STING antagonist, and for the treatment or prophylaxis of autoimmune diseases, inflammatory diseases, neurological disorders diseases, metabolic diseases, cardiovascular diseases, or selective types of cancers where overexpression or activation of STING is implicated. The compounds of formula (I) or (Ia) show superior STING antagonism activity. In addition, the compounds of formula (I) or (Ia) also show good cytotoxicity, phototoxicity, solubility, hPBMC, human microsome stability and SDPK profiles, as well as low CYP inhibition.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term "deuterio" or "deuterium" denotes the isotope of hydrogen that has a single neutron as well as a proton in the nucleus.

The term "C_{1-6}alkyl" denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups are methyl, ethyl and *n*-propyl.

The term "C_{1-6}alkylene" denotes a linear or branched saturated divalent hydrocarbon group of 1 to 6 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 6 carbon atoms. Examples of C_{1-6}alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

The term "C_{1-6}alkoxy" denotes C_{1-6}alkyl-O-.

The term "trideuterioC_{1-6}alkyl" denotes a C_{1-6}alkyl group wherein three of the hydrogen atoms of the C_{1-6}alkyl group has been replaced by deuterium. Example of trideuterioC_{1-6}alkyl includes trideuteriomethyl.

The term "C_{2-6}alkenyl" denotes a monovalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one double bond. In particular embodiments, alkenyl has 2 to 4 carbon atoms with at least one double bond. Examples of C_{2-6}alkenyl include ethenyl (or vinyl), propenyl, prop-2-enyl, isopropenyl, n-butenyl, and iso-butenyl.

The term "C_{2-6}alkynyl" denotes a monovalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one triple bond. In particular embodiments, alkynyl has 2 to 4 carbon atoms with at least one triple bond. Examples of C_{2-6}alkynyl include ethynyl (–C≡CH), prop-1-ynyl (–C≡CCH_3), prop-2-ynyl (propargyl, –CH_2C≡CH), but-1-ynyl, but-2-ynyl, and but-3-ynyl.The term "halogen" and "halo" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term "haloC_{1-6}alkyl" denotes a C_{1-6}alkyl group wherein at least one of the hydrogen atoms of the C_{1-6}alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl.

The term "haloC_{1-6}alkoxy" denotes haloC_{1-6}alkyl-O-.

The term "haloazetidinyl" denotes an azetidinyl group wherein at least one of the hydrogen atoms of the azetidinyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of halopiperidinyl include fluoroazetidinyl and difluoroazetidinyl.

The term "pyrimidinyloxy" denotes pyrimidinyl-O-.

The term "trideuterioC_{1-6}alkoxy" denotes trideuterioC_{1-6}alkyl-O-.

The term "carboxy" denotes -COOH.

The term "C_{3-7}cycloalkyl" denotes a monovalent saturated monocyclic or bicyclic hydrocarbon group of 3 to 7 ring carbon atoms. Bicyclic means consisting of two saturated carbocycles having one or more carbon atoms in common. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[1.1.0]butyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, or bicyclo[2.2.2]octanyl.

The term "haloC_{3-7}cycloalkyl" denotes a C_{3-7}cycloalkyl group wherein at least one of the hydrogen atoms of the C_{3-7}cycloalkyl group has been replaced by same or different halogen atoms, particularly fluoro atom.

The term "halo-1,2,3,5,6,7-hexahydropyrrolizinyl" denotes a 1,2,3,5,6,7-hexahydropyrrolizinyl group wherein at least one of the hydrogen atoms of the C_{3-7}cycloalkyl group has been replaced by same or different halogen atoms, particularly fluoro atom.

The term "C_{3-7}cycloalkoxy" denotes C_{3-7}cycloalkyl-O-.

The term "oxetanyloxy" denotes oxetanyl-O-.

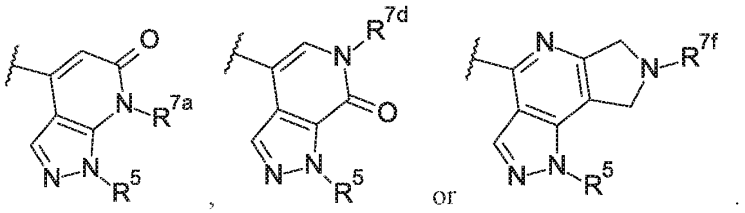
The term "azetidinyloxy" denotes azetidinyl-O-.

The term "C_{1-6}alkylcarbonyloxy" denotes C_{1-6}alkyl-C(O)-O-.

The terms "heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" are used interchangeably and refer to any mono-, bi-, tricyclic, spiro or bridged, saturated, partially saturated or unsaturated, non-aromatic ring system, having 3 to 20 ring atoms, where the ring atoms are carbon, and at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur, oxygen or silicon. If any ring atom of a cyclic system is a

heteroatom, that system is a heterocycle, regardless of the point of attachment of the cyclic system to the rest of the molecule. In one example, heterocyclyl includes 3-11 ring atoms ("members") and includes monocycles, bicycles, tricycles, spiro, and bridged ring systems, wherein the ring atoms are carbon, where at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur, oxygen or silicon. In other examples, heterocyclyl includes 4-10 or 5-10 ring atoms. In one example, heterocyclyl includes 1 to 4 heteroatoms. In one example, heterocyclyl includes 1 to 3 heteroatoms. In another example, heterocyclyl includes 3- to 7-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur, oxygen or silicon. In another example, heterocyclyl includes 4- to 6-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur, oxygen or silicon. In another example, heterocyclyl includes 3-membered monocycles. In another example, heterocyclyl includes 4-membered monocycles. In another example, heterocyclyl includes 5-6 membered monocycles. In some embodiments, a heterocycloalkyl includes at least one nitrogen. In one example, the heterocyclyl group includes 0 to 3 double bonds. Any nitrogen or sulfur heteroatom may optionally be oxidized (e.g., NO, SO, SO_2), and any nitrogen heteroatom may optionally be quaternized (e.g., $[NR_4]^+Cl^-$, $[NR_4]^+OH^-$). Examples of heterocycles include oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, isoquinolinyl, tetrahydroisoquinolinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, 1,1-dioxoisothiazolyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-

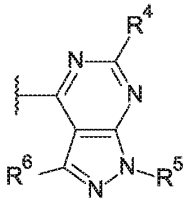
azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-onyl, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisoindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl, and 2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl. Particularly, heterocyclyl herein can be



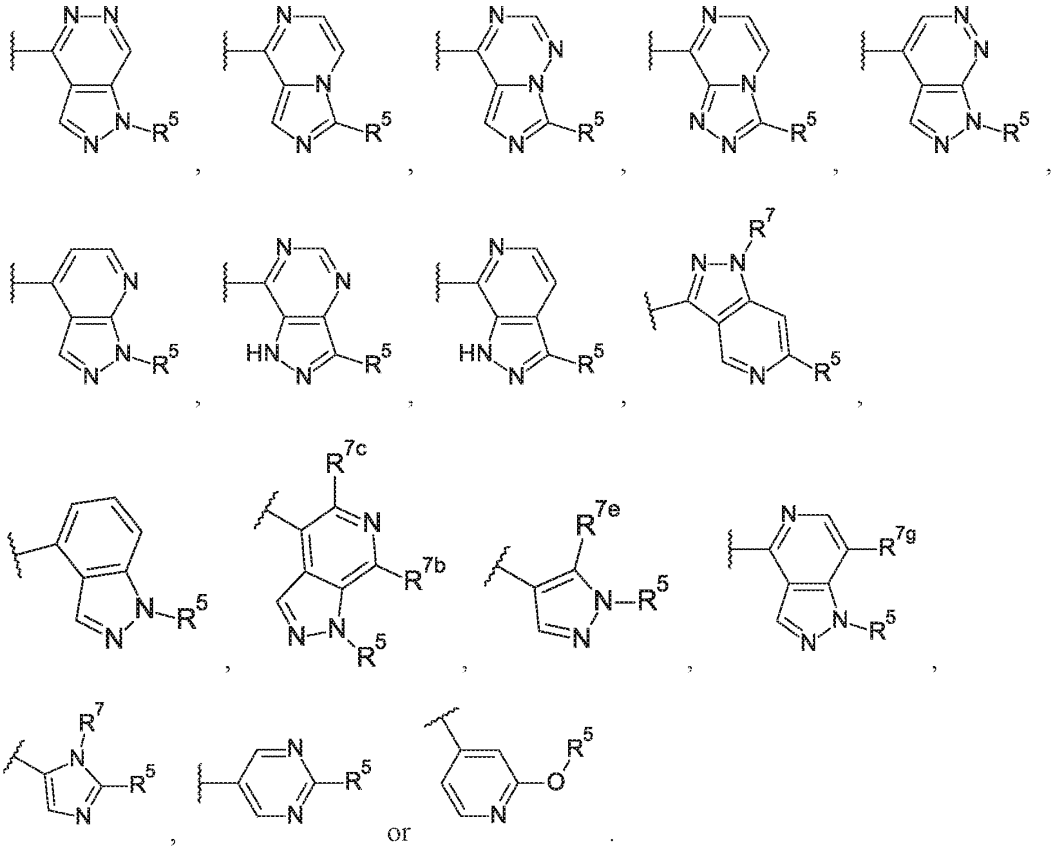
The term "heterocyclylene" denotes a divalent heterocyclyl group.

The term "aryl" denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms. Examples of aryl moieties include phenyl and naphthyl. The term "arylene" denotes a divalent aryl group.

The term "heteroaryl" refers to any mono-, bi-, or tricyclic aromatic ring system containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, and in an example embodiment, at least one heteroatom is nitrogen. See, for example, Lang's Handbook of Chemistry (Dean, J. A., ed.) 13th ed. Table 7-2 [1985]. Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to an aryl ring, wherein the aryl ring or the heteroaryl ring is joined to the remainder of the molecule. In one embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. In one embodiment, heteroaryl includes 7-12 membered bicyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Example heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, imidazol[1,2-a]pyrimidinyl, 1H-pyrazolo[3,4-d]pyrimidine, 1H-pyrazolo[3,4-d]pyridazine, imidazo[1,5-a]pyrazine, imidazo[5,1-f][1,2,4]triazine, [1,2,4]triazolo[4,3-a]pyrazine, 1H-pyrazolo[3,4-c]pyridazine, 1H-pyrazolo[3,4-b]pyridine, 1H-pyrazolo[4,3-d]pyrimidine, 1H-pyrazolo[3,4-c]pyridine, 1H-pyrazolo[4,3-c]pyridine and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl,



benzoimidazolyl, indazolyl and indolyl. Particularly, heteroaryl herein can be



or

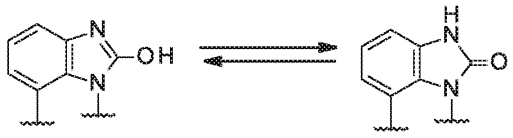
The term "heteroarylene" denotes a divalent heteroaryl group.

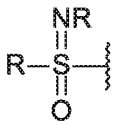
In particular embodiments, a heterocyclyl group or a heteroaryl group is attached at a carbon atom of the heterocyclyl group or the heteroaryl group. By way of example, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine ring, position 3, 4, 5, or 6 of a pyridazine ring, position 2, 4, 5, or 6 of a pyrimidine ring, position 2, 3, 5, or 6 of a pyrazine ring, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole ring, position 2, 4, or 5 of an oxazole, imidazole or thiazole ring, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole ring, position 2 or 3 of an aziridine ring, position 2, 3, or 4 of an azetidine ring, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline ring or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline ring.

In certain embodiments, the heterocyclyl group or heteroaryl group is N-attached. By way of example, nitrogen bonded heterocyclyl or heteroaryl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

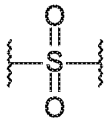
The term "optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 0, 1, 2, 3, 4, or 5 or more, or any range derivable therein) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment, an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents. In another embodiment an optionally substituted group has 4 substituents. In another embodiment an optionally substituted group has 5 substituents.

In one embodiment, the skill in the art can understand the keto-enol tautomerism exists for certain structures as illustrated below:





The term "RSO(NR)" denotes .



The term "SO_2" or "sulfonyl" denotes .



The term "sulfonimidoyl" denotes .

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, *N*-ethylpiperidine, and polyamine resins.

The term "A pharmaceutically active metabolite" denotes a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. After entry into the body, most drugs are substrates for chemical reactions that may change their physical properties and biologic effects. These metabolic conversions, which usually affect the polarity of the compounds of the invention, alter the way in which drugs are distributed in and excreted from the body. However, in some cases, metabolism of a drug is required for therapeutic effect.

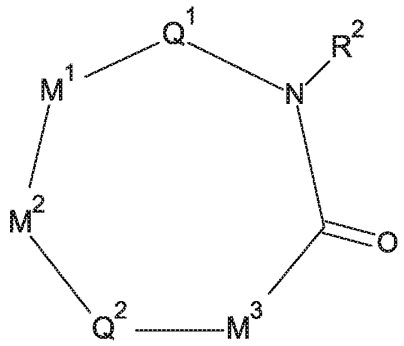
The term "therapeutically effective amount" denotes an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more

symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

The term "pharmaceutical composition" denotes a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

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The present invention relates to (i) a compound of formula (Ia),



(Ia),

wherein

M^1 is heteroarylene optionally substituted by R^1; wherein

R^1 is deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, $(R)_2N$, RCO, RSO_2, $RNHSO_2$, R_2NSO_2, RSO(NR), R_3Si, $ROC_{1\text{-}6}alkyl$, $RSC_{1\text{-}6}alkyl$, $RNHC_{1\text{-}6}alkyl$, $(R)_2NC_{1\text{-}6}alkyl$, $RSO_2C_{1\text{-}6}alkyl$, $RNHSO_2C_{1\text{-}6}alkyl$, $R_2NSO_2C_{1\text{-}6}alkyl$, $RSO(NR)C_{1\text{-}6}alkyl$ or $R_3SiC_{1\text{-}6}alkyl$; wherein R is H, R^a, R^b or R^c;

R^a is $C_{1\text{-}6}alkyl$ optionally substituted by R^b or R^c;

R^b is $C_{3\text{-}7}cycloalkyl$, heterocyclyl, heteroaryl or aryl, said $C_{3\text{-}7}cycloalkyl$, heterocyclyl, heteroaryl and aryl being unsubstituted or optionally substituted by deuterio, halogen or R^c;

R^c is selected from deuterio, $C_{1\text{-}6}alkyl$, $(C_{1\text{-}6}alkyl)_3Si$, $haloC_{1\text{-}6}alkyl$, $deuterioC_{1\text{-}6}alkyl$, $C_{1\text{-}6}alkoxy$, $haloC_{1\text{-}6}alkoxy$, $deuterioC_{1\text{-}6}alkoxy$, $C_{2\text{-}6}alkenyl$, $haloC_{2\text{-}6}alkenyl$,

deuterioC_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{2-6}alkynyl, deuterioC_{2-6}alkynyl, C_{3-7}cycloalkyl, haloC_{3-7}cycloalkyl, deuterioC_{3-7}cycloalkyl, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylcarbonylamino, haloC_{1-6}alkylamino, haloC_{1-6}alkylcarbonylamino, $(haloC_{1-6}alkyl)_2$amino, C_{3-7}cycloalkylamino, C_{3-7}cycloalkylcarbonylamino, $(C_{3-7}cycloalkyl)_2$amino, haloC_{3-7}cycloalkylamino, $(haloC_{3-7}cycloalkyl)_2$amino, C_{3-7}cycloalkyl(C_{1-6}alkyl)amino, haloC_{3-7}cycloalkyl(C_{1-6}alkyl)amino, C_{1-6}alkylsulfonylamino, haloC_{1-6}alkylsulfonylamino, C_{1-6}alkoxyC_{1-6}alkyl, (haloC_{1-6}alkoxy)C_{1-6}alkyl, C_{1-6}alkoxy(halo)C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-7}cycloalkylhaloC_{1-6}alkyl, C_{1-6}alkylcarbonyl, haloC_{1-6}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, haloC_{3-7}cycloalkylcarbonyl, C_{1-6}alkoxycarbonyl, haloC_{1-6}alkoxycarbonyl, C_{3-7}cycloalkoxycarbonyl, haloC_{3-7}cycloalkoxycarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, C_{3-7}cycloalkylaminocarbonyl, $(C_{3-7}cycloalkyl)_2$aminocarbonyl, C_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, haloC_{1-6}alkylaminocarbonyl, halo$(C_{1-6}alkyl)_2$aminocarbonyl, haloC_{3-7}cycloalkylaminocarbonyl, halo$(C_{3-7}cycloalkyl)_2$aminocarbonyl, haloC_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, C_{1-6}alkylhaloC_{3-7}cycloalkylaminocarbonyl, $(C_{1-6}alkyl)_3$ammonio, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfanyl, C_{3-7}cycloalkylsulfinyl, C_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkylsulfanyl, haloC_{1-6}alkylsulfinyl, haloC_{1-6}alkylsulfonyl, haloC_{3-7}cycloalkylsulfanyl, haloC_{3-7}cycloalkylsulfinyl, haloC_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, (haloC_{1-6}alkylamino)sulfonyl, $(C_{1-6}alkyl)_2$aminosulfonyl, $(haloC_{1-6}alkyl)_2$aminosulfonyl, $(C_{1-6}alkyl)_2$phosphoryl, $(C_{1-6}alkoxy)_2$phosphoryl, hydroxy(C_{1-6}alkoxy)phosphoryl, C_{1-6}alkoxyphosphoryl, hydroxy, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, hydroxylhaloC_{1-6}alkoxy, hydroxyC_{3-7}cycloalkyl, hydroxyhaloC_{3-7}cycloalkyl and sulfonimidoyl optionally substituted by H, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, heteroaryl and heterocyclyl;

M^2 is arylene, heterocyclylene or heteroarylene, said arylene, heterocyclylene or heteroarylene being optionally substituted by R^1;

M^3 is heterocyclylene which is unsubstituted or optionally substituted by R^3;

R^2 is deuterio, R, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RSO_2C_{1-6}alkyl, RNHC_{1-6}alkyl or $(R)_2NC_{1-6}$alkyl;

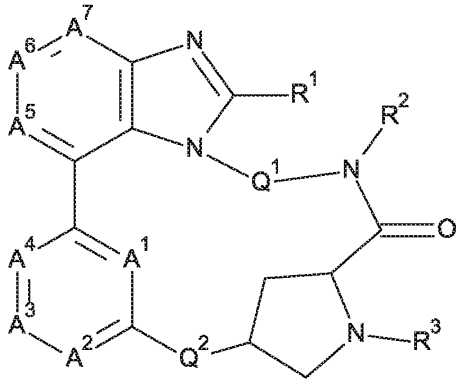
R^3 is heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl or arylcarbonyl, said heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl and arylcarbonyl being unsubstituted or optionally substituted by R^1;

Q^1 is -M-, -M-O-M-, -M-S-M-, -M-SO_2-M-, -M-SO(NH)-M-, -M-SO(NR)-M-, -M-SiR_2-M- or -M-N(R)-M-; wherein M is C_{1-6}alkylene unsubstituted or optionally substituted by the substituents independently selected from deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, R_2N, RSO_2, ROC_{1-6}alkyl, RSC_{1-6}alkyl, $RNHC_{1-6}$alkyl, $(R)_2NC_{1-6}$alkyl and RSO_2C_{1-6}alkyl;

Q^2 is NH, O, S, SO, SO_2, P(O)R, PO(NR), Se, N(R), SiR_2, heterocyclyl, heteroaryl or aryl;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (ii) a compound of formula (I),



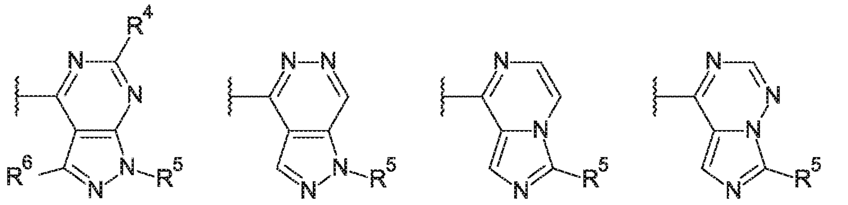
(I),

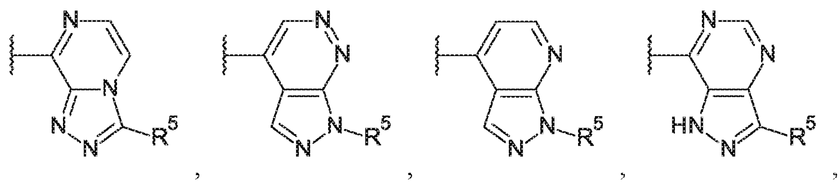
wherein

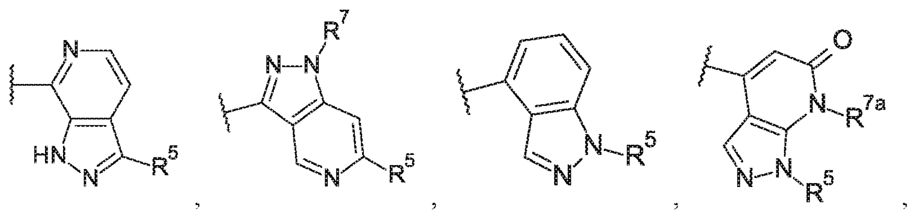
R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

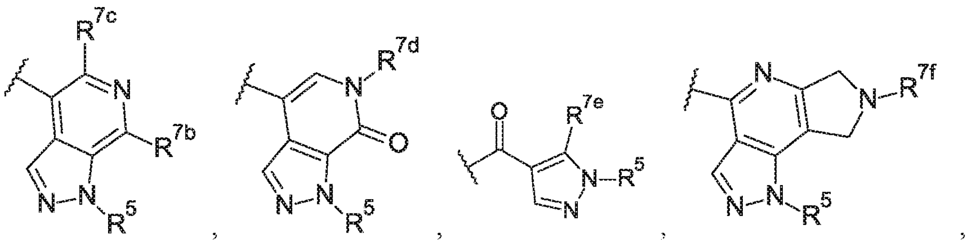
R^2 is H, (2-oxa-5-azabicyclo[2.2.1]heptanyl)C_{1-6}alkyl, (2-oxa-6-azaspiro[3.3]heptanyl)C_{1-6}alkyl, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, ((C_{1-6}alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-}

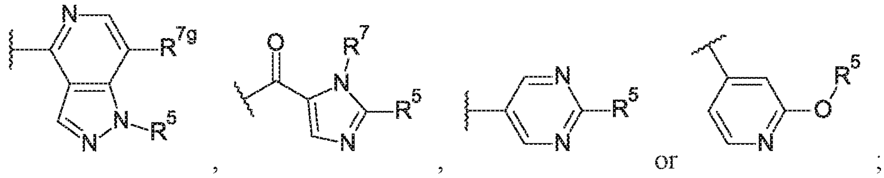
${}_{6}$alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is 









wherein

R^4 is H,

(C_{1-6}alkyl)$_2$amino,

(C_{1-6}alkyl)$_2$aminocarbonyl,

(C_{1-6}alkyl)$_2$phosphoryl,

1,1-dioxothianyl,

1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by C_{1-6}alkyl,

1,6-diazaspiro[3.3]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

1,7-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or oxetanyl,
2,2-dioxo-2λ^6-thia-6-azaspiro[3.3]heptanyl,
2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C_{1-6}alkyl,
2,5-diazabicyclo[2.2.1]heptanyl substituted by C_{1-6}alkyl, haloC_{1-6}alkyl or oxetanyl,
2-azaspiro[3.3]heptanyl once or twice substituted by substituents independently selected from haloC_{1-6}alkyl and hydroxy,
2-oxa-5-azabicyclo[2.2.1]heptanyl,
2-oxa-6-azaspiro[3.3]heptanyl,
3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl,
3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,
3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylcarbonyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, haloC_{3-7}cycloalkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,
3,6-diazabicyclo[3.2.0]heptanyl substituted by oxetanyl,
3,7-diazabicyclo[4.2.0]octanyl substituted by oxetanyl,
3,8-diazabicyclo[3.2.1]octanyl substituted by haloC_{1-6}alkyl,
3-oxa-6-azabicyclo[3.1.1]heptanyl,
3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,
3-oxa-8-azabicyclo[3.2.1]octanyl,
4,7-diazaspiro[2.5]octanyl unsubstituted or substituted by C_{1-6}alkyl,
4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,
5-oxa-2,8-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl,
6,6-dioxo-6λ^6-thia-1-azaspiro[3.3]heptanyl,
6-oxa-1-azaspiro[3.3]heptanyl,
6-oxa-3-azabicyclo[3.1.1]heptanyl,
8-oxa-2,5-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl,
8-oxa-3-azabicyclo[3.2.1]octanyl,
amino,
aminocarbonyl,
azetidinyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkyl)$_2$amino, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, amino, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylC_{1-6}alkyl, C_{3-7}cycloalkyl,

cyano, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinyl and morpholinylC_{1-6}alkyl,

azetidinyloxy substituted by haloC_{1-6}alkyl or C_{3-7}cycloalkyl,

C_{1-6}alkoxy unsubstituted or substituted by (haloC_{1-6}alkylcarbonyl)azetidinyl, C_{1-6}alkylazetidinyl, C_{1-6}alkylpiperazinyl, C_{1-6}alkylpyrrolidinyl, halo-1,2,3,5,6,7-hexahydropyrrolizinyl, haloC_{1-6}alkylazetidinyl, morpholinyl, oxetanyl or tetrahydrofuranyl,

C_{1-6}alkoxyC_{1-6}alkylamino,

C_{1-6}alkoxycarbonyl,

C_{1-6}alkyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkylcarbonyl)azetidinyl, (haloC_{1-6}alkylcarbonyl)pyrrolidinyl, 1,1-dioxothietanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 4,7-diazaspiro[2.5]octanyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkylcarbonylpyrrolidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{1-6}alkylsulfonylpyrrolidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, cyano, haloC_{1-6}alkylazetidinyl, hydroxy, hydroxyC_{1-6}alkyl, morpholinyl and oxetanyl,

C_{1-6}alkylamino,

C_{1-6}alkylsulfanyl unsubstituted or substituted by 1,1-dioxothietanyl,

C_{1-6}alkylsulfonyl,

C_{3-7}cycloalkyl unsubstituted or substituted by C_{1-6}alkoxy or hydroxy,

carboxy,

cyano,

haloC_{1-6}alkoxy,

haloC_{1-6}alkyl substituted by hydroxy,

hydroxy,

hydroxyC_{1-6}alkylcarbamoyl,

imidazolyl,

morpholinyl,

morpholinylcarbonyl,

oxetanyl,

oxomorpholinyl,

oxooxazolidinyl,

oxopiperazinyl substituted by C_{1-6}alkyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy,

piperazinyl once or twice substituted by substituents independently selected from C_{1-6}alkyl, carboxy, oxetanyl and phenylC_{1-6}alkyl,

piperidinyl substituted by C_{1-6}alkyl, 2H-tetrazolyl or oxazolyl,

pyrrolidinyl once or twice substituted by substituents independently selected from amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, cyano, haloC_{1-6}alkylcarbonyl and halogen,

pyrrolidinylcarbonyl,

tetrahydrofuranyl, or

tetrahydropyranyl;

R^5 is 1,3-dihydroisobenzofuranyl,

1H-indazolyl substituted by halogen,

C_{2-6}alkynyl,

thienyl,

bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,

phenyl substituted once, twice or three times by the substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkyl)C_{3-7}cycloalkyloxy, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkylmorpholinyl)C_{1-6}alkoxy, (C_{1-6}alkylsulfonylazetidinyl)C_{1-6}alkoxy, 2-oxa-6-azaspiro[3.3]heptanyl, azetidinyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{2-6}alkynyl, C_{1-6}alkoxyC_{3-7}cycloalkyloxy, C_{1-6}alkoxypyrrolidinyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, carboxy, cyano, cyanoC_{1-6}alkoxy, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, halogen, hydroxy, morpholinyl, morpholinylC_{1-6}alkoxy, oxetanylC_{1-6}alkoxy, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl, tetrahydrofuranyloxy and trideuterioC_{1-6}alkoxy,

pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy, C_{1-6}alkylsulfanyl and C_{1-6}alkoxy, or

pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or C_{1-6}alkyl;

R^7 is C_{1-6}alkyl;

R^{7a} is C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7b} is H, C_{1-6}alkoxy or phenylC_{1-6}alkoxy;

R^{7c} is H or C_{1-6}alkoxy;

R^{7d} is C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7e} is H, amino, phenylC_{1-6}alkylamino or morpholinylC_{1-6}alkylamino;

R^{7f} is C_{1-6}alkyl, phenylC_{1-6}alkyl or oxetanyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene unsubstituted or substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylcarbonyloxy, carboxy, hydroxy, hydroxyC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkoxy and trideuterioC_{1-6}alkoxy, or

-M-O-M-, wherein M is C_{1-6}alkylene;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8 or N, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkoxyamino, cyano, haloazetidinylC_{1-6}alkyl, haloC_{1-6}alkoxy, halogen, morpholinylC_{1-6}alkyl or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

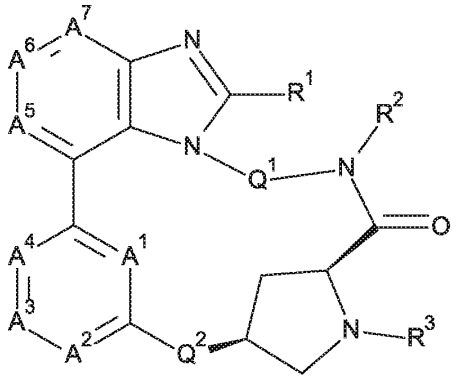
A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (iii) a compound of formula (Ib),

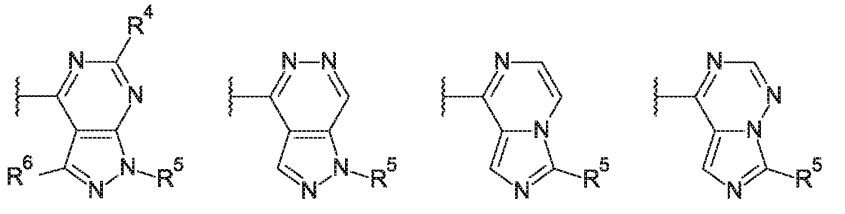


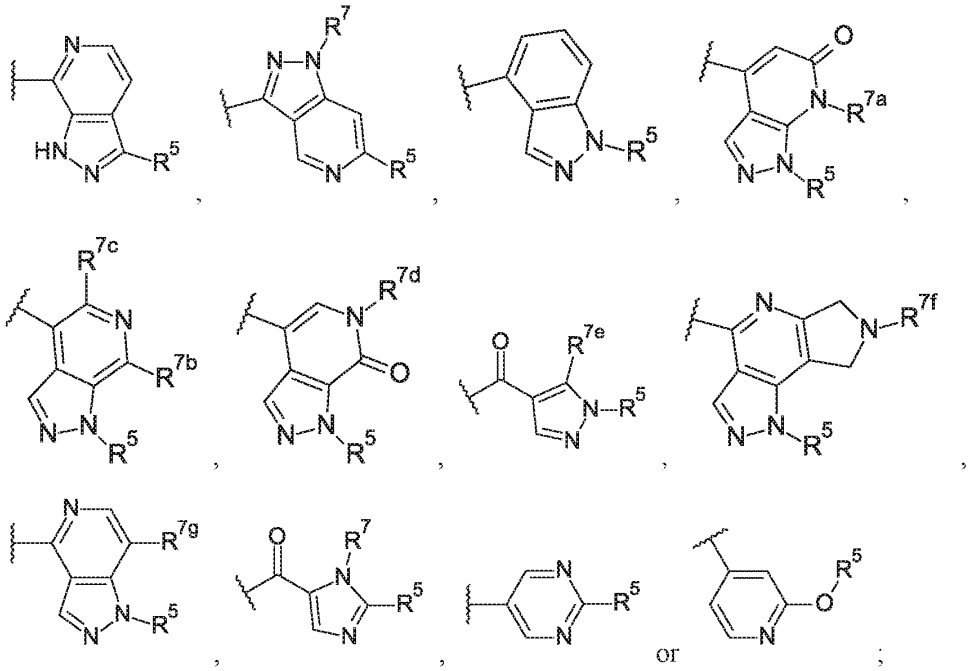
(I),

wherein

R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

R^2 is H, (2-oxa-5-azabicyclo[2.2.1]heptanyl)C_{1-6}alkyl, (2-oxa-6-azaspiro[3.3]heptanyl)C_{1-6}alkyl, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, ((C_{1-6}alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is 



wherein

R^4 is H,

$(C_{1-6}alkyl)_2amino$,

$(C_{1-6}alkyl)_2aminocarbonyl$,

$(C_{1-6}alkyl)_2phosphoryl$,

1,1-dioxothianyl,

1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by $C_{1-6}alkyl$,

1,6-diazaspiro[3.3]heptanyl substituted by $haloC_{1-6}alkyl$ or oxetanyl,

1,7-diazaspiro[3.5]nonanyl substituted by $haloC_{1-6}alkyl$ or oxetanyl,

2,2-dioxo-2λ⁶-thia-6-azaspiro[3.3]heptanyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by $C_{1-6}alkyl$,

2,5-diazabicyclo[2.2.1]heptanyl substituted by $C_{1-6}alkyl$, $haloC_{1-6}alkyl$ or oxetanyl,

2-azaspiro[3.3]heptanyl once or twice substituted by substituents independently selected from $haloC_{1-6}alkyl$ and hydroxy,

2-oxa-5-azabicyclo[2.2.1]heptanyl,

2-oxa-6-azaspiro[3.3]heptanyl,

3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylcarbonyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, haloC_{3-7}cycloalkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3,6-diazabicyclo[3.2.0]heptanyl substituted by oxetanyl,

3,7-diazabicyclo[4.2.0]octanyl substituted by oxetanyl,

3,8-diazabicyclo[3.2.1]octanyl substituted by haloC_{1-6}alkyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

3-oxa-8-azabicyclo[3.2.1]octanyl,

4,7-diazaspiro[2.5]octanyl unsubstituted or substituted by C_{1-6}alkyl,

4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

5-oxa-2,8-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl,

6,6-dioxo-6λ^6-thia-1-azaspiro[3.3]heptanyl,

6-oxa-1-azaspiro[3.3]heptanyl,

6-oxa-3-azabicyclo[3.1.1]heptanyl,

8-oxa-2,5-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl,

8-oxa-3-azabicyclo[3.2.1]octanyl,

amino,

aminocarbonyl,

azetidinyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkyl)$_2$amino, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, amino, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylC_{1-6}alkyl, C_{3-7}cycloalkyl, cyano, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinyl and morpholinylC_{1-6}alkyl,

azetidinyloxy substituted by haloC_{1-6}alkyl or C_{3-7}cycloalkyl,

C_{1-6}alkoxy unsubstituted or substituted by (haloC_{1-6}alkylcarbonyl)azetidinyl, C_{1-6}alkylazetidinyl, C_{1-6}alkylpiperazinyl, C_{1-6}alkylpyrrolidinyl, halo-1,2,3,5,6,7-hexahydropyrrolizinyl, haloC_{1-6}alkylazetidinyl, morpholinyl, oxetanyl or tetrahydrofuranyl,

C_{1-6}alkoxyC_{1-6}alkylamino,

C_{1-6}alkoxycarbonyl,

C_{1-6}alkyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkylcarbonyl)azetidinyl, (haloC_{1-6}alkylcarbonyl)pyrrolidinyl, 1,1-dioxothietanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 4,7-diazaspiro[2.5]octanyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkylcarbonylpyrrolidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{1-6}alkylsulfonylpyrrolidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, cyano, haloC_{1-6}alkylazetidinyl, hydroxy, hydroxyC_{1-6}alkyl, morpholinyl and oxetanyl,

C_{1-6}alkylamino,

C_{1-6}alkylsulfanyl unsubstituted or substituted by 1,1-dioxothietanyl,

C_{1-6}alkylsulfonyl,

C_{3-7}cycloalkyl unsubstituted or substituted by C_{1-6}alkoxy or hydroxy,

carboxy,

cyano,

haloC_{1-6}alkoxy,

haloC_{1-6}alkyl substituted by hydroxy,

hydroxy,

hydroxyC_{1-6}alkylcarbamoyl,

imidazolyl,

morpholinyl,

morpholinylcarbonyl,

oxetanyl,

oxomorpholinyl,

oxooxazolidinyl,

oxopiperazinyl substituted by C_{1-6}alkyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy,

piperazinyl once or twice substituted by substituents independently selected from C_{1-6}alkyl, carboxy, oxetanyl and phenylC_{1-6}alkyl,

piperidinyl substituted by C_{1-6}alkyl, 2H-tetrazolyl or oxazolyl,

pyrrolidinyl once or twice substituted by substituents independently selected from amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, cyano, haloC_{1-6}alkylcarbonyl and halogen,

pyrrolidinylcarbonyl,

tetrahydrofuranyl, or
tetrahydropyranyl;

R^5 is 1,3-dihydroisobenzofuranyl,
1H-indazolyl substituted by halogen,
C_{2-6}alkynyl,
thienyl,
bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,
phenyl substituted once, twice or three times by the substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkyl)C_{3-7}cycloalkyloxy, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkylmorpholinyl)C_{1-6}alkoxy, (C_{1-6}alkylsulfonylazetidinyl)C_{1-6}alkoxy, 2-oxa-6-azaspiro[3.3]heptanyl, azetidinyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{2-6}alkynyl, C_{1-6}alkoxyC_{3-7}cycloalkyloxy, C_{1-6}alkoxypyrrolidinyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, carboxy, cyano, cyanoC_{1-6}alkoxy, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, halogen, hydroxy, morpholinyl, morpholinylC_{1-6}alkoxy, oxetanylC_{1-6}alkoxy, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl, tetrahydrofuranyloxy and trideuterioC_{1-6}alkoxy,
pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy, C_{1-6}alkylsulfanyl and C_{1-6}alkoxy, or
pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or C_{1-6}alkyl;

R^7 is C_{1-6}alkyl;

R^{7a} is C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7b} is H, C_{1-6}alkoxy or phenylC_{1-6}alkoxy;

R^{7c} is H or C_{1-6}alkoxy;

R^{7d} is C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7e} is H, amino, phenylC_{1-6}alkylamino or morpholinylC_{1-6}alkylamino;

R^{7f} is C_{1-6}alkyl, phenylC_{1-6}alkyl or oxetanyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene unsubstituted or substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkyl, C_{1-}

$_{6}$alkylcarbonyloxy, carboxy, hydroxy, hydroxyC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkoxy and trideuterioC_{1-6}alkoxy, or

-M-O-M-, wherein M is C_{1-6}alkylene;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8 or N, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkoxyamino, cyano, haloazetidinylC_{1-6}alkyl, haloC_{1-6}alkoxy, halogen, morpholinylC_{1-6}alkyl or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

or a pharmaceutically acceptable salt thereof.

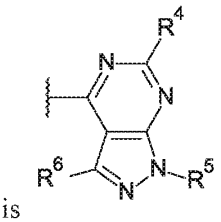
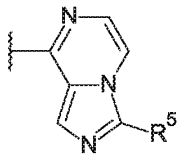
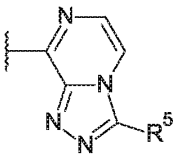
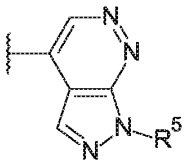
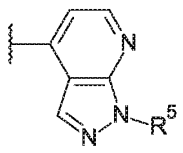
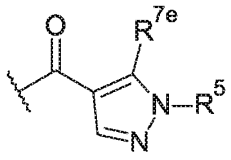
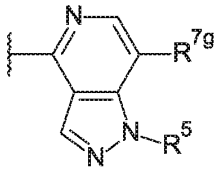
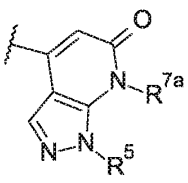
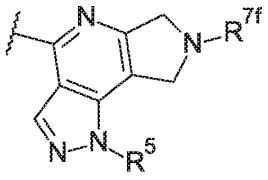
A further embodiment of present invention is (iv) a compound of formula (I) or (Ia) according to (i) or (iii), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_{1-6}alkyl.

A further embodiment of present invention is (v) a compound of formula (I) or (Ia), according to any one of (i) to (iv), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or methyl.

A further embodiment of present invention is (vi) a compound of formula (I) or (Ia) according to any one of (i) to (v), wherein R^2 is C_{1-6}alkyl or trideuterioC_{1-6}alkyl.

A further embodiment of present invention is (vii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (vi), wherein R^2 is methyl, ethyl or trideuteriomethyl.

A further embodiment of present invention is (viii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (vii), wherein R^3

is  ,  ,  ,  ,  ,  ,  ,  or  ;

wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl, or

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

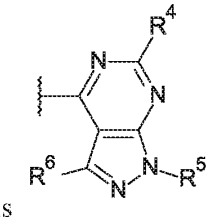
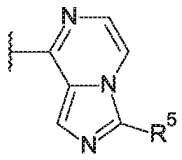
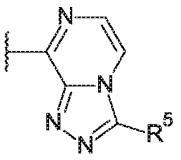
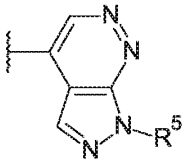
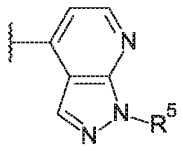
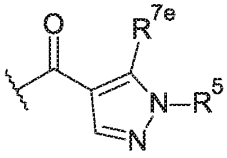
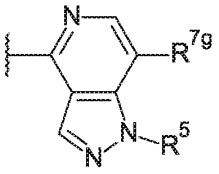
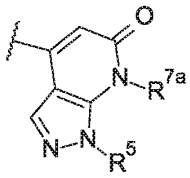
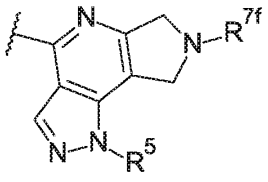
R^6 is H;

R^{7a} is C_{1-6}alkyl;

R^{7e} is amino;

R^{7f} is C_{1-6}alkyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl.

A further embodiment of present invention is (ix) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (viii), wherein R^3 is  ,  ,  ,  ,  ,  ,  ,  or  ; wherein

R^4 is H,

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-

yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H;

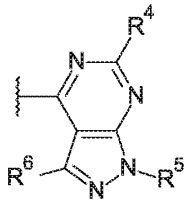
R^{7a} is methyl;

R^{7e} is amino;

R^{7f} is methyl;

R^{7g} is H or methoxymethyl.

A further embodiment of present invention is (x) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (ix), wherein R^3



is ; wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl, or

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

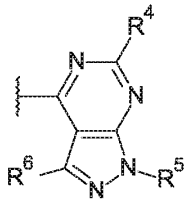
R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H.

A further embodiment of present invention is (xi) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (x), wherein R^3



is ; wherein

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-

diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H.

A further embodiment of present invention is (xii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xi), wherein Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy, C_{1-6}alkyl and trideuterioC_{1-6}alkoxy.

A further embodiment of present invention is (xiii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xii), wherein Q^1 is propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl, acetoxy and trideuteriomethoxy.

A further embodiment of present invention is (xiv) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xiii), wherein Q^1 is C_{1-6}alkylene substituted by C_{1-6}alkoxy.

A further embodiment of present invention is (xv) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xiv), wherein Q^1 is propylene substituted by methoxy or ethoxy.

A further embodiment of present invention is (xvi) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xv), wherein Q^2 is NH or O.

A further embodiment of present invention is (xvii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xvi), wherein A^1 is N.

A further embodiment of present invention is (xviii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xvii), wherein A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy or halogen.

A further embodiment of present invention is (xix) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xviii), wherein A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy, difluoromethoxy or fluoro.

A further embodiment of present invention is (xx) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xix), wherein A^3 is CR^8, wherein R^8 is H.

A further embodiment of present invention is (xxi) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xx), wherein A^4 is CR^9, wherein R^9 is H.

A further embodiment of present invention is (xxii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxi), wherein A^5 is CR^{10} or N, wherein R^{10} is H or fluoro.

A further embodiment of present invention is (xxiii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxii), wherein A^5 is CR^{10}, wherein R^{10} is H.

A further embodiment of present invention is (xxiv) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxiii), wherein A^6 is CR^{11}, wherein R^{11} is H or halogen.

A further embodiment of present invention is (xxv) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxiv), wherein A^6 is CR^{11}, wherein R^{11} is H or fluoro.

A further embodiment of present invention is (xxvi) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxv), wherein A^6 is CR^{11}, wherein R^{11} is halogen.

A further embodiment of present invention is (xxvii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxvi), wherein A^6 is CR^{11}, wherein R^{11} is fluoro.

A further embodiment of present invention is (xxviii) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxvii), wherein A^7 is CR^{12}, wherein R^{12} is H or halogen.

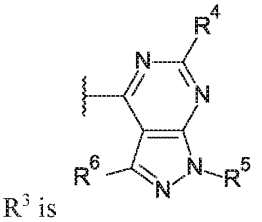
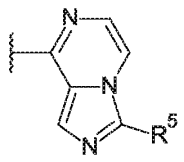
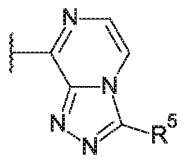
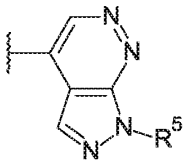
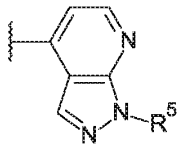
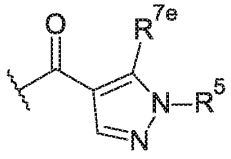
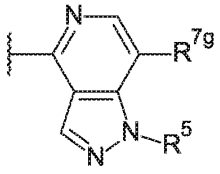
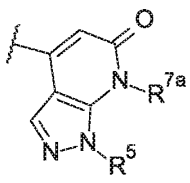
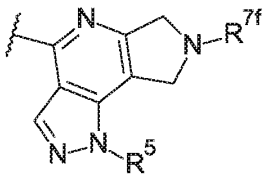
A further embodiment of present invention is (xxix) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxviii), wherein A^7 is CR^{12}, wherein R^{12} is H or fluoro.

A further embodiment of present invention is (xxx) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xxix), wherein A^7 is CR^{12}, wherein R^{12} is H.

A further embodiment of present invention is (xxxi) a compound of formula (I) or (Ia), according to any one of (i) or (ii) or (iii), wherein

R^1 is H or $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl or trideuterio$C_{1\text{-}6}$alkyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  or  ; wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by halo$C_{1\text{-}6}$alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H;

R^{7a} is C_{1-6}alkyl;

R^{7e} is amino;

R^{7f} is C_{1-6}alkyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy, C_{1-6}alkyl and trideuterioC_{1-6}alkoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy or halogen;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11}, wherein R^{11} is H or halogen;

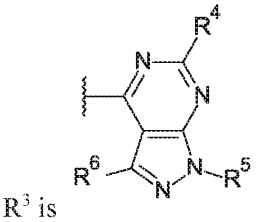
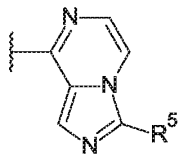
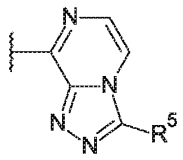
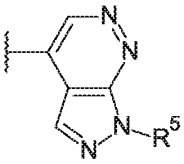
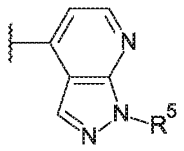
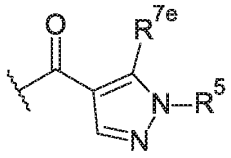
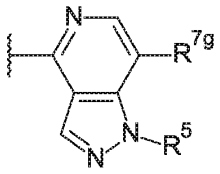
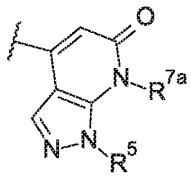
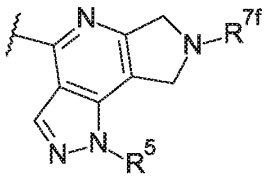
A^7 is CR^{12}, wherein R^{12} is H or halogen;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxii) a compound of formula (I) or (Ia), according to (xxxi), wherein

R^1 is H or methyl;

R^2 is methyl, ethyl or trideuteriomethyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  or  ; wherein

R^4 is H,

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-

methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,
pyridinyl twice substituted by fluoro, or
pyrimidinyl substituted by fluoro;

R^6 is H;

R^{7a} is methyl;

R^{7e} is amino;

R^{7f} is methyl;

R^{7g} is H or methoxymethyl;

Q^1 is propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl, acetoxy and trideuteriomethoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is methyl;

A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy, difluoromethoxy or fluoro;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or fluoro;

A^6 is CR^{11}, wherein R^{11} is H or fluoro;

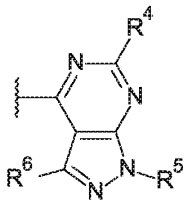
A^7 is CR^{12}, wherein R^{12} is H or fluoro;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxiii) a compound of formula (I) or (Ia), according to (xxxii), wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl;

R^3 is  ; wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H;

Q^1 is C_{1-6}alkylene substituted by C_{1-6}alkoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is halogen;

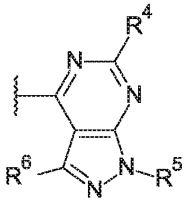
A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxiv) a compound of formula (I) or (Ia), according to (xxxiii), wherein

R^1 is methyl;

R^2 is methyl;

R^3 is  ; wherein

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H;

Q^1 is propylene substituted by methoxy or ethoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

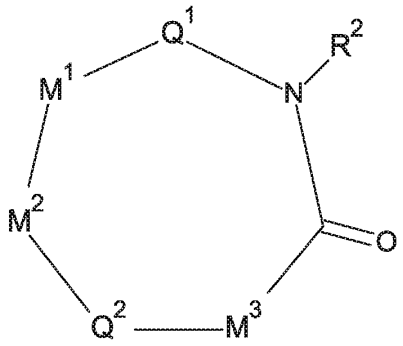
A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is fluoro;

A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

The present invention relates to (i') a compound of formula (Ia),



(Ia),

wherein

M^1 is heteroarylene optionally substituted by R^1; wherein

R^1 is deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, $(R)_2N$, RCO, RSO_2, $RNHSO_2$, R_2NSO_2, RSO(NR), $ROC_{1\text{-}6}$alkyl, $RSC_{1\text{-}6}$alkyl, $RNHC_{1\text{-}6}$alkyl, $(R)_2NC_{1\text{-}6}$alkyl, $RSO_2C_{1\text{-}6}$alkyl, $RNHSO_2C_{1\text{-}6}$alkyl, $R_2NSO_2C_{1\text{-}6}$alkyl or $RSO(NR)C_{1\text{-}6}$alkyl; wherein R is H, R^a, R^b or R^c;

R^a is $C_{1\text{-}6}$alkyl optionally substituted by R^b or R^c;

R^b is C_{3-7}cycloalkyl, heterocyclyl, heteroaryl or aryl, said C_{3-7}cycloalkyl,heterocyclyl, heteroaryl and aryl being unsubstituted or optionally substituted by halogen or R^c;

R^c is selected from C_{1-6}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, haloC_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{2-6}alkynyl, C_{3-7}cycloalkyl, haloC_{3-7}cycloalkyl, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, haloC_{1-6}alkylamino, halo$(C_{1-6}alkyl)_2$amino, C_{3-7}cycloalkylamino, $(C_{3-7}cycloalkyl)_2$amino, haloC_{3-7}cycloalkylamino, $(haloC_{3-7}cycloalkyl)_2$amino, C_{3-7}cycloalkyl(C_{1-6}alkyl)amino, haloC_{3-7}cycloalkyl(C_{1-6}alkyl)amino, C_{1-6}alkoxyC_{1-6}alkyl, (haloC_{1-6}alkoxy)C_{1-6}alkyl, C_{1-6}alkoxy(halo)C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-7}cycloalkylhaloC_{1-6}alkyl, C_{1-6}alkylcarbonyl, haloC_{1-6}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, haloC_{3-7}cycloalkylcarbonyl, C_{1-6}alkoxycarbonyl, haloC_{1-6}alkoxycarbonyl, C_{3-7}cycloalkoxycarbonyl, haloC_{3-7}cycloalkoxycarbonyl, haloC_{1-6}alkoxycarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, C_{3-7}cycloalkylaminocarbonyl, $(C_{3-7}cycloalkyl)_2$aminocarbonyl, C_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, haloC_{1-6}alkylaminocarbonyl, halo$(C_{1-6}alkyl)_2$aminocarbonyl, haloC_{3-7}cycloalkylaminocarbonyl, halo$(C_{3-7}cycloalkyl)_2$aminocarbonyl, haloC_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, C_{1-6}alkylhaloC_{3-7}cycloalkylaminocarbonyl, $(C_{1-6}alkyl)_3$ammonio, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfanyl, C_{3-7}cycloalkylsulfinyl, C_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkylsulfanyl, haloC_{1-6}alkylsulfinyl, haloC_{1-6}alkylsulfonyl, haloC_{3-7}cycloalkylsulfanyl, haloC_{3-7}cycloalkylsulfinyl, haloC_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, (haloC_{1-6}alkylamino)sulfonyl, $(C_{1-6}alkyl)_2$aminosulfonyl, $(haloC_{1-6}alkyl)_2$aminosulfonyl, $(C_{1-6}alkyl)_2$phosphoryl, $(C_{1-6}alkoxy)_2$phosphoryl, hydroxy(C_{1-6}alkoxy)phosphoryl, C_{1-6}alkoxyphosphoryl, hydroxy, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, hydroxylhaloC_{1-6}alkoxy, hydroxyC_{3-7}cycloalkyl, hydroxyhaloC_{3-7}cycloalkyl and sulfonimidoyl optionally substituted by H, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, heteroaryl and heterocyclyl;

M^2 is arylene, heterocyclylene or heteroarylene, said arylene, heterocyclylene or heteroarylene being optionally substituted by R^1;

M^3 is heterocyclylene which is unsubstituted or optionally substituted by R^3;

R^2 is deuterio, R, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RSO_2C_{1-6}alkyl, $RNHC_{1-6}$alkyl or $(R)_2NC_{1-6}$alkyl;

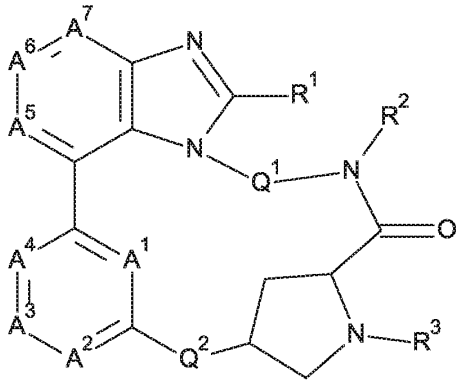
R^3 is heteroaryl, aryl, heteroarylcarbonyl or arylcarbonyl, said heteroaryl and aryl being optionally substituted by R^1;

Q^1 is -M-, -M-O-M-, -M-S-M-, -M-N(R)-M-; wherein M is C_{1-6}alkylene unsubstituted or optionally substituted by the substituents independently selected from deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, R_2N, RSO_2, ROC_{1-6}alkyl, RSC_{1-6}alkyl, $RNHC_{1-6}$alkyl, $(R)_2NC_{1-6}$alkyl and RSO_2C_{1-6}alkyl;

Q^2 is NH, O or S;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (ii') a compound of formula (I),

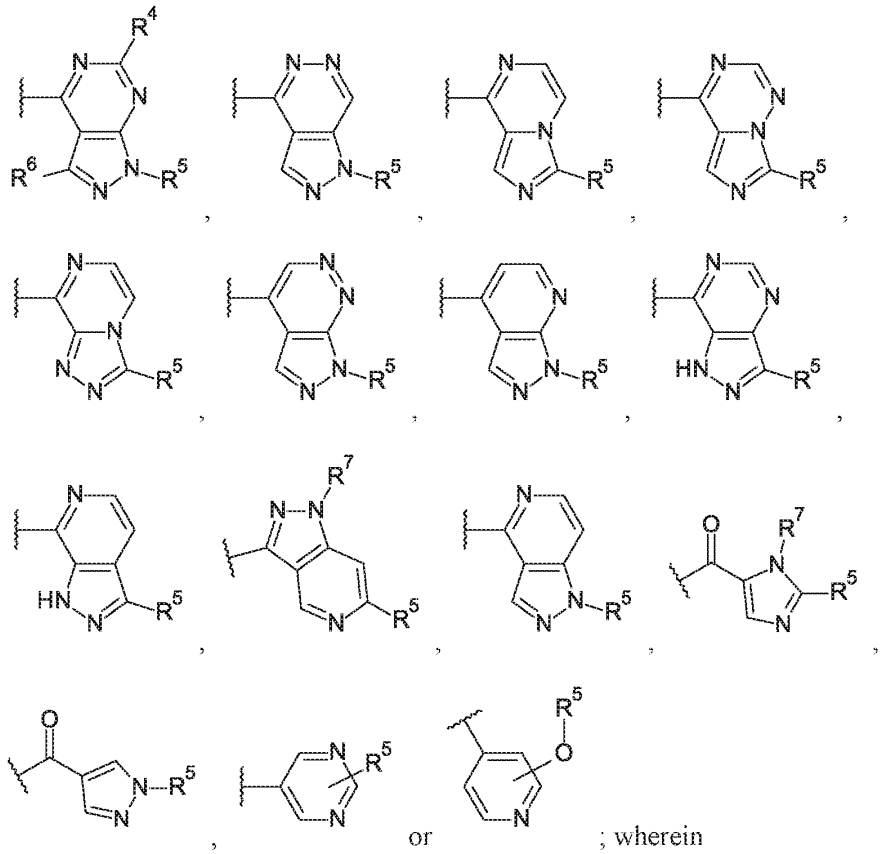


(I),

wherein

R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

R^2 is H, ((C_{1-6}alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is 

; wherein

R^4 is H, $(C_{1-6}alkyl)_2$aminocarbonyl, $(C_{1-6}alkyl)_2$phosphoryl, amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkylamino, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{3-7}cycloalkyl, carboxy, cyano, hydroxy, hydroxyC_{1-6}alkyl, morpholinyl, morpholinylC_{1-6}alkoxy or morpholinylC_{1-6}alkyl;

R^5 is thienyl,

bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,

phenyl substituted once, twice or three times by the substituents independently selected from $(C_{1-6}alkyl)_2$phosphoryl, $(C_{1-6}$alkylmorpholinyl$)C_{1-6}$alkoxy, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{2-6}alkenyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkyl, carboxy, cyano, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, halogen, hydroxy, morpholinylC_{1-6}alkoxy, oxetanylC_{1-6}alkoxy, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl and trideuterioC_{1-6}alkoxy,

pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy and C_{1-6}alkoxy, or

pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or C_{1-6}alkyl;

R^7 is C_{1-6}alkyl;

Q^1 is C_{1-6}alkylene unsubstituted or substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylcarbonyloxy, carboxy, hydroxy, hydroxyC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkoxy and trideuterioC_{1-6}alkoxy, or

-M-O-M-, wherein M is C_{1-6}alkylene;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH or N;

A^3 is CR^8 or N, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkoxy, cyano, haloazetidinylC_{1-6}alkyl, haloC_{1-6}alkoxy, morpholinylC_{1-6}alkyl or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

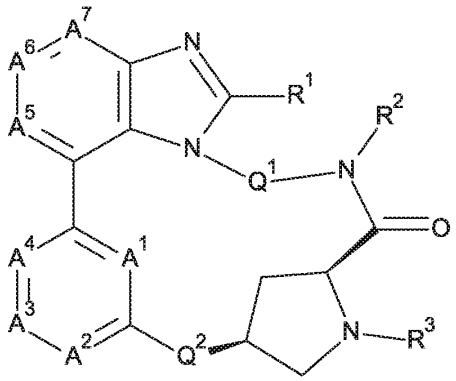
A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (iii') a compound of formula (Ib),

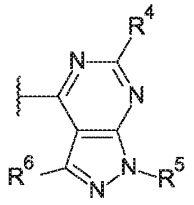
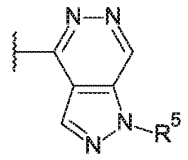
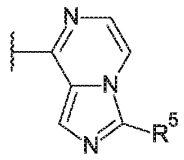
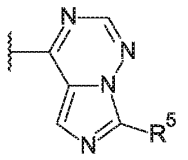
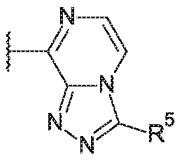
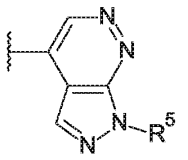
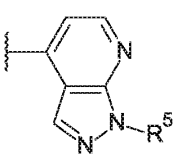
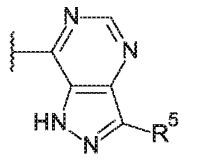
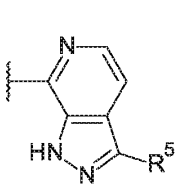
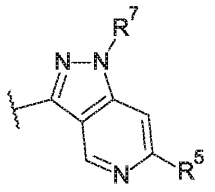
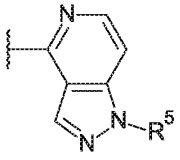
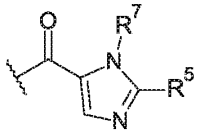
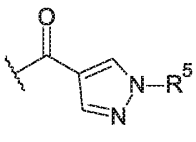
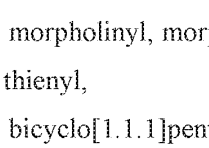
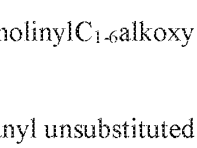
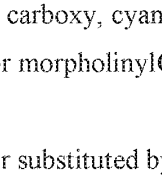


(I),

wherein

R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

R^2 is H, ((C_{1-6}alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein

R^4 is H, (C_{1-6}alkyl)$_2$aminocarbonyl, (C_{1-6}alkyl)$_2$phosphoryl, amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkylamino, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{3-7}cycloalkyl, carboxy, cyano, hydroxy, hydroxyC_{1-6}alkyl, morpholinyl, morpholinylC_{1-6}alkoxy or morpholinylC_{1-6}alkyl;

R^5 is thienyl,

bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,

phenyl substituted once, twice or three times by the substituents independently selected from $(C_{1-6}alkyl)_2$phosphoryl, $(C_{1-6}alkylmorpholinyl)C_{1-6}alkoxy$, $C_{1-6}alkoxy$, $C_{1-6}alkoxyC_{1-6}alkoxy$, $C_{1-6}alkoxyC_{1-6}alkyl$, $C_{1-6}alkyl$, $C_{1-6}alkylamino$, $C_{1-6}alkylsulfanyl$, $C_{1-6}alkylsulfinyl$, $C_{1-6}alkylsulfonyl$, $C_{2-6}alkenyl$, $C_{3-7}cycloalkoxy$, $C_{3-7}cycloalkyl$, carboxy, cyano, $haloC_{1-6}alkoxy$, $haloC_{1-6}alkyl$, halogen, hydroxy, $morpholinylC_{1-6}alkoxy$, $oxetanylC_{1-6}alkoxy$, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl and $trideuterioC_{1-6}alkoxy$,

pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy and $C_{1-6}alkoxy$, or

pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or $C_{1-6}alkyl$;

R^7 is $C_{1-6}alkyl$;

Q^1 is $C_{1-6}alkylene$ unsubstituted or substituted once or twice by the substituents independently selected from $C_{1-6}alkoxy$, $C_{1-6}alkoxyC_{1-6}alkoxy$, $C_{1-6}alkyl$, $C_{1-6}alkylcarbonyloxy$, carboxy, hydroxy, $hydroxyC_{1-6}alkoxy$, $hydroxyC_{1-6}alkyl$, $morpholinylC_{1-6}alkoxy$ and $trideuterioC_{1-6}alkoxy$, or

-M-O-M-, wherein M is $C_{1-6}alkylene$;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH or N;

A^3 is CR^8 or N, wherein R^8 is H, $C_{1-6}alkoxy$, $C_{1-6}alkoxyC_{1-6}alkyl$, $C_{1-6}alkyl$, $C_{3-7}cycloalkoxy$, cyano, $haloazetidinylC_{1-6}alkyl$, $haloC_{1-6}alkoxy$, $morpholinylC_{1-6}alkyl$ or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, $C_{1-6}alkyl$ or $C_{1-6}alkoxy$;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

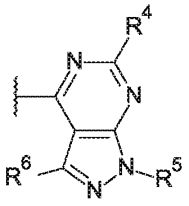
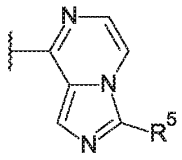
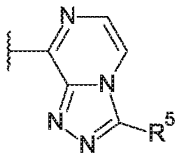
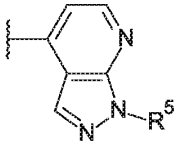
or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (iv') a compound of formula (I) or (Ia) according to (i') or (iii'), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_{1-6}alkyl.

A further embodiment of present invention is (v') a compound of formula (I) or (Ia), according to any one of (i') to (iv'), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or methyl.

A further embodiment of present invention is (vi') a compound of formula (I) or (Ia) according to any one of (i') to (v'), wherein R^2 is H or C_{1-6}alkyl.

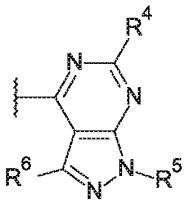
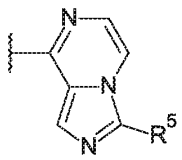
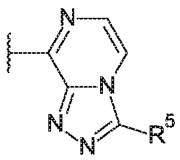
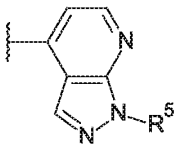
A further embodiment of present invention is (vii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (vi'), wherein R^2 is H, methyl or ethyl.

A further embodiment of present invention is (viii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (vii'), wherein R^3 is  ,  ,  or  ; wherein

R^4 is H, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or morpholinylC_{1-6}alkyl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy;

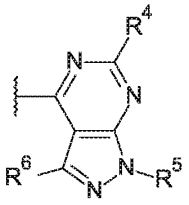
R^6 is H.

A further embodiment of present invention is (ix) a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (viii'), wherein R^3 is  ,  ,  or  ; wherein

R^4 is H, amino, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl or morpholinylmethyl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from fluoro, methoxy, trideuteriomethoxy, difluoromethoxy, ethoxy, cyclopropoxy and hydroxy;

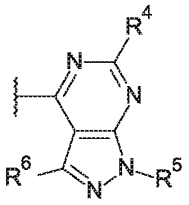
R^6 is H.

A further embodiment of present invention is (x') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (ix'), wherein R^3 is  ; wherein

R^4 is H or C_{1-6}alkoxyC_{1-6}alkyl;

R^5 is phenyl substituted twice or three times by the substituents independently selected from C_{1-6}alkoxy and halogen;

R^6 is H.

A further embodiment of present invention is (xi') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (x'), wherein R^3 is  ; wherein

R^4 is H or methoxymethyl;

R^5 is phenyl substituted twice or three times by the substituents independently selected from methoxy and fluoro;

R^6 is H.

A further embodiment of present invention is (xii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xi'), wherein Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy and C_{1-6}alkyl.

A further embodiment of present invention is (xiii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xii'), wherein Q^1 is

propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl and acetoxy.

A further embodiment of present invention is (xiv') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xiii'), wherein Q^1 is C_{1-6}alkylene substituted by C_{1-6}alkoxy.

A further embodiment of present invention is (xv') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xiv'), wherein Q^1 is propylene substituted by methoxy or ethoxy.

A further embodiment of present invention is (xvi') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xv'), wherein Q^2 is NH or O.

A further embodiment of present invention is (xvii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xvi'), wherein A^1 is N.

A further embodiment of present invention is (xviii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xvii'), wherein A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy or haloC_{1-6}alkoxy.

A further embodiment of present invention is (xix') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xviii'), wherein A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy or difluoromethoxy.

A further embodiment of present invention is (xx') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xix'), wherein A^3 is CR^8, wherein R^8 is H.

A further embodiment of present invention is (xxi') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xx'), wherein A^4 is CR^9, wherein R^9 is H.

A further embodiment of present invention is (xxii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxi'), wherein A^5 is CR^{10} or N, wherein R^{10} is H or fluoro.

A further embodiment of present invention is (xxiii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxii'), wherein A^5 is CR^{10}, wherein R^{10} is H.

A further embodiment of present invention is (xxiv') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxiii'), wherein A^6 is CR^{11}, wherein R^{11} is H or halogen.

A further embodiment of present invention is (xxv') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxiv'), wherein A^6 is CR^{11}, wherein R^{11} is H or fluoro.

A further embodiment of present invention is (xxvi') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxv'), wherein A^6 is CR^{11}, wherein R^{11} is halogen.

A further embodiment of present invention is (xxvii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxvi'), wherein A^6 is CR^{11}, wherein R^{11} is fluoro.

A further embodiment of present invention is (xxviii') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxvii'), wherein A^7 is CR^{12}, wherein R^{12} is H or halogen.

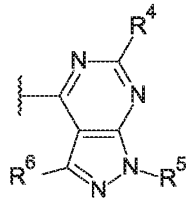
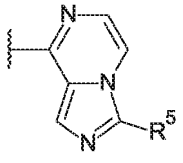
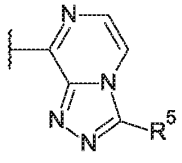
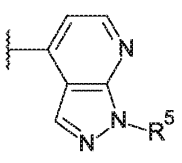
A further embodiment of present invention is (xxix') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxviii'), wherein A^7 is CR^{12}, wherein R^{12} is H or fluoro.

A further embodiment of present invention is (xxx') a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, according to any one of (i') to (xxix'), wherein A^7 is CR^{12}, wherein R^{12} is H.

A further embodiment of present invention is (xxxi') a compound of formula (I) or (Ia), according to any one of (i') or (ii') or (iii'), wherein

R^1 is H or $C_{1\text{-}6}$alkyl;

R^2 is H or $C_{1\text{-}6}$alkyl;

R^3 is  ,  ,  or  ; wherein

R^4 is H, amino, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl or morpholinyl$C_{1\text{-}6}$alkyl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy, halogen, hydroxy, and trideuterioC_{1-6}alkoxy;

R^6 is H;

Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy and C_{1-6}alkyl;

Q^2 is NH or O;

A^1 is CH or N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy or haloC_{1-6}alkoxy;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11}, wherein R^{11} is H or halogen;

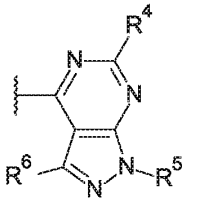
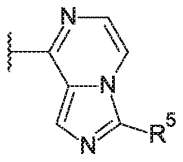
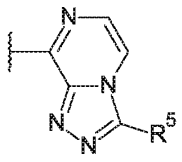
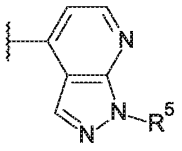
A^7 is CR^{12}, wherein R^{12} is H or halogen;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxii') a compound of formula (I) or (Ia), according to (xxxi'), wherein

R^1 is H or methyl;

R^2 is H, methyl or ethyl;

R^3 is  ,  ,  or  ; wherein

R^4 is H, amino, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from fluoro, methoxy, trideuteriomethoxy, difluoromethoxy, ethoxy, cyclopropoxy and hydroxy;

R^6 is H;

Q^1 is propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl and acetoxy;

Q^2 is NH or O;

A^1 is CH or N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy or difluoromethoxy;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or fluoro;

A^6 is CR^{11}, wherein R^{11} is H or fluoro;

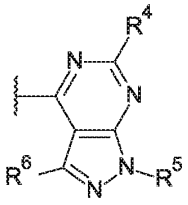
A^7 is CR^{12}, wherein R^{12} is H or fluoro;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxiii') a compound of formula (I) or (Ia), according to (xxxi'), wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl;

R^3 is  ; wherein

R^4 is H or $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl;

R^5 is phenyl substituted twice or three times by the substituents independently selected from $C_{1\text{-}6}$alkoxy and halogen;

R^6 is H;

Q^1 is $C_{1\text{-}6}$alkylene substituted by $C_{1\text{-}6}$alkoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is halogen;

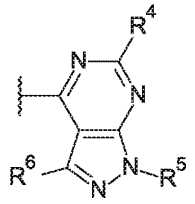
A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xxxiv') a compound of formula (I) or (Ia), according to (xxxiii'), wherein

R^1 is methyl;

R^2 is methyl;

R^3 is  ; wherein

R^4 is H or methoxymethyl;

R^5 is phenyl substituted twice or three times by the substituents independently selected from methoxy and fluoro;

R^6 is H;

Q^1 is propylene substituted by methoxy or ethoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is fluoro;

A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention (xxxv) is a compound of formula (I) or (Ia) selected from the following:

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carbonyl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,16,18-tetrazapentacyclo[14.6.1.$1^{2,6}$.$1^{8,11}$.$0^{19,23}$]pentacosa-1(22),2,4,6(25),17,19(23),20-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-hydroxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-benzyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-morpholinopropyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

3-[(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaen-13-yl]propyl-trimethyl-ammonium;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-methyl-10-[3-(3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[7-(2,4-difluorophenyl)imidazo[5,1-f][1,2,4]triazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl] -15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl] -15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15- (2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(oxetan-3-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[3-(2,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(3,4-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-(3-methyl-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

5-fluoro-2-[4-[(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile;

[(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl) pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy) -4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-(4-fluoro-2-methoxy-phenyl)-4-[(8S,11S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide;

1-(4-fluoro-2-methoxy-phenyl)-N,N-dimethyl-4-[(8S,11S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-hydroxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

8S,11S)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(2-morpholinoethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(6-fluoro-2-hydroxy-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,6-difluoro-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-methyl-10-[3-(2-thienyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(5-fluoro-3-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(3-fluoro-5-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(3,5-difluoro-2-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2-chloro-4-fluoro-phenyl)pyrimidin-5-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(methylamino)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,22,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(oxetan-3-ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(oxetan-3-ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-[(4-methylmorpholin-2-yl)methoxy]phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-methoxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-(2-hydroxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-[2-[(4aR,7aS)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]ethyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(4-methylsulfonylpiperazin-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(1,2,4-triazol-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(2-pyrazol-1-ylethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-23-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-3-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(trifluoromethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

5-fluoro-2-[4-[(8S,11S)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile;

5-fluoro-2-[4-[(8S,11S)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzoic acid;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-ethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-2-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(4-methylsulfonylpiperazin-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18,22-dideuterio-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-hydroxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

[(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylic acid;

1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carbonitrile;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-23-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-morpholino-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

Ethyl 1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylate;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfonyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-dimethylphosphoryl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-[(3,3-difluoroazetidin-1-yl)methyl]-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(morpholinomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-hydroxy-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-vinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,22-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-(difluoromethoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-(cyclopropoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-(difluoromethyl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-ethyl-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-18-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(hydroxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4,5-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-15-methoxy-10-[1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(5-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-4-(methoxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S)-10-[1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(trifluoromethyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-3,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-3,5,7,10,13,17,19-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-thia-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)triazolo[4,5-c]pyridin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(methoxymethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[4,3-c]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(4,4,4-trifluorobutyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carbonyl]-22-fluoro-13-(3-pyrimidin-2-yloxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-22-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-21-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15R)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-methoxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-16-oxa-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-(1-pyrimidin-5-ylpyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(11S,14S,18R)-13-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-25-fluoro-18-methoxy-16,21-dimethyl-5-oxa-10,13,16,20,22,29-hexazahexacyclo[18.6.1.1^{2,9}.1^{11,14}.0^{3,7}.0^{23,27}]nonacosa-1(26),2(29),3(7),8,21,23(27),24-heptaen-15-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-methyl-6-(3-thienyl)pyrazolo[4,3-c]pyridin-3-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridin-3-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-21,23-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2,4-difluorophenoxy)-4-pyridyl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-15-ethoxy-10-[1-[4-fluoro-2-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-18-hydroxy-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid;

(8S,11S,15R)-10-[6-ethoxy-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(morpholinomethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-isopropyl-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

methyl (8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxylate;

(8S,11S)-18-(chloromethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-hydroxy-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-amino-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-N,13-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxamide;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

N-[(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-18-yl]acetamide;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-fluoro-4-tetrahydrofuran-3-yl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22,23-difluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydrofuran-3-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydropyran-4-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-2-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-acetylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-hydroxy-1-(hydroxymethyl)ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(hydroxymethyl)-2-methoxy-ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylazetidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-acetylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylpyrrolidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-acetylpyrrolidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylpyrrolidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-acetylpyrrolidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methyl-4-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-(3-morpholinopropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-13-[3-[(4a*R*,7a*S*)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]propyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-ethylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-cyclopropylsulfonylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(pyrrolidine-1-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-(2,4-difluorophenyl)-4-[(8S,11S)-22-fluoro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]-N-(2-hydroxyethyl)pyrazolo[3,4-d]pyrimidine-6-carboxamide;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(morpholine-4-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(methoxymethyl)pyrazolo[4,3-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-5,13,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(1,3-dihydroisobenzofuran-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methyl-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoro-1-hydroxy-ethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[7-cyclopropyl-1-(2,4-difluorophenyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(2-methoxyethyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26- hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methoxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-hydroxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-[2-(azetidin-1-yl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(2-fluoro-4-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluor-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo [15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-[1-(methoxymethyl)cyclopropoxy]phenyl] pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-4,22-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2-dioxo-2λ^6-thia-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(hydroxymethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxy-1-methyl-ethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3*R*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(dimethylamino)methyl]azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methylsulfonylazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(tetrahydrofuran-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-cyclopropylazetidin-3-yl)oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(4-methylpiperazin-1-yl)ethoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroacetyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methylpiperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylazetidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylpyrrolidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-fluoroethyl)azetidin-3-yl]oxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(dimethylamino)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(3-amino-3-methyl-azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo [3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroethyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]ethyl acetate;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoro-3-methylsulfanyl-2-pyridyl)-6-methylsulfanyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(morpholinomethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-ylmethyl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(2H-tetrazol-5-yl)-1-piperidyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(3,5-difluoro-2-pyridyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3a*R*,6a*S*)-2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-cyclopentyl-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(4a*R*,7a*R*)-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-benzyl-4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]piperazine-2-carboxylic acid;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-oxazol-5-yl-1-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(3-prop-1-ynylimidazo[1,5-*a*]pyrazin-8-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-[[1-(2-methoxyacetyl)azetidin-3-yl]methyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxypyrrolidin-1-yl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-tetrahydrofuran-3-yloxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[2-[4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-1-yl]-3,5-difluoro-phenoxy]acetonitrile;

(8*S*,11*S*,15*S*)-10-[1-[2,4-difluoro-6-[(1-methylsulfonylazetidin-3-yl)methoxy]phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-4-(cyclopropylamino)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)indazol-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methyl-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[7-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-(cyclopropylmethyl)-1-(2,4-difluorophenyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[3-[1-(2,4-difluorophenyl)-4-[(8S,11S,15S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothian-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(methylsulfonylmethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[6-(1-cyclopropylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methylsulfanyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(dimethylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-imidazol-1-yl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoroethoxy)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(3*S*)-1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidine-3-carbonitrile;

8-[1-(2,4-difluorophenyl)-4-[(8S,11S,15R)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6,7,9,9a-tetrahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-4-one;

(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-fluoroethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-methoxyethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[5-(2-fluoroethyl)-8-oxa-2,5-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(3-phenylpropylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*S*)-3-cyclopropyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-hydroxy-6-(trifluoromethyl)-2-azaspiro[3.3]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-1,6-diazaspiro[3.3]heptan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

2-[3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

3-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(2-morpholinoethylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[11-benzyl-3-(2,4-difluorophenyl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-methyl-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[5-amino-1-(2,4-difluorophenyl)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-

diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

2-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11S,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(2-fluoroethyl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(oxetan-3-yl)-1,6-diazaspiro[3.3]heptan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6,6-dioxo-6λ^{6}-thia-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,7-diazabicyclo[4.2.0]octan-7-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-(oxetan-3-yl)-3,4,8,11-tetrazatricyclo[7.3.0.$0^{2,6}$]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(oxetan-3-yl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-

diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-

heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one;

3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-2-oxo-piperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

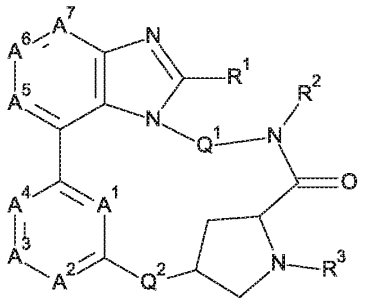
(8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one; and

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-fluorocyclobutyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

or a pharmaceutically acceptable salt thereof.

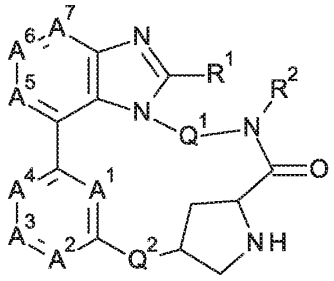
Another embodiment of present invention (xxxvi) is a process for the preparation of a compound according to any one of (i) to (xxxv) comprising any of the following steps:

a) the formation of compound of formula (I),



(I),

via nucleophilic substitution between compound of formula (VIII),

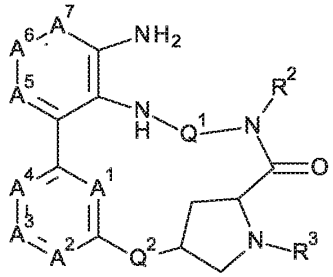


(VIII), and R^3X, in the presence of a base;

b) the formation of compound of formula (I) via Buchwald-Hartwig reaction between compound of formula (VIII) and R^3X, in the presence of a catalyst;

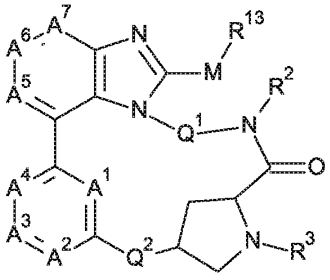
c) the formation of compound of formula (I) via condensation reaction between compound of formula (VIII) and R^3OH, in the presence of coupling reagent;

d) the formation of compound of formula (I) via cyclization reaction between compound of formula (XVIII) ,

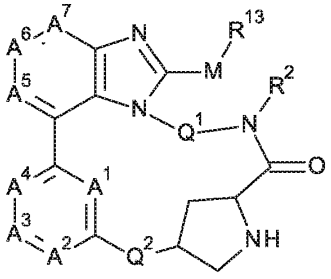


(XVIII), and regents;

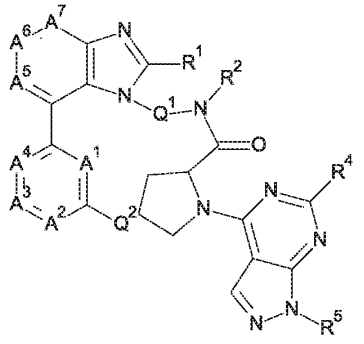
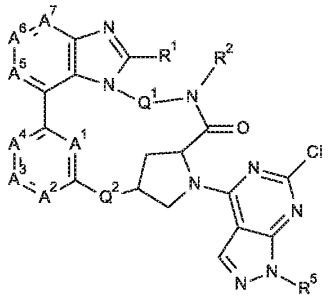
e) the formation of compound of formula (XXI),

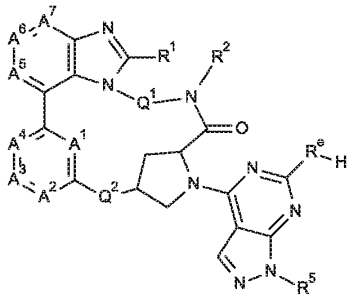


(XXI), via nucleophilic substitution between compound of formula (XX),



(XX), and R^3X in the presence of a base;

f) the formation of compound of formula (XXII),  (XXII), via reaction between compound of formula (Ic),  (Ic), and alcohols or amines (R^4-X) in the presence of a base;

g) the amino group of compound of formula (XXIV),  (XXIV), reacts with halide via nucleophilic substitution or with ketone via reductive amination to provide final compound of formula (XXII);

wherein

in step a) and e) , the base is DIEA;

in step b), the catalyst is $Pd_2(dba)_3$;

in step c), the coupling reagent is HATU;

in step d), the regents is CDI, BrCN or $R^1(OCH_3)_3$;

in step e), the base is DIEA;

in step f), the base is DIPEA, K_2CO_3 or NaH;

X is halogen; R^{13} is R^a, R^b or R^c; M is C_{1-6}alkylene; R^e is a substituent bearing primary or secondary amino groups; R^1 to R^7, Q^1, Q^2, A^1 to A^7 are as defined as in any one of (i) to (xxxv) or (i') to (xxxiv').

Another embodiment of present invention (xxxvii) is related to a compound or pharmaceutically acceptable salt according to any one of (i) to (xxxv) or (i') to (xxxiv') for use as therapeutically active substance.

Another embodiment of present invention (xxxviii) is related to a pharmaceutical composition comprising a compound in accordance with any one of (i) to (xxxv) or (i') to (xxxiv') and a therapeutically inert carrier.

Another embodiment of present invention (xxxix) is related to the use of a compound according to any one of (i) to (xxxv) or (i') to (xxxiv') for the treatment or prophylaxis of autoimmune diseases, inflammatory diseases, neurological disorders diseases, metabolic diseases, cardiovascular diseases, ocular diseases, or selective types of cancers where overexpression or activation of STING is implicated.

Another embodiment of present invention (xl) is related to the use of a compound according to any one of (i) to (xxxv) or (i') to (xxxiv') for the treatment to subjects suffered from an inteferonopathy or auto-inflammatory diseases in which the STING activation are the root-cause of disease pathologies.

Another embodiment of present invention (xli) is related to the use of a compound according to any one of (i) to (xxxv) or (i') to (xxxiv') for the inhibition of STING.

Another embodiment of present invention (xlii) is related to the use of a compound according to any one of (i) to (xxxv) or (i') to (xxxiv') for the preparation of a medicament for the inhibition of STING.

Another embodiment of present invention (xliii) is related to a compound or pharmaceutically acceptable salt according to any one of (i) to (xxxv) or (i') to (xxxiv'), when manufactured according to a process of (xxxvi).

Another embodiment of present invention (xliv) is related to a method for the treatment or prophylaxis of autoimmune diseases, which method comprises administering a therapeutically effective amount of a compound as defined in any one of (i) to (xxxv) or (i') to (xxxiv').

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as

methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (I) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit STING interaction with IRF3, NF-kB, NLRP3 etc., for blocking downstream type I IFN and pro-inflammatory cytokine (e.g. IL-6, TNFa, ISGs) production, cellular responses/conditions (e.g. autophagy, apoptosis, cell senescence). For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.1 to 1000 mg/kg, alternatively about 0.1 to 1000 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.1 to 1000 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 0.1 to about 1000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 0.1 to 1000 mg of the compound of the invention compounded with about 0.1 to 1000 mg anhydrous lactose, about 0.1 to 1000 mg sodium croscarmellose, about 0.1 to 1000 mg polyvinylpyrrolidone (PVP) K30, and about 0.1 to 1000 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 0.1 to 1000 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

Another embodiment includes a pharmaceutical composition comprising a compound of formula (I) for use in the treatment of interferonopathies, autoimmune and inflammatory diseases. Another embodiment includes a pharmaceutical composition comprising a compound of formula (I) for use in the treatment of infection or selective type of cancer.

The following composition A and B illustrate typical compositions of the present invention, but serve merely as representative thereof.

Composition A

A compound of the present invention can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

Composition B

A compound of the present invention can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention inhibit STING, including its signaling and activities. Accordingly, the compounds of the invention are useful for infection, inflammation, auto-immune, degenerative diseases and cancer therapy.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of autoimmune diseases.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of inflammatory diseases.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of neurological disorders diseases.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of cardiovascular diseases.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of ocular diseases.

In some embodiments, compounds of the invention are useful for the treatment or prophylaxis of selective types of cancers where overexpression or activation of STING is implicated.

Alternatively, compounds of the invention are useful for the treatment of subjects suffered from an inteferonopathy or auto-inflammatory diseases in which the STING activation are the root-cause of disease pathologies. More broadly, the compounds can be used for the treatment of all pathological cellular processes which are STING dependent.

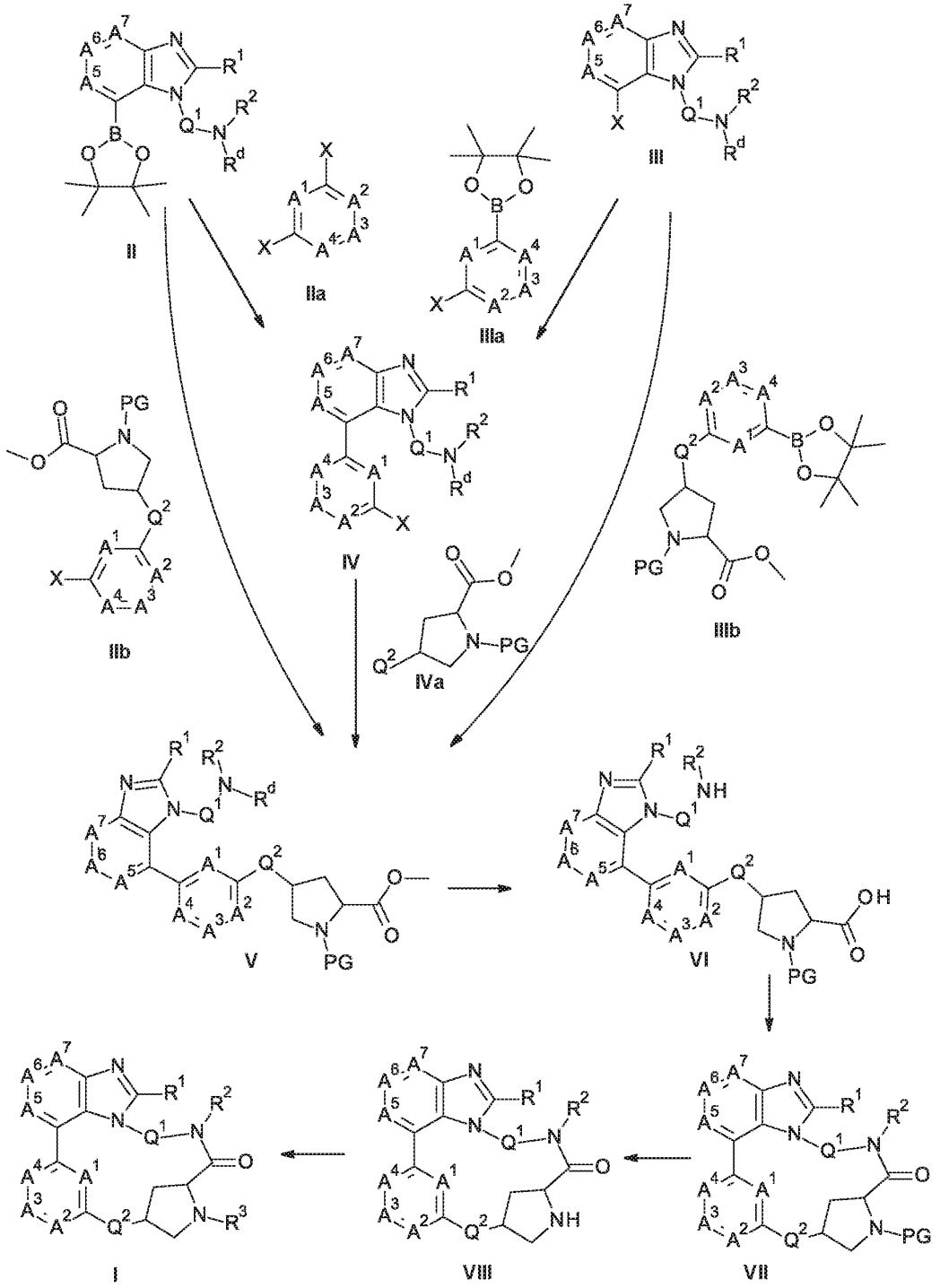
Another embodiment includes a method of treating or preventing cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1 to R^7, Q^1, Q^2, A^1 to A^7 are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic routes for preparing the compound of the invention are shown in following schemes.

Scheme 1

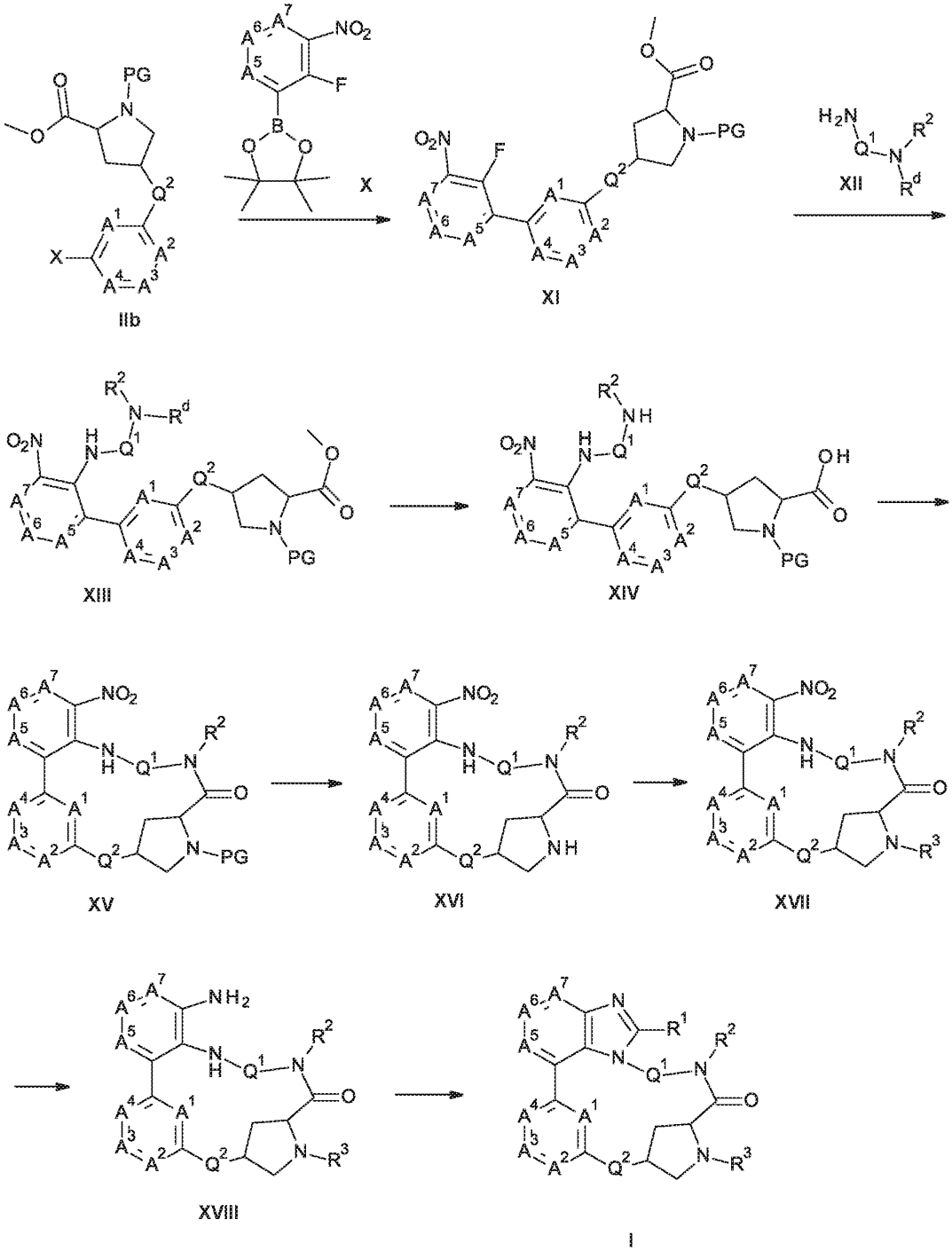


Wherein R^d is H or PG, wherein PG can be, for example, Boc or Cbz; X is halogen.

As depicted in **Scheme 1**, the synthesis of compounds of the present invention started from bronic ester compound of formula (**II**) or halide (**III**). Suzuki coupling between compound of

formula (**II**) and compound of formula (**IIb**) with a catalyst, such as $Pd(dppf)Cl_2$, and a base, such as K_2CO_3, provides compound of formula (**V**), which can also be obtained via the Suzuki coupling between bronic ester compound of formula (**IIIb**) and halide (**III**). On the other hand, Suzuki coupling between compound of formula (**II**) and halide (**IIa**) or between compound of formula (**IIIa**) and halide (**III**) provides an intermediate of formula (**IV**), which is reacted with compound of formula (**IVa**) via Buchwald-Hartwig amination or nucleophilic substitution to give compound of formula (**V**). Compound of formula (**V**) is hydrolyzed in the presence of LiOH directly and followed by appropriate deprotection to give compound of formula (**VI**) (Boc deprotection: HCl in dioxane or TFA in DCM; Cbz deprotection: Pd/C or $Pd(OH)_2/C$ under H_2). Compound of formula (**VI**) can be cyclized to give compound of formula (**VII**) in the presence of a coupling reagent, such as HATU, and a base, such as DIPEA. The following Boc deprotection in acidic condition (HCl in dioxane or TFA in DCM) or Cbz deprotection by catalytic hydrogenation (Pd/C or $Pd(OH)_2/C$ under H_2) or in acidic condition (TFA) to give compound of formula (**VIII**). Compound of formula (**I**) can be obtained by the reaction between compound of formula (**VIII**) and $\mathbf{R^3X}$ via nucleophilic substitution in the presence of a base, such as DIEA, or via Buchwald-Hartwig reaction in the presence of a catalyst, such as $Pd_2(dba)_3$. On the other hand, compound of formula (**IX**) can also be obtained via condensation reaction between compound of formula (**VIII**) and $\mathbf{R^3OH}$ in the presence of coupling reagent, such as HATU.

Scheme 2

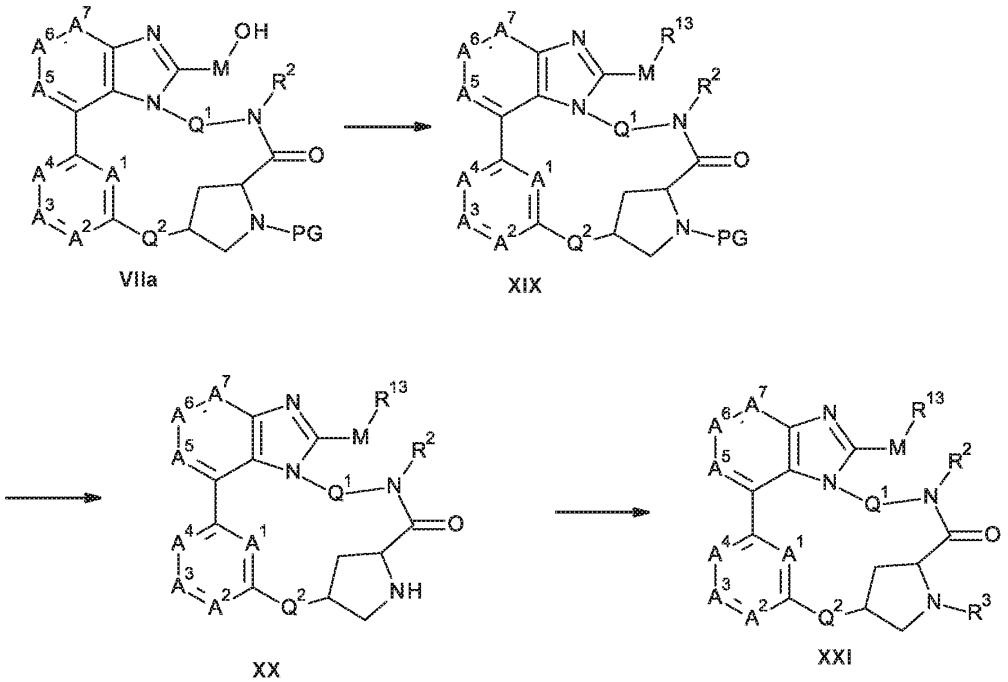


As depicted in **Scheme 2**, Suzuki coupling between halide (**IIb**) and bronic ester compound of formula (**X**) provides compound of formula (**XI**), which reacts with compound of formula (**XII**) via nucleophilic substitution in the presence of a base, such as DIPEA, K_2CO_3 to give compound of formula (**XIII**). The preparation of compounds of formula (**XIV**), (**XV**),

(**XVI**), (**XVII**) are in analogy to the preparation of compounds of formula (**VI**), (**VII**), (**VIII**), (**IX**) that described above in **scheme 1**. Compound of formula (**XVII**) is hydrogenated in the presence of zinc and ammonium chloride to give compound of formula (**XVIII**), which reacts with CDI, BrCN or $R^1(OCH_3)_3$ to give compound of formula (**I**).

General synthetic routes for preparing the compound of formula (**XXI**) is shown below.

Scheme 3

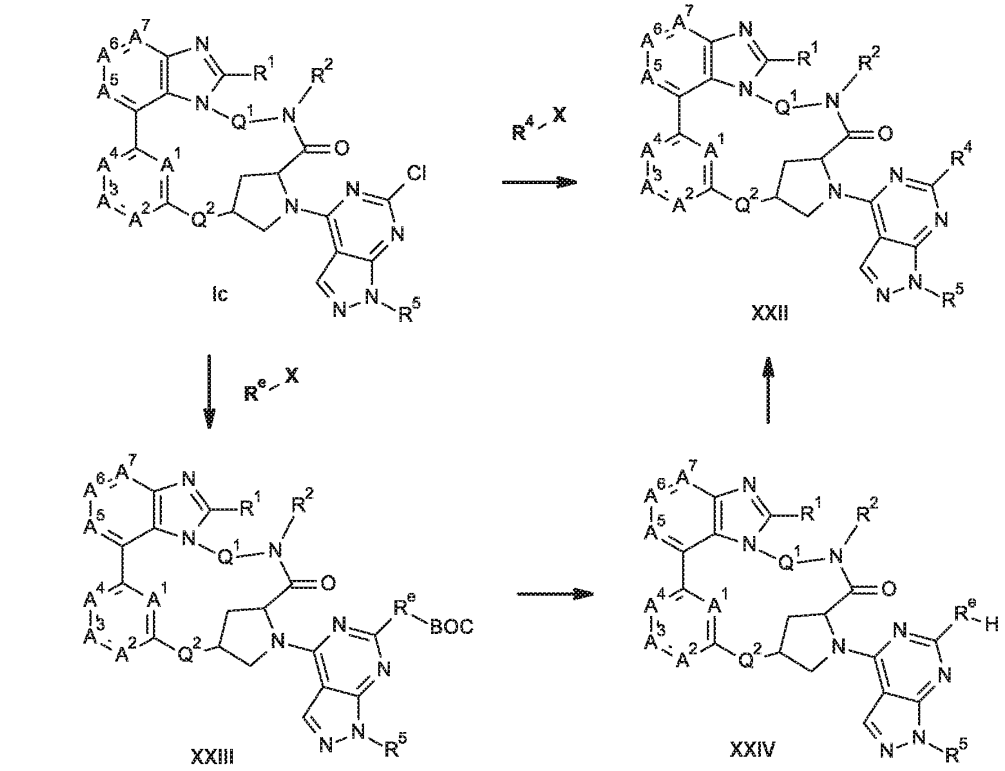


Wherein R^{13} is R^a, R^b or R^c.

As depicted in **Scheme 3**, compound of formula (**VIIa**) is presented when R^1 in formula (**VII**) is hydroxy$C_{1\text{-}6}$alkyl. Compound of formula (**VIIa**) reacts with methanesulfonic anhydride or methanesulfonyl chloride in the presence of a base, such as DIPEA or TEA to give a methanesulfonate ester intermediate, which was treated with amine to provide compound of formula (**XIX**). The preparation of compounds of formula (**XX**) is in analogy to the preparation of compounds of formula (**VIII**) in **scheme 1**. Compound of formula (**XXI**) can be obtained via nucleophilic substitution between compound of formula (**XX**) and $\mathbf{R^3X}$ in the presence of a base, such as DIEA.

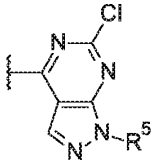
General synthetic routes for preparing the compound of formula (**XXII**) is shown below.

Scheme 4



Wherein X is OH, NH, SH or halogen; R^e is a substituent bearing primary or secondary amino groups.

As depicted in **Scheme 4**, compound of formula (**Ic**) is presented when R^3 in formula (**I**) is



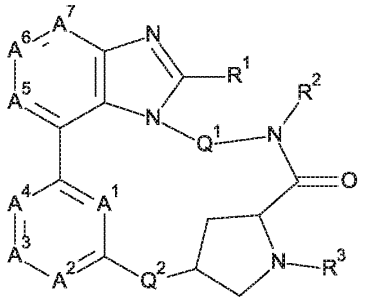
. Compound of formula (**Ic**) reacts with alcohols or amines (R^4-X) in the presence of a base, such as DIPEA, K_2CO_3 or NaH to directly give compound of formula (**XXII**) or give intermediate compound of formula (**XXIII**), which was then deprotected in acidic condition to give compound of formula (**XXIV**). The amino group of compound of formula (**XXIV**) reacts with halide via nucleophilic substitution or with ketone via reductive amination to provide final compound of formula (**XXII**). On the other hand, photoredox coupling between compound of formula (**Ic**) and alkyl halide (R^4X) in the presence of a catalyst, such as $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ to directly give compound of formula (**XXII**) or give Boc-protected compound of formula (**XXIII**), which was then deprotected in acidic condition to give compound of formula (**XXIV**). Nucleophilic substitution with halide or reductive amination with ketone of compound of formula (**XXIV**) to provide final compound of formula (**XXII**). Thirdly,

Buchwald coupling between compound of formula (**Ic**) and lactams (such as pyrrolidin-2-one, morpholin-3-one) in the presence of a catalyst, such as Pd_2dba_3 to give compound of formula (**XXII**).

Compounds of this invention can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or SFC.

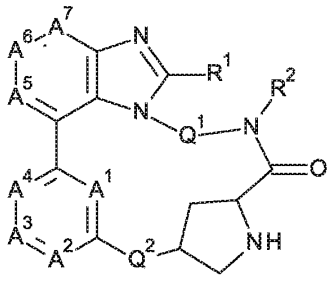
This invention also relates to a process for the preparation of a compound of formula (I) or (I) comprising any of the following steps:

a) the formation of compound of formula (I),



(I),

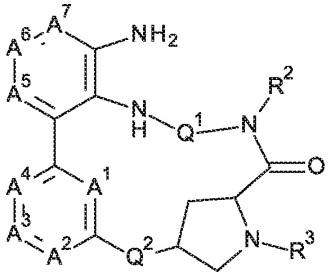
via nucleophilic substitution between compound of formula (VIII),

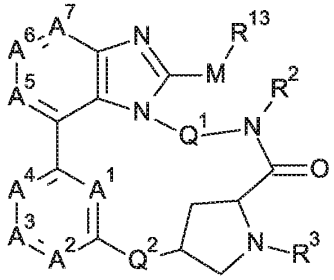
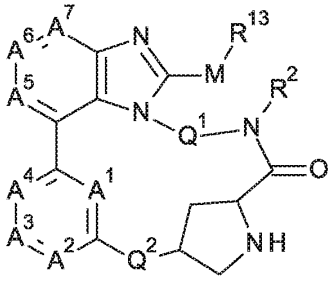


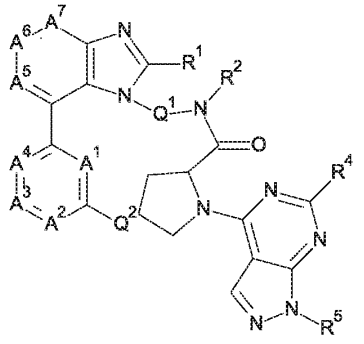
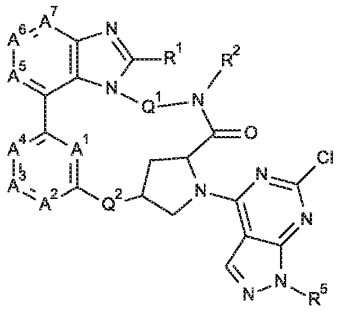
(VIII), and R^3X, in the presence of a base;

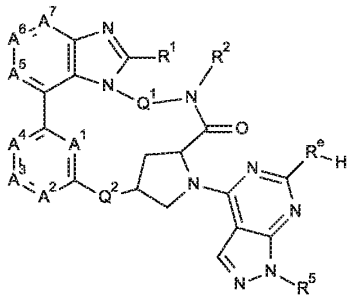
b) the formation of compound of formula (I) via Buchwald-Hartwig reaction between compound of formula (VIII) and R^3X, in the presence of a catalyst;

c) the formation of compound of formula (I) via condensation reaction between compound of formula (VIII) and R^3OH, in the presence of coupling reagent;

d) the formation of compound of formula (I) via cyclization reaction between compound of formula (XVIII),  (XVIII), and regents;

e) the formation of compound of formula (XXI),  (XXI), via nucleophilic substitution between compound of formula (XX),  (XX), and R^3X in the presence of a base;

f) the formation of compound of formula (XXII),  (XXII), via reaction between compound of formula (Ic),  (Ic), and alcohols or amines (R^4-X) in the presence of a base;

g) the amino group of compound of formula (XXIV),  (XXIV), reacts with halide via nucleophilic substitution or with ketone via reductive amination to provide final compound of formula (XXII);

wherein

in step a) and e) , the base can be, for example, DIEA;

in step b), the catalyst can be, for example, $Pd_2(dba)_3$;

in step c), the coupling reagent can be, for example, HATU;

in step d), the regents can be, for example, CDI, BrCN or $R^1(OCH_3)_3$;

in step e), the base can be, for example, DIEA;

in step f), the base can be, for example, DIPEA, K_2CO_3 or NaH;

X is halogen; R^{13} is R^a, R^b or R^c; M is $C_{1\text{-}6}$alkylene; R^e is a substituent bearing primary or secondary amino groups.

A compound of formula (I) or (Ia) when manufactured according to the above process is also an object of the invention.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

ABBREVIATIONS

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations used herein are as follows:

ACN:	acetonitrile
Boc_2O:	di-*tert* butyl dicarbonate
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-dinaphthalene
DCM:	dichloromethane
DCE:	dichloroethane
DIPEA or DIEA:	*N*,*N*-diisopropylethylamine
DIBAL-H:	diisobutylaluminium hydride
DIAD:	diisopropyl azodicarboxylate
DMA:	*N*,*N*-Dimethylacetylamine
DMAP:	4-dimethylaminopyridine
DMF:	*N*,*N*-Dimethylformamide
DMSO:	dimethyl sulfoxide
DPPP:	1,3-Bis(diphenylphosphino)propane
EA or EtOAc:	ethyl acetate
FA:	formic acid
HATU:	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
h(s) or hr(s):	hour (s)
hPBMC:	human peripheral blood mononuclear cells
IC_{50}:	half inhibition concentration

Ir[dF(CF_3)ppy]$_2$(dtbpy)(PF_6): [4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate

IPA: isopropanol

LCMS: liquid chromatography-mass spectrometry

mCPBA: meta-chloroperoxybenzoic acid

min(s): minute(s)

MS: mass spectrometry

MsCl: methanesulfonyl chloride

Ms_2O: methanesulfonic anhydride

NBS: *N*-bromosuccinimide

NIS: *N*-iodosuccinimide

NMP: *N*-Methylpyrrolidone

$NiCl_2$.dtbbpy: [4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride

PE: petroleum ether

prep-HPLC: preparative high performance liquid chromatography

prep-TLC: preparative thin layer chromatography

PyBOP/BOP: (1-hydroxy-1*H*-benzotriazolato-o)tri-1-pyrrolidinylphosphorus hexafluorophosphate

PPh_3: triphenylphosphine

$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0)

(R)-binap : (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene

Rf: retention factor

rt, r.t: room temperature

RT: retention time

RuPhos Pd G2: chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) 2nd generation

Selectfluor 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

SFC: supercritical fluid chromatography

S-Phos: 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBSCl: tert-butyldimethylsilyl chloride

t-BuXPhos: 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl

*t*BuXPhos Pd G3: Methanesulfonato(2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)

*t*Bu$_3$P-Pd-G2 Chloro[(tri-tert-butylphosphine)(2-aminobiphenyl-2-yl)palladium(II)

T_3P: Propylphosphonic anhydride

TEA: trimethylamine

TFA: trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

THF: tetrahydrofuran

TLC: thin layer chromatography

XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

XPhos Pd G2: chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

v/v volume ratio

GENERAL EXPERIMENTAL CONDITIONS

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 µm; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using XBridge™ Prep-C18 (5 µm, OBDTM 30 × 100 mm) column, SunFire™ Prep-C18 (5 µm, OBD™ 30 × 100 mm) column, Phenomenex Synergi-C18 (10 µm, 25 × 150 mm) or Phenomenex Gemini-C18 (10 µm, 25 × 150 mm). Waters AutoP purification System (Sample Manager 2767, Pump 2525, Detector: Micromass ZQ and UV 2487, solvent system: acetonitrile and 0.1% ammonium hydroxide in water; acetonitrile and 0.1% FA in water or acetonitrile and 0.1% TFA in water). Or Gilson-281 purification System (Pump 322, Detector: UV 156, solvent system: acetonitrile and 0.05% ammonium hydroxide in water; acetonitrile and 0.225% FA in water; acetonitrile and 0.05% HCl in water; acetonitrile and 0.075% TFA in water; or acetonitrile and water).

For SFC chiral separation, intermediates were separated by chiral column (Daicel chiralpak IC, 5 μm, 30 × 250 mm), AS (10 μm, 30 × 250 mm) or AD (10 μm, 30 × 250 mm) using Mettler Toledo Multigram III system SFC, Waters 80Q preparative SFC or Thar 80 preparative SFC, solvent system: CO_2 and IPA (0.5% TEA in IPA) or CO_2 and MeOH (0.1% $NH_3 \cdot H_2O$ in MeOH), back pressure 100bar, detection UV@ 254 or 220 nm.

LC/MS spectra of compounds were obtained using a LC/MS (Waters™ Alliance 2795-Micromass ZQ, Shimadzu Alliance 2020-Micromass ZQ or Agilent Alliance 6110-Micromass ZQ), LC/MS conditions were as follows (running time 3 or 1.5 mins):

Acidic condition I: A: 0.1% TFA in H_2O; B: 0.1% TFA in acetonitrile;

Acidic condition II: A: 0.0375% TFA in H_2O; B: 0.01875% TFA in acetonitrile;

Basic condition I: A: 0.1% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Basic condition II: A: 0.025% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Neutral condition: A: H_2O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion $(MH)^+$.

NMR Spectra were obtained using Bruker Avance 400 MHz, 500 MHz.

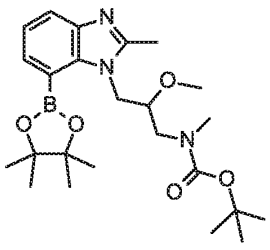
The microwave assisted reactions were carried out in a Biotage Initiator Sixty microwave synthesizer. All reactions involving air-sensitive reagents were performed under an argon or nitrogen atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

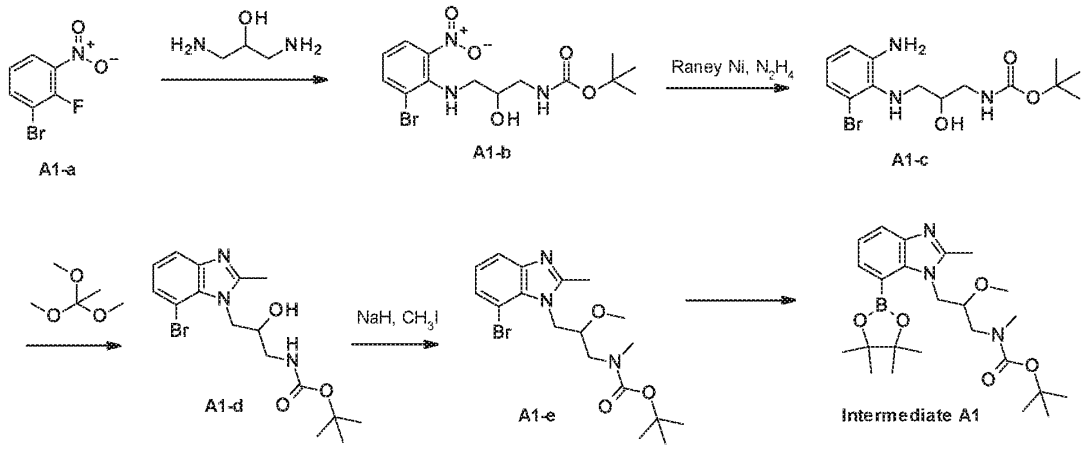
The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

Intermediate A1

***tert*-butyl *N*-[2-methoxy-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(2-bromo-6-nitro-anilino)-2-hydroxy-propyl]carbamate (compound A1-b)

To a solution of 1,3-diamino-2-propanol (35.64 g, 395.45 mmol, as the "**AMINE**" in table 1) in ACN was added 3-bromo-2-fluoronitrobenzene (**compound A1-a**, 43.5 g, 197.73 mmol, as the "**ARYL FLUORIDE**" in table 1) slowly at 25 °C. After being stirred at 20 °C for 0.5 hours, the mixture was filtered, and the filtered cake was collected and dissolved in methanol. Then *tert*-butyl (2-methylpropan-2-yl)oxycarbonyl carbonate (106.8 g, 489.47 mmol) and DIPEA (63.26 g, 489.47 mmol) was added. After being stirred at 20 °C for 1 h, the mixture was concentrated, the residue was purified prep-HPLC to afford **compound A1-b** (51.5 g). LCMS $(M-56+H)^+$:336.

Step 2: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)-2-hydroxy-propyl]carbamate (compound A1-c)

To a solution of *tert*-butyl *N*-[3-(2-bromo-6-nitro-anilino)-2-hydroxy-propyl]carbamate (**compound A1-b**, 50.5 g, 129.41 mmol) in methanol (846 mL) was added Raney Ni (30.38 g, 517.64 mmol) and hydrazine hydrate (34.79 g, 694.97 mmol). After being stirred at 25 °C for 1 h, the mixture was filtered and concentrated. The crude product was dissolved in DCM (500 mL), washed with water (300 mL). The organic layer was dried and concentrated to give **compound A1-c** (43 g). LCMS $(M+H)^+$: 360.

Step 3: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl] carbamate (compound A1-d)

To a solution of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)-2-hydroxy-propyl]carbamate (**compound A1-c**, 37.5 g, 104.09 mmol) in anhydrous THF (496 mL) was added trimethyl orthoacetate (45 mL, as the "**SOLVENT**" in table 1) and pyridinium *p*-toluenesulfonate (3.75 g,

14.92 mmol). After being stirred for 1 h at 20 °C, the mixture was concentrated and the residue was triturated by PE/EA(1/1, 150 mL) to give **compound A1-d** (39 g). LCMS $(M+H)^+$: 384.

Step 4: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (compound A1-e)

To a solution of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (**compound A1-d**, 10.0 g, 26.02 mmol) in DMF (200 mL) was added CH_3I (11.08 g, 78.07 mmol, as the "**ALKYL IODIDE**" in table 1) at -10 °C under N_2, then NaH (2.6 g, 65.06 mmol) was added slowly in portions. The mixture was stirred at -10 °C for 5 hours. The mixture was then stirred at 20 °C for another 12 h. The reaction was quenched with ice cold NH_4Cl solution and extracted with EA twice, the organic layer was dried and concentrated to afford **compound A1-e** (11.7 g). LCMS $(M+H)^+$: 412.

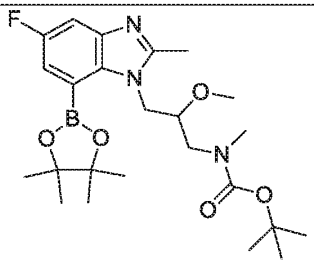
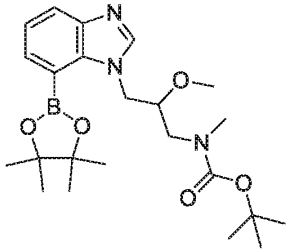
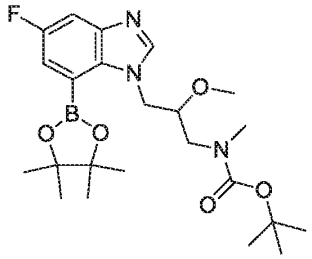
Step 5: preparation of *tert*-butyl *N*-[2-methoxy-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (Intermediate A1)

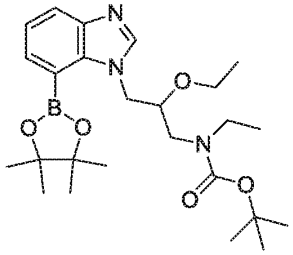
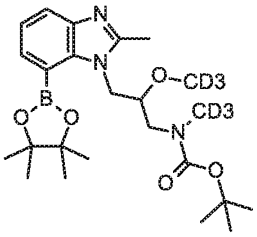
To a mixture of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (**compound A1-e**, 10.5 g, 25.47 mmol) in DMSO (150 mL) was added potassium acetate (5.0 g, 50.93 mmol), bis(triphenylphosphine)palladium(II) chloride (2.68 g, 3.82 mmol) and BUTYLDI-1-ADAMANTYLPHOSPHINE (2.74 g, 7.64 mmol). The mixture was degassed with N_2 for three times and stirred at 130 °C for 2 hours. The reaction mixture was poured into water (1000 mL) and extracted with EA (300 mL) twice. The organic phase was washed with brine (300 mL), dried and concentrated, the residue was purified by silica gel to afford **Intermediate A1** (8.8 g). LCMS $(M+H)^+$: 460.

The following intermediates in Table 1 were prepared in analogy to **Intermediate A1** by replacing **compound A1-a** with the "**ARYL FLUORIDE**" and 1,3-diamino-2-propanol with the "**AMINE**" in step 1, trimethyl orthoacetate with the "**SOLVENT**" in step 3, CH_3I with the "**ALKYL IODIDE**" in step 4 by the reagents indicated in Table 1.

Table 1. Compound synthesis and characterization

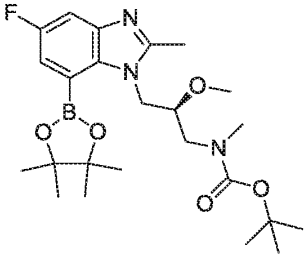
No.	Compound Name and Structure	AMINE, ARYL FLUORIDE, SOLVENT, ALKYL IODIDE	LCMS $(M+H)^+$
A2	***tert*-butyl *N*-[3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate**	**AMINE:** 1,3-diamino-2-propanol **ARYL FLUORIDE:** 1-bromo-2,5-difluoro-3-	478

		nitro-benzene **SOLVENT:** 1,1,1-trimethoxyethane **ALKYL IODIDE:** methyl iodide	
A3	***tert*-butyl *N*-[2-methoxy-3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate** 	**AMINE:** 1,3-diamino-2-propanol **ARYL FLUORIDE:** 3-bromo-2-fluoronitrobenzene **SOLVENT:** trimethoxymethane **ALKYL IODIDE:** methyl iodide	446
A4	***tert*-butyl *N*-[3-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate** 	**AMINE:** 1,3-diamino-2-propanol **ARYL FLUORIDE:** 1-bromo-2,5-difluoro-3-nitro-benzene **SOLVENT:** trimethoxymethane **ALKYL IODIDE:** methyl iodide	464
A5	***tert*-butyl *N*-[2-ethoxy-3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-ethyl-carbamate**	**AMINE:** 1,3-diamino-2-propanol **ARYL FLUORIDE:** 3-bromo-2-fluoronitrobenzene **SOLVENT:** trimethoxymethane **ALKYL IODIDE:**	474

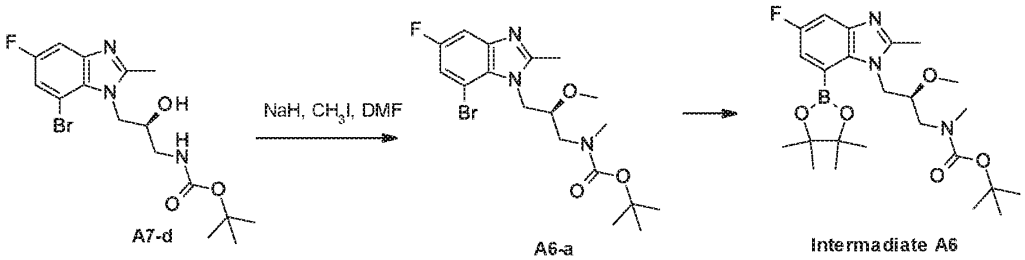
		ethyl iodide	
A21	*tert*-butyl *N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-(trideuteriomethoxy)propyl]-*N*-(trideuteriomethyl)carbamate 	**AMINE:** 1,3-diamino-2-propanol **ARYL FLUORIDE:** 3-bromo-2-fluoronitrobenzene **SOLVENT:** trimethoxymethane **ALKYL IODIDE:** trideuterio(iodo)methane	452

Intermediate A6

***tert*-butyl *N*-[(2*R*)-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate**



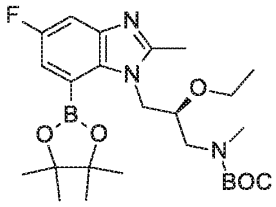
The title compound was prepared according to the following scheme:



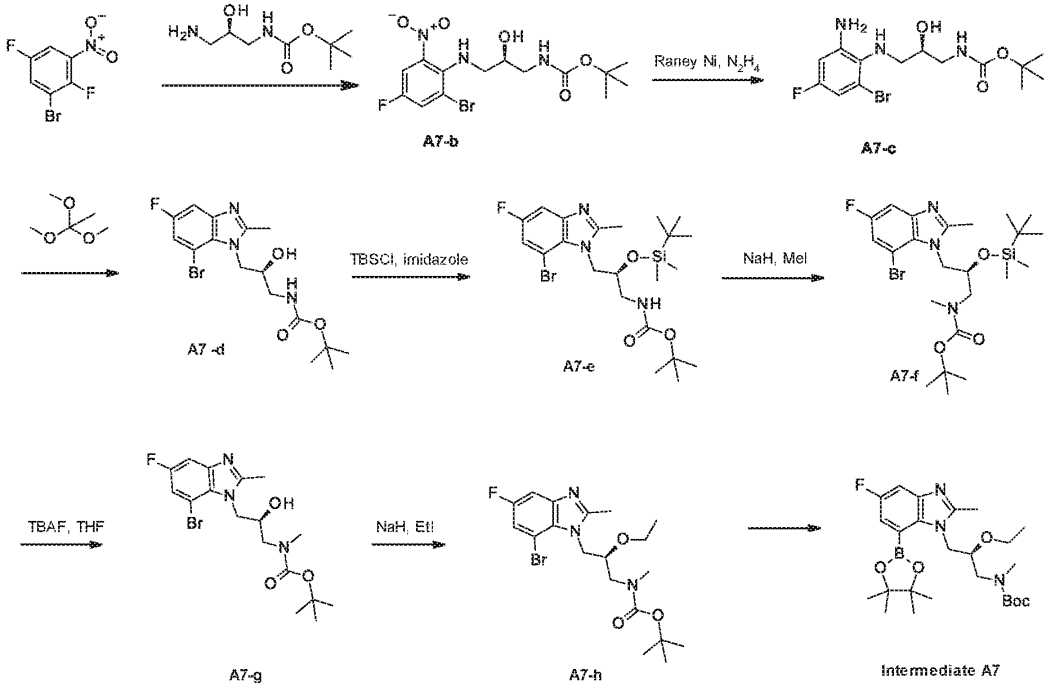
The title compound was prepared in analogy to the preparation of **Intermediate A1** by using **compound A7-d** instead of **compound A1-d.** LCMS $(M+H)^+$: 478.

Intermediate A7

***tert*-butyl *N*-[(2*R*)-2-ethoxy-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[(2*R*)-3-(2-bromo-4-fluoro-6-nitro-anilino)-2-hydroxy-propyl]carbamate (compound A7-b)

To a mixture of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate (59.59 g, 313.25 mmol) and 1-bromo-2,5-difluoro-3-nitro-benzene (71.0 g, 298.33 mmol) in ACN (710 mL) was added potassium carbonate (82.46 g, 596.66 mmol). After being stirred at 50 °C for 2 hours, the mixture was filtered and the filtrate was concentrated to give **compound A7-b** (131 g). LCMS $(M+H)^+$: 352.

Step 2: preparation of *tert*-butyl *N*-[(2*R*)-3-(2-amino-6-bromo-4-fluoro-anilino)-2-

hydroxy-propyl]carbamate (compound A7-c)

To a solution of **compound A7-b** (63.0 g, 154.33 mmol) in methanol (1000 mL) was added Raney Ni (36.23 g, 617.31 mmol) and hydrazine hydrate (29.19 g, 583.1 mmol). After being stirred at 25 °C for 1 h, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in DCM, washed with water and brine. The organic layer was dried and concentrated to give **compound A7-c** (128 g). LCMS $(M+H)^+$: 378.

Step 3: preparation of *tert*-butyl *N*-[(2*S*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (compound A7-d)

To a solution of **compound A7-c** (123.0 g, 325.19 mmol) in anhydrous THF (1500 mL) was added trimethyl orthoacetate (136.74 mL, 1104 mmol) and pyridinium *p*-toluenesulfonate (11.71 g, 46.62 mmol). The reaction was stirred for 1 h at 20 °C. The mixture was concentrated under reduced pressure to give **compound A7-d** (160 g). LCMS $(M+H)^+$: 400.

Step 4: preparation of *tert*-butyl *N*-[(2*S*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]carbamate (compound A7-e)

To a solution of **compound A7-d** (80.0 g, 198.88 mmol) and imidazole (40.62 g, 596.63 mmol) in DMF (765 mL) was added *tert*-butyldimethylchlorosilane (59.95 g, 397.75 mmol), then the mixture was stirred for 18 hours at 30 °C. The mixture was poured into ice-aq.NH_4Cl (2000 mL), extracted with EtOAc (800 mL) twice. The organic layer was dried and concentrated to give **compound A7-e** (94 g). LCMS $(M+H)^+$: 518.

Step 5: preparation of *tert*-butyl *N*-[(2*R*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]-*N*-methyl-carbamate (compound A7-f)

To a solution of **compound A7-e** (82.0 g, 158.75 mmol) in DMF (800 mL) was added sodium hydride (60% in oil, 15.87 g, 396.89 mmol) at 0°C and then stirred at 0 °C for 1 h. Iodomethane (90.13 g, 635.02 mmol) was then added at 0°C and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extracted with EA. The organic layer was dried and concentrated, the crude product was purified by column chromatography to give **compound A7-f** (44.4 g). LCMS $(M+H-56)^+$: 530.

Step 6: preparation of *tert*-butyl *N*-[(2*R*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]-*N*-methyl-carbamate (compound A7-g)

A mixture of **compound A7-f** (39.8 g, 75.02 mmol) and TBAF/THF (1M, 150.0 mL, 150 mmol) was stirred at 20 °C for 2 hours. Then the mixture was concentrated and the crude product was diluted with EtOAc (600mL), washed with water and brine. The organic layer was dried and concentrated to give **compound A7-g** (39.4 g). LCMS$(M+H)^+$: 416.

Step 7: preparation of *tert*-butyl *N*-[(2*R*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-ethoxy-propyl]-*N*-methyl-carbamate (compound A7-h)

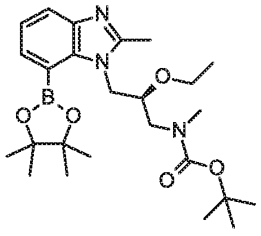
To a solution of **compound A7-g** (17.4 g, 41.8 mmol) and iodoethane (5.01 mL, 62.7 mmol) in DMF (174 mL) was added sodium hydride (2.17 g, 54.34 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. The reaction was then quenched with water, and the mixture was extracted with EA. The organic layer was dried and concentrated to give **compound A7-h** (20.4 g). LCMS $(M+H)^+$: 444.

Step 8: preparation of *tert*-butyl *N*-[(2*R*)-2-ethoxy-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (Intermediate A7)

To a mixture of **compound A7-h** (19.4 g, 43.66 mmol) and bis(pinacolato)diboron (27.72 g, 109.15 mmol) in DMSO (194 mL) was added potassium acetate (8.57 g, 87.32 mmol), bis(triphenylphosphine)palladium(II) chloride (4.6 g, 6.55 mmol) and butyldi-1-adamantylphospine (4.7 g, 13.1 mmol). The mixture was degassed with N_2 for three times, and then stirred at 130 °C for 2 hours. The reaction mixture was then poured into water (1000 mL) and extracted with EA (500 mL). The organic layer was dried and concentrated, the crude product was purified by column chromatography to give **Intermediate A7** (15 g). LCMS $(M+H)^+$: 478.

Intermediate A8

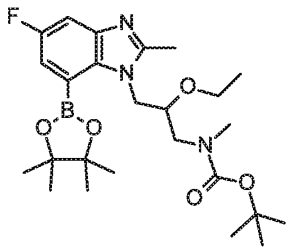
***tert*-butyl *N*-[(2*R*)-2-ethoxy-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared in analogy to the preparation of **Intermediate A7** by using 3-bromo-2-fluoronitrobenzene instead of 1-bromo-2,5-difluoro-3-nitro-benzene. LCMS $(M+H)^+$: 474.

Intermediate A9

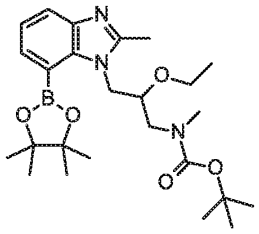
***tert*-butyl *N*-[2-ethoxy-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared in analogy to the preparation of **Intermediate A7** by using *tert*-butyl *N*-[(3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate. LCMS $(M+H)^+$: 492.

Intermediate A10

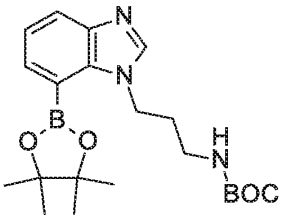
***tert*-butyl *N*-[2-ethoxy-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



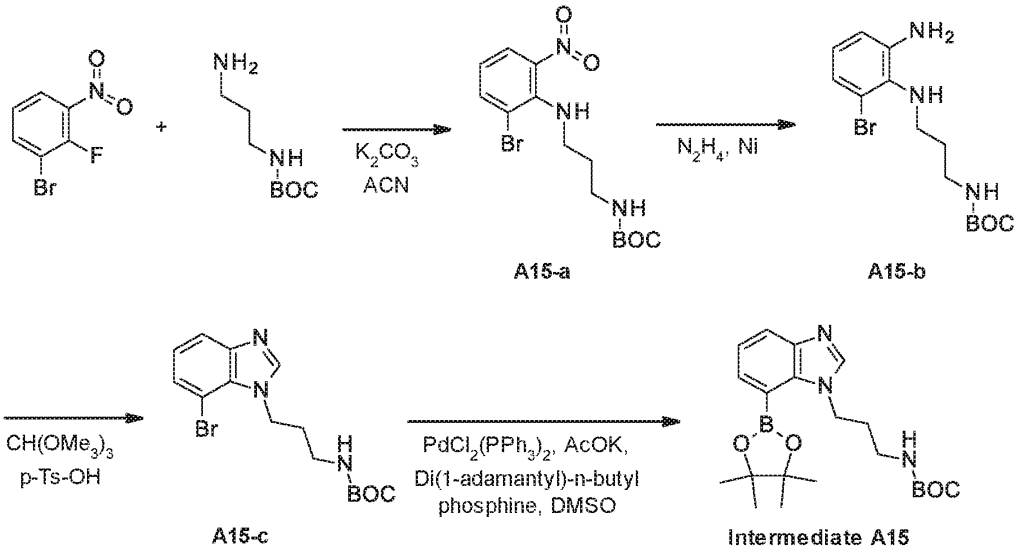
The title compound was prepared in analogy to the preparation of **Intermediate A7** by using *tert*-butyl *N*-[(3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate and 3-bromo-2-fluoronitrobenzene instead of 1-bromo-2,5-difluoro-3-nitro-benzene. LCMS $(M+H)^+$: 474.

Intermediate A15

***tert*-butyl *N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl] carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(2-bromo-6-nitro-anilino)propyl]carbamate (intermediate A15-a)

To a microwave tube was added 1-bromo-2-fluoro-3-nitro-benzene (2.7 g, 12.3 mmol, as the "**ARYL FLUORIDE**" in table 2), *tert*-butyl *N*-(3-aminopropyl)carbamate (2.14 g, 12.3 mmol, as the "**AMINE**" in table 2), K_2CO_3 (1.7 g, 12.3 mmol) and acetonitrile (15 mL). The tube was sealed and heated to 90 °C for 3 hrs. The mixture was cooled and filtered, the filtrate was concentrated and the residue was purified by silica gel to give **intermediate A15-a** (4.8 g). LCMS ($M+H^+$): 374.

Step 2: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)propyl]carbamate (intermediate A15-b)

To a flask was added nickel (2.9 g, 49.4 mmol), MeOH (100mL) and *tert*-butyl *N*-[3-(2-bromo-6-nitro-anilino)propyl]carbamate (**intermediate A15-a**, 5 g, 13.4 mmol), the suspension was stirred vigorously and hydrazine (8.56 g, 8.32 mL, 134 mmol) was then added. After being stirred at r.t. for 1 hr, the mixture was filtered and filtrate was concentrated. The residue was dissolved in DCM and washed with water and brine. The organic layer was dried and concentrated to give **intermediate A15-b** (4.6 g), LCMS ($M+H^+$): 344.

Step 3: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (intermediate A15-c)

To a flask containing *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)propyl]carbamate (**intermediate A15-b**, 3.5 g, 10.2 mmol) was added trimethyl orthoformate (9.7 g, 10 mL, 91.4 mmol, as the "**SOLVENT**" in table 2) and *p*-toluenesulfonic acid monohydrate (387 mg, 2.03 mmol), a light yellow solution formed. The mixture was stirred at r.t. for 5 hrs. The mixture was

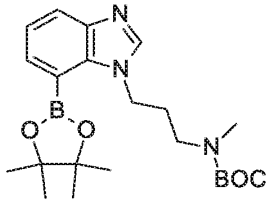
concentrated and the residue was purified by silica gel to give **intermediate A15-c** (3.2 g). LCMS ($M+H^+$): 354.

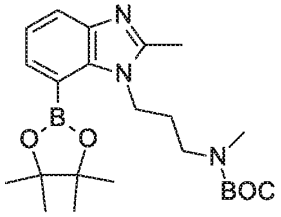
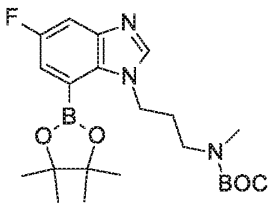
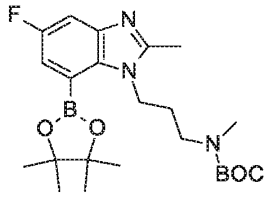
Step 4: preparation of *tert*-butyl *N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (intermediate A15)

To a tube was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (**intermediate A15-c**, 2.7 g, 7.62 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.84 g, 19.1 mmol), potassium acetate (1.5 g, 15.2 mmol) and DMSO (12 mL). The solution was bubbled with N_2 for 5 mins and then Butyldi-1-adamantylphosphine (820 mg, 2.29 mmol) and bis(triphenylphosphine)palladium(II) dichloride (802 mg, 1.14 mmol) were added. The tube was sealed, and heated to 130 °C for 4 hrs. The mixture was diluted with water and then it was extracted with EA. The organic layer was dried and concentrated, the residue was purified by silica gel to give **intermediate A15** (2.1 g). LCMS ($M+H^+$): 402.

The following intermediates in Table 2 were prepared in analogy to **Intermediate A15** by replacing **1-bromo-2-fluoro-3-nitro-benzene** with the "**ARYL FLUORIDE**" and ***tert*-butyl *N*-(3-aminopropyl)carbamate** with the "**AMINE**" in step 1, **trimethyl orthoformate** with the "**SOLVENT**" in step 3 by the reagents indicated in Table 2.

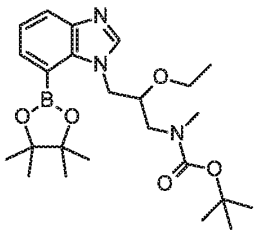
Table 2. Compound synthesis and characterization

No.	Compound Name and Structure	AMINE, ARYL FLUORIDE, SOLVENT	LCMS $(M+H)^+$
A11	***tert*-butyl *N*-methyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate** 	**AMINE:** *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate **ARYL FLUORIDE:** 3-bromo-2-fluoronitrobenzene **SOLVENT:** trimethoxymethane	416
A12	***tert*-butyl *N*-methyl-*N*-[3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate**	**AMINE:** *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate **ARYL FLUORIDE:**	430

		3-bromo-2-fluoronitrobenzene **SOLVENT:** 1,1,1-trimethoxyethane	
A13	***tert*-butyl *N*-[3-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate** 	**AMINE:** *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate **ARYL FLUORIDE:** 1-bromo-2,5-difluoro-3-nitro-benzene **SOLVENT:** trimethoxymethane	434
A14	***tert*-butyl *N*-[3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate** 	**AMINE:** *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate **ARYL FLUORIDE:** 1-bromo-2,5-difluoro-3-nitro-benzene **SOLVENT:** 1,1,1-trimethoxyethane	448

Intermediate A17

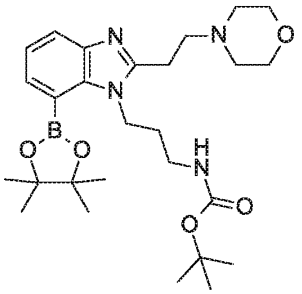
***tert*-butyl *N*-[2-ethoxy-3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



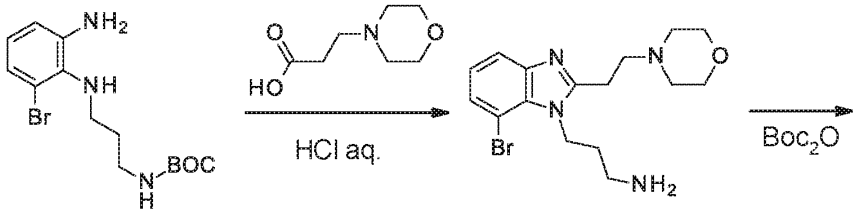
The title compound was prepared in analogy to the preparation of **intermediate A7** by using *tert*-butyl *N*-[(3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2R)-3-amino-2-hydroxy-propyl]carbamate, trimethoxymethane instead of 1,1,1-trimethoxyethane and 3-bromo-2-fluoronitrobenzene instead of 1-bromo-2,5-difluoro-3-nitro-benzene. LCMS $(M+H)^+$: 474.

Intermediate A18

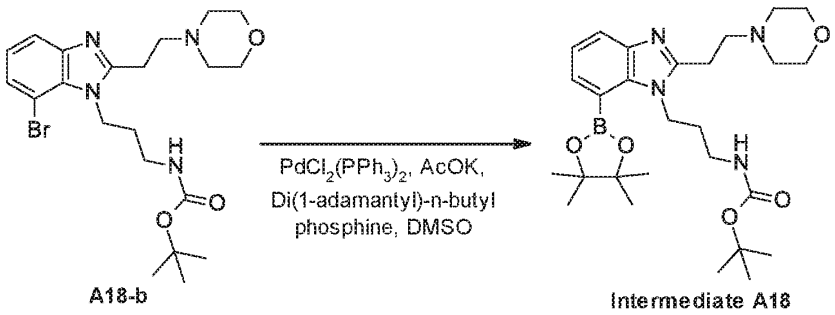
***tert*-butyl N-[3-[2-(2-morpholinoethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate**



The title compound was prepared according to the following scheme:



A15-b A18-a



A18-b Intermediate A18

Step 1: preparation of 3-[7-bromo-2-(2-morpholinoethyl)benzimidazol-1-yl]propan-1-amine (Intermediate A18-a)

A mixture of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino) propyl]carbamate (**compound**

A15-b 4.5 g, 13.07 mmol) and 3-morpholinopropanoic acid (2.08 g, 13.07 mmol) in con.HCl (45.0 mL, 13.07 mmol) and water (45 mL) was stirred at 100 °C for 40 h. After adjusting the reaction mixture's pH to 8~10 with NaOH (20%), the reaction mixture was extracted with DCM, the organic layer was dried concentrated to give compound **A18-a** (3.7 g). LCMS ($M+H^+$): 367.

Step 2: preparation of *tert*-butyl *N*-[3-[7-bromo-2-(2-morpholinoethyl)benzimidazol-1-yl]propyl]carbamate (Intermediate A18-b)

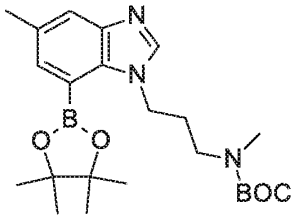
A mixture of compound **A18-a** (3.7g, 10.21 mmol) and di-*t*-butyldicarbonate (3.34 g, 15.32 mmol) in methanol was stirred at 20 °C for 16 hr. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give **intermediate A18-b** (1 g). LCMS ($M+H^+$): 467.

Step 3: preparation of *tert*-butyl *N*-[3-[2-(2-morpholinoethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (Intermediate A18)

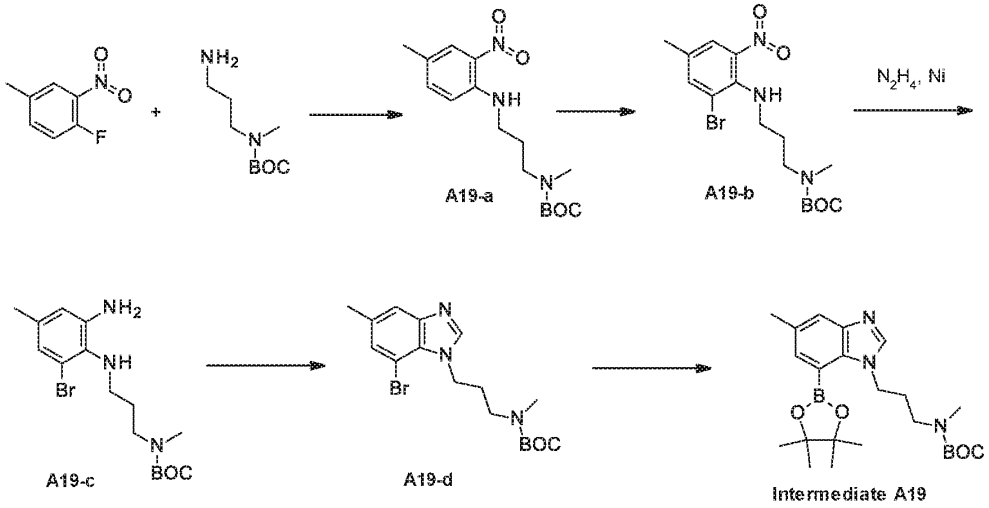
To a tube was added *tert*-butyl *N*-[3-[7-bromo-2-(2-morpholinoethyl)benzimidazol-1-yl]propyl]carbamate (**Intermediate A18-b**, 560 mg, 1.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (700 mg, 2.76 mmol), potassium acetate (235 mg, 2.4 mmol), and DMSO (6 mL). The solution was bubbled with N_2 for 5 mins and then butyldi-1-adamantylphosphine (85.9 mg, 240 μmol) and bis(triphenylphosphine)palladium(II) dichloride (84.1 mg, 120 μmol) were added. The tube was heated to 130 °C for about 6 hrs. The mixture was diluted with water and then extracted with EA, the organic layer was dried and concentrated. The residue was purified by silica gel to give **Intermediate A18** (180 mg). LCMS ($M+H^+$): 515.

Intermediate A19

***tert*-butyl *N*-methyl-*N*-[3-[5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-methyl-*N*-[3-(4-methyl-2-nitro-anilino)propyl]carbamate (compound A19-a)

To a mixture of 4-fluoro-3-nitrotoluene (5.0 g, 32 mmol) and potassium carbonate (8.9 g, 64 mmol) in ACN (100 mL) was added *N*-(3-aminopropyl)-*N*-methylcarbamic acid *tert*-butylester (6.7 g, 35.5 mmol) slowly at 25 °C. After being stirred at 85 °C for 2 hours, the mixture was filtered and concentrated to afford compound **A19-a** (11.6 g). LCMS $(M+H)^+$: 324.

Step 2: preparation of *tert*-butyl *N*-[3-(2-bromo-4-methyl-6-nitro-anilino)propyl]-*N*-methyl-carbamate (compound A19-b)

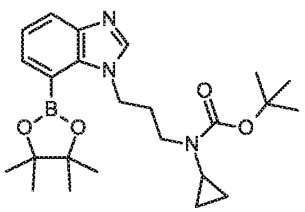
A mixture of compound **A19-a** (10.0 g, 31 mmol) and NBS (6.73 g, 37.82 mmol) in ACN (100 mL) was stirred at 85 °C for 12 hours. Then the reaction was concentrated and the residue was purified by flash chromatography to give compound **A19-b** (4.75 g). LCMS $(M+H)^+$: 402.

Step 3~5: preparation of *tert*-butyl *N*-methyl-*N*-[3-[5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (intermediate A19)

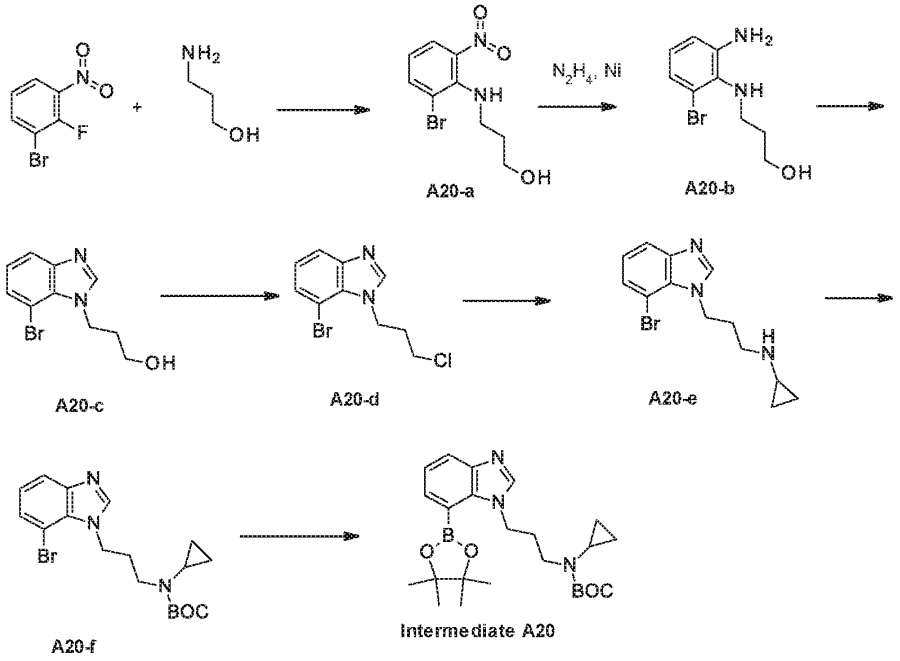
The title compound was prepared in analogy to the preparation of **intermediate A15** by using compound **A19-b** instead of compound **A15-a**. LCMS $(M+H)^+$: 430.

Intermediate A20

***tert*-butyl *N*-cyclopropyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate**



The title compound was prepared according to the following scheme:



Step 1~3: preparation of 3-(7-bromobenzimidazol-1-yl)propan-1-ol (compound A20-c)

Compound **A20-c** was prepared in analogy to the preparation of **intermediate A15-c** by using 3-aminopropan-1-ol instead of *tert*-butyl *N*-(3-aminopropyl)carbamate, LCMS $(M+H)^+$: 255.

Step 4: preparation of 7-bromo-1-(3-chloropropyl)benzimidazole (compound A20-d)

A mixture of compound **A20-c** (10 g, 39 mmol) in $SOCl_2$ (40 mL) was stirred at 80 °C for 1 h. Then the mixture was concentrated, the residue was dissolved in EtOAc, washed with 5% $NaHCO_3$ and brine (50.0mL). The organic layer was dried and concentrated to give compound **A20-d** (7.0 g). LCMS $(M+H)^+$: 273.

Step 5: preparation of *N*-[3-(7-bromobenzimidazol-1-yl)propyl]cyclopropanamine (compound A20-e)

A mixture of compound **A20-d** (1.6 g, 5.85 mmol), cyclopropylamine (1.6 g, 28.03 mmol), DIPEA (1.6 g, 12.38 mmol) in NMP (10.0 mL) was stirred for 12 hours at 110 °C. Then the mixture was diluted with DCM, washed with water and brine. The organic layer was dried and concentrated to give the crude compound **A20-e** (560 mg). LCMS $(M+H)^+$: 295.

Step 6: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-*N*-cyclopropyl-carbamate (compound A20-f)

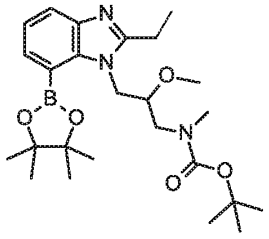
A mixture of compound **A20-e** (500 mg, 1.7 mmol) and di-t-butyldicarbonate (500 mg, 2.29 mmol) in DCM (10 mL) was stirred for 1 h at 20 °C. The mixture was concentrated and the residue was purified by prep-TLC to give compound **A20-f** (560 mg), which was used in next step directly. LCMS $(M+H)^+$: 396.

Step 7: preparation of *tert*-butyl *N*-cyclopropyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (Intermediate A20)

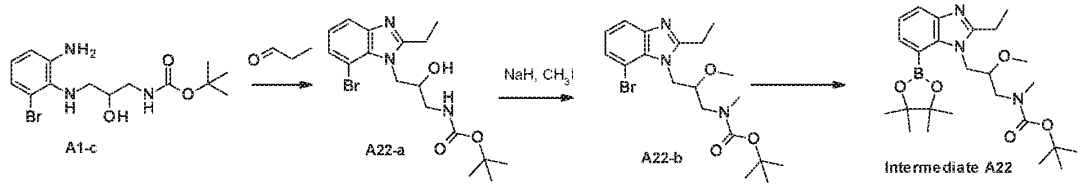
The title compound was prepared in analogy to the preparation of **intermediate A15** by using compound **A20-f** instead of compound **A15-c**. LCMS $(M+H)^+$: 442.

Intermediate A22

***tert*-butyl *N*-[3-[2-ethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-ethyl-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (compound A22-a)

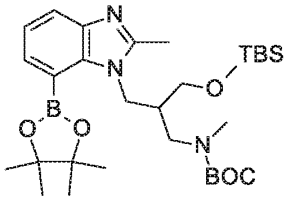
To a solution of compound **A1-c** (7.3 g, 20 mmol) in water (8 mL) and DMF (80 mL) was added oxone (3.41 g, 20.26 mmol), propionaldehyde (1.35 g, 23.3 mmol) in turns at 0 °C and then stirred at 20 °C for 12 hours. The reaction was quenched with saturated ammonium chloride solution (500 mL), extracted with EA (1000 mL). The organic layer was dried and concentrated; the residue was purified by column chromatography to give compound **A22-a** (2.5 g). LCMS $(M+H)^+$: 398.

Step 2~3: *tert*-butyl *N*-[3-[2-ethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (intermediate A22)

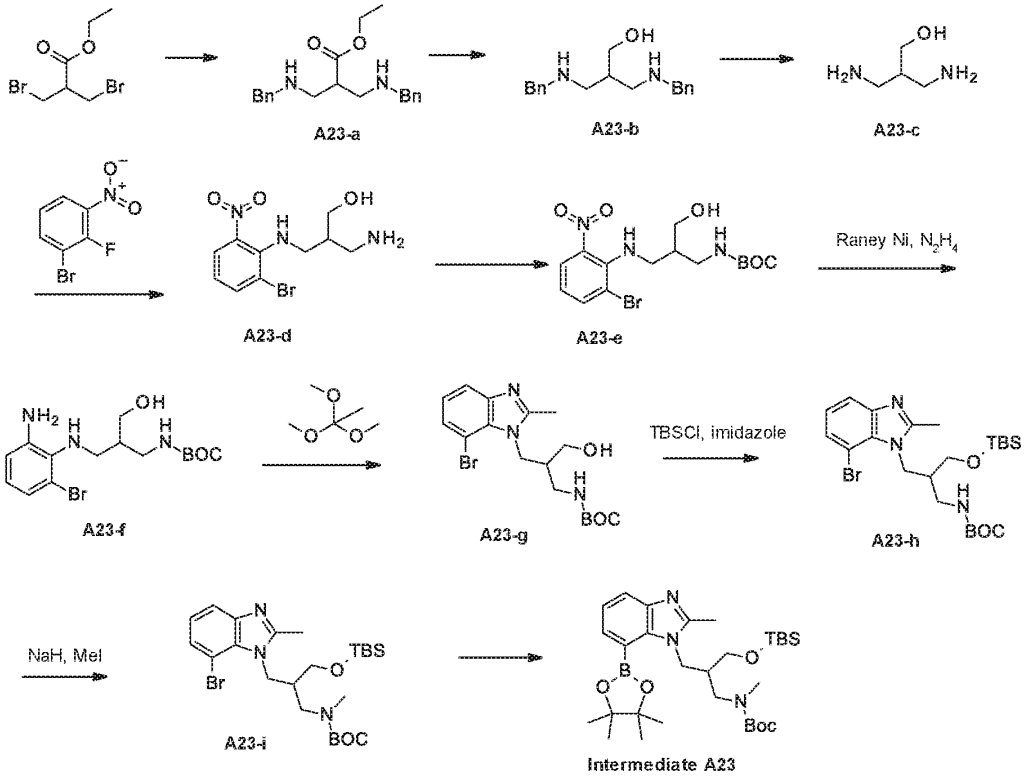
The title compound was prepared in analogy to the preparation of **intermediate A1** by using compound **A22-a** instead of compound **A1-d**. LCMS$(M+H)^+$: 474.

Intermediate A23

***tert*-butyl *N*-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 3-(benzylamino)-2-[(benzylamino)methyl]propanoate (compound A23-a)

To a mixture of benzylamine (7.97 mL, 73.01 mmol) and DIPEA (12.72 mL, 73.01 mmol) in ACN (80 mL) was added ethyl-3-bromo-2-(bromomethyl)propionate (10 g, 36.5 mmol) in ACN (20 mL) slowly at 80 °C in 1 h. Then the mixture was stirred at 80 °C for 6 hours. The reaction was concentrated and the residue was purified by flash chromatography to give compound **A23-a** (5.9 g). LCMS ($M+H^+$): 327.

Step 2: preparation of 3-(benzylamino)-2-[(benzylamino)methyl]propan-1-ol (compound A23-b)

To a solution of compound **A23-a** (8.7 g, 26.65 mmol) in THF (120 mL) was added $LiAlH_4$ (1.2 g, 32 mmol) at 0 °C, then the mixture was stirred at 0 °C for 2 hours. The reaction was quenched with H_2O (1.2 mL), 10% aq.NaOH(3.6 mL). Then the mixture was diluted with EA (100 mL), dried over anhydrous magnesium sulfate. The organic layer was concentrated to give compound **A23-b** (6.1 g). LCMS $(M+H)^+$: 285.

Step 3: preparation of 3-amino-2-(aminomethyl)propan-1-ol (compound A23-c)

To a solution of compound **A23-b** (11 g, 38.68 mmol) in methanol (80 mL) and acetic acid (10 mL) was added $Pd(OH)_2/C$ (2.2 g) under N_2. The mixture was stirred under hydrogen at 60 °C for 48 hours. The reaction mixture was filtered and concentrated to give compound **A23-c** (5 g). LCMS $(M+H)^+$: 105.

Step 4~7: preparation of *tert*-butyl *N*-[2-[(7-bromo-2-methyl-benzimidazol-1-yl)methyl]-3-hydroxy-propyl]carbamate (compound A23-g)

Compound **A23-g** was prepared in analogy to the preparation of **intermediate A1-d** by using compound **A23-c** instead of 1,3-diamino-2-propanol, LCMS $(M+H)^+$: 398.

Step 8~9: preparation of *tert*-butyl *N*-[2-[(7-bromo-2-methyl-benzimidazol-1-yl)methyl]-3-[*tert*-butyl(dimethyl)silyl]oxy-propyl]carbamate (compound A23-i)

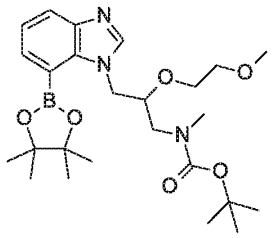
Compound **A23-i** was prepared in analogy to the preparation of **intermediate A7-f** by using compound **A23-g** instead of compound **A7-d**. LCMS $(M+H^+)$: 526.

Step 10: preparation of *tert*-butyl *N*-[2-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (intermediate A23)

The title compound was prepared in analogy to the preparation of **intermediate A1** by using compound **A23-i** instead of compound **A1-e**. LCMS $(M+H^+)$: 574.

Intermediate A24

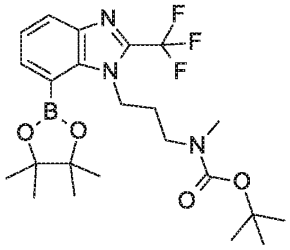
***tert*-butyl *N*-[2-(2-methoxyethoxy)-3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



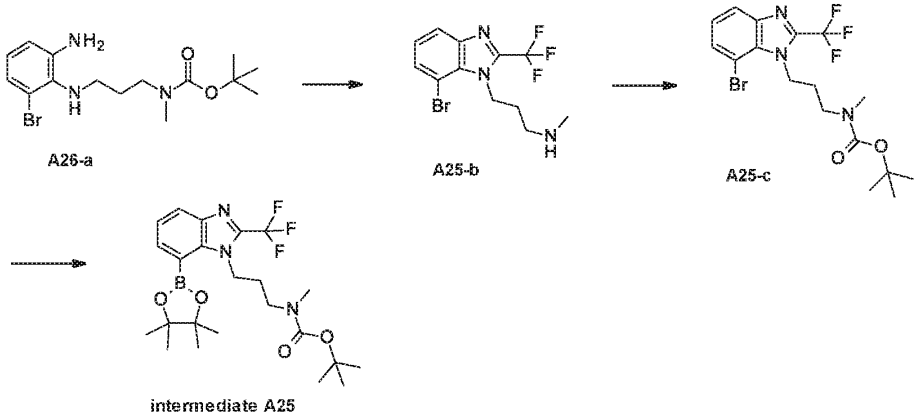
The title compound was prepared in analogy to the preparation of **Intermediate A7** by using *tert*-butyl *N*-[(3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2R)-3-amino-2-hydroxy-propyl]carbamate, 3-bromo-2-fluoronitrobenzene instead of 1-bromo-2,5-difluoro-3-nitro-benzene, trimethoxymethane instead of trimethoxymethane and 1-bromo-2-methoxy-ethane instead of ethyl iodide. LCMS $(M+H)^+$: 490.

Intermediate A25

***tert*-butyl *N*-methyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzimidazol-1-yl]propyl]carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of 3-[7-bromo-2-(trifluoromethyl)benzimidazol-1-yl]-N-methyl-propan-1-amine (compound A25-b)

A mixture of compound **A26-a** (7.65 g, 21.35 mmol) and con.HCl (1 mL) in TFA (70.0 mL) was stirred at 70 °C for 12 h. The mixture was concentrated to give compound **A25-b** (6.6 g). LCMS$(M+H)^+$: 336

Step 2: preparation of 3-[7-bromo-2-(trifluoromethyl)benzimidazol-1-yl]-*N*-methyl-propan-1-amine (compound A25-c)

A mixture of compound **A25-b** (3.25 g, 9.67 mmol), Boc_2O (4.36 g, 20 mmol) and DIPEA (3.37 mL, 19.34 mmol) in methanol (30 mL) was stirred at 20 °C for 1 h. Then the mixture was

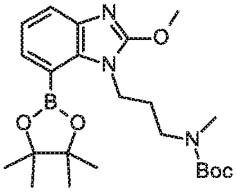
concentrated, the residue was purified by silica gel to give compound **A25-c** (3.25 g). LCMS(M+H)$^+$: 436.

Step 3: preparation of *tert*-butyl *N*-methyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzimidazol-1-yl]propyl]carbamate (intermediate A25)

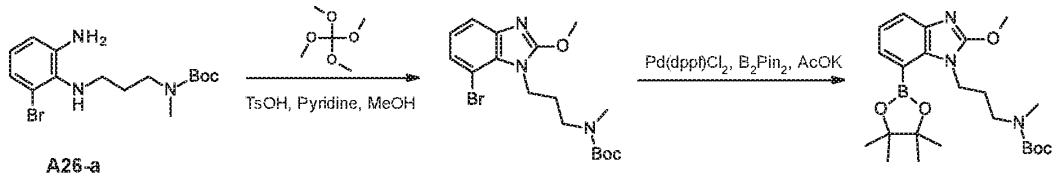
To a mixture of compound **A25-c** (3.2 g, 7.33 mmol) and bis(pinacolato)diboron (4.66 g, 18.34 mmol) in DMSO (44.73 mL) was added potassium acetate (1.44 g, 14.67 mmol), bis(triphenylphosphine)palladium(II) chloride (0.77 g, 1.1 mmol) and butyldi-1-adamantylphosphine(0.79 g, 2.2 mmol). The mixture was degassed with N_2 for three times and stirred at 130 °C for 2 h. The reaction mixture was poured into water and extracted with EA. The organic layer was dried and concentrated, the residue was purified by silica gel to give **intermediate A25** (1.46 g). LCMS (M+H)$^+$: 484.

Intermediate A26

***tert*-butyl *N*-[3-[2-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



A26-a A26-b intermediate A26

Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methoxy-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound A26-b)

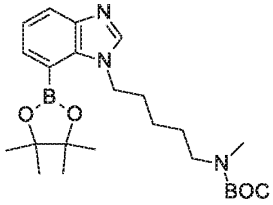
To a solution of compound **A26-a** (9.0 g, 26.1 mmol, the synthesis was refer to **A15-b**) in methanol (50 mL) was added tetramethoxymethane (7.1 g, 52.2 mmol) and TsOH•pyridine (1.3 g, 5.2 mmol). After being stirred at 60 °C for 12 h, the mixture was concentrated and then purified by prep-HPLC to give compound **A26-b** (4.0 g). LCMS (M+H$^+$): 454.

Step 2: preparation of *tert*-butyl *N*-[3-[2-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (Intermediate A26)

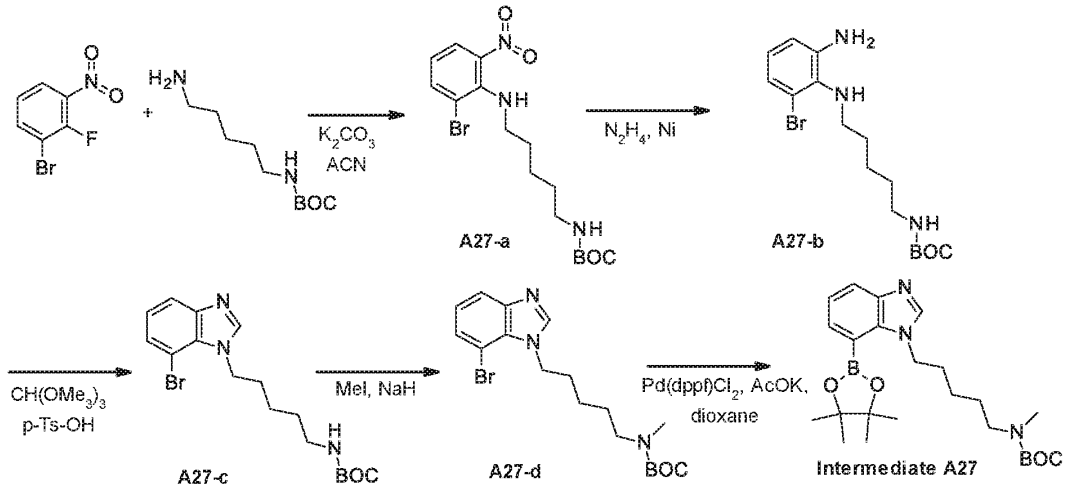
To a mixture of compound **A26-b** (2.0 g, 5.0 mmol) and bis(pinacolato)diboron (1.9 g, 7.5 mmol) in 1,4-dioxane (20 mL) was added potassium acetate (1.0 g, 10.04 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.6 g, 0.7 mmol). After being stirred at 100 °C for 2 h under N_2 atmosphere, the mixture was poured into water (20.0 mL), extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give **Intermediate A26** (0.5 g). LCMS ($M+H^+$): 446.

Intermediate A27

***tert*-butyl *N*-methyl-*N*-[5-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]pentyl]carbamate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[5-(2-bromo-6-nitro-anilino)pentyl]carbamate (compound A27-a)

A mixture of 1-bromo-2-fluoro-3-nitro-benzene (660 mg, 3 mmol), *tert*-butyl *N*-(5-aminopentyl)carbamate (667 mg, 3.3 mmol), K_2CO_3 (622 mg, 4.5 mmol) in acetonitrile (10 mL) was heated to 85 °C for 2 hours. After cooling to room temperature, the reaction mixture was partitioned between water and DCM. The separated aqueous layer were extracted with DCM, the combined organic layer was washed with brine, dried and concentrated to give crude compound **A27-a** (1.43 g), which was directly used for next step without purification. LCMS ($M+H^+$): 302.

Step 2: preparation of *tert*-butyl *N*-[5-(2-amino-6-bromo-anilino)pentyl]carbamate (compound A27-b)

To a mixture of *tert*-butyl *N*-[5-(2-bromo-6-nitro-anilino)pentyl]carbamate (compound **A27-a**, 1.43 g, 3.0 mmol) and Raney-nickel (197 mg, 3.0 mmol) in methanol (10 mL) was added hydrazine hydrate (698 mg, 9.0 mmol) dropwise, after 30 minutes later (no more bubbles), the reaction mixture was filtered carefully. The filtrate was concentrated, the residue was dissolved in EtOAc, then washed with water and brine, the organic layer was dried and concentrated to afford crude compound **A27-b** (1.54 g), which was directly used for next step without purification. LCMS ($M+H^+$): 372.

Step 3: preparation of *tert*-butyl *N*-[5-(7-bromobenzimidazol-1-yl)pentyl]carbamate (compound A27-c)

A mixture of *tert*-butyl *N*-[5-(7-bromobenzimidazol-1-yl)pentyl]carbamate (**A27-b**, 1.54 g, 2.9 mmol), trimethyl orthoformate (922 mg, 8.7 mmol) and p-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol) in anhydrous THF was stirred at room temperature for 16 hours. The reaction mixture was concentrated to give some oil; the oil was dissolved in DCM and then washed with sat.aq.$NaHCO_3$, and brine. The organic layer was dried and concentrated to afford crude compound **A27-c** (1.59 g), which was directly used for next step without purification. LCMS ($M+H^+$): 382.

Step 4: preparation of *tert*-butyl *N*-[5-(7-bromobenzimidazol-1-yl)pentyl]-*N*-methyl-carbamate (compound A27-d)

To a mixture of *tert*-butyl *N*-[5-(7-bromobenzimidazol-1-yl)pentyl]-*N*-methyl-carbamate (**A27-c**, 1.59 g, 2.08 mmol) and iodomethane (886 mg, 6.24 mmol) in anhydrous DMF (8 mL) was added NaH (333 mg, 8.32 mmol) in one portion, the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water, and then extracted with EtOAc. The separated organic layer was washed with water and brine, the organic layer was dried and concentrated and the residue was purified by flash column to afford compound **A27-d** (595 mg). LCMS ($M+H^+$): 396.

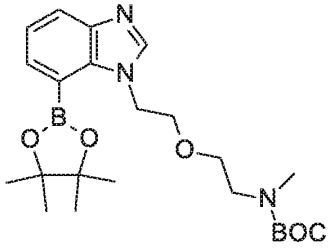
Step 5: preparation of *tert*-butyl *N*-methyl-*N*-[5-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]pentyl]carbamate (intermediate A27)

A mixture of tert-butyl *N*-[5-(7-bromobenzimidazol-1-yl)pentyl]-*N*-methyl-carbamate (compound **A27-d**, 595 mg, 1.13 mmol), bis(pinacolato)diboron (572 mg, 2.25 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (47 mg, 0.056 mmol) and potassium acetate (332 mg, 3.38 mmol) in anhydrous 1,4-dioxane (10 mL)

was heated at 110 °C for 16 hours under nitrogen with conventional heating. After cooling to room temperature, the reaction mixture was partitioned between water and DCM. The separated aqueous layer was extracted with DCM, the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated. The residue was purified by flash chromatography to afford crude Intermediate **A27** (429 mg). LCMS ($M+H^+$): 444.

Intermediate A28

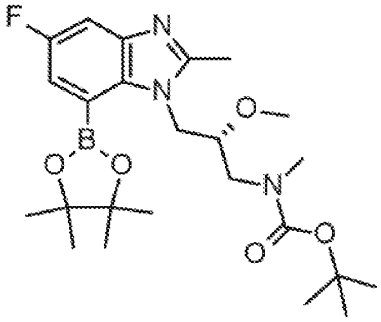
***tert*-butyl *N*-methyl-*N*-[2-[2-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]ethoxy]ethyl]carbamate**



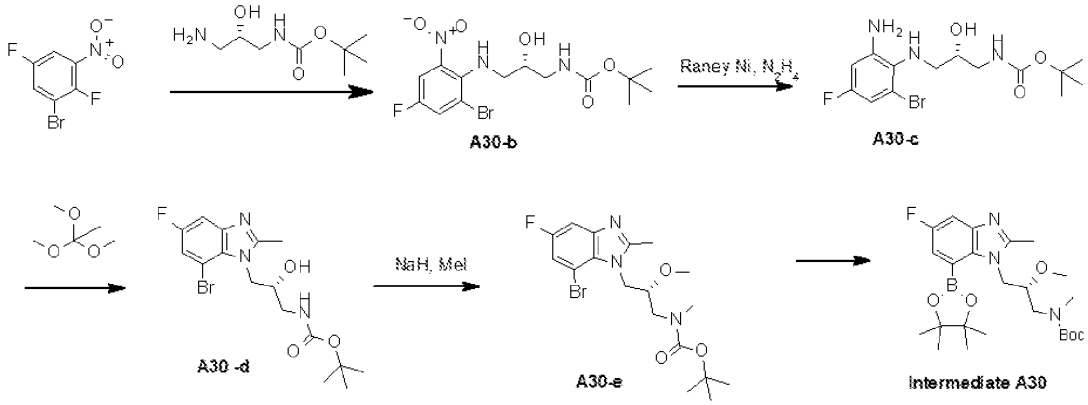
The title **Intermediate A28** was prepared in analogy to the preparation of **Intermediate A27** by replacing *tert*-butyl *N*-(5-aminopentyl)carbamate with *tert*-butyl *N*-[2-(2-aminoethoxy)ethyl]carbamate. LCMS ($M+H^+$): 446.

Intermediate A30

***tert*-butyl *N*-[(2*S*)-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate**



The title compound was prepared according to the following scheme:



Step 1~3: preparation of *tert*-butyl *N*-[(2*S*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (compound A30-d)

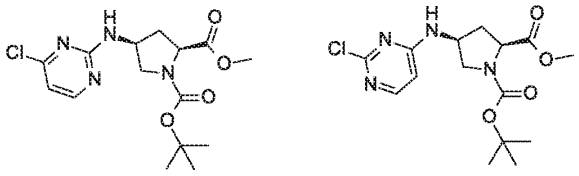
The title compound was prepared in analogy to the preparation of compound **A7-d** by using *tert*-butyl *N*-[(2*S*)-3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate, LCMS $(M+H)^+$: 400.

Step 4~5: preparation of *tert*-butyl *N*-[(2*S*)-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (Intermediate A30)

The title compound was prepared in analogy to the preparation of **Intermediate A1** by using **compound A30-d** instead of **compound A1-d.** LCMS $(M+H)^+$: 478.

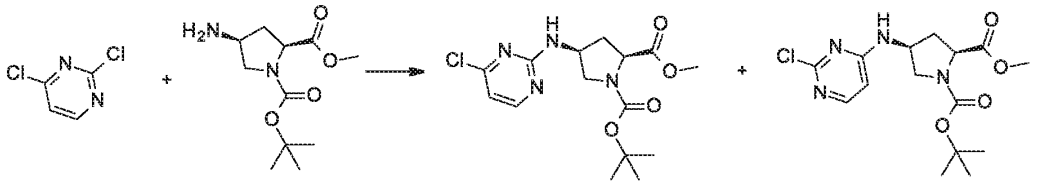
Intermediate B1 and B2

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(4-chloropyrimidin-2-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B1) and *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(2-chloropyrimidin-4-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B2)**



Intermediate B1 Intermediate B2

The title compound was prepared according to the following scheme:

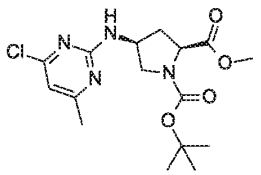


Intermediate B1 Intermediate B2

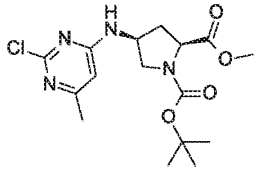
A mixture of 2,4-dichloropyrimidine (19.21 g, 128.94 mmol), 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (21 g, 85.96 mmol) and K_2CO_3 (35.64 g, 257.89 mmol) in DMF (100 mL) was stirred at 80 °C for 16 hours. Then the reaction was diluted with EtOAc, washed with water and brine, the organic layer was concentrated, the residue was purified by silica gel (eluting with 10%-30% PE in EtOAc) to give **intermediate B1** (faster eluted, 5 g), LCMS ($M+H^+$): 357; and **intermediate B2** (slower eluted, 25 g), LCMS ($M+H^+$): 357.

Intermediate B3 and B4

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(4-chloro-6-methyl-pyrimidin-2-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B3) and *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(2-chloro-6-methyl-pyrimidin-4-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B4)**

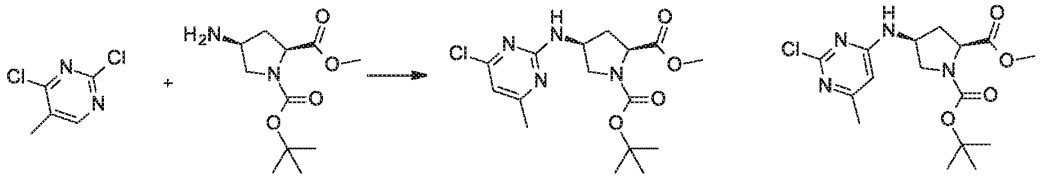


Intermediate B3



Intermediate B4

The title compound was prepared according to the following scheme:

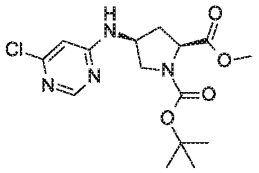


Intermediate B3 Intermediate B4

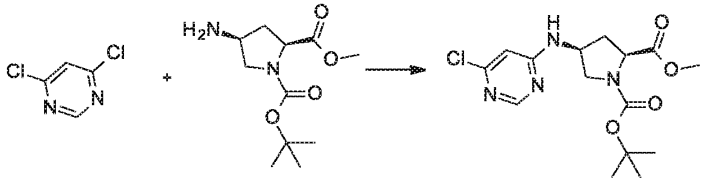
A mixture of 2,4-dichloro-6-methyl-pyrimidine (1.2 g, 7.37 mmol), 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (1.2 g, 4.91 mmol), DIPEA (634.85 mg, 4.91 mmol) and K_2CO_3 (2.04 g, 14.74 mmol) in acetonitrile (24 mL) was stirred at 80 °C for 16 hours. Then the reaction was filtered and concentrated, the residue was purified by silica gel (eluting with 10%-30% PE in EtOAc) to give **intermediate B3** (faster eluted, 300 mg), LCMS ($M+H^+$): 371; and **intermediate B4** (slower eluted, 700 mg), LCMS ($M+H^+$): 371.

Intermediate B5

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-chloropyrimidin-4-yl)amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

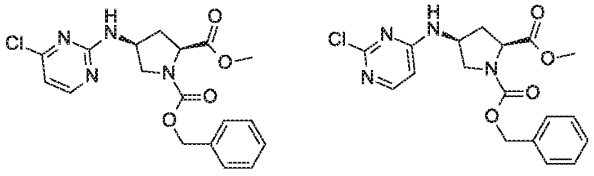


Intermediate B5

A mixture of 4,6-dichloropyrimidine (2.29 g, 15.35 mmol), 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (2.5 g, 10.23 mmol, 1 eq) and K_2CO_3 (4.24 g, 30.7 mmol) in acetonitrile (50 mL) was stirred at 80 °C for 16 hours. Then the reaction was filtered and concentrated, the residue was purified by silica gel to give **intermediate B5** (3.5 g), LCMS ($M+H^+$): 357.

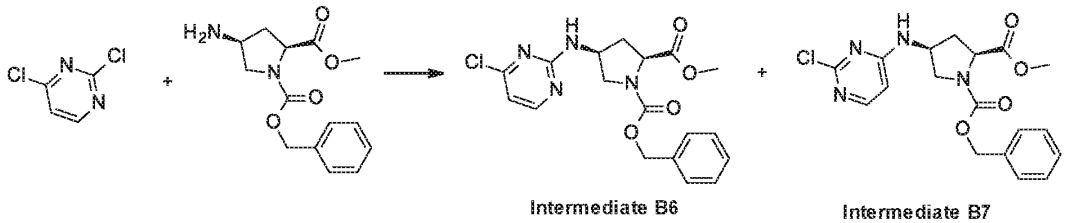
Intermediate B6 and B7

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(4-chloropyrimidin-2-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B6) and O1-benzyl O2-methyl (2*S*,4*S*)-4-[(2-chloropyrimidin-4-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B7)**



Intermediate B6 Intermediate B7

The title compound was prepared according to the following scheme



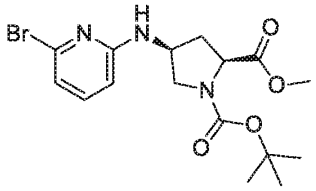
Intermediate B6 Intermediate B7

A mixture of 2,4-dichloropyrimidine (5.35 g, 35.9 mmol), 1-benzyl 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (5 g, 18 mmol), K_2CO_3 (4.97 g, 35.9 mmol) and DIPEA

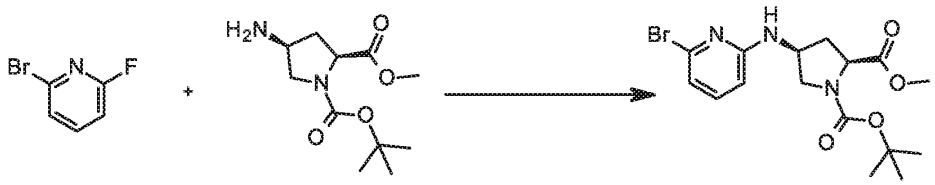
(4.64 g, 35.9 mmol) in MeCN was stirred at rt for 48 hours. Then the reaction was filtered and concentrated, the residue was purified by silica gel (eluting with 10%-30% PE in EtOAc) to give **intermediate B6** (faster eluted, 1 g), LCMS ($M+H^+$): 391; and **intermediate B7** (slower eluted, 6 g), LCMS ($M+H^+$): 391.

Intermediate B8

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

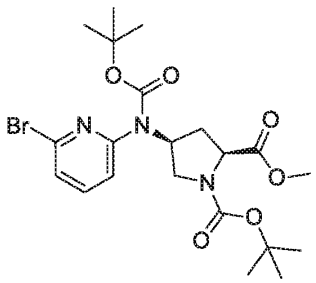


Intermediate B8

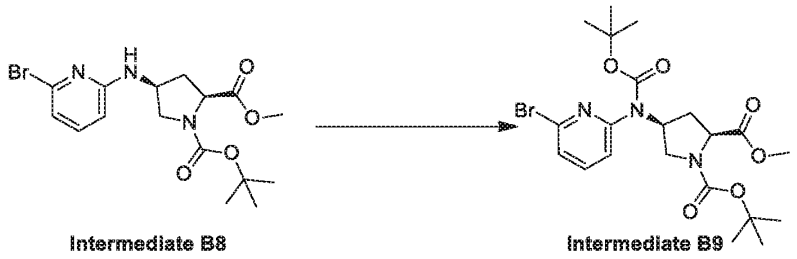
A mixture of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (28.0 g, 99.73 mmol), DIPEA (69.49 mL, 398.93 mmol) and 2-bromo-6-fluoropyridine (21.06 g, 119.68 mmol) in DMSO (140 mL) was heated to 110 °C for 16 hours. The mixture was diluted with water and extracted with EA, the organic layer was concentrated to give **intermediate B8** (34 g), LCMS ($M+H^+$): 400.

Intermediate B9

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)-*tert*-butoxycarbonyl-amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

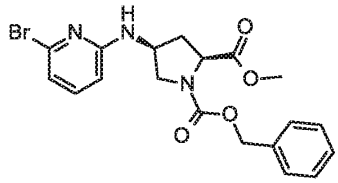


Intermediate B8 Intermediate B9

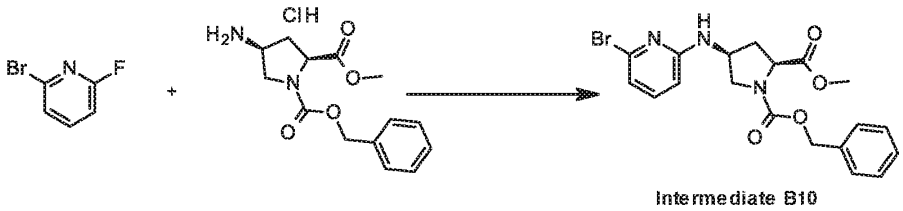
A mixture of **intermediate B8** (12.0 g, 29.98 mmol), 4-dimethylaminopyridine (0.73 g, 6 mmol), di-t-butyldicarbonate (19.63 g, 89.94 mmol) and triethylamine (10.45 mL, 74.95 mmol) in DCM (60 mL) was stirred at 40 °C for 16 hours. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give **intermediate B9** (11.8 g), LCMS ($M+H^+$): 500.

Intermediate B10

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

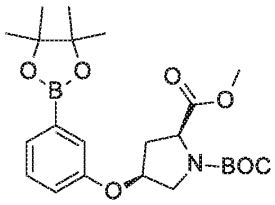


Intermediate B10

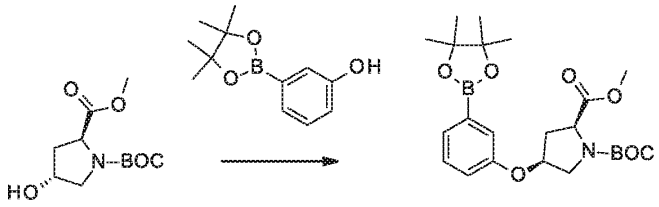
A mixture of O1-benzyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate;hydrochloride (4.7 g, 14.93 mmol), 2-bromo-6-fluoropyridine (3.15 g, 17.92 mmol) and DIPEA (13.0 mL, 74.66 mmol) in DMSO (20 mL) was stirred at 110 °C for 16 h. The mixture was concentrated, the residue was purified by prep-HPLC to give **intermediate B10** (5.1 g), LCMS (M+H+): 434.

Intermediate B11

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

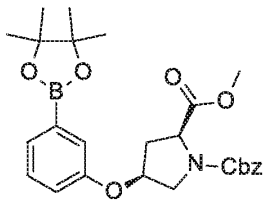


Intermediate B11

To a stirred solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (2 g, 8.15 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.79 g, 8.15 mmol) and Ph_3P (2.46 g, 9.38 mmol) in THF (50 mL) was added DIAD (1.9 g, 9.38 mmol) in THF (10 mL) dropwise at 0 °C. After being stirred at 20 °C overnight, the reaction mixture was concentrated, and the residue was s purified by silica gel to give **intermediate B11**, LCMS: $(M+H)^+$: 448.

Intermediate B12

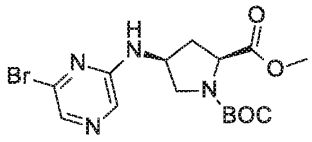
***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]pyrrolidine-1,2-dicarboxylate**



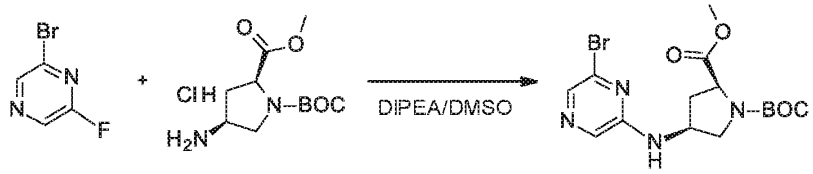
The title compound was prepared in analogy to the preparation of intermediate **B11** by using 1-benzyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate instead of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate. LCMS: $(M+H)^+$: 482.

Intermediate B13

O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[(6-bromopyrazin-2-yl)amino]pyrrolidine-1,2-dicarboxylate



The title compound was prepared according to the following scheme:

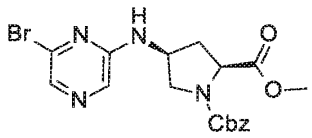


Intermediate B13

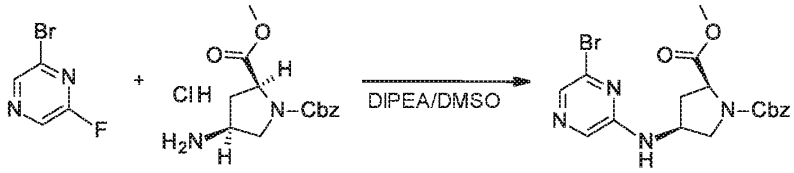
A mixture of 2-bromo-6-fluoro-pyrazine (3.12 g, 17.63 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (4.5 g, 16.03 mmol) and DIPEA (6.21 g, 8.4mL, 48.09 mmol) in DMSO was heated to 110 °C for 12 hrs. The mixture was diluted with EA, washed with water, the organic layer was dried and concentrated to give **intermediate B13** (7 g), LCMS ($M+H^+$): 401.

Intermediate B14

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromopyrazin-2-yl)amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

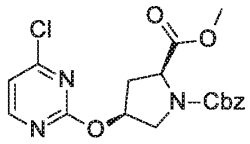


Intermediate B14

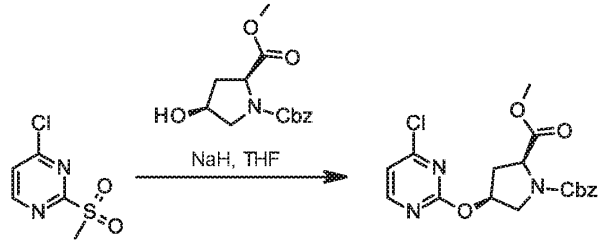
A mixture of 2-bromo-6-fluoro-pyrazine (1.05 g, 5.72 mmol), O1-benzyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (1.5 g, 4.77 mmol) and DIPEA (1.85 g, 2.5mL, 14.3 mmol) in DMSO was heated to 110 °C for 12 hrs. The mixture was diluted with EA, washed with water, the organic layer was dried and concentrated to give **intermediate B14** (2.4 g), LCMS ($M+H^+$): 435.

Intermediate B15

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-(4-chloropyrimidin-2-yl)oxypyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

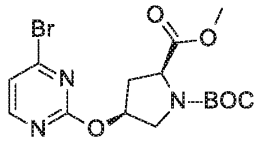


Intermediate B15

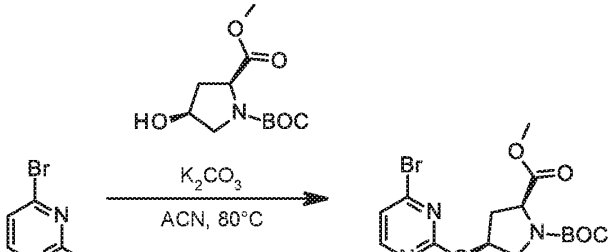
To a mixture of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (30.0 g, 107.4 mmol) and 4-chloro-2-methylsulfonyl-pyrimidine (20.0 g, 103.8 mmol) in anhydrous THF (340 mL) was added sodium hydride (60% in oil, 4.4 g, 110 mmol) in portions at room temperature under nitrogen, the resulting mixture was stirred at room temperature for 16 hours. The mixture was poured into aq.NH_4Cl (200 mL) and extracted with EtOAc. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel to give Intermediate **B15** (27.0 g). LCMS $(M+H)^+$: 392.

Intermediate B16

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-(4-bromopyrimidin-2-yl)oxypyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

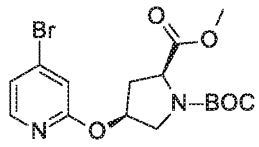


Intermediate B16

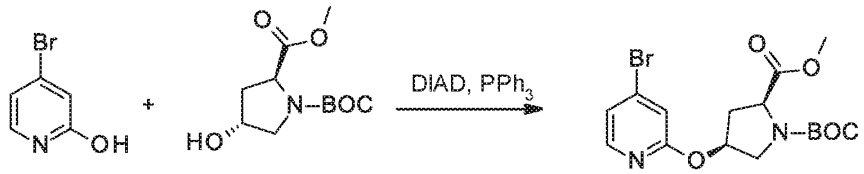
To a solution of O1-tert-*butyl* O2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (5.0 g, 20.4 mmol), potassium carbonate (8.45 g, 61.2 mmol) in acetonitrile (100 mL) was added 4-bromo-2-chloropyrimidine (3.94 g, 20.4 mmol) and then stirred at 80°C for 16 hours. The reaction mixture was poured into aq.NH_4Cl (200 mL) and then extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by column chromatography to afford Intermediate **B16** (2.69 g). LCMS $(M-100+H)^+$: 302.

Intermediate B20

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(4-bromo-2-pyridyl)oxy]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

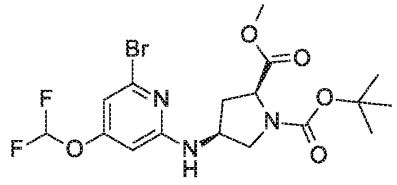


Intermediate B20

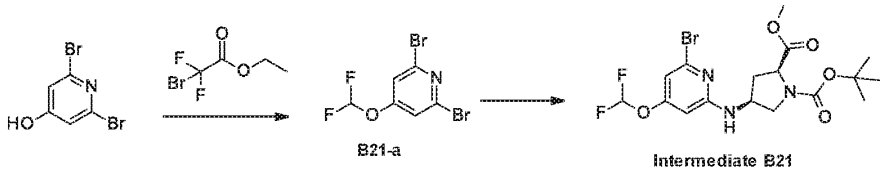
To a mixture of 4-bromo-2-hydroxypyridine (10.64 g, 61.16 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (10.0 g, 40.77 mmol) and PPh_3 (16.04 g, 61.16 mmol) in Toluene (100 mL) was added DIAD (12.37 g, 61.16 mmol) at 0 °C under N_2, then the mixture was stirred at 100 °C for 1 h. The mixture was concentrated and the residue was purified by prep-HPLC to afford **intermediate B20** (12.5 g). LCMS $(M-56+H)^+$: 345.

Intermediate B21

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(difluoromethoxy)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:



Step 1: preparation of 2,6-dibromo-4-(difluoromethoxy)pyridine (compound B21-a)

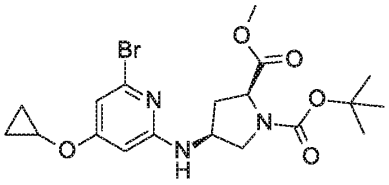
To a stirred solution of 2,6-dibromopyridin-4-ol (2.0 g, 7.91 mmol) and potassium carbonate (2.19 g, 15.82 mmol) in DMF (20 mL) was added ethyl bromodifluoroacetate (4.82 g, 23.73 mmol) at 25°C. After being stirred for 16 h at 80 °C, the reaction mixture was poured into water and extracted with EA. The organic phase was concentrated and the residue was purified by silica gel to afford compound **B21-a** (2.7 g), LCMS $(M+H)^+$: 304.

Step 2: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(difluoromethoxy)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (Intermediate B21)

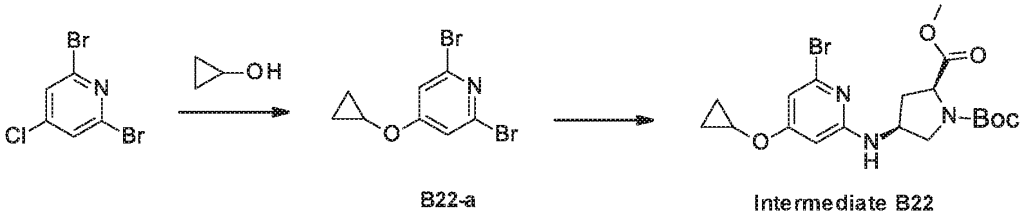
To a solution of compound **B21** (1186.79 mg, 3.92 mmol) in 1,4-dioxane (20 mL) was added O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (1 g, 3.56 mmol), cesium carbonate (3481.6 mg, 10.69 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (343.5 mg, 0.590 mmol) and tris(dibenzylideneacetone)dipalladium (0) (400.0 mg, 0.440 mmol). The reaction was stirred at 85 °C for 12 h under N_2. The reaction mixture was filtered and concentrated, the residue was purified by prep-HPLC to give **intermediate B21** (200 mg), LCMS $(M+H)^+$: 466.

Intermediate B22

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(cyclopropoxy)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:



Step 1: preparation of 2,6-dibromo-4-(cyclopropoxy)pyridine (compound B22-a)

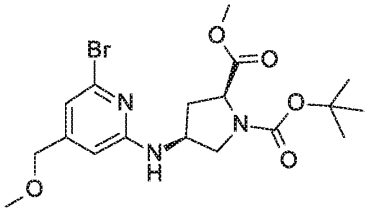
To a solution of 2,6-dibromo-4-chloro-pyridine (5.0 g, 18.4 mmol) in DMF (40 mL) was added NaH (0.88 g, 22 mmol, 60%) at 0 °C, then cyclopropanol (1.28 g, 22 mmol) was added and stirred at 0 °C for 1 h. The reaction was quenched with water and extracted with EA. The organic layer was concentrated, and the residue was purified by prep-HPLC to give compound **B22-a** (2.6 g). LCMS $(M+H)^+$: 294.

Step 2: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(cyclopropoxy)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (intermediate B22)

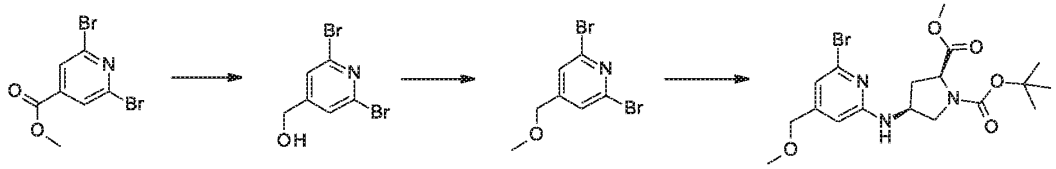
To a solution of compound **B21-a** (1.1 g, 3.7 mmol) in 1,4-dioxane (18 mL) was added O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (0.9 g, 3.2 mmol), cesium carbonate (3.1 g, 9.6 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (309 mg, 0.5 mmol) and $Pd(OAc)_2$ (120 mg, 0.5 mmol). The reaction was stirred at 90 °C for 12 h under N_2. The reaction mixture was concentrated, the residue was purified by silica gel to give **intermediate B22** (550 mg). LCMS $(M+H)^+$: 456.

Intermediate B23

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(methoxymethyl)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:



B23-a B23-b intermediate B23

Step 1: preparation of (2,6-dibromo-4-pyridyl)methanol (compound B23-a)

To a solution of methyl 2,6-dibromopyridine-4-carboxylate (2.5 g, 8.5 mmol) in methanol (30 mL) was added sodium borohydride (1.3 g, 34 mmol) at 0 °C, and then the solution was stirred at 65 °C for 3 hours. The reaction mixture was poured into ice water and adjusted the pH around 7 by adding 1 N aq. HCl solution. The mixture was extracted with EtOAc, and then the organic layer was dried and concentrated to give compound **B23-a** (2.3 g). LCMS $(M+H)^+$: 268.

Step 2: preparation of 2,6-dibromo-4-(methoxymethyl)pyridine (compound B23-b)

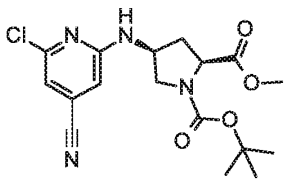
To a solution of compound **B23-a** (2.1 mg, 7.9 mmol) in THF (20 mL) was added sodium hydride (378 mg, 9.4 mmol) at 0 °C slowly, after being stirred at 0 °C for 20 mins, iodomethane (0.54 mL, 8.65 mmol) was added. After stirring at 0 °C for 2 hours, the reaction was quenched with water and extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by flash chromatography to give compound **B23-b** (1.75 g). LCMS $(M+H)^+$: 282.

Step 3: : preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-bromo-4-(methoxymethyl)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (Intermediate B23)

To a solution of compound **B23-b** (1 g, 3.56 mmol) in 1,4-dioxane (20 mL) was added O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (700 mg, 2.5 mmol), cesium carbonate (3.48 g, 10.7 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (345 mg, 0.6 mmol) and tris(dibenzylideneacetone)dipalladium (0) (391 mg, 0.43 mmol). The reaction was stirred at 85 °C for 16 hs under N_2. The reaction mixture was poured into water, and extracted with EA, the organic layer was dried and concentrated. The residue was purified by flash chromatography to give **intermediate B23** (500 mg). LCMS $(M+H)^+$: 444.

Intermediate B24

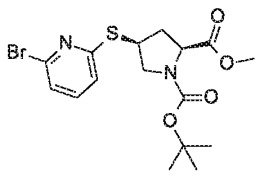
***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-chloro-4-cyano-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate**



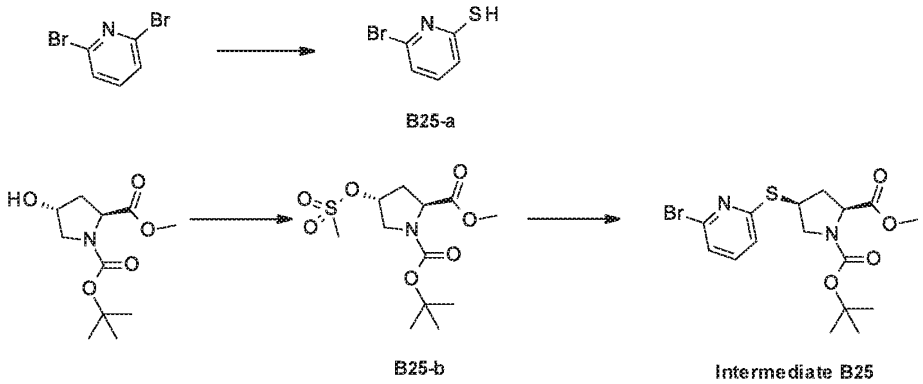
The title compounds were prepared in analogy to the preparation of **Intermediate B8** by using 2,6-dichloroisonicotinonitrile instead of 2-bromo-6-fluoropyridine, LCMS $(M+H)^+$: 381.

Intermediate B25

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)sulfanyl]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:



Step 1: preparation of 6-bromopyridine-2-thiol (compound B25-a)

A mixture of 2,6-dibromopyridine (10 g, 42 mmol), MeONa (5.7 g, 105 mmol) and methyl 3-mercaptopropionate (11 mL, 97 mmol) in DMF (100 mL) was stirred at 70 °C for 12 hours. Then the reaction was concentrated, methanol (100 mL) and MeONa (5.7 g, 105 mmol) was added to the residue, the resulted mixture was heated at 70 °C for 4 hours. The mixture was concentrated and the residue was dissolved in water (100 mL), after adjusting the solution pH to 5 with FA, a solid precipitated, which was collected by filtration to give compound **B25-a** (1.9 g). LCMS $(M+H)^+$: 190.

Step 2: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*R*)-4-methylsulfonyloxypyrrolidine-1,2-dicarboxylate (compound B25-b)

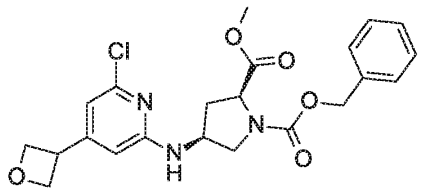
To a solution of O1-*tert*-butyl O2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (15 g, 61 mmol) and TEA (18.5 g, 183.5 mmol) in anhydrous THF (100 mL) was added Ms_2O (13.85 g, 79.5 mmol) in THF (30 mL) dropwise, then the reaction mixture was stirred for 4 h at 50 °C. The reaction mixture was quenched with $NaHCO_3$, extracted with EA, the organic phase was dried and concentrated to give **compound B25-b** (18 g). LCMS $(M+H)^+$: 324.

Step 3: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)sulfanyl]pyrrolidine-1,2-dicarboxylate (Intermediate B25)

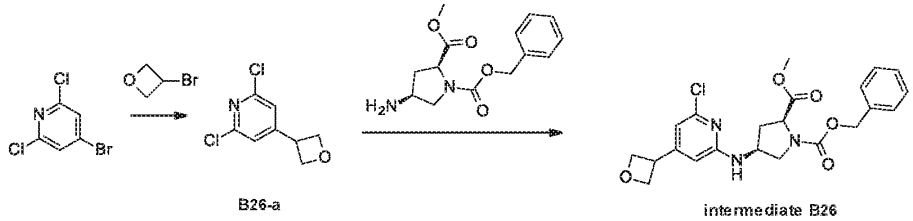
A mixture of compound **B25-a** (1.9 g, 10 mmol), K_2CO_3 (2.1 g, 15 mmol) and compound **B25-b** (3.9 mg, 12 mmol) in anhydrous DMF (15 mL) was stirred at 70 °C for 12 hours. The reaction mixture was poured into water and then extracted with EA. The combined organic layer was dried and concentrated, the residue was purified by column chromatography to give **intermediate B25** (1.9 g). LCMS $(M\text{-}Boc+H)^+$: 317.

Intermediate B26

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[6-chloro-4-(oxetan-3-yl)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (intermediate B26)**



The title compound was prepared according to the following scheme:



Step 1: preparation of 2,6-dichloro-4-(oxetan-3-yl)pyridine (compound B26-a)

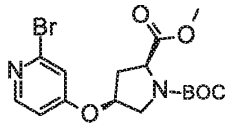
To a 15 mL vial was added 4-bromo-2,6-dichloro-pyridine (500.0 mg, 2.2 mmol), 3-bromooxetane (392.42 mg, 2.86 mmol), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (24.72 mg, 0.020 mmol), $NiCl_2$.dtbbpy (4.39 mg, 0.010 mmol), TTMSS (547.97 mg, 2.2 mmol), Na_2CO_3 (467.19 mg, 4.41 mmol) in 1,2-dimethoxyethane (22.04 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25 °C for 14 h (Three batch, total 1.5 g). Then the mixture was concentrated, the residue was purified by prep-HPLC to give compound **B26-a** (280 mg). LCMS $(M+H)^+$: 204.

Step 2: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[6-chloro-4-(oxetan-3-yl)-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (intermediate B26)

To a mixture of compound **B26-a** (225 mg, 1.1 mmol) in 1,4-dioxane (6 mL) was added O1-benzyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (300.0 mg, 0.950 mmol), cesium carbonate (931.62 mg, 2.86 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (91.92 mg, 0.160 mmol) and $Pd(OAc)_2$ (35.58 mg, 0.160 mmol). The reaction was stirred at 85 °C for 12 h under N_2. The reaction mixture was purified by silica gel to give intermediate **B26** (210 mg). LCMS $(M+H)^+$: 446.

Intermediate B30

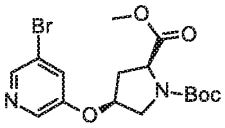
***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(2-bromo-4-pyridyl)oxy]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared in the analogy to the preparation of intermediate **B20** by using 2-bromo-4-hydroxypyridine instead of 4-bromo-2-hydroxypyridine. LCMS ($M+H^+$): 401.

Intermediate B31

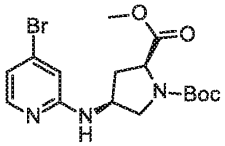
***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(5-bromo-3-pyridyl)oxy]pyrrolidine-1,2-dicarboxylate**



The title compound was prepared in the analogy to the preparation of intermediate **B20** by using 3-bromo-5-hydroxypyridine instead of 4-bromo-2-hydroxypyridine. LCMS ($M+H^+$): 401.

Intermediate B32

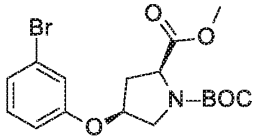
***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(4-bromo-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate**



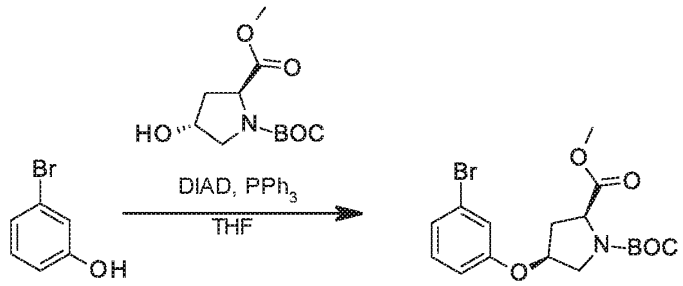
The title compound was prepared in the analogy to the preparation of intermediate **B8** by using 4-bromo-2-fluoropyridine instead of 2-bromo-6-fluoropyridine. LCMS ($M+H^+$): 400.

Intermediate B33

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-(3-bromophenoxy)pyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:

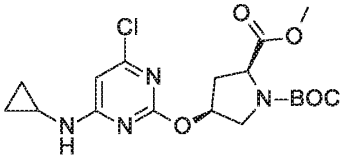


Intermediate B33

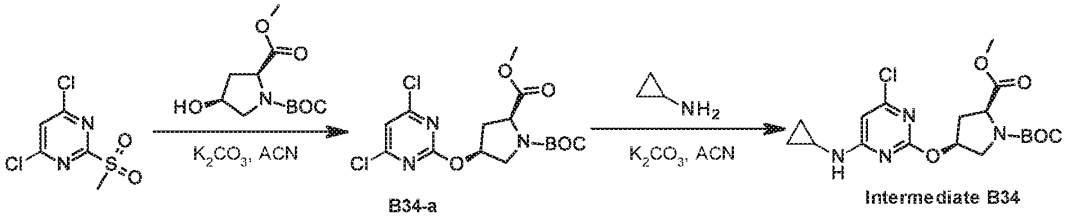
To a mixture of 3-bromophenol (4.23 g, 24.5 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (4 g, 16.3 mmol), triphenylphosphine (6.42 g, 24.5 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate (4.95 g, 24.5 mmol) dropwise. The resulting mixture was stirred at room temperature for 4 hours, then concentrated and the residue was purified by flash chromatography to afford **Intermediate B33** (5.5 g). LCMS $(M+H)^+$: 400.

Intermediate B34

***O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[4-chloro-6-(cyclopropylamino)pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate**



The title compound was prepared according to the following scheme:



Step 1: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-(4,6-dichloropyrimidin-2-yl)oxypyrrolidine-1,2-dicarboxylate (compound B34-a)

A mixture of 4,6-dichloro-2-methylsulfonyl-pyrimidine (2.0 g, 8.81 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (2.2 g, 8.81 mmol) and potassium carbonate (3.6 g, 26.42 mmol) in acetonitrile (20 mL) was stirred at room temperature for 1 hr. The reaction was quenched by water, then the mixture was extracted with EtOAc for three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated

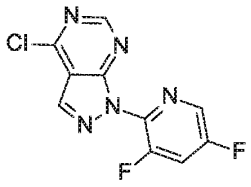
under reduced pressure to give a residue. The residue was purified by flash column chromatography to afford compound **B34-a** (1.0 g) as a colorless oil. LCMS $(M+H)^+$: 392.

Step 2: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[4-chloro-6-(cyclopropylamino)pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (Intermediate B34)

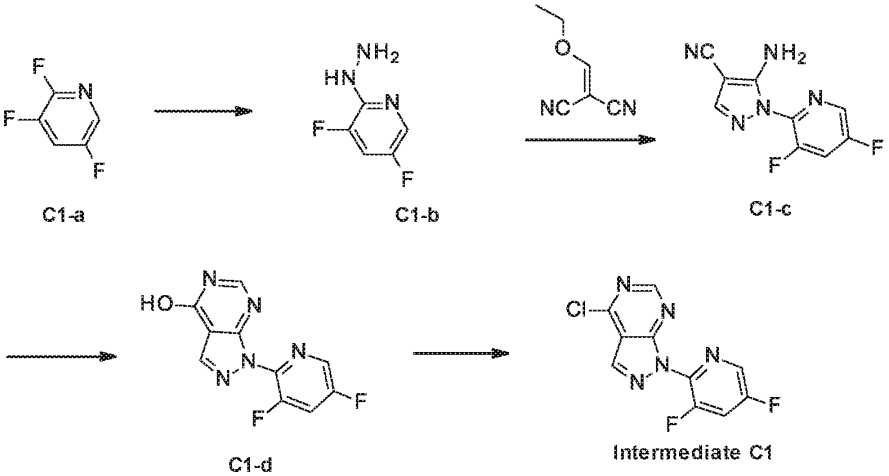
To a mixture of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-(4,6-dichloropyrimidin-2-yl)oxypyrrolidine-1,2-dicarboxylate (1.0 g, 2.55 mmol) and cyclopropylamine (0.18 mL, 2.55 mmol) in acetonitrile (1 mL) was added potassium carbonate (1.06 g, 7.65 mmol), the resulting mixture was stirred at 90 °C for 1 hr. The reaction was quenched by water, then the mixture was extracted with EtOAc for three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give desired **Intermediate B34** (0.83 g) as a light yellow oil. LCMS $(M+H)^+$: 413.

Intermediate C1

4-chloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1: preparation of (3,5-difluoro-2-pyridyl)hydrazine (compound C1-b)

To a solution of 2,3,5-trifluoropyridine (compound **C1-a**, 6.0 g, 45 mmol) in ethanol (60 mL) was added hydrazine hydrate (21.87 mL, 450 mmol). After being stirred at 65 °C for 16 h, the reaction mixture was concentrated to afford compound **C1-b** (6.5 g). LCMS $(M+H)^+$: 146.

Step 2: preparation of 5-amino-1-(3,5-difluoro-2-pyridyl)pyrazole-4-carbonitrile (compound C1-c)

A mixture of (3,5-difluoro-2-pyridyl)hydrazine (compound **C1-b**, 6.5 g, 45 mmol), DIEA (11.74 mL, 67.39 mmol) and ethoxymethylenemalononitrile (6.05 g, 50 mmol) in ethanol (65 mL) was stirred at 80 °C for 16 hrs. After cooling the reaction mixture to 0 °C, solid precipitated, which was collected and dried to afford compound **C1-c** (3.8 g). LCMS $(M+H)^+$: 222.

Step 3: preparation of 1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C1-d)

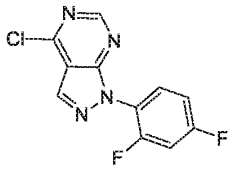
A solution of 5-amino-1-(3,5-difluoro-2-pyridyl)pyrazole-4-carbonitrile (compound **C1-c**, 3.8 g, 17.18 mmol) in formic acid (38.0 mL, 17.18 mmol) was stirred at 100 °C for 16 hrs. The reaction was concentrated and the solid was washed with MeCN to afford compound **C1-d** (2.9 g). LCMS $(M+H)^+$: 250.

Step 4: preparation of 4-chloro-1-(3,5-difluoro-2-pyridyl) pyrazolo[3,4-d] pyrimidine (Intermediate C1)

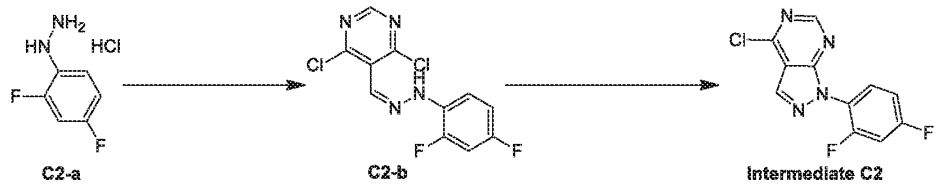
To a solution of 1-(3,5-difluoro-2-pyridyl) pyrazolo[3,4-d]pyrimidin-4-ol (compound **C1-d**, 1.8 g, 7.22 mmol) was added phosphorus oxychloride (19.29 mL, 206.91 mmol) and then stirred at 100 °C for 1 h. The reaction mixture was concentrated and the residue was diluted with DCM (10 mL). The mixture was concentrated and the residual solid was washed with DCM to give **intermediate C1** (1.33 g). LCMS $(M+H)^+$: 268.

Intermediate C2

4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1: preparation of *N*-[(4,6-dichloropyrimidin-5-yl)methyleneamino]-2,4-difluoro-aniline (compound C2-b)

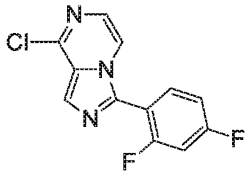
A mixture of 4,6-dichloro-5-pyrimidinecarbaldehyde (**compound C2-a**, 20.0 g, 113 mmol), 2,4-difluorophenylhydrazine hydrochloride (24.91 g, 137.95 mmol) and potassium carbonate (21.17 g, 153.21 mmol) in DCM (400 mL) was stirred at 20 °C for 12 h. Then the mixture was washed with water and brine, the organic layer was dried and concentrated to give the crude compound **C2-b** (34.5 g). LCMS $(M+H)^+$: 303.

Step 2: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C2)

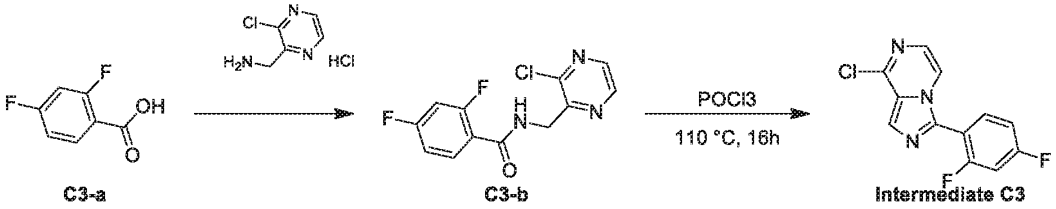
To a solution of *N*-[(4,6-dichloropyrimidin-5-yl)methyleneamino]-2,4-difluoro-aniline (compound **C2-b**,18.5 g, 61.04 mmol) in NMP (185 mL) was added 4A molecular sieve (2 g). The mixture was stirred at 110 °C for 40 h. The reaction was cooled and 300 mL of water was added into the reaction mixture within 20 min. The precipitate was collected and dried to give **intermediate C2** (8.5 g). LCMS $(M+H)^+$: 267.

Intermediate C3

8-chloro-3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazine



The title compound was prepared according to the following scheme:.



Step 1: preparation of 8-chloro-3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazine (compound C3-b)

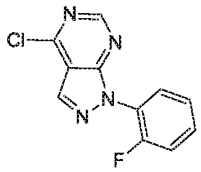
To a mixture of 2,4-difluorobenzoic acid (**compound C3-a**, 8 g, 50.6 mmol) in DCM (100 mL) was added thionyl chloride (260 mL) at 25 °C. After being stirred at 80 °C for 2 h, the mixture was concentrated and diluted with DCM. Then to the reaction mixture was added (3-chloropyrazin-2-yl)methanamine hydrochloride (9.12 g, 50.66 mmol) and triethylamine (14.33 mL, 102.78 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. Then the mixture was concentrated, the residue was diluted with DCM (400 mL), washed with water (500 mL) and brine. The organic layer was dried and concentrated to afford **compound C3-b** (7620 mg). LCMS $(M+H)^+$: 284.

Step 2: preparation of 8-chloro-3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazine (Intermediate C3)

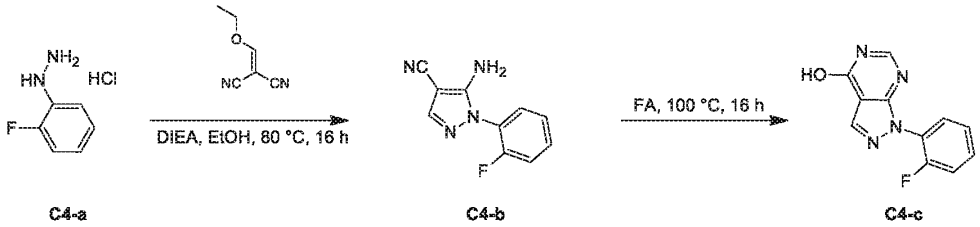
To a solution of compound **C3-b** (16.2 g, 57.11 mmol) in toluene (320 mL) was added phosphorus oxychloride (26.62 mL, 285.55 mmol). The mixture was stirred at 110 °C for 16 h. Then mixture was concentrated, the residue was added to a vigorous stirring mixture of EA (300 mL, contained 10 mL of triethylamine) and 50 g $NaHCO_3$ in 300 mL water at 0 °C. The organic layer was separated, dried and concentrated to give **intermediate C3** (15.4 g). LCMS $(M+H)^+$: 266.

Intermediate C4

4-chloro-1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 5-amino-1-(2-fluorophenyl)pyrazole-4-carbonitrile (compound C4-b)

To a solution of ethoxymethylenemalononitrile (11.27 g, 92.26 mmol) in ethanol (70 mL) was added 2-fluorophenylhydrazine hydrochloride (compound **C4-a**, 15.0 g, 92.26 mmol) and DIEA (49.27 mL, 276.77 mmol). The mixture was stirred at 25 °C for 1 h and then at 80 °C for 16 h. The reaction mixture was concentrated and the residue was purified by column chromatography to give compound **C4-b** (17.8 g). LCMS $(M+H^+)$: 202.

Step 2: preparation of 1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C4-c)

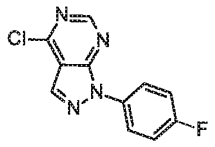
A solution of 5-amino-1-(2-fluorophenyl)pyrazole-4-carbonitrile (compound **C4-b**, 5.0 g, 24.73 mmol) in formic acid (25.0 mL, 24.73 mmol) was stirred at 100 °C for 16 h. Then the mixture was concentrated, the crude product was recrystallized in MeOH to give compound **C4-c** (3.5 g), LCMS ($M+H^+$): 231.

Step 3: preparation of 4-chloro-1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C4)

A mixture of phosphorus oxychloride (10.0 mL, 107.28 mmol) and 1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (**C4-c**, 1.5 g, 6.52 mmol) was stirred at 100 °C for 3 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted with DCM (50 mL) twice. The organic layer was dried and concentrated to give **intermediate C4** (1.4 g), LCMS ($M+H^+$): 248.

Intermediate C5

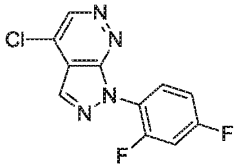
4-chloro-1-(4-fluorophenyl)pyrazolo[3,4-d]pyrimidine 4



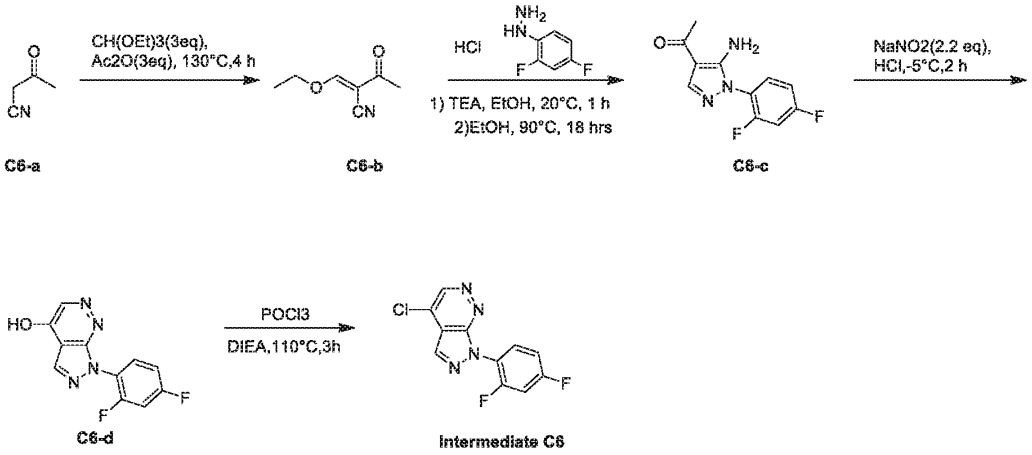
The title compound was prepared in analogy to the preparation of intermediate **C4** by using 4-fluorophenylhydrazine hydrochloride instead of 2-fluorophenylhydrazine hydrochloride. LCMS ($M+H^+$): 248.

Intermediate C6

4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazine



The title compound was prepared according to the following scheme:



Step 1: preparation of (2E)-2-(ethoxymethylene)-3-oxo-butanenitrile (compound C6-b)

A mixture of triethyl orthoformate (90.08 mL, 541.58 mmol) and 3-oxobutanenitrile (compound **C6-a**15.0 g, 180.53 mmol) in acetic anhydride (18.4 g, 180.53 mmol) was stirred at 130 °C for 4 h under N_2 atmosphere. The reaction was concentrated to give the crude product compound **C6-b** (25 g), LCMS ($M+H^+$): 140.

Step 2: preparation of 1-[5-amino-1-(2,4-difluorophenyl)pyrazol-4-yl]ethanone (compound C6-c)

To a solution of (2E)-2-(ethoxymethylene)-3-oxo-butanenitrile (compound **C6-b**, 25.0 g, 89.83 mmol) in ethanol (80 mL) was added triethylamine (25.04 mL, 179.66 mmol) at 0 °C, then the mixture was stirred at 0 °C for 30 mins, then 2,4-difluorophenylhydrazine hydrochloride (16221.7 mg, 89.83 mmol) was added slowly (about 30 min) at 0 °C. The reaction mixture was stirred at 90 °C for 18 h and then concentrated; the residue was purified by flash chromatography to give compound **C6-c** (5 g), LCMS ($M+H^+$): 238.

Step 3: preparation of 1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-ol (compound C6-d)

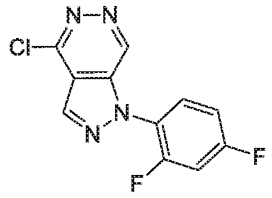
A mixture of 1-[5-amino-1-(2,4-difluorophenyl)pyrazol-4-yl]ethanone (compound **C6-c**, 4 g, 16.86 mmol) in hydrochloride acid (50 mL) and water (25 mL) was stirred at -5 °C for 1 h. Then sodium nitrite (2560 mg, 37 mmol) in water (25 mL) was added, the mixture was stirred at -5°C for 1 h and 25 °C for 1 h. After heating at 65°C for 4 h, the reaction mixture was adjusted pH to 7 using aq.$NaHCO_3$ solution at 0 °C. Then the mixture was extracted with EtOAc, dried and concentrated to give compound **C6-d** (4 g), LCMS ($M+H^+$): 248.

Step 4: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazine (Intermediate C6)

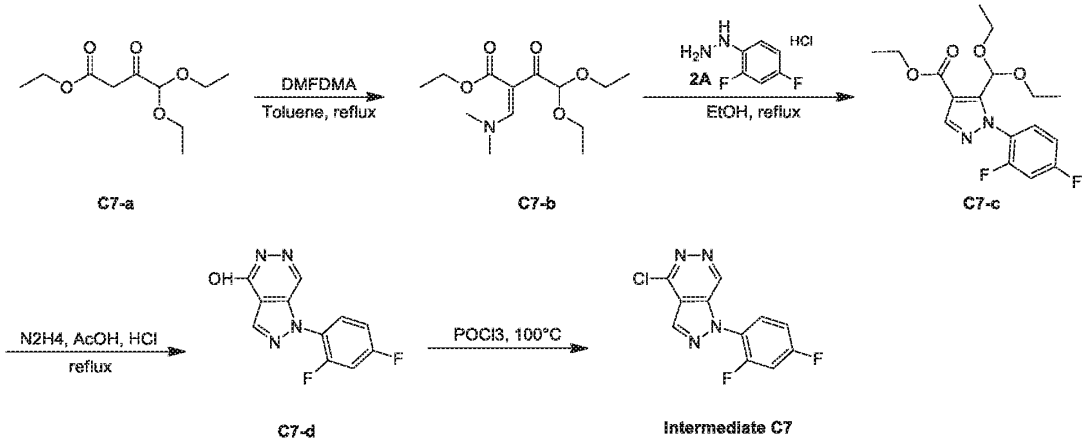
A mixture of 1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-ol (compound **C6-d**, 5 g, 20.15 mmol) and DIPEA (7.02 mL, 40.29 mmol) in phosphorus oxychloride (50.0 mL) was heated to 110 °C for 3 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted with DCM (50 mL) twice. The organic layer was dried and concentrated to give the crude product, which was purified by flash chromatography to give **intermediate C6** (395 mg), LCMS ($M+H^+$): 266.

Intermediate C7

4-chloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1: preparation of ethyl (2Z)-2-(dimethylaminomethylene)-4,4-diethoxy-3-oxo-butanoate (compound C7-b)

A mixture of ethyl 4,4-diethoxy-3-oxo-butanoate (2.0 g, 9.16 mmol) and DMF dimethyl acetal (1.31 g, 11 mmol) in toluene (20 mL) was stirred at 110 °C for 2 h. The reaction mixture was concentrated to give compound **C7-b** (2.45 g). LCMS ($M+H)^+$: 274.

Step 2: preparation of ethyl 5-(diethoxymethyl)-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound C7-c)

A mixture of ethyl (2Z)-2-(dimethylaminomethylene)-4,4-diethoxy-3-oxo-butanoate (compound **C7-b**, 1.95 g, 7.13 mmol) and 2,4-difluorophenylhydrazine hydrochloride (1.42 g,

7.85 mmol) in ethanol (20 mL) was stirred at 80 °C for 1 h. Then the reaction was concentrated, the residue was diluted with EA, washed with water and brine. The organic layer was dried and concentrated; the residue was purified by flash column chromatography to give compound **C7-c** (2 g). LCMS $(M+H)^+$: 355.

Step 3: preparation of 1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazin-4-ol (compound C7-d)

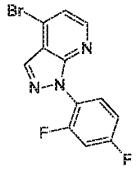
To a solution of ethyl-5-(diethoxymethyl)-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (**compound C7-c**, 1.0 g, 2.82 mmol) in Acetic acid (10 mL) was added hydrazine hydrate (0.28 g, 5.64 mmol). The reaction was stirred at 90 °C for 12 h. Then hydrazine hydrate (0.28 g, 5.64 mmol, 2 eq) was added and the reaction was stirred at 120 °C for 12 h. After cooling to 0°C, a solid precipitated, which was collected and dried in vacuo to give compound **C7-d** (500 mg). LCMS $(M+H)^+$: 249.

Step 4: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazine (Intermediate C7)

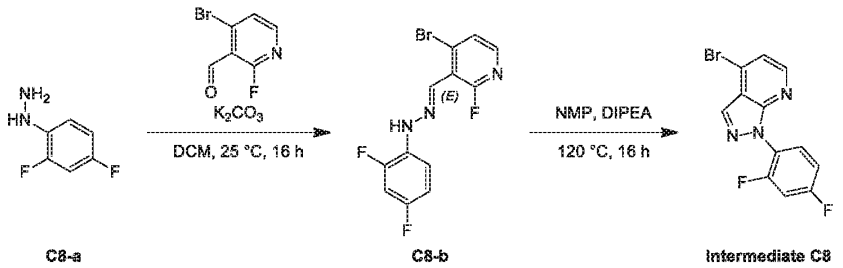
A solution of 1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazin-4-ol (**C7-d**, 100.0 mg, 0.400 mmol) in phosphoryl trichloride (1.06 mL, 11.35 mmol) was stirred at 100 °C for 12 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted with DCM (50 mL) twice. The organic layer was dried and concentrated, the crude compound was purified by pre-TLC to give **intermediate C7** (50 mg). LCMS $(M+H)^+$: 267.

Intermediate C8

4-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridine



The title compound was prepared according to the following scheme:



Step 1: preparation of *N*-[(4-bromo-2-fluoro-3-pyridyl)methyleneamino]-2,4-difluoro-aniline (compound C8-b)

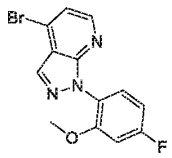
A mixture of 4-bromo-2-fluoro-pyridine-3-carbaldehyde (1.5 g, 7.35 mmol), 2,4-difluorophenylhydrazine hydrochloride (1.5 g, 8.31 mmol) and potassium carbonate (1.2 g, 8.68 mmol) in DCM (30 mL) was stirred at 25 °C for 16 h. The mixture was diluted with EA (50 mL), washed with water (100 mL) and brine (100 mL). The organic layer was dried and concentrated, the residue was purified by silica gel to afford compound **C8-b** (2.35 g). LCMS $(M+H)^+$: 330.

Step 2: preparation of 4-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridine (Intermediate C8)

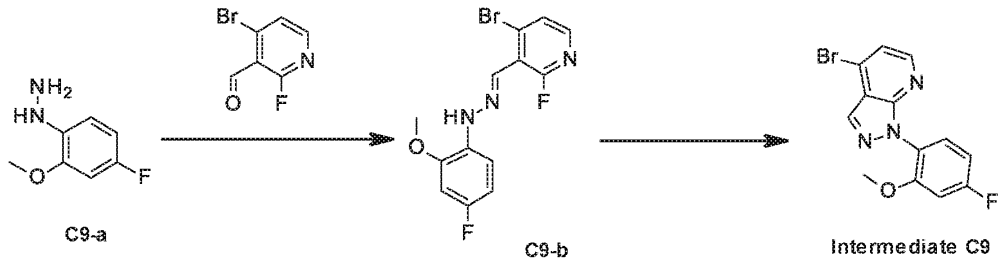
A mixture of compound **C8-b** (2.25 g, 6.82 mmol) and DIPEA (2.4 mL, 14.51 mmol) in anhydrous NMP (40 mL) was stirred for 16 h at 120 °C. The mixture was diluted with EA (50 mL), washed with water (100 mL) and brine (100 mL). The organic layer was dried and concentrated; the residue was purified by silica gel to afford **intermediate C8** (644 mg). LCMS $(M+H)^+$: 310.

Intermediate C9

4-bromo-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridine



The title compound was prepared according to the following scheme:



Step 1: preparation of *N*-[(4-bromo-2-fluoro-3-pyridyl)methyleneamino]-4-fluoro-2-methoxy-aniline (compound C9-b)

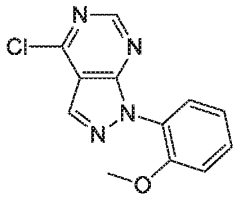
A mixture of 4-bromo-2-fluoro-pyridine-3-carbaldehyde (3.0 g, 14.71 mmol), (4-fluoro-2-methoxy-phenyl)hydrazine hydrochloride (compound **C9-a**, 3.5 g, 14.9 mmol) and potassium carbonate (2.4 g, 17.37 mmol) in DCM (30 mL) was stirred at 25 °C for 16 h. The mixture was diluted with EtOAc (150 mL), washed with water and brine. The organic layer was dried and concentrated to give compound **C9-b** (4.2 g). LCMS $(M+H)^+$: 342.

Step 2: preparation of 4-bromo-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridine (Intermediate C9)

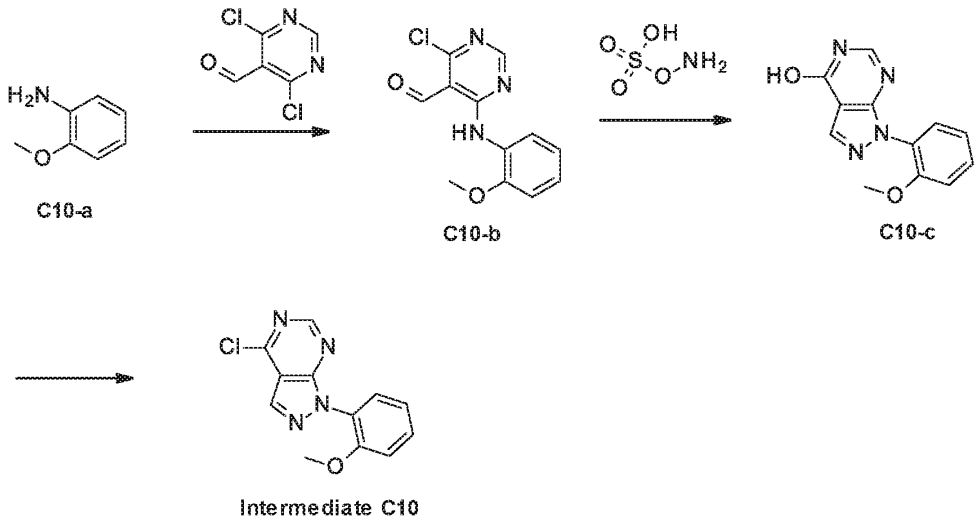
A mixture of *N*-[(4-bromo-2-fluoro-3-pyridyl)methyleneamino]-4-fluoro-2-methoxy-aniline (compound **C9-b**, 4.2 g, 12.28 mmol) and DIPEA (4.32 mL, 26.13 mmol) in anhydrous NMP (60 mL) was stirred for 72 h at 130 °C. The reaction was poured into water (200 mL) and extracted with EtOAc (150 mL). The organic phase dried and concentrated, the residue was purified by prep-HPLC to afford **intermediate C9** (1066 mg). LCMS $(M+H)^+$: 310.

Intermediate C10

4-chloro-1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1: preparation of 4-chloro-6-(2-methoxyanilino)pyrimidine-5-carbaldehyde (compound C10-b)

A mixture of O-anisidine (5.0 g, 40.6 mmol), TEA (8.2 g, 81.2 mmol) and 4,6-dichloro-5-pyrimidinecarbaldehyde (**C10-a** 7.19 g, 40.6 mmol) in chloroform (20 mL) was stirred at 20 °C for 12 h. To the mixture was added water (50 mL) and EtOAc(50 mL), the mixture was filtered and the filter cake was collected to give compound **C10-b** (8.1 g). LCMS $(M+H)^+$: 264.

Step 2: preparation of 1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C10-c)

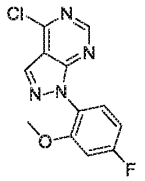
To a solution of 4-chloro-6-(2-methoxyanilino)pyrimidine-5-carbaldehyde (**C10-b** ,1.0 g, 3.79 mmol) in ACN (20 mL) was added hydroxylamine-o-sulfonic acid (2.57 g, 22.75 mmol), and the reaction mixture was stirred at 20 °C for 12 h. Then aq. NaOH (1N, 16 mL) was added and the reaction mixture was stirred at 20 °C for another 4 h. The reaction mixture was poured into water (100 mL), extracted with EA (150 mL), the organic layer was dried and concentrated. The residue was purified by prep-HPLC to give compound **C10-c** (102 mg). LCMS $(M+H)^+$: 244.

Step 3: preparation of 4-chloro-1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C10)

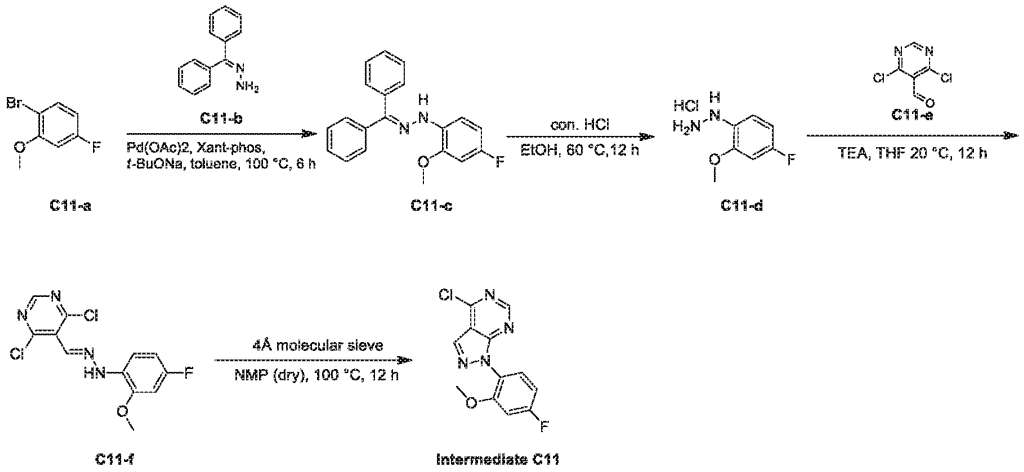
A solution of compound **C10-c** (102 mg, 0.42 mmol) in $POCl_3$ (5.0 mL) was stirred at 80 °C for 2 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted with DCM (50 mL) twice. The organic layer was dried and concentrated to give **intermediate C10** (80 mg). LCMS $(M+H)^+$: 261.

Intermediate C11

4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of *N*-(benzhydrylideneamino)-4-fluoro-2-methoxy-aniline (compound C11-c)

A solution of 2-bromo-5-fluoroanisole (compound **C11-a**, 10.0 g, 48.78 mmol), benzophenone hydrazone (compound **C11-b**, 10.0 g, 50.96 mmol), palladium (II) acetate (200.0 mg, 0.89 mmol), xant-phos (400.0 mg, 0.69 mmol) and sodium *tert*-butoxide (6.7 g, 69.72 mmol) in anhydrous toluene (150.0 mL) was stirred for 12 h at 100 °C under N_2. The mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried and concentrated to give crude product, which was recrystallized from PE (200 mL) to give compound **C11-c** (12 g), used in next step directly. LCMS $(M+H)^+$: 321.

Step 2: preparation of (4-fluoro-2-methoxy-phenyl)hydrazine hydrochloride (compound C11-d)

A mixture of compound **C11-c** (11.0 g, 34.34 mmol) in ethanol (100.0 mL) and con. HCl (10.0 mL, 120 mmol) was stirred for 12 h at 60 °C. The mixture was concentrated, and then EtOAc (100 mL) was added. After stirring for 5 mins, the mixture was filtered, the filter cake was washed with PE (50 mL) and dried to give compound **C11-d** (4.5 g), which was used in next step directly. LCMS $(M+H)^+$: 141.

Step 3: preparation of *N*-[(4,6-dichloropyrimidin-5-yl)methyleneamino]-4-fluoro-2-methoxy-aniline (compound C11-f)

A mixture of compound **C11-d** (4.3 g, 22.32 mmol), 4,6-dichloro-5-pyrimidinecarbaldehyde (compound **C11-e,** 4.3 g, 24.3 mmol) and triethylamine (3.5 g, 34.59 mmol) in anhydrous THF (100.0 mL) was stirred for 12 h at 20 °C. The reaction solution was diluted with EtOAc (100.0 mL), washed with water and brine. The organic layer was dried and

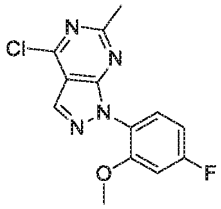
concentrated to give crude compound **C11-f** (5.2 g), used in next step directly. LCMS $(M+H)^+$: 315.

Step 4: preparation of 4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C11)

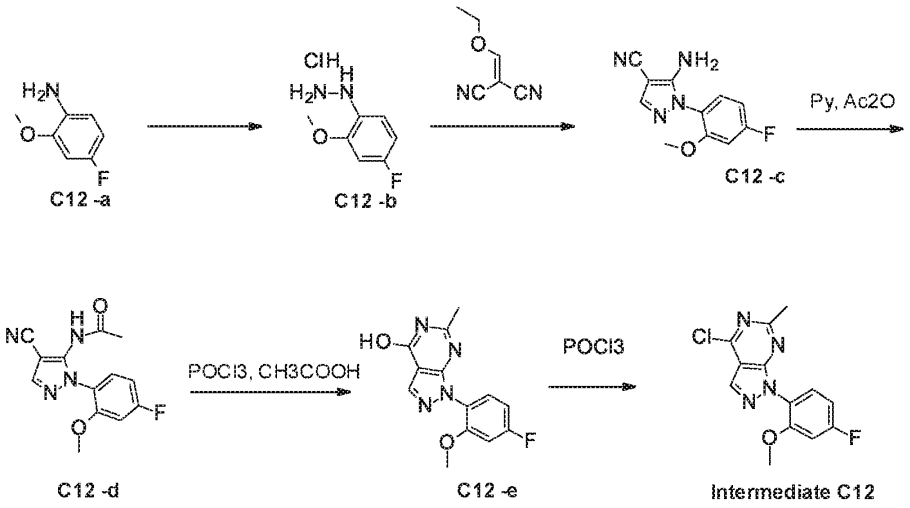
A mixture of *N*-[(E)-(4,6-dichloropyrimidin-5-yl)methyleneamino]-4-fluoro-2-methoxy-aniline (compound **C11-f**, 4.0 g, 12.69 mmol) and 4A MS (1.0 g) in anhydrous DMF (10.0 mL) was stirred for 12 h at 100 °C. The mixture was diluted with EtOAc (200.0 mL), washed with water and brine. The organic layer was dried and concentrated to give crude product, which was purified by prep-TLC to give **intermediate C11** (747 mg). LCMS $(M+H)^+$: 279.

Intermediate C12

4-chloro-1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of ((4-fluoro-2-methoxy-phenyl)hydrazine hydrochloride (compound C12-b)

To a stirring solution of 4-fluoro-2-methoxy-aniline (compound **C12-a,** 30.0 g, 212.55 mmol) in HCl/water (297.58 mL, 1488 mmol) was added a solution of $NaNO_2$ (22.0 g, 318.9 mmol) in water (300 mL) at 0 °C. After stirring for 30 mins, a solution of tin (II) chloride dihydrate (119.92 g, 531.45 mmol) in conc. HCl (53.14 mL, 637.65 mmol) was added dropwise.

The mixture was stirred at 15 °C for 12 h. The mixture was adjusted to pH 10-12 with 20% aqueous sodium hydroxide, and then extracted with EA. The organic phase were dried and concentrated. The residue was acidified with HCl in dioxane to pH 3~4, then the solid was collected and dried to give compound **C12-b** (26 g). LCMS $(M+H)^+$: 157.

Step 2: preparation of (5-amino-1-(4-fluoro-2-methoxy-phenyl)pyrazole-4-carbonitrile (compound C12-c)

To a solution of (4-fluoro-2-methoxy-phenyl)hydrazine;hydrochloride (compound **C12-b**, 11.5 g, 59.7 mmol) in ethanol (10 mL) was added ethoxymethylenemalononitrile (7.29 g, 59.7 mmol) and DIEA (31.88 mL, 179.11 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated and the residue was diluted with EA. The organic layer was washed with water and brine (100 mL), and then concentrated, the residue was purified by column chromatography to give compound **C12-c** (5.2 g). LCMS $(M+H)^+$: 233.

Step 3: preparation of (*N*-[4-cyano-2-(4-fluoro-2-methoxy-phenyl)pyrazol-3-yl]acetamide (compound C12-d)

A solution of 5-amino-1-(4-fluoro-2-methoxy-phenyl)pyrazole-4-carbonitrile (compound **C12-c**, 5.2 g, 22.39 mmol) in acetic anhydride (2286.13 mg, 22.39 mmol) was stirred at 100 °C for 12 h. The reaction was quenched with aq. NaOH (1 M, 30 mL) at 0~20 °C and then stirred at 100°C for 1 h. The reaction mixture was diluted with water, extracted with EA, the organic layer was concentrated and the residue was recrystallized (PE:EA=3:1) to give compound **C12-d** (3.9 g). LCMS $(M+H)^+$: 275.

Step 4: preparation of 1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-ol (compound C12-e)

To a solution of *N*-[4-cyano-2-(4-fluoro-2-methoxy-phenyl)pyrazol-3-yl]acetamide (**C12-d**, 1300.0 mg, 4.74 mmol) in acetic acid (13 mL) was added phosphorus oxychloride (1.3 mL, 13.95 mmol), then the reaction was stirred at 110 °C for 2 h. The reaction mixture was poured into water (100 mL), the solid was collected and dried to give compound **C12-e** (1.1 g). LCMS $(M+H)^+$: 275.

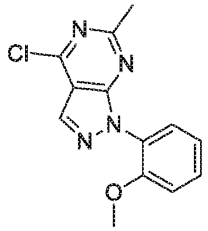
Step 5: preparation of 4-chloro-1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidine (Intermediate C12)

A mixture of 1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-ol (compound **C12-e**, 1100 mg, 4 mmol) in phosphorus oxychloride (11 mL) was stirred at 100 °C for 12 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted

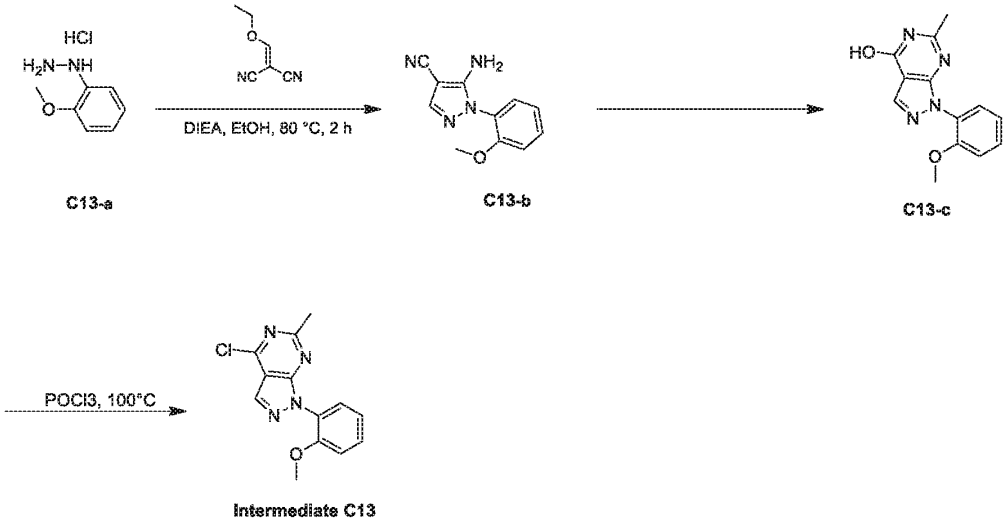
with DCM (50 mL) twice. The organic layer was dried and concentrated to give **intermediate C12** (1.1 g). LCMS $(M+H)^+$: 293.

Intermediate C13

4-chloro-1-(2-ethoxyphenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 5-amino-1-(2-ethoxyphenyl)pyrazole-4-carbonitrile (compound C13-b)

To a solution of ethoxymethylenemalononitrile (compound **C13-a,** 8.42 g, 68.91 mmol) in ethanol (70 mL) was added (2-ethoxyphenyl)hydrazine; hydrochloride (13.0 g, 68.91 mmol) and DIEA (36.8 mL, 206.73 mmol). The mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated and the residue was purified by silica gel to give compound **C13-b** (15 g). LCMS $(M+H)^+$: 229.

Step 2: preparation of 1-(2-ethoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C13-c)

A mixture of 5-amino-1-(2-ethoxyphenyl)pyrazole-4-carbonitrile (compound **C13-b,** 5.0 g, 21.91 mmol) in formic acid (50 mL) was stirred at 100 °C for 16 h. The mixture was

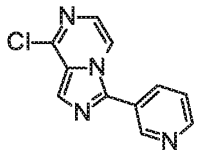
concentrated and the residue was recrystallized in MeOH (12 mL) to give compound **C13-c** (4.5 g). LCMS $(M+H)^+$: 257.

Step 3: preparation of 4-chloro-1-(2-ethoxyphenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C13)

A mixture of 1-(2-ethoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound **C13-c**, 4.5 g, 17.56 mmol) in phosphorus oxychloride (50 mL) was stirred at 100 °C for 12 h. The reaction mixture was added into ice-$NaHCO_3$ solution slowly, and then extracted with DCM (50 mL) twice. The organic layer was dried and concentrated to give **intermediate C13** (4.44 g). LCMS $(M+H)^+$: 275.

Intermediate C14

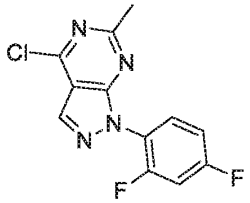
8-chloro-3-(3-pyridyl)imidazo[1,5-a]pyrazine



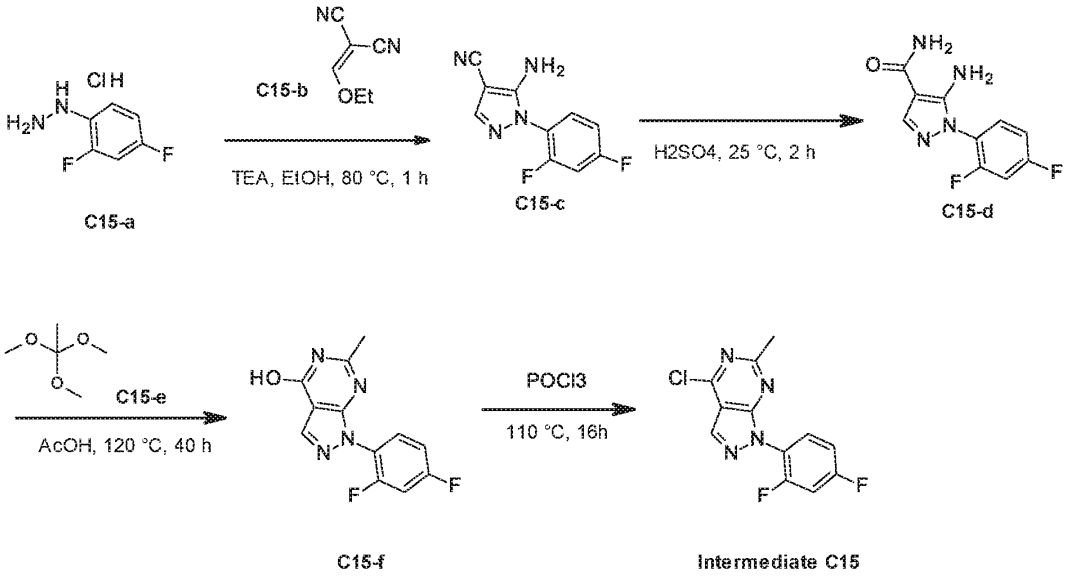
The title compound was prepared in analogy to the preparation of intermediate **C3** by using nicotinic acid instead of 2,4-difluorobenzoic acid. LCMS $(M+H^+)$: 231.

Intermediate C15

4-chloro-1-(2,4-difluorophenyl)-6-methyl-1H-pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1: preparation of 5-amino-1-(2,4-difluorophenyl)-1*H*-pyrazole-4-carbonitrile (compound C15-c)

To a solution of 2,4-difluorophenylhydrazine hydrochloride (compound **C15-a**, 5.0 g, 27.69 mmol) in ethanol (80 mL) was added ethoxymethylenemalononitrile (compound **C15-b**, 3.38 g, 27.69 mmol) and triethylamine (7.72 mL, 55.38 mmol). The mixture was stirred at 25 °C for 0.5 hours, and then heated to 80 °C for 1 h. The mixture was concentrated, the residue was dissolved in EA, washed with water and brine. The organic layer was dried and concentrated to give compound **C15-c** (5.5 g). LCMS $(M+H)^+$: 221.

Step 2: preparation of 5-amino-1-(2,4-difluorophenyl)-1*H*-pyrazole-4-carboxamide (compound C15-d)

5-amino-1-(2,4-difluorophenyl)pyrazole-4-carbonitrile (compound **C15-c**, 4.5 g, 20.44 mmol) was added to ice-cold sulfuric acid (50.0 g, 509.79 mmol). After stirring at 25 °C for 2 h, the mixture was poured into ice-water, and then basified with ammonia. The precipitate was collected and then dissolved in 60 mL of 6 M HCl solution and basified with 10 M NaOH solution to pH 8~9. The precipitate was collected and dried to give **compound C15-d** (4.5 g). LCMS $(M+H)^+$: 239.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-ol (compound C15-f)

A mixture of 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxamide (compound **C15-d**, 1.0 g, 4.2 mmol) in trimethyl orthoacetate (compound **C15-e,** 5.0 mL, 8.4 mmol) was stirred at

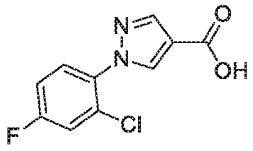
120 °C for 40 h. Then the reaction mixture was concentrated, the residue was purified by prep-HPLC to give compound **C15-f** (80 mg). LCMS $(M+H)^+$: 263.

Step 4: preparation of 4-chloro-1-(2,4-difluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-d]pyrimidine (Intermediate C15)

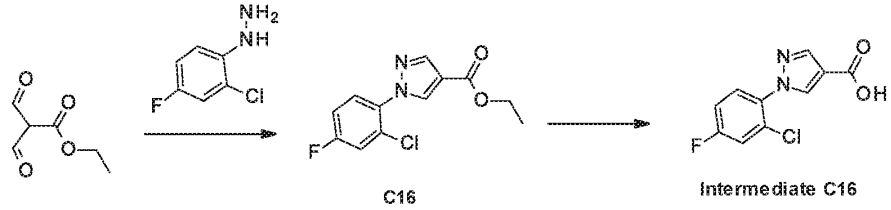
A mixture of 1-(2,4-difluorophenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-ol (compound **C15-f**, 70.0 mg, 0.270 mmol) in phosphorus oxychloride (2.0 mL) was stirred at 110 °C for 16 h under N_2. The mixture was quenched with 100 mL of $NaHCO_3$ and extracted with EA (50 mL). The organic layer was dried and concentrated to give **intermediate C15** (35 mg). LCMS $(M+H)^+$: 281.

Intermediate C16

1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carboxylic acid



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carboxylate (compound C16-a)

A mixture of 2-chloro-4-fluorophenylhydrazine hydrochloride (6 g, 30.5 mmol) and ethyl 2-formyl-3-oxopropanoate (4.4 g, 30.5 mmol) in ethanol (120 mL) and was stirred for 16 hs at 25 °C. Then the mixture was diluted with DCM and adjusted to pH=3 with aq. HCl (1 M). The organic layer was separated; dried and concentrated to give the crude compound **C16**-a (8.18 g). LCMS $(M+H)^+$: 269.

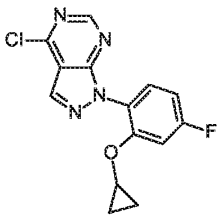
Step 2: preparation of 1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carboxylic acid (Intermediate C16)

A mixture of compound C16-a (8.18 g, 30.5 mmol) and lithium hydroxide monohydrate (3.8 g, 91 mmol) in ethanol (100 mL) was stirred at 45 °C for 4 hrs. The mixture was concentrated to about 20 mL and diluted with 80 mL of water, acidified to pH 3~4 with 1 M HCl

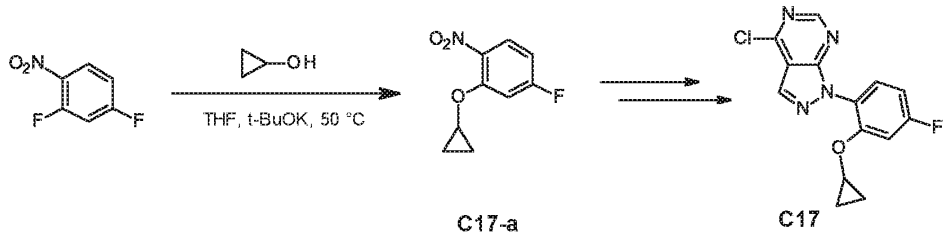
solution. The solid was filtered and the filter cake was dried to give **intermediate C16** (6.2 g). LCMS $(M+H)^+$: 241.

Intermediate C17

4-chloro-1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-(cyclopropoxy)-4-fluoro-1-nitro-benzene (compound C17-a)

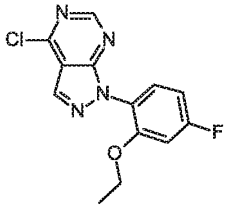
A mixture of 2,4-difluoro-1-nitro-benzene (10.0 g, 62.86 mmol), cyclopropanol (5.0 g, 86.09 mmol) and sodium tert-butoxide (12.1 g, 0.12 mol) in THF (0.2 L) was stirred at 50 °C for 1 h. The mixture was poured into water (0.2 L) and extracted with EtOAc (0.2 L twice). The combined organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography to give compound **C17-a** (8.0 g).

Step 2~6: preparation of 4-chloro-1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C17)

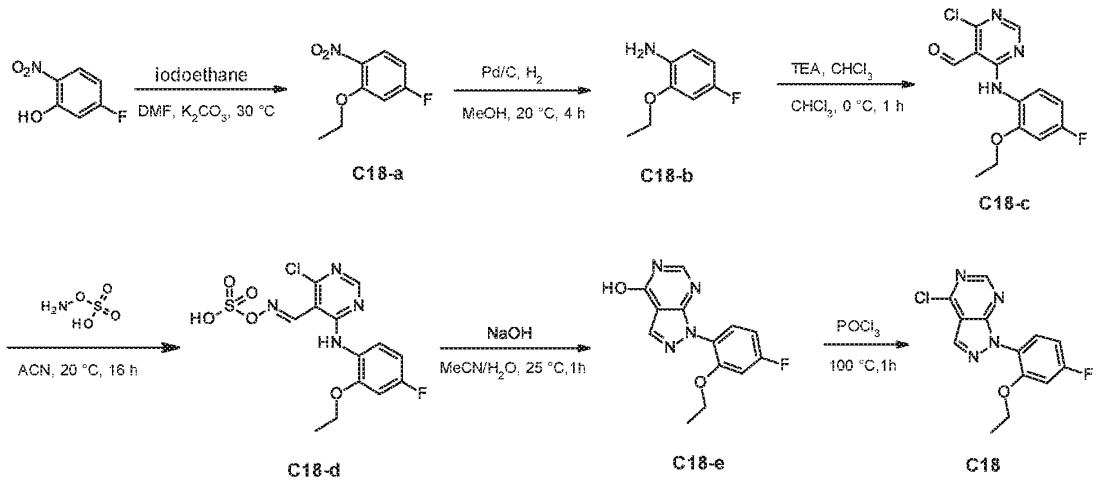
The title compound was prepared in analogy to the preparation of **intermediate C18** by using compound **C17-a** instead of compound **C18-a**. LCMS $(M+H)^+$: 305.

Intermediate C18

4-chloro-1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-ethoxy-4-fluoro-1-nitro-benzene (compound C18-a)

A mixture of 5-fluoro-2-nitro-phenol (1.0 g, 6.4 mmol), potassium carbonate (1.7 g, 12.7 mmol) and iodoethane (0.6 mL, 7.64 mmol, 1.2 eq) in DMF (10.0 mL) was stirred at 30 °C for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was dried and concentrated to give compound **C18-a** (1.0 g).

Step 2: preparation of 2-ethoxy-4-fluoro-aniline (compound C18-b)

To the mixture of 2-ethoxy-4-fluoro-1-nitro-benzene (compound **C18-a**, 1.0 g, 5.4 mmol) in methanol (10.0 mL) was added Pd/C (0.1 g) and the mixture was stirred at 20 °C for 4 h under H_2 atmosphere. The mixture was poured into water (20.0 mL) and extracted with EtOAc (20.0 mL twice). The organic layer was concentrated, the residue was purified by flash chromatography column to give compound **C18-b**, (0.8 g). LCMS ($M+H^+$): 156.

Step 3: preparation of 4-chloro-6-(2-ethoxy-4-fluoro-anilino)pyrimidine-5-carbaldehyde (compound C18-c)

To a mixture of 4,6-dichloropyrimidine-5-carbaldehyde (0.8 g, 4.51 mmol) and TEA (0.9 g, 9.0 mmol) in chloroform (20.0 mL) was added 2-ethoxy-4-fluoro-aniline (compound **C18-b**, 0.7 g, 4.5 mmol) dropwise and the mixture was stirred at 0 °C for 1 h. The mixture was washed with water, the organic layer was concentrated, and the residue was purified by silica gel to give compound **C18-c** (0.1 g). LCMS ($M+H^+$): 296.

Step 4: preparation of [[4-chloro-6-(2-ethoxy-4-fluoro-anilino)pyrimidin-5-yl]methyleneamino] hydrogen sulfate (compound C18-d)

A mixture of amino hydrogen sulfate (0.2 g, 1.7 mmol) and 4-chloro-6-(2-ethoxy-4-fluoro-

anilino)pyrimidine-5-carbaldehyde (compound **C18-c**, 0.1 g, 0.34 mmol) in MeCN (5.0 mL) was stirred at 20 °C for 16 h. The mixture was used in next step directly. LCMS ($M+H^+$): 311.

Step 5: preparation of 1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C18-e)

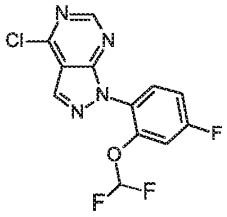
To the mixture of compound **C18-d** (0.1 g, 0.3 mmol) in ACN (5.0 mL) was added NaOH a.q (2.0 mL, 1M) and the reaction mixture was stirred at 25 °C for 2 h under N_2. The mixture was purified by prep-HPLC to give compound **C18-e** (30.0 mg). LCMS ($M+H^+$): 275.

Step 6: preparation of 4-chloro-1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidine (compound C18-f)

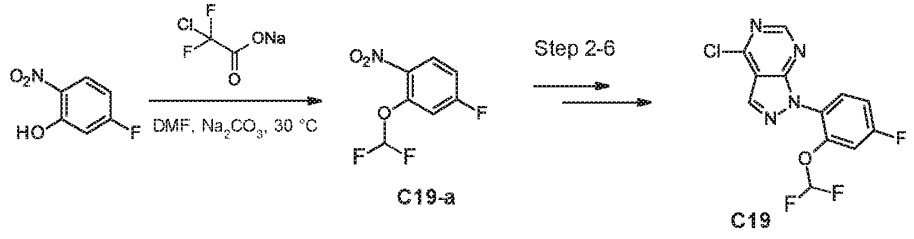
A solution of 1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound **C18-e**, 20.0 mg, 0.07 mmol) in $POCl_3$ (1.0 mL) was stirred at 100 °C for 1 h. The mixture was concentrated to give intermediate **C18** (20.0 mg). LCMS ($M+H^+$): 293.

Intermediate C19

4-chloro-1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-(difluoromethoxy)-4-fluoro-1-nitro-benzene (C19-a)

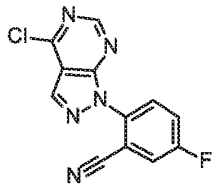
To a solution of 5-fluoro-2-nitro-phenol (5.0 g, 31.83 mmol) and sodium chlorodifluoroacetate (5.8 g, 38.2mmol) in DMF (60.0 mL) was added Na_2CO_3 (6.75 g, 63.65 mmol). The mixture was stirred at 100 °C for 2 h, and then poured into water (200.0 mL). The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried and concentrated to give compound **C19-a** (5.0 g).

Step 2-6: preparation of 4-chloro-1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C19)

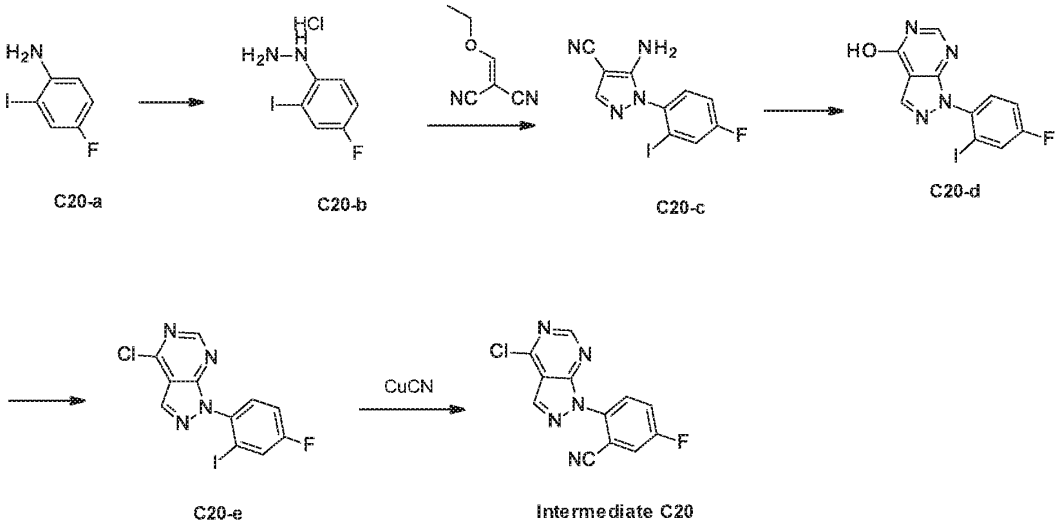
The title compound was prepared in analogy to the preparation of intermediate **C18** by using compound **C19-a** instead of compound **C18-a**. LCMS $(M+H)^+$: 315.

Intermediate C20

2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-benzonitrile



The title compound was prepared according to the following scheme:



Step 1~3: preparation of 1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C20-d)

Compound **C20-d** was prepared in analogy to the preparation of intermediate **C43** by using 4-fluoro-2-iodo-aniline instead of 2-bromo-4-fluoro-aniline. LCMS $(M+H)^+$: 356.

Step 4: preparation of 4-chloro-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-d]pyrimidine (compound C20-e)

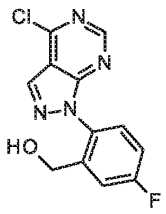
A solution of 4-chloro-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-d]pyrimidine (compound **C20-d**, 5 g, 14.0 mmol) in $POCl_3$ (15 mL) was stirred at 80 °C for 2 hours. Then the reaction mixture was concentrated, the residue was diluted with EtOAc (100 mL), and poured into aq.$NaHCO_3$. The organic layer was separated and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated to give compound **C20-e** (4.5 g). LCMS $(M+H)^+$: 375.

Step 5: preparation of 2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-benzonitrile (Intermediate C20)

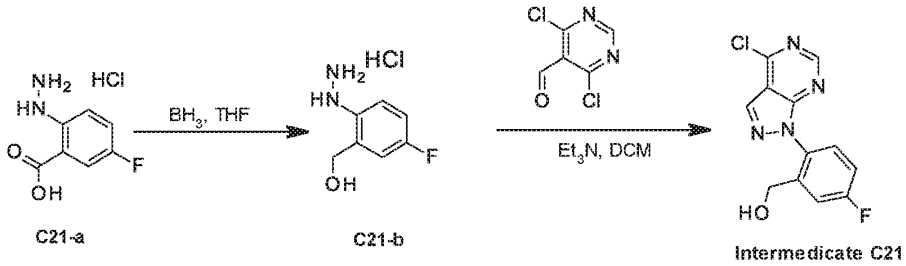
To a solution of 4-chloro-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-d]pyrimidine (compound **C20-e**, 2 g, 5.3 mmol) in DMF (50 mL) was added cuprous cyanide (1.0 g, 5.9 mmol) under nitrogen at room temperature. The reaction mixture was stirred at 100 °C for 3 hours. After cooling to room temperature, the reaction mixture was poured into water (200 mL), and extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated to get crude product, which was purified by column chromatography to give Intermediate **C20** (0.8 g). LCMS $(M+H)^+$: 274.

Intermediate C21

[2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenyl]methanol



The title compound was prepared according to the following scheme:



Step 1: preparation of (5-fluoro-2-hydrazino-phenyl)methanol;hydrochloride (compound C21-b)

To a solution of 5-fluoro-2-hydrazino-benzoic acid hydrochloride (compound **C21-a**, 1.24 g, 6 mmol) in anhydrous THF (15 mL) was added 1M borane tetrahydrofuran complex (30 mL, 30 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was carefully quenched by adding MeOH, then 4M HCl in 1,4-dioxane solution was added and stirred for 1 h. The white suspension was concentrated in *vacuo* to give crude compound **C21-b** (1.12 g).

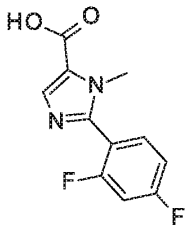
Step 2: preparation of [2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenyl]methanol (Intermediate C21)

To a mixture of (5-fluoro-2-hydrazino-phenyl)methanol hydrochloride (compound **C21-b**, 930 mg, 4.8 mmol) in DCM (12 mL) was added Et_3N (2.44 g, 24.14 mmol), then 4,6-dichloropyrimidine-5-carbaldehyde (854.54 mg, 4.83 mmol) was added and stirred at room

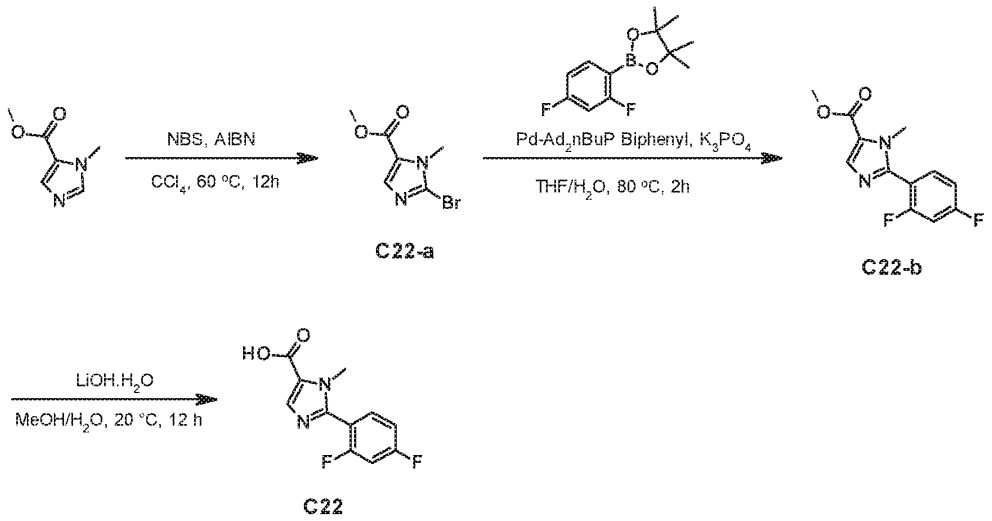
temperature for 16 hours. The reaction mixture was partitioned between water and DCM, the separated aqueous layer was extracted with DCM. The combined organic layer was dried and concentrated, the residue was purified by flash chromatography to afford Intermediate **C21** (270 mg). LCMS $(M+H)^+$: 279.

Intermediate C22

2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carboxylic acid



The title compound was prepared according to the following scheme:



Step 1: preparation of methyl 2-bromo-3-methyl-imidazole-4-carboxylate (compound C22-a)

To a solution of methyl 3-methylimidazole-4-carboxylate (5.0 g, 35.6 mmol) in carbon tetrachloride (300.0 mL) was added NBS (12.7 g, 71.4 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.3 g, 1.8 mmol). The mixture was stirred at 60 °C for 12 h and then concentrated. The residue was purified by silica gel to give compound **C22-a** (1.5 g). LCMS $(M+H)^+$: 219.

Step 2: preparation of methyl 2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carboxylate (compound C22-b)

A solution of 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 g, 5.1

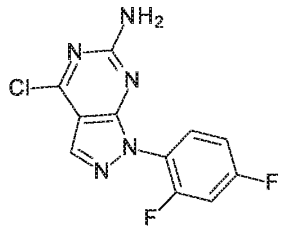
mmol), compound **C22-a** (1.0 g, 4.6 mmol), Pd-Ad$_2$nBuP Biphenyl (0.3 g, 0.46 mmol) and K_3PO4 (2.9 g, 13.7 mmol) in THF (10.0 mL) and water (1.0 mL) was stirred at 80 °C for 2 h under N_2. The mixture was quenched with water (20.0 mL) and then extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **C22-b** (0.7 g) as a white solid. LCMS $(M+H)^+$: 253.

Step 3: preparation of 2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carboxylic acid (Intermediate C22)

A solution of compound **C22-b** (0.7 g, 2.78 mmol) and LiOH•H_2O (0.35 g, 8.33 mmol) in methanol (15.0 mL) and water (2.0 mL) was stirred at 20 °C for 12 h. The mixture was concentrated, the residue was dissolved in water (20 mL) and acidified with HCl (1M) to pH=4. The mixture was extracted with EtOAc, and the organic layer was dried and concentrated to give **Intermediate C22** (0.6 g). LCMS $(M+H)^+$: 238.

Intermediate C23

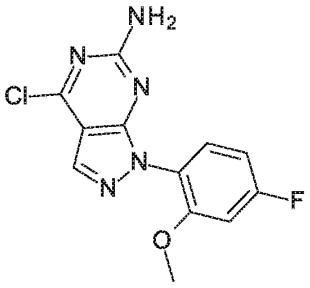
[4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]amine



The title compound was prepared in analogy to the preparation of intermediate **C2** by using 2-amino-4,6-dichloro-pyrimidine-5-carbaldehyde instead of 4,6-dichloro-5-pyrimidinecarbaldehyde (**compound C2-a**). LCMS $(M+H^+)$: 282.

Intermediate C24

[4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-6-yl]amine

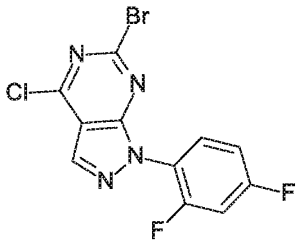


The title compound was prepared in analogy to the preparation of intermediate **C2** by using 2-amino-4,6-dichloro-pyrimidine-5-carbaldehyde and (4-fluoro-2-methoxy-

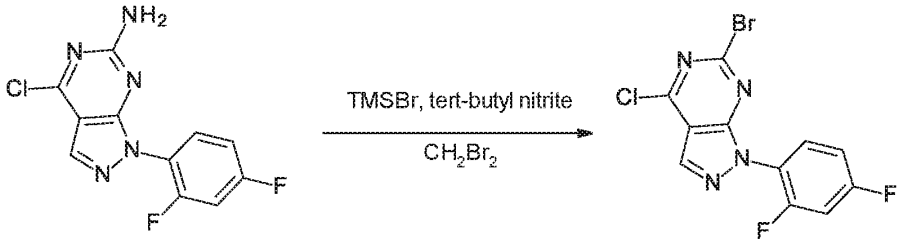
phenyl)hydrazine;hydrochloride (**C9-a)** instead of 4,6-dichloro-5-pyrimidinecarbaldehyde (**compound C2-a)** and 2,4-difluorophenylhydrazine hydrochloride. LCMS ($M+H^+$): 294.

Intermediate C25

[4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-6-yl]amine



The title compound was prepared according to the following scheme:

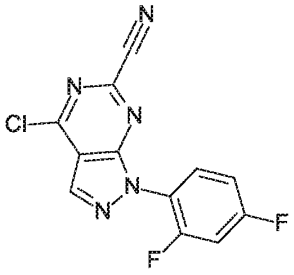


Intermediate C23 **Intermediate C25**

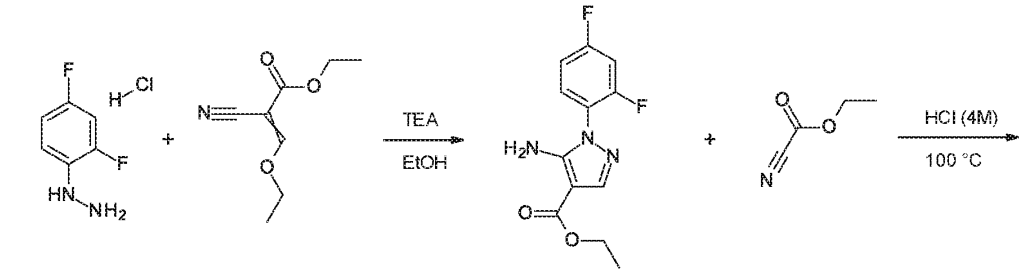
Bromotrimethylsilane (2.45 g, 2.07 mL, 15.98 mmol) was added dropwise to a stirred solution of [4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]amine (compound **C23,** 500 mg, 1.78 mmol) in dibromomethane (54 mL) under N_2 atmosphere. Then *tert*-butyl nitrite (4.21 mL, 35.51 mmol) was added dropwise, and stirring was continued at ambient temperature for 1 h. The mixture was cooled for 15 min and added dropwise to a cold, vigorously stirred mixture of saturated $NaHCO_3/H_2O$ (50 mL)/CH_2Cl_2 (50 mL). The aqueous layer was extracted with DCM (30 mL, twice) and the combined organic phase was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel to afford **intermediate C25** (450 mg). LCMS ($M+H^+$): 346.

Intermediate C27

4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxylic acid ethyl ester (compound C27-a)

A solution of 2-cyano-3-ethoxy-acrylic acid ethyl ester (507 mg, 3 mmol), (2,4-difluorophenyl)hydrazine;hydrochloride (540 mg, 3 mmol) and Et_3N (836 µL, 6 mmol) in ethanol (10 mL) was stirred at 90 °C for 12 hours. The solvent was removed by reduce pressure and then purified by silica gel to afford compound **C27-a** (635 mg), LCMS ($M+H^+$): 268.

Step 2: preparation of 1-(2,4-difluorophenyl)-4-keto-5*H*-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid ethyl ester (compound C27-b)

To a suspension of compound **C27-a** (635 mg, 2.38 mmol) in 4 M HCl in dioxane (12 mL) was added cyanoformic acid ethyl ester (470 mg, 4.75 mmol). The mixture was stirred at 100 °C for 14 hours and then was cooled to room temperature. After 1,4-dioxane was removed in *vacuo*, the residue was partitioned between methylene chloride and water. The organic layer was dried

and concentrated, the residue was purified by silica gel to afford compound **C27-b** (700 mg), LCMS ($M+H^+$): 321.

Step 3: preparation of 1-(2,4-difluorophenyl)-4-keto-5H-pyrazolo[3,4-d]pyrimidine-6-carboxamide (compound C27-c)

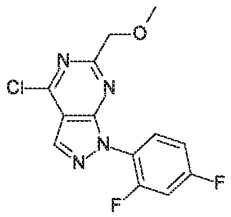
A suspension of compound **C27-b** (260 mg, 0.812 mmol) in 7 M ammonia in MeOH (4 mL) was stirred at room temperature for 12 hours. The mixture was concentrated to afford compound **C27-c**, (220 mg).

Step 4: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carbonitrile (Intermediate C27)

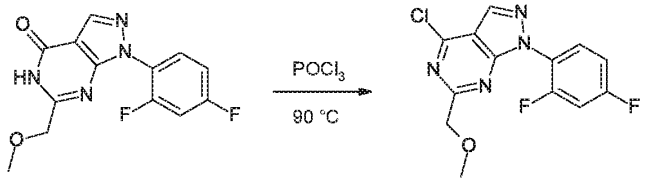
A suspension of compound **C27-c** (160 mg, 0.522 mmol) in phosphorus oxychloride (2 mL) was stirred at 90 °C for 2 hours. The mixture was concentrated and the residue was purified by silica gel to afford **intermediate C27** (123 mg), LCMS ($M+H^+$): 292.

Intermediate C28

[4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-6-yl]amine



The title compound was prepared according to the following scheme:

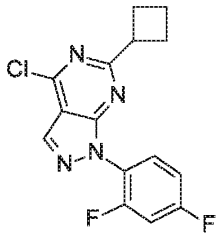


C28-a Intermediate C28

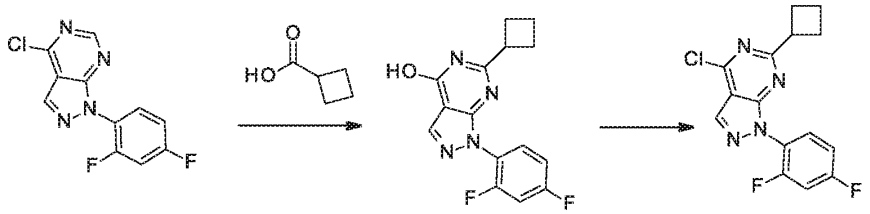
A suspension of compound **C28-a** (200 mg, 0.684 mmol, the synthesis refer to **C27-b** by using 2-methoxyacetonitrile instead of cyanoformic acid ethyl ester in step 2) in phosphorus oxychloride (mL, 21.46 mmol) was stirred at 90 °C for 0.5 hours. Then the reaction mixture was concentrated to give an oil, which was purified by silica gel to give intermediate **C28** (182 mg) as white solid. LCMS ($M+H^+$): 311.

Intermediate C30

4-chloro-6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Intermediate C2 C30-a Intermediate C30

Step 1: preparation of 6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C30-a)

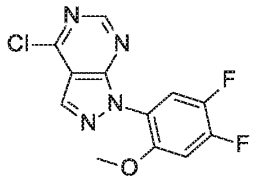
To a solution of **intermediate C2** (50 mg, 0.19 mmol) in acetonitrile (1 mL) was added cyclobutanecarboxylic acid (56.0 mg, 0.56 mmol), silver nitrate (255 mg, 1.5 mmol). The reaction mixture was heated at 60 °C for 2 hours, and then a solution of ammonium persulfate (214 mg, 0.94 mmol) in water (1 mL) was added. After being stirred at 60 °C for another 2 hours, the mixture was concentrated and the residue was purified by prep-HPLC to afford compound **C30-a** (15 mg). LCMS $(M+H)^+$: 357.

Step 2: preparation of 4-chloro-6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (intermediate C30)

A solution of compound **C30-a** (15.0 mg, 0.050 mmol) in phosphorus oxychloride (0.5 mL, 5.36 mmol) was stirred at 80 °C for 2 hrs. The reaction mixture was cooled to 0 °C and then diluted with EA. The mixture was quenched with sat.$NaHCO_3$ (30 mL) at 0 °C. The organic phase was separated, dried and concentrated to afford **intermediate C30** (15 mg). LCMS $(M+H)^+$: 321.

Intermediate C31

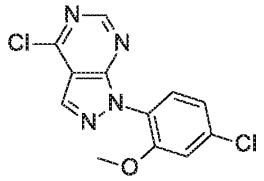
4-chloro-1-(4,5-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



The title compounds were prepared in analogy to the preparation of intermediate **C10** by using 4,5-difluoro-2-methoxy-aniline instead of O-anisidine, LCMS $(M+H)^+$: 297.

Intermediate C32

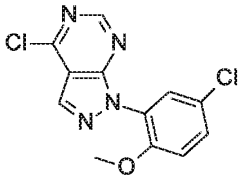
4-chloro-1-(4-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



The title compounds were prepared in analogy to the preparation of intermediate **C10** by using 4-chloro-2-methoxyaniline instead of O-anisidine, LCMS $(M+H)^+$: 295.

Intermediate C33

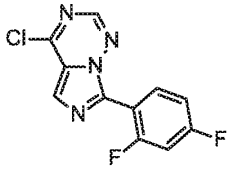
4-chloro-1-(5-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



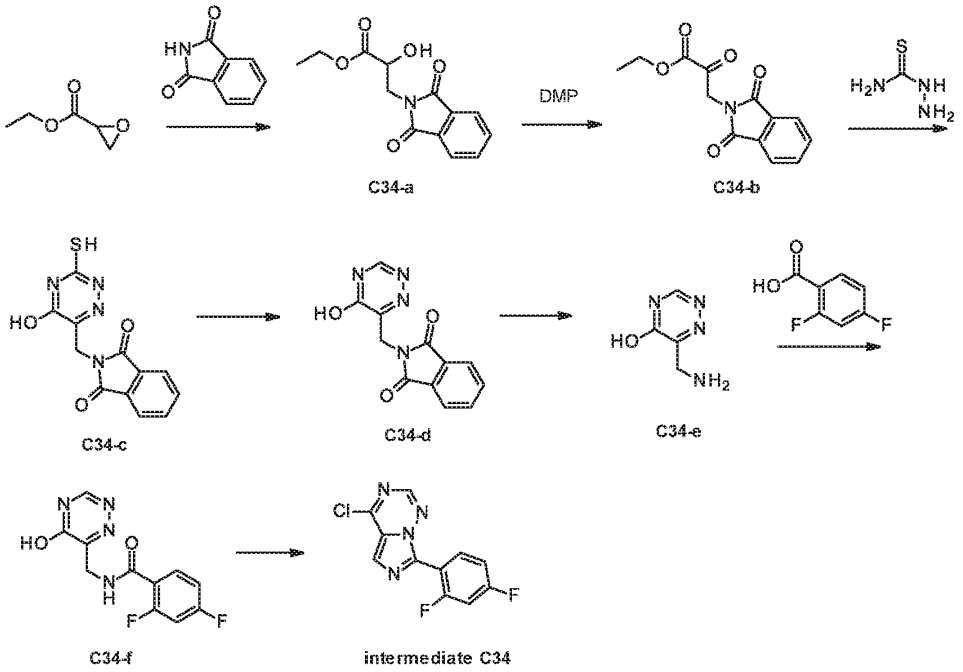
The title compounds were prepared in analogy to the preparation of intermediate **C10** by using 5-chloro-2-methoxyaniline instead of O-anisidine, LCMS $(M+H)^+$: 295.

Intermediate C34

4-chloro-7-(2,4-difluorophenyl)imidazo[5,1-f][1,2,4]triazine



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropanoate (compound C34-a)

To a solution of ethyl 2,3-epoxypropanoate (10.0 g, 86.12 mmol) in DMF (200 mL) was added phthalimide (11.0 g, 74.76 mmol) and potassium phthalimide (2 g, 10.8 mmol), the mixture was stirred at 90 °C for 5 hours. The mixture was diluted with EA, washed with water and brine, the organic layer was dried and concentrated to give compound **C34-a** (19 g). LCMS $(M+H)^+$: 264.

Step 2: preparation of ethyl 3-(1,3-dioxoisoindolin-2-yl)-2-oxopropanoate (compound C34-b)

To a solution of compound **C34-a** (18.0 g, 68.38 mmol) in DCM (200 mL) was added Dess-Martin periodinane (43.5 g, 102.56 mmol) at 0 °C. The mixture was stirred at 20 °C for 3 h. The mixture was filtered through celite and the filtrate was concentrated to give compound **C34-b** (14 g). LCMS $(M+H)^+$: 262.

Step 3: preparation of 2-((5-hydroxy-3-mercapto-1,2,4-triazin-6-yl)methyl)isoindoline-1,3-dione (compound C34-c)

A slurry of compound **C34-b** (10.0 g, 38.28 mmol) in anhydrous ethanol (200 mL) was charged with thiosemicarbazide (3.49 g, 38.28 mmol) in one portion and heated to 80 °C for 2 h. The reaction mixture was charged with DIPEA (6.67 mL, 38.28 mmol) and heated to 40 °C for 16 hours. The mixture was concentrated, and the residue was dissolved in acetonitrile (80 mL).

After water (300 mL) was added to the solution, solid precipitated, which was collected by filtration to give compound **C34-c** (5.6 g). LCMS $(M+H)^+$: 289.

Step 4: preparation of 2-((5-hydroxy-1,2,4-triazin-6-yl)methyl)isoindoline-1,3-dione (compound C34-d)

A mixture of compound **C34-c** (4.6 g, 15.96 mmol), Et_3SiH (3.6 g) and Raney Ni (6.0 g, 15.96 mmol) in ethanol (130 mL) was stirred at 80 °C for 12 hours. Then the mixture was filtered through celite and the filtrate was concentrated to give compound **C34-d** (2.8 g). LCMS $(M+H)^+$: 257.

Step 5: preparation of 6-(aminomethyl)-1,2,4-triazin-5-ol (compound C34-e)

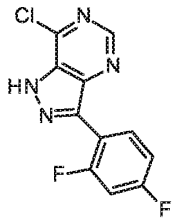
To a solution of compound **C34-d** (100 mg) in ethanol (1 mL) was added methylamine (1.0 mL, 2 M in EtOH) at 20 °C, then the mixture was stirred at 60 °C for 1 h. The reaction solution was concentrated to give compound **C34-e**. LCMS $(M+H)^+$: 127.

Step 6~7: preparation of 4-chloro-7-(2,4-difluorophenyl)imidazo[5,1-f][1,2,4]triazine (intermediate C34)

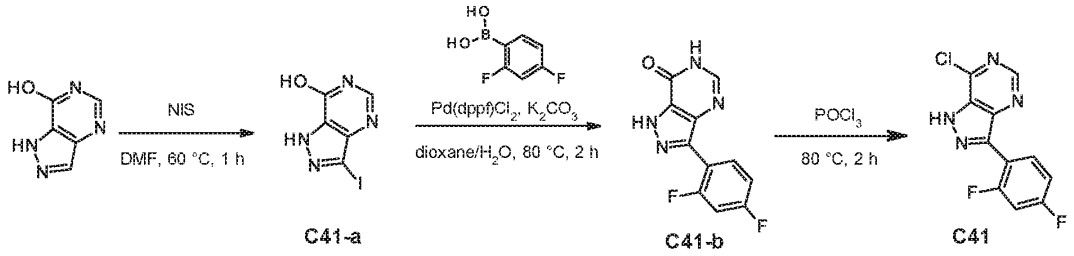
The title compound was prepared in analogy to the preparation of intermediate **C3** by using compound **C34-e** instead of (3-chloropyrazin-2-yl)methanamine hydrochloride. LCMS $(M+H)^+$: 267.

Intermediate C41

7-chloro-3-(2,4-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 3-iodo-1*H*-pyrazolo[4,3-d]pyrimidin-7-ol (compound C41-a)

A mixture of 1*H*-pyrazolo[4,3-d]pyrimidin-7-ol (0.3 g, 2.2 mmol) and NIS (0.8 g, 4.4 mmol) in DMF (10.0 mL) was stirred at 60 °C for 1 h, and then the mixture was concentrated ,

the residue was triturated in MeOH (5.0 mL) to give compound **C41-a**, (0.5 g). LCMS ($M+H^+$): 262.

Step 2: preparation of 3-(2,4-difluorophenyl)-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one (compound C41-b)

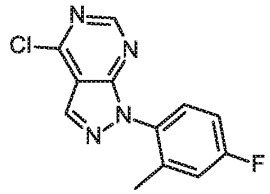
To a mixture of (2,4-difluorophenyl)boronic acid (0.7 g, 4.6 mmol) and 3-iodo-1H-pyrazolo[4,3-d]pyrimidin-7-ol (compound **C41-a**, 0.5 g, 2.3 mmol) in 1,4-dioxane (5.0 mL) and water (1.0 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (170.1 mg, 0.2 mmol) and potassium carbonate (1.0 g, 7.0 mmol) under N_2 atmosphere. The mixture was stirred at 80 °C for 2 h under N_2 atmosphere and then filtered. The filter cake was washed with ACN (20.0 mL) and MeOH (20.0 mL). The solid was dried to give compound **C41-b** (0.2 g). LCMS ($M+H^+$): 249.

Step 3: preparation of 7-chloro-3-(2,4-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidine (Intermediate C41)

A mixture of 3-(2,4-difluorophenyl)-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one (**C41-b**, 0.1 g, 0.4 mmol) in $POCl_3$ (5.0 mL) was stirred at 80 °C for 2 h. The mixture was then concentrated under reduce pressure and the residue was partitioned between EtOAc (20.0 mL) and aqueous solution of $NaHCO_3$ (20.0 mL). The organic layer was separated, dried and concentrated to give **intermediate C41** (60.0 mg). LCMS ($M+H^+$): 267.

Intermediate C42

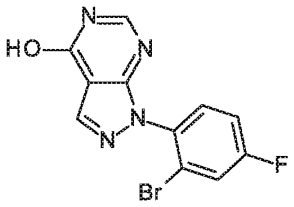
4-chloro-1-(4-fluoro-2-methyl-phenyl)pyrazolo[3,4-d]pyrimidine



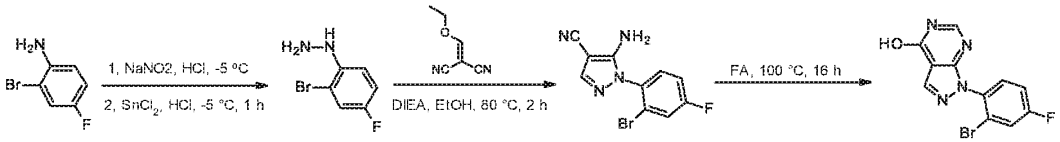
The title compound was prepared in analogy to the preparation of intermediate **C18** by using (4-fluoro-2-methyl-phenyl)hydrazine hydrochloride instead of compound **C2-a**. LCMS ($M+H^+$): 263.

Intermediate C43

1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



Step 1: preparation of (2-bromo-4-fluoro-phenyl)hydrazine (compound C43-a)

To a solution of 2-bromo-4-fluoro-aniline (5.0 g, 26.3 mmol) in hydrochloric acid (12 M) (50.0 mL) and water (25.0 mL) was added a solution of sodium nitrite (2.0 g, 28.9 mmol) in water (3.0 mL) dropwise at -5 °C. After addition, the reaction mixture was stirred at -5 °C for 0.5 h. Then a solution of tin(II) chloride dihydrate (17.8 g, 78.9 mmol) in hydrochloric acid (12 M) (50.0 mL) was added into this mixture at -5 °C drop wise. The mixture was stirred for additional 2 hours and then filtered. This filter cake was washed with cold brine and dried to give compound **C43-a** (5.0 g).

Step 2: Preparation of 5-amino-1-(2-bromo-4-fluoro-phenyl)pyrazole-4-carbonitrile (compound C43-b)

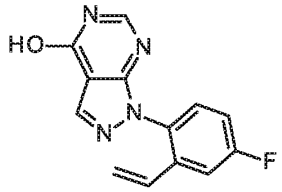
A mixture of compound **43-a** (4.0 g, 19.5 mmol), 2-(ethoxymethylene)propanedinitrile (2.4 g, 19.5 mmol) and DIEA (7.5 g, 58.5 mmol, 3.0 eq) in ethanol (0.1 L) was stirred at 80 °C for 2 h. The mixture was poured into waster (0.1 L) and extracted with EtOAc (0.1 L twice). The combined organic layer was dried and concentrated to give compound **C43-b** (4.5 g). LCMS ($M+H^+$): 281.

Step 3: preparation of 1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (Intermediate C43)

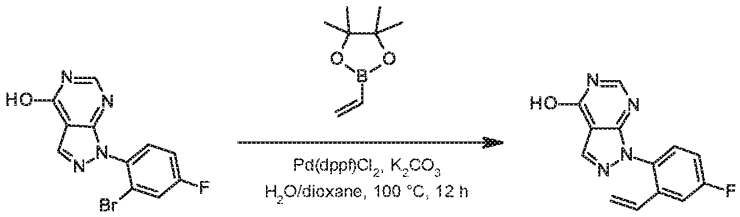
A solution of compound **C43-b** (4.0 g, 14.23 mmol) in formic acid (20.0 mL) was stirred at 80 °C for 1 h. The mixture was concentrated and the residue was recrystallized in MeOH to give **intermediate C43** (2.0 g). LCMS ($M+H^+$): 309.

Intermediate C44

1-(4-fluoro-2-vinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:

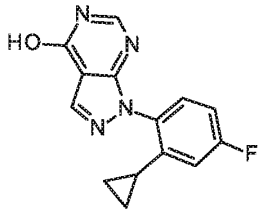


Intermediate C43 Intermediate C44

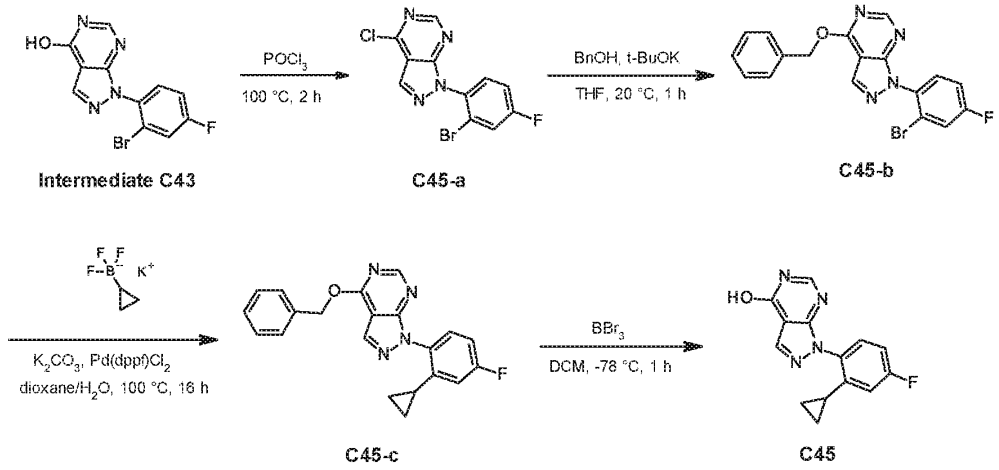
To a mixture of intermediate **C43** (0.5 g, 1.6 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.37 g, 1.6 mmol) and potassium carbonate (0.7 g, 4.85 mmol) in 1,4-dioxane (10.0 mL) and water (2 mL) was added 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride toluene (0.13 g, 0.16 mmol, 0.1 eq). The mixture was stirred at 100 °C for 12 h under N_2. The mixture was filtered and the filtrate was concentrated, the residue was purified by chromatography column to give **intermediate C44** (0.2 g). LCMS ($M+H^+$): 257.

Intermediate C45

1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-(2-bromo-4-fluoro-phenyl)-4-chloro-pyrazolo[3,4-d]pyrimidine (compound C45-a)

A solution of intermediate **C43** (4.5 g, 14.5 mmol) in $POCl_3$ (50.0 mL) was stirred at 100 °C for 2 h. The mixture was concentrated and the residue was dissolved in EtOAc (0.3 L). The solution was poured into aq. $NaHCO_3$ (0.3 L). The organic phase was separated, washed with brine, dried and concentrated to compound **C45-a** (4.0 g). LCMS ($M+H^+$): 327.

Step 2: preparation of 4-benzyloxy-1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidine (compound C45-b)

A mixture of compound **C45-a** (4.0 g, 12.2 mmol), benzyl alcohol (1.1 mL, 14.6 mmol) and t-BuOK (24.4 mL, 24.4 mmol) in THF (50.0 mL) was stirred at 20 °C for 1 h. The mixture was poured into water (50.0 mL) and extracted with EtOAc (50 mL twice). The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give compound **C45-b** (3.1 g). LCMS ($M+H^+$): 399.

Step 3: preparation of 4-benzyloxy-1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidine (compound C45-c)

To a mixture of compound **C45-b** (1.0 g), potassium cyclopropyltrifluoroborate (0.7 g, 5.0 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in 1,4-dioxane (20.0 mL) and water (2.0 mL) was added 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride toluene (0.21 g, 0.25 mmol). The mixture was stirred at 100 °C for 16 h under N_2. After cooled to r.t., the mixture was poured into brine (20.0 mL) and extracted with EtOAc (20.0 mL twice). The combined organic layer was dried and concentrated, the residue was purified by pre-TLC to compound **C45-c** (50.0 mg). LCMS ($M+H^+$): 361.

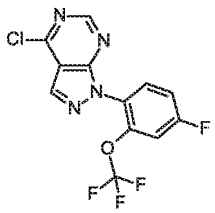
Step 4: preparation of 1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-

ol (Intermediate C45)

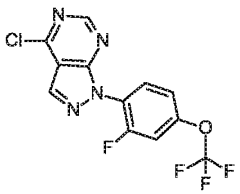
To a mixture of compound **C45-c** (50.0 mg, 0.14 mmol) in DCM (3.0 mL) was added BBr_3 (34.3 mg, 0.14 mmol) at -78 °C dropwise and the mixture was stirred at -78 °C for 1 h under N_2. The reaction was quenched water (3.0 mL) and then concentrated, the residue was purified by prep-HPLC to give **intermediate C45** (25.0 mg). LCMS ($M+H^+$): 271.

Intermediate C46A and C46B

4-chloro-1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C46A) and 4-chloro-1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C46B)

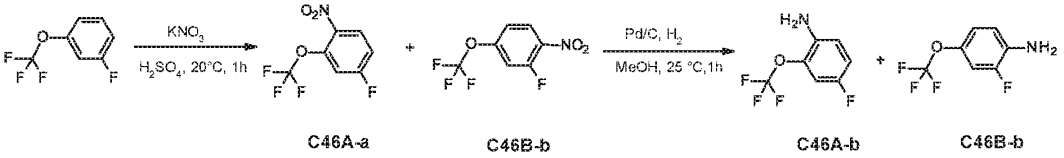


C46A

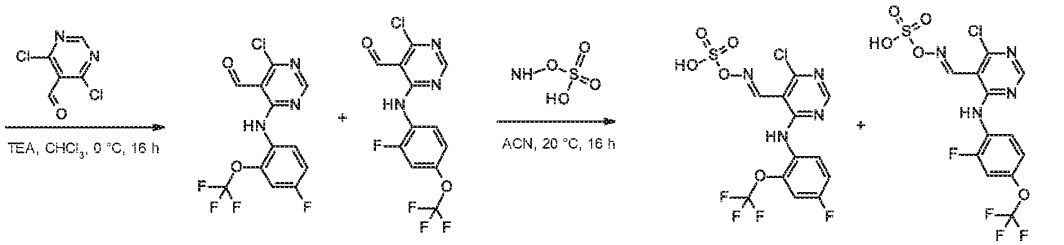


C46B

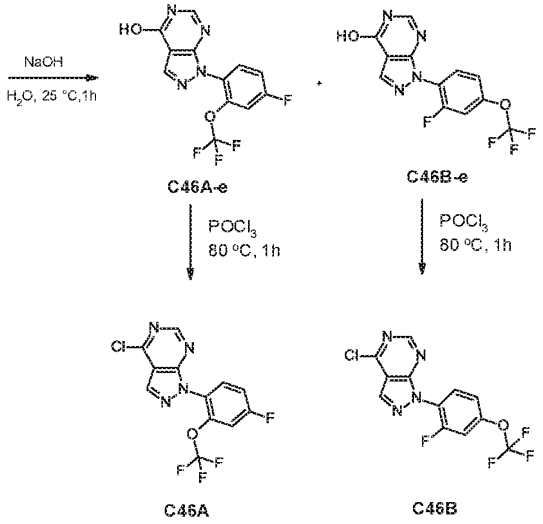
The title compounds were prepared according to the following scheme:



C46A-a **C46B-b** **C46A-b** **C46B-b**



C46A-c **C46B-c** **C46A-d** **C46A-d**



Step 1: preparation of 4-fluoro-1-nitro-2-(trifluoromethoxy)benzene (compound C46A-a) and 2-fluoro-1-nitro-4-(trifluoromethoxy)benzene (compound C46B-a)

1-fluoro-3-(trifluoromethoxy)benzene (10.0 g, 55.5 mmol) was dissolved in H_2SO_4 (40.0 mL) and the mixture was cooled to 0 °C in ice bath. Then to the mixture was added KNO_3 (1.4 g, 13.86 mmol) portion-wise with internal temperature below 5 °C. Upon completion of the addition, the mixture was stirred at 0 °C for 1 h. The mixture was poured into ice (200.0 g) and extracted with EtOAc (100.0 mL twice). The mixture was dried and concentrated to give a mixture of compound **C46A-a** and **C46B-a** (1.5 g).

Step 2: preparation of 4-fluoro-2-(trifluoromethoxy)aniline (C46A-b) and 2-fluoro-4-(trifluoromethoxy)aniline (C46B-b)

To a mixture of Pd/C (0.3 g) in methanol (10.0 mL) was added a mixture of compound **C46A-a** and **C46B-a** (1.5 g, 6.6 mmol) and the resulting mixture was stirred at 20 °C for 16 h. The mixture was filtered and the filtrate was concentrated to give a mixture of compound **C46A-b** and **C46B-b** (0.6 g). LCMS ($M+H^+$): 196.

Step 3: preparation of 4-chloro-6-[4-fluoro-2-(trifluoromethoxy)anilino]pyrimidine-5-carbaldehyde (compound C46A-c) and 4-chloro-6-((2-fluoro-4-(trifluoromethoxy)phenyl)amino)pyrimidine-5-carbaldehyde (compound C46B-c)

To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (1.3 g, 7.3 mmol) and TEA (2.2 g, 22.04 mmol) in chloroform (20.0 mL) was added a mixture of compound **C46A-b** and **C46B-b** (0.6 g, 3.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1h and then stirred at 20 °C for another 16 h. The mixture was poured into water (30.0 mL), and the organic layer was separated, dried and concentrated. The residue was purified by TLC to give a mixture of

compound **C46A-c** and **C46B-c** (250 mg). LCMS ($M+H^+$): 336.

Step 4: preparation of [(E)-[4-chloro-6-[4-fluoro-2-(trifluoromethoxy)anilino]pyrimidin-5-yl]methyleneamino] hydrogen sulfate (compound C46A-d) and [(E)-[4-chloro-6-[2-fluoro-4-(trifluoromethoxy)anilino]pyrimidin-5-yl]methyleneamino] hydrogen sulfate (compound C46B-d)

To a solution of amino hydrogen sulfate (0.5 g, 4.5 mmol) in ACN (20.0 mL) was added a mixture of compound **C46A-c** and **C46B-c** (0.25 g, 0.7 mmol). The reaction mixture was stirred at 20 °C for 16 h under N_2. Then the mixture containing compound **C46A-d** and **C46B-d** was used in next step directly. LCMS ($M+H^+$): 351.

Step 5: preparation of 1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-ol (compound C46A-e) and 1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-ol (compound C46B-e)

To a solution of $NaOH/H_2O$ (1.2 mL,1.0 M) in ACN (10.0 mL) was added the mixture of compound **C46A-d** and **C46B-d** in step 4 and the resulting mixture was stirred at 25 °C for 1 h under N_2. The mixture was purified by prep-HPLC to give compound **C46A-e** (faster eluted, 50.0 mg) and **C46B-e** (slower eluted, 30.0 mg). LCMS ($M+H^+$): 315.

Step 6: preparation of 4-chloro-1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C46A)

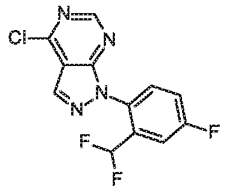
A solution of compound **C46A-e** (20.0 mg, 0.06 mmol) in $POCl_3$ (1.0 mL) was stirred at 80 °C for 1 h. The mixture was poured into a mixture of saturated aqueous $NaHCO_3$ solution (20.0 mL) and EtOAc (20.0 mL). The organic layer was washed with water, dried and concentrated to give intermediate **C46A** (8.0 mg). LCMS ($M+H^+$): 333.

Step 7: Preparation of 4-chloro-1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C46B)

The title compound was prepared in analogy to the preparation of intermediate **C46A** by using compound **C46B-e** instead of compound **C46A-e**. LCMS ($M+H^+$): 333.

Intermediate C47

4-chloro-1-[2-(difluoromethyl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine

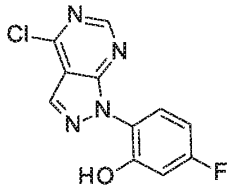


The title compound was prepared in analogy to the preparation of intermediate **C2** by using

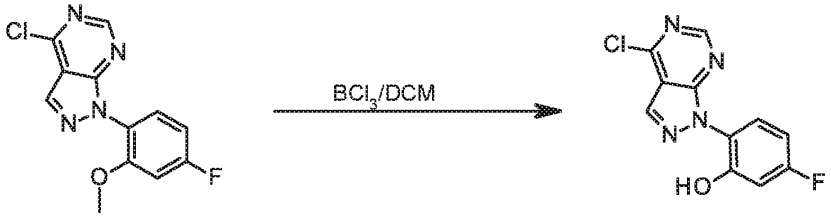
[2-(difluoromethyl)-4-fluoro-phenyl]hydrazine hydrochloride instead of compound **C2-a**. LCMS ($M+H^+$): 299.

Intermediate C50

2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenol



The title compound was prepared according to the following scheme:.

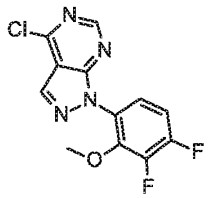


intermediate C50

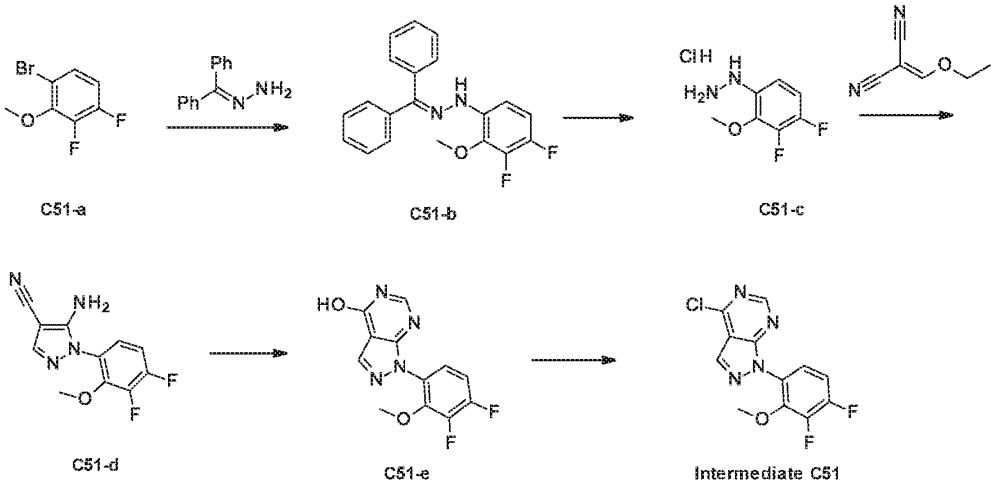
To a solution of 4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (200.0 mg, 0.72 mmol, **Intermediate C11**) in DCM (5 mL) was added BCl_3/DCM (2.15 mL, 2.15 mmol) at -78 °C. After being stirred at 20 °C for 2 h, the reaction mixture was poured into ice-water and extracted with EA, the organic layer was dried and concentrated to give intermediate **C50** (190 mg). LCMS $(M+H)^+$: 265.

Intermediate C51

4-chloro-1-(3,4-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.



Step 1~2: preparation of (3,4-difluoro-2-methoxy-phenyl)hydrazine hydrochloride (compound C51-c)

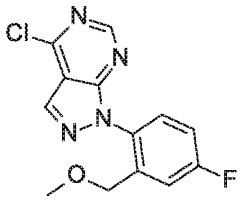
Compound **C51-c** was prepared in analogy to the preparation of compound **C11-d** by using compound **C51-a** instead of compound **C11-a**. LCMS $(M+H)^+$: 158.

Step 3~5: preparation of 4-chloro-1-(3,4-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C51)

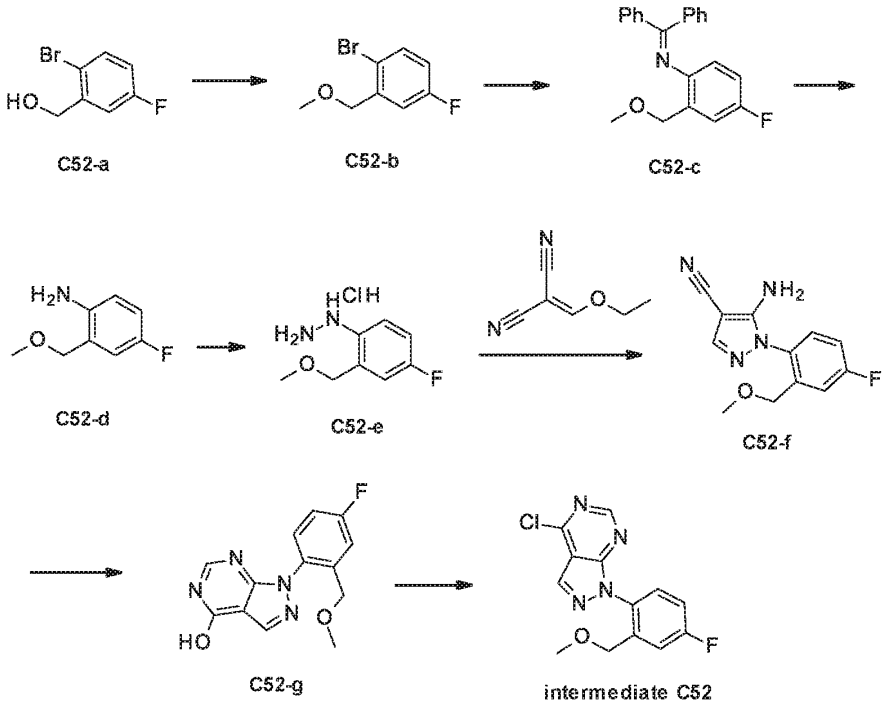
Intermediate **C51** was prepared in analogy to the preparation of Intermediate **C4** by using compound **C51-c** instead of compound **C4-a**. LCMS $(M+H)^+$: 297.

Intermediate C52

4-chloro-1-[4-fluoro-2-(methoxymethyl)phenyl]pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-bromo-4-fluoro-2-(methoxymethyl)benzene (compound C52-b)

To a solution of 2-bromo-5-fluorobenzyl alcohol (compound **C52-a**, 3 g, 14.63 mmol) and iodomethane (4.2 g, 29.27 mmol) in THF (30 mL) was added NaH (1.2 g, 29.27 mmol) at 0 °C, and then the mixture was stirred at 20 °C for 2 hours. The reaction was quenched with water and extracted with EA, the organic layer was dried and concentrated to give compound **C52-b** (3.4 g).

Step 2: preparation of *N*-[4-fluoro-2-(methoxymethyl)phenyl]-1,1-diphenyl-methanimine (compound C52-c)

A mixture of compound **C52-b** (1 g, 4.57 mmol), diphenylmethanimine (0.92 mL, 5.48 mmol), (R)-binap (625 mg, 1 mmol), tris(dibenzylideneacetone)dipalladium (418 mg, 0.46 mmol) and cesium carbonate (2231 mg, 6.85 mmol) in 1,4-dioxane (20 mL) was stirred at 100 °C for 12 hours under N_2. The reaction mixture was filtered, the filtrate was concentrated and the residue was purified by silica gel to give compound **C52-c** (1.4 g). LCMS $(M+H)^+$: 320.

Step 3: preparation of 4-fluoro-2-(methoxymethyl)aniline (compound C52-d)

A mixture of compound **C52-c** (1.4 g, 2.76 mmol), sodium acetate (0.5 mL, 6.63 mmol) and NH_2OH•HCl (0.38 g, 5.52 mmol) in methanol (8 mL) was stirred at 20 °C for 2 hours. The reaction mixture was filtered and the filtrate was poured into water, acidified pH to 1~2 with HCl (1 M). The resulting solution was extracted with EA to remove organic impurity, the aqueous

layer was then basified pH to 8~9 with NaOH (1 M) and extracted with EA. The organic layer was dried and concentrated to give compound **C52-d** (230 mg).

Step 4: preparation of [4-fluoro-2-(methoxymethyl)phenyl]hydrazine (compound C52-e)

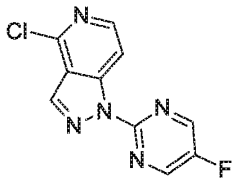
To a stirring solution of 4-fluoro-2-(methoxymethyl)aniline (compound **C52-d** 230 mg, 1.48 mmol) in HCl/water (2.08 mL, 10.38 mmol) was added a solution of $NaNO_2$ (0.15 g, 2.22 mmol) in water (2 mL) at 0 °C. After stirring for 30 mins, a solution of tin(II) chloride dihydrate (0.84 g, 3.71 mmol) in conc. HCl (0.37 mL, 4.45 mmol) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hours and then adjusted pH to 10~12 with 20% aqueous sodium hydroxide. The resulting solution was extracted with EA, the organic layer was added HCl in dioxane (4 M) while white solid precipitated, which was collected by filtration to give compound **C52-e** (130 mg). LCMS $(M-NH_2+H)^+$: 154.

Step 5~7: preparation of 4-chloro-1-[4-fluoro-2-(methoxymethyl)phenyl]pyrazolo[3,4-d]pyrimidine (Intermediate C52)

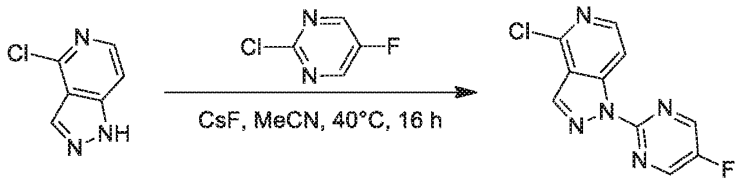
Intermediate **C52** was prepared in analogy to the preparation of Intermediate **C4** by using compound **C52-e** instead of compound **C4-a**. LCMS $(M+H)^+$: 293.

Intermediate C53

4-chloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:.

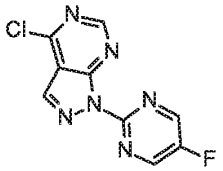


C53-a **Intermediate C53**

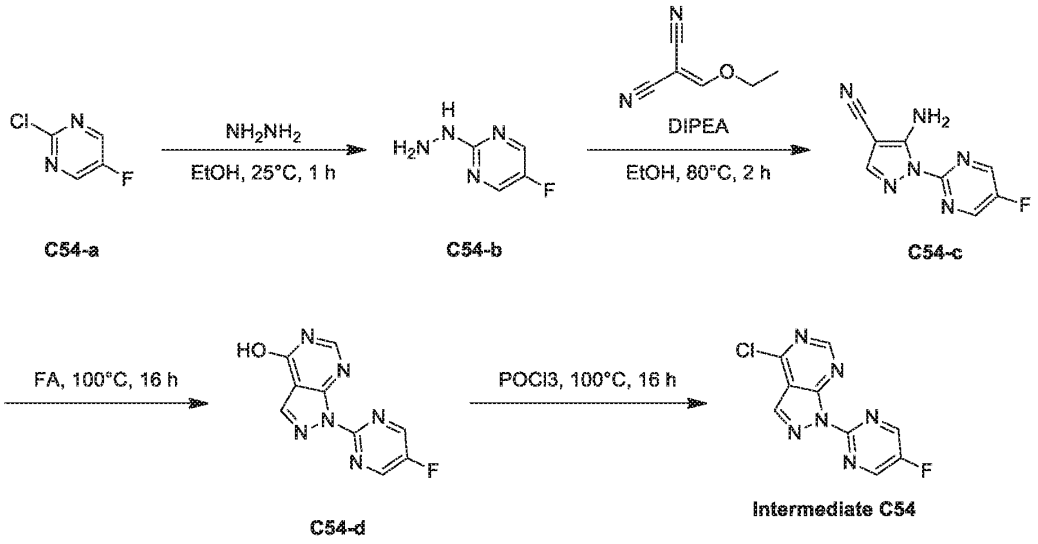
To a stirred solution of 2-chloro-5-fluoropyrimidine (compound **C53-a**, 60 mg, 0.45 mmol) and cesium fluoride (100 mg, 0.66 mmol) in acetonitrile (3 mL) was added 4-chloro-1H-pyrazolo[4,3-c]pyridine (50 mg, 0.33 mmol) at 40 °C, and the reaction mixture was stirred at 40 °C for 16 hours. The reaction mixture was concentrated and the residue was purified by prep-TLC to afford intermediate **C53** (60 mg). LCMS $(M+H)^+$: 250.

Intermediate C54

4-chloro-1-(5-fluoropyrimidin-2-yl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of (5-fluoropyrimidin-2-yl)hydrazine (compound C54-b)

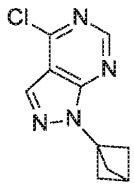
To a stirred solution of 2-chloro-5-fluoropyrimidine (compound **C54-a**, 2.0 g, 15.09 mmol) in ethanol (12 mL) was added hydrazine hydrate (3.66 mL, 75.46 mmol), then the mixture was stirred at 25 °C for 1 h. The reaction was concentrated to afford compound **C54-b** (1.9 g). LCMS $(M+H)^+$: 129.

Step 2~4: preparation of 4-chloro-1-(5-fluoropyrimidin-2-yl)pyrazolo[3,4-d] pyrimidine (Intermediate C54)

Intermediate **C54** was prepared in analogy to the preparation of Intermediate **C4** by using compound **C54-b** instead of compound **C4-a**. LCMS $(M+H)^+$: 251.

Intermediate C56

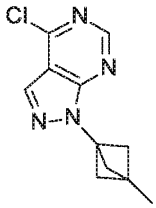
1-(1-bicyclo[1.1.1]pentanyl)-4-chloro-pyrazolo[3,4-d]pyrimidine



The title compounds were prepared in analogy to the preparation of intermediate **C10** by using bicyclo[1.1.1]pentan-1-amine instead of O-anisidine, LCMS $(M+H)^+$: 211.

Intermediate C57

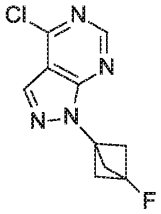
4-chloro-1-(3-methyl-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared in analogy to the preparation of intermediate **C10** by using 3-methylbicyclo[1.1.1]pentan-1-amine instead of O-anisidine, LCMS $(M+H)^+$: 235.

Intermediate C58

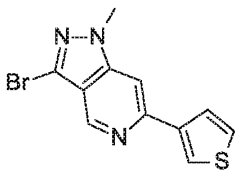
4-chloro-1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidine



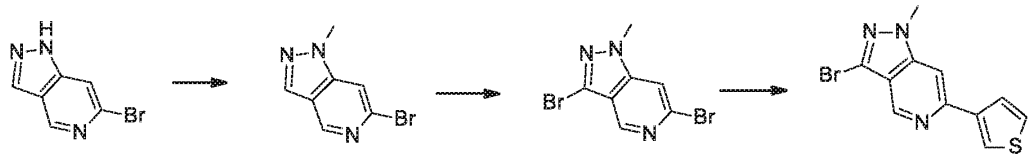
The title compound was prepared in analogy to the preparation of intermediate **C10** by using 3-fluorobicyclo[1.1.1]pentan-1-amine instead of O-anisidine. LCMS $(M+H)^+$: 239.

Intermediate C59

4-chloro-1-(2-ethoxyphenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



C59-a C59-b C59-c intermediated C59

Step 1: preparation of 6-bromo-1-methyl-pyrazolo [4,3-c]pyridine (compound C59-b)

A solution of 6-bromo-1*H*-pyrazolo[4,3-c]pyridine (compound **C59-a**, 4.0 g, 20.2 mmol) in DMFDMA (15.0 mL) was stirred at 120 °C for 12 h. The reaction mixture was concentrated and the residue was purified by silica gel to give compound **C59-b** (2.3 g). LCMS $(M+H)^+$: 212.

Step 2: preparation of 3-bromo-6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridine (compound C59-c)

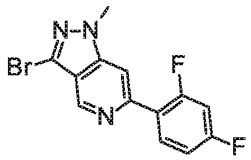
To a solution of compound **C59-b** (300 mg, 1.22 mmol) in DMF (6.2 mL) was added NBS (435 mg, 2.45 mmol) and then stirred at 80 °C for 2 hours. The reaction mixture was quenched with water, extracted with EA, the organic layer was dried and concentrated. The residue was purified by silica gel to afford compound **C59 c** (140 mg). LCMS $(M+H)^+$: 292.

Step 3: preparation of 3-bromo-1-methyl-6-(3-thienyl)-pyrazolo-[4,3-c]pyridine (intermediate C59)

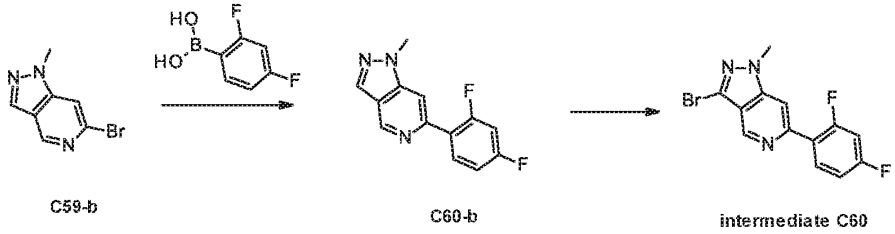
To a solution of compound **C59-c** (100 mg, 0.34 mmol) in THF (2 mL) and water (2 mL) was added tetrakis (triphenylphosphine) palladium (40 mg, 0.03 mmol), thiophene-2-boronic acid (66 mg, 0.52 mmol) and Na_2CO_3 (108 mg, 0.86 mmol). After stirring at 85 °C for 16 hours, the mixture was concentrated and the residue was purified by pre-TLC to afford intermediate **C59** (60 mg). LCMS $(M+H)^+$: 296.

Intermediate C60

3-bromo-6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridine



The title compound was prepared according to the following scheme:



C59-b C60-b intermediate C60

Step 1: preparation of 6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridine (compound C60-b)

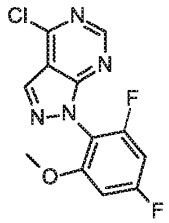
To a solution of compound **C59-b** (500 mg, 2.36 mmol), 2,4-difluorobenzeneboronic acid (447 mg, 2.83 mmol,) and potassium carbonate (652 mg, 4.72 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (173 mg, 0.240 mmol) under N_2, and the mixture was stirred at 90 °C for 3 h under N_2. The mixture was concentrated and the residue was purified by silica gel to give compound **C60-b** (540 mg). LCMS $(M+H)^+$:246.

Step 2: preparation of 3-bromo-6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridine (intermediated C60)

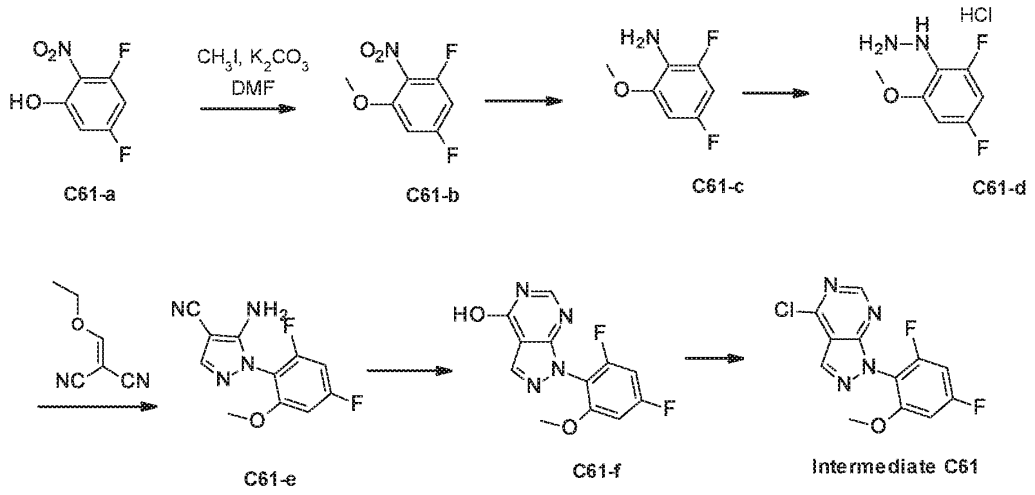
To a solution of compound **C60-b** (300 mg) in DMF (6 mL) was added NBS (435 mg, 2.45 mmol) and then stirred at 80 °C for 2 hours. The reaction mixture was quenched with water, extracted with EA, the organic layer was dried and concentrated. The residue was purified by silica gel to give intermediate **C60** (80 mg). LCMS $(M+H)^+$: 324.

Intermediate C61

4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 1,5-difluoro-3-methoxy-2-nitro-benzene (compound C61-b)

A mixture of 3,5-difluoro-2-nitro-phenol (compound **C61-a**, 9.5 g, 54.3 mmol), iodomethane (10.0 g, 70.5 mmol) and potassium carbonate (10.0 g, 72.4 mmol) in anhydrous DMF (250 mL) was stirred at room temperature for 12 hours. The mixture was diluted with EtOAc (500 mL), and washed with water (200 mL) and brine (200 mL). The organic layer was dried and concentrated to give the crude product, which was purified by flash chromatography to give compound **C61-b** (10.0 g). LCMS $(M+H)^+$: 190.

Step 2: preparation of 2,4-difluoro-6-methoxy-aniline (compound C61-c)

To a mixture of 1,5-difluoro-3-methoxy-2-nitro-benzene (compound **C61-b**, 10.0 g, 52.9 mmol) in anhydrous EtOAc (200 mL) was added Pd/C (1.0 g) and the reaction mixture was stirred at room temperature for 12 h under hydrogen. The mixture was filtered, the filtrate was concentrated to give compound **C61-c** (7.5 g). LCMS $(M+H)^+$: 160.

Step 3~5: preparation of 1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C61-f)

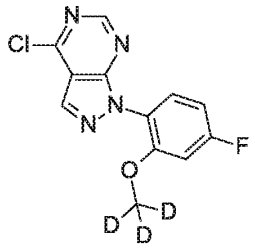
Compound **C61-f** was prepared in analogy to the preparation of intermediate **C43** by using 2,4-difluoro-6-methoxy-aniline instead of 2-bromo-4-fluoro-aniline. LCMS $(M+H)^+$: 279.

Step 6: preparation of 4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C61)

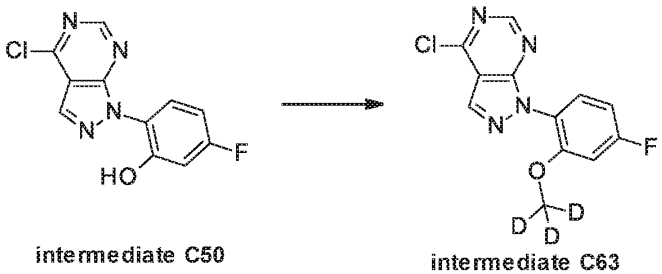
A mixture of 1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound **C61-f**, 4.6 g, 16.5 mmol) in $POCl_3$ (18 mL) was stirred at 100 °C for 2 h. The mixture was concentrated, the residue was taken in EtOAc (100 mL) and poured into aq.$NaHCO_3$ (100 mL). The separated organic layer was washed with brine, dried and concentrated to give Intermediate **C61** (4.14 g). LCMS $(M+H)^+$: 297.

Intermediate C62

4-chloro-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:

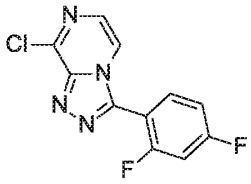


intermediate C50 intermediate C63

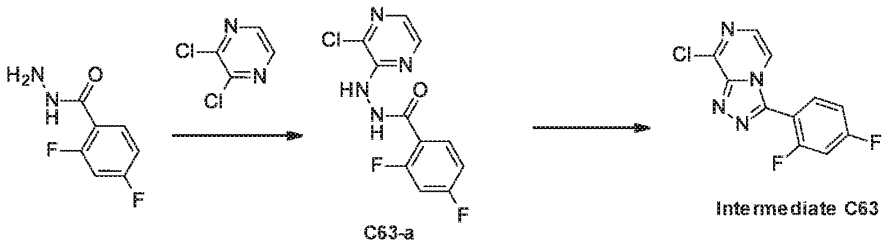
To a mixture of intermediate **C50** (100 mg, 0.38 mmol), trideuterio(deuteriooxy)methane (40.89 mg, 1.13 mmol) and triphenylphosphine (198 mg, 0.76 mmol) in THF (1 mL) was added DIAD (153 mg, 0.76 mmol) in one portion. The mixture was stirred at rt for 1 h and then concentrated, the residue was purified by silica gel to give intermediate **C62** (50 mg), LCMS: $(M+H)^+$: 282.

Intermediate C63

8-chloro-3-(2,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine



The title compound was prepared according to the following scheme:



C63-a Intermediate C63

Step 1: preparation of *N*'-(3-chloropyrazin-2-yl)-2,4-difluoro-benzohydrazide (compound C63-a)

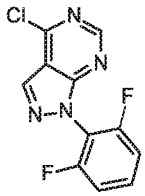
A mixture of 2,3-dichloropyrazine (1 g, 6.71 mmol), 2,4-difluorobenzohydrazide (1.16 g, 6.71 mmol), and Cs_2CO_3 (4.37 g, 13.42 mmol) in DMF was stirred at 100 °C for 2 hours, then the reaction was diluted with EA, washed with water and brine, the organic layer was dried and concentrated to give compound **C63-a** (1.5 g). LCMS: $(M+H)^+$: 285.

Step 2: preparation of 8-chloro-3-(2,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (Intermediate C63)

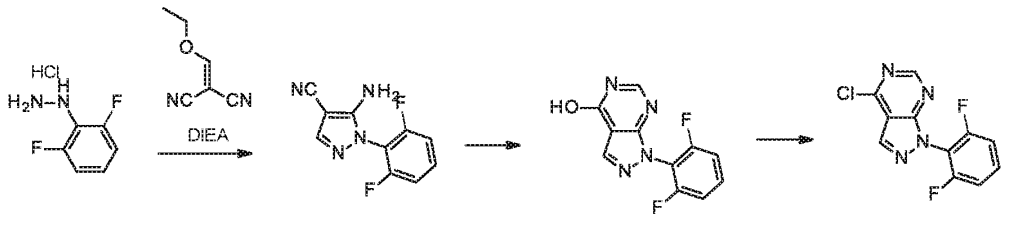
A mixture of compound **C63-a**(1.5 g, 5.27 mmol) in phosphorus oxychloride (10 mL) was stirred at 100 °C for 16 hours, then the reaction was diluted with EA, quench by adding to $NaHCO_3$ (5%, 100 mL). The organic layer was separated and concentrated, the residue was purified by flash preparation to give **Intermediate C63** (300 mg). LCMS: $(M+H)^+$: 267.

Intermediate C64

4-chloro-1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



C64-a C64-b C64-c Intermediate C64

Step 1~2: preparation of 1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C64-c)

Compound **C64-c** was prepared in analogy to the preparation of intermediate **C43** by using 2,6-difluoro-aniline instead of 2-bromo-4-fluoro-aniline. LCMS $(M+H)^+$: 249.

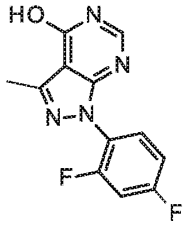
Step 3: preparation of 4-chloro-1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C64)

A mixture of 1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound **C64-c**, 3.7 g, 14.9 mmol) in $POCl_3$ (18 mL) was stirred at 100 °C for 4 h. The mixture was concentrated, the

residue was diluted with EtOAc (200 mL) and poured into aq.$NaHCO_3$ (200 mL). The separated organic layer was washed with brine, dried and concentrated to give Intermediate **C64** (3.7 g). LCMS $(M+H)^+$: 267.

Intermediate C65

1-(2,4-difluorophenyl)-3-methyl-pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:

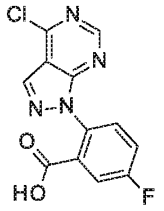


C65-a **Intermediate C65**

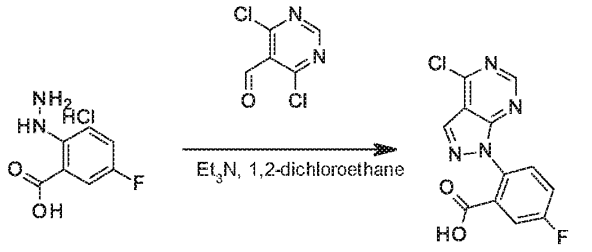
A mixture of 5-amino-1-(2,4-difluorophenyl)-3-methyl-pyrazole-4-carbonitrile (compound **C65-a**, 234 mg, 1 mmol) in formic acid (3 mL) was stirred at 120 °C for 2 h under microwave irritation. After removing excess formic acid in *vacuo*, the residue formed a slurry in EtOAc/hexane, then filtered. The filter cake was collected and dried to give Intermediate **C65** (241 mg). LCMS $(M+H)^+$: 263.

Intermediate C66

2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-benzoic acid



The title compound was prepared according to the following scheme:

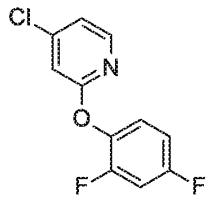


C66-a Intermedicate C66

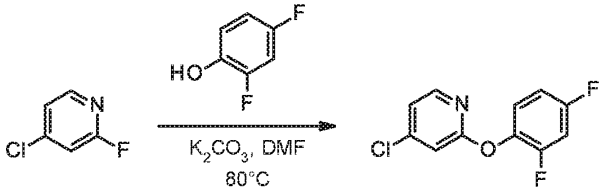
A mixture of 5-fluoro-2-hydrazino-benzoic acid hydrochloride (620 mg, 3 mmol), 4,6-dichloropyrimidine-5-carbaldehyde (531 mg, 3 mmol) and Et_3N (911 mg, 9 mmol) in anhydrous 1,2-dichloroethane (8 mL) was stirred at room temperature for 3 h. After removing solvent in *vacuo*, the residue formed a slurry in EtOAc/hexane, then filtered. The filtrate was concentrated and the residue was purified by flash chromatography to afford Intermediate **C66** (404 mg). LCMS $(M+H)^+$: 293.

Intermediate C67

4-chloro-2-(2,4-difluorophenoxy)pyridine



The title compound was prepared according to the following scheme:

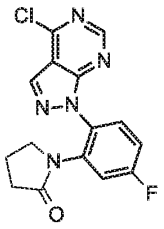


Intermedicate C67

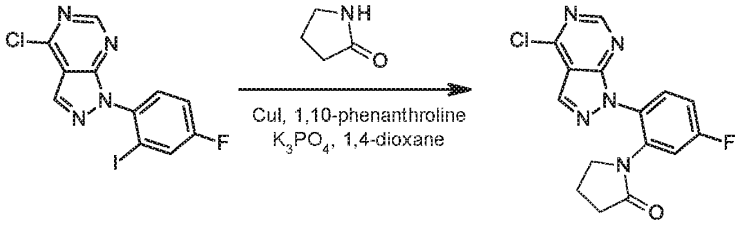
A mixture of 4-chloro-2-fluoropyridine (2.0 g, 15.2 mmol), 2,4-difluorophenol (2.2 g, 16.7 mmol) and potassium carbonate (4.2 g, 30.4 mmol) in DMF (60 mL) was stirred at 80 °C for 12 hours. After being cooled to room temperature, the reaction mixture was diluted with EtOAc (200 mL), washed with water and brine, the organic layer was dried and concentrated. The residue was purified by column chromatography to afford Intermediate **C67** (2.9 g). LCMS $(M+H)^+$: 242.

Intermediate C68

1-[2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenyl]pyrrolidin-2-one



The title compound was prepared according to the following scheme:

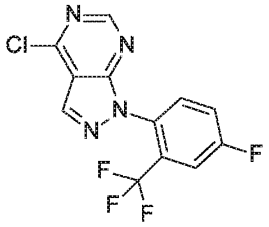


C20-e Intermediate C68

To a solution of **compound C20-e** (0.5 g, 1.1 mmol), 2-pyrrolidone (0.11 mL, 1.5 mmol), CuI (0.1 g, 0.5 mmol) and 1,10-phenanthroline (0.1 g, 0.55 mmol) in 1,4-dioxane (20 mL) was added potassium phosphate (283.0 mg, 1.3 mmol, 1.0 eq) and the reaction mixture was stirred at 75 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried and concentrated to get crude product, which was purified by column chromatography to afford Intermediate **C68** (0.1 g). LCMS $(M+H)^+$: 332.

Intermediate C69

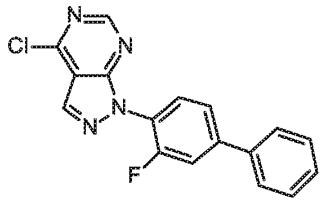
4-chloro-1-[4-fluoro-2-(trifluoromethyl)phenyl]pyrazolo[3,4-d]pyrimidine



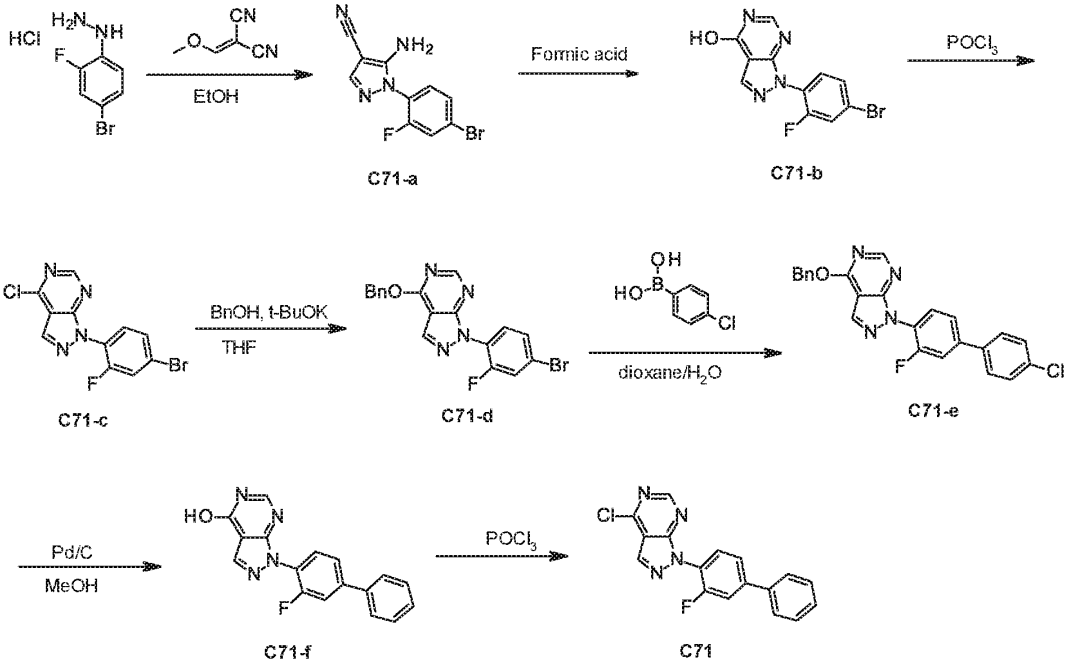
The title compound was prepared in analogy to the preparation of Intermediate **C2** by using [4-fluoro-2-(trifluoromethyl)phenyl]hydrazine hydrochloride instead of 2,4-difluorophenylhydrazine hydrochloride. LCMS $(M+H^+)$: 317.

Intermediate C71

4-chloro-1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



Step 1: preparation of 5-amino-1-(4-bromo-2-fluoro-phenyl)pyrazole-4-carbonitrile (compound C71-a)

A mixture of 2-(methoxymethylene)propanedinitrile (2.5 g, 20.7 mmol), DIEA (8.0 g, 62.1 mmol) and (4-bromo-2-fluoro-phenyl)hydrazine hydrochloride (5.0 g, 20.7 mmol) in ethanol (150 mL) was stirred at 60 °C for 2 hours. The mixture was poured into water (200 mL) and extracted with EtOAc (200 mL twice). The combined organic layer was dried and concentrated to give compound **C71-a** (5.5 g). LCMS ($M+H^+$): 281.

Step 2: preparation of 1-(4-bromo-2-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C71-b)

A mixture of compound **C71-a** (5.5 g, 19.6 mmol) in formic acid (20.0 mL) was stirred at 120 °C for 12 hours. The mixture was concentrated, and the residue was triturated in MeOH (0.1 L) to give compound **C71-b** (5.0 g). LCMS ($M+H^+$): 309.

Step 3: preparation of 1-(4-bromo-2-fluoro-phenyl)-4-chloro-pyrazolo[3,4-

d]pyrimidine (compound C71-c)

The mixture of compound **C71-b** (4.0 g, 12.9 mmol) in $POCl_3$ (10.0 mL) was stirred at 100 °C for 2 hours. The mixture was concentrated. The residue was triturated in MeOH (0.1 L) to give compound **C71-c** (4.0 g) as a yellow solid. LCMS ($M+H^+$): 327.

Step 4: preparation of 4-benzyloxy-1-(4-bromo-2-fluoro-phenyl)pyrazolo[3,4-d]pyrimidine (compound C71-d)

A mixture of compound **C71-c** (1.0 g, 3.0 mmol), benzyl alcohol (0.4 g, 3.9 mmol) and t-BuOK (0.6 g, 6.0 mmol) in THF (5 mL) was stirred at 0 °C for 1 h. The mixture was poured into water (20 mL) and extracted with EA (20 mL twice). The combined organic layer was dried and concentrated to give compound **C71-d** (0.3 g). LCMS ($M+H^+$): 399.

Step 5: preparation of 4-benzyloxy-1-[4-(4-chlorophenyl)-2-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine (compound C71-e)

To a mixture of compound **C71-d** (0.2 g, 0.5 mmol) and Na_2CO_3 (0.1 g, 1.0 mmol) in 1,4-dioxane (2 mL) and water (0.4 mL) was added (4-chlorophenyl)boronic acid (131.4 mg, 0.6mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and toluene (41.21 mg, 0.05 mmol). Then the mixture was stirred at 50 °C for 12 hours under N_2. The mixture was filtered and concentrated, the residue was purified by pre-HPLC to compound **C71-e** (0.2 g). LCMS ($M+H^+$): 431.

Step 6: preparation of 1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C71-f)

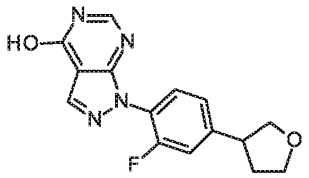
To a mixture of compound **C71-e** (0.1 g, 0.2 mmol) in methanol (1 mL) was added Pd/C (20 mg) and the mixture was stirred at 20 °C for 2 hours under H_2. The mixture was filtered and concentrated to give crude compound **C71-f** (30 mg). LCMS ($M+H^+$): 307.

Step 6: preparation of 4-chloro-1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidine (Intermediate C71)

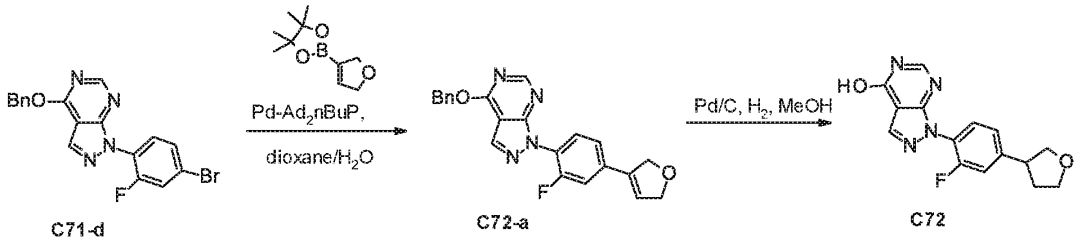
A mixture of crude compound **C71-f** (30.0 mg) in $POCl_3$ (1.0 mL) was stirred at 100 °C for 2 hours. The mixture was partitioned between $NaHCO_3$ a.q. (30 mL) and EA (30 mL). The organic layer was dried and concentrated to give crude Intermediate **C71** (30 mg). LCMS ($M+H^+$): 325.

Intermediate C72

1-(2-fluoro-4-tetrahydrofuran-3-yl-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-benzyloxy-1-[4-(2,5-dihydrofuran-3-yl)-2-fluoro-phenyl]pyrazolo[3,4-d]pyrimidine (compound C72-a)

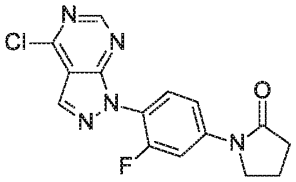
To a mixture of compound **C71-d** (0.2 g, 0.5 mmol) and K_3PO_4 (0.2 g, 1 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.1 g, 0.6 mmol) and Pd-Ad$_2$nBuP Biphenyl Precat (G1) (33.4 mg, 0.05 mmol). Then the mixture was stirred at 60 °C for 1 h under N_2. The mixture was filtered and the filtrate was concentrated, the residue was purified by pre-HPLC to give compound **C72-a** (120 mg). LCMS ($M+H^+$): 389.

Step 2: preparation of 1-(2-fluoro-4-tetrahydrofuran-3-yl-phenyl)pyrazolo[3,4-d]pyrimidin-4-ol (Intermediate C72)

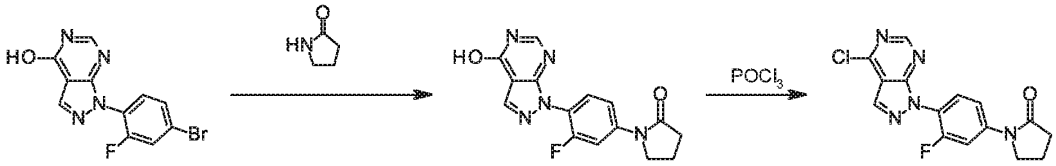
To a mixture of compound **C72-a** (0.1 g, 0.3 mmol) in MeOH (5 mL) was added Pd/C (50 mg) and then the mixture was stirred at 20 °C for 1 h under H_2. The mixture was filtered and the filtrate was concentrated to give intermediate **C72** (70.0 mg). LCMS ($M+H^+$): 301.

Intermediate C73

1-[4-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-3-fluoro-phenyl]pyrrolidin-2-one



The title compound was prepared according to the following scheme:



C71-b C73-a C73

Step 1: preparation of 1-[3-fluoro-4-(4-hydroxypyrazolo[3,4-d]pyrimidin-1-yl)phenyl]pyrrolidin-2-one (compound C73-a)

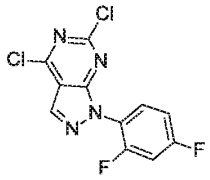
To a mixture of pyrrolidin-2-one (1.0 mL, 12.9 mmol), compound **C71-b** (1.0 g, 3.24 mmol) and TMEDA (0.4 g, 6.5 mmol) in DMF (10 mL) was added K_2CO_3 (1.4 g, 9.7 mmol) and CuI (1.2 g, 6.4 mmol). After being stirred at 120 °C for 2 h, the mixture was filtered and the filtrate was concentrated, the residue was purified by pre-HPLC to give compound **C73-a** (0.1 g). LCMS ($M+H^+$): 314.

Step 2: preparation of 1-[4-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-3-fluoro-phenyl]pyrrolidin-2-one (Intermediate C73)

A mixture of compound **C73-a** (20.0 mg, 0.06 mmol) in $POCl_3$ (1.0 mL) was stirred at 100 °C for 1 h, and then poured into a mixture of $NaHCO_3$ a.q. (50 mL) and EtOAc (50 mL). The organic layer was separated, washed with brine and concentrated to give Intermediate **C73** (15 mg). LCMS ($M+H^+$): 332.

Intermediate C74

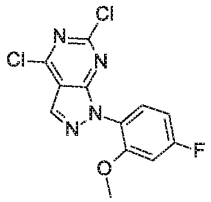
4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared in analogy to the preparation of Intermediate **C1** by using 2,4,6-trichloropyrimidine-5-carbaldehyde instead of 4,6-dichloropyrimidine-5-carbaldehyde. LCMS ($M+H^+$): 301.

Intermediate C75

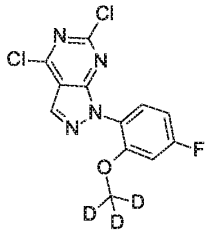
4,6-dichloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



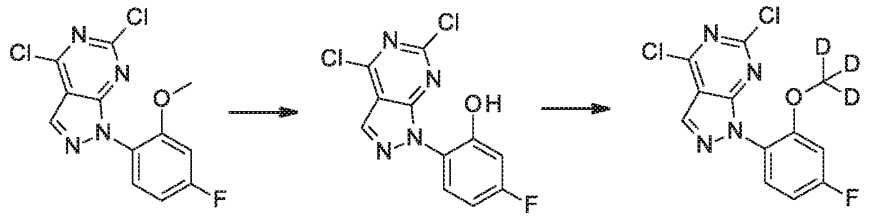
The title compound was prepared in analogy to the preparation of Intermediate **C2** by using 2,4,6-trichloropyrimidine-5-carbaldehyde instead of 4,6-dichloropyrimidine-5-carbaldehyde and compound **C11-d** instead of compound **C2-a**. LCMS ($M+H^+$): 313.

Intermediate C76

4,6-dichloro-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:



intermediate C75 C76-a intermediate C76

Step 1: preparation of 2-(4,6-dichloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenol (compound C76-a)

To a solution of intermediate **C75** (2.0 g, 6.39 mmol) in DCM (40 mL) was added BCl_3/THF (31.94 mL, 31.94 mmol) at -78 °C and the reaction mixture was stirred at 25 °C for 12 hours, then poured into ice-water (100 mL), extracted with DCM. The organic layer was dried and concentrated to give compound **C76-a** (1.51 g), LCMS ($M+H^+$): 299.

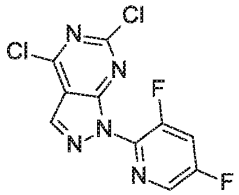
Step 2: preparation of 4,6-dichloro-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d] pyrimidine (Intermediate C76)

To a mixture of compound **C76-a** (1 g, 3.34 mmol), trideuterio(deuteriooxy) methane (350 mg, 10.92 mmol) and TPP (1.3 g, 5 mmol) in toluene (15 mL) was added DEAD (873 mg, 5 mmol) at 0 °C under N_2, then the mixture was stirred at 50 °C for 1 h under N_2. The reaction was

quenched with water (100 mL) and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by column chromatography to Intermediate **C76** (800 mg). LCMS ($M+H^+$): 316.

Intermediate C77

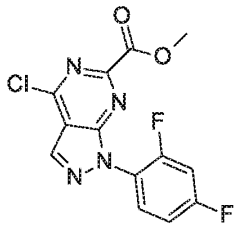
4,6-dichloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine



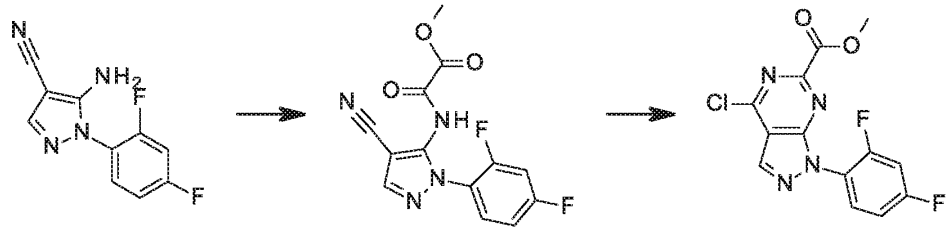
The title compound was prepared in analogy to the preparation of Intermediate **C2** by using 2,4,6-trichloropyrimidine-5-carbaldehyde instead of 4,6-dichloropyrimidine-5-carbaldehyde and compound **C1-b** instead of compound **C2-a**. LCMS ($M+H^+$): 302.

Intermediate C78

methyl 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carboxylate



The title compound was prepared according to the following scheme:



C4-b C78-b Intermediate C78

Step 1 : preparation of methyl 2-[[4-cyano-2-(2,4-difluorophenyl)pyrazol-3-yl]amino]-2-oxo-acetate (compound C78-b)

To a solution of **compound C4-b** (5.0 g, 22.71 mmol) in sulfolane (50 mL) at 10 °C was added methyl oxalyl chloride (3.07 mL, 34.06 mmol) slowly (about 30 min). Then the mixture was stirred at 110 °C for 16 h. The mixture was cooled to 25 °C and poured into a stirred ice water (500 mL) and EtOAc (100 mL). The organic layer was separated, dried and concentrated,

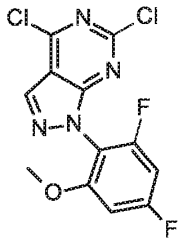
the residue was purified by silica gel and prep-HPLC to give compound **C78-b** (5 g). LCMS ($M+H^+$): 307.

Step 2 : preparation of methyl 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carboxylate (Intermediate C78)

To the compound **C78-b** (2.2 g, 7.18 mmol) was added $POCl_3$ (30 mL) at 0 °C. After being stirred at 110 °C for 36 hours, the mixture was concentrated to give the crude product, which was diluted with DCM (30 mL) and then poured into ice-$NaHCO_3$. Then the mixture was extracted with DCM, the organic layer was dried and concentrated, the residue was purified by flash chromatography to give Intermediate **C78** (1.5 g). LCMS ($M+H^+$): 325

Intermediate C79

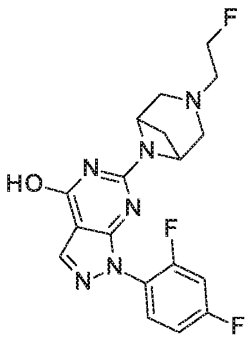
4,6-dichloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidine



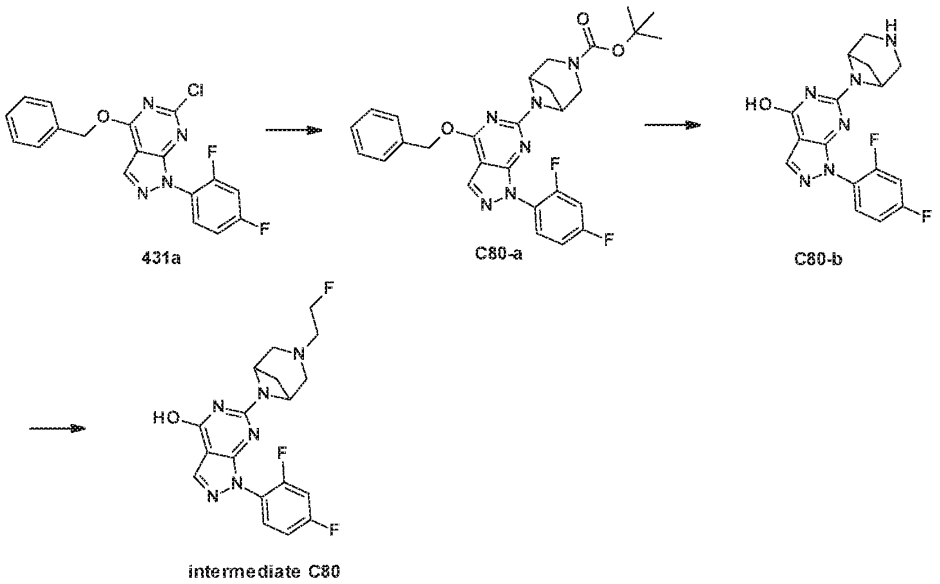
The title compound was prepared in analogy to the preparation of Intermediate **C2** by using 2,4,6-trichloropyrimidine-5-carbaldehyde instead of 4,6-dichloropyrimidine-5-carbaldehyde and compound **C61-d** instead of compound **C2-a**. LCMS ($M+H^+$): 331.

Intermediate C80

1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 6-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (compound C80-a)

To a solution of compound **431a** (1.25 g, 3.35 mmol), *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (731.32 mg, 3.69 mmol) in DMSO (20 mL) was added *N,N*-diisopropylethylamine (1.75 mL, 10 mmol) and then stirred at 100 °C for 1 h. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give compound **C80-a** (2.0 g) as a brow oil. LCMS ($M+H^+$):535.

Step 2: preparation of 6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C80-b)

To a solution of **compound C80-a** (4.0 g, 7.48 mmol) in DCM (20 mL) was added TFA at 0 °C and then stirred at 25 °C for 2 hrs. The reaction mixture was concentrated and the residue was diluted with water (50 mL), which was lyophilized to give **compound C80-b** (2.5 g) as a yellow solid. LCMS ($M+H^+$):345.

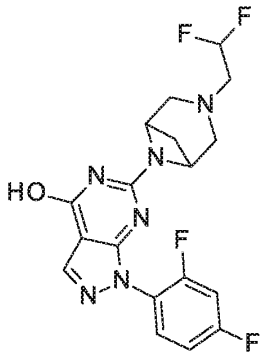
Step 3: preparation of 1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol (intermediate C80)

To a solution of **compound C80-b** (500.0 mg, 1.09 mmol), 1-fluoro-2-iodoethane (1.90 g, 10.91 mmol) in ACN (20 mL) was added triethylamine (1.52 mL, 10.91 mmol) and then the mixture was stirred at 80 °C for 12 hrs. The reaction was quenched with water (200 mL) and the mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash-

HPLC (TFA as additive) to give **intermediate C80** (300.0 mg) as a yellow solid. LCMS ($M+H^+$):391.

Intermediate C81

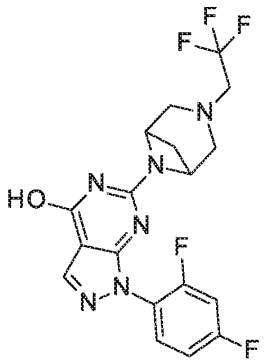
6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C81 was prepared in analogy to the preparation of **Intermediate C80** by using 2,2-difluoroethyl methanesulfonate instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):409.

Intermediate C82

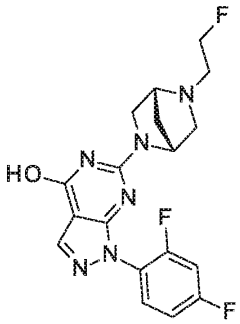
1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C82 was prepared in analogy to the preparation of **Intermediate C80** by using 2,2,2-trifluoroethyl trifluoromethanesulfonate instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):427.

Intermediate C83

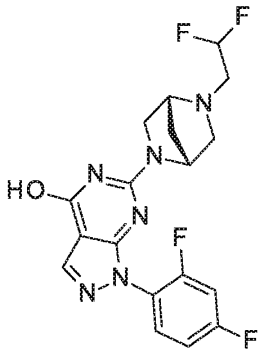
1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C83 was prepared in analogy to the preparation of **Intermediate C80** by using *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS ($M+H^+$):391.

Intermediate C84

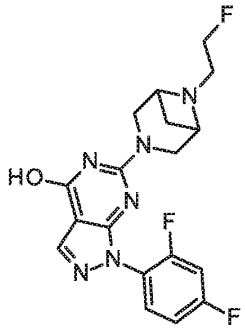
6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C84 was prepared in analogy to the preparation of **Intermediate C80** by using *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate and 2,2-difluoroethyl methanesulfonate instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):409.

Intermediate C85

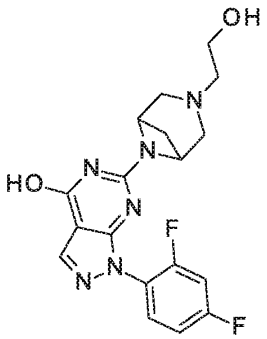
1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C85 was prepared in analogy to the preparation of **Intermediate C80** by using *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS ($M+H^+$):391.

Intermediate C86

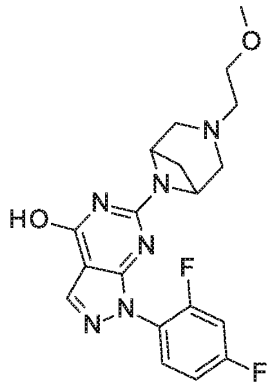
1-(2,4-difluorophenyl)-6-[3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C86 was prepared in analogy to the preparation of **Intermediate C80** by using ethylene oxide instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):389.

Intermediate C87

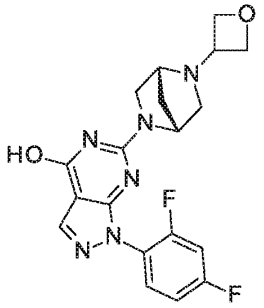
1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



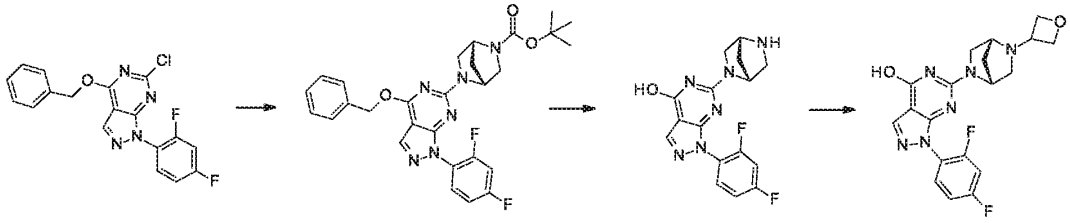
Intermediate C87 was prepared in analogy to the preparation of **Intermediate C80** by using 1-iodo-2-methoxy-ethane instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):403.

Intermediate C88

1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl (1*R*,4*R*)-5-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (compound C88-a)

To a solution of **compound 431a** (1.0 g, 2.68 mmol) and *tert*-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (585 mg, 2.95 mmol) in DMSO (16 mL) was added *N,N*-diisopropylethylamine (1.4 mL, 8.05 mmol) and then stirred at 90 °C for 1 h. The reaction

mixture was poured into water (400 mL) and extracted with ethyl acetate (100 ml×3). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to give **compound C88-a** (3.5 g) as a brown oil. LCMS ($M+H^+$): 535.

Step 2: preparation of 6-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound C88-b)

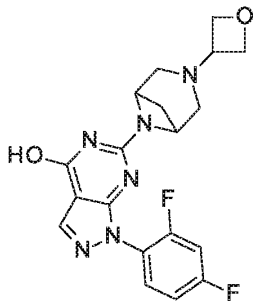
To a solution of **compound C88-a** (650 mg, 1.22 mmol) in DCM (10 mL) was added TFA (3.04 mL, 12.16 mmol) at 0 °C and then stirred at 25 °C for 1 h. The reaction mixture was concentrated to give **compound c88-b** (1500 mg) as a yellow oil. LCMS ($M+H^+$): 345.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-ol (Intermediate C88)

To a solution of **compound C88-b** (450.0 mg, 0.98 mmol), 3-oxetanone (720.0 mg, 9.99 mmol) in DCE (9 mL) was added sodium triacetoxyborohydride (1.04 g, 4.91 mmol) at 0 °C and then stirred at 25 °C for 1 h. The mixture was diluted with H_2O (30 mL) and extracted with EA (20 mL×2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give **intermediate C88** (200.0) as a brown solid. LCMS ($M+H^+$): 401.

Intermediate C89

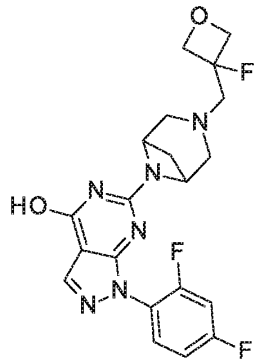
1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C89 was prepared in analogy to the preparation of **Intermediate C88** by using *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate instead of *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. LCMS ($M+H^+$): 401.

Intermediate C90

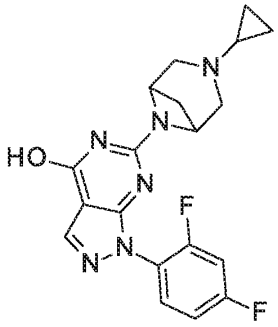
1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C90 was prepared in analogy to the preparation of **Intermediate C88** by using *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate instead of *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and 3-fluorooxetane-3-carbaldehyde instead of cyclobutanone. LCMS ($M+H^+$): 433.

Intermediate C91

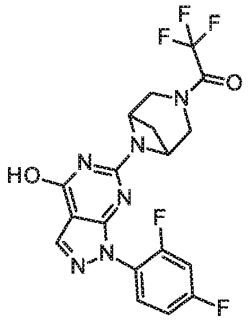
6-[3-cyclopropyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol



Intermediate C91 was prepared in analogy to the preparation of **Intermediate C88** by using *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate instead of *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and (1-ethoxycyclopropoxy)trimethylsilane instead of cyclobutanone. LCMS ($M+H^+$): 385.

Intermediate C92

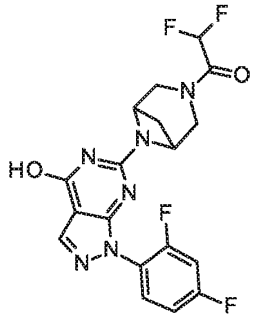
1-[6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]-2,2,2-trifluoro-ethanone



To a solution of **compound C80-b** (100.0 mg, 0.22 mmol), triethylamine (0.09 mL, 0.65 mmol) in DCM (2 mL) was added trifluoroacetic anhydride (0.05 mL, 0.33 mmol) at 0 °C and then stirred at 25 °C for 1 h. The reaction mixture was poured into water (20 mL) and extracted with DCM (20mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated to give **intermediate C92** (100.0 mg) as a white solid. LCMS ($M+H^+$): 441.

Intermediate C93

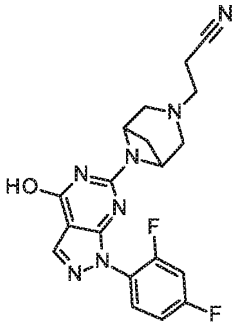
1-[6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]-2,2-difluoro-ethanone



Intermediate C93 was prepared in analogy to the preparation of **Intermediate C92** by using (2,2-difluoroacetyl) 2,2-difluoroacetate instead of trifluoroacetic anhydride. LCMS ($M+H^+$): 423.

Intermediate C94

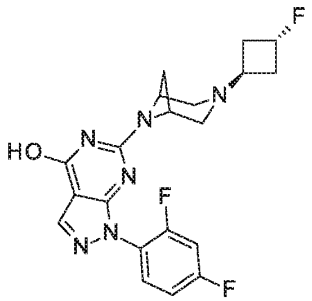
3-[6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile



Intermediate C94 was prepared in analogy to the preparation of **Intermediate C80** by using 3-bromopropionitrile instead of 1-fluoro-2-iodoethane. LCMS ($M+H^+$):398.

Intermediate C95

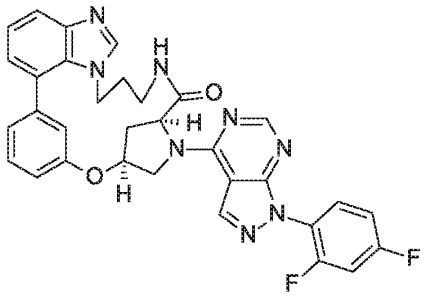
1-(2,4-difluorophenyl)-6-[3-(3-fluorocyclobutyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol



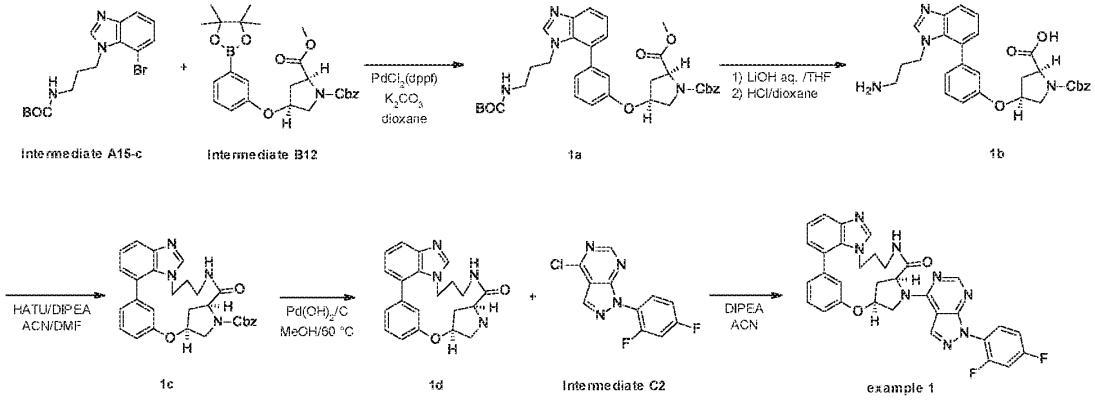
Intermediate C95 was prepared in analogy to the preparation of **Intermediate C88** by using *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate instead of *tert*-butyl (1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate and 3-fluorocyclobutanone instead of cyclobutanone. LCMS ($M+H^+$): 417.

Example 1

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[3-[3-[3-(*tert*-butoxycarbonylamino)propyl]benzimidazol-4-yl]phenoxy]pyrrolidine-1,2-dicarboxylate (compound 1a)

To a flask was added *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]pyrrolidine-1,2-dicarboxylate (compound **B12**, 1.63 g, 3.39 mmol) , *tert*-butyl N-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (compound **A15-c**, 1 g, 2.82 mmol,), K_2CO_3 (780 mg, 5.65 mmol), 1,4-dioxane (15mL) and water (0.5mL), the suspension was bubbled with N_2 for 5 mins and $PdCl_2(DPPF)$-CH_2Cl_2 adduct (207 mg, 282 μmol) was added. The mixture was heated to 100 °C for 2 hrs. The mixture was diluted with 40 mL water and then it was extracted with EA three times, the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel to give compound **1a** (688 mg), LCMS ($M+H^+$): 629.

Step 2: preparation of (2*S*,4*S*)-4-[3-[3-(3-aminopropyl)benzimidazol-4-yl]phenoxy]-1-benzyloxycarbonyl-pyrrolidine-2-carboxylic acid;hydrochloride (compound 1b)

To the flask containing *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[3-[3-[3-(*tert*-butoxycarbonylamino)propyl]benzimidazol-4-yl]phenoxy]pyrrolidine-1,2-dicarboxylate (compound **1a**, 866 mg, 1.38 mmol) was added THF (8mL) and 2 N aqueous solution of LiOH

(4mL, 8 mmol). The mixture was stirred at r.t. for 3 hrs. To the mixture was added 20 mL DCM and then it was acidified with 1 N aqueous solution of HCl (pH ~ 5). The mixture was separated, the organic layer was dried concentrated to give (2*S*,4*S*)-1-benzyloxycarbonyl-4-[3-[3-[3-(*tert*-butoxycarbonylamino) propyl]benzimidazol-4-yl]phenoxy]pyrrolidine-2-carboxylic acid which was obtained as brown oil, then dissolved in EtOAc (2mL) and HCl 4 N in dioxane (4.8 g, 4mL, 16 mmol) was added. The mixture was stirred at r.t. for 3 hrs. The mixture was concentrated directly to give compound **1b** (650 mg), LCMS ($M+H^+$): 515.

Step 3: preparation of benzyl (8*S*,11*S*)-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 1c)

To a 1000 mL flask was added 2-(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (720 mg, 1.89 mmol), DIPEA (408 mg, 552 μL, 3.16 mmol) and acetonitrile (325mL), the solution was cooled with ice bath and then a solution of (2*S*,4*S*)-4-(3-(1-(3-aminopropyl)-1*H*-benzo[d]imidazol-7-yl)phenoxy)-1-((benzyloxy) carbonyl)pyrrolidine-2-carboxylic acid (compound **1b**, 650 mg, 1.26 mmol) in DMF (65mL) was added via dropping funnel for about 20 min. The mixture was concentrated to remove the ACN, the residue was poured into 200 mL water and extracted with EA/MeOH=50:1 (150 mL for 3 times), the organic layer was dried over Na_2SO_4 and concentrated to give an oil, which was dried to give compound **1c** (440 mg), LCMS ($M+H^+$): 497.

Step 4: preparation of (8*S*,11*S*)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 1d)

The benzyl (8*S*,11*S*)-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound **1c**, 440 mg, 0.88 mmol) was dissolved in MeOH (50mL) and then $Pd(OH)_2$ (20% on carbon with 50% H_2O) (177 mg, 1.26 mmol) was added. The mixture was purged with H_2 for 5 times. The mixture was heated to 60 °C and stirred under H_2 balloon for about 16 hrs. The mixture was concentrated to give compound **1d** (~800 mg, containing some DMF), LCMS ($M+H^+$): 363.

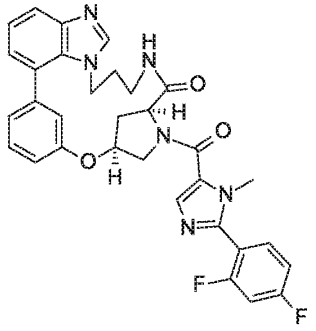
Step 5: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (example 1)

To a microwave tube was added (8*S*,11*S*)-7-oxa-10,13,17,19-

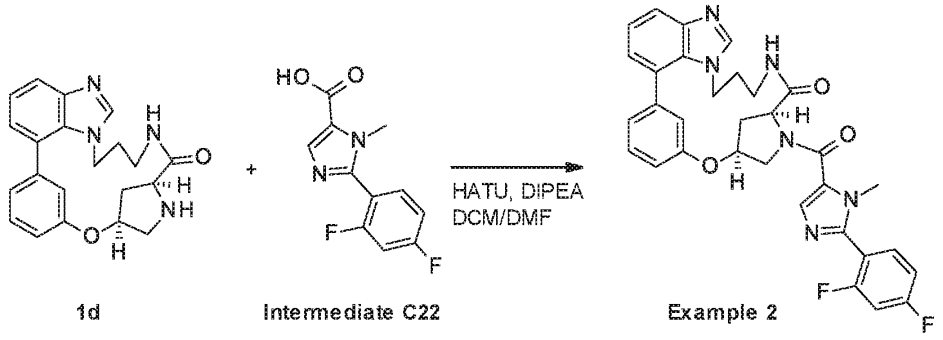
tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **1d**, 30 mg, 82.8 µmol), 4-chloro-1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound **C2**, 22.1 mg, 82.8 µmol,), DIPEA (32.1 mg, 43.4 µL, 248 µmol) and acetonitrile (2mL). The mixture was heated to 90 °C and stirred for about 1 hr, then concentrated to give an oil which was purified via prep-HPLC to give Example **1** (3.7 mg), LCMS (M+H$^+$): 593. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.31 - 7.94 (m, 2H), 7.70 - 7.59 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.32 - 7.24 (m, 2H), 7.23 - 7.18 (m, 1H), 7.18 - 7.12 (m, 2H), 7.09 (br s, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 5.53 - 5.33 (m, 1H), 5.06 (br d, *J* = 9.7 Hz, 1H), 4.54 (br d, *J* = 11.4 Hz, 1H), 4.42 - 4.28 (m, 1H), 4.23 - 4.07 (m, 1H), 4.05 - 3.91 (m, 1H), 3.52 - 3.37 (m, 1H), 3.20 - 3.08 (m, 1H), 2.86 (br d, *J* = 14.2 Hz, 1H), 2.76 - 2.50 (m, 1H), 2.29 - 2.13 (m, 1H), 2.03 - 1.86 (m, 1H).

Example 2

(8*S*,11*S*)-10-[2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carbonyl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



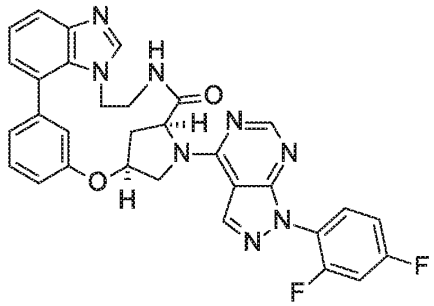
1d Intermediate C22 Example 2

To a microwave tube was added 2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carboxylic acid (compound **C22**, 65.7 mg, 276 µmol), 2-(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-

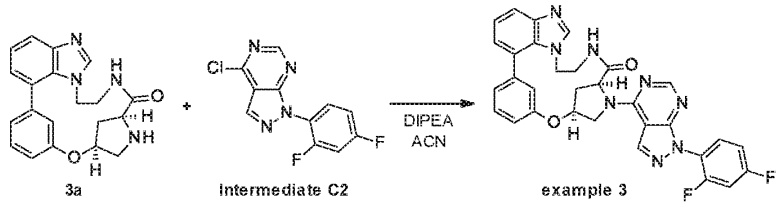
tetramethylisouronium hexafluorophosphate(V) (157 mg, 414 μmol,), DIPEA (107 mg, 145 μL, 828 μmol) and DCM (2mL), the suspension was stirred for a while and a solution of (8*S*,11*S*)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26), 3,5,18,20(24),21-heptaen-12-one (compound **1d**, 100 mg, 276 μmol) in DMF (0.5mL) was added. After being stirred at r.t. for 16 hrs, the mixture was filtered, the filtrate was concentrated to give an oil which was purified via prep-HPLC to give Example **2** (23 mg), LCMS (M+H$^+$): 583. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.50 - 9.38 (m, 1H), 8.10 - 8.01 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.69 - 7.63 (m, 1H), 7.60 - 7.54 (m, 1H), 7.51 - 7.45 (m, 1H), 7.37 - 7.23 (m, 3H), 7.11 - 7.01 (m, 2H), 5.43 - 5.35 (m, 1H), 4.96 - 4.91 (m, 1H), 4.17 - 4.00 (m, 2H), 3.94 - 3.87 (m, 3H), 3.87 - 3.83 (m, 2H), 3.56 - 3.39 (m, 1H), 3.10 - 2.88 (m, 1H), 2.86 - 2.72 (m, 1H), 2.71 - 2.47 (m, 1H), 2.45 - 2.20 (m, 1H), 2.05 - 1.74 (m, 1H).

Example 3

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,16,18-tetrazapentacyclo[14.6.1.1^{2,6}.1^{8,11}.0^{19,23}]pentacosa-1(22),2,4,6(25),17,19(23),20-heptaen-12-one



The title compound was prepared according to the following scheme:



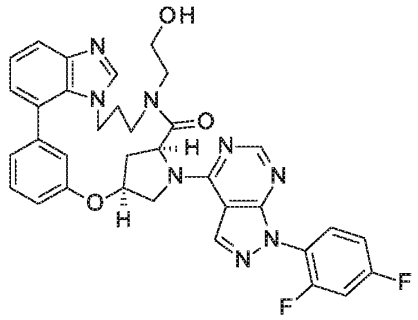
3a Intermediate C2 example 3

To a microwave tube was added (8*S*,11*S*)-7-oxa-10,13,16,18-tetrazapentacyclo [14.6.1.1^{2,6}.1^{8,11}.0^{19,23}]pentacosa-1(22),2,4,6(25),17,19(23),20-heptaen-12-one (compound **3a**, 40 mg, 115 μmol, the synthesis refers to compound **1d** by using *tert*-butyl *N*-(2-aminoethyl)carbamate instead of *tert*-butyl N-(3-aminopropyl)carbamate), 4-chloro-1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidine (Intermediate **C2**, 36.7 mg, 138 μmol, Eq: 1.2),

DIPEA (59.4 mg, 80.2 µL, 459 µmol) and acetonitrile (4 mL), a yellow solution formed. The mixture was heated to 90 °C for 2 hrs, then the mixture was concentrated to give an oil, which was purified via prep-HPLC to give the Example **3** (9 mg), LCMS ($M+H^+$): 579. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.33 (s, 1H), 8.59 - 8.36 (m, 1H), 8.27 - 7.95 (m, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.71 - 7.62 (m, 2H), 7.59 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 7.1 Hz, 1H), 7.37 - 7.32 (m, 1H), 7.32 - 7.25 (m, 1H), 7.24 - 7.16 (m, 1H), 7.04 (br d, J = 7.5 Hz, 1H), 7.01 - 6.96 (m, 1H), 5.66 - 5.50 (m, 1H), 5.12 - 5.02 (m, 1H), 4.62 - 4.45 (m, 2H), 4.39 (br dd, J = 3.7, 11.2 Hz, 1H), 3.80 - 3.68 (m, 1H), 3.62 - 3.51 (m, 2H), 2.79 - 2.67 (m, 1H), 2.63 - 2.50 (m, 1H).

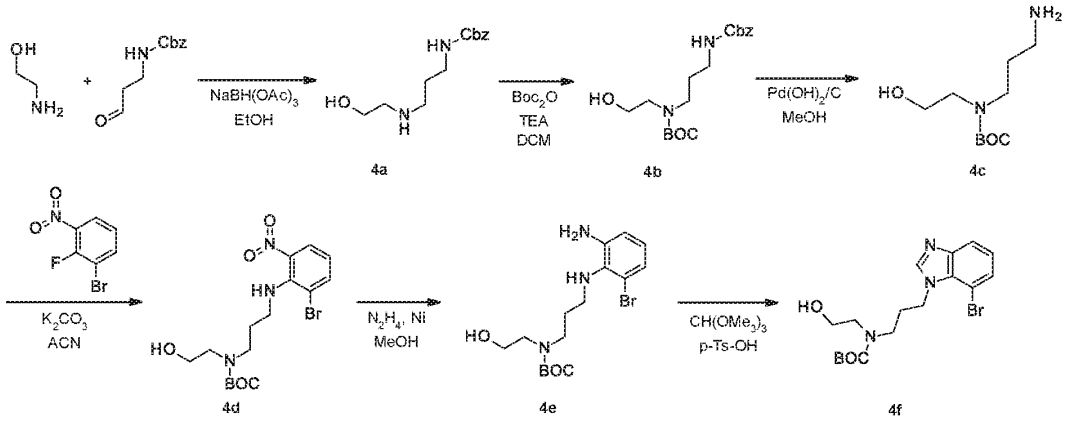
Example 4

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-hydroxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of example **1** by using compound **4f** instead of intermediate **A15-c**. Example **4** (6.4 mg), LCMS ($M+H^+$): 637. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.49 - 9.41 (m, 1H), 8.58 - 8.47 (m, 1H), 8.38 - 8.22 (m, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.72 - 7.60 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.33 - 7.24 (m, 2H), 7.24 - 7.16 (m, 1H), 7.09 - 6.99 (m, 2H), 5.64 - 5.45 (m, 2H), 4.41 - 4.28 (m, 1H), 4.26 - 4.17 (m, 1H), 4.17 - 3.99 (m, 2H), 3.84 - 3.72 (m, 1H), 3.71 - 3.58 (m, 2H), 3.46 - 3.40 (m, 1H), 3.18 - 3.10 (m, 1H), 3.09 - 3.00 (m, 1H), 2.97 - 2.86 (m, 1H), 2.83 - 2.64 (m, 2H), 1.85 - 1.72 (m, 1H).

The compound **4f** was prepared according to the following scheme:



Step 1 ~ 2: preparation of *tert*-butyl *N*-[3-(benzyloxycarbonylamino)propyl]-*N*-(2-hydroxyethyl)carbamate (compound 4b)

To a flask was added benzyl (3-oxopropyl)carbamate (2 g, 9.65 mmol), 2-aminoethan-1-ol (1.18 g, 19.3 mmol), EtOH (50mL) and 5 drops of AcOH. The mixture was heated to 60 °C for about 30 mins and then sodium triacetoxyborohydride (3.07 g, 14.5 mmol) was added. The mixture was stirred at the same temperature for about 16 hrs. The mixture was concentrated to give compound **4a**, then DCM (30mL), TEA (4.89 g, 6.73mL, 48.3 mmol) and Boc_2O (7.38 g, 7.85mL, 33.8 mmol) were added. After being stirred at r.t. for 2 hrs, the mixture was filtered through celite, the filtrate was concentrated to give an oil, which was purified by silica gel to give compound **4b** (1.95 g), LCMS ($M+H^+$): 353.

Step 3: preparation of *tert*-butyl *N*-(3-aminopropyl)-*N*-(2-hydroxyethyl)carbamate (compound 4c)

To a flask was added *tert*-butyl *N*-[3-(benzyloxycarbonylamino)propyl]-*N*-(2-hydroxyethyl)carbamate (**4b**, 1.95 g, 5.53 mmol), $Pd(OH)_2$ 20% on carbon with 50% H_2O (200 mg, 1.42 mmol) and MeOH (50 mL), the suspension was purged with H_2 for 5 times. After being stirred at r.t. for 2 hrs, the mixture was filtered, the filtrate was concentrated to give compound **4c** (1.2 g), LCMS ($M+H^+$): 219.

Step 4: preparation of *tert*-butyl *N*-[3-(2-bromo-6-nitro-anilino)propyl]-*N*-(2-hydroxyethyl)carbamate (compound 4d)

To a microwave tube was added 1-bromo-2-fluoro-3-nitrobenzene (1.45 g, 6.6 mmol), *tert*-butyl N-(3-aminopropyl)-N-(2-hydroxyethyl)carbamate (compound **4c**, 1.2 g, 5.5 mmol), K_2CO_3 (1.52 g, 11 mmol) and acetonitrile (30 mL). The tube was sealed and heated to 90 °C for 2 hrs. The mixture was cooled and filtered, the filtrate was concentrated to give an oil. The oil was purified by silica gel to give compound **4d** (1.78 g), LCMS ($M+H^+$): 418.

Step 5: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)propyl]-*N*-(2-hydroxyethyl)carbamate (compound 4e)

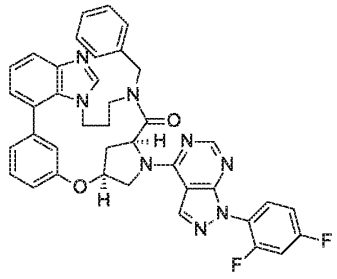
To a flask was added: nickel (1 g, 17 mmol), MeOH (50mL), *tert*-butyl N-[3-(2-bromo-6-nitro-anilino)propyl]-N-(2-hydroxyethyl)carbamate (compound **4d**, 1.7 g, 4.06 mmol), the suspension was stirred vigorously and hydrazine monohydrate (1.02 g, 1.02mL, 20 mmol) was added. After being stirred at r.t. for 1 hr, the mixture was filtered through celite, the filtrate was concentrated to give an oil. The oil was dissolved in 40 mL DCM and washed with 20 mL water for three times. The organic layer was dried over Na_2SO_4 and concentrated to give compound **4e** (1 g), LCMS ($M+H^+$): 388.

Step 6: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-N-(2-hydroxyethyl)carbamate (compound 4f)

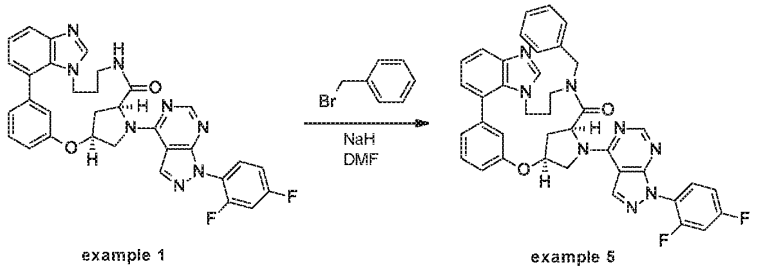
To the flask containing the *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)propyl]-N-(2-hydroxyethyl)carbamate (**4e**, 1 g, 2.58 mmol) was added trimethyl orthoformate (2.91 g, 3mL, 27.4 mmol) and 4-methylbenzenesulfonic acid hydrate (98 mg, 515 μmol2), a light yellow solution formed. After being stirred at r.t. for 16 hrs, the mixture was concentrated to give an oil. The oil was purified by silica gel to give compound **4f** (367 mg), LCMS ($M+H^+$): 398.

Example 5

(8*S*,11*S*)-13-benzyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

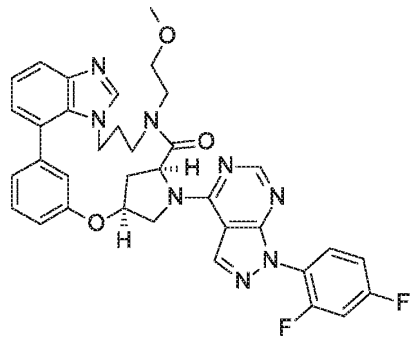


example 1 example 5

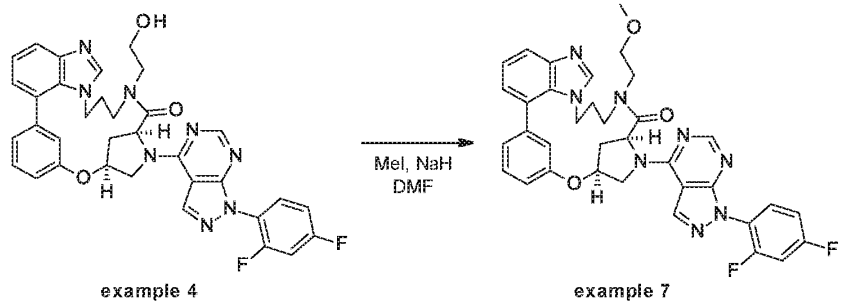
To a mixture of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example **1**, 130 mg, 219 μmol) in DMF (2mL) was added NaH (35.1 mg, 877 μmol) slowly. The mixture was stirred for about 10 mins and (bromomethyl)benzene (75 mg, 52.1 μL, 439 μmol) was added. After being stirred at 40 °C for 16 hrs, the mixture was quenched with 2 mL water and then it was purified via prep-HPLC to give Example **5** (28.6 mg), LCMS (M+H$^+$): 683. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.37 (s, 1H), 8.57 (s, 1H), 8.32 (s, 1H), 7.86 - 7.80 (m, 1H), 7.72 - 7.60 (m, 3H), 7.49 - 7.42 (m, 1H), 7.41 - 7.33 (m, 3H), 7.33 - 7.25 (m, 4H), 7.24 - 7.16 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.07 (s, 1H), 5.68 (br s, 1H), 5.61 (d, *J* = 9.4 Hz, 1H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.59 - 4.52 (m, 2H), 4.51 - 4.39 (m, 1H), 4.01 - 3.87 (m, 2H), 3.78 - 3.66 (m, 1H), 2.93 (br d, *J* = 14.4 Hz, 1H), 2.84 - 2.61 (m, 3H), 1.77 - 1.63 (m, 1H).

Example 7

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



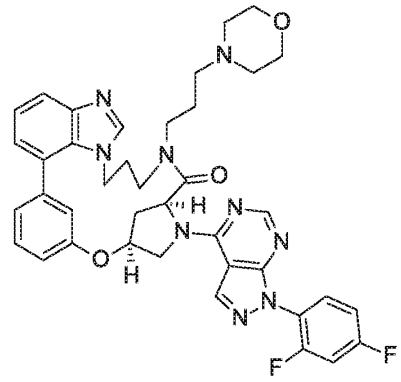
example 4 example 7

To a tube was added (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-hydroxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

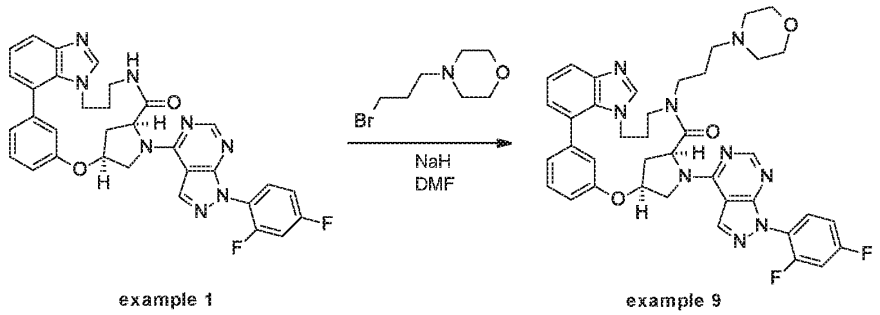
1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example **4**, 25 mg, 39.3 µmol) and DMF (1 mL), the solution was cooled with ice bath and NaH (7.85 mg, 196 µmol) was added. The mixture was stirred for a while and iodomethane (27.9 mg, 18.2 µL, 196 µmol) was added. The mixture was heated to 50 °C and stirred for 4 hrs. The mixture solution was purified via prep-HPLC directly to give Example **7** (2.3 mg), LCMS ($M+H^+$): 651.

Example 9

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-morpholinopropyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



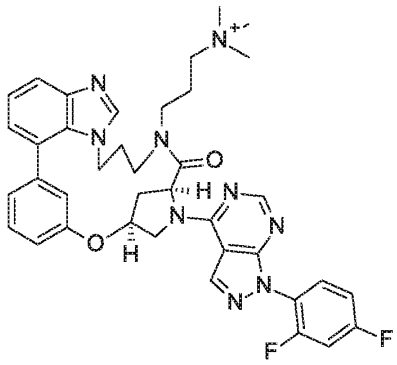
example 1 example 9

The title compound was prepared in analogy to example **5** by using 4-(3-bromopropyl)morpholine hydrobromide instead of (bromomethyl)benzene. Example **9**, LCMS ($M+H^+$): 720. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.22 (s, 1H), 8.20 (s, 1H), 7.69 - 7.61 (m, 2H), 7.50 (t, J = 7.9 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.23 - 7.16 (m, 2H), 7.08 (dd, J = 0.9, 7.3 Hz, 1H), 7.02 - 6.99 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 5.66 - 5.58 (m, 2H), 4.59 - 4.46 (m, 2H), 4.02 (dt, J = 3.3, 13.0 Hz, 1H), 3.97 - 3.90 (m, 1H), 3.82 (dt, J = 6.1, 12.8 Hz, 1H), 3.77 - 3.66 (m, 4H), 3.52 - 3.40 (m, 1H), 3.34 - 3.31 (m, 1H), 3.23 - 3.14 (m, 1H), 2.99 - 2.87 (m, 1H), 2.71 (br d, J = 3.1 Hz, 2H), 2.62 - 2.50 (m, 4H), 2.50 - 2.33 (m, 2H), 1.92 - 1.80 (m, 1H), 1.76 -

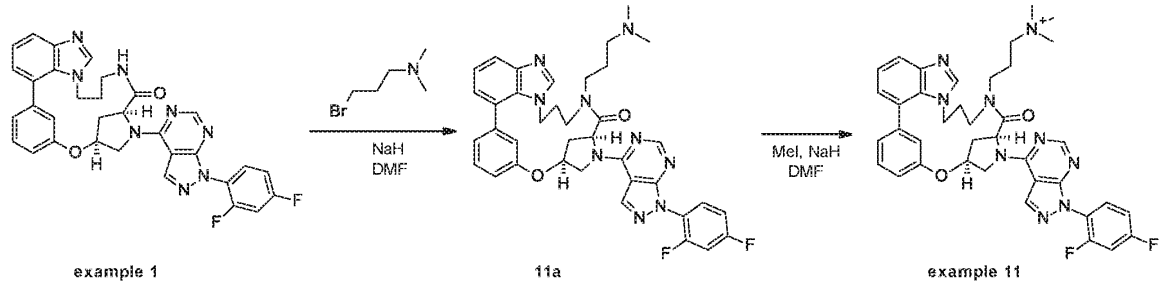
1.57 (m, 2H).

Example 11

3-[(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaen-13-yl]propyl-trimethyl-ammonium



The title compound was prepared according to the following scheme:



example 1 11a example 11

Step 1: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(dimethylamino)propyl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 11a)

To a microwave tube was added (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (example **1**, 40 mg, 67.5 μmol), 3-bromo-N,N-dimethylpropan-1-amine hydrobromide (33.3 mg, 135 μmol) and DMF (0.5mL), a light yellow solution formed, and then NaH (21.6 mg, 540 μmol) was added in one portion. After being stirred at r.t. for 1 hr, the mixture was quenched with 10 mL water and neutralized with 1 N HCl aq., then it was extracted with 15 mL DCM twice, the organic layer was dried over Na_2OS_4 and

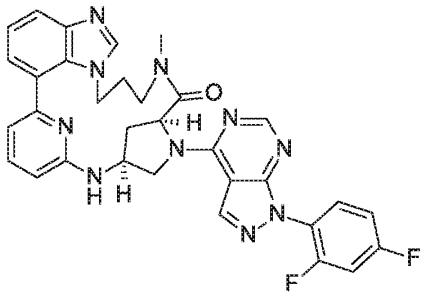
concentrated, the residue was purified by silica gel to give compound **11a** (22 mg), LCMS ($M+H^+$): 678.

Step 2: preparation of 3-[(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaen-13-yl]propyl-trimethyl-ammonium (Example 11)

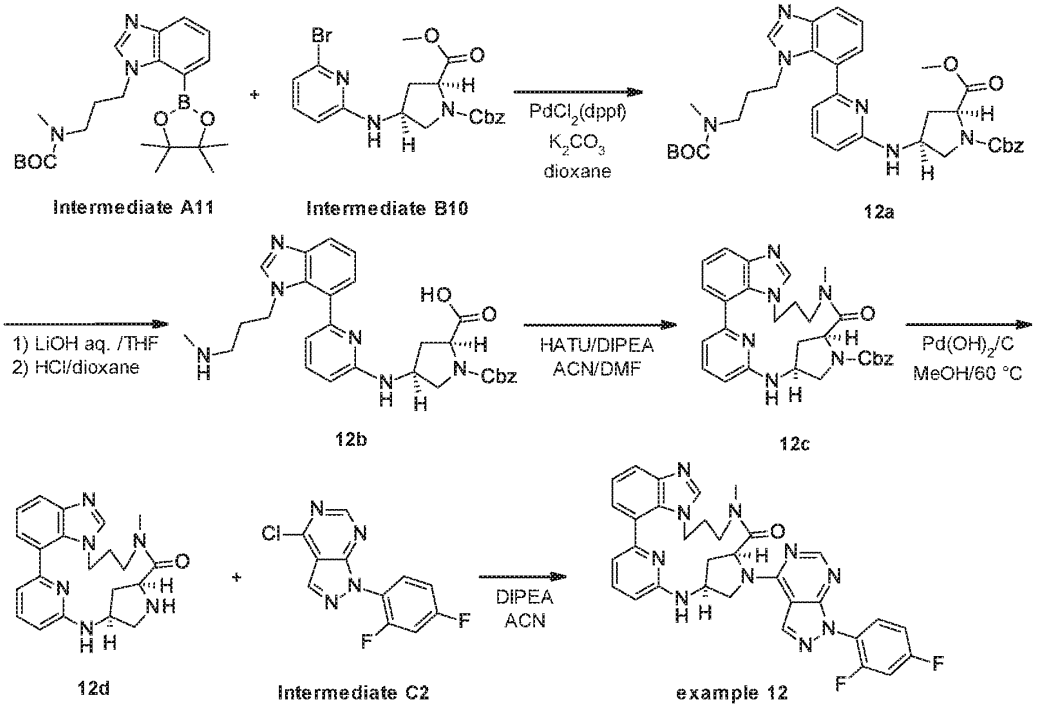
To a tube was added (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(dimethylamino)propyl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **11a**, 22 mg, 31.8 μmol), DMF (0.5mL) and methyl iodide (45.1 mg, 19.9 μL, 318 μmol). The mixture was stirred at r.t. for 2 hrs and then it was purified via prep-HPLC directly to give example **11** (9.9 mg), LCMS (M^+): 692. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.47 (br s, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 7.70 - 7.61 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.24 - 7.17 (m, 2H), 7.10 (dd, *J* = 0.8, 7.3 Hz, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 5.68 - 5.62 (m, 1H), 5.47 (br d, *J* = 8.7 Hz, 1H), 4.55 - 4.49 (m, 2H), 4.08 - 3.93 (m, 2H), 3.91 - 3.78 (m, 1H), 3.57 (td, *J* = 7.4, 15.2 Hz, 1H), 3.49 - 3.40 (m, 2H), 3.20 (s, 9H), 3.17 - 3.13 (m, 1H), 3.06 - 2.93 (m, 1H), 2.78 - 2.62 (m, 3H), 2.34 - 2.18 (m, 1H), 2.12 - 2.00 (m, 1H), 1.69 - 1.56 (m, 1H).

Example 12

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 12a)

To a tube was added O1-benzyl O2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)amino] pyrrolidine-1,2-dicarboxylate (**intermediate B10**, 750 mg, 1.73 mmol, as the "**HALIDE 1**" in table 3), *tert*-butyl *N*-methyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (**intermediate A11**, 500 mg, 1.2 mmol, as the "**BORONIC REAGENT**" in table 3), K_2CO_3 (333 mg, 2.41 mmol), water (0.5mL) and 1,4-dioxane (15mL), the suspension was bubbled with N_2 for 5 mins. Then $PdCl_2(DPPF)$-CH_2Cl_2 adduct (88.1 mg, 120 μmol) was added and the mixture was heated to 100 °C for 3 hrs. The mixture was diluted with EA and filtered, the filtrate was concentrated to give an oil, which was purified by silica gel to give compound **12a** (860 mg), LCMS ($M+H^+$): 643.

Step 2: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 12b)

A mixture of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-

dicarboxylate (compound **12a**, 977 mg, 1.52 mmol) and LiOH (6 mL, 2 N) in THF (2 mL) and MeOH (4 mL) was stirred at rt for 2 hrs. The mixture was diluted with 30 mL DCM and adjusted pH to 4, the mixture was extracted with DCM, the organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in EA (3 mL) and then treated with 4 N HCl in dioxane (3 mL). After being stirred at r.t. for 4 hrs, the mixture was concentrated, the residue was purified via prep- HPLC to give compound **12b** (684 mg), LCMS ($M+H^+$): 529.

Step 3: preparation of benzyl (8*S*,11*S*)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 12c)

To a solution of HATU (1.08 g, 2.84 mmol) and DIPEA (611 mg, 826 μL, 4.73 mmol) in DMF (20 mL) was added a solution of compound (compound **12b**, 500 mg, 946 μmol) in DMF (20 mL) and acetonitrile (200 mL) dropwise in 1 hr. After being stirred at r.t. for16 hrs, the mixture was concentrated, the residue was purified by silica gel to give compound **12c** (480 mg), LCMS ($M+H^+$): 511.

Step 4: preparation of (8*S*,11*S*)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 12d)

A mixture of compound **1c** (480 mg, 940 μmol) and $Pd(OH)_2$ 20% on carbon with 50% H_2O (132 mg, 940 μmol) in MeOH (50 mL) was purged with H_2 for three times. After being stirred at 65 °C for 2 hrs, the mixture was cooled and filtered, the filtrate was concentrated to give **compound 12d** (410 mg), LCMS ($M+H^+$): 377.

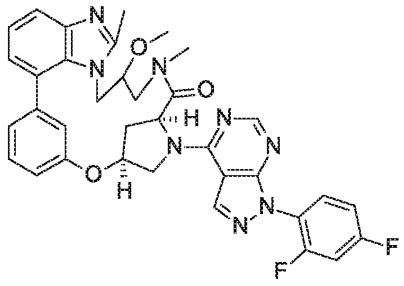
Step 5: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 12)

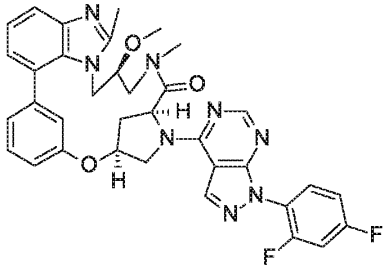
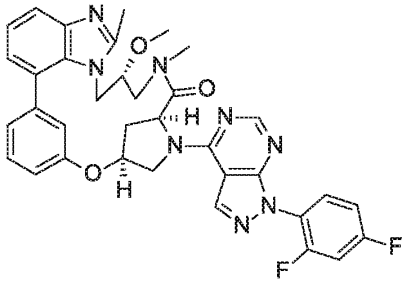
To a microwave tube was added (8*S*,11*S*)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **6d**, 50 mg, 133 μmol), 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (**intermediate C2**, 39 mg, 146 μmol, as the "**HALIDE 2**" in table 3), DIPEA (51.5 mg, 69.6 μL, 398 μmol) and acetonitrile (3 mL). After being stirred at 85 °C for 2 hrs, the mixture was concentrated to give an oil, which was purified via prep-HPLC to give Example **12** (23.3 mg), LCMS ($M+H^+$): 607. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.52 (s, 1H), 8.34 - 8.28 (m, 1H), 8.22 (s, 1H), 7.82 - 7.76 (m, 1H), 7.72 (dd, J = 1.5, 7.6 Hz, 1H), 7.69 - 7.59 (m, 1H), 7.40 - 7.35 (m, 1H), 7.35 - 7.31 (m, 1H), 7.28 (ddd, J = 2.7, 8.8, 10.2 Hz, 1H), 7.22 - 7.16 (m, 1H), 6.99

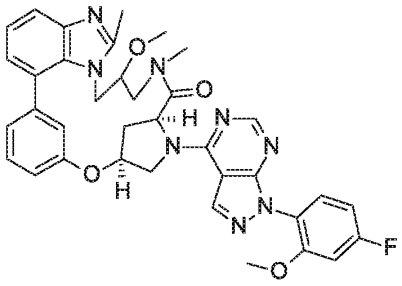
(d, J = 7.5 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 5.50 (d, J = 8.4 Hz, 1H), 4.98 - 4.91 (m, 1H), 4.75 - 4.68 (m, 1H), 4.55 (dd, J = 6.5, 11.4 Hz, 1H), 4.37 - 4.24 (m, 1H), 4.19 - 4.05 (m, 2H), 3.04 (s, 3H), 2.92 - 2.83 (m, 1H), 2.68 - 2.61 (m, 1H), 2.60 - 2.52 (m, 1H), 2.20 - 1.95 (m, 1H), 1.59 - 1.40 (m, 1H).

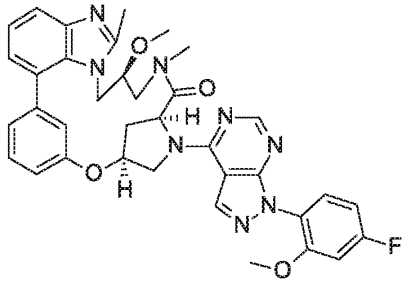
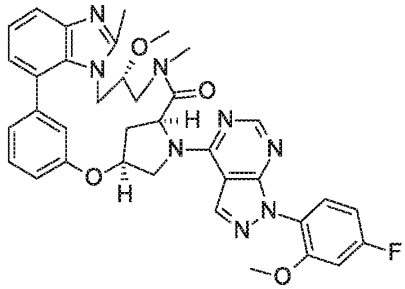
The following examples in Table 3 were prepared in analogy to Example **12**, replacing **Intermediate A11** with the "**BORONIC REAGENT**" in step 1, **Intermediate B10** with the "**HALIDE 1**" in step 1, **Intermediate C2** with the "**HALIDE 2**" in step 5 by the reagents indicated in Table 3.

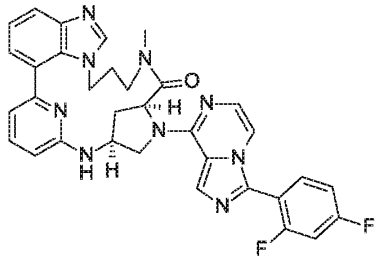
Table 3. Compound synthesis and characterization

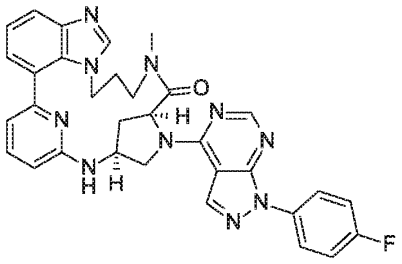
No.	Compound Name and Structure	BORONIC REAGENT, HALIDE 1, HALIDE 2	^{1}H NMR and MS (ESI)
13	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B12a** **HALIDE 2**: Intermediate **C2**	LCMS (M+H$^+$): 651
13A &13B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}**	SFC separation of Example **13** to give Example **13A** (Faster eluted) and Example **13B**	**Example 13A** LCMS (M+H$^+$): 651. ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.55 (s, 1H), 8.22 (s,

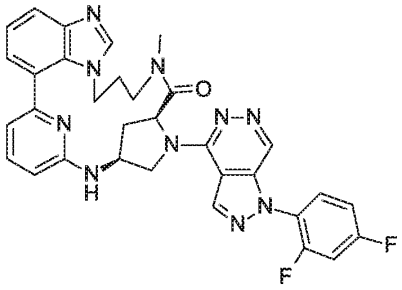
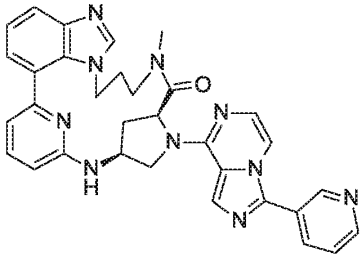
	^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2} ^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	(Slower eluted) **SFC condition:** Instrument: SFC 80 Column: C-4, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	1H), 7.70 - 7.60 (m, 1H), 7.56 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.32 - 7.25 (m, 1H), 7.24 - 7.16 (m, 3H), 7.03 - 6.97 (m, 1H), 6.93 (dd, *J* = 0.8, 7.3 Hz, 1H), 6.79 (br d, *J* = 7.5 Hz, 1H), 5.59 (t, *J* = 3.8 Hz, 1H), 5.44 (d, *J* = 9.5 Hz, 1H), 4.55 - 4.40 (m, 2H), 4.19 - 4.10 (m, 1H), 3.94 (dd, *J* = 11.1, 14.4 Hz, 1H), 3.71 - 3.61 (m, 1H), 3.53 (dd, *J* = 3.8, 14.5 Hz, 1H), 3.10 - 2.97 (m, 3H), 2.92 (d, *J* = 14.3 Hz, 1H), 2.79 - 2.73 (m, 3H), 2.66 - 2.56 (m, 2H), 2.55 (s, 3H) **Example 13B** LCMS (M+H$^+$): 651. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.22 (s, 1H), 7.72 - 7.60 (m, 1H), 7.57 (dd, *J* = 0.9, 7.9 Hz, 1H), 7.53 - 7.46 (m, 1H), 7.33 - 7.28 (m, 1H), 7.28 - 7.24 (m, 1H), 7.23 - 7.20 (m, 1H), 7.20 - 7.16 (m, 1H), 7.16 - 7.13 (m,

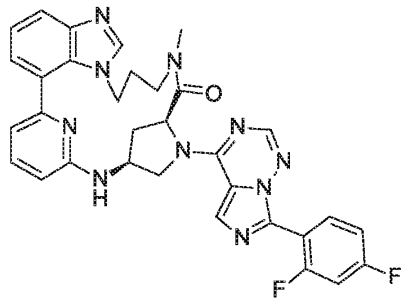
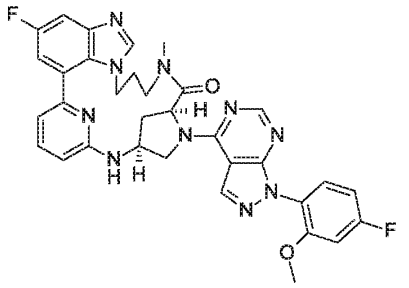
			1H), 7.12 - 7.08 (m, 1H), 7.06 - 7.00 (m, 1H), 5.56 - 5.51 (m, 1H), 5.50 - 5.44 (m, 1H), 4.75 - 4.66 (m, 1H), 4.57 - 4.51 (m, 1H), 4.50 - 4.41 (m, 1H), 4.22 - 4.07 (m, 2H), 3.30 - 3.26 (m, 1H), 3.12 - 3.00 (m, 3H), 2.93 - 2.88 (m, 3H), 2.83 - 2.76 (m, 1H), 2.69 - 2.63 (m, 1H), 2.62 (s, 1H), 2.59 - 2.55 (m, 3H)
14	**(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B12a** **HALIDE 2**: Intermediate **C11**	LCMS (M+H$^+$): 663
14A &14B	**(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}**	SFC separation of Example **14** to give **Example 14A** (Faster eluted) and **Example 14B**	**Example 14A** LCMS (M+H$^+$): 663。 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.49 (s, 1H), 8.16 (s,

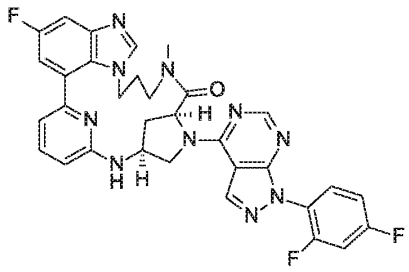
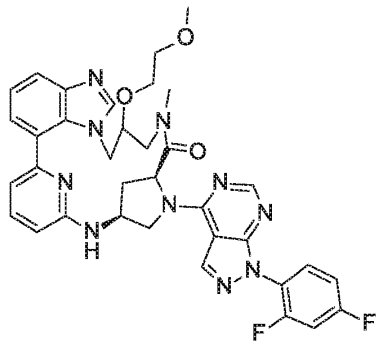
	^{0,24}] **hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**  	(Slower eluted) SFC condition: Instrument: SFC 80 Column: C-4, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	1H), 7.55 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.48 - 7.37 (m, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.18 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.07 - 7.02 (m, 1H), 7.01 - 6.97 (m, 1H), 6.95 - 6.91 (m, 1H), 6.87 (dt, *J* = 2.5, 8.4 Hz, 1H), 6.78 (br d, *J* = 7.6 Hz, 1H), 5.58 (t, *J* = 3.8 Hz, 1H), 5.42 (d, *J* = 9.5 Hz, 1H), 4.54 - 4.38 (m, 2H), 4.17 - 4.10 (m, 1H), 4.00 - 3.89 (m, 1H), 3.76 - 3.71 (m, 3H), 3.70 - 3.60 (m, 1H), 3.57 - 3.50 (m, 1H), 3.10 - 2.96 (m, 3H), 2.91 (br d, *J* = 14.5 Hz, 1H), 2.79 - 2.74 (m, 3H), 2.65 - 2.56 (m, 2H), 2.55 (s, 3H) **Example 14B** LCMS ($M+H^+$): 663。 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.16 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.18 - 7.08 (m, 3H), 7.07 - 7.01 (m, 2H), 6.91 - 6.84 (m, 1H), 5.53

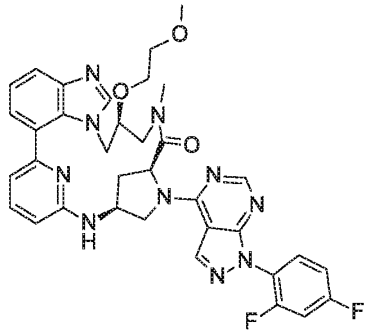
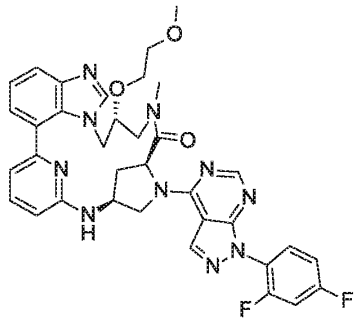
			(t, *J* = 4.0 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 4.76 - 4.66 (m, 1H), 4.59 - 4.39 (m, 2H), 4.21 - 4.07 (m, 2H), 3.77 - 3.71 (m, 3H), 3.29 - 3.25 (m, 1H), 3.12 - 3.00 (m, 3H), 2.92 - 2.87 (m, 3H), 2.79 (br d, *J* = 14.5 Hz, 1H), 2.68 - 2.59 (m, 2H), 2.59 - 2.55 (m, 3H)
101	**(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C3**	LCMS (M+H$^+$) 606 ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.28 (s, 1H), 8.18 - 7.86 (m, 1H), 7.82 - 7.75 (m, 1H), 7.74 - 7.64 (m, 2H), 7.37 - 7.29 (m, 2H), 7.28 - 7.17 (m, 3H), 7.08 (br d, *J* = 4.3 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.41 (br s, 1H), 5.02 - 4.93 (m, 1H), 4.68 - 4.48 (m, 2H), 4.38 - 4.22 (m, 1H), 4.18 - 4.05 (m, 2H), 3.06 (s, 3H), 2.88 (br dd, *J* = 7.2, 13.7 Hz, 1H), 2.68 - 2.48 (m, 2H), 2.22 - 2.08 (m, 1H), 1.58 - 1.43 (m, 1H)
103	**(8*S*,11*S*)-10-[1-(4-fluorophenyl)pyrazolo[3,4-**	**BORONIC REAGENT:**	LCMS (M+H$^+$) 589 ^{1}H NMR (400 MHz,

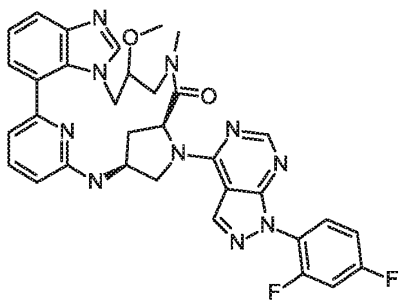
	d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **A11** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C5**	DMSO-d_6) δ = 8.59 (s, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 8.27 - 8.18 (m, 2H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.68 (dd, *J* = 1.8, 7.4 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.29 - 7.20 (m, 2H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.77 - 6.65 (m, 1H), 5.62 - 5.51 (m, 1H), 5.50 - 5.43 (m, 1H), 4.88 - 4.76 (m, 1H), 4.73 - 4.65 (m, 1H), 4.54 - 4.44 (m, 1H), 4.27 - 4.16 (m, 2H), 3.98 - 3.89 (m, 1H), 3.05 - 2.92 (m, 4H), 2.90 - 2.72 (m, 2H), 2.66 - 2.58 (m, 1H), 2.43 - 2.34 (m, 1H)
107	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C7**	LCMS $(M+H)^+$: 607. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.50 - 9.39 (m, 1H), 9.07 (br s, 1H), 8.85 (br s, 1H), 7.93 - 7.81 (m, 3H), 7.79 - 7.66 (m, 2H), 7.50 - 7.41 (m, 1H), 7.37 - 7.30 (m, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.58 - 5.30 (m, 2H), 4.80 - 4.60 (m, 3H), 4.48 - 4.26 (m, 2H), 4.23 - 4.08 (m, 1H),

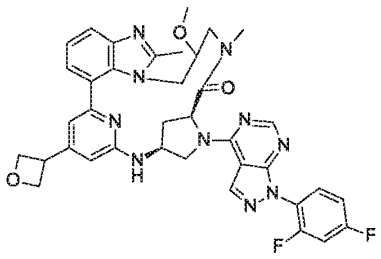
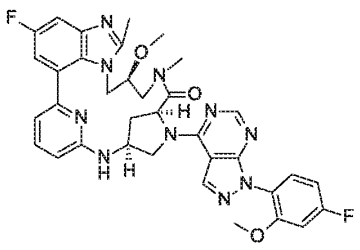
			3.16 - 3.05 (m, 2H), 3.03 - 2.95 (m, 1H), 2.97 - 2.95 (m, 1H), 2.83 - 2.68 (m, 1H), 2.00 - 1.84 (m, 1H), 1.55 - 1.38 (m, 1H).
108	**(8*S*,11*S*)-13-methyl-10-[3-(3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C14**	LCMS (M+H)$^{+}$: 571. ^{1}H NMR (400 MHz, DMSO-*d*6) δ = 9.02 (d, *J*=1.88 Hz, 1H), 8.69 (dd, *J*=4.83, 1.44 Hz, 1H), 8.30 (s, 1H), 8.24 (dt, *J*=8.03, 1.82 Hz, 1H), 7.80 - 7.72 (m, 2H), 7.68 (dd, *J*=7.15, 1.88 Hz, 1H), 7.60 (dd, *J*=7.78, 4.89 Hz, 1H), 7.29 - 7.20 (m, 3H), 7.13 (br s, 1H), 6.93 (d, *J*=7.40 Hz, 1H), 6.71 (br d, *J*=8.41 Hz, 1H), 5.49 (br s, 2H), 4.88 - 3.84 (m, 6H), 2.98 (br s, 3H), 2.81 (br dd, *J*=12.49, 7.22 Hz, 1H), 2.09 - 1.96 (m, 1H), 1.42 - 1.20 (m, 2H).
109	**(8*S*,11*S*)-10-[7-(2,4-difluorophenyl)imidazo[5,1-f][1,2,4]triazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}**	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B8**	LCMS (M+H)$^{+}$: 607. ^{1}H NMR (400 MHz, METHANOL-*d*4) δ = 9.53 - 9.45 (m, 1H), 8.16 (s, 1H), 7.93 - 7.84 (m,

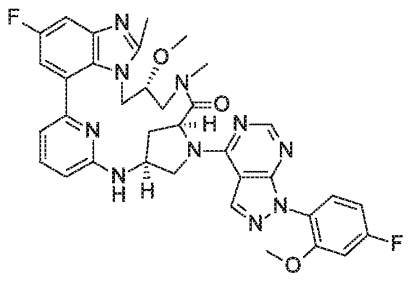
	^{0,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one 	**HALIDE 2**: Intermediate **C34**	4H), 7.74 - 7.67 (m, 2H), 7.22 - 7.10 (m, 3H), 6.87 - 6.79 (m, 1H), 5.61 - 5.44 (m, 1H), 5.17 - 5.04 (m, 1H), 4.77 - 4.55 (m, 2H), 4.48 - 4.17 (m, 3H), 3.15 - 3.04 (m, 3H), 3.02 - 2.81 (m, 2H), 2.76 - 2.58 (m, 1H), 2.20 - 1.93 (m, 1H), 1.78 - 1.49 (m, 1H).
136	**(8*S*,11*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A13** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C11**	LCMS (M+H$^+$) 637
137	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-**	**BORONIC REAGENT:** Intermediate **A13** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C2**	LCMS (M+H$^+$) 635 ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.64 - 8.56 (m, 1H), 8.37 (d, *J* = 4.5 Hz, 1H), 8.25 (s, 1H), 7.83 - 7.69 (m, 2H), 7.64 - 7.56 (m, 1H), 7.50

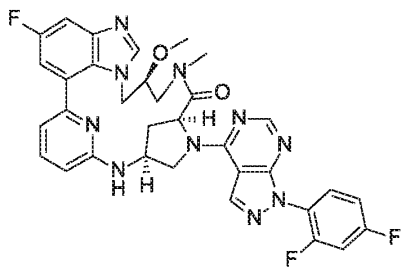
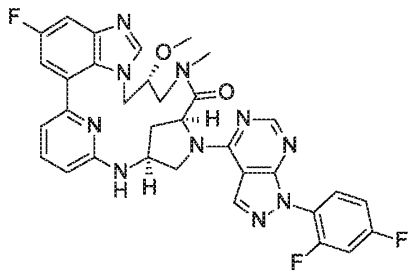
	heptaen-12-one 		(dd, *J* = 2.5, 9.1 Hz, 1H), 7.37 - 7.29 (m, 1H), 7.20 - 7.13 (m, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.79 - 6.68 (m, 1H), 5.64 (br d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 8.6 Hz, 1H), 4.99 - 4.74 (m, 1H), 4.72 - 4.63 (m, 1H), 4.54 - 4.43 (m, 1H), 4.27 - 4.16 (m, 1H), 4.07 - 3.89 (m, 2H), 3.04 - 2.90 (m, 3H), 2.86 - 2.73 (m, 1H), 2.66 - 2.55 (m, 1H), 2.42 - 2.33 (m, 1H), 2.02 - 1.79 (m, 1H), 1.42 - 1.21 (m, 1H)
165	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT**: Intermediate **A24** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C2**	

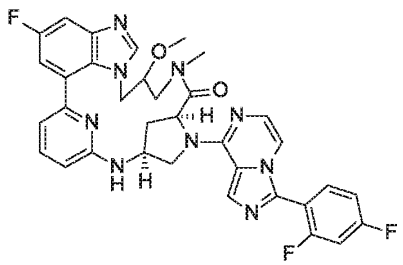
166A & 166B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl] -15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15- (2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one**  	SFC separation of Example **166** to give Example **166A** (Faster eluted) and Example **166B** (Slower eluted) **SFC condition:** Instrument: Waters 80Q Preparative SFC system Column: DAICEL CHIRALPAK AD(250mm×30mm ,10μm) Mobile phase: Phase A for Supercritical CO_2, and Phase B for IPA+ACN(0.1%NH_3H_2O); Gradient: 70%Phase B (30% Phase A) Flow rate: 70g/min Back pressure: 100 bar to keep the CO_2 in Supercritical flow. Column temperature: 30°C	**Example 166A** LCMS (M+H)$^+$:681.. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.64 (s, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 7.75- 7.94 (m, 3H), 7.25 - 7.48 (m, 3H), 7.09 - 7.20 (m, 1H), 6.61 - 6.77 (m, 1H), 5.80 – 5.82 (m, 1H), 5.71 – 5.73 (m, 1H), 5.47 - 5.66 (m, 1H), 5.32 - 5.45 (m, 1H), 4.59 - 4.71 (m, 1H), 4.45 - 455 (m, 1H), 4.32 – 4.40 (m, 1H), 4.12 - 4.29 (m, 2H), 3.75 - 3.80 (m, 1H), 3.34 - 3.38 (m, 1H), 3.04 - 3.25 (m, 4H), 2.58 - 3.00 (m, 5H), 2.01 - 2.17 (m, 1H). **Example 166B** LCMS (M+H)$^+$:681. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.55 (s, 1H), 8.31 (s, 1H), 8.19 -8.22 (m, 1H), 7.55 - 7.75 (m, 5H), 7.20 - 7.25 (m, 2H), 6.85 - 6.90 (m, 1H), 6.53 - 6.70 (m, 1H), 5.41 (m, 1H), 5.22 - 5.34 (m, 2H), 4.96 - 5.13 (m, 1H), 4.61 – 4.65 (m,

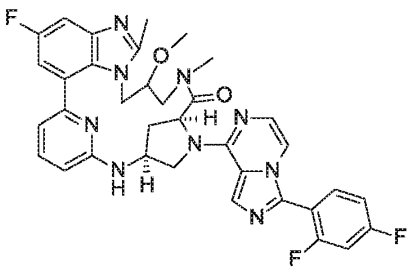
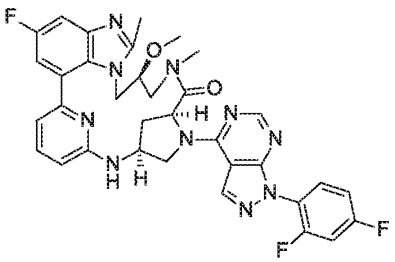
			1H), 4.36 - 4.52 (m, 1H), 4.07 - 4.21 (m, 2H), 3.84 - 3.96 (m, 2H), 3.40 – 3.44 (m, 1H), 3.13 - 3.23 (m, 1H), 2.94 - 3.09 (m, 3H), 2.77 - 2.88 (m, 5H), 1.85 - 2.12 (m, 1H).
168	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT**: Intermediate **A3** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C2**	LCMS (M+H)$^{+}$: 637. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.21 - 9.40 (m, 1H), 8.59 -8.62 (m, 1H), 8.26 (s, 1H), 7.87 - 7.89 (m, 1H), 7.79 - 7.84 (m, 2H), 7.58 - 7.61 (m, 2H), 7.47 (m, 1H), 7.27 - 7.38 (m, 1H), 7.01 - 7.21 (m,1H), 6.75 - 6.80 (m, 1H), 5.85 - 5.95 (m, 1H), 5.47 - 5.52 (m, 2H), 4.18 - 4.44 (m, 4H), 3.12 (s, 3H), 3.01 - 3.09 (m, 1H), 2.90 - 2.96 (m, 2H), 2.81 - 2.90 (m, 1H), 2.81 - 2.83 (m, 3H).
227	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(oxetan-3-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT**: Intermediate **A1** **HALIDE 1**: Intermediate **B26** **HALIDE 2**: Intermediate **C2**	LCMS (M+H)$^{+}$: 707. ^{1}H NMR (400 MHz, METHANOL-*d*4) δ = 8.55 (s, 1H), 8.42 - 8.20 (m, 1H), 7.69 - 7.56 (m, 2H), 7.39 - 6.92 (m, 5H), 6.68 (d, *J* = 6.4 Hz, 1H), 5.57 - 5.42 (m, 1H), 5.24 - 5.09 (m, 3H), 4.83 -

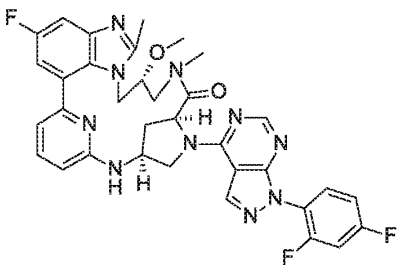
			4.75 (m, 1H), 4.67 - 4.49 (m, 1H), 4.43 - 4.26 (m, 2H), 4.17 - 3.89 (m, 2H), 3.22 - 3.00 (m, 5H), 2.92 - 2.71 (m, 5H), 2.63 - 2.50 (m, 5H).
243 & 244	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT**: Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C11** SFC separation to give Example 243 (Faster eluted) and Example 244 (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 35% Flow rate: 60 mL /min Back pressure: 100 bar Column	**Example 243** LCMS (M+H$^+$) 681 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.47 (s, 1H), 8.16 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 6.1, 8.7 Hz, 1H), 7.31 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.21 - 7.14 (m, 1H), 7.12 - 7.08 (m, 1H), 7.05 (dd, *J* = 2.4, 10.7 Hz, 1H), 6.87 (dt, *J* = 2.6, 8.3 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.77 (dd, *J* = 4.3, 15.6 Hz, 1H), 5.46 (d, *J* = 8.9 Hz, 1H), 4.66 (t, *J* = 5.0 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.27 - 4.14 (m, 1H), 4.13 - 4.05 (m, 1H), 3.98 - 3.89 (m, 1H), 3.76 (s, 3H), 3.03 (s, 3H), 2.92 - 2.86 (m, 1H), 2.84 (s, 3H), 2.57 (s, 3H), 2.54 - 2.45 (m, 2H) **Example 244**,

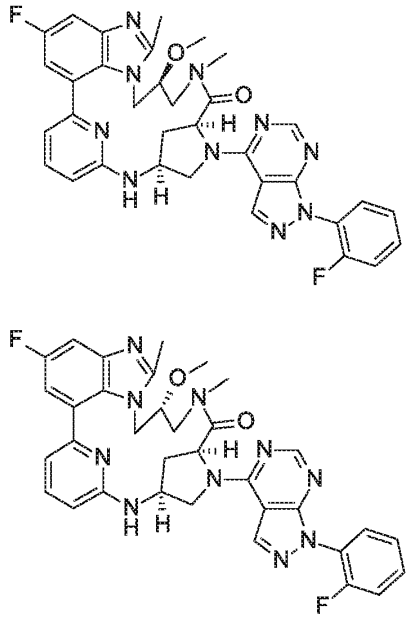
		temperature: 35°C	LCMS (M+H$^+$) 681 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.16 (s, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.27 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.09 - 6.99 (m, 2H), 6.93 - 6.83 (m, 2H), 6.72 - 6.65 (m, 1H), 5.48 (d, *J* = 9.0 Hz, 1H), 5.32 - 5.13 (m, 1H), 4.72 (br t, *J* = 5.3 Hz, 1H), 4.55 (dd, *J* = 6.4, 11.4 Hz, 1H), 4.29 (br d, *J* = 11.4 Hz, 1H), 4.08 - 4.03 (m, 1H), 4.02 - 3.91 (m, 1H), 3.75 (s, 3H), 3.73 - 3.68 (m, 1H), 3.07 (s, 3H), 3.04 - 2.90 (m, 1H), 2.84 (s, 3H), 2.75 - 2.67 (m, 1H), 2.57 (s, 3H), 2.55 - 2.50 (m, 1H)
245 & 246	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-**	**BORONIC REAGENT: Intermediate A4** **HALIDE 1: Intermediate B10** **HALIDE 2: Intermediate C2** **SFC separation to give Example 245**	**Example 245** LCMS (M+H$^+$) 655 ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.58 (s, 1H), 8.26 (s, 1H), 8.18 - 8.13 (m, 1H), 7.82 - 7.77 (m, 1H), 7.77 - 7.69 (m, 1H), 7.61 (ddd, *J* = 2.6, 9.1, 10.4 Hz, 1H), 7.52 (dd, *J* = 2.4, 8.9 Hz, 1H),

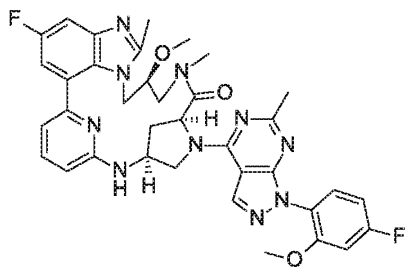
	difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	**(Faster eluted) and Example 246 (Slower eluted)** **SFC condition:** Instrument: SFC 80 Column: AS, 250×20 mm I.D., 5μm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 20% Flow rate: 50 mL /min Back pressure: 100 bar Column temperature: 35°C	7.37 - 7.30 (m, 1H), 7.30 - 7.23 (m, 1H), 7.15 - 7.09 (m, 1H), 6.71 - 6.62 (m, 1H), 5.91 - 5.75 (m, 1H), 5.57 - 5.40 (m, 2H), 4.66 - 4.56 (m, 1H), 4.49 - 4.38 (m, 1H), 4.31 (br d, *J* = 11.4 Hz, 1H), 4.21 - 4.09 (m, 2H), 3.85 - 3.74 (m, 1H), 3.06 - 2.92 (m, 3H), 2.82 (br d, *J* = 13.6 Hz, 1H), 2.77 - 2.70 (m, 3H), 2.62 (br d, *J* = 13.3 Hz, 1H), 2.40 - 2.28 (m, 1H) **Example 246** LCMS ($M+H^+$) 655 ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.61 (s, 1H), 8.38 (d, *J* = 3.8 Hz, 1H), 8.27 (s, 1H), 7.80 - 7.69 (m, 2H), 7.60 (ddd, *J* = 2.8, 9.1, 10.4 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.36 - 7.28 (m, 1H), 7.19 - 7.12 (m, 1H), 7.01 - 6.94 (m, 1H), 6.78 - 6.66 (m, 1H), 5.54 - 5.40 (m, 2H), 5.06 - 4.88 (m, 1H), 4.77 - 4.67 (m, 1H), 4.57 - 4.47 (m, 1H), 4.29 - 4.16 (m, 2H), 4.05 - 3.95 (m, 1H), 3.90 - 3.70 (m,

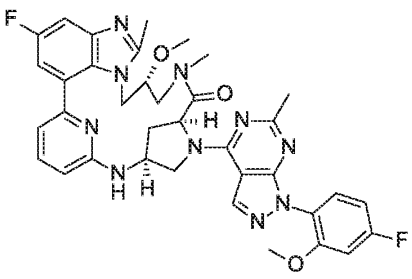
			1H), 3.27 - 3.13 (m, 1H), 3.12 - 2.98 (m, 3H), 2.90 - 2.83 (m, 3H), 2.64 - 2.52 (m, 1H), 2.36 - 2.28 (m, 1H)
247	**(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A4** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C3**	LCMS (M+H$^+$) 654 ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.12 (s, 1H), 7.82 - 7.70 (m, 2H), 7.58 - 7.46 (m, 3H), 7.33 (dt, *J* = 2.3, 8.5 Hz, 1H), 7.26 (dd, *J* = 2.4, 10.6 Hz, 2H), 7.18 - 7.05 (m, 2H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.70 - 5.61 (m, 1H), 5.59 - 5.46 (m, 1H), 5.46 - 5.30 (m, 1H), 4.71 - 4.41 (m, 2H), 4.19 - 4.08 (m, 1H), 3.82 - 3.72 (m, 1H), 3.12 - 2.92 (m, 4H), 2.90 - 2.80 (m, 2H), 2.75 (s, 3H), 2.58 - 2.52 (m, 1H), 2.38 (m, 1H)
248	**(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C3**	LCMS (M+H$^+$) 668 ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.35 - 8.13 (m, 1H), 7.87 - 7.69 (m, 2H), 7.62 - 7.51 (m, 1H), 7.48 - 7.40 (m, 1H), 7.39 - 7.27 (m, 2H), 7.25 - 7.09 (m, 2H), 7.09 - 6.90 (m, 1H), 6.73 - 6.63 (m, 1H), 5.87 - 5.52 (m,

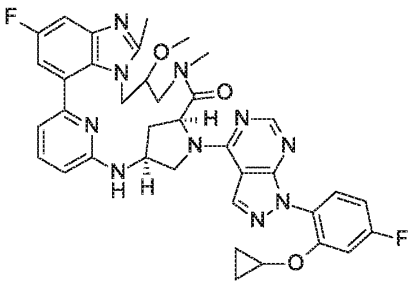
			1H), 5.21 (br dd, *J* = 2.4, 8.6 Hz, 1H), 4.76 - 4.44 (m, 1H), 4.15 - 3.74 (m, 2H), 3.70 - 3.58 (m, 1H), 3.13 - 2.90 (m, 5H), 2.77 - 2.73 (m, 3H), 2.56 (s, 2H), 2.52 (br s, 3H), 2.47 - 2.29 (m, 2H)
252 & 253	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C2** SFC separation to give Example **252** (Faster eluted) and Example **253** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: TCI Chiral MB-S 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA ($0.1\%NH_3H_2O$) Gradient: B 10%	LCMS ($M+H^+$) 669 **Example 252** LCMS ($M+H^+$) 669 ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.52 (s, 1H), 8.20 (s, 1H), 7.84 - 7.76 (m, 1H), 7.70 - 7.57 (m, 1H), 7.33 - 7.24 (m, 2H), 7.22 - 7.13 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.70 - 6.62 (m, 1H), 5.79 - 5.64 (m, 1H), 5.49 - 5.37 (m, 1H), 4.67 - 4.56 (m, 1H), 4.52 - 4.42 (m, 1H), 4.38 - 4.25 (m, 1H), 4.19 - 4.06 (m, 1H), 3.93 (dd, *J* = 9.4, 14.2 Hz, 1H), 3.12 - 2.99 (m, 3H), 2.92 - 2.84 (m, 2H), 2.83 (s, 3H), 2.57 - 2.53 (m, 3H), 2.52 - 2.42 (m, 2H) **Example 253** LCMS ($M+H^+$) 669 ^{1}H NMR (400 MHz,

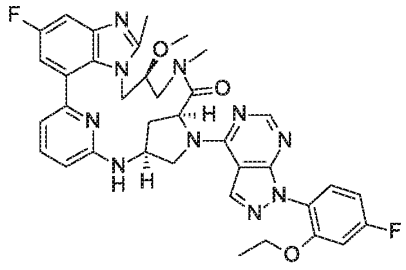
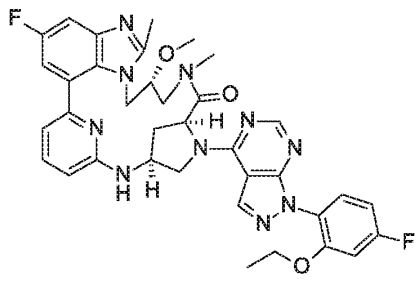
		Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	METHANOL-d_4) δ = 8.54 (s, 1H), 8.22 (s, 1H), 7.80 - 7.73 (m, 1H), 7.71 - 7.59 (m, 1H), 7.32 - 7.24 (m, 2H), 7.23 - 7.16 (m, 1H), 7.04 (dd, *J* = 2.3, 10.1 Hz, 1H), 6.95 - 6.87 (m, 1H), 6.74 - 6.66 (m, 1H), 5.50 (d, *J* = 8.9 Hz, 1H), 5.32 - 5.10 (m, 1H), 4.77 - 4.69 (m, 1H), 4.56 (dd, *J* = 6.4, 11.4 Hz, 1H), 4.36 - 4.26 (m, 1H), 4.11 - 4.04 (m, 1H), 4.04 - 3.91 (m, 1H), 3.78 - 3.63 (m, 1H), 3.19 - 3.05 (m, 3H), 3.05 - 2.95 (m, 1H), 2.85 (s, 3H), 2.76 - 2.66 (m, 1H), 2.59 - 2.56 (m, 3H), 2.56 - 2.50 (m, 1H)
254 & 255	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C4** SFC separation to give Example **254** (Faster eluted) and Example **255**	**Example 254** LCMS (M+H$^+$) 651 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.21 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.64 - 7.59 (m, 1H), 7.59 - 7.54 (m, 1H), 7.43 - 7.36 (m, 2H), 7.29 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.19 - 7.13 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.71

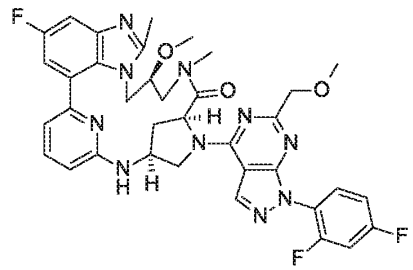
	hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	(Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	- 6.63 (m, 1H), 5.75 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.45 - 5.45 (m, 1H), 5.49 - 5.37 (m, 1H), 4.68 - 4.63 (m, 1H), 4.49 (td, *J* = 5.5, 11.3 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.18 - 4.08 (m, 1H), 3.99 - 3.90 (m, 1H), 3.13 - 3.00 (m, 3H), 2.92 - 2.86 (m, 1H), 2.83 (s, 3H), 2.57 - 2.54 (m, 3H), 2.53 - 2.44 (m, 2H) **Example 255** LCMS ($M+H^+$) 651 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.21 (s, 1H), 7.75 (dd, *J* = 7.7, 8.3 Hz, 1H), 7.64 - 7.53 (m, 2H), 7.42 - 7.34 (m, 2H), 7.27 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.10 - 6.99 (m, 1H), 6.94 - 6.85 (m, 1H), 6.71 - 6.64 (m, 1H), 5.48 (d, *J* = 9.0 Hz, 1H), 5.36 - 5.13 (m, 1H), 4.73 - 4.67 (m, 1H), 4.54 (dd, *J* = 6.4, 11.4 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 4.10 - 4.03 (m, 1H), 4.02 - 3.90 (m, 1H), 3.75 - 3.61 (m, 1H), 3.18 -

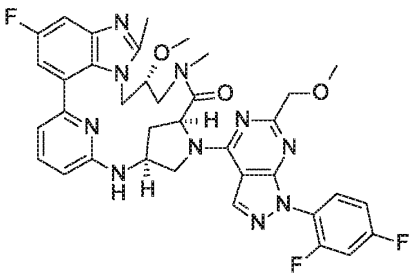
			3.05 (m, 3H), 3.03 - 2.91 (m, 1H), 2.84 (s, 3H), 2.73 - 2.66 (m, 1H), 2.57 - 2.54 (m, 3H), 2.53 (s, 1H)
256 & 257	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C12** SFC separation to give Example **256** (Faster eluted) and Example **257** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: Pyridine, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 35% Flow rate: 60 mL /min Back pressure: 100 bar	**Example 256** LCMS (M+H$^+$) 695 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.39 (s, 1H), 7.77 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.41 (dd, *J* = 6.1, 8.5 Hz, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.04 (dd, *J* = 2.7, 10.8 Hz, 1H), 6.95 - 6.89 (m, 1H), 6.89 - 6.82 (m, 1H), 6.74 - 6.67 (m, 1H), 5.54 (d, *J* = 9.0 Hz, 1H), 5.36 - 5.17 (m, 1H), 4.74 - 4.68 (m, 1H), 4.57 - 4.49 (m, 1H), 4.28 - 4.17 (m, 1H), 4.08 (br s, 1H), 4.05 - 3.96 (m, 1H), 3.77 - 3.75 (m, 3H), 3.74 - 3.70 (m, 1H), 3.09 (s, 3H), 3.07 - 2.99 (m, 1H), 2.87 - 2.82 (m, 3H), 2.72 - 2.66 (m, 1H), 2.60 (s, 3H), 2.56 - 2.51 (m, 1H), 2.51 - 2.37 (m, 3H) **Example 257** LCMS (M+H$^+$) 695

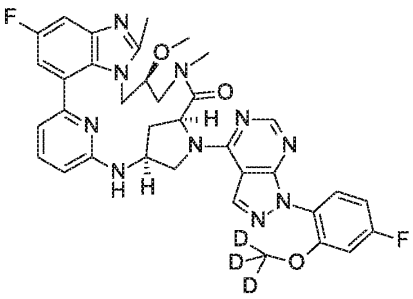
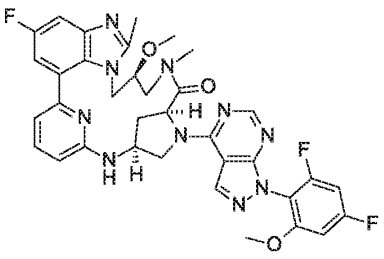
		Column temperature: 35°C	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 6.1, 8.7 Hz, 1H), 7.37 (dd, *J* = 2.4, 8.1 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.13 - 7.09 (m, 1H), 7.05 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.90 - 6.84 (m, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.87 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.52 (d, *J* = 8.9 Hz, 1H), 4.68 - 4.64 (m, 1H), 4.53 - 4.45 (m, 1H), 4.33 - 4.28 (m, 1H), 4.28 - 4.21 (m, 1H), 4.20 - 4.14 (m, 1H), 3.98 - 3.90 (m, 1H), 3.78 - 3.74 (m, 3H), 3.13 - 3.03 (m, 3H), 2.94 - 2.88 (m, 1H), 2.87 (s, 3H), 2.64 - 2.60 (m, 3H), 2.54 - 2.50 (m, 2H), 2.40 (s, 3H)
258	**(8*S*,11*S*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C17**	LCMS (M+H$^+$) 707 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.48 - 8.44 (m, 1H), 8.16 (s, 1H), 7.85 - 7.73 (m, 1H), 7.46 - 7.37 (m, 1H), 7.35 - 7.26 (m, 2H), 7.16 (dd, *J* = 2.6, 10.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz,

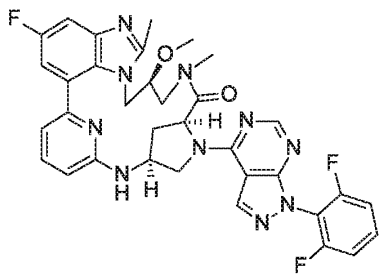
			1H), 6.94 - 6.87 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.76 (dd, *J* = 4.3, 15.6 Hz, 1H), 5.53 - 5.38 (m, 1H), 4.73 - 4.64 (m, 1H), 4.61 - 4.48 (m, 1H), 4.35 - 4.21 (m, 1H), 4.18 - 4.03 (m, 1H), 3.99 - 3.91 (m, 1H), 3.88 - 3.81 (m, 1H), 3.75 - 3.57 (m, 1H), 3.13 - 3.02 (m, 3H), 2.93 - 2.86 (m, 1H), 2.85 - 2.81 (m, 3H), 2.75 - 2.60 (m, 1H), 2.59 - 2.55 (m, 3H), 2.54 - 2.45 (m, 1H), 0.79 - 0.70 (m, 2H), 0.62 - 0.54 (m, 2H)
265 & 266	**(8*S*,11*S*,15*R*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C18** SFC separation to give Example **265** (Faster eluted) and Example **266** (Slower eluted) **SFC condition:** Instrument: SFC 80	**Example 265** LCMS (M+H$^+$) 695 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.48 (s, 1H), 8.18 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 6.1, 8.5 Hz, 1H), 7.30 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.19 - 7.13 (m, 1H), 7.12 - 7.07 (m, 1H), 7.03 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.86 (dt, *J* = 2.4, 8.2 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.76 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.47 (d, *J* = 9.0

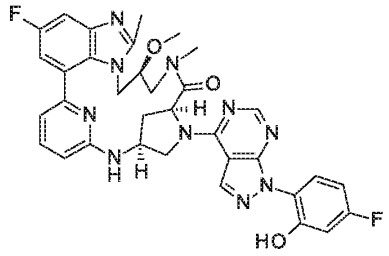
	1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	Hz, 1H), 4.69 - 4.63 (m, 1H), 4.54 - 4.48 (m, 1H), 4.37 - 4.32 (m, 1H), 4.19 - 4.09 (m, 1H), 4.05 (q, *J* = 6.9 Hz, 2H), 3.94 (dd, *J* = 9.3, 14.2 Hz, 1H), 3.14 - 3.01 (m, 3H), 2.93 - 2.85 (m, 2H), 2.84 (s, 3H), 2.59 - 2.54 (m, 3H), 2.54 - 2.45 (m, 2H), 1.15 (t, *J* = 7.0 Hz, 3H) **Example 266** LCMS ($M+H^+$) 695 ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.18 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.43 (dd, *J* = 6.2, 8.6 Hz, 1H), 7.28 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.09 - 6.99 (m, 2H), 6.95 - 6.89 (m, 1H), 6.86 (dt, *J* = 2.7, 8.3 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.50 (d, *J* = 9.2 Hz, 1H), 5.34 - 5.14 (m, 1H), 4.76 - 4.69 (m, 1H), 4.57 (dd, *J* = 6.5, 11.4 Hz, 1H), 4.37 - 4.28 (m, 1H), 4.12 - 4.07 (m, 1H), 4.05 (q, *J* = 6.9 Hz, 2H), 4.02 - 3.93 (m, 1H), 3.78 - 3.65 (m, 1H), 3.19 - 3.06 (m, 3H), 3.05

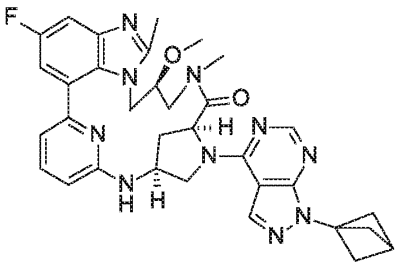
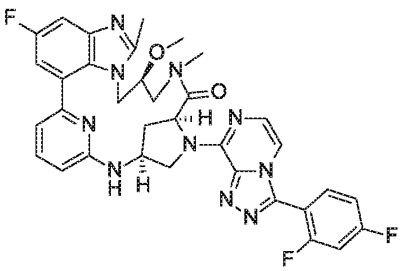
			- 2.98 (m, 1H), 2.85 (s, 3H), 2.76 - 2.69 (m, 1H), 2.61 - 2.56 (m, 3H), 2.56 - 2.52 (m, 1H), 1.15 (t, *J* = 7.0 Hz, 3H)
267 & 268	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C28** SFC separation to give Example **267** (Faster eluted) and Example **268** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: Pyridine, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 25% Flow rate: 60 mL /min Back pressure: 100bar	**Example 267** LCMS (M+H$^+$): 713 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 7.80 - 7.73 (m, 1H), 7.69 - 7.59 (m, 1H), 7.28 (dd, *J* = 2.5, 8.6 Hz, 2H), 7.21 - 7.14 (m, 1H), 7.03 (dd, *J* = 2.3, 10.1 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.61 (d, *J* = 9.0 Hz, 1H), 5.32 - 5.11 (m, 1H), 4.76 - 4.71 (m, 1H), 4.60 - 4.53 (m, 1H), 4.53 - 4.46 (m, 1H), 4.46 - 4.37 (m, 1H), 4.30 - 4.21 (m, 1H), 4.08 - 3.92 (m, 2H), 3.78 - 3.63 (m, 1H), 3.42 (s, 3H), 3.09 (s, 3H), 3.05 - 2.97 (m, 1H), 2.84 (s, 3H), 2.74 - 2.68 (m, 1H), 2.57 (s, 3H), 2.56 - 2.50 (m, 1H) **Example 268** LCMS (M+H$^+$): 713 ^{1}H NMR (500 MHz,

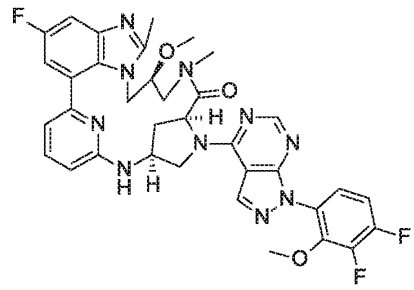
		Column temperature: 35°C	METHANOL-d4) δ = 8.49 (s, 1H), 7.85 - 7.77 (m, 1H), 7.70 - 7.60 (m, 1H), 7.32 - 7.23 (m, 2H), 7.21 - 7.13 (m, 2H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.77 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.59 (d, *J* = 8.9 Hz, 1H), 4.67 (t, *J* = 5.0 Hz, 1H), 4.52 (s, 1H), 4.52 - 4.46 (m, 1H), 4.46 - 4.37 (m, 1H), 4.34 - 4.27 (m, 1H), 4.19 - 4.09 (m, 1H), 3.90 (br dd, *J* = 9.3, 14.2 Hz, 1H), 3.51 - 3.41 (m, 3H), 3.14 - 3.02 (m, 3H), 2.98 - 2.86 (m, 2H), 2.84 (s, 3H), 2.56 (s, 3H), 2.50 (tt, *J* = 4.4, 9.0 Hz, 2H)
360	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C62**	LCMS (M+H$^+$): 684 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.55 (s, 1H), 8.23 (s, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 2.5, 7.2 Hz, 1H), 7.56 (dd, *J* = 2.6, 10.2 Hz, 1H), 7.47 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.08 (dd, *J* = 2.6, 10.7

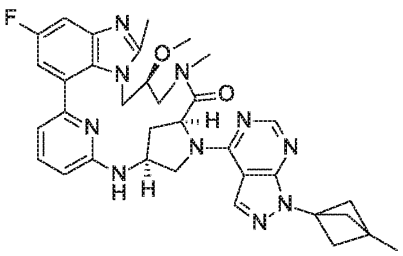
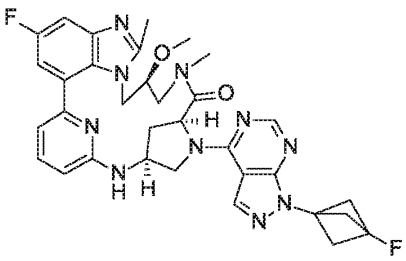
			Hz, 1H), 6.93 - 6.87 (m, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.14 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.49 (d, *J* = 8.9 Hz, 1H), 4.70 (t, *J* = 4.9 Hz, 1H), 4.55 (dd, *J* = 5.8, 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.34 - 4.27 (m, 1H), 3.95 (dd, *J* = 9.3, 14.3 Hz, 1H), 3.17 - 3.10 (m, 1H), 3.06 (s, 3H), 2.97 (s, 3H), 2.92 (br d, *J* = 13.7 Hz, 1H), 2.84 (s, 3H), 2.62 - 2.53 (m, 2H)
361	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C61**	LCMS (M+H$^+$): 699 ^{1}H NMR (500 MHz, METHANOL-*d*$_4$) δ = 8.53 (d, *J* = 0.9 Hz, 1H), 8.19 (s, 1H), 7.85 - 7.79 (m, 1H), 7.33 - 7.28 (m, 1H), 7.17 (dd, *J* = 2.6, 10.4 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.97 - 6.91 (m, 1H), 6.88 - 6.82 (m, 1H), 6.68 (dd, *J* = 0.8, 8.4 Hz, 1H), 5.77 (td, *J* = 3.8, 15.1 Hz, 1H), 5.48 (d, *J* = 8.9 Hz, 1H), 4.66 (t, *J* = 5.0 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.33 (dd, *J* = 4.9, 11.4

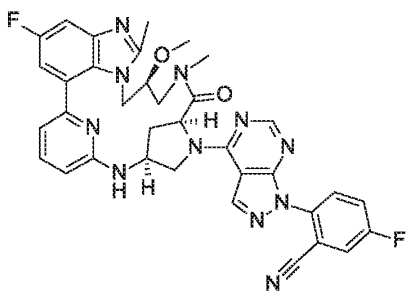
			Hz, 1H), 4.19 - 4.10 (m, 1H), 3.93 (dd, *J* = 9.4, 14.3 Hz, 1H), 3.83 - 3.75 (m, 3H), 3.03 (s, 3H), 2.93 - 2.85 (m, 2H), 2.85 - 2.82 (m, 3H), 2.59 - 2.55 (m, 3H), 2.55 - 2.45 (m, 2H)
362	**(8*S*,11*S*,15*R*)-10-[1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C64**	LCMS (M+H$^+$): 669 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.58 (s, 1H), 8.23 (s, 1H), 7.83 - 7.77 (m, 1H), 7.69 - 7.61 (m, 1H), 7.33 - 7.29 (m, 1H), 7.27 (t, *J* = 8.3 Hz, 2H), 7.17 (dd, *J* = 2.6, 10.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.77 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.48 (d, *J* = 8.9 Hz, 1H), 4.67 - 4.62 (m, 1H), 4.52 - 4.45 (m, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.14 (dd, *J* = 10.9, 15.5 Hz, 1H), 3.93 (dd, *J* = 9.4, 14.3 Hz, 1H), 3.02 (s, 3H), 2.92 - 2.85 (m, 2H), 2.83 (s, 3H), 2.57 (s, 3H), 2.53 - 2.44 (m, 2H)
364	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-**	**BORONIC REAGENT:**	LCMS (M+H$^+$): 667 ^{1}H NMR (500 MHz,

	phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C50**	METHANOL-d_4) δ = 8.51 - 8.47 (m, 1H), 8.21 - 8.16 (m, 1H), 7.84 - 7.79 (m, 1H), 7.49 (dd, *J* = 6.2, 8.6 Hz, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.17 (dd, *J* = 2.6, 10.5 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.82 - 6.77 (m, 1H), 6.77 - 6.72 (m, 1H), 6.70 - 6.64 (m, 1H), 5.81 - 5.65 (m, 1H), 5.47 (br dd, *J* = 4.3, 8.5 Hz, 1H), 4.68 - 4.61 (m, 1H), 4.55 - 4.43 (m, 1H), 4.36 - 4.26 (m, 1H), 4.14 (dd, *J* = 10.9, 15.5 Hz, 1H), 3.94 (dd, *J* = 9.3, 14.2 Hz, 1H), 3.02 (s, 3H), 2.92 - 2.84 (m, 2H), 2.83 (s, 3H), 2.56 (s, 3H), 2.53 - 2.44 (m, 2H)
365	**(8*S*,11*S*,15*R*)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C56**	LCMS (M+H$^+$): 623 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 8.20 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 2.3, 8.4 Hz, 1H), 7.19 (dd, *J* = 2.4, 10.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.78 (dd, *J* = 4.3, 15.4 Hz,

			1H), 5.41 (d, *J* = 8.9 Hz, 1H), 4.63 (br t, *J* = 5.0 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.19 - 4.06 (m, 1H), 3.92 (dd, *J* = 9.3, 14.2 Hz, 1H), 3.02 (s, 3H), 2.90 - 2.85 (m, 2H), 2.84 (s, 3H), 2.67 (s, 1H), 2.58 (s, 3H), 2.52 - 2.44 (m, 8H)
366	**(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C63**	LCMS (M+H$^+$): 669 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 7.84 (t, *J* = 7.9 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.48 - 7.45 (m, 2H), 7.44 - 7.23 (m, 4H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.78 - 6.68 (m, 1H), 6.25 (d, *J* = 8.7 Hz, 1H), 5.98 (dd, *J* = 4.3, 15.5 Hz, 1H), 4.53 (br t, *J* = 4.7 Hz, 1H), 4.31 - 4.14 (m, 3H), 3.81 (dd, *J* = 9.4, 14.1 Hz, 1H), 3.12 (s, 3H), 2.99 - 2.91 (m, 2H), 2.91 (s, 3H), 2.73 - 2.69 (m, 1H), 2.68 (s, 3H), 2.59 - 2.51 (m, 1H)
367	**(8*S*,11*S*,15*R*)-10-[1-(3,4-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-**	**BORONIC REAGENT:** Intermediate **A6**	LCMS (M+H$^+$): 699 ^{1}H NMR (500 MHz, METHANOL-d_4) δ =

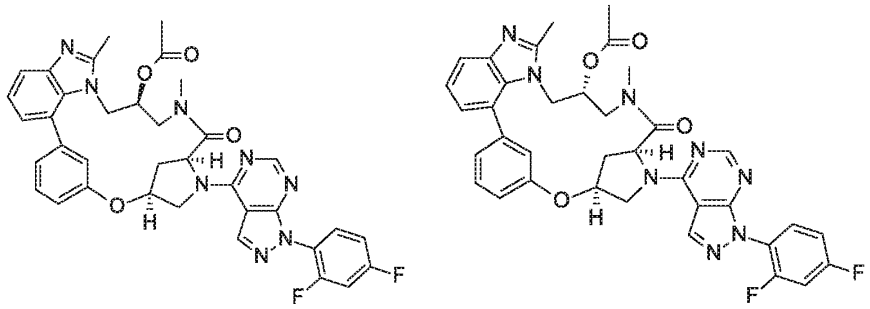
	methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	**HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C51**	8.53 (s, 1H), 8.22 (s, 1H), 7.88 (t, *J* = 7.9 Hz, 1H), 7.59 (dd, *J* = 2.5, 7.2 Hz, 1H), 7.55 (dd, *J* = 2.5, 10.3 Hz, 1H), 7.34 - 7.29 (m, 1H), 7.25 - 7.19 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.15 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.49 (d, *J* = 8.9 Hz, 1H), 4.70 (t, *J* = 4.8 Hz, 1H), 4.57 - 4.51 (m, 1H), 4.39 - 4.33 (m, 1H), 4.32 - 4.25 (m, 1H), 3.99 - 3.90 (m, 1H), 3.87 - 3.80 (m, 3H), 3.07 (s, 3H), 3.06 - 2.99 (m, 1H), 2.97 (s, 3H), 2.91 - 2.86 (m, 1H), 2.83 (s, 3H), 2.62 - 2.51 (m, 2H)
368	**(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-(3-methyl-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C57**	LCMS (M+H$^+$): 637 ^{1}H NMR (500 MHz, METHANOL-*d*$_4$) δ = 8.30 (s, 1H), 8.23 (s, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.61 - 7.57 (m, 1H), 7.56 - 7.50 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.10 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.40 (d, *J* = 8.9 Hz, 1H), 4.66 (t, *J* = 4.9 Hz,

			1H), 4.47 (dd, *J* = 6.0, 11.4 Hz, 1H), 4.35 - 4.28 (m, 1H), 4.28 - 4.21 (m, 1H), 3.94 (dd, *J* = 9.4, 14.3 Hz, 1H), 3.04 (s, 3H), 2.96 (s, 4H), 2.91 - 2.85 (m, 1H), 2.82 (s, 3H), 2.60 - 2.49 (m, 2H), 2.36 (s, 6H), 1.39 (s, 3H)
369	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2}^{0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C58**	LCMS (M+H$^+$): 641 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.33 (s, 1H), 8.24 (s, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.61 - 7.57 (m, 1H), 7.54 (dd, *J* = 2.4, 10.2 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.12 (dd, *J* = 4.5, 15.3 Hz, 1H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.68 - 4.64 (m, 1H), 4.46 (dd, *J* = 6.0, 11.4 Hz, 1H), 4.32 - 4.21 (m, 2H), 3.93 (dd, *J* = 9.4, 14.3 Hz, 1H), 3.05 (s, 3H), 2.96 (s, 4H), 2.88 - 2.84 (m, 1H), 2.82 (d, *J* = 1.7 Hz, 6H), 2.80 - 2.78 (m, 3H), 2.61 - 2.48 (m, 2H)
371	**5-fluoro-2-[4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-**	**BORONIC REAGENT:** Intermediate **A6**	LCMS (M+H$^+$): 676 ^{1}H NMR (500 MHz, METHANOL-d_4) δ =

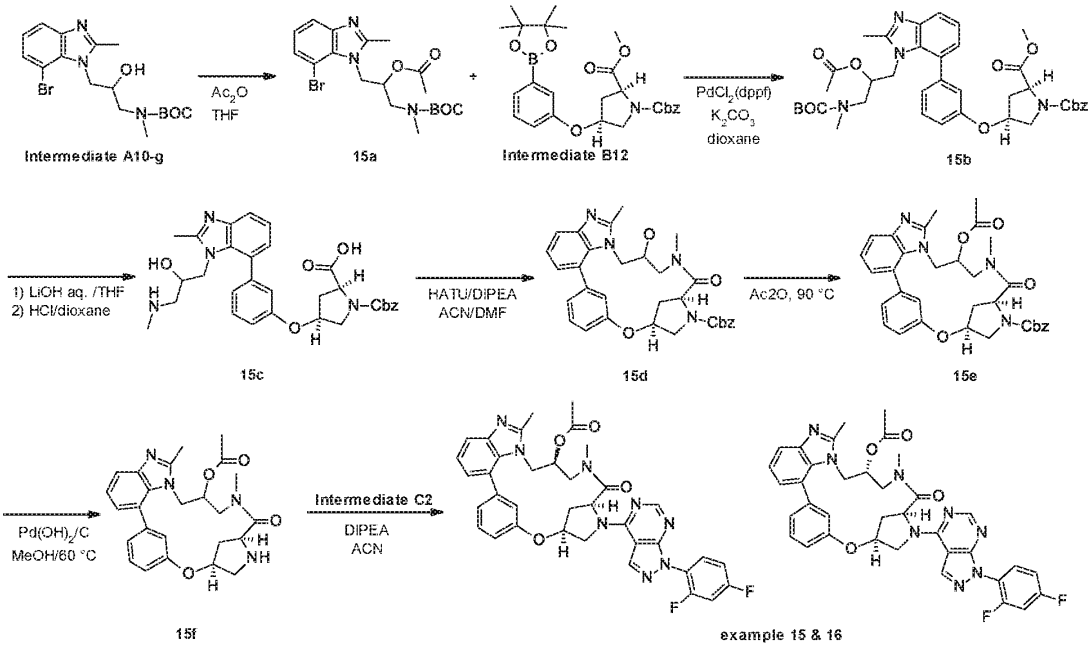
	hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile 	**HALIDE 1**: Intermediate **B10** **HALIDE 2**: Intermediate **C20**	8.60 (s, 1H), 8.28 (s, 1H), 7.91 - 7.87 (m, 2H), 7.87 - 7.82 (m, 1H), 7.73 - 7.66 (m, 1H), 7.59 (dd, *J* = 2.5, 7.2 Hz, 1H), 7.55 (dd, *J* = 2.6, 10.2 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.14 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.50 (d, *J* = 8.9 Hz, 1H), 4.72 - 4.67 (m, 1H), 4.57 - 4.51 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.32 - 4.26 (m, 1H), 3.95 (dd, *J* = 9.5, 14.3 Hz, 1H), 3.07 (s, 3H), 3.02 - 2.98 (m, 1H), 2.97 (s, 3H), 2.91 - 2.86 (m, 1H), 2.82 (s, 3H), 2.62 - 2.50 (m, 2H)

Example 15 and Example 16

[(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26), 3,5,18,20(24),21-heptaen-15-yl] acetate



The title compound was prepared according to the following scheme:



Step 1: preparation of [1-[(7-bromo-2-methyl-benzimidazol-1-yl)methyl]-2-[*tert*-butoxycarbonyl(methyl)amino]ethyl] acetate (compound 15a)

A mixture of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]-*N*-methyl-carbamate (**intermediate A10-g**, 1.1 g, 2.76 mmol, the synthesis refers to **intermediate A7-g**) and Ac_2O (4.33 g, 4 mL, 42.39 mmol) in THF (4 mL) was heated to 70 °C for 16 hrs. The mixture was concentrated, the residue was purified by silica gel to give compound **17a** (1.3 g), LCMS ($M+H^+$): 440.

Step 2~4: preparation of benzyl (8*S*,11*S*)-15-hydroxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaene-10-carboxylate (compound 15d)

Compound **15d** was prepared in analogy to the preparation of compound **1c** by using

compound **15a** instead of intermediate **A15-c**. LCMS ($M+H^+$): 541.

Step 5: preparation of benzyl (8*S*,11*S*)-15-acetoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaene-10-carboxylate (compound 15e)

To a microwave tube was added (8*S*,11*S*)-15-hydroxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (**15d** , 594.67 mg, 1.1 mmol) and Ac_2O (12.87 g, 11.89 mL, 126.05 mmol), a brown suspension formed. Then it was reacted under microwave at 90 °C for 150 mins. The mixture was concentrated, the residue was dissolved in 100 mL DCM and washed with brine, the organic layer was dried and concentrated. The crude product was purified by silica gel to give compound **15e** (550 mg), LCMS ($M+H^+$): 583.

Step 6: preparation of [(8*S*,11*S*)-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (compound 15f)

Compound **15f** was prepared in analogy to step 4 in the preparation of **Example 1** by using compound **15e**) instead of compound **1c**. LCMS ($M+H^+$): 449.

Step 7: preparation of [(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.12,6.18,11.020,24]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaen-15-yl] acetate (Example 15 & 16)

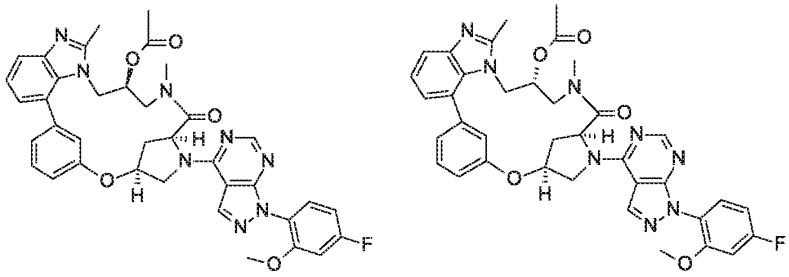
Example 15 & **16** were prepared in analogy to step 5 in the preparation of **Example 1** by using compound **15f** instead of compound **1d**. The mixture was purified via prep-HPLC and SFC. (**SFC condition:** Instrument: SFC 80; Column: Pyridine, 250×30 mm I.D., 5μm; Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O); Gradient: B 35%; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35°C)

Example 15, faster eluted, LCMS ($M+H^+$): 679. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.21 (s, 1H), 7.70 - 7.63 (m, 1H), 7.56 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.32 - 7.25 (m, 2H), 7.24 - 7.22 (m, 1H), 7.21 - 7.16 (m, 2H), 7.08 - 7.01 (m, 1H), 6.96 - 6.87 (m, 1H), 5.61 - 5.56 (m, 1H), 5.48 (d, *J* = 9.5 Hz, 1H), 4.73 - 4.58 (m, 1H), 4.55 - 4.48 (m, 2H), 4.34 - 4.20 (m, 2H), 3.14 - 3.00 (m, 4H), 2.96 - 2.89 (m, 1H), 2.71 - 2.66 (m, 1H), 2.66 - 2.57 (m, 4H), 1.64 (s, 3H).

Example 16, slower eluted, LCMS ($M+H^+$): 679. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.19 (s, 1H), 7.70 - 7.63 (m, 1H), 7.53 - 7.50 (m, 1H), 7.50 - 7.44 (m, 1H), 7.31 - 7.25 (m, 1H), 7.23 - 7.16 (m, 4H), 7.00 - 6.95 (m, 1H), 6.86 - 6.79 (m, 1H), 5.62 - 5.57 (m, 1H), 5.51 - 5.39 (m, 2H), 4.56 - 4.40 (m, 2H), 4.31 - 4.22 (m, 1H), 4.08 - 3.99 (m, 1H), 3.71 (dd, *J* = 3.9, 14.9 Hz, 1H), 3.15 - 2.99 (m, 4H), 2.95 - 2.88 (m, 1H), 2.68 - 2.63 (m, 1H), 2.61 (s, 3H), 1.65 (s, 3H).

Example 17 and Example 18

[(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate



The title compounds were prepared in analogy to the preparation of **Example 15** and **Example 16** by using **intermediate C11** instead of **intermediate C2**. (**SFC condition:** Instrument: SFC 80; Column: Pyridine, 250×30 mm I.D., 5μm; Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O); Gradient: B 35%; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35°C)

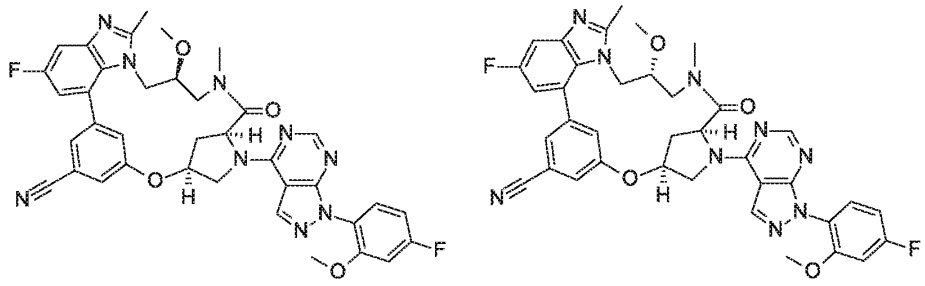
Example 17, faster eluted, LCMS ($M+H^+$): 691. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.50 (s, 1H), 8.15 (s, 1H), 7.56 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.45 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.28 - 7.21 (m, 2H), 7.19 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.08 - 7.03 (m, 2H), 6.94 - 6.85 (m, 2H), 5.60 - 5.56 (m, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 4.59 - 4.47 (m, 3H), 4.33 - 4.21 (m, 2H), 3.77 - 3.75 (m, 1H), 3.75 (s, 3H), 3.14 - 3.00 (m, 4H), 2.92 (br d, *J* = 13.6 Hz, 1H), 2.70 - 2.65 (m, 1H), 2.65 - 2.63 (m, 3H), 1.64 (s, 3H).

Example 18, slower eluted, LCMS ($M+H^+$): 691. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.54 (s, 1H), 8.14 (s, 1H), 7.59 (br d, *J* = 8.1 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.44 (dd, *J* = 6.3, 8.7 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.19 (dd, *J* = 2.7, 11.0 Hz, 1H), 7.09 - 7.01 (m, 1H), 7.00 - 6.92 (m,

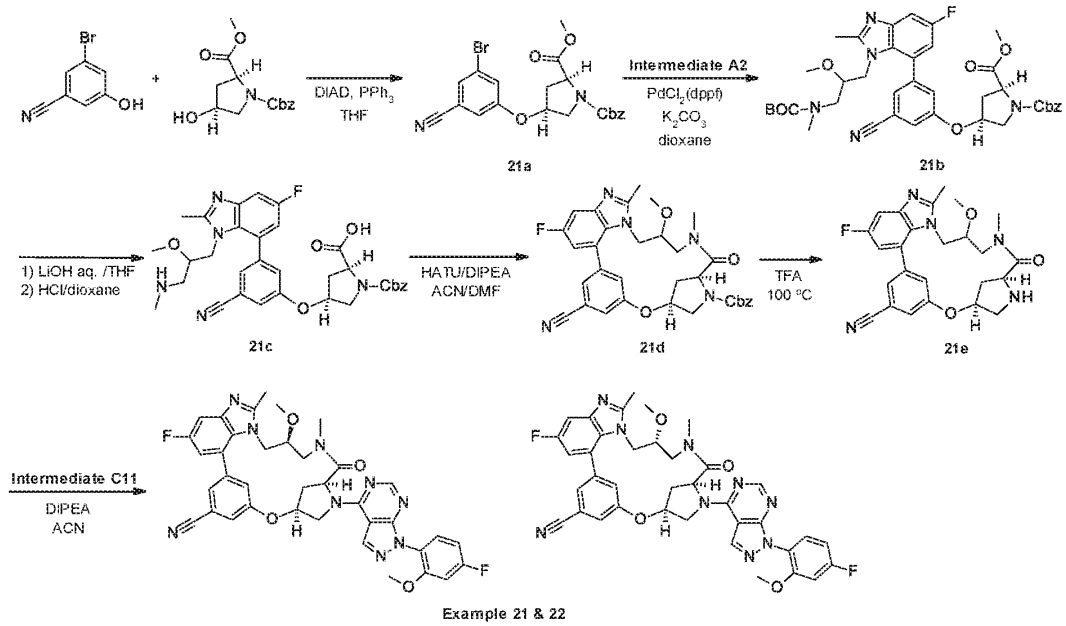
2H), 6.87 - 6.82 (m, 1H), 5.59 (t, *J* = 4.3 Hz, 1H), 5.43 - 5.38 (m, 1H), 5.28 - 5.18 (m, 1H), 4.48 - 4.41 (m, 1H), 4.35 (br d, *J* = 11.7 Hz, 1H), 4.20 - 4.16 (m, 1H), 3.93 - 3.84 (m, 1H), 3.73 - 3.72 (m, 5H), 3.03 - 2.90 (m, 4H), 2.66 - 2.63 (m, 3H), 2.63 - 2.57 (m, 1H), 1.64 - 1.58 (m, 3H).

Example 21 and Example 22

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile



The title compounds were prepared according to the following scheme:



Step 1: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-(3-bromo-5-cyano-

phenoxy)pyrrolidine-1,2-dicarboxylate (compound 21a)

To a flask was added 3-bromo-5-hydroxy-benzonitrile (4.17 g, 21.05 mmol, as the "**ArOH**" in table 4), *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (5.6 g, 20.05 mmol), THF (25 mL) and triphenylphosphine (6.31 g, 24.06 mmol). And then to the solution was added DIAD (5.27 g, 26.07 mmol) dropwise. After being stirred at r.t. for 3 hrs, the mixture was concentrated, the residue was purified by silica gel to give compound **21a** (13.8 g), LCMS ($M+H^+$): 459.

Step 2: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[3-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-5-cyano-phenoxy]pyrrolidine-1,2-dicarboxylate (compound 21b)

To a flask was added *tert*-butyl *N*-[3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-N-methyl-carbamate(**intermediate A2**, 2 g, 4.19 mmol, as the "**BORONIC REAGENT**" in table 4), compound **21a** (3.21 g, 4.19 mmol), K_2CO_3 (1.16 g, 8.38 mmol), 1,4-dioxane (20 mL) and water (1 mL). The suspension was bubbled with N_2 for 5 mins, then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), dichloromethane adduct (342.13 mg, 0.419 mmol) was added. After being heated to 90 °C for 16 hrs, the mixture was diluted with 200 mL water and extracted with 50 mL EA for three times. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **21b** (1.9 g), LCMS ($M+H^+$): 730.

Step 3: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[3-cyano-5-[6-fluoro-3-[2-methoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]phenoxy]pyrrolidine-2-carboxylic acid (compound 21c)

A mixture of compound **21b** (1.9 g, 2.6 mmol) and LiOH (2 N, 3 mL) in THF (2 mL) and methanol (2 mL) was stirred at rt for 2 hrs. The mixture was diluted with 20 mL water and adjusted pH to about 4 with 2 N aq. solution of HCl, then it was extracted with 30 mL DCM for three times. The organic layer was dried and concentrated, the residue was dissolved in DCM (5 mL) and TFA (5 mL), the mixture was stirred at r.t. for 1 hr and then concentrated. The crude product was purified via prep-HPLC to give compound **21c** (1.47 g), LCMS ($M+H^+$): 616.

Step 4: preparation of benzyl (8*S*,11*S*)-4-cyano-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 21d)

To a solution of HATU (1.66 g, 4.36 mmol) and DIEA (1.8 g, 13.94 mmol) in acetonitrile (400 mL) was added another solution of compound **21c** (1.47 g, 1.74 mmol) in acetonitrile (350

mL) dropwise in 3 hrs. The mixture was concentrated and the residue was dissolved in 150 mL EA, which was washed with water and brine, the organic layer was dried and concentrated, the residue was purified via prep-HPLC to give compound **21d** (850 mg, LCMS ($M+H^+$): 598.

Step 5: preparation of (8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaene-4-carbonitrile (compound 21e)

To a microwave tube was added compound **21d** (450 mg, 0.670 mmol) and TFA (1 mL). The mixture was reacted under microwave at 100 °C for 10 mins, and then the mixture was concentrated to give compound **21d** (700 mg), LCMS ($M+H^+$): 464.

Step 6: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21 -heptaene-4-carbonitrile and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl) pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21 -heptaene-4-carbonitrile (Example 21 & 22)

To a flask was added compound **21e** (103.96 mg, 0.180 mmol), intermediate **C11** (47.99 mg, 0.180 mmol as "**HALIDE**" in table 4), DIEA (93.05 mg, 125.75 μL, 0.720 mmol) and acetonitrile (4.69 mL). The mixture was heated to 85 °C for 1 hr, then the mixture was concentrated and the residue was purified by silica gel and SFC (as "**SFC condition**" in table 4) to give Example **21** and Example **22**. (SFC condition: Instrument: SFC 80; Column: IA, 250×30 mm I.D., 5μm; Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O); Gradient: B 40%; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35°C)

Example 21 (77.3 mg), faster eluted, LCMS ($M+H^+$): 706. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.17 (s, 1H), 7.67 (s, 1H), 7.44 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.32 - 7.28 (m, 2H), 7.26 - 7.22 (m, 1H), 7.05 (dd, *J* = 2.7, 10.7 Hz, 1H), 6.88 (dt, *J* = 2.6, 8.4 Hz, 1H), 6.81 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.67 - 5.63 (m, 1H), 5.45 (d, *J* = 9.3 Hz, 1H), 4.57 - 4.40 (m, 2H), 4.17 - 4.10 (m, 1H), 4.07 - 3.98 (m, 1H), 3.76 - 3.71 (m, 3H), 3.64 - 3.56 (m, 1H), 3.49 - 3.42 (m, 1H), 3.15 - 2.99 (m, 3H), 2.84 - 2.81 (m, 3H), 2.79 (br d, *J* = 14.6 Hz, 1H), 2.72 - 2.60 (m, 2H), 2.56 (s, 3H).

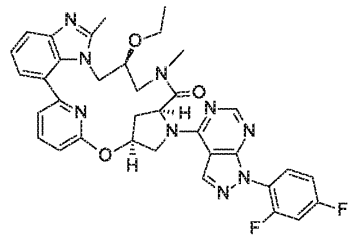
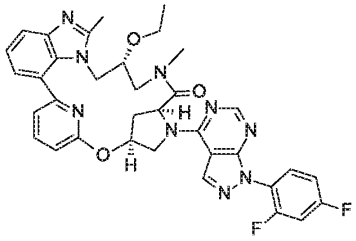
Example 22 (7 mg), slower eluted, LCMS ($M+H^+$): 706. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.17 (s, 1H), 7.68 - 7.57 (m, 2H), 7.44 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.32 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.05 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.97 -

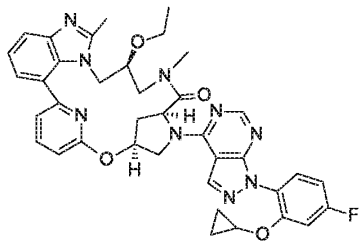
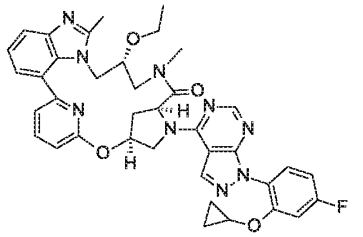
6.92 (m, 1H), 6.90 - 6.84 (m, 1H), 5.69 - 5.59 (m, 1H), 5.52 (d, *J* = 9.5 Hz, 1H), 4.58 - 4.37 (m, 3H), 4.32 - 4.19 (m, 1H), 4.14 - 4.01 (m, 1H), 3.75 (s, 3H), 3.16 - 3.04 (m, 3H), 3.03 - 2.96 (m, 3H), 2.96 - 2.78 (m, 3H), 2.75 - 2.67 (m, 1H), 2.66 - 2.57 (m, 3H).

The following examples in Table 4 were prepared in analogy to **Example 21** & **22**, replacing 3-bromo-5-hydroxy-benzonitrile with "**ArOH**" in step 1, **Intermediate A2** with the "**BORONIC REAGENT**" in step 2, **Intermediate C11** with the "**HALIDE**" in step 6 by the reagents indicated in Table 4.

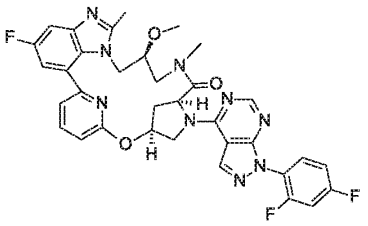
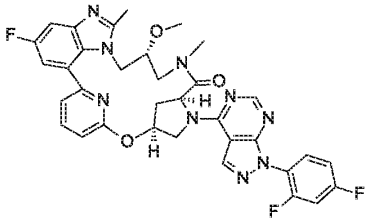
Table 4. Compound synthesis and characterization

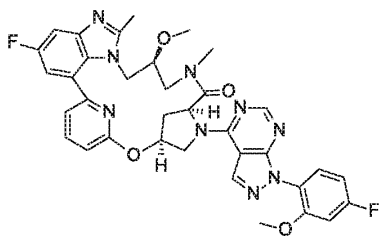
No.	Compound Name and Structure	ArOH, BORONIC REAGENT, HALIDE, SFC CONDITION	^{1}H NMR and MS (ESI)
23 & 24	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** and **(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl) pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**ArOH:** bromopyridin-2-ol **BORONIC REAGENT:** Intermediate **A10** **HALIDE**: Intermediate **C2** SFC separation to give Example **23** (Faster eluted) & **24** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: Pyridine, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA	**Example 23** LCMS (M+H$^+$): 666 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.54 (s, 1H), 8.23 (s, 1H), 7.97 (t, *J* = 7.9 Hz, 1H), 7.67 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.64 - 7.61 (m, 1H), 7.41 - 7.33 (m, 2H), 7.32 - 7.25 (m, 2H), 7.23 - 7.17 (m, 1H), 7.03 (br d, *J* = 8.2 Hz, 1H), 5.64 - 5.44 (m, 2H), 4.63 - 4.50 (m, 2H), 4.44 - 4.35 (m, 1H), 4.16 - 3.99 (m, 2H), 3.75 - 3.55 (m, 1H), 3.27 - 3.19 (m, 1H), 3.15 - 2.96 (m, 4H), 2.91 - 2.81 (m, 1H), 2.79 - 2.70 (m, 2H), 2.59 (s, 3H), 0.56 (t, *J* = 6.9 Hz, 3H)

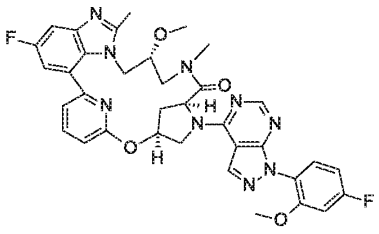
	 	(0.1% NH_3H_2O) Gradient: B 35% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	**Example 24** LCMS ($M+H^+$): 666 ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.24 (s, 1H), 8.07 - 7.99 (m, 1H), 7.70 - 7.61 (m, 2H), 7.58 - 7.53 (m, 1H), 7.50 - 7.43 (m, 1H), 7.37 - 7.26 (m, 2H), 7.24 - 7.17 (m, 1H), 7.10 - 7.03 (m, 1H), 5.89 (dd, *J* = 4.0, 15.5 Hz, 1H), 5.61 - 5.58 (m, 1H), 4.61 - 4.49 (m, 2H), 4.40 - 4.24 (m, 1H), 4.20 - 4.13 (m, 1H), 4.03 - 3.94 (m, 1H), 3.27 - 3.20 (m, 1H), 3.07 - 2.95 (m, 3H), 2.95 - 2.86 (m, 1H), 2.80 (dd, *J* = 1.9, 14.0 Hz, 1H), 2.75 - 2.68 (m, 1H), 2.67 - 2.63 (m, 1H), 2.62 - 2.59 (m, 3H), 2.58 - 2.53 (m, 1H), 0.60 - 0.55 (m, 3H)
25 & 26	**(8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-**	**ArOH:** bromopyridin-2-ol **BORONIC REAGENT:**	LCMS ($M+H^+$): 704 **Example 25** LCMS ($M+H^+$): 704 ^1H NMR (500 MHz,

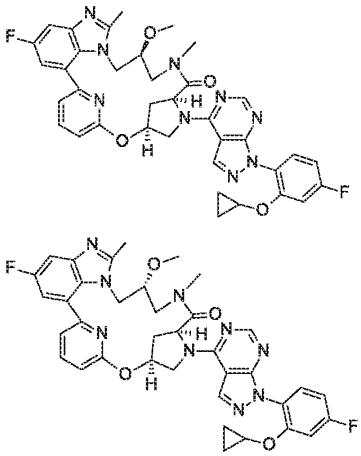
	pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-[2-(cyclopropoxy) -4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	Intermediate **A10** **HALIDE**: Intermediate **C17** SFC separation to give Example **25** (Faster eluted) & **26** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: Pyridine, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 30% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	METHANOL-d_4) δ = 8.48 (s, 1H), 8.16 (s, 1H), 7.98 (t, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.46 - 7.40 (m, 1H), 7.39 - 7.34 (m, 2H), 7.34 - 7.30 (m, 1H), 7.29 - 7.25 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.93 - 6.86 (m, 1H), 5.64 - 5.60 (m, 1H), 5.60 - 5.46 (m, 1H), 4.62 - 4.52 (m, 2H), 4.40 (d, *J* = 2.4 Hz, 1H), 4.15 - 4.09 (m, 1H), 4.09 - 4.03 (m, 1H), 3.85 (tt, *J* = 2.9, 6.0 Hz, 1H), 3.74 - 3.60 (m, 1H), 3.28 - 3.21 (m, 1H), 3.15 - 3.09 (m, 1H), 3.07 - 2.96 (m, 3H), 2.93 - 2.83 (m, 1H), 2.80 - 2.70 (m, 2H), 2.61 (s, 3H), 0.78 - 0.71 (m, 2H), 0.63 - 0.59 (m, 2H), 0.58 - 0.55 (m, 3H) **Example 26** LCMS ($M+H^+$): 704 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.17 (s, 1H), 8.07 - 8.00 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H),

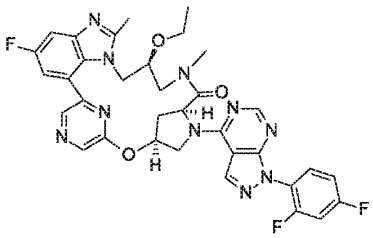
			7.56 (d, *J* = 7.6 Hz, 1H), 7.49 - 7.40 (m, 2H), 7.35 - 7.27 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.95 - 6.87 (m, 1H), 5.89 (dd, *J* = 4.0, 15.5 Hz, 1H), 5.60 - 5.56 (m, 1H), 4.60 - 4.47 (m, 2H), 4.39 - 4.29 (m, 1H), 4.20 - 4.12 (m, 2H), 4.03 - 3.95 (m, 1H), 3.89 - 3.82 (m, 1H), 3.27 - 3.20 (m, 1H), 3.07 - 2.97 (m, 3H), 2.96 - 2.92 (m, 1H), 2.80 (dd, *J* = 1.8, 13.9 Hz, 1H), 2.67 - 2.63 (m, 1H), 2.62 (s, 3H), 2.58 - 2.54 (m, 1H), 0.77 - 0.72 (m, 2H), 0.62 - 0.59 (m, 2H), 0.59 - 0.55 (m, 3H)
27 & 28	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-**	**ArOH:** bromopyridin-2-ol **BORONIC REAGENT:** Intermediate **A2** **HALIDE**: Intermediate **C2** SFC separation to give Example **27** (Faster eluted) & **28** (Slower	**Example 27** LCMS (M+H$^+$): 670 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.55 (s, 1H), 8.24 (s, 1H), 8.11 - 8.03 (m, 1H), 7.68 (dt, *J* = 5.8, 8.5 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.33 - 7.26 (m, 2H), 7.24 - 7.17 (m, 1H), 7.15 - 7.10 (m, 1H), 5.90 (dd, *J*

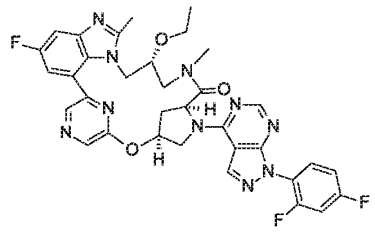
	oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one  	eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	= 4.0, 15.6 Hz, 1H), 5.62 - 5.57 (m, 1H), 4.61 - 4.54 (m, 1H), 4.53 - 4.36 (m, 1H), 4.22 - 4.11 (m, 1H), 4.00 - 3.89 (m, 1H), 3.09 - 2.97 (m, 3H), 2.96 - 2.90 (m, 1H), 2.88 - 2.83 (m, 1H), 2.82 (s, 3H), 2.76 - 2.68 (m, 1H), 2.60 (s, 3H), 2.59 - 2.54 (m, 1H), 2.54 - 2.45 (m, 1H). **Example 28** LCMS ($M+H^+$): 670 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.23 (s, 1H), 7.99 (t, *J* = 7.9 Hz, 1H), 7.71 - 7.59 (m, 1H), 7.37 (br d, *J* = 7.5 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.23 - 7.18 (m, 1H), 7.15 (br d, *J* = 10.1 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.60 (br d, *J* = 9.0 Hz, 2H), 5.52 - 5.44 (m, 1H), 4.61 - 4.51 (m, 1H), 4.44 - 4.34 (m, 1H), 4.12 - 4.01 (m, 2H), 3.58 - 3.47 (m, 1H), 3.17 - 3.09 (m, 1H), 3.02 (s, 3H), 2.92 -

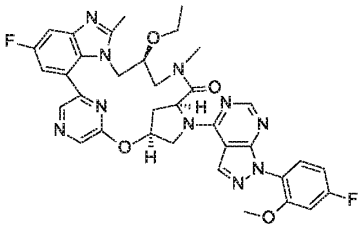
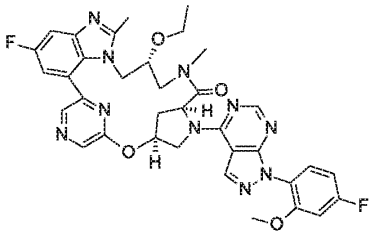
			2.83 (m, 1H), 2.82 (s, 3H), 2.78 - 2.69 (m, 1H), 2.60 - 2.54 (m, 3H).
29 & 30	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**ArOH:** bromopyridin-2-ol **BORONIC REAGENT:** Intermediate **A2** **HALIDE**: Intermediate **C11** SFC separation to give Example **29** (Faster eluted) & **30** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100bar Column temperature:	**Example 29** LCMS (M+H$^+$): 682 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.18 (s, 1H), 8.09 - 8.02 (m, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 6.1, 8.7 Hz, 1H), 7.34 (dd, *J* = 2.6, 8.4 Hz, 1H), 7.29 - 7.23 (m, 1H), 7.13 - 7.08 (m, 1H), 7.06 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.92 - 6.84 (m, 1H), 5.87 (dd, *J* = 4.0, 15.6 Hz, 1H), 5.60 - 5.43 (m, 2H), 4.56 - 4.49 (m, 1H), 4.42 - 4.32 (m, 1H), 4.21 - 4.10 (m, 1H), 4.00 - 3.89 (m, 1H), 3.77 (s, 3H), 3.08 - 2.96 (m, 3H), 2.96 - 2.89 (m, 1H), 2.87 - 2.82 (m, 1H), 2.81 (s, 3H), 2.75 - 2.67 (m, 1H), 2.58 (s, 3H), 2.53 - 2.46 (m, 1H) **Example 30** LCMS (M+H$^+$): 682

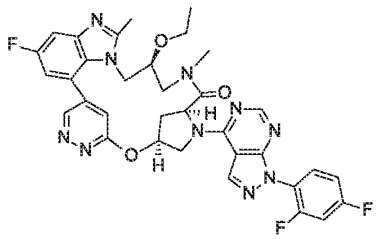
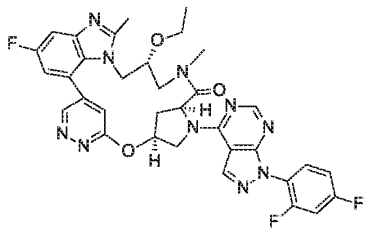
		35°C	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 8.17 (s, 1H), 8.01 - 7.94 (m, 1H), 7.44 (dd, *J* = 6.1, 8.7 Hz, 1H), 7.38 - 7.33 (m, 1H), 7.32 - 7.29 (m, 1H), 7.15 (br d, *J* = 9.9 Hz, 1H), 7.08 - 7.00 (m, 2H), 6.92 - 6.82 (m, 1H), 5.67 - 5.52 (m, 2H), 5.50 - 5.42 (m, 1H), 4.57 - 4.48 (m, 1H), 4.42 - 4.32 (m, 1H), 4.12 - 4.02 (m, 2H), 3.76 (s, 3H), 3.58 - 3.46 (m, 1H), 3.17 - 3.09 (m, 1H), 3.01 (s, 3H), 2.85 (s, 1H), 2.82 (s, 3H), 2.77 - 2.68 (m, 1H), 2.58 (s, 3H).
31 &32	**(8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-**	**ArOH:** bromopyridin-2-ol **BORONIC REAGENT:** Intermediate **A2** **HALIDE**: Intermediate **C17** SFC separation to give Example **31** (Faster	**Example 31** LCMS (M+H$^+$): 708 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.38 (s, 1H), 8.07 (s, 1H), 8.00 - 7.93 (m, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 6.0, 8.7 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.19 - 7.12 (m, 1H), 7.05 - 6.99 (m, 1H), 6.84 - 6.77 (m, 1H), 5.77 (dd, *J*

	d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	eluted) & **32** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 45% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	= 4.1, 15.6 Hz, 1H), 5.52 - 5.46 (m, 1H), 4.47 - 4.42 (m, 1H), 4.09 - 4.03 (m, 1H), 4.02 - 3.96 (m, 1H), 3.90 - 3.82 (m, 1H), 3.79 - 3.72 (m, 1H), 3.00 - 2.87 (m, 3H), 2.85 - 2.79 (m, 1H), 2.78 - 2.74 (m, 1H), 2.74 - 2.69 (m, 3H), 2.65 - 2.58 (m, 1H), 2.54 - 2.50 (m, 1H), 2.49 - 2.45 (m, 3H), 2.43 - 2.36 (m, 1H), 0.68 - 0.60 (m, 2H), 0.50 (td, *J* = 2.7, 6.7 Hz, 2H) **Example 32** LCMS ($M+H^+$): 708 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.37 (s, 1H), 8.06 (s, 1H), 7.89 (t, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 6.0, 8.7 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.24 - 7.18 (m, 2H), 7.05 (br d, *J* = 10.1 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.84 - 6.76 (m, 1H), 5.53 - 5.42 (m, 2H), 4.48 - 4.41 (m, 1H), 4.32 - 4.25 (m, 1H), 4.09 - 3.94 (m, 3H), 3.75 (tt, *J*

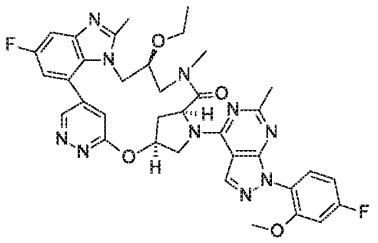
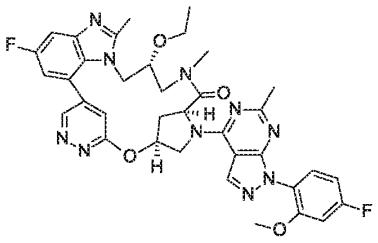
			= 2.9, 5.9 Hz, 1H), 3.49 - 3.39 (m, 1H), 3.03 - 2.87 (m, 4H), 2.77 - 2.69 (m, 4H), 2.67 - 2.58 (m, 1H), 2.49 (s, 3H), 0.68 - 0.60 (m, 2H), 0.54 - 0.46 (m, 2H)
85 & 86	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**ArOH:** 6-chloropyrazin-2-ol **BORONIC REAGENT:** Intermediate **A9** **HALIDE**: Intermediate **C2** SFC separation to give Example **85** (Faster eluted) & **86** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O)	**Example 85** LCMS (M+H$^+$): 685 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.85 (s, 1H), 8.56 (d, *J* = 2.3 Hz, 2H), 8.24 (s, 1H), 7.68 (dt, *J* = 6.0, 8.5 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.33 - 7.27 (m, 1H), 7.24 - 7.16 (m, 1H), 5.84 - 5.68 (m, 1H), 5.68 - 5.58 (m, 1H), 4.64 - 4.55 (m, 2H), 4.54 - 4.35 (m, 1H), 4.21 - 4.11 (m, 1H), 4.03 - 3.94 (m, 1H), 3.30 - 3.25 (m, 1H), 3.09 - 2.97 (m, 3H), 2.87 - 2.78 (m, 2H), 2.70 - 2.65 (m, 1H), 2.65 - 2.51 (m, 5H), 0.61 (t, *J* = 6.9 Hz, 3H) **Example 86** LCMS (M+H$^+$): 685 ^{1}H NMR (500 MHz,

		Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	METHANOL-d_4) δ = 8.66 (s, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 8.24 (s, 1H), 7.71 - 7.60 (m, 1H), 7.39 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.16 (m, 1H), 5.86 - 5.69 (m, 1H), 5.64 (br d, *J* = 8.4 Hz, 1H), 4.65 - 4.58 (m, 1H), 4.51 - 4.37 (m, 1H), 4.16 - 4.03 (m, 2H), 3.66 - 3.55 (m, 1H), 3.30 - 3.22 (m, 2H), 3.16 - 3.12 (m, 1H), 3.05 (s, 3H), 3.02 - 2.96 (m, 1H), 2.88 - 2.80 (m, 1H), 2.80 - 2.73 (m, 1H), 2.63 - 2.57 (m, 3H), 0.56 (t, *J* = 6.9 Hz, 3H)
89 & 90	**(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-**	**ArOH:** 6-chloropyrazin-2-ol **BORONIC REAGENT:** Intermediate **A9** **HALIDE**: Intermediate **C11** SFC separation to give Example **89** (Faster eluted) & **90** (Slower	**Example 89** LCMS (M+H$^+$): 697 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.85 (s, 1H), 8.56 (s, 1H), 8.51 (s, 1H), 8.19 (s, 1H), 7.49 - 7.36 (m, 3H), 7.07 (dd, *J* = 2.4, 10.6 Hz, 1H), 6.89 (dt, *J* = 2.5, 8.4 Hz, 1H), 5.73 - 5.64 (m, 1H), 5.63 - 5.50 (m, 1H), 4.64 - 4.56 (m, 2H), 4.47 - 4.30 (m, 1H),

	dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100 bar Column temperature: 35°C	4.17 (br dd, *J* = 11.3, 15.6 Hz, 1H), 4.05 - 3.94 (m, 1H), 3.80 - 3.74 (m, 3H), 3.29 - 3.24 (m, 1H), 3.10 - 2.97 (m, 3H), 2.86 - 2.77 (m, 2H), 2.69 - 2.54 (m, 6H), 0.73 - 0.57 (m, 3H) **Example 90** LCMS (M+H$^+$): 697 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.66 (s, 1H), 8.52 - 8.45 (m, 2H), 8.18 (s, 1H), 7.45 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.31 (br d, *J* = 9.5 Hz, 1H), 7.06 (dd, *J* = 2.3, 10.7 Hz, 1H), 6.92 - 6.84 (m, 1H), 5.86 - 5.68 (m, 1H), 5.65 - 5.50 (m, 1H), 4.61 - 4.57 (m, 1H), 4.49 - 4.29 (m, 1H), 4.16 - 4.03 (m, 2H), 3.76 (s, 3H), 3.65 - 3.54 (m, 1H), 3.31 - 3.21 (m, 2H), 3.19 - 3.12 (m, 1H), 3.04 (s, 3H), 3.00 - 2.91 (m, 1H), 2.88 - 2.79 (m, 1H), 2.79 - 2.72 (m, 1H), 2.61 (s, 3H), 0.56 (t, *J* = 6.9 Hz,

			3H)
91 & 92	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one**  	**ArOH:** 5-chloropyridazin-3-ol **BORONIC REAGENT:** Intermediate **A9** **HALIDE**: Intermediate **C2** prep-HPLC separation to give Example **91** (Faster eluted) & **92** (Slower eluted)	**Example 91** LCMS (M+H$^+$): 685 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.94 (d, *J* = 1.2 Hz, 1H), 8.60 (s, 1H), 8.25 (s, 1H), 7.71 - 7.61 (m, 2H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.35 (dd, *J* = 2.2, 9.4 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.24 - 7.17 (m, 1H), 6.14 - 5.93 (m, 1H), 5.48 (d, *J* = 9.5 Hz, 1H), 4.67 - 4.62 (m, 1H), 4.55 (dd, *J* = 3.9, 11.8 Hz, 1H), 4.46 - 4.29 (m, 1H), 4.22 - 4.08 (m, 1H), 3.79 - 3.65 (m, 2H), 3.51 - 3.39 (m, 1H), 3.36 - 3.31 (m, 1H), 3.16 - 3.03 (m, 3H), 3.02 - 2.90 (m, 2H), 2.89 - 2.84 (m, 1H), 2.84 - 2.82 (m, 3H), 0.74 - 0.66 (m, 3H) **Example 92** LCMS (M+H$^+$): 685 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.92 - 8.84 (m, 1H), 8.48

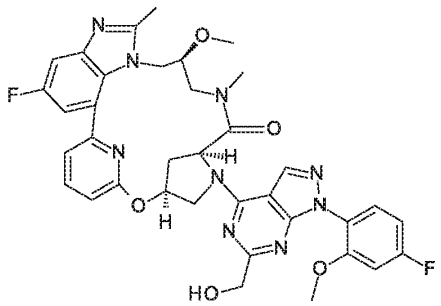
			(s, 1H), 8.14 (s, 1H), 7.58 (dt, *J* = 6.0, 8.5 Hz, 1H), 7.55 - 7.47 (m, 1H), 7.31 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.24 - 7.15 (m, 1H), 7.14 - 7.07 (m, 1H), 7.05 - 6.96 (m, 1H), 6.03 - 5.90 (m, 1H), 5.41 (br d, *J* = 9.6 Hz, 1H), 4.55 - 4.38 (m, 3H), 4.32 (br d, *J* = 15.9 Hz, 1H), 4.21 - 4.04 (m, 1H), 4.01 - 3.82 (m, 1H), 3.50 - 3.36 (m, 1H), 3.03 - 2.90 (m, 3H), 2.86 - 2.74 (m, 1H), 2.73 - 2.61 (m, 3H), 2.55 - 2.49 (m, 3H), 0.60 - 0.52 (m, 3H)
93 & 94	**(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-**	**ArOH:** 5-chloropyridazin-3-ol **BORONIC REAGENT:** Intermediate **A9** **HALIDE**: Intermediate **C12** prep-HPLC separation to give Example **93** (Faster eluted) & **94** (Slower eluted)	**Example 93** LCMS (M+H$^+$): 711 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.95 (d, *J* = 1.5 Hz, 1H), 8.62 (s, 1H), 7.67 (dd, *J* = 2.4, 7.7 Hz, 1H), 7.53 (dd, *J* = 6.1, 8.7 Hz, 1H), 7.44 - 7.40 (m, 1H), 7.40 - 7.33 (m, 1H), 7.14 - 7.07 (m, 1H), 6.97 - 6.88 (m, 1H), 6.15 - 5.96 (m, 1H), 5.60 (d, *J* = 9.5 Hz, 1H), 4.70 - 4.64 (m, 1H),

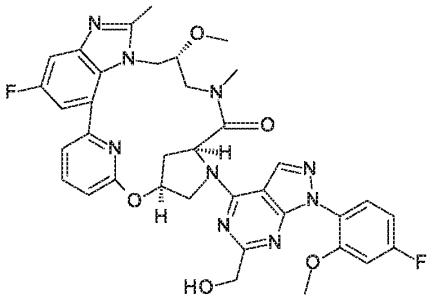
	4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  		4.61 (br d, *J* = 4.1 Hz, 1H), 4.45 - 4.33 (m, 1H), 4.21 - 4.10 (m, 1H), 3.82 - 3.78 (m, 3H), 3.75 - 3.65 (m, 2H), 3.50 - 3.41 (m, 1H), 3.15 - 3.11 (m, 1H), 3.04 (s, 3H), 3.01 - 2.92 (m, 2H), 2.91 - 2.84 (m, 1H), 2.84 - 2.80 (m, 3H), 2.64 - 2.49 (m, 3H), 0.72 (t, *J* = 6.9 Hz, 3H) **Example 94** LCMS (M+H$^+$): 711 ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 9.01 (br s, 1H), 8.55 (s, 1H), 7.71 - 7.61 (m, 1H), 7.59 (br d, *J* = 7.8 Hz, 1H), 7.49 (dd, *J* = 6.2, 8.5 Hz, 1H), 7.36 - 7.29 (m, 1H), 7.12 - 7.06 (m, 1H), 6.95 - 6.87 (m, 1H), 6.13 - 5.92 (m, 1H), 5.59 (br d, *J* = 9.5 Hz, 1H), 4.66 - 4.61 (m, 1H), 4.60 - 4.49 (m, 2H), 4.31 - 4.17 (m, 1H), 4.16 - 4.01 (m, 1H), 3.78 (s, 3H), 3.63 - 3.53 (m, 1H), 3.18 - 3.12 (m, 1H), 3.03 (s, 3H), 2.98 - 2.89 (m, 1H),

			2.89 - 2.78 (m, 3H), 2.78 - 2.72 (m, 3H), 2.60 - 2.44 (m, 3H), 0.74 - 0.67 (m, 3H)

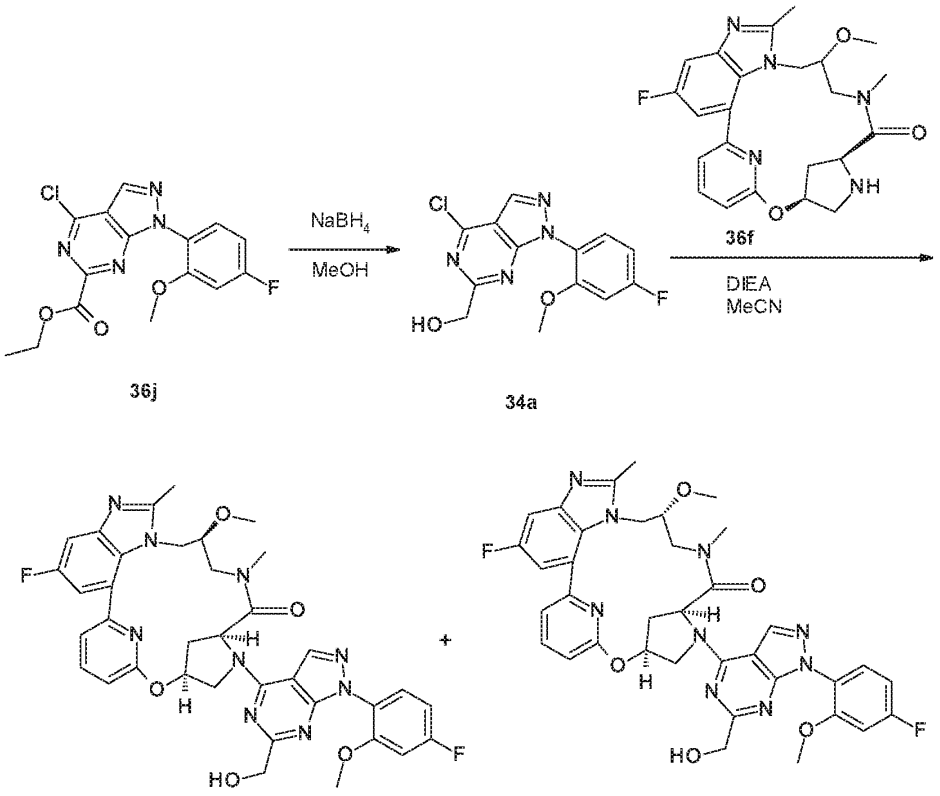
Example 34 and Example 35

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared according to the following scheme:



Example 34 and 35

Step 1: preparation of [4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methanol (compound 34a)

$NaBH_4$ (13 mg, 0.342 mmol) was added to a solution of compound **36j** (100 mg, 0.285 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. Then the reaction mixture was added methanol (4 mL) and $NaBH_4$ (13 mg, 0.342 mmol) , and stirred for another 4 hours. Saturated NH_4Cl solution was added to quenched the reaction and then the solution was extracted with DCM (20 mL). The organic layer was dried and concentrated, the residue was by silica gel to afford compound **34a** (35 mg, 37.78%). LCMS ($M+H^+$): 309.

Step 2: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 34) and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-

pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 35)

A suspension of compound **36f** (47 mg, 0.108 mmol), [4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methanol (**compound 34a,** 35 mg, 0.108 mmol) and DIEA (56 µL, 0.323 mmol) in acetonitrile (1 mL) was stirred at 70 °C for 0.5 hours. The reaction was concentrated and the residue was purified by reversed-phase Chromatography to afford product (54 mg), which was separated via SFC to give **example 34** and **35**.

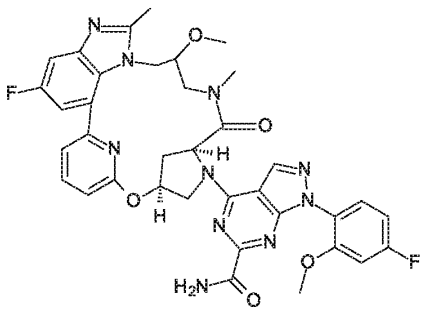
SFC conditions: Instrument: SFC 80; Column: OD, 250×20 mm I.D., 5µm.; Mobile phase: A for CO_2 and B for ethanol (0.1% NH_3H_2O); Gradient: B 35%; Flow rate: 40 mL /min; Back pressure: 100bar; Column temperature: 35°C.

Example 34 (24 mg), faster eluted, LCMS (M+H$^+$): 712. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.44 - 8.37 (m, 1H), 7.98 (t, *J* = 7.9 Hz, 1H), 7.45 - 7.34 (m, 2H), 7.31 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.15 (br d, *J* = 9.9 Hz, 1H), 7.07 - 7.00 (m, 2H), 6.89 - 6.82 (m, 1H), 5.74 (d, *J* = 9.3 Hz, 1H), 5.58 (br t, *J* = 4.0 Hz, 1H), 5.47 - 5.40 (m, 1H), 4.59 - 4.49 (m, 2H), 4.49 - 4.46 (m, 1H), 4.45 - 4.35 (m, 1H), 4.08 (br dd, *J* = 3.3, 14.3 Hz, 2H), 3.74 (s, 3H), 3.58 - 3.47 (m, 1H), 3.17 - 3.09 (m, 1H), 3.06 - 2.96 (m, 3H), 2.81 (d, *J* = 2.3 Hz, 4H), 2.74 - 2.65 (m, 1H), 2.60 - 2.54 (m, 3H).

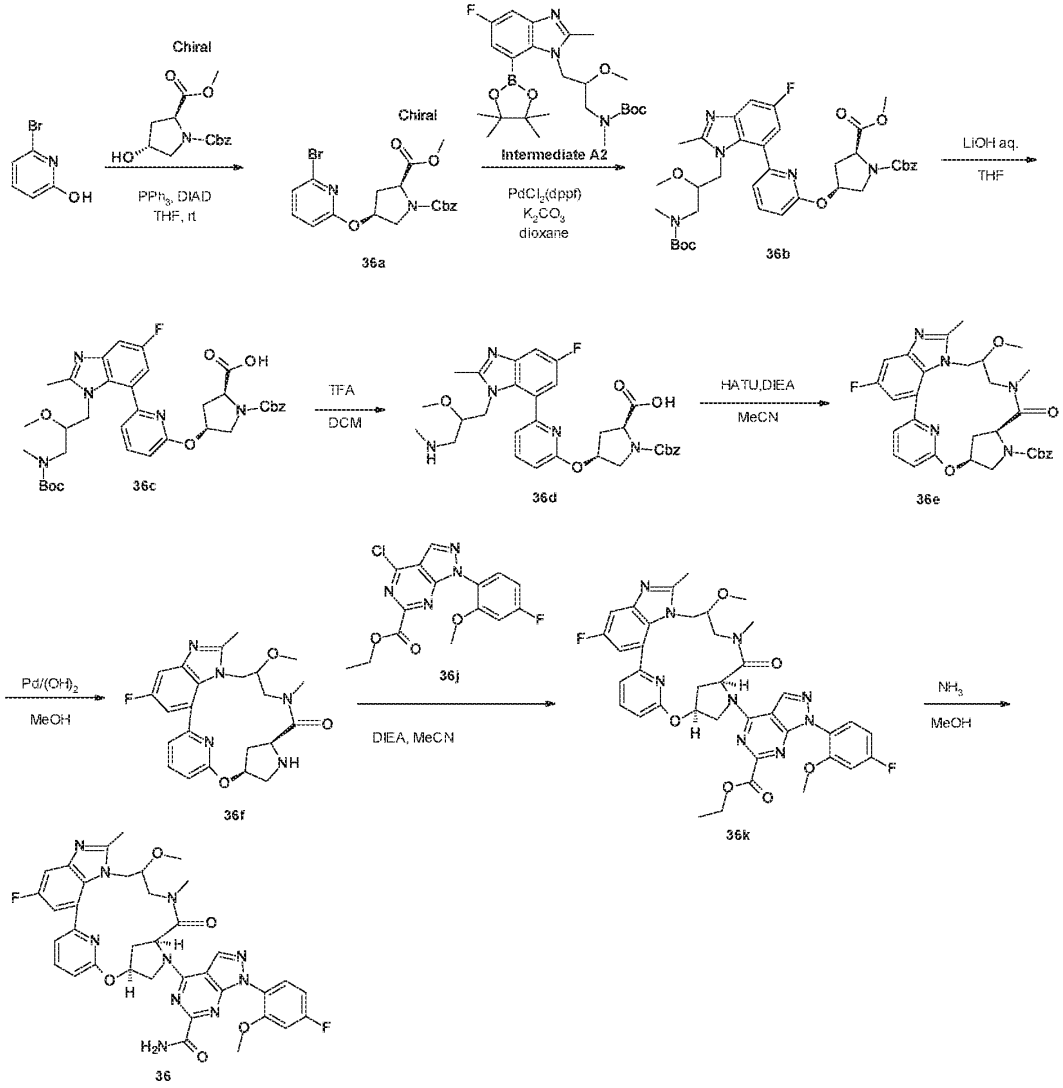
Example 35 (7 mg), slower eluted LCMS (M+H$^+$): 712. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.47 - 8.38 (m, 1H), 8.09 - 7.96 (m, 1H), 7.59 - 7.52 (m, 1H), 7.46 - 7.23 (m, 3H), 7.13 - 7.01 (m, 2H), 6.89 - 6.82 (m, 1H), 5.91 - 5.71 (m, 2H), 5.60 - 5.41 (m, 1H), 4.60 - 4.39 (m, 4H), 4.19 - 4.08 (m, 1H), 4.01 - 3.91 (m, 1H), 3.79 - 3.72 (m, 3H), 3.10 - 3.04 (m, 1H), 3.01 - 2.89 (m, 3H), 2.86 - 2.78 (m, 4H), 2.72 - 2.65 (m, 1H), 2.63 - 2.46 (m, 5H).

Example 36

1-(4-fluoro-2-methoxy-phenyl)-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of (2*S*, 4*S*)-4-[(6-bromo-2-pyridyl)oxy]pyrrolidine-1,2-dicarboxylic acid O1-benzyl ester O2-methyl ester (compound 36a)

To a flask was added 6-bromopyridin-2-ol (6.04 g, 34.7 mmol), (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylic acid O_1-benzyl ester O_2-methyl ester (9.41 g, 33.69 mmol, 1 eq), THF (37.64 mL) and triphenylphosphine (17.67 g, 67.39 mmol), a brown solution formed. To the solution was added DIAD (10.22 g, 9.92 mL, 50.54 mmol) dropwise. The mixture was stirred at room temperature for 3 hours. The mixture was concentrated and the residue was purified by silica gel and prep-HPLC to afford compound **36a** (13.6 g). LCMS ($M+H^+$): 435.

Step 2: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-2-pyridyl]oxy]pyrrolidine-1,2-dicarboxylate (compound 36b)

To a flask was added intermediate **A2** (28.77 g, 18.38 mmol), compound **36a** (8 g, 18.38 mmol), K_2CO_3 (5.08 g, 36.76 mmol), 1,4-dioxane (80 mL) and water (4 mL), the suspension was bubbled with N_2 for 5 mins and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.5 g, 1.84 mmol) was added. After being heated to 90 °C for 2 hours, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel to afford compound **36b** (12.46 g). LCMS ($M+H^+$): 706.

Step 3: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-2-pyridyl]oxy]pyrrolidine-2-carboxylic acid (compound 36c)

To a solution of compound **36b** (6.9 g, 9.78 mmol) in THF (60 mL)/water (60 mL) was added hydroxylithium (468 mg, 19.55 mmol), the mixture was stirred at room temperature for 2 hours. The mixture was concentrated and adjusted pH to about 4 with HCl (1 M), then it was extracted with DCM. The organic layer was dried and concentrated to afford compound **36c** (6.6 g). LCMS ($M+H^+$): 692.

Step 4: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[6-fluoro-3-[2-methoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]oxy]pyrrolidine-2-carboxylic acid;2,2,2-trifluoroacetic acid (compound 36d)

A mixture of compound **36c** (6.6 g, 9.54 mmol) in DCM (10 mL) and TFA (12 mL) was stirred at room temperature for 2 hours. The mixture was concentrated to afford compound **36d** (8.9 g). LCMS ($M+H^+$): 592.

Step 5: preparation of benzyl (8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 36e)

To a solution of HATU (5.75 g, 15.13 mmol) and DIEA (15.0 mL, 85.79 mmol) in acetonitrile (1200 mL) was added another solution of compound **36d** (8.9 g, 9.53 mmol) in acetonitrile (1180 mL) dropwise in 2 hours. The mixture was concentrated and the residue was purified via reversed phase chromatography to afford compound **36e** (2200 mg). LCMS ($M+H^+$): 574.

Step 6: preparation of (8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 36f)

A mixture of compound **36e** (2200 mg, 3.84 mmol) and palladium hydroxide (20% on carbon with 50% H_2O) (440 mg, 3.13 mmol) in methanol (263 mL) was purged with H_2 for 3 times. After being heated to 50 °C for 3 hours, the mixture was filtered, the filtrate was concentrated to afford compound **36f** (1570 mg). LCMS ($M+H^+$): 440.

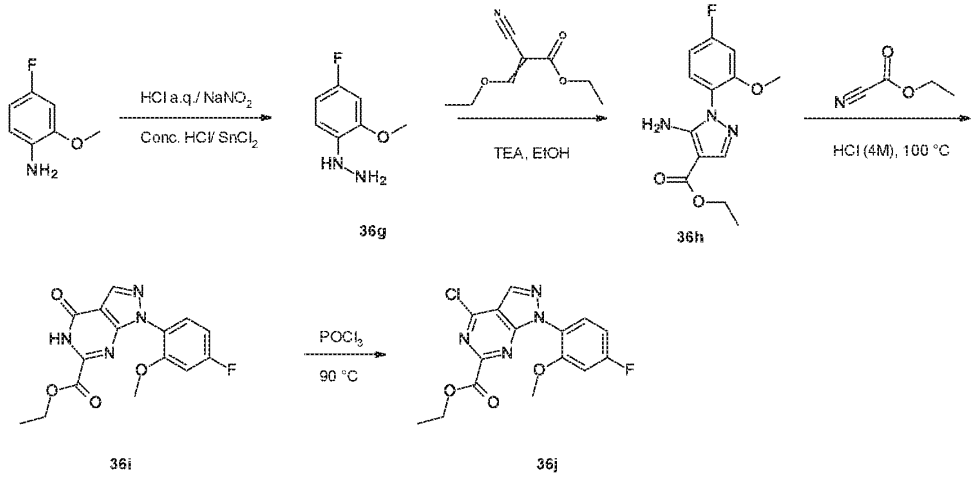
Step 7: preparation of ethyl 1-(4-fluoro-2-methoxy-phenyl)-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylate (compound 36k)

A suspension of compound **36f** (40 mg, 0.091 mmol), compound **36j** (35 mg, 0.100 mmol) and DIEA (32 μL, 0.182 mmol) in acetonitrile (1 mL) was stirred at 70 °C for 0.5 hours. The mixture was concentrated and the residue was purified by reversed-phase chromatography to afford compound **36k** (60 mg). LCMS ($M+H^+$): 754.

Step 8: preparation of 1-(4-fluoro-2-methoxy-phenyl)-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide (Example 36)

A solution of **compound 36k** (20 mg, 0.027 mmol) in 7 M ammonia (7M in MeOH, 1 mL, 7 mmol) was stirred at room temperature for 3 hours. The mixture was concentrated and the residue was purified by reversed-phase chromatography to afford **Example 36** (8 mg), LCMS ($M+H^+$): 725. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.57 - 8.51 (m, 1H), 8.18 - 8.02 (m, 1H), 7.69 - 7.53 (m, 2H), 7.51 - 7.38 (m, 2H), 7.27 - 7.14 (m, 1H), 7.08 - 7.02 (m, 1H), 6.92 - 6.83 (m, 1H), 6.25 - 5.90 (m, 1H), 5.67 - 5.48 (m, 1H), 4.64 - 4.42 (m, 3H), 4.34 - 4.19 (m, 1H), 4.16 - 3.93 (m, 1H), 3.84 - 3.73 (m, 3H), 3.67 - 3.58 (m, 1H), 3.17 - 3.02 (m, 4H), 2.96 - 2.88 (m, 4H), 2.86 - 2.80 (m, 3H), 2.79 - 2.69 (m, 1H).

The preparation of compound **36j** was prepared according to the following scheme:



36g 36h 36i 36j

Step 1: preparation of (4-fluoro-2-methoxy-phenyl)hydrazine (compound 36g)

To a stirring solution of (4-fluoro-2-methoxy-phenyl)amine (3 g, 21.26 mmol) in 5 M HCl (30 mL) was added a solution of sodium nitrite (2.2 g, 31.87 mmol) in water (30 mL) at 0° C. After stirring for 30 mins, a solution of tin (II) chloride (10 g, 53.14 mmol,) in Conc. HCl (12 N, 6 mL) was added dropwise to the mixture. Then the mixture was stirred at room temperature overnight. After being adjusted pH to 10-12 with 20% aqueous sodium hydroxide, the mixture was extracted with CH_2Cl_2. The organic layer was dried and concentrated to afford compound **36g** (3 g). LCMS ($M+H^+$): 157.

Step 2: preparation of 5-amino-1-(4-fluoro-2-methoxy-phenyl)pyrazole-4-carboxylic acid ethyl ester (compound 36h)

A solution of compound **36g** (1.5 g, 9.61 mmol), 2-cyano-3-ethoxy-acrylic acid ethyl ester (1.63 g, 9.61 mmol) and Et_3N (2.68 mL, 19.21 mmol) in ethanol (20 mL) was stirred at 90 °C for 12 hours. The mixture was concentrated, and the residue was purified by silica gel to afford compound **36h** (1.91 g). LCMS ($M+H^+$): 280.

Step 3: preparation of 1-(4-fluoro-2-methoxy-phenyl)-4-keto-5H-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid ethyl ester (compound 36i)

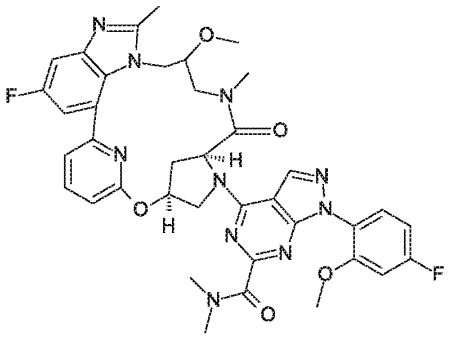
To a solution of compound **36h** (1.91 g, 6.84 mmol) in 4 M HCl in dioxane) (15 mL) at room temperature was added cyanoformic acid ethyl ester (1.36 g, 13.68 mmol). The mixture was stirred at 100 °C for 14 hours and then was cooled to room temperature. The reaction mixture was concentrated and the residue was purified by silica gel to afford compound **36i** (763 mg). LCMS ($M+H^+$): 333.

Step 4: preparation of 4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine-6-carboxylic acid ethyl ester (compound 36j)

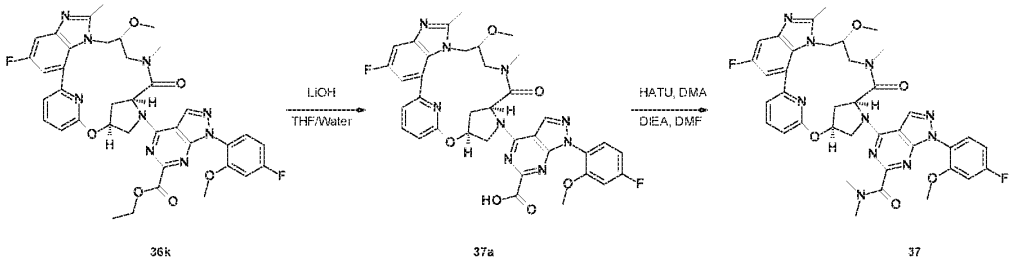
A suspension of compound **36i** (300 mg, 0.858 mmol) in phosphorus oxychloride (6.58 g, 4 mL, 42.91 mmol) was stirred at 90 °C for 2 hours. The reaction mixture was cooled to room temperature and then poured into the saturated $NaHCO_3$ (30 mL) at 0°C. The mixture was adjusted pH to 8 and extracted with EtOAc (50 mL, three times). The organic layer was dried and concentrated, the residue was purified by silica gel to afford compound **36j** (250 mg). LCMS ($M+H^+$): 351.

Example 37

1-(4-fluoro-2-methoxy-phenyl)-*N*,*N*-dimethyl-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carboxamide



The title compounds were prepared according to the following scheme:



Step 1: preparation of 1-(4-fluoro-2-methoxy-phenyl)-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylic acid (compound 37a)

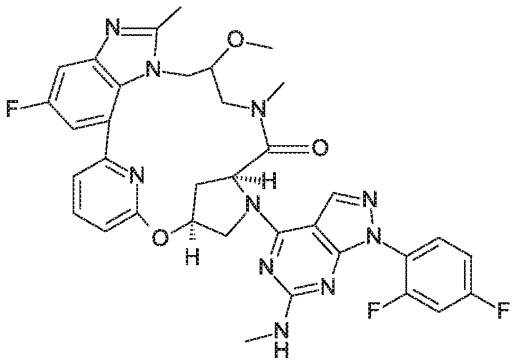
A mixture of compound **36k** (40 mg, 0.054 mmol) and hydroxylithium (5 mg, 0.212 mmol) in THF (4 mL)/water (4 mL) was stirred at room temperature for 0.5 hours. After adjusting the pH to 5, the reaction mixture was extracted with EtOAc (20 mL, three times). The combined organic layer was dried and concentrated to afford compound **37a** (37 mg). LCMS ($M+H^+$): 726.

Step 2: preparation of 1-(4-fluoro-2-methoxy-phenyl)-*N*,*N*-dimethyl-4-[(8*S*,11*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (Example 37)

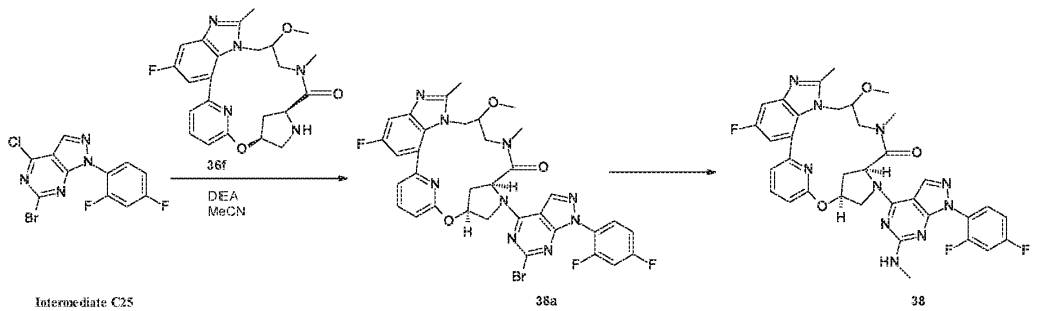
A suspension of compound **37a** (20 mg, 0.028 mmol), HATU (14 mg, 0.036 mmol) and DIEA (10 µL, 0.055 mmol) in DMF (2 mL) was stirred at room temperature for 0.5 hours. 2 M dimethylamine (28 µL, 0.055 mmol) was added and the reaction mixture was stirred at room temperature for another 15 mins. The reaction mixture was directly purified by reversed-phase chromatography to afford Example **37** (7 mg), LCMS (M+H$^+$): 753. ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.52 (s, 1H), 8.16 - 8.04 (m, 1H), 7.68 - 7.52 (m, 2H), 7.50 - 7.36 (m, 2H), 7.24 - 7.13 (m, 1H), 7.08 - 6.99 (m, 1H), 6.90 - 6.83 (m, 1H), 6.21 (br dd, *J* = 4.1, 15.6 Hz, 1H), 5.70 - 5.47 (m, 2H), 4.63 - 4.53 (m, 1H), 4.41 - 4.19 (m, 2H), 4.14 - 3.92 (m, 1H), 3.77 - 3.71 (m, 3H), 3.67 - 3.56 (m, 1H), 3.18 - 2.80 (m, 18H).

Example 38

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(methylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Intermediate C25 38a 38

Step 1: preparation of (8*S*,11*S*)-10-[6-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 38a)

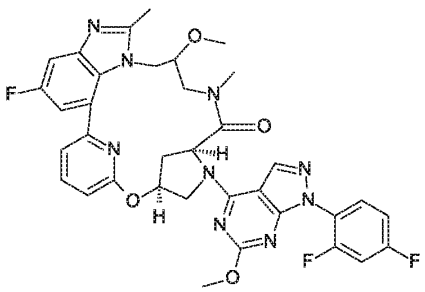
A suspension of intermediate **C25** (100 mg, 0.256 mmol), compound **36f** (113 mg, 0.256 mmol) and DIEA (90 µL, 0.513 mmol) in ethanol (5 mL) was stirred at room temperature for 12 hours. The solvent was removed under reduce pressure and then the residue was purified by reversed-phase chromatography to afford compound **38a** (157 mg). LCMS (M+H$^+$): 748.

Step 2: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(methylamino)-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 38)

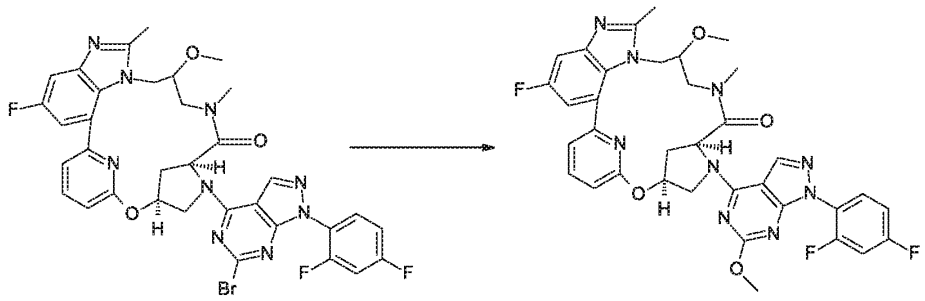
A suspension of compound **38a** (20 mg, 0.027 mmol), 2 M methylamine (2 mL, 4 mmol) and K_2CO_3 (7 mg, 0.053 mmol) was microwaved at 120 °C for 3 hours. The suspension was filtered and the filtrate was concentrated. The residue was purified by reversed-phase chromatography to afford **Example 38** (12 mg), LCMS (M+H$^+$): 699. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.37 - 8.31 (m, 1H), 8.17 - 8.04 (m, 1H), 7.70 - 7.59 (m, 2H), 7.59 - 7.45 (m, 2H), 7.32 - 7.25 (m, 1H), 7.24 - 7.12 (m, 2H), 6.24 - 6.01 (m, 1H), 5.64 - 5.59 (m, 1H), 5.51 - 5.46 (m, 1H), 4.59 - 4.48 (m, 2H), 4.42 - 4.36 (m, 1H), 4.31 - 4.23 (m, 1H), 4.09 (br dd, *J* = 4.6, 14.5 Hz, 1H), 3.98 - 3.90 (m, 1H), 3.67 - 3.59 (m, 1H), 3.13 - 3.08 (m, 1H), 3.05 - 2.98 (m, 3H), 2.94 - 2.80 (m, 8H), 2.79 - 2.71 (m, 1H).

Example 40

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

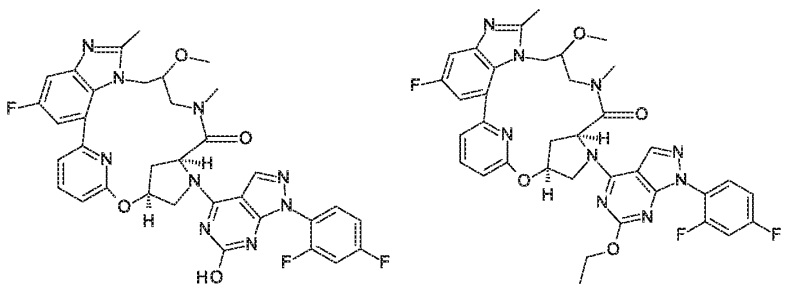


38a 40

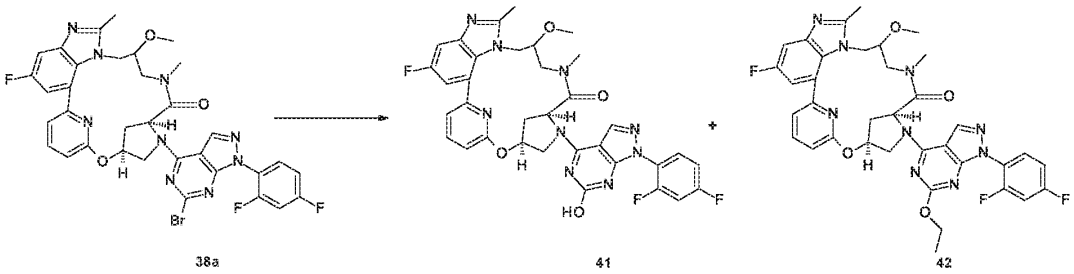
A suspension of **compound 38a** (20 mg, 0.027 mmol), 5 M Sodium methoxide (11 µL, 0.053 mmol) in methanol (64 µL) was stirred at room temperature for 0.5 hours. After being stirred at 40 °C for 2 hours, the reaction mixture was concentrated and the residue was purified by reversed-phase chromatography to afford **Example 40** (10 mg), LCMS ($M+H^+$): 700. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.45 - 8.40 (m, 1H), 8.16 - 8.04 (m, 1H), 7.73 - 7.46 (m, 4H), 7.30 - 7.14 (m, 3H), 6.25 - 6.08 (m, 1H), 5.65 - 5.55 (m, 2H), 4.58 - 4.55 (m, 1H), 4.50 (br d, J = 11.4 Hz, 1H), 4.40 - 4.29 (m, 2H), 4.12 - 4.06 (m, 1H), 3.97 (s, 1H), 3.87 - 3.85 (m, 2H), 3.15 - 3.12 (m, 1H), 3.04 (s, 2H), 2.95 - 2.89 (m, 4H), 2.85 - 2.81 (m, 4H), 2.79 - 2.73 (m, 1H).

Example 41 and Example 42

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-hydroxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



38a 41 42

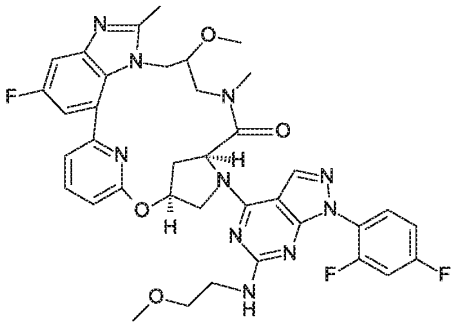
A suspension of compound **38a** (20 mg, 0.027 mmol) in 2 M sodium hydroxide (2 mL, 4 mmol)/ethanol (2 mL) was stirred at room temperature for 0.5 hours. After being stirred at 70 °C for 12 hours, the reaction mixture was concentrated. The residue was purified by reversed-phase chromatography to afford **example 41** (3 mg) and **example 42** (12 mg).

Example 41, LCMS ($M+H^+$): 686. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.39 - 8.33 (m, 1H), 8.16 - 8.02 (m, 1H), 7.72 (br d, J = 2.6 Hz, 2H), 7.56 - 7.41 (m, 2H), 7.34 - 7.11 (m, 3H), 5.62 - 5.47 (m, 2H), 4.58 (br dd, J = 5.0, 12.2 Hz, 2H), 4.53 - 4.50 (m, 1H), 4.38 - 4.32 (m, 1H), 4.11 (br d, J = 14.2 Hz, 1H), 3.67 - 3.61 (m, 2H), 3.18 - 3.06 (m, 2H), 3.02 - 2.96 (m, 3H), 2.93 - 2.87 (m, 4H), 2.84 - 2.77 (m, 3H).

Example 42, LCMS ($M+H^+$): 714. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 8.16 - 8.03 (m, 1H), 7.70 - 7.43 (m, 4H), 7.29 - 7.12 (m, 3H), 6.25 - 5.87 (m, 1H), 5.66 - 5.43 (m, 2H), 4.59 - 4.39 (m, 2H), 4.39 - 4.20 (m, 3H), 4.14 - 3.90 (m, 1H), 3.71 - 3.53 (m, 1H), 3.34 (s, 1H), 3.18 - 3.06 (m, 2H), 3.05 - 3.00 (m, 2H), 2.95 - 2.88 (m, 3H), 2.85 - 2.70 (m, 4H), 1.38 (t, J = 7.1 Hz, 1H), 1.34 - 1.29 (m, 2H).

Example 43

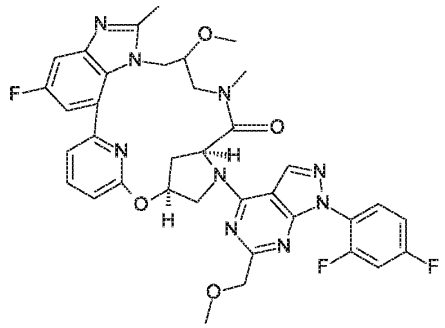
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethylamino)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **38** by using 2-methoxyethylamine instead of methylamine. LCMS ($M+H^+$): 743. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.23 - 8.17 (m, 1H), 8.05 - 7.94 (m, 1H), 7.58 - 7.36 (m, 4H), 7.20 - 7.03 (m, 3H), 5.56 - 5.47 (m, 1H), 5.40 - 5.33 (m, 1H), 4.47 - 4.36 (m, 2H), 4.29 - 4.24 (m, 1H), 4.21 - 4.13 (m, 1H), 4.03 - 3.95 (m, 1H), 3.57 - 3.47 (m, 3H), 3.42 - 3.31 (m, 5H), 3.07 - 3.02 (m, 2H), 2.96 - 2.92 (m, 2H), 2.81 (s, 3H), 2.75 - 2.67 (m, 4H).

Example 44

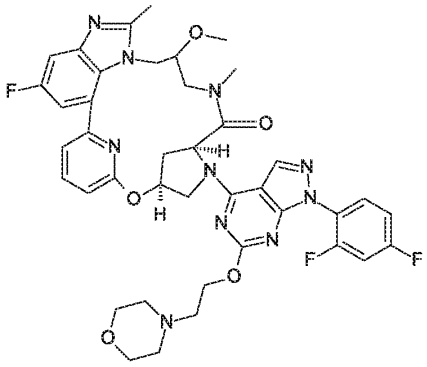
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **36** by using 2-methoxyacetonitrile (step 9) instead of cyanoformic acid ethyl ester. LCMS ($M+H^+$): 714. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.45 - 8.37 (m, 1H), 8.09 - 7.93 (m, 1H), 7.60 - 7.33 (m, 4H), 7.27 - 7.02 (m, 3H), 6.17 - 5.84 (m, 1H), 5.66 - 5.37 (m, 2H), 4.52 - 4.26 (m, 4H), 4.25 - 4.12 (m, 1H), 4.02 - 3.75 (m, 2H), 3.59 - 3.44 (m, 1H), 3.42 - 3.36 (m, 1H), 3.34 - 3.28 (m, 2H), 3.07 - 2.89 (m, 4H), 2.85 - 2.78 (m, 3H), 2.76 - 2.71 (m, 3H), 2.66 - 2.46 (m, 1H).

Example 45

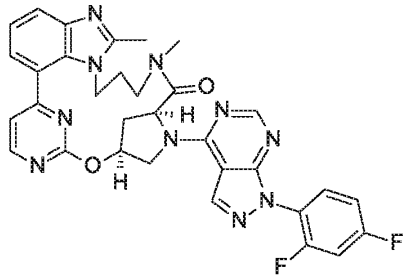
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(2-morpholinoethoxy)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **40** by using 2-morpholinoethanol and sodium hydride instead of sodium methoxide. LCMS ($M+H^+$): 799. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.38 - 8.32 (m, 1H), 8.10 - 7.91 (m, 1H), 7.60 - 7.33 (m, 4H), 7.21 - 7.03 (m, 3H), 6.15 - 5.63 (m, 1H), 5.56 - 5.36 (m, 2H), 4.69 - 4.67 (m, 1H), 4.55 - 4.50 (m, 2H), 4.48 - 4.41 (m, 2H), 4.33 - 4.23 (m, 2H), 4.18 - 4.13 (m, 1H), 4.03 - 3.94 (m, 2H), 3.89 - 3.81 (m, 2H), 3.75 - 3.69 (m, 1H), 3.56 - 3.53 (m, 1H), 3.47 (br s, 1H), 3.07 - 2.98 (m, 3H), 2.97 - 2.89 (m, 3H), 2.86 - 2.78 (m, 4H), 2.76 - 2.69 (m, 4H).

Example 53

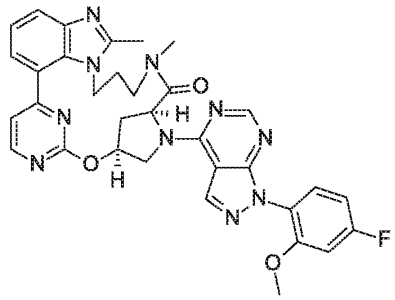
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of example **289** by using **Intermediate B16** instead of **Intermediate B1** and **Intermediate C2** instead of **Intermediate C11**. LCMS ($M+H^+$): 623. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.85 - 8.75 (m, 1H), 8.66 - 8.33 (m, 1H), 8.28 - 7.86 (m, 1H), 7.79 - 7.67 (m, 2H), 7.65 - 7.54 (m, 2H), 7.47 - 7.38 (m, 1H), 7.36 - 7.18 (m, 2H), 5.85 - 5.65 (m, 1H), 5.58 - 5.40 (m, 1H), 5.23 - 5.04 (m, 1H), 4.55 - 4.12 (m, 2H), 4.04 - 3.88 (m, 2H), 2.99 - 2.93 (m, 1H), 2.87 (s, 2H), 2.84 - 2.74 (m, 1H), 2.73 - 2.59 (m, 2H), 2.57 (s, 3H), 1.83 - 1.59 (m, 1H), 1.20 - 1.09 (m, 1H).

Example 54

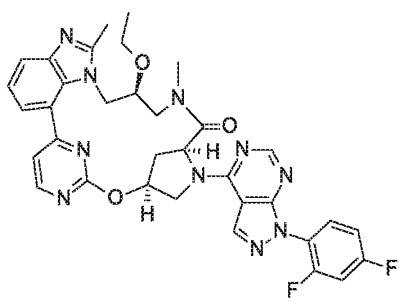
(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

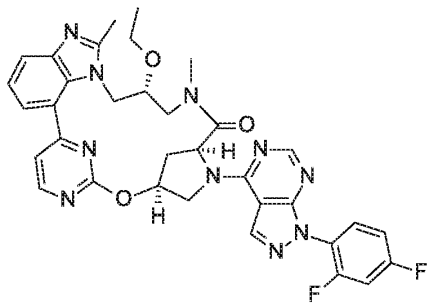


The title compound was prepared in analogy to the preparation of example **289** by using **Intermediate B16** instead of **Intermediate B1**. LCMS (M+H$^+$): 635. ^{1}H NMR (500 MHz, DMSO-d6) δ = 8.87 - 8.73 (m, 1H), 8.57 - 7.76 (m, 2H), 7.73 - 7.66 (m, 1H), 7.60 - 7.52 (m, 1H), 7.49 - 7.37 (m, 2H), 7.31 - 7.24 (m, 1H), 7.23 - 7.15 (m, 1H), 6.98 - 6.88 (m, 1H), 5.86 - 5.42 (m, 2H), 5.25 - 5.03 (m, 1H), 4.56 - 4.10 (m, 2H), 4.05 - 3.87 (m, 2H), 3.74 (s, 3H), 2.99 - 2.84 (m, 3H), 2.83 - 2.74 (m, 1H), 2.72 - 2.65 (m, 1H), 2.59 (br d, *J* = 15.3 Hz, 1H), 2.57 (s, 3H), 1.75 (br dd, *J* = 4.0, 8.2 Hz, 1H), 1.15 (br dd, *J* = 8.2, 12.8 Hz, 1H).

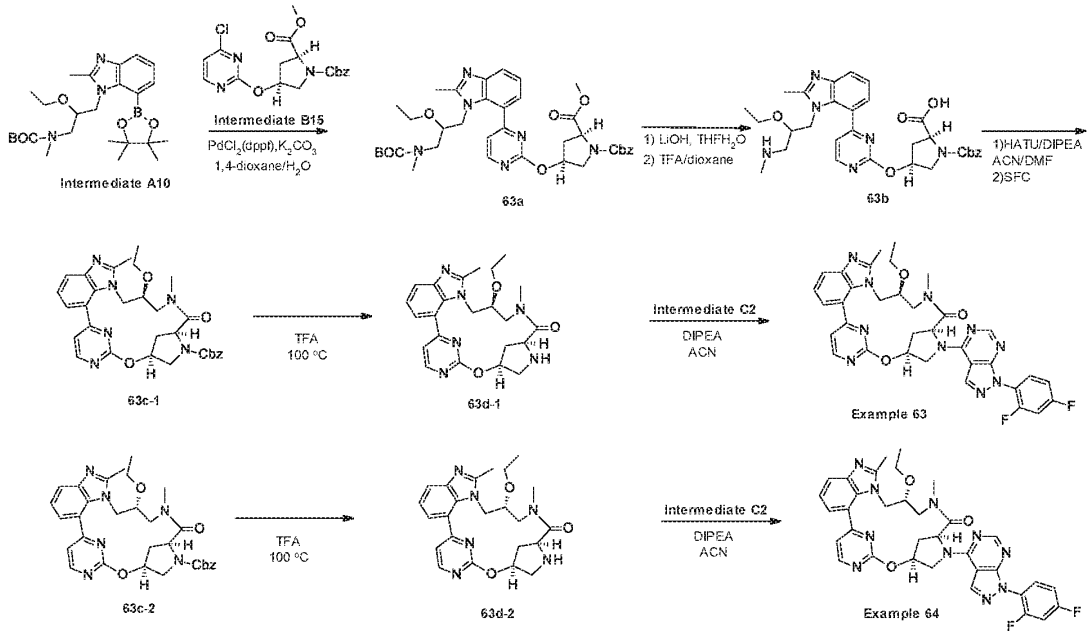
Example 63 and Example 64

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared according to the following scheme:



Step 1: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[4-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]-2-ethoxy-propyl]-2-methyl-benzimidazol-4-yl]pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 63a)

A mixture of K_2CO_3 (2.96 g, 21.44 mmol), **intermediate A10** (3.38 g, 7.15 mmol), intermediate **B15** (3.50 g, 7.15 mmol) and $PdCl_2$(dppf) DCM(261.45 mg, 0.357 mmol) in 1,4-dioxane (30 mL) and water (3 mL) was heated to 100°C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **63a** (4.0 g). LCMS ($M+H^+$): 703.

Step 2: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[4-[3-[2-ethoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]pyrimidin-2-yl]oxy-pyrrolidine-2-carboxylic acid (compound 63b)

A mixture of compound **63a** (3.60 g, 5.12 mmol) and $LiOH.H_2O$ (2.15 g, 51.22 mmol) in tetrahydrofuran (15 mL) and water (3 mL) was stirred at 25 °C for 12 hours. The reaction mixture was adjusted PH = 5 with HCl (1 M) and extracted with MeOH/DCM. The organic layer was dried and concentrated, the residue was dissolved in 1,4-dioxane (5 mL) and TFA (5 mL). After stirred at 25 °C for 4 hours, the mixture was concentrated to give crude compound **63b** (3.2 g). LCMS ($M+H^+$): 589.

Step 3: preparation of benzyl (8*S*,11*S*,15*R*)-15-ethoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate and benzyl (8S,11S,15S)-15-ethoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 63c-1&63c-2)

To a solution of HATU (4.13 g, 10.87 mmol) and DIPEA (3.51 g, 27.18 mmol) in acetonitrile (800 mL) was added a solution of compound **63b** (3.2 g, 5.44 mmol) in acetonitrile (2400 mL) dropwise at rt. The mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, the residue was diluted with EtOAc, washed with water and brine. The organic layer was dried and concentrated, the residue was purified by SFC (Instrument: SFC 80, Column: IA, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 50%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C) to give faster eluted compound **63c-1** (500 mg) and slower eluted compound **63c-2**(400 mg), LCMS ($M+H^+$): 571.

Step 4: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one(compound 63d-1&63d-2)

A mixture of compound **63c-1** (500 mg, 0.876 mmol) in TFA (2.0 mL) was stirred for 100 °C for 10 mins under microwave. The reaction mixture was concentrated to give compound **63d-1** (380 mg). LCMS ($M+H^+$): 437.

A mixture of compound **63c-2** (400 mg, 0.701 mmol) in TFA (2.0 mL) was stirred for 100 °C for 10 mins under microwave. The reaction mixture was concentrated to give compound **63d-2** (300 mg). LCMS ($M+H^+$): 437.

Step 5: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one(example 63&64)

A mixture of compound **63d-1** (50 mg, 0.115 mmol), DIPEA (44 mg, 0.344 mmol) and **intermediate C2** (30 mg, 0.115 mmol, as the "**HALIDE 1**" in table 5) in DMSO (1 mL) was stirred for 1 hour at 80 °C. The reaction mixture was purified by prep-HPLC to give **Example 63**

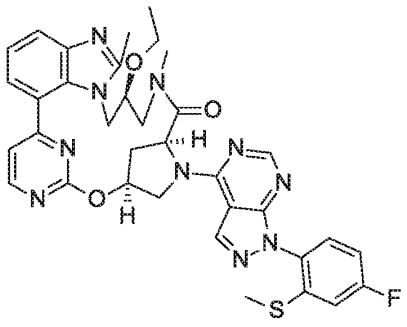
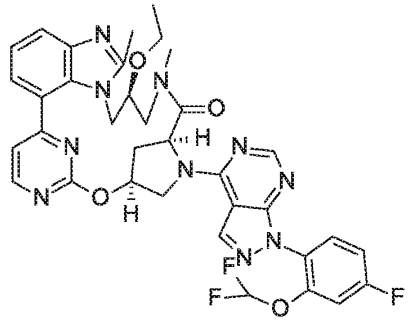
(9.3 mg). LCMS ($M+H^+$): 667. ^{1}H NMR (500 MHz, DMSO-d6) δ = 8.87 - 8.76 (m, 1H), 8.68 - 8.35 (m, 1H), 8.29 - 7.87 (m, 1H), 7.80 - 7.68 (m, 3H), 7.65 - 7.53 (m, 2H), 7.39 - 7.26 (m, 2H), 5.76 - 5.47 (m, 3H), 4.51 - 4.38 (m, 1H), 4.37 - 4.15 (m, 1H), 4.11 - 3.99 (m, 1H), 3.94 - 3.80 (m, 1H), 3.20 - 3.10 (m, 1H), 3.00 - 2.86 (m, 3H), 2.84 - 2.75 (m, 1H), 2.75 - 2.66 (m, 2H), 2.55 - 2.53 (m, 3H), 2.48 - 2.39 (m, 2H), 0.45 - 0.35 (m, 3H).

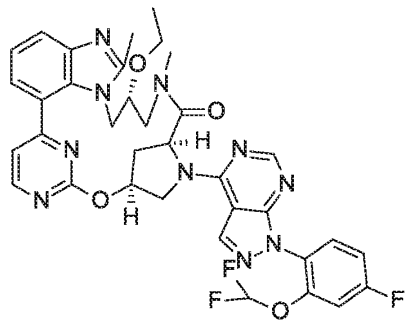
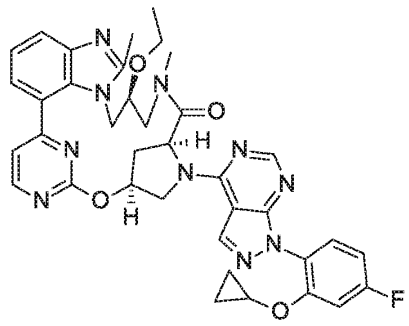
A mixture of compound **63d-2** (50 mg, 0.115 mmol), DIPEA (44 mg, 0.344 mmol) and **intermediate C2** (30 mg, 0.115 mmol, as the "**HALIDE 2**" in table 5) in DMSO (1 mL) was stirred for 1 hour at 80 °C. The reaction mixture was purified by prep-HPLC to give **Example 64** (7.0 mg). LCMS ($M+H^+$): 667. ^{1}H NMR (500 MHz, DMSO-d6) δ = 8.81 - 8.70 (m, 1H), 8.68 - 8.34 (m, 1H), 8.28 - 7.84 (m, 1H), 7.79 - 7.71 (m, 1H), 7.70 - 7.66 (m, 1H), 7.64 - 7.56 (m, 1H), 7.54 - 7.42 (m, 2H), 7.37 - 7.30 (m, 1H), 7.29 - 7.20 (m, 1H), 5.82 - 5.47 (m, 3H), 4.51 - 4.36 (m, 1H), 4.25 - 4.14 (m, 1H), 4.07 - 3.85 (m, 2H), 3.51 - 3.39 (m, 1H), 3.29 (br s, 1H), 3.18 - 3.09 (m, 1H), 3.03 - 2.89 (m, 3H), 2.85 (br s, 1H), 2.78 - 2.66 (m, 1H), 2.64 - 2.56 (m, 1H), 2.54 (d, *J* = 2.9 Hz, 3H), 0.47 - 0.40 (m, 3H).

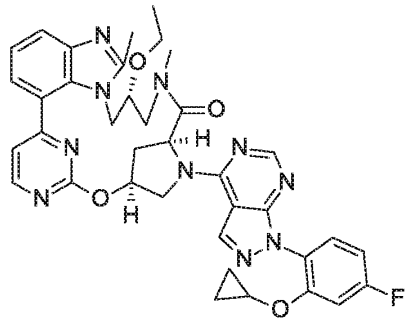
The following examples in Table 5 were prepared in analogy to **Example 63** & **64** by replacing **Intermediate C2** with the "**HALIDE**" in step 5 by the reagents indicated in Table 5.

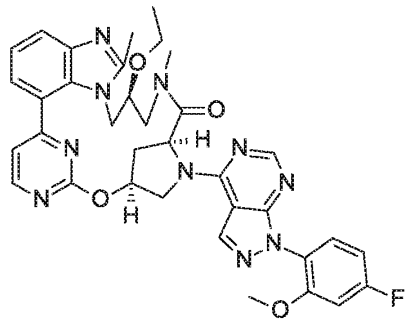
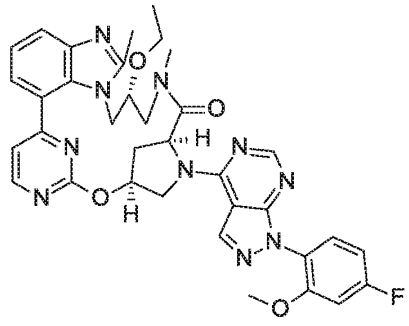
Table 5. Compound synthesis and characterization

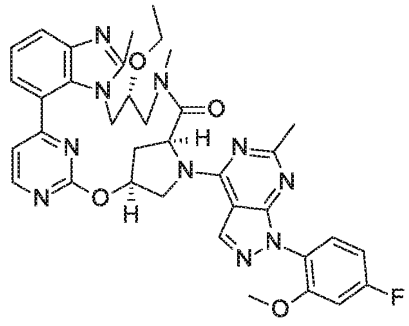
No.	Compound Name and Structure	HALIDE 1 and HALIDE 2	^{1}H NMR and MS (ESI)
55	**(8*S*,11*S*,15*R*)-15-ethoxy-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**HALIDE 1:** Compound **291e**	LCMS ($M+H^+$): 695. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.91 - 8.80 (m, 1H), 8.63 - 7.84 (m, 2H), 7.84 - 7.64 (m, 3H), 7.52 - 7.39 (m, 2H), 7.39 - 7.31 (m, 1H), 7.22 - 7.13 (m, 1H), 5.79 - 5.45 (m, 3H), 4.51 - 4.32 (m, 1H), 4.24 - 4.04 (m, 2H), 3.96 - 3.80 (m, 1H), 3.23 - 3.11 (m, 2H), 3.01 - 2.89 (m, 3H), 2.86 - 2.67 (m, 3H), 2.63 (br s,

			3H), 2.59 - 2.54 (m, 1H), 2.43 - 2.39 (m, 3H), 0.45 - 0.38 (m, 3H)
56	**(8*S*,11*S*,15*R*)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**HALIDE1:** Intermediate **C19**	LCMS (M+H$^+$): 715 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.80 - 8.69 (m, 1H), 8.58 - 7.84 (m, 2H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.69 - 7.55 (m, 3H), 7.42 - 7.34 (m, 1H), 7.31 - 7.19 (m, 2H), 7.06 - 6.68 (m, 1H), 5.90 - 5.68 (m, 2H), 5.64 - 5.43 (m, 1H), 4.59 - 4.30 (m, 2H), 4.24 - 4.13 (m, 1H), 4.08 - 3.97 (m, 1H), 3.30 - 3.12 (m, 2H), 3.10 - 2.98 (m, 3H), 2.97 - 2.89 (m, 1H), 2.88 - 2.79 (m, 1H), 2.78 - 2.69 (m, 1H), 2.66 - 2.62 (m, 3H), 2.56 (dd, *J* = 7.0, 9.3 Hz, 1H), 0.61 - 0.52 (m, 3H)
57	**(8*S*,11*S*,15*S*)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-**	**HALIDE 1:** Intermediate **C19**	LCMS (M+H$^+$): 715 ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.79 - 8.70 (m, 1H), 8.64 - 7.79 (m, 2H), 7.74 - 7.63 (m,

	hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 		2H), 7.58 - 7.47 (m, 2H), 7.46 - 7.40 (m, 1H), 7.38 - 7.32 (m, 1H), 7.31 - 7.08 (m, 2H), 5.84 - 5.46 (m, 3H), 4.54 - 4.18 (m, 2H), 4.14 - 3.88 (m, 2H), 3.53 - 3.42 (m, 1H), 3.20 - 3.05 (m, 2H), 3.04 - 2.92 (m, 3H), 2.91 - 2.78 (m, 1H), 2.77 - 2.60 (m, 2H), 2.59 - 2.55 (m, 3H), 0.45 (dt, *J* = 4.1, 6.9 Hz, 3H)
58	**(8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**HALIDE 1**: Intermediate **C17**	LCMS (M+H$^+$): 705 ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.89 - 8.73 (m, 1H), 8.50 - 7.92 (m, 2H), 7.91 - 7.84 (m, 1H), 7.83 - 7.76 (m, 1H), 7.69 (d, *J* = 5.2 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.47 - 7.37 (m, 1H), 7.37 - 7.30 (m, 1H), 6.94 - 6.85 (m, 1H), 6.05 - 5.90 (m, 1H), 5.89 - 5.70 (m, 1H), 5.61 - 5.44 (m, 1H), 4.56 - 4.31 (m, 2H), 4.31 - 4.20 (m, 1H), 4.08 - 3.97 (m, 1H), 3.86 (qd, *J* = 3.0, 5.9 Hz, 1H), 3.39 - 3.33 (m, 1H), 3.10 - 2.99 (m, 3H), 2.97 - 2.83 (m, 2H), 2.80 - 2.75

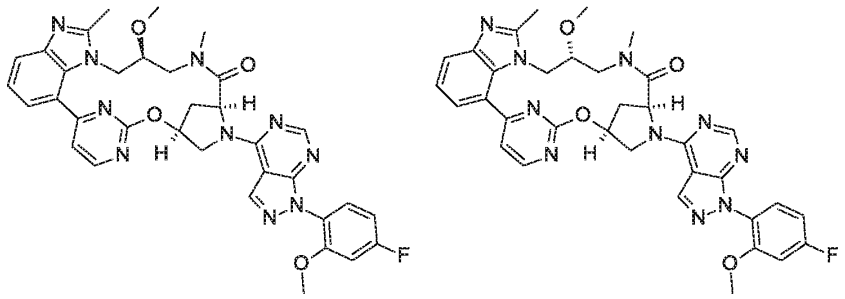
			(m, 3H), 2.75 - 2.68 (m, 2H), 2.68 - 2.61 (m, 1H), 0.79 - 0.70 (m, 2H), 0.63 - 0.59 (m, 3H), 0.59 - 0.55 (m, 2H)
59	**(8*S*,11*S*,15*S*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**HALIDE 1**: Intermediate **C17**	LCMS (M+H$^+$): 705 ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.79 - 8.68 (m, 1H), 8.56 - 7.74 (m, 2H), 7.73 - 7.67 (m, 1H), 7.58 - 7.49 (m, 2H), 7.46 - 7.38 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.03 - 6.91 (m, 1H), 5.83 - 5.45 (m, 3H), 4.51 - 4.02 (m, 3H), 4.00 - 3.89 (m, 2H), 3.53 - 3.43 (m, 1H), 3.20 - 3.07 (m, 2H), 3.03 - 2.92 (m, 3H), 2.91 - 2.78 (m, 1H), 2.76 - 2.61 (m, 2H), 2.58 (s, 3H), 0.81 - 0.67 (m, 2H), 0.61 - 0.49 (m, 2H), 0.48 - 0.41 (m, 3H)
60	**(8*S*,11*S*,15*R*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**HALIDE 1**: Intermediate **C11**	LCMS (M+H$^+$): 679 ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.86 - 8.78 (m, 1H), 8.57 - 7.78 (m, 2H), 7.78 - 7.70 (m, 2H), 7.62 - 7.54 (m, 1H), 7.48 - 7.39 (m, 1H), 7.34 - 7.26 (m, 1H), 7.24 - 7.15 (m, 1H), 7.01 - 6.90

			(m, 1H), 5.80 - 5.45 (m, 3H), 4.50 - 4.15 (m, 2H), 4.11 - 3.98 (m, 1H), 3.93 - 3.79 (m, 1H), 3.78 - 3.72 (m, 3H), 3.19 - 3.08 (m, 1H), 3.00 - 2.87 (m, 3H), 2.84 - 2.71 (m, 2H), 2.71 - 2.63 (m, 1H), 2.54 (s, 3H), 2.53 - 2.51 (m, 1H), 2.47 - 2.42 (m, 1H), 0.45 - 0.36 (m, 3H)
61	**(8*S*,11*S*,15*S*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{2,0,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**HALIDE 1**: Intermediate **C11**	LCMS (M+H$^+$): 679 ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.82 - 8.67 (m, 1H), 8.58 - 7.73 (m, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.59 - 7.36 (m, 3H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.22 - 7.15 (m, 1H), 7.00 - 6.90 (m, 1H), 5.81 - 5.44 (m, 3H), 4.51 - 4.17 (m, 2H), 4.11 - 3.99 (m, 1H), 3.98 - 3.88 (m, 1H), 3.79 - 3.70 (m, 3H), 3.49 - 3.39 (m, 1H), 3.23 - 3.03 (m, 2H), 3.03 - 2.89 (m, 3H), 2.88 - 2.78 (m, 1H), 2.77 - 2.59 (m, 2H), 2.55 (s, 3H), 0.49 - 0.38 (m, 3H)
62	**(8*S*,11*S*,15*S*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-**	**HALIDE 2**: Intermediate **C12**	LCMS (M+H$^+$): 693 ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.77 -

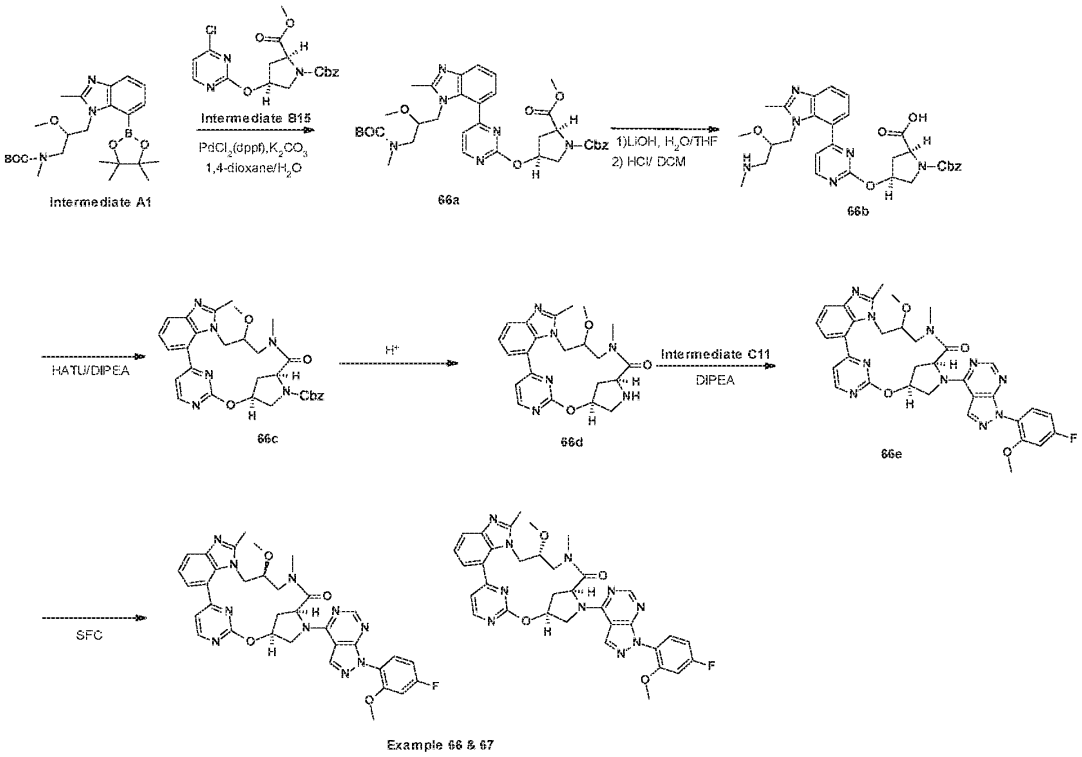
	4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 		8.65 (m, 1H), 8.47 - 7.62 (m, 2H), 7.57 - 7.45 (m, 2H), 7.45 - 7.33 (m, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 2.5, 10.9 Hz, 1H), 6.99 - 6.90 (m, 1H), 5.83 - 5.39 (m, 3H), 4.48 - 4.26 (m, 1H), 4.21 - 4.13 (m, 1H), 4.10 - 3.98 (m, 1H), 3.98 - 3.91 (m, 1H), 3.79 - 3.71 (m, 3H), 3.51 - 3.40 (m, 1H), 3.20 - 3.04 (m, 2H), 3.04 - 2.92 (m, 3H), 2.90 - 2.78 (m, 1H), 2.73 - 2.59 (m, 2H), 2.56 (d, *J* = 3.4 Hz, 3H), 2.43 - 2.30 (m, 3H), 0.45 (dt, *J* = 2.4, 6.8 Hz, 3H)

Example 66 and Example 67

(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[4-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-2-methyl-benzimidazol-4-yl]pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 66a)

A mixture of K_2CO_3 (619.07 mg, 4.48 mmol), **Intermediate A1** (754.49 mg, 1.64 mmol) intermediate **B15** (900 mg, 1.49 mmol) and Pd(dppf)Cl_2 DCM(54.62 mg, 0.075 mmol) in dioxane (20 mL) and water (2 mL) was heated to 100°C for 12 h under N_2 atmosphere. The reaction mixture was diluted with water and extracted two times with EtOAc. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **66a** (680 mg), LCMS ($M+H^+$): 689.

Step 2: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[4-[3-[2-methoxy-3-

(methylamino)propyl]-2-methyl-benzimidazol-4-yl]pyrimidin-2-yl]oxy-pyrrolidine-2-carboxylic acid (compound 66b)

A mixture of compound **66a** (680 mg, 0.987 mmol) and lithium hydroxide monohydrate (207.13 mg, 4.94 mmol) in tetrahydrofuran (8 mL) and water (2 mL) was stirred at 25 °C for 12 hours. The reaction mixture was adjusted pH = 5 with HCl (1M), then extracted with MeOH/DCM. The organic layer was dried and concentrated, the residue was dissolved in dichloromethane (6 mL) and 4 M HCl in dioxane (2 mL). After being stirred at 25 °C for 3 hours, the reaction mixture was concentrated to give crude compound **66b** (740 mg), LCMS ($M+H^+$): 575.

Step 3: preparation of benzyl (8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 66c)

To a mixture of HATU (992.54 mg, 2.61 mmol) and DIEA (843.41 mg, 6.53 mmol) in DMF (10 mL) and acetonitrile (60 mL) was added a solution of compound **66b** (750 mg, 1.31 mmol) in DMF (30 mL) and acetonitrile (600 mL) dropwise at rt. After being stirred at room temperature for 1 hour, the reaction mixture was concentrated, the residue was diluted with EtOAc. The organic layer was washed with water and brine, then it was dried and concentrated, further purified by silica gel to give compound **66c** (560 mg), LCMS ($M+H^+$): 557.

Step 4: preparation of *tert*-butyl (8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 66d)

To a flask containing compound **66c** (560 mg, 1.01 mmol) was added methanol (50 mL) and palladium hydroxide (20% on carbon with 50% H_2O) (114.02 mg, 0.812 mmol). The suspension was purged with H_2 for 3 times. After heated to 60 °C for 1.5 hrs, the mixture was filtered and the filtrate was concentrated to give compound **66d**, used in the next step directly. LCMS ($M+H^+$): 423.

Step 5: preparation of (8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 66e)

Compound **66d** (151.61 mg, 0.36 mmol) and DIEA (183.54 mg, 1.42 mmol) were dissolved in dimethyl sulfoxide (4 mL) and **Intermediate C11** (100 mg, 0.36 mmol) was added. The mixture was stirred for 1 hours at 80 °C. The reaction mixture was concentrated, the residue

was purified by prep-HPLC to give compound **66e** (200 mg), LCMS ($M+H^+$): 665.

Step 6: preparation of (8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one(Example 66&67)

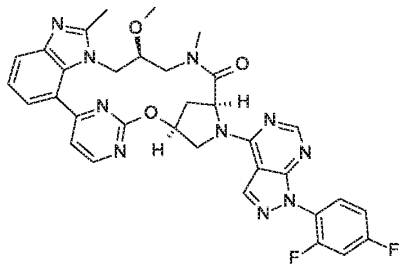
Compound **66e** was separated by SFC (Instrument: SFC 80, Column: Pyridine, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 35%, Flow rate: 60 mL /min, Back pressure: 100 bar, Column temperature: 35°C) to give Example **66** (slower eluted) and Example **67** (faster eluted).

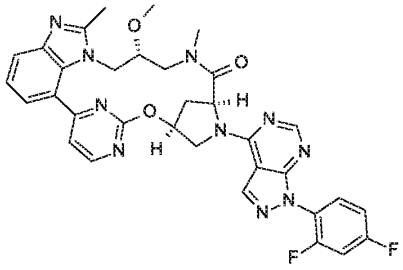
Example 66 (44 mg, slower eluted), LCMS ($M+H^+$): 665. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.84 - 8.77 (m, 1H), 8.68 - 7.88 (m, 2H), 7.80 - 7.67 (m, 3H), 7.65 - 7.51 (m, 2H), 7.40 - 7.24 (m, 2H), 5.76 - 5.32 (m, 3H), 4.53 - 4.16 (m, 2H), 4.11 - 3.99 (m, 1H), 3.94 - 3.77 (m, 1H), 3.33 - 3.33 (m, 3H), 3.01 - 2.89 (m, 3H), 2.89 - 2.81 (m, 1H), 2.79 - 2.74 (m, 1H), 2.69 - 2.66 (m, 3H), 2.51 (s, 3H), 2.45 - 2.37 (m, 1H), 2.04 - 1.94 (m, 1H).

Example 67 (47 mg, faster eluted), LCMS ($M+H^+$): 665. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.82 - 8.66 (m, 1H), 8.59 - 7.73 (m, 2H), 7.71 - 7.64 (m, 1H), 7.56 - 7.36 (m, 3H), 7.33 - 7.11 (m, 2H), 7.03 - 6.88 (m, 1H), 5.86 - 5.38 (m, 3H), 4.54 - 4.19 (m, 2H), 4.14 - 4.01 (m, 1H), 3.99 - 3.88 (m, 1H), 3.74 (d, J = 2.4 Hz, 3H), 3.55 - 3.46 (m, 1H), 3.20 - 3.09 (m, 1H), 3.04 - 2.91 (m, 3H), 2.89 - 2.79 (m, 1H), 2.79 - 2.71 (m, 1H), 2.69 (br d, J = 4.4 Hz, 3H), 2.53 (s, 3H).

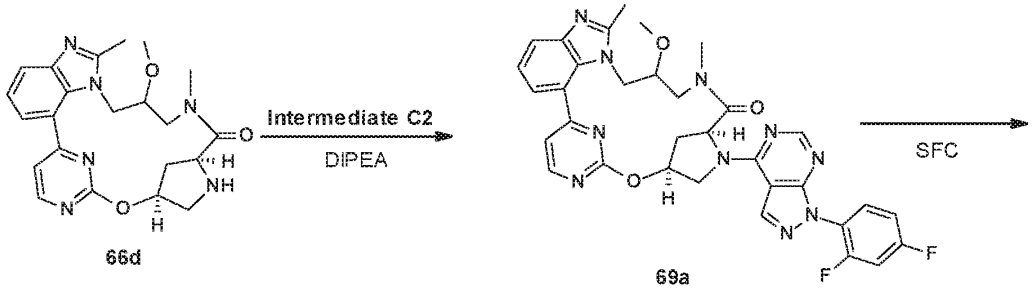
Example 69 and Example 70

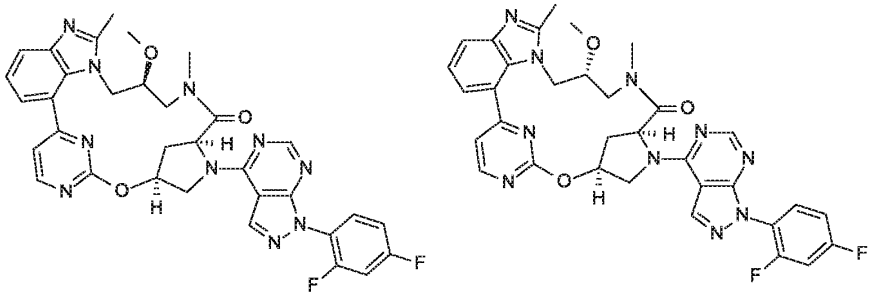
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compound was prepared according to the following scheme:





Example 69 & 70

The title compounds were prepared in analogy to the preparation of Example **66** and Example **67** by using **Intermediate C2** instead of **Intermediate C11**. Compound **69a** was separated by SFC (Instrument: SFC 80, Column: Pyridine, 250×30 mm I.D., 5µm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 35%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C) to give Example **69** and Example **70**.

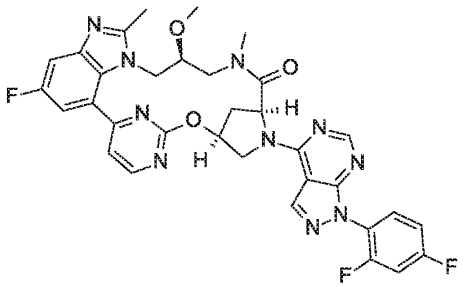
Example **69** (slower eluted), LCMS ($M+H^+$): 653. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.89 - 8.78 (m, 1H), 8.67 - 8.28 (m, 1H), 8.27 - 7.80 (m, 1H), 7.78 - 7.52 (m, 4H), 7.50 - 7.25 (m, 2H), 7.23 - 6.90 (m, 1H), 5.77 - 5.37 (m, 3H), 4.52 - 4.16 (m, 2H), 4.13 - 3.99 (m, 1H), 3.93 - 3.79 (m, 1H), 3.78 - 3.68 (m, 1H), 3.02 - 2.88 (m, 3H), 2.87 - 2.73 (m, 2H), 2.72 - 2.66 (m, 3H), 2.51 (br s, 3H), 2.46 - 2.34 (m, 1H).

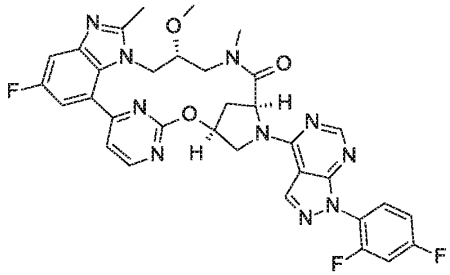
Example **70** (faster eluted), LCMS ($M+H^+$): 653. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.78

- 8.69 (m, 1H), 8.67 - 7.81 (m, 2H), 7.79 - 7.70 (m, 1H), 7.70 - 7.65 (m, 1H), 7.64 - 7.56 (m, 1H), 7.54 - 7.48 (m, 1H), 7.47 - 7.39 (m, 1H), 7.37 - 7.29 (m, 1H), 7.28 - 7.20 (m, 1H), 5.84 - 5.45 (m, 3H), 5.38 - 5.26 (m, 1H), 4.51 - 4.18 (m, 2H), 4.09 - 4.00 (m, 1H), 3.98 - 3.88 (m, 1H), 3.04 - 2.91 (m, 3H), 2.90 - 2.83 (m, 1H), 2.77 - 2.71 (m, 1H), 2.69 (d, *J* = 3.4 Hz, 3H), 2.53 (d, *J* = 2.9 Hz, 3H), 1.99 - 1.93 (m, 1H).

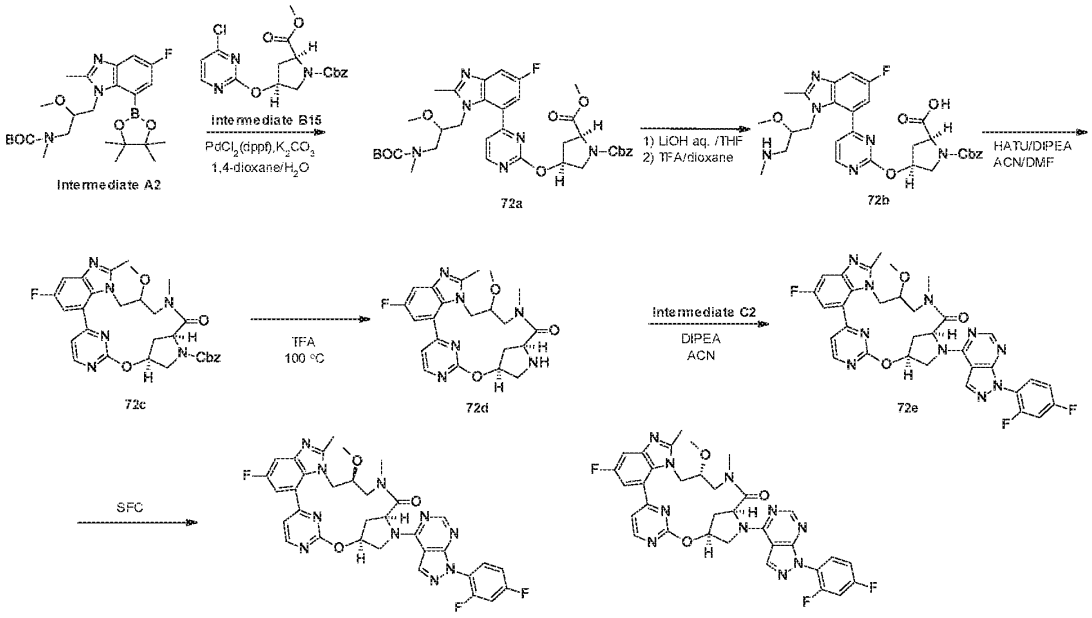
Example 72 and Example 73

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compound was prepared according to the following scheme:



Example 72 & 73

The title compounds were prepared in analogy to the preparation of Example **66** and Example **67** by using **Intermediate A2** instead of **Intermediate A1**. SFC condition of compound **72e**: Instrument: SFC 80, Column: Pyridine, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 50%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C.

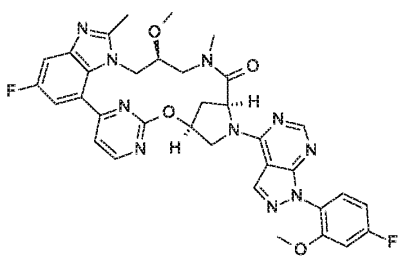
Example **72** (faster eluted), LCMS ($M+H^+$): 671. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.82 - 8.70 (m, 1H), 8.67 - 7.82 (m, 2H), 7.79 - 7.69 (m, 1H), 7.65 - 7.54 (m, 2H), 7.50 (td, J = 2.8, 8.9 Hz, 1H), 7.42 - 7.27 (m, 2H), 5.80 - 5.45 (m, 3H), 4.52 - 4.14 (m, 2H), 4.09 - 3.84 (m, 2H), 3.43 - 3.33 (m, 1H), 3.19 - 3.03 (m, 1H), 3.03 - 2.90 (m, 3H), 2.89 - 2.82 (m, 1H), 2.73 (br d, J = 4.0 Hz, 1H), 2.70 (d, J = 3.7 Hz, 3H), 2.56 - 2.52 (m, 3H).

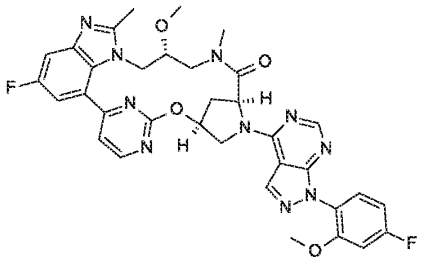
Example **73** (slower eluted), LCMS ($M+H^+$): 671. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.90 - 8.80 (m, 1H), 8.67 - 7.90 (m, 2H), 7.80 - 7.68 (m, 2H), 7.64 - 7.54 (m, 2H), 7.53 - 7.44 (m, 1H), 7.38 - 7.27 (m, 1H), 5.78 - 5.43 (m, 3H), 4.53 - 4.20 (m, 2H), 4.19 - 3.90 (m, 2H), 3.88 - 3.72 (m, 1H), 3.01 - 2.88 (m, 3H), 2.86 - 2.73 (m, 2H), 2.70 - 2.68 (m, 3H), 2.51 (br s, 3H), 2.42 - 2.34 (m, 1H).

Example 75 and Example 76

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





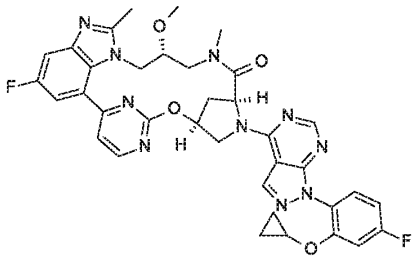
The title compounds were prepared in analogy to the preparation of Example **72** and Example **73** by using **Intermediate C11** instead of **Intermediate C2**. SFC condition of compound **72e**: Instrument: SFC 80, Column: Pyridine, 250×30 mm I.D., 5µm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 50%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C.

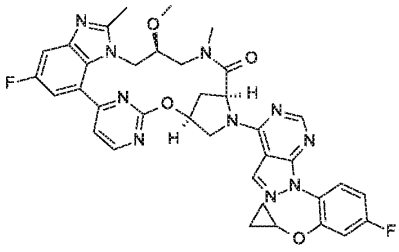
Example **75** (faster eluted), LCMS (M+H$^+$): 683. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.80 - 8.72 (m, 1H), 8.56 - 7.70 (m, 2H), 7.56 (t, *J* = 4.5 Hz, 1H), 7.51 (td, *J* = 2.6, 8.9 Hz, 1H), 7.47 - 7.38 (m, 1H), 7.34 (br dd, *J* = 2.0, 6.3 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.99 - 6.91 (m, 1H), 5.80 - 5.32 (m, 3H), 4.51 - 4.17 (m, 2H), 4.07 - 3.85 (m, 2H), 3.74 (d, *J* = 2.0 Hz, 3H), 3.42 - 3.34 (m, 1H), 3.05 - 2.92 (m, 3H), 2.88 - 2.81 (m, 1H), 2.70 (d, *J* = 4.9 Hz, 3H), 2.69 - 2.61 (m, 1H), 2.54 (s, 3H), 2.07 - 1.92 (m, 1H).

Example **76** (slower eluted), LCMS (M+H+): 683. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.88 - 8.81 (m, 1H), 8.56 - 7.80 (m, 2H), 7.79 - 7.75 (m, 1H), 7.61 - 7.54 (m, 1H), 7.52 - 7.38 (m, 2H), 7.20 (dd, J = 2.7, 11.1 Hz, 1H), 7.00 - 6.92 (m, 1H), 5.81 - 5.35 (m, 3H), 4.52 - 3.94 (m, 4H), 3.90 - 3.77 (m, 1H), 3.76 - 3.70 (m, 3H), 3.02 - 2.89 (m, 3H), 2.88 - 2.72 (m, 2H), 2.71 - 2.66 (m, 3H), 2.51 (d, J = 1.4 Hz, 3H), 2.43 - 2.36 (m, 1H).

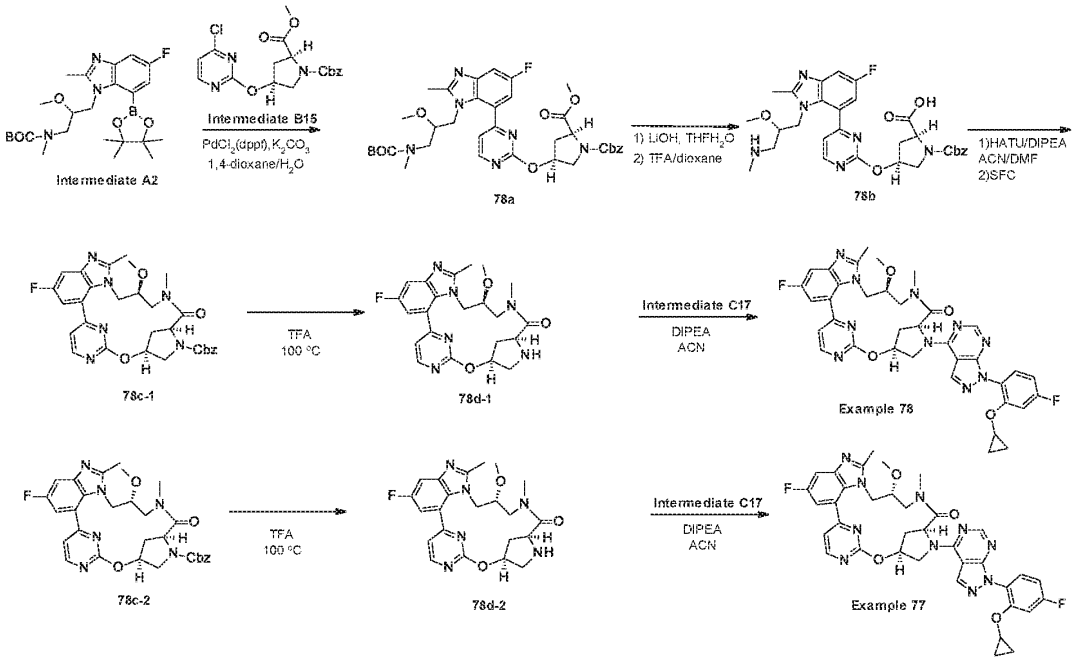
Example 77 and Example 78

(8*S*,11*S*,15*S*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared according to the following scheme:



The title compounds were prepared in analogy to the preparation of Example **63** and Example **64** by using intermediate **C17** instead of Intermediate **C2**, and intermediate **A2** instead of intermediate **A10**.

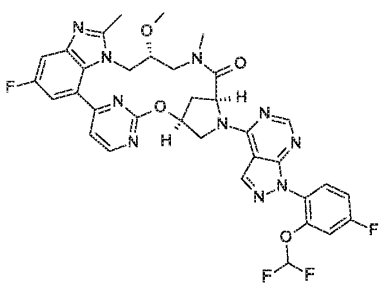
SFC preparation (Instrument: SFC 80, Column: IA, 250×30 mm I.D., 5µm, Mobile phase: A for CO_2 and B for IPA (0.1% $NH_3.H_2O$), Gradient: B 50%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C) to give faster eluted compound **78c-1** and slower eluted compound **78c-2**.

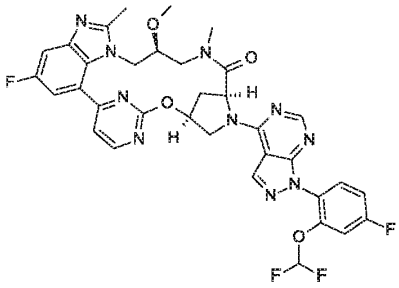
Example 77, LCMS ($M+H^+$): 709. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.82 - 8.74 (m, 1H), 8.54 - 7.72 (m, 2H), 7.61 - 7.54 (m, 2H), 7.47 - 7.35 (m, 3H), 7.02 - 6.94 (m, 1H), 5.80 - 5.41 (m, 3H), 4.49 - 4.14 (m, 2H), 4.12 - 4.02 (m, 1H), 4.00 - 3.88 (m, 2H), 3.52 (br d, J = 11.4 Hz, 1H), 3.18 - 3.04 (m, 1H), 3.03 - 2.91 (m, 3H), 2.88 - 2.82 (m, 1H), 2.73 - 2.70 (m, 3H), 2.70 - 2.63 (m, 1H), 2.62 - 2.56 (m, 3H), 0.79 - 0.68 (m, 2H), 0.58 - 0.46 (m, 2H)

Example **78**, LCMS (M+H$^+$): 709. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.92 - 8.82 (m, 1H), 8.53 - 7.80 (m, 2H), 7.80 - 7.77 (m, 1H), 7.65 - 7.60 (m, 1H), 7.57 - 7.50 (m, 1H), 7.47 - 7.36 (m, 2H), 7.04 - 6.95 (m, 1H), 5.76 - 5.45 (m, 3H), 4.48 - 4.16 (m, 2H), 4.15 - 4.05 (m, 1H), 4.00 - 3.93 (m, 1H), 3.90 - 3.79 (m, 1H), 3.01 - 2.89 (m, 3H), 2.88 - 2.82 (m, 1H), 2.82 - 2.74 (m, 1H), 2.73 - 2.71 (m, 3H), 2.70 - 2.62 (m, 1H), 2.57 - 2.53 (m, 3H), 2.44 - 2.37 (m, 1H), 0.78 - 0.70 (m, 2H), 0.58 - 0.49 (m, 2H).

Example 79 and Example 80

(8*S*,11*S*,15*S*)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





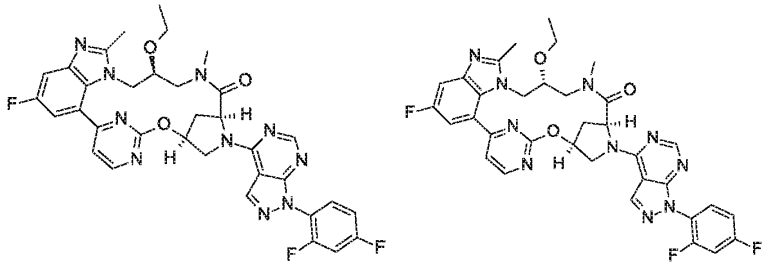
The title compounds were prepared in analogy to the preparation of Example **77** and Example **78** by using intermediate **C19** instead of intermediate **C17**.

Example **79** (prepared in analogy to Example 77), LCMS (M+H$^+$): 719. ^{1}H NMR (500 MHz, DMSO-d6) δ = 8.86 - 8.73 (m, 1H), 8.67 - 7.80 (m, 2H), 7.73 - 7.64 (m, 1H), 7.62 - 7.52 (m, 2H), 7.48 - 7.39 (m, 2H), 7.38 - 7.31 (m, 1H), 7.30 - 7.09 (m, 1H), 5.80 - 5.43 (m, 3H), 4.51 - 4.17 (m, 2H), 4.14 - 4.01 (m, 1H), 4.00 - 3.86 (m, 1H), 3.51 - 3.45 (m, 1H), 3.17 - 3.04 (m, 1H), 3.04 - 2.91 (m, 3H), 2.91 - 2.80 (m, 1H), 2.71 (d, J = 4.4 Hz, 3H), 2.71 - 2.65 (m, 1H), 2.59 (s, 3H).

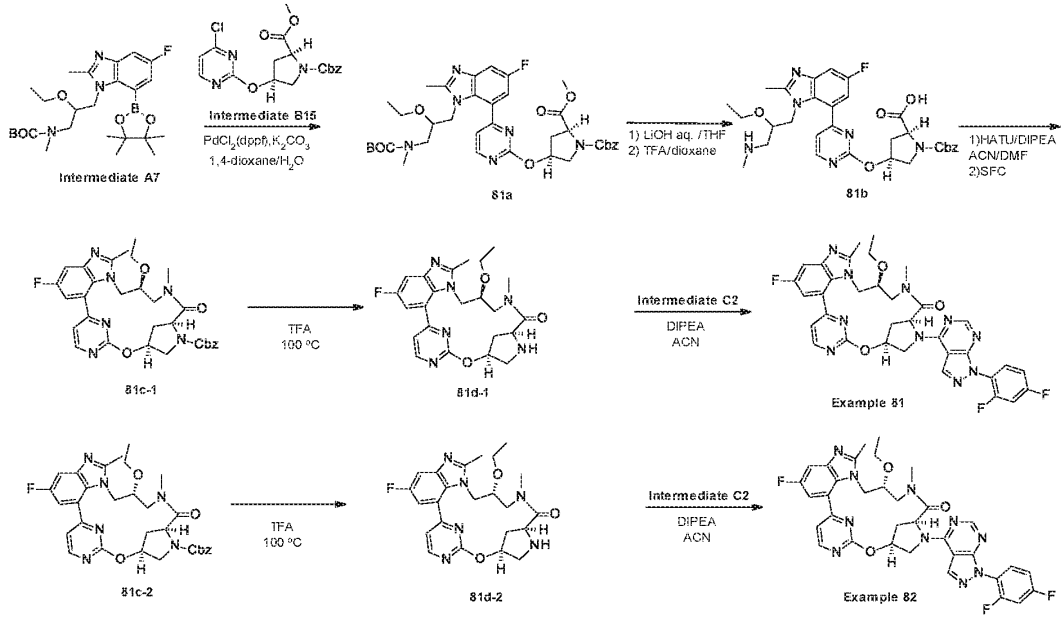
Example **80** (prepared in analogy to Example 78), LCMS (M+H$^+$): 719. ^{1}H NMR (500 MHz, DMSO-d6) δ = 8.91 - 8.79 (m, 1H), 8.64 - 7.85 (m, 2H), 7.82 - 7.76 (m, 1H), 7.72 - 7.64 (m, 1H), 7.61 (br d, J = 8.5 Hz, 1H), 7.54 (br d, J = 9.5 Hz, 1H), 7.47 - 7.39 (m, 1H), 7.38 - 7.31 (m, 1H), 7.30 - 7.06 (m, 1H), 5.78 - 5.44 (m, 3H), 4.50 - 4.17 (m, 2H), 4.13 - 4.02 (m, 1H), 3.90 - 3.79 (m, 1H), 3.02 - 2.88 (m, 3H), 2.87 - 2.82 (m, 1H), 2.81 - 2.75 (m, 1H), 2.73 (br s, 1H), 2.72 - 2.66 (m, 3H), 2.57 - 2.53 (m, 3H), 2.45 - 2.38 (m, 1H).

Example 81 and Example 82

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



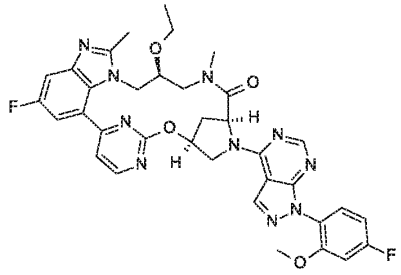
The title compounds were prepared in analogy to the preparation of Example **63** and Example **64** by using **Intermediate A7** instead of **Intermediate A8** to give compound **81c-1** (faster eluted) and compound **81c-2** (slower eluted). SFC condition of compound **81c**: Instrument: SFC 80, Column: Pyridine, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 50%, Flow rate: 60 mL /min, Back pressure: 100bar, Column temperature: 35°C.

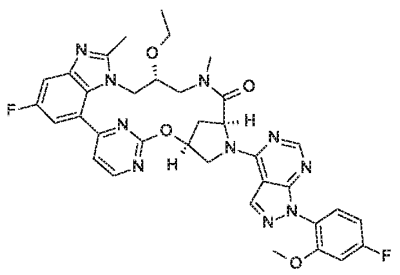
Example **81**, LCMS (M+H$^+$): 685. ^{1}H NMR (500 MHz, DMSO-d_6) δ =1H NMR (500 MHz, DMSO-d6) δ = 8.88 - 8.80 (m, 1H), 8.68 - 7.88 (m, 2H), 7.82 - 7.69 (m, 2H), 7.65 - 7.55 (m, 2H), 7.54 - 7.46 (m, 1H), 7.38 - 7.28 (m, 1H), 5.79 - 5.43 (m, 3H), 4.51 - 4.17 (m, 2H), 4.11 - 3.80 (m, 2H), 3.53 - 3.42 (m, 1H), 3.22 - 3.11 (m, 1H), 2.98 - 2.86 (m, 3H), 2.85 - 2.77 (m, 1H), 2.75 - 2.64 (m, 2H), 2.57 - 2.52 (m, 3H), 2.49 - 2.44 (m, 1H), 0.45 - 0.36 (m, 3H).

Example **82**, LCMS (M+H$^+$): 685. ^{1}H NMR (500 MHz, DMSO-d_6) δ =1H NMR (500 MHz, DMSO-d6) δ = 8.80 - 8.73 (m, 1H), 8.68 - 7.83 (m, 2H), 7.80 - 7.69 (m, 1H), 7.64 - 7.56 (m, 2H), 7.56 - 7.49 (m, 1H), 7.47 - 7.37 (m, 1H), 7.37 - 7.27 (m, 1H), 5.82 - 5.44 (m, 3H), 4.53 - 4.15 (m, 2H), 4.08 - 3.85 (m, 2H), 3.51 - 3.43 (m, 1H), 3.21 - 3.10 (m, 1H), 3.04 - 2.91 (m, 3H), 2.89 - 2.79 (m, 1H), 2.77 - 2.69 (m, 1H), 2.68 - 2.58 (m, 2H), 2.58 - 2.53 (m, 3H), 0.46 (dt, *J* = 4.3, 6.9 Hz, 3H).

Example 83 and Example 84

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared in analogy to the preparation of Example **81** and Example **82** by using **Intermediate C11** instead of **Intermediate C2**.

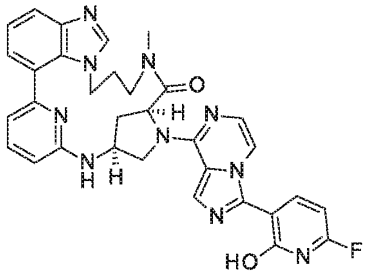
Example **83** (prepared in analogy to Example **81**), LCMS (M+H$^+$): 697. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.90 - 8.83 (m, 1H), 8.55 - 7.79 (m, 2H), 7.79 - 7.76 (m, 1H), 7.62 - 7.57 (m, 1H), 7.55 - 7.48 (m, 1H), 7.47 - 7.39 (m, 1H), 7.20 (dd, J = 2.6, 11.0 Hz, 1H), 6.99 - 6.92 (m, 1H), 5.75 - 5.46 (m, 3H), 4.49 - 4.16 (m, 2H), 4.09 - 3.99 (m, 1H), 3.91 - 3.79 (m, 1H), 3.75 (s, 3H), 3.33 - 3.28 (m, 1H), 3.21 - 3.14 (m, 1H), 2.99 - 2.87 (m, 3H), 2.84 - 2.75 (m, 1H), 2.74 - 2.64 (m, 2H), 2.55 (s, 3H), 2.47 (br d, *J* = 7.0 Hz, 1H), 0.45 - 0.37 (m, 3H).

Example **84** (prepared in analogy to Example **82**), LCMS (M+H$^+$): 697. ^{1}H NMR (500

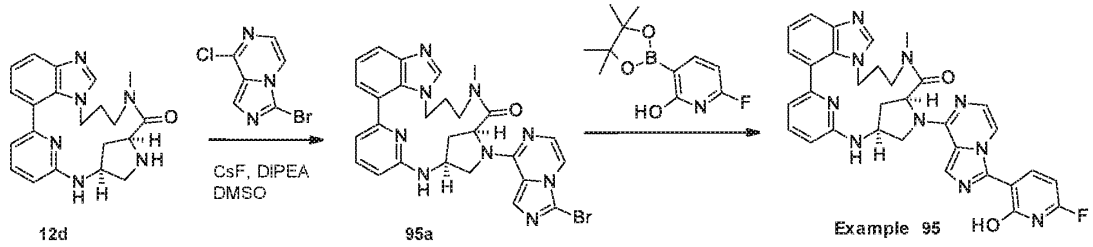
MHz, DMSO-d_6) δ = 8.79 - 8.72 (m, 1H), 8.58 - 7.71 (m, 2H), 7.63 - 7.50 (m, 2H), 7.49 - 7.36 (m, 2H), 7.20 (dd, J = 2.6, 11.0 Hz, 1H), 6.99 - 6.91 (m, 1H), 5.84 - 5.46 (m, 3H), 4.55 - 4.16 (m, 2H), 4.09 - 3.86 (m, 2H), 3.74 (s, 3H), 3.49 - 3.43 (m, 1H), 3.20 - 3.06 (m, 2H), 3.03 - 2.91 (m, 3H), 2.86 - 2.80 (m, 1H), 2.76 - 2.61 (m, 2H), 2.56 (s, 3H), 0.48 - 0.40 (m, 3H).

Example 95

(8*S*,11*S*)-10-[3-(6-fluoro-2-hydroxy-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*)-10-(3-bromoimidazo[1,5-a]pyrazin-8-yl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 95a)

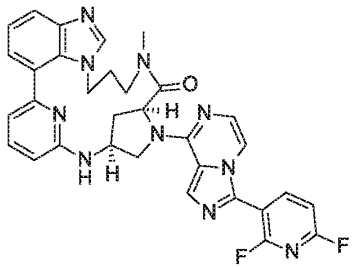
To a flask was added (8*S*,11*S*)-13-methyl-7,10,13,17,19,26-hexazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound **12d**, 100 mg, 239 μmol), 3-bromo-8-chloro-imidazo[1,5-a]pyrazine (100 mg, 478 μmol), CsF (181 mg, 1.2 mmol), DIPEA (155 mg, 208 μL, 1.2 mmol), DMSO (2 mL). The mixture was heated to 90 °C for 12 hrs. The mixture was diluted with 40 mL EA and then it was washed with water 25 mL for three times, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel to give compound **95a** (69 mg), LCMS ($M+H^+$): 579.

Step 2: preparation of (8*S*,11*S*)-10-[3-(6-fluoro-2-hydroxy-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 95)

To a microwave tube was added (8*S*,11*S*)-10-(3-bromoimidazo[1,5-a]pyrazin-8-yl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound **95a**, 10 mg, 17 µmol), 6-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol (12.6 mg, 52 µmol), Cs_2CO_3 (22.8 mg, 70 µmol), 1,4-dioxane (1 mL) and Water (0.4 mL). The suspension was bubbled with N_2 for 5 mins and $PdCl_2$(DPPF)-CH_2Cl_2 adduct (5.1 mg, 7 µmol) was added. The mixture was heated to 110 °C for 16 hrs. The mixture was concentrated and purified by prep-HPLC to give Example **95** (2 mg). LCMS (M+H$^+$): 605. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.53 - 8.40 (m, 1H), 8.10 - 8.02 (m, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.72 (br d, *J* = 7.3 Hz, 1H), 7.36 - 7.25 (m, 2H), 7.24 - 7.17 (m, 1H), 7.12 - 7.02 (m, 1H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.83 - 6.79 (m, 1H), 6.79 - 6.76 (m, 1H), 6.74 - 6.69 (m, 1H), 6.55 - 6.49 (m, 1H), 5.73 - 5.49 (m, 1H), 5.46 - 5.28 (m, 1H), 4.94 - 4.76 (m, 1H), 4.67 - 4.51 (m, 2H), 4.11 - 4.03 (m, 2H), 4.01 - 3.92 (m, 2H), 2.97 (br s, 3H), 2.86 - 2.75 (m, 2H), 2.09 - 1.89 (m, 1H), 1.45 - 1.29 (m, 1H).

Example 96

(8*S*,11*S*)-10-[3-(2,6-difluoro-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one

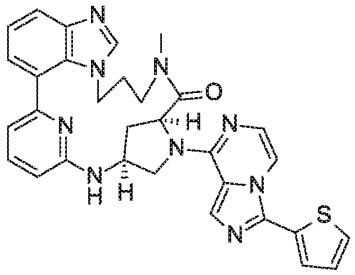


Example **96** was prepared in analogy to the preparation of Example **95** by using 2,6-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine instead of 6-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol. LCMS (M+H$^+$): 607. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 - 8.41 (m, 1H), 8.31 – 8.28 (m, 2H), 7.79 - 7.73 (m, 1H), 7.68 (dd, *J* = 1.8, 7.2 Hz, 1H), 7.42 (dd, *J* = 2.0, 8.2 Hz, 2H), 7.27 - 7.21 (m, 2H), 7.18 - 7.09 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.54 - 5.35 (m, 2H), 4.88 - 4.72 (m, 1H), 4.64 - 4.53 (m,

2H), 4.07 - 3.91 (m, 4H), 2.98 (br s, 3H), 2.87 - 2.77 (m, 2H), 2.12 - 1.95 (m, 1H), 1.45 - 1.32 (m, 1H).

Example 97

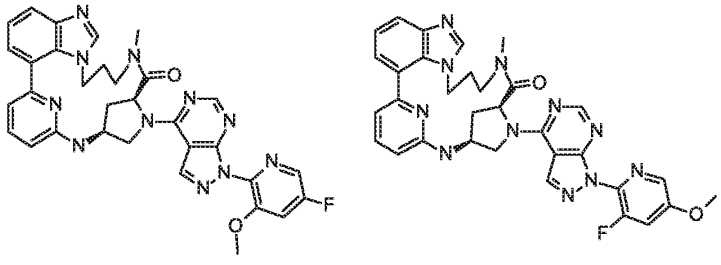
(8*S*,11*S*)-13-methyl-10-[3-(2-thienyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



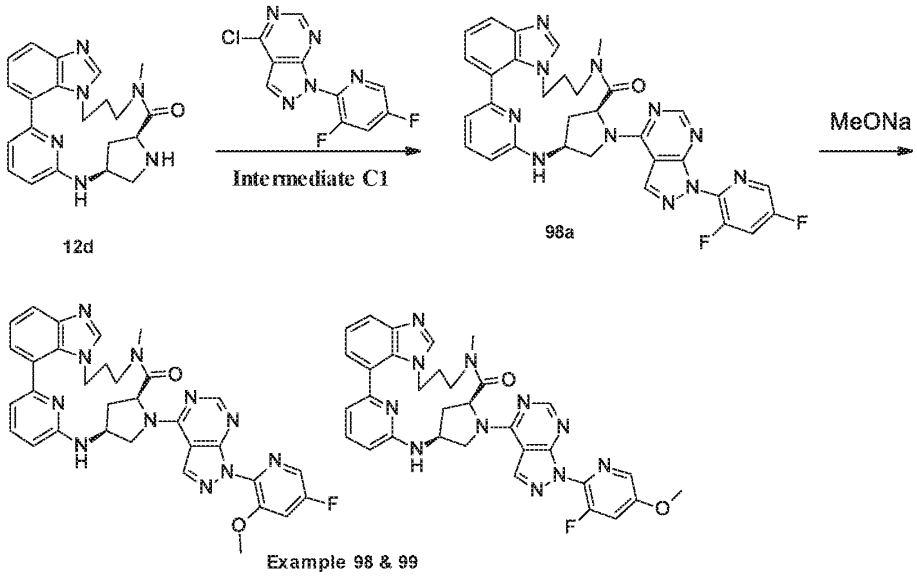
Example **97** was prepared in analogy to the preparation of Example **95** by using 4,4,5,5-tetramethyl-2-(2-thienyl)-1,3,2-dioxaborolane instead of 6-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol. Example **97** (1.5 mg) was obtained. LCMS (M+H$^+$): 576. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.92 - 7.86 (m, 1H), 7.82 - 7.75 (m, 6H), 7.44 - 7.37 (m, 3H), 7.28 (dd, *J* = 4.0, 5.0 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.81 - 5.61 (m, 1H), 5.45 - 5.31 (m, 1H), 4.95-4.81 (m, 1H), 4.65 - 4.53 (m, 2H), 4.16 - 4.07 (m, 2H), 4.03 - 3.93 (m, 2H), 2.97 (br s, 3H), 2.85 - 2.79 (m, 2H), 2.05 - 1.89 (m, 1H), 1.46 - 1.31 (m, 1H).

Exemple 98 & 99

(8*S*,11*S*)-10-[1-(5-fluoro-3-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-(3-fluoro-5-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 98a)

A mixture of intermediate **C1** (38 mg, 0.1 mmol), compound **12d** (36 mg, 0.1 mmol) and DIPEA (0.05 mL, 0.29 mmol) in ACN (1.5 mL) was stirred at 85 °C for 2 h. The mixture was concentrated to give crude compound **98a** (60 mg). LCMS $(M+H)^+$: 608.

Step 2: preparation of 8*S*,11*S*)-10-[1-(5-fluoro-3-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-(3-fluoro-5-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 98 & 99)

To a solution of compound **98a** (60 mg, 0.1 mmol) in methanol (1.5 mL) was added MeONa (1.5 mL, 5 M in MeOH) at 25 °C, then the mixture was stirred at 25 °C for 4 hours. The mixture was quenched with sat. NH_4Cl (10 mL), extracted with EtOAc (10 mL). The organic layer was concentrated and the residue was purified by prep-HPLC to give **Example 98** (9 mg) and **Example 99** (1.6 mg).

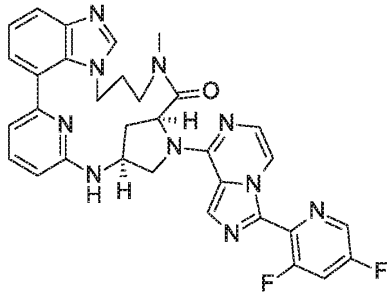
Example 98: LCMS$(M+H)^+$: 620, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.44 - 9.31 (m, 1H), 8.54 - 8.46 (m, 1H), 8.25 - 8.22 (m, 1H), 8.20 - 8.15 (m, 1H), 7.92 - 7.80 (m, 3H), 7.62 - 7.52 (m, 2H), 7.03 (br d, *J* =7.21 Hz, 1H), 6.85 - 6.72 (m, 1H), 5.85 - 5.69 (m, 1H), 5.51 - 5.37 (m, 1H),

5.11 – 4.83 (m, 1H), 4.73 - 4.61 (m, 1H), 4.51 - 4.42 (m, 1H), 4.28 - 4.13 (m, 3H), 4.05 - 3.94 (m, 1H), 3.80 - 3.78 (m, 3H), 3.04 (s, 1H), 2.96 (s, 2H), 2.89 - 2.78 (m, 1H), 2.70 - 2.57 (m, 1H), 2.41 - 2.29 (m, 1H).

Example 99: LCMS(M+H)$^+$: 620, ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.28 - 8.16 (m, 3H), 7.84 - 7.76 (m, 1H), 7.71 (br d, *J*=7.46 Hz, 1H), 7.60 (dd, *J*=10.94, 2.26 Hz, 1H), 7.39 - 7.28 (m, 2H), 6.99 (br d, *J*=7.21 Hz, 1H), 6.78 - 6.69 (m, 1H), 5.54 - 5.41 (m, 1H), 4.77 - 4.69 (m, 1H), 4.66 (br s, 2H), 4.58 - 4.52 (m, 2H), 4.30 (br d, *J*=12.47 Hz, 1H), 4.20 - 4.06 (m, 2H), 4.00 (s, 3H), 3.18 - 3.00 (m, 3H), 2.96 - 2.83 (m, 1H), 2.75 - 2.51 (m, 2H).

Example 100

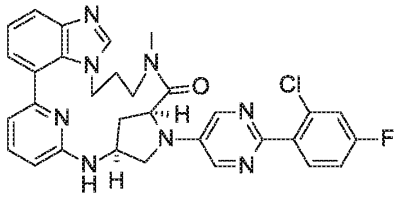
(8*S*,11*S*)-10-[3-(3,5-difluoro-2-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



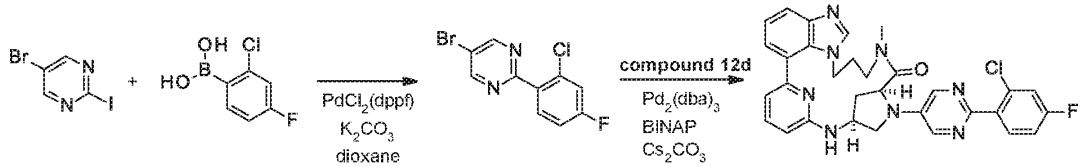
Example **100** was prepared in analogy to the preparation of Example **95** by using 3,5-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine instead of 6-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol. LCMS (M+H$^+$): 607. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.81 (br s, 1H), 8.73 (d, *J* = 2.3 Hz, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 8.20 (ddd, *J* = 2.4, 8.8, 10.8 Hz, 1H), 7.83 - 7.79 (m, 1H), 7.79 - 7.77 (m, 1H), 7.77 - 7.75 (m, 1H), 7.46 - 7.36 (m, 2H), 7.21 (br s, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.86 - 5.58 (m, 1H), 5.54 - 5.26 (m, 1H), 4.99 - 4.78 (m, 1H), 4.71 - 4.48 (m, 2H), 4.19 - 4.06 (m, 2H), 4.02 – 3.97 (m, 2H), 2.98 (br s, 3H), 2.85 – 2.80 (m, 2H), 1.99 (br s, 1H), 1.40 (br s, 1H).

Example 102

(8*S*,11*S*)-10-[2-(2-chloro-4-fluoro-phenyl)pyrimidin-5-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



102a example 102

Step 1: preparation of 5-bromo-2-(2-chloro-4-fluoro-phenyl)pyrimidine (compound 102a)

A solution of 5-bromo-2-iodopyrimidine (1.7 g, 5.97 mmol), $PdCl_2$(dppf) (487 mg, 597 µmol), (2-chloro-4-fluorophenyl)boronic acid (1.04 g, 5.97 mmol and K_2CO_3 (2.47 g, 17.9 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was stirred at 120 °C for 16 hrs. The mixture was cooled and diluted with EA (20 mL), and then it was washed with brine (20 mL). The organic layer was dried and concentrated. The crude product was purified by silica gel to give the compound **102a** (420 mg), LCMS ($M+H^+$): 287.

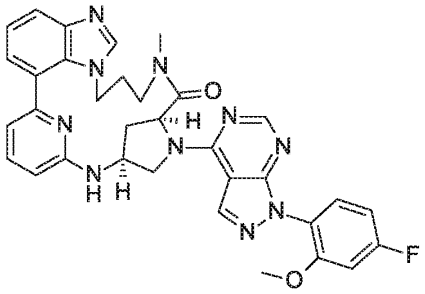
Step 2: preparation of (8*S*,11*S*)-10-[2-(2-chloro-4-fluoro-phenyl)pyrimidin-5-yl]-13-methyl-7,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (example 102)

To a solution of (8*S*,11*S*)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[**15.6.1.1**^{2,6}**.1**^{8,11}**.0**^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (**12d**, 50 mg, 133 µmol) in 1,4-dioxane (3 mL) was added 5-bromo-2-(2-chloro-4-fluorophenyl)pyrimidine (**102a**, 57.3 mg, 199 µmol), 2,2'-bis(diphenylphosphaneyl)-1,1'-binaphthalene (33.1 mg, 53.1 µmol), $Pd_2(dba)_3$ (24.3 mg, 26.6 µmol) and Cs_2CO_3 (108 mg, 332 µmol). The reaction mixture was bubbled with N_2 for 5 mins and then heated to 110 °C for 16 hrs. The reaction mixture was filtered and the filtrate was concentrated, the residue was purified by prep-HPLC to give Example **102** (7.3 mg), LCMS ($M+H^+$): 584. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.47 (s, 1H), 8.19 (s, 2H), 7.89 (dd, *J* = 2.0, 5.1 Hz, 1H), 7.87 - 7.83 (m, 1H), 7.73 - 7.68 (m, 2H), 7.67 - 7.62 (m, 1H), 7.34 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.19 (dt, *J* = 2.6, 8.4 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.93 (d, *J* = 8.8 Hz, 1H), 4.64 - 4.58 (m, 1H), 4.41 - 4.31 (m, 1H), 4.22 (dd, *J* = 10.7, 13.8 Hz, 1H), 4.01 (dd,

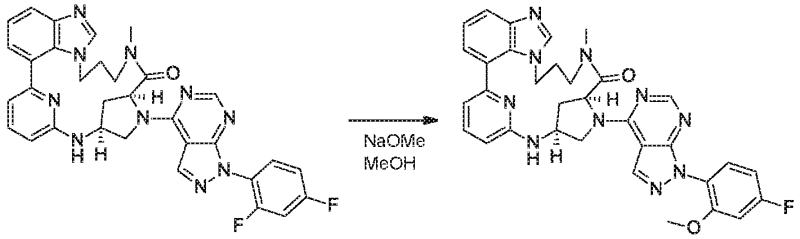
J = 5.7, 10.6 Hz, 1H), 3.82 (d, *J* = 10.6 Hz, 1H), 3.04 (s, 3H), 2.96 - 2.87 (m, 1H), 2.77 - 2.68 (m, 1H), 2.66 - 2.56 (m, 1H), 2.08 - 1.95 (m, 1H), 1.68 - 1.53 (m, 1H).

Example 104

(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

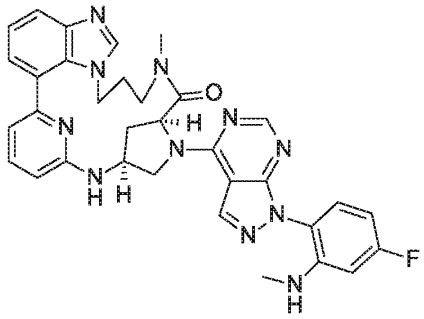


Example 12 Example 104

To a tube was added (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (**Example 12**, 33 mg, 54.4 µmol), MeOH (2mL) and sodium methanolate (4 N in methanol) (3mL, 12 mmol), a suspension formed. The mixture was heated to 70 °C for 16 hrs. The mixture was concentrated and then it was purified via prep-HPLC to give the Example **104** (6.6 mg). LCMS (M+H$^+$) 619. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.48 (s, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.47 - 7.40 (m, 1H), 7.29 - 7.22 (m, 2H), 7.22 - 7.16 (m, 1H), 6.99 - 6.91 (m, 2H), 6.79 - 6.67 (m, 1H), 5.54 (br d, *J* = 8.4 Hz, 1H), 5.44 (d, *J* = 8.6 Hz, 1H), 4.96 - 4.76 (m, 1H), 4.72 - 4.60 (m, 1H), 4.55 - 4.43 (m, 1H), 4.28 - 4.14 (m, 1H), 4.09 - 3.89 (m, 3H), 3.73 (s, 3H), 2.95 (s, 3H), 2.90 - 2.75 (m, 1H), 2.41 - 2.34 (m, 1H), 2.09 - 1.83 (m, 1H), 1.45 - 1.24 (m, 1H)

Example 106

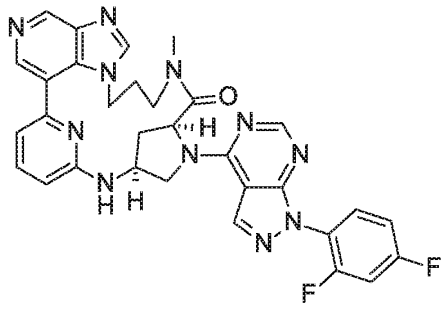
(8*S*,11*S*)-10-[1-[4-fluoro-2-(methylamino)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



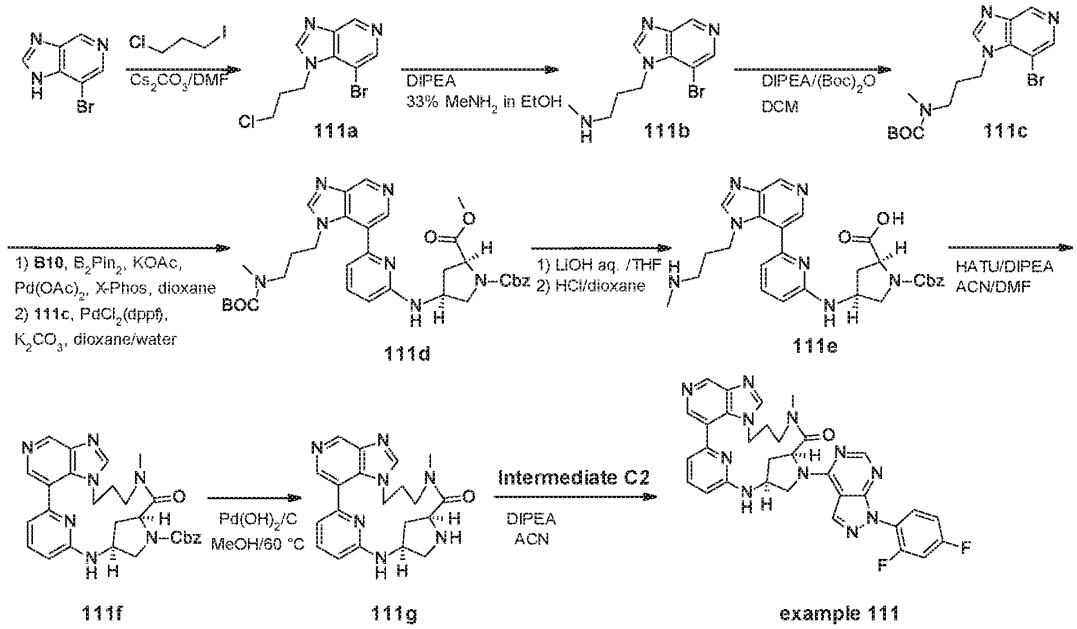
The title compound was prepared in analogy to the preparation of Example **104** by using the reaction condition with methanamine (33% in ethanol) instead of NaOMe and MeOH. LCMS (M+H$^+$) 618. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (s, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 7.83 - 7.76 (m, 1H), 7.71 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.19 - 7.11 (m, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.77 - 6.71 (m, 1H), 6.54 (dd, *J* = 2.7, 11.6 Hz, 1H), 6.45 (dt, *J* = 2.8, 8.4 Hz, 1H), 5.50 (d, *J* = 8.6 Hz, 1H), 4.78 - 4.72 (m, 1H), 4.57 - 4.53 (m, 2H), 4.29 (d, *J* = 11.7 Hz, 1H), 4.20 - 4.04 (m, 2H), 3.05 (s, 3H), 2.96 - 2.84 (m, 1H), 2.75 (s, 3H), 2.68 - 2.62 (m, 1H), 2.62 - 2.53 (m, 1H), 2.23 - 2.00 (m, 1H), 1.61 - 1.41 (m, 1H).

Example 111

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,22,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 7-bromo-1-(3-chloropropyl)imidazo[4,5-c]pyridine (compound 111a)

To a flask was added 7-bromo-1*H*-imidazo[4,5-c]pyridine (2 g, 10.1 mmol), 1-chloro-3-iodo-propane (2.68 g, 1.41mL, 13.13 mmol), Cs_2CO_3 (6.58 g, 20.2 mmol), DMF (15 mL). The mixture was heated to 55 °C for 3 hrs. The mixture was diluted with 40 mL EA, which was washed with water 25 mL for three times, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel to give compound **111a** (470 mg), LCMS ($M+H^+$): 274.

Step 2: preparation of 3-(7-bromoimidazo[4,5-c]pyridin-1-yl)-*N*-methyl-propan-1-amine (compound 111b)

To a flask was added 7-bromo-1-(3-chloropropyl)imidazo[4,5-c]pyridine (compound **111a**, 470 mg, 1.71 mmol), DIPEA (442 mg, 598 μL, 3.42 mmol), 33% $MeNH_2$ in EtOH (6 mL), The mixture was heated to 90 °C for 16 hrs, then the mixture was concentrated to give compound **111b** (500 mg), LCMS ($M+H^+$): 269.

Step 3: preparation of *tert*-butyl *N*-[3-(7-bromoimidazo[4,5-c]pyridin-1-yl)propyl]-*N*-methyl-carbamate (compound 111c)

To a flask was added 3-(7-bromoimidazo[4,5-c]pyridin-1-yl)-*N*-methyl-propan-1-amine (compound **111b**, 460 mg, 1.71 mmol), DIPEA (663 mg, 895 μL, 5.13 mmol), *tert*-butoxycarbonyl *tert*-butyl carbonate (448 mg, 2.05 mmol), DCM (6 mL), the suspension was stirred at room temperature for 1 hr. Then the mixture was concentrated, the crude product was

purified by silica gel to give compound **111c** (430 mg), LCMS ($M+H^+$): 369.

Step 4: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[1-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]imidazo[4,5-c]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 111d)

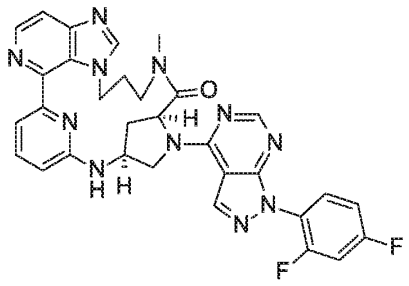
To a flask was added O1-benzyl O2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate (**Intermediate B10**, 1 g, 2.3 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.17 g, 4.6 mmol), KOAc (452 mg, 4.6 mmol) and 1,4-dioxane (8 mL). The suspension was bubbled with N_2 for 5 mins, then $Pd(OAc)_2$ (103 mg, 461 μmol) and dicyclohexyl-[3-(2,4,6-triisopropylphenyl)phenyl]phosphane (439 mg, 921 μmol) were added. The mixture was heated to 80 °C for 12 hrs, then the mixture was filtered, *tert*-butyl *N*-[3-(7-bromoimidazo[4,5-c]pyridin-1-yl)propyl]-*N*-methyl-carbamate (compound **111c**, 425 mg, 1.15 mmol), K_2CO_3 (477 mg, 3.45 mmol), and water (1 mL) were added into the filtrate. The suspension was bubbled with N_2 for 5 mins and $PdCl_2(DPPF)$-CH_2Cl_2 adduct (207 mg, 282 μmol) was added. After being heated to 90 °C for 2 hrs, the mixture was diluted with 40 mL water and extracted with EA 25 mL for three times, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel to give compound **111d** (460 mg), LCMS ($M+H^+$): 644.

Step 5~8: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,22,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 111)

Example **111** was prepared in analogy to the preparation of Example **1** by using compound **111d** instead of compound **1a**. LCMS ($M+H^+$): 608. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.93 (s, 1H), 8.53 (s, 1H), 8.46 - 8.40 (m, 2H), 8.24 - 8.21 (m, 1H), 7.89 - 7.79 (m, 1H), 7.71 - 7.59 (m, 1H), 7.33 - 7.24 (m, 1H), 7.23 - 7.14 (m, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.84 - 6.76 (m, 1H), 5.55 - 5.41 (m, 1H), 5.41 - 5.20 (m, 1H), 4.62 - 4.50 (m, 3H), 4.39 - 4.20 (m, 2H), 4.15 - 4.03 (m, 1H), 3.13 (s, 1H), 3.04 (s, 2H), 2.94 - 2.82 (m, 1H), 2.63 - 2.58 (m, 1H), 2.11 - 1.89 (m, 1H), 1.62 - 1.41 (m, 1H).

Example 112

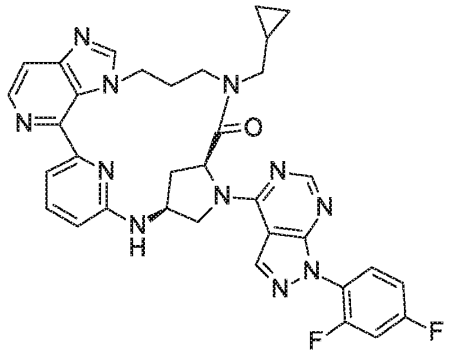
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



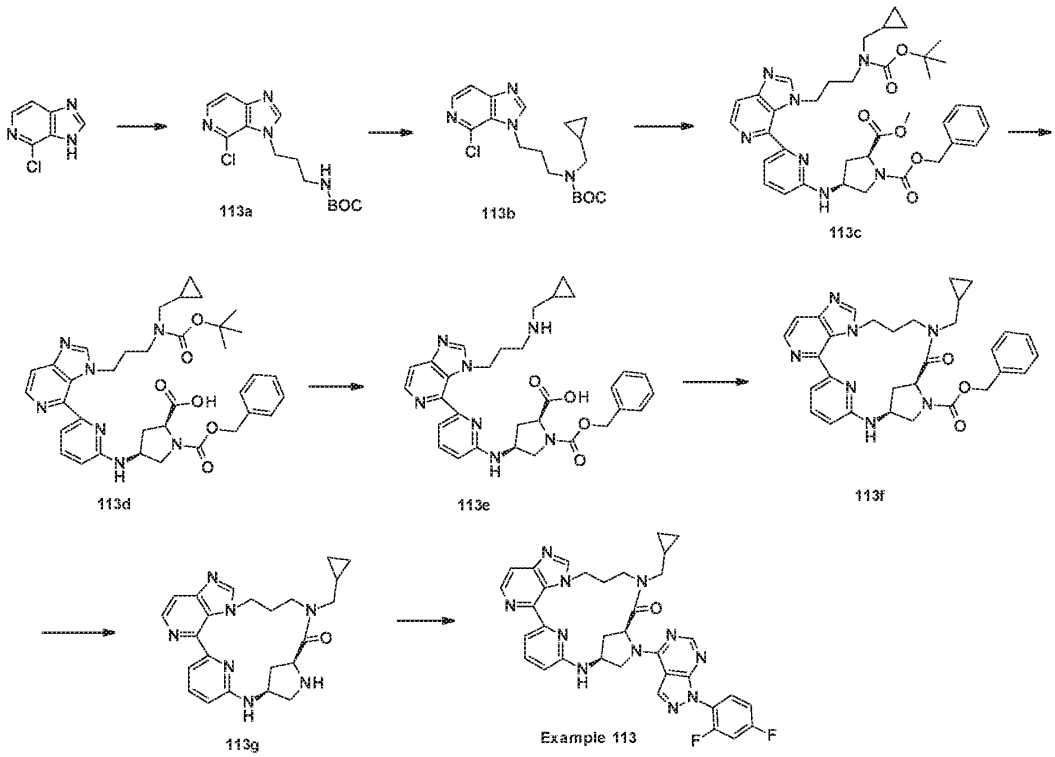
Example **112** was prepared in analogy to the preparation of Example **111** by using 4-chloro-3*H*-imidazo[4,5-c]pyridine instead of 7-bromo-1*H*-imidazo[4,5-c]pyridine. Example **112** (7 mg) was obtained. LCMS ($M+H^+$): 608. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.61 - 8.47 (m, 2H), 8.38 (d, *J* = 3.2 Hz, 1H), 8.37 - 8.25 (m, 1H), 7.86 - 7.80 (m, 1H), 7.78 - 7.71 (m, 1H), 7.71 - 7.69 (m, 1H), 7.64 - 7.57 (m, 1H), 7.43 - 7.38 (m, 1H), 7.37 - 7.30 (m, 1H), 6.83 - 6.73 (m, 1H), 5.59 (br d, *J* = 8.6 Hz, 1H), 5.48 (d, *J* = 8.7 Hz, 1H), 5.43 - 5.31 (m, 1H), 4.76 - 4.67 (m, 1H), 4.55 – 4.49 (m, 1H), 4.30 - 4.20 (m, 2H), 4.21 - 4.08 (m, 1H), 3.98 - 3.90 (m, 1H), 3.02 (s, 1H), 2.93 (s, 2H), 2.90 - 2.75 (m, 1H), 2.64 - 2.35 (m, 1H), 1.82 - 1.56 (m, 1H), 1.46 - 1.25 (m, 1H).

Example 113

(8*S*,11*S*)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(4-chloroimidazo[4,5-c]pyridin-3-yl)propyl]carbamate (compound 113a)

The mixture of 4-chloro-3*H*-imidazo[4,5-c]pyridine (6.0 g, 39.07 mmol), 3-(BOC-amino)propyl bromide (10.23 g, 42.98 mmol) and cesium carbonate (19.09 g, 58.61 mmol) in ACN (50 mL) was stirred at 90 °C for 2 h. The mixture was filtered and the filtrate was concentrated, the residue was purified by prep-HPLC to give compound **113a** (3.5 g), LCMS $(M+H)^+$: 311.

Step 2: preparation of *tert*-butyl *N*-[3-(4-chloroimidazo[4,5-c]pyridin-3-yl)propyl]-*N*-(cyclopropylmethyl)carbamate (compound 113b)

To a solution of compound **113a** (3.4 g, 11 mmol) in DMF (30 mL) was added sodium hydride, 60% in oil (880. mg, 22 mmol) at -10 °C. The mixture was stirred at -10 °C for 0.5 h. Then (bromomethyl)cyclopropane (1.17 mL, 12 mmol) was added and then stirred at 25 °C for 16 hours. The reaction was quenched with aq. NH_4Cl solution, the mixture was extracted with EA, the organic layer was dried and concentrated, the residue was purified by silica gel to give compound **113b** (3.5 g), LCMS $(M+H)^+$: 365.

Step 3: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(cyclopropylmethyl)amino]propyl]imidazo[4,5-c]pyridin-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 113c)

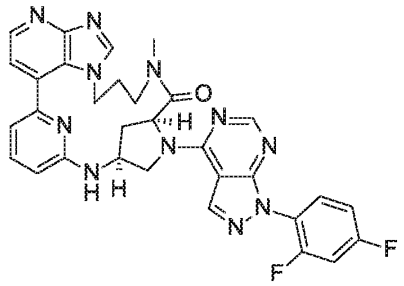
To a mixture of compound **113b** (420 mg, 1.15 mmol), intermediate **B10** (500 mg, 1.15 mmol), Zn (301.1 mg, 4.61 mmol) in DMA (8 mL) was added pyridine-2-carboximindamide hydrochloride (54.43 mg, 0.350 mmol), Nickel chloride dimethoxyethane adduct (75.89 mg, 0.350 mmol) at 25 °C under N_2 atmosphere. The reaction was stirred at 25 °C for 15 hours. Then the reaction was filtered and the filtrate was concentrated, the residue was purified by flash chromatography column to give compound **113c** (155 mg), LCMS $(M+H)^+$: 684.

Step 4~8: preparation of (8*S*,11*S*)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 113)

The title compound was prepared in analogy to the preparation of **Example 12** by using compound **113c** instead of compound **12a**. LCMS $(M+H)^+$: 648. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.98 - 9.95 (m, 1H), 8.56 (s, 1H), 8.53 - 8.51 (m, 1H), 8.39 - 8.25 (m, 1H), 8.20 - 8.19 (m, 1H), 7.98 - 7.83 (m, 1H), 7.83 - 7.68 (m, 1H), 7.34 -7.20 (m, 3H), 7.06 - 7.04 (m, 1H), 5.60 - 5.51 (m, 2H), 4.82 - 4.80 (m, 2H), 4.61 - 4.58 (m, 1H), 4.46 - 4.33 (m, 2H), 4.11 - 3.98 (m, 1H), 3.60 - 3.55 (m, 1H), 3.33 - 3.32 (m, 1H), 3.15 - 3.10 (m, 1H), 2.68 - 2.66 (m, 1H), 2.15 - 1.90 (m, 1H), 1.62 - 1.59 (m, 1H), 0.64 - 0.26 (m, 5H).

Example 114

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

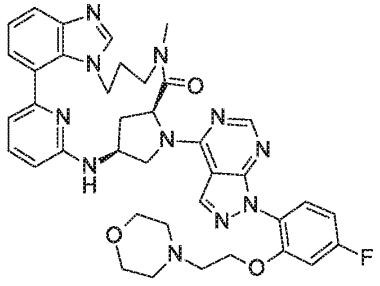


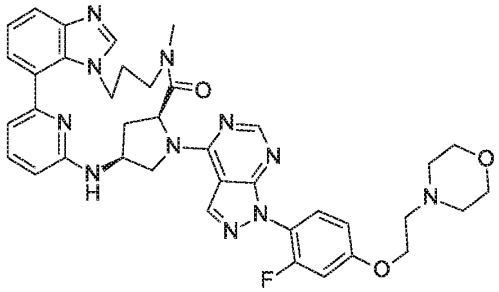
Example **114** was prepared in analogy to the preparation of Example **111** by using 7-chloro-1*H*-imidazo[4,5-b]pyridine instead of 7-bromo-1*H*-imidazo[4,5-c]pyridine. LCMS $(M+H^+)$: 608. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.62 - 8.51 (m, 2H), 8.44 (d, J = 4.9 Hz, 1H), 8.38 - 8.22 (m, 1H), 7.87 - 7.79 (m, 1H), 7.78 - 7.69 (m, 1H), 7.60 (ddd, J = 2.8, 9.1, 10.4 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.08 (d, J = 7.3 Hz, 1H), 6.86 - 6.75 (m, 1H), 5.70 – 5.67 (m, 1H), 5.46

(d, *J* = 8.7 Hz, 1H), 5.17 - 4.98 (m, 1H), 4.75 - 4.65 (m, 1H), 4.52 - 4.47 (m, 1H), 4.28 - 4.18 (m, 2H), 4.17 - 4.05 (m, 1H), 3.97 – 3.90 (m, 1H), 3.03 (s, 1H), 2.94 (s, 2H), 2.90 - 2.61 (m, 1H), 2.61 - 2.34 (m, 1H), 1.99 - 1.74 (m, 1H), 1.43 - 1.21 (m, 1H).

Exemple 115 & 116

(8*S*,11*S*)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one





To a solution of 2-morpholinoethanol (86.49 mg, 0.660 mmol) in DMF (1 mL) was added NaH (21.1 mg, 0.530 mmol) at 0°C and the mixture was stirred at 0°C for 30 mins, **Example 12** (40 mg, 0.07 mmol) in DMF (0.5 mL) was added at 0 °C. The mixture was stirred at 80 °C for 2 h, then the mixture was quenched with water, the solution was purified by prep-HPLC to afford Example **115** (3.8 mg) and Example **116** (3 mg).

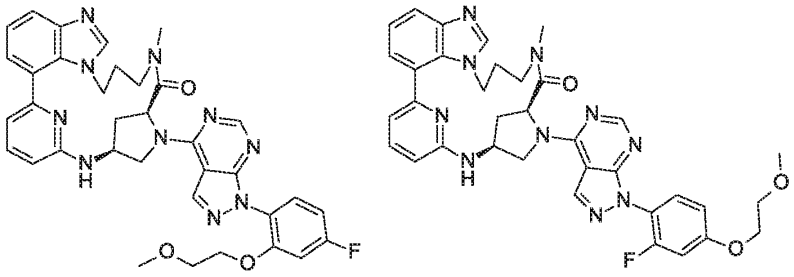
Example 115: LCMS (M+H)$^+$: 718. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.52 - 9.44 (m, 1H), 8.58 - 8.51 (m, 1H), 8.25 (s, 1H), 7.94 - 7.84 (m, 2H), 7.72 - 7.68 (m, 2H), 7.55 - 7.46 (m, 1H), 7.22 - 7.17 (m, 1H), 7.13 - 7.09 (m, 1H), 7.04 - 6.95 (m, 1H), 6.89 - 6.84 (m, 1H), 5.54 - 5.44 (m, 1H), 5.17 – 5.01 (m, 2H), 4.65 - 4.55 (m, 2H), 4.50 - 4.44 (m, 2H), 4.37 - 4.31 (m, 2H), 4.28 - 4.13 (m, 2H), 3.96 - 3.72 (m, 4H), 3.48 - 3.43 (m, 2H), 3.09 - 3.06 (m, 3H), 2.98 - 2.88 (m, 2H), 2.68 - 2.59 (m, 2H), 2.24 - 2.11 (m, 1H), 2.07 - 1.98 (m, 1H), 1.76 - 1.63 (m, 1H).

Example 116: LCMS (M+H)$^+$: 718. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.37 - 9.15 (m, 1H), 8.17 - 7.98 (m, 1H), 7.93 - 7.76 (m, 3H), 7.74 - 7.57 (m, 3H), 7.09 - 7.03 (m, 1H), 7.01 - 6.93 (m, 1H), 6.86 - 6.75 (m, 2H), 5.57 - 5.39 (m, 1H), 4.75 - 4.55 (m, 3H), 4.49 - 4.44 (m, 2H), 4.35 - 4.24 (m, 2H), 4.21 - 4.10 (m, 2H), 4.01 - 3.81 (m, 4H), 3.67 - 3.59 (m, 2H), 3.46 - 3.37 (m,

2H), 3.05 - 2.99 (m, 3H), 2.97 - 2.80 (m, 1H), 2.80 - 2.59 (m, 1H), 2.55 - 2.41 (m, 1H), 2.26 - 2.14 (m, 1H), 2.07 - 2.02 (m, 1H), 1.75 - 1.52 (m, 1H).

Example 118 & 119

(8*S*,11*S*)-10-[1-[4-fluoro-2-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-[2-fluoro-4-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



Example 118 & 119 were prepared in analogy to the preparation of **Example 115 & 116** by using 2-methoxyethanol instead of 2-morpholinoethanol.

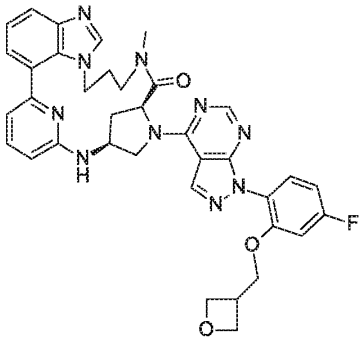
Example 118: LCMS $(M+H)^+$: 663. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.27 - 8.22 (m, 1H), 8.18 (s, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.77 - 7.68 (m, 1H), 7.45 (br dd, *J* = 6.1, 8.7 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.08 (dd, *J* = 2.3, 10.7 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.89 (dt, *J* = 2.4, 8.3 Hz, 1H), 6.78 - 6.70 (m, 1H), 5.49 (br d, *J* = 8.6 Hz, 1H), 4.77 - 4.70 (m, 2H), 4.30 (br d, *J* = 11.4 Hz, 1H), 4.22 - 4.10 (m, 4H), 3.53 - 3.46 (m, 2H), 3.14 (s, 3H), 3.05 (s, 3H), 2.88 (br dd, *J* = 6.9, 13.8 Hz, 1H), 2.69 - 2.54 (m, 2H), 2.20 - 2.12(m, 1H), 1.73 - 1.44 (m, 2H).

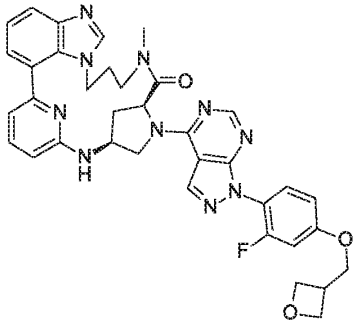
Example 119: LCMS $(M+H)^+$: 663. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.51 (s, 1H), 8.35 - 8.20 (m, 2H), 7.84 - 7.77 (m, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.53 - 7.43 (m, 1H), 7.39 - 7.28 (m, 2H), 7.04 - 6.95 (m, 3H), 6.75 (br d, *J* = 8.3 Hz, 1H), 5.50 (br d, *J* = 8.9 Hz, 1H), 4.76 - 4.72 (m, 2H), 4.33 - 4.27 (m, 1H), 4.25 - 4.20 (m, 2H), 4.18 - 4.08 (m, 2H), 3.82 - 3.77 (m, 2H), 3.45 (s, 3H), 3.05 (s, 3H), 2.94 - 2.84 (m, 1H), 2.72 - 2.57 (m, 2H), 2.25 - 2.17 (m, 1H), 1.75 - 1.46 (m, 2H).

Example 120 & 121

(8*S*,11*S*)-10-[1-[4-fluoro-2-(oxetan-3-ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-[2-fluoro-4-(oxetan-3-

ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





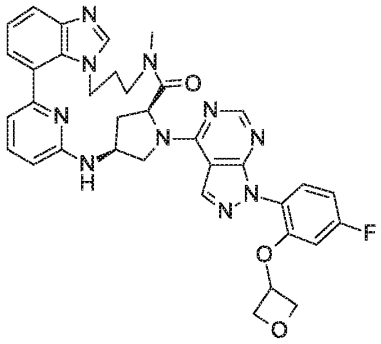
Example 120 & 121 were prepared in analogy to the preparation of **Example 115 & 116** by using oxetan-3-ylmethanol instead of 2-morpholinoethanol.

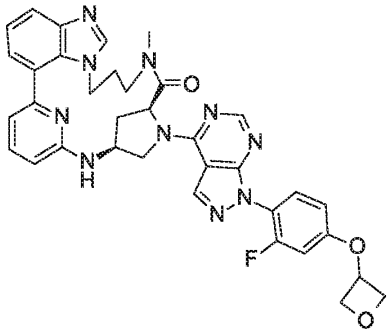
Example 120: LCMS (M+H)$^+$: 675. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.5 - 8.45 (m, 1H), 8.30 – 8.25 (m, 1H), 8.17 (s, 1H), 7.78 - 7.67 (m, 2H), 7.55 - 7.51 (m, 1H), 7.31 – 7.27 (m, 2H), 7.20 – 7.15 (m, 1H), 7.05 – 6.95 (m, 1H), 6.9 – 6.8 (m, 1H), 6.85 – 6.75 (m, 1H), 5.63 - 5.44 (m, 1H), 4.55 – 4.61 (m, 10H), 4.35 - 4.25 (m, 2H), 4.23 - 4.05 (m, 4H), 3.05 (s, 3H), 2.95 - 2.75 (m, 1H), 2.68 - 2.55 (m, 1H).

Example 121: LCMS (M+H)$^+$: 675. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.01 - 8.55 (m, 1H), 8.26 (s, 1H), 8.15 – 7.95 (m, 1H), 7.75 – 7.65 (m, 2H), 7.26 – 7.2 (m, 3H), 6.95 – 6.90 (m, 2H), 6.85 – 6.75 (m, 1H), 6.65 - 6.60 (m, 1H), 5.63 - 5.44 (m, 1H), 5.43 - 5.29 (m, 1H), 4.88 - 4.56 (m, 4H), 4.53 - 4.30 (m, 4H), 4.22 (br d, J = 6.8 Hz, 2H), 4.18 - 3.89 (m, 4H), 2.88 (s, 3H), 2.80 - 2.71 (m, 1H), 2.03 - 1.94 (m, 2H).

Example 122 & 123

(8*S*,11*S*)-10-[1-[4-fluoro-2-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-[2-fluoro-4-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





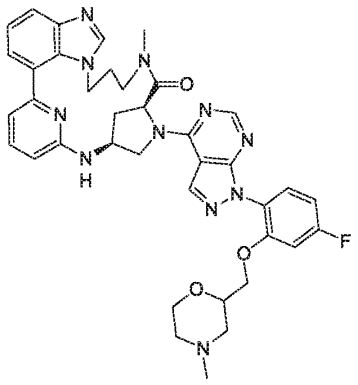
Example 122 & 123 were prepared in analogy to the preparation of **Example 115 & 116** by using oxetan-3-ol instead of 2-morpholinoethanol.

Example 122: LCMS(M+H)$^+$: 661. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 - 8.3 (m, 1H), 8.34 - 8.28 (m, 1H), 8.27 - 8.16 (m, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.68 (br d, J = 7.3 Hz, 1H), 7.52 - 7.45 (m, 1H), 7.29 - 7.20 (m, 2H), 7.00 (dt, J = 2.3, 8.3 Hz, 1H), 6.96 - 6.88 (m, 2H), 6.76 - 6.65 (m, 1H), 5.62 - 5.49 (m, 1H), 5.45 (br d, J = 8.7 Hz, 1H), 5.36 (td, J = 5.4, 11.1 Hz, 1H), 4.99 - 4.79 (m, 2H), 4.72 - 4.55 (m, 1H), 4.53 - 4.44 (m, 1H), 4.36 - 4.26 (m, 2H), 4.26 - 4.18 (m, 1H), 4.12 - 3.91 (m, 2H), 3.32 - 3.23 (m, 2H), 2.94 (s, 3H), 2.90 - 2.74 (m, 1H), 2.71 - 2.57 (m, 1H), 2.41 - 2.30 (m, 1H).

Example 123: LCMS(M+H)$^+$: 661. ^{1}H NMR (400 MHz, DMSO--d_6) δ = 8.55 - 8.41 (m, 1H), 8.35 - 8.27 (m, 1H), 8.27 - 8.20 (m, 1H), 7.80 - 7.73 (m, 1H), 7.68 (br d, J = 7.5 Hz, 1H), 7.59 - 7.50 (m, 1H), 7.30 - 7.20 (m, 2H), 7.03 - 6.91 (m, 2H), 6.85 (br d, J = 8.6 Hz, 1H), 6.76 - 6.64 (m, 1H), 5.59 - 5.49 (m, 1H), 5.47 - 5.36 (m, 2H), 4.97 (br t, J = 6.7 Hz, 2H), 4.72 - 4.63 (m, 1H), 4.59 (dd, J = 5.2, 6.9 Hz, 2H), 4.53 - 4.43 (m, 1H), 4.19 (br d, J = 11.5 Hz, 1H), 4.05 - 3.93 (m, 2H), 3.32 - 3.26 (m, 2H), 3.02 (s, 3H), 2.87 - 2.74 (m, 1H), 2.70 - 2.61 (m, 1H), 2.41 - 2.30 (m, 1H).

Example 124

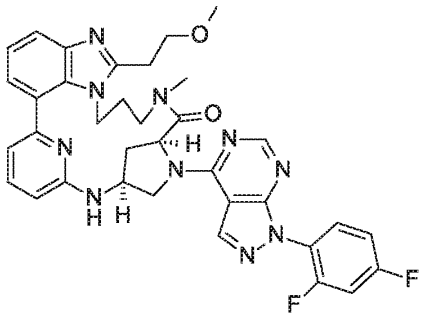
(8*S*,11*S*)-10-[1-[4-fluoro-2-[(4-methylmorpholin-2-yl)methoxy]phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example 124 were prepared in analogy to the preparation of **Example 115 & 116** by using (4-methylmorpholin-2-yl)methanol instead of 2-morpholinoethanol. LCMS(M+H)$^+$: 718. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.58 - 8.48 (m, 1H), 8.38 - 8.13 (m, 2H), 7.80 - 7.72 (m, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.56 - 7.40 (m, 1H), 7.30 - 7.10 (m, 3H), 7.01 - 6.89 (m, 2H), 6.76 - 6.64 (m, 1H), 5.61 - 5.48 (m, 1H), 5.44 (br dd, J = 5.4, 8.3 Hz, 1H), 4.98 - 4.76 (m, 1H), 4.74 - 4.61 (m, 1H), 4.55 - 4.41 (m, 1H), 4.21 (br dd, J = 6.2, 10.9 Hz, 1H), 4.12 - 3.86 (m, 4H), 3.85 - 3.79 (m, 1H), 3.73 - 3.63 (m, 1H), 3.60 - 3.53 (m, 1H), 2.95 (s, 3H), 2.90 - 2.75 (m, 2H), 2.69 - 2.56 (m, 2H), 2.43 - 2.30 (m, 2H), 2.21 (s, 1H), 2.09 - 1.99 (m, 3H), 1.93 - 1.81 (m, 1H).

Example 126

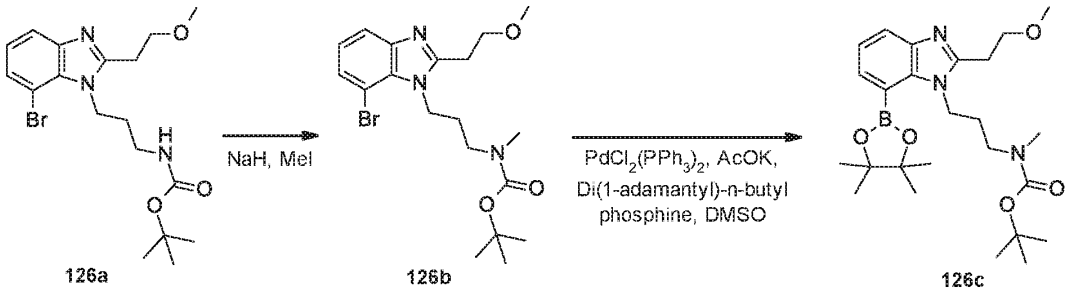
(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-methoxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of **Example 12** by using **126c** instead of **Intermediate A11** in step one. LCMS (M+H$^+$) 665. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.22 (s, 1H), 7.82 - 7.75 (m, 1H), 7.70 - 7.59 (m, 2H), 7.32 - 7.23 (m, 3H), 7.22 - 7.15 (m, 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.49 (d, J = 8.7 Hz, 1H), 4.75 - 4.72 (m, 1H), 4.59 - 4.54 (m, 2H), 4.32 - 4.23 (m, 1H), 4.08 - 3.94 (m, 2H),

3.92 - 3.81 (m, 2H), 3.34 - 3.32 (m, 3H), 3.19 (t, *J* = 6.3 Hz, 2H), 3.04 (s, 3H), 2.98 - 2.83 (m, 1H), 2.75 - 2.68 (m, 1H), 2.62 - 2.49 (m, 1H), 2.23 - 1.99 (m, 1H), 1.38 - 1.23 (m, 1H).

The compound **126c** was prepared according to the following scheme:

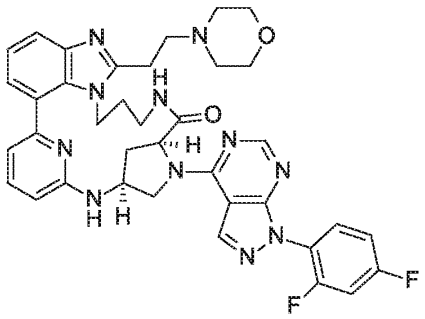


126a 126b 126c

The compound **126c** was prepared in analogy to the preparation of **intermediate A18** by using 3-methoxypropanoic acid instead of 3-morpholinopropanoic acid in step one. LCMS ($M+H^+$) 474.

Example 127

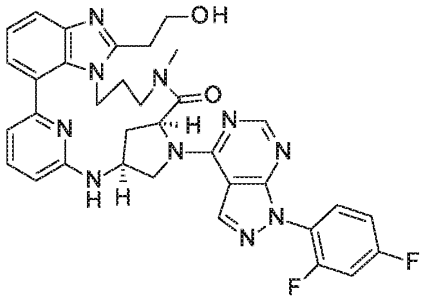
(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



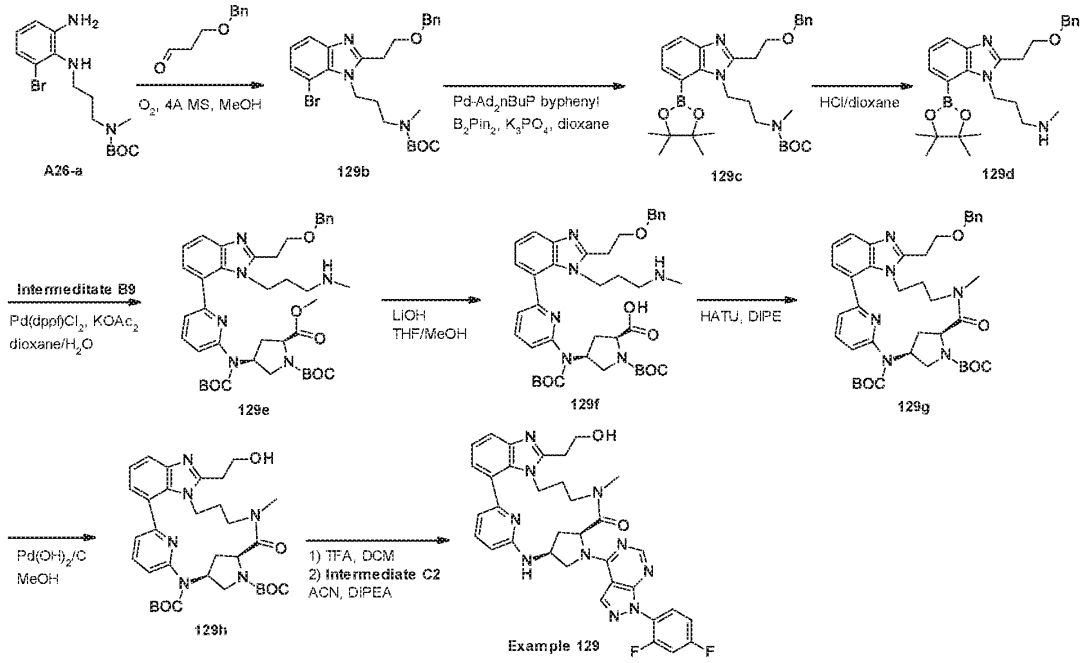
The title compound was prepared in analogy to the preparation of **Example 12** by using **Intermediate A18** instead of **Intermediate A11** in step one. LCMS ($M+H^+$) 706. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.41 - 8.25 (m, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.32 - 7.24 (m, 3H), 7.23 - 7.17 (m, 1H), 6.90 (br d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.17 - 5.07 (m, 1H), 5.03 - 4.92 (m, 1H), 4.67 - 4.52 (m, 3H), 4.39 - 4.30 (m, 1H), 4.27 - 4.15 (m, 1H), 4.14 - 4.03 (m, 1H), 3.70 (br t, *J* = 4.2 Hz, 4H), 3.17 - 3.09 (m, 2H), 2.99 - 2.87 (m, 3H), 2.67 - 2.59 (m, 4H), 2.58 - 2.37 (m, 1H), 1.87 - 1.63 (m, 1H), 1.45 - 1.25 (m, 1H).

Example 129

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-(2-hydroxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-[2-(2-benzyloxyethyl)-7-bromo-benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 129b)

To a solution of *tert*-butyl *N*-[3-(2-amino-6-bromo-anilino)propyl]-*N*-methyl-carbamate (compound **A26-a**, 19 g, 53.03 mmol) in methanol (558.24 mL) was added 3-benzyloxypropanal (9578.75 mg, 58.34 mmol) and 4A MS (38 g). After being stirred at 70 °C for 48 hrs, the mixture was filtered, the filtrate was concentrated and the residue was purified by flash-HPLC to give compound **129b** (12.9 g), LCMS ($M+H^+$): 502.

Step 2: preparation of *tert*-butyl *N*-[3-[2-(2-benzyloxyethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 129c)

To a solution of compound **129b** (12.7 g, 25.28 mmol) in 1,4-dioxane (127 mL) was added bis(pinacolato)diboron (12837.5 mg, 50.55 mmol), catacxium a-Pd-G2 (1.35 mg, 2.02 mmol) and K_3PO_4 (4.19 mL, 50.55 mmol) under Ar. The mixture was stirred at 110 °C for 16 hrs, then the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel to give compound **129c** (6.7 g), LCMS ($M+H^+$): 550.

Step 3: preparation of 3-[2-(2-benzyloxyethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-*N*-methyl-propan-1-amine (compound 129d)

To a solution of compound **129c** (3.7 g, 6.73 mmol) in DCM (20 mL) was added HCl/dioxane (20.0 mL, 4 M) at 0°C. The reaction was stirred at 25°C for 2 hrs, then the mixture was concentrated to give compound **129d** (3.7 g), LCMS ($M+H^+$): 450.

Step 4: preparation of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[[6-[2-(2-benzyloxyethyl)-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]-*tert*-butoxycarbonyl-amino]pyrrolidine-1,2-dicarboxylate (compound 129e)

To a solution of compound **129d** (3.5 g, 7.2 mmol), intermediate **B9** (3.6 g, 7.2 mmol), $Pd(dppf)Cl_2$ (510 mg, 0.7 mmol) in 1,4-dioxane (35 mL) and water (4 mL) was added Na_2CO_3 (2.2 g, 21 mmol) in glovebox under Ar. The reaction solution was stirred at 85 °C for 12 hrs. The mixture was poured into 100 mL water, and then it was extracted with EtOAc. The organic layer was dried and concentrated to give crude compound **129e** (7.6 g), which was used in next step directly, LCMS ($M+H^+$): 743.

Step 5: preparation of (2*S*,4*S*)-4-[[6-[2-(2-benzyloxyethyl)-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]-*tert*-butoxycarbonyl-amino]-1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylic acid (compound 129f)

To a solution of compound **129e** (7.45 g, 10.03 mmol) in the mixture solvent of methanol (16 mL) and THF (50 mL) was added a solution of Lithium hydroxide (30.08 mL, 1 M) in water (30.81 mL) at 0 °C. The solution was stirred at 15 °C for 18 hrs, then the reaction mixture was acidified with 5% citric acid to pH=4~5, the mixture solution was directly purified by prep-HPLC to give compound **129f** (1.5 g), LCMS ($M+H^+$): 729.

Step 6: preparation of *ditert*-butyl (8*S*,11*S*)-18-(2-benzyloxyethyl)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound 129g)

To a solution of DIPEA (0.6 mL, 3.43 mmol) and HATU (782.5 mg, 2.06 mmol) in DMF (68.6 mL) was added a solution of compound **129f** (1.0 g, 1.37 mmol) in THF (200 mL) dropwise in 1 h at 0 °C. The mixture was concentrated to give an oil and then it was purified by Flash-HPLC to give the compound **129g** (800 mg), LCMS ($M+H^+$): 711.

Step 7: preparation of *ditert*-butyl (8*S*,11*S*)-18-(2-hydroxyethyl)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound 129h)

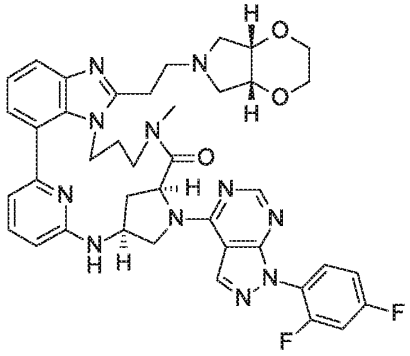
To a solution of compound **129g** (900.0 mg, 1.27 mmol) in methanol (50 mL) was added $Pd(OH)_2/C$ (900.0 mg, 6.96 mmol). The reaction was stirred at 20°C for 72 hrs under H_2. The mixture was filtered and the filtrate was concentrated to give compound **129h** (605 mg), LCMS ($M+H^+$): 621.

Step 8: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-(2-hydroxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 129)

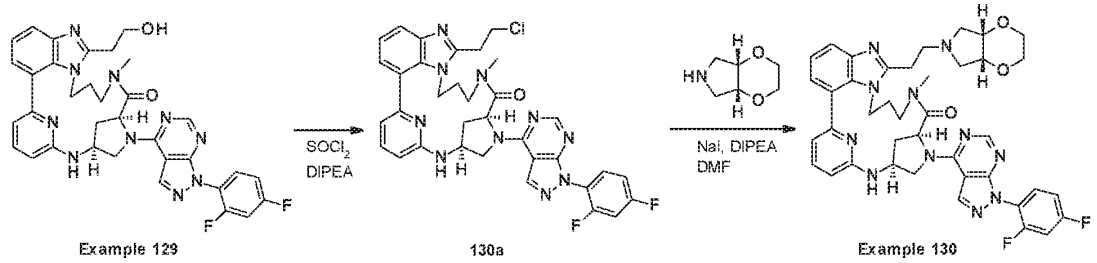
A mixture of compound **129h** (500 mg, 0.805 mmol) in DCM (4 mL) and TFA (2 mL) was stirred at r.t. for 1 hr. The mixture was concentrated, the residue was dissolved in acetonitrile (8 mL) and then DIPEA (832.86 mg, 1.13 mL, 6.44 mmol), intermediate **C2** (236.25 mg, 0.886 mmol) was added. The mixture was heated to 85 °C for 2 hrs and then concentrated. The residue was purified via prep-HPLC to give compound **129** (64 mg). LCMS ($M+H^+$) 651. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.61 (s, 1H), 8.26 - 8.11 (m, 1H), 7.81 - 7.68 (m, 2H), 7.66 - 7.55 (m, 2H), 7.38 - 7.28 (m, 1H), 7.28 - 7.13 (m, 2H), 6.92 - 6.84 (m, 1H), 6.78 - 6.65 (m, 1H), 5.55 - 5.41 (m, 2H), 5.21 - 4.97 (m, 1H), 4.95 - 4.77 (m, 1H), 4.73 - 4.64 (m, 1H), 4.56 - 4.45 (m, 1H), 4.26 - 4.07 (m, 1H), 3.97 - 3.80 (m, 4H), 3.08 - 2.99 (m, 3H), 2.97 - 2.90 (m, 2H), 2.89 - 2.69 (m, 1H), 2.63 - 2.53 (m, 1H), 2.48 - 2.40 (m, 1H), 2.10 - 1.80 (m, 1H), 1.22 - 1.07 (m, 1H).

Example 130

(8*S*,11*S*)-18-[2-[(4aR,7aS)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]ethyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*)-18-(2-chloroethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 130a)

To a tube was added Example **129** (200 mg, 0.307 mmol), DIPEA (79.45 mg, 107.37 μL, 0.615 mmol) and DCM (10 mL), the white suspension was stirred at r.t. and $SOCl_2$ (731.29 mg, 448.64 μL, 6.15 mmol) was added. After being stirred at r.t. for 5 hrs, the mixture was quenched with water and then it was adjusted pH to 7, the mixture was extracted with 10 mL DCM twice, the organic layer was dried over Na_2SO_4 and concentrated to give compound **130a**. LCMS ($M+H^+$): 669.

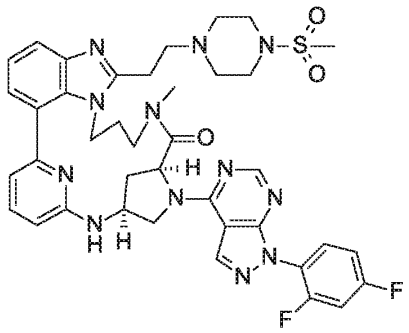
Step 2: preparation of (8*S*,11*S*)-18-[2-[(4aR,7aS)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]ethyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 130)

To a microwave tube was added compound **130a** (50 mg, 0.044 mmol), sodium iodide (26.19 mg, 0.175 mmol), (4a*S*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole hydrochloride (14.47 mg, 0.087 mmol), DIPEA (28.22 mg, 38.14 μL, 0.218 mmol) and DMF (0.860 mL), the mixture was stirred at 70 °C for 16 hrs. The mixture was diluted with 10 mL

DCM and washed with 10 mL sat. NH_4Cl for 3 times. The organic layer was concentrated, the residue was purified via prep-HPLC to give Example **130** (12.4 mg). LCMS ($M+H^+$) 762. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.22 (s, 1H), 7.82 - 7.75 (m, 1H), 7.70 - 7.59 (m, 2H), 7.32 - 7.16 (m, 4H), 6.95 - 6.87 (m, 1H), 6.78 - 6.69 (m, 1H), 5.53 - 5.41 (m, 1H), 5.16 - 5.01 (m, 1H), 4.75 - 4.69 (m, 1H), 4.67 - 4.49 (m, 3H), 4.36 - 4.17 (m, 2H), 4.17 - 4.09 (m, 2H), 4.09 - 4.02 (m, 1H), 4.01 - 3.89 (m, 1H), 3.83 - 3.71 (m, 2H), 3.58 - 3.47 (m, 2H), 3.18 - 3.01 (m, 6H), 3.00 - 2.85 (m, 3H), 2.75 - 2.64 (m, 1H), 2.63 - 2.50 (m, 1H), 2.25 - 1.91 (m, 1H), 1.38 - 1.23 (m, 1H).

Example 131

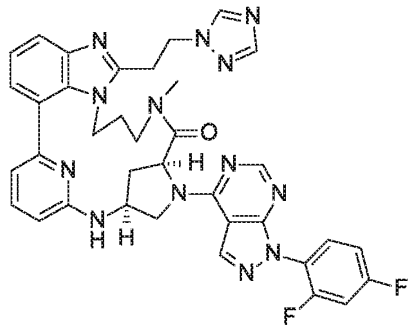
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(4-methylsulfonylpiperazin-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of **Example 130** by using 1-mesylpiperazine instead of (4a*S*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole in step two. LCMS ($M+H^+$) 797. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.58 (s, 1H), 8.25 (s, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.84 - 7.78 (m, 1H), 7.71 - 7.59 (m, 1H), 7.55 - 7.46 (m, 2H), 7.34 - 7.26 (m, 1H), 7.25 - 7.17 (m, 1H), 7.06 - 6.99 (m, 1H), 6.90 - 6.83 (m, 1H), 5.53 - 5.45 (m, 1H), 5.43 - 5.31 (m, 1H), 4.79 - 4.75 (m, 1H), 4.64 - 4.55 (m, 1H), 4.40 - 4.26 (m, 1H), 4.14 - 4.01 (m, 2H), 3.62 - 3.44 (m, 8H), 3.39 - 3.32 (m, 3H), 3.05 (s, 3H), 3.04 - 2.91 (m, 2H), 2.91 - 2.86 (m, 3H), 2.80 - 2.71 (m, 1H), 2.66 - 2.55 (m, 1H), 2.14 - 2.03 (m, 1H), 1.43 - 1.28 (m, 1H).

Example 132

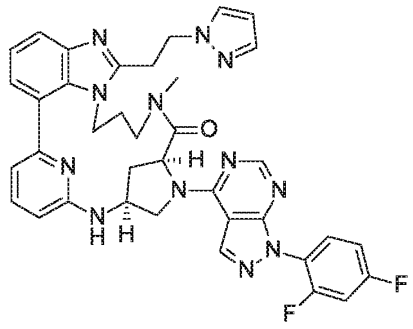
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(1,2,4-triazol-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of **Example 130** by using 1,2,4-triazole instead of (4a*S*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole in step two. LCMS ($M+H^+$): 702.

Example 133

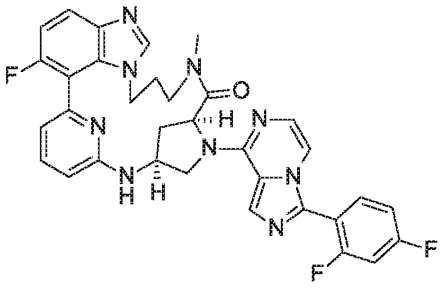
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(2-pyrazol-1-ylethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



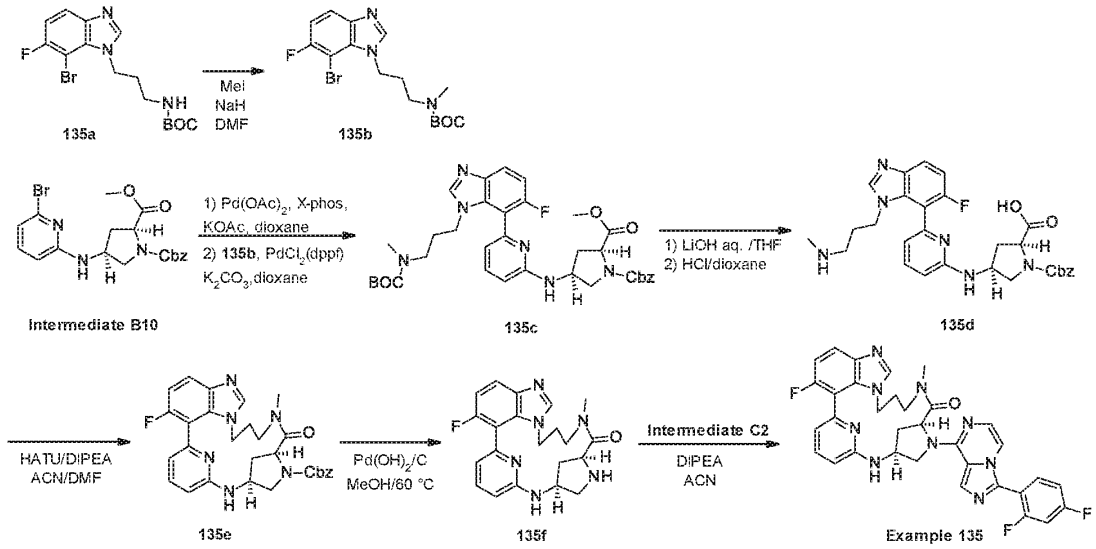
The title compound was prepared in analogy to the preparation of **Example 130** by using 1H-pyrazole instead of (4a*S*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole in step two. LCMS ($M+H^+$) 701.

Example 135

(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-23-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-6-fluoro-benzimidazol-1-yl)propyl]-N-methyl-carbamate (compound 135b)

To a flask was added *tert*-butyl *N*-[3-(7-bromo-6-fluoro-benzimidazol-1-yl)propyl]carbamate (compound **135a**, 520 mg, 1.4 mmol, the synthesis refers to the **intermediate 15A-c** by using 2-bromo-1,3-difluoro-4-nitro-benzene instead of 1-bromo-2-fluoro-3-nitro-benzene in step 1), MeI (594.86 mg, 262.05 μL, 4.19 mmol) and DMF (6 mL). The solution was stirred at r.t. and then NaH (223.5 mg, 5.59 mmol) was added in one portion. After being stirred at rt for 1 hour, the mixture was poured into 50 mL water and then extracted with 15 mL EA for three times. The organic layer was dried and concentrated, the crude product was purified by silica gel to give compound **135b** (574 mg), LCMS ($M+H^+$): 386.

Step 2: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-5-fluoro-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 135c)

To a microwave tube was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (761.82 mg, 3 mmol), *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate (compound **B10**, 651.4 mg, 1.5 mmol), potassium acetate (294.4 mg, 3 mmol) and 1,4-dioxane (7 mL). The suspension was bubbled with N_2 for 5 mins and then dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-3-yl)phosphane (143.0 mg, 0.300 mmol) & $Pd(OAc)_2$ (33.7 mg, 0.150 mmol) were added. After being heated 85 °C for 16 hrs, to the mixture was added compound **135b** (270.0 mg, 0.7 mmol), K_2CO_3 (193.5 mg, 1.4 mmol), 1,4-dioxane (2 mL) and water (1 mL), the suspension was bubbled with N_2 for 5 mins and then $PdCl_2(dppf)$-CH_2Cl_2 adduct (51.2 mg, 0.070 mmol) was added. The mixture was stirred at 100 °C for 4 hrs, and then diluted with water, extracted with EA. The organic layer was dried and concentrated, the crude product was purified by silica gel to give compound **135c** (320 mg), LCMS ($M+H^+$): 661.

Step 3: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[5-fluoro-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 135d)

A mixture of compound **135c** (320 mg, 0.315 mmol) and LiOH (1.39 mL, 2 N) was stirred at r.t. for 2 hrs. The mixture was diluted with water and adjusted pH to 4, then it was extracted with DCM twice. The organic layer was dried and concentrated, the residue was dissolved in DCM (2 mL) and TFA (2 mL). After being stirred at r.t. for 1 hr, the mixture was concentrated and the residue was purified via prep-HPLC to give compound **135d** (110 mg), LCMS ($M+H^+$): 547.

Step 4: preparation of benzyl (8*S*,11*S*)-23-fluoro-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 135e)

To a solution of HATU (126.6 mg, 0.333 mmol), DIEA (129.1 mg, 174 μL, 0.999 mmol) in DMF (2 mL) and acetonitrile (30 mL) was added another suspension of compound **135d** (110 mg, 0.167 mmol) in DMF (2 mL) and acetonitrile (30 mL) dropwise in 1 hr. Then the mixture was concentrated, the residue was purified by silica gel to give compound **135e** (120 mg), LCMS ($M+H^+$): 529.

Step 5: preparation of (8*S*,11*S*)-23-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 135f)

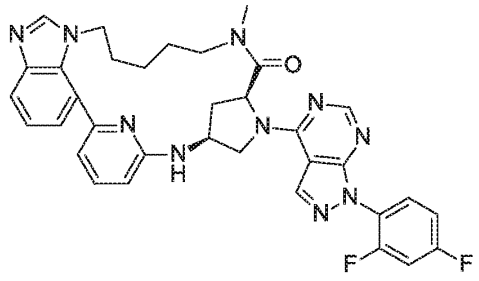
To a 100 mL flask was added compound **135e** (80 mg, 0.151 mmol), palladium hydroxide (20% on carbon with 50% H_2O) (16 mg, 0.023 mmol) and MeOH (20 mL), the suspension was purged with H_2 for 3 times. The mixture was heated to 65 °C and stirred for about 2 hrs. The mixture was filtered, the filtrate was concentrated to compound **135f** (91 mg), LCMS ($M+H^+$): 395.

Step 6: preparation of (8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-23-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 135)

To a microwave tube was added compound **135f** (19.72 mg, 0.050 mmol), intermediate **C3** (17.27 mg, 0.065 mmol), cesium fluoride (15.19 mg, 0.100 mmol), DIPEA (12.92 mg, 17.47 µL, 0.100 mmol) and DMSO (1 mL). The brown suspension was heated to 90 °C and stirred for about 16 hrs. The mixture was concentrated, the residue was purified via prep-HPLC to give Example **135** (8.7 mg), LCMS ($M+H^+$): 624. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.30 (s, 1H), 8.24 - 7.91 (m, 1H), 7.78 - 7.69 (m, 2H), 7.67 (dd, J = 4.8, 8.9 Hz, 1H), 7.53 (ddd, J = 2.4, 9.4, 10.5 Hz, 1H), 7.32 (dt, J = 2.4, 8.3 Hz, 1H), 7.24 (br s, 1H), 7.18 - 7.03 (m, 2H), 6.81 (dd, J = 1.4, 7.3 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 5.63 - 5.24 (m, 2H), 4.69 - 4.44 (m, 1H), 4.42 - 4.07 (m, 2H), 4.04 - 3.92 (m, 1H), 3.70 - 3.55 (m, 1H), 3.31 - 3.23 (m, 2H), 3.01 (br s, 3H), 2.84 - 2.73 (m, 1H), 2.45 - 2.23 (m, 2H), 1.45 - 1.31 (m, 1H).

Example 139

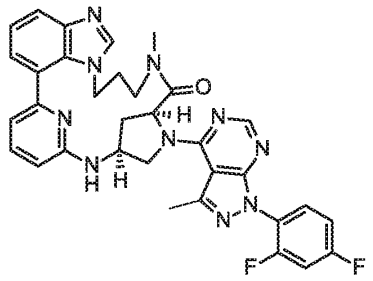
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one



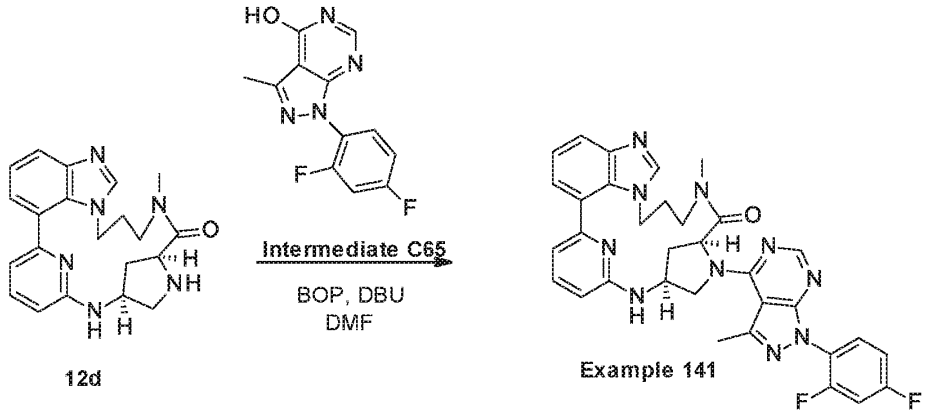
The title compound was prepared in analogy to the preparation of Example **12** by using Intermediate **A27** instead of Intermediate **A12**. Example **139** was obtained. LCMS ($M+H^+$): 635. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 - 8.16 (m, 3H), 7.78 - 7.57 (m, 3H), 7.36 - 7.13 (m, 4H), 6.88 (d, J = 7.3 Hz, 1H), 6.77 - 6.65 (m, 1H), 5.60 - 5.31 (m, 1H), 4.73 - 4.46 (m, 3H), 4.38 - 3.88 (m, 5H), 3.27 - 3.14 (m, 3H), 2.81 - 2.65 (m, 2H), 1.88 - 1.44 (m, 5H).

Example 141

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-3-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

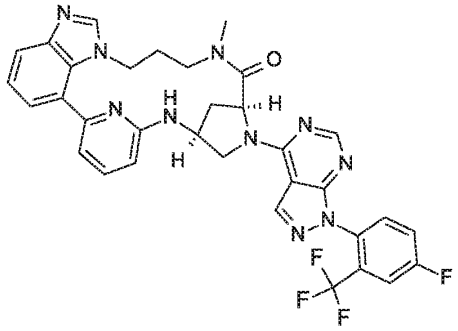


A mixture of Intermediate **C65** (26 mg, 0.1 mmol), benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (53 mg, 0.12 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (23 mg, 0.15 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) was stirred at room temperature for 15 mins, then compound **12d** (38 mg, 0.1 mmol) was added and stirred at room temperature for 16 hours. The reaction mixture was directly purified by prep-HPLC to afford Example **141** (19 mg). LCMS (M+H$^+$): 621. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.44 - 8.09 (m, 2H), 7.87 - 7.68 (m, 2H), 7.65 - 7.56 (m, 1H), 7.40 - 7.30 (m, 2H), 7.29 - 7.22 (m, 1H), 7.17 (br t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.71 (br d, *J* = 8.4 Hz, 1H), 5.62 (br d, *J* = 6.1 Hz, 1H), 5.00 - 4.75 (m, 1H), 4.72 - 4.49 (m, 2H), 4.35 - 4.06 (m, 3H), 3.05 (s, 3H), 2.94 - 2.71 (m, 4H), 2.67 - 2.44 (m, 2H), 2.23 - 2.06 (m, 1H), 1.53 (br s, 1H).

Example 146

(8*S*,11*S*)-10-[1-[4-fluoro-2-(trifluoromethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-

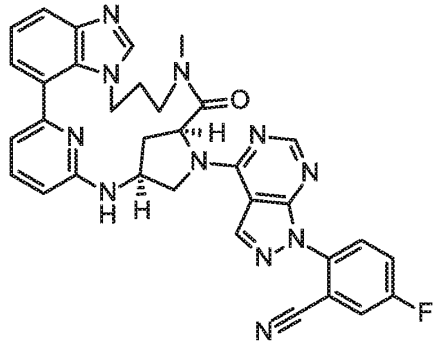
methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



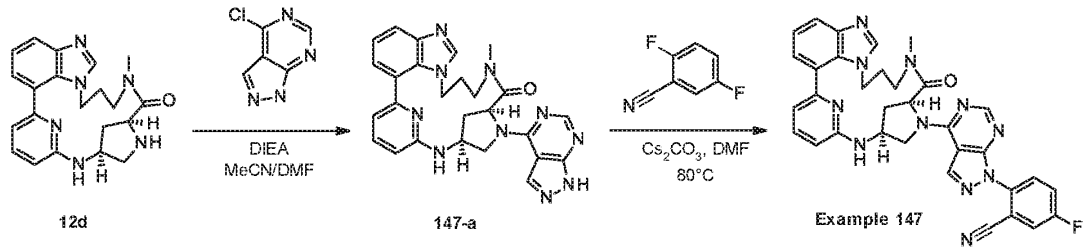
Example **146** was prepared in analogy to the preparation of Example **12** by using intermediate **C69** instead of intermediate **C2**., LCMS (M+H$^+$): 657. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.58 (s, 1H), 8.34 - 8.17 (m, 2H), 8.01 - 7.91 (m, 1H), 7.82 - 7.72 (m, 3H), 7.71 - 7.64 (m, 1H), 7.30 - 7.18 (m, 2H), 6.98 - 6.87 (m, 1H), 6.76 - 6.63 (m, 1H), 5.65 - 5.34 (m, 2H), 5.00 - 4.77 (m, 1H), 4.74 - 4.57 (m, 1H), 4.54 - 4.41 (m, 1H), 4.26 - 4.15 (m, 1H), 4.09 - 3.93 (m, 2H), 3.05 - 2.88 (m, 3H), 2.86 - 2.74 (m, 1H), 2.39 - 2.30 (m, 1H), 2.07 - 1.90 (m, 1H), 1.89 - 1.18 (m, 2H).

Example 147

5-fluoro-2-[4-[(8*S*,11*S*)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile



The title compound was prepared according to the following scheme:



12d 147-a Example 147

Step 1: preparation of (8*S*,11*S*)-13-methyl-10-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 147-a)

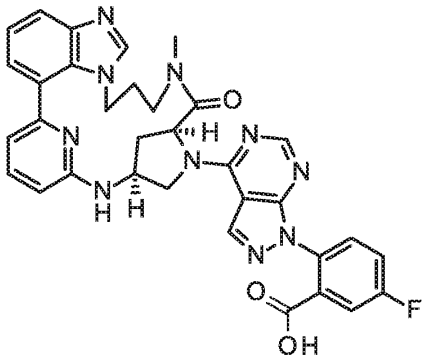
A mixture of (8*S*,11*S*)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound **12d**, 92 mg, 0.25 mmol), 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (38 mg, 0.25 mmol,) and *N*,*N*-diisopropylethylamine (95 mg, 0.73 mmol) in anhydrous acetonitrile and *N*,*N*-dimethylformamide (1 mL) was stirred at room temperature for 1 h. The reaction mixture was partitioned between water and EtOAc, the organic layer was separated and the aqueous layer was further extracted with EtOAc for three times. The organic layer was washed with brine, dried and concentrated. The residue was purified by precipitation from EtOAc/PE, the solid was collected to afford compound **147-a** (65 mg). LCMS (M+H)$^+$: 495.

Step 2: preparation of 5-fluoro-2-[4-[(8*S*,11*S*)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile (Example 147)

A mixture of (8*S*,11*S*)-13-methyl-10-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound **147-a**, 65 mg, 0.13 mmol), 2,5-difluorobenzonitrile (55 mg, 0.39 mmol) and cesium carbonate (86 mg, 0.26 mmol) in *N*,*N*-dimethylformamide (1 mL) was heated at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was directly purified by prep-HPLC to afford Example **147** (10 mg). LCMS (M+H)$^+$: 614. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.61 - 8.20 (m, 3H), 7.92 - 7.77 (m, 3H), 7.75 - 7.64 (m, 2H), 7.39 - 7.26 (m, 2H), 7.04 - 6.94 (m, 1H), 6.77 - 6.69 (m, 1H), 5.55 - 5.42 (m, 1H), 4.62 - 4.53 (m, 2H), 4.34 - 4.08 (m, 3H), 3.15 - 3.03 (m, 3H), 2.89 (td, *J* = 6.8, 13.7 Hz, 1H), 2.69 - 2.50 (m, 2H), 2.16 - 1.97 (m, 2H), 1.65 - 1.54 (m, 1H).

Example 148

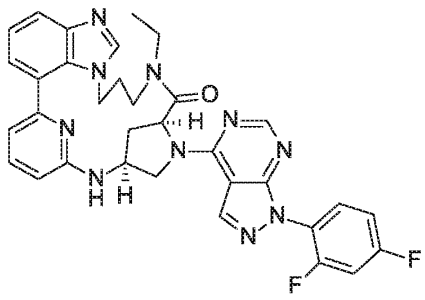
5-fluoro-2-[4-[(8*S*,11*S*)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzoic acid



The title compound was prepared in analogy to the preparation of Example **12** by using Intermediate **C66** instead of Intermediate **C2**. Example **148** was obtained. LCMS (M+H$^+$): 633. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.52 - 8.14 (m, 3H), 7.86 - 7.73 (m, 3H), 7.68 - 7.61 (m, 1H), 7.53 (dt, J = 2.6, 8.2 Hz, 1H), 7.44 - 7.36 (m, 2H), 7.01 (d, J = 7.5 Hz, 1H), 6.79 - 6.71 (m, 1H), 5.53 - 5.40 (m, 1H), 4.78 - 4.69 (m, 1H), 4.60 - 4.26 (m, 1H), 4.38 - 4.26 (m, 1H), 4.24 - 4.08 (m, 2H), 3.18 - 3.01 (m, 3H), 2.89 (br dd, J = 7.6, 14.0 Hz, 1H), 2.69 - 2.52 (m, 2H), 2.16 - 1.96 (m, 2H), 1.65 - 1.44 (m, 1H).

Example 150

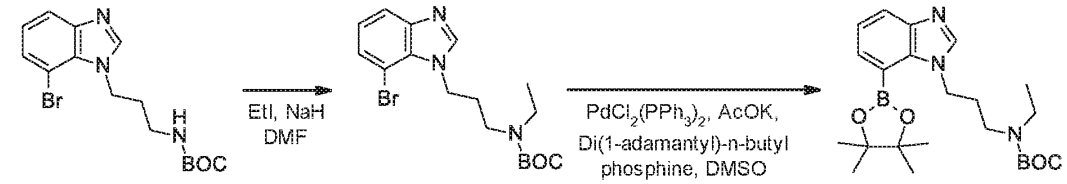
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-ethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **12** by using compound **150b** instead of intermediate **A11**. LCMS (M+H$^+$): 621. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.52 (s, 1H), 8.28 - 8.18 (m, 2H), 7.83 - 7.76 (m, 1H), 7.71 (br d, J = 7.5

Hz, 1H), 7.66 (dt, *J* = 6.0, 8.6 Hz, 1H), 7.41 - 7.24 (m, 4H), 7.19 (br t, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.51 (br d, *J* = 6.2 Hz, 1H), 5.04 - 4.93 (m, 1H), 4.78 - 4.66 (m, 1H), 4.60 - 4.49 (m, 1H), 4.34 - 4.27 (m, 1H), 4.18 - 4.08 (m, 1H), 4.02 - 3.87 (m, 1H), 3.45 - 3.34 (m, 2H), 2.98 - 2.83 (m, 1H), 2.62 - 2.55 (m, 1H), 2.23 - 2.06 (m, 1H), 1.55 - 1.38 (m, 1H), 1.15 - 0.99 (m, 3H).

The compound **150b** was prepared according to the following scheme:



Intermediate A15-c 150a 150b

Step 1: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-*N*-ethyl-carbamate (compound 150a)

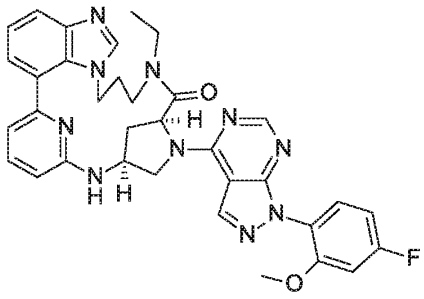
To a flask was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (compound **A15-c**, 4 g, 11.29 mmol), ethyl iodide (4.4 g, 2.28 mL, 28.23 mmol) and DMF (40 mL), the solution was stirred at r.t. and then NaH (903.26 mg, 22.58 mmol) was added in one portion. After being stirred at rt for 1 h, the mixture was poured into water and then extracted with EA for three times. The organic layer was dried and concentrated, the crude product was purified by silica gel to give compound **150a** (3.85 g), LCMS ($M+H^+$): 383.

Step 2: preparation of *tert*-butyl *N*-ethyl-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (compound 150b)

To a seal tube was added *tert*-butyl N-[3-(7-bromobenzimidazol-1-yl)propyl]-N-ethyl-carbamate (compound **150a**, 1.47 g, 3.85 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.96 g, 7.7 mmol), potassium acetate (755.7 mg, 7.7 mmol), DMSO (30 mL). The solution was bubbled with N_2 for 5 mins and then bis(triphenylphosphine)palladium(ii) dichloride (270.23 mg, 0.385 mmol) & Butyldi-1-adamantylphosphine (276.08 mg, 0.770 mmol) were added. The tube was heated to 130 °C and stirred for about 16 hrs. The mixture was diluted with 200 mL water and then it was extracted with 50 mL EA for 3 times. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **150b** (1.42g), LCMS ($M+H^+$): 430.

Example 151

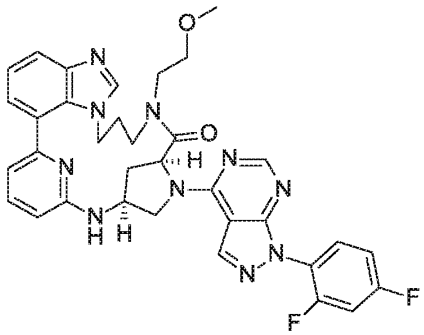
(8*S*,11*S*)-13-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **12** by using compound **150b** instead of intermediate **A11** in step 1 and using intermediate **C11** instead of intermediate **C2** in step 5. LCMS ($M+H^+$) 633. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.46 (s, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 7.82 - 7.77 (m, 1H), 7.73 - 7.68 (m, 1H), 7.46 - 7.41 (m, 1H), 7.39 - 7.34 (m, 1H), 7.34 - 7.29 (m, 1H), 7.05 (dd, *J* = 2.4, 10.7 Hz, 1H), 7.02 - 6.98 (m, 1H), 6.87 (dt, *J* = 2.4, 8.3 Hz, 1H), 6.75 - 6.69 (m, 1H), 5.50 (br d, *J* = 7.3 Hz, 1H), 5.04 - 4.95 (m, 1H), 4.74 - 4.67 (m, 1H), 4.56 - 4.48 (m, 1H), 4.29 (br d, *J* = 11.3 Hz, 1H), 4.18 - 4.09 (m, 1H), 4.00 - 3.89 (m, 1H), 3.75 (s, 3H), 3.44 - 3.33 (m, 2H), 3.03 - 2.89 (m, 1H), 2.63 - 2.50 (m, 2H), 2.20 - 2.08 (m, 1H), 1.53 - 1.41 (m, 1H), 1.11 (br t, *J* = 6.9 Hz, 3H).

Example 153

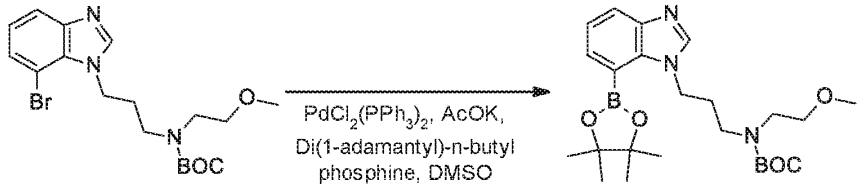
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **12** by using compound **153b** instead of intermediate **A11** in step 1. LCMS ($M+H^+$) 651. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 - 8.50 (m, 1H), 8.36 - 8.31 (m, 1H), 8.29 - 8.19 (m, 1H), 7.85 - 7.78 (m, 1H), 7.72 (br d, *J* = 7.6 Hz, 1H), 7.69 - 7.59 (m, 1H), 7.40 - 7.31 (m, 2H), 7.31 - 7.25 (m, 1H), 7.23 - 7.14 (m, 1H), 7.00 (dd, *J* = 2.4, 7.3 Hz, 1H), 6.77 - 6.68 (m, 1H), 5.62 - 5.42 (m, 1H), 5.15 - 4.95 (m, 1H), 4.74 - 4.67 (m, 1H), 4.58 - 4.50 (m, 1H), 4.36 - 4.26 (m, 1H), 4.25 - 4.10 (m,

1H), 4.04 - 3.80 (m, 1H), 3.76 - 3.57 (m, 1H), 3.55 - 3.38 (m, 2H), 3.38 (s, 1H), 3.18 (s, 2H), 3.17 - 3.01 (m, 1H), 2.99 - 2.78 (m, 1H), 2.78 - 2.46 (m, 1H), 2.32 - 1.95 (m, 1H), 1.60 - 1.34 (m, 1H).

The compound **153b** was prepared according to the following scheme:

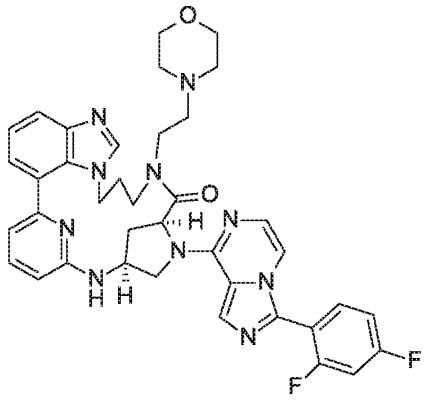


153a 153b

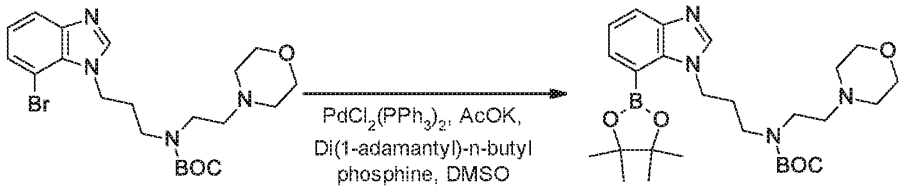
To a tube was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-N-(2-methoxyethyl)carbamate (compound **153a**, 720 mg, 1.75 mmol, the synthesis refer to the preparation of compound **4f** by using 2-methoxyethanamine instead of 2-aminoethan-1-ol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.33 mmol), potassium acetate (343 mg, 3.49 mmol), DMSO (15 mL). The mixture was bubbled with N_2 for 5 mins and then bis(triphenylphosphine)palladium(ii) dichloride (123 mg, 175 μmol) and butyldi-1-adamantylphosphine (125 mg, 349 μmol) were added. After being heated to 130 °C for 5 hrs, the mixture was diluted with water and extracted with EA for 3 times. The organic layer was dried over and concentrated, the residue was purified by silica gel to give compound **153b** (540 mg), LCMS ($M+H^+$): 460.

Example 155

(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **12** by using compound **155b** instead of intermediate **A11** in step 1 and intermediate **C3** instead of intermediate **C2** in step 5. LCMS ($M+H^+$) 705. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.23 (s, 1H), 8.12 - 7.91 (m, 1H), 7.83 - 7.75 (m, 1H), 7.73 - 7.64 (m, 2H), 7.38 - 7.34 (m, 1H), 7.34 - 7.28 (m, 1H), 7.28 - 7.17 (m, 3H), 7.09 (br d, J = 4.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 5.47 (br s, 1H), 5.12 - 4.94 (m, 1H), 4.68 - 4.50 (m, 2H), 4.44 - 4.27 (m, 1H), 4.23 - 4.12 (m, 1H), 4.07 - 3.89 (m, 1H), 3.73 - 3.60 (m, 4H), 3.54 - 3.44 (m, 2H), 3.00 (br dd, J = 6.8, 13.7 Hz, 1H), 2.70 - 2.42 (m, 7H), 2.39 - 2.24 (m, 1H), 2.16 - 2.00 (m, 1H), 1.53 - 1.39 (m, 1H).

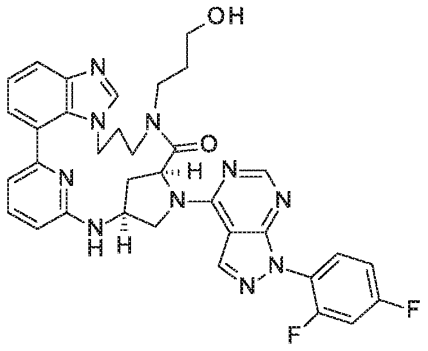


155a **155b**

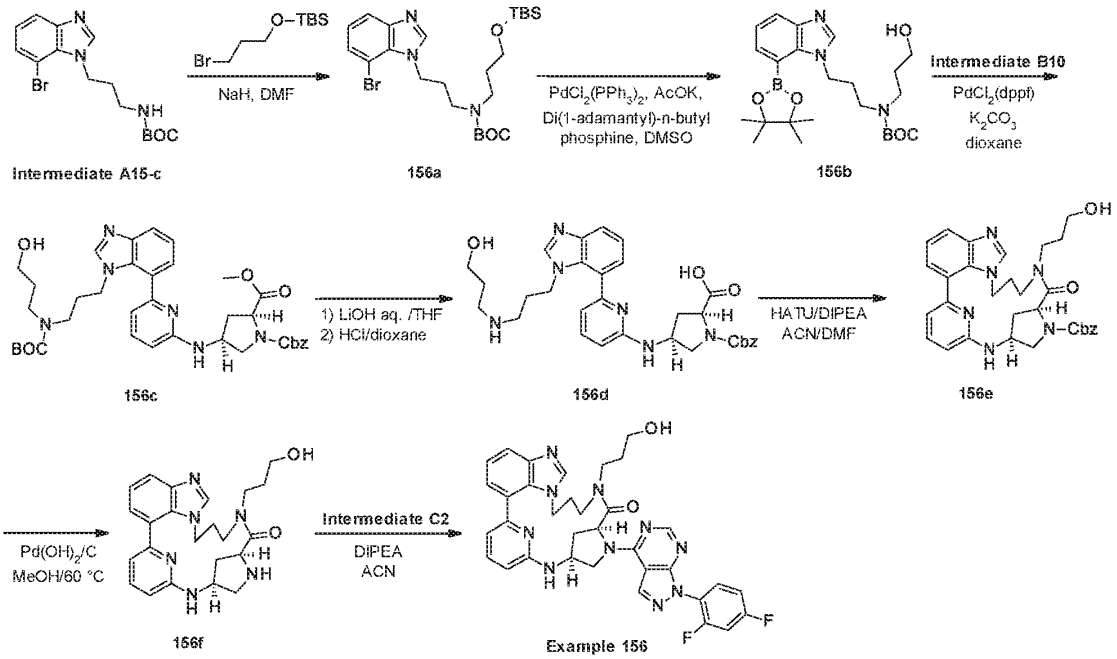
Compound **155b** was prepared in analogy to the preparation of compound **153b** by using compound **155a** (the synthesis refer to the preparation of compound **4f** by using 2-morpholinoethanamine instead of 2-aminoethan-1-ol) instead of compound **153a** according to the following scheme. LCMS ($M+H^+$): 515.

Example 156

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-*N*-[3-[*tert*-butyl(dimethyl)silyl]oxypropyl]carbamate (compound 156a)

To a flask was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (**A15-c**, 2.3 g, 6.49 mmol), (3-bromopropoxy)(tert-butyl)dimethylsilane (3.29 g, 13 mmol) and DMF (15 mL), the solution was stirred at r.t. and then NaH (623 mg, 26 mmol) was added in one portion. The mixture was poured into 50 mL water and then extracted with 15 mL EA for three times. The organic layer was dried over Na_2SO_4 and concentrated to give compound **156a** (2.7 g). LCMS ($M+H^+$): 484.

Step 2: preparation of *tert*-butyl *N*-(3-hydroxypropyl)-N-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (compound 156b)

To a tube was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-*N*-[3-[*tert*-butyl(dimethyl)silyl]oxypropyl]carbamate (compound **156a**, 1 g, 1.9 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (964.49 mg, 3.8 mmol), potassium acetate (372.75 mg, 3.8 mmol), DMSO (15 mL). The mixture was bubbled with N_2 for 5 mins and then bis(triphenylphosphine)palladium(ii) dichloride (133.29 mg, 0.190 mmol) & Butyldi-1-adamantylphosphine (136.18 mg, 0.380 mmol) were added. After being heated to 130 °C for 4 hrs, the mixture was diluted with water and then it was extracted with EA. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **156b** (364 mg) and TBS-compound **156b** (470 mg). LCMS ($M+H^+$): 460 and LCMS ($M+H^+$): 574.

Step 3: preparation of O1-benzyl O2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(3-hydroxypropyl)amino]propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 156c)

To a flask was added K_2CO_3 (782.19 mg, 5.66 mmol), compound **156b** (1.3 g, 2.83 mmol), Intermediate **B10** (1.23 g, 2.83 mmol), 1,4-dioxane (10 mL) and water (0.200 mL), the suspension was bubbled with N_2 for 5 mins and $PdCl_2(dppf)$-CH_2Cl_2 adduct (207.06 mg, 0.283 mmol) was added. After being heated to 90 °C for 3 hrs, then the mixture was diluted water and extracted with EA. The organic layer was dried concentrated the residue was purified by silica gel to give compound **156c** (1 g). LCMS ($M+H^+$): 687.

Step 4: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[3-[3-(3-hydroxypropylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 156d)

A mixture of compound **156c** (500 mg, 0.728 mmol) and hydroxylithium (3 mL, 2 N) in THF (1.5 mL) and methanol (1.5 mL) was stirred at rt for 2 hrs. The mixture was diluted with 5 mL water and adjusted pH to about 4, then it was extracted with 100 mL DCM twice. The organic layer was dried and concentrated, the residue was dissolved in 1,4-dioxane (1 mL), and then it was treated with 4 N HCl in dioxane) (1 mL). The mixture was stirred at r.t. for 4 hrs and then concentrated to give compound **156d** (500 mg). LCMS ($M+H^+$): 573.

Step 5: preparation of benzyl (8*S*,11*S*)-13-(3-hydroxypropyl)-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 156e)

To a solution of HATU (557.49 mg, 1.47 mmol), DIEA (568.47 mg, 768.2 μL, 4.4 mmol), in DMF (20 mL) and acetonitrile (130 mL) was added another suspension of compound **156d** (500 mg, 0.733 mmol) in DMF (20 mL) and acetonitrile (130 mL) dropwise in 2 hrs. The mixture was concentrated, the residue was purified by silica gel to give compound **156e** (270 mg). LCMS ($M+H^+$): 555.

Step 6: preparation of (8*S*,11*S*)-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 156f)

To a 100 mL flask was added (8*S*,11*S*)-13-(3-hydroxypropyl)-12-oxo-7,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (**156e**, 270 mg, 0.487 mmol), palladium hydroxide on carbon (49.48 mg, 0.352 mmol) and MeOH (40 mL), the suspension was purged with H_2 for 5 times. The mixture was

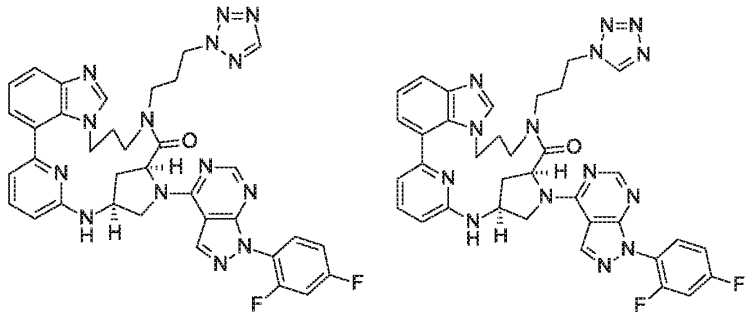
heated to 65 °C and stirred for about 4 hrs. The mixture was filtered, the filtrate was concentrated to give compound **156e** (400 mg). LCMS ($M+H^+$): 421.

Step 7: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 156)

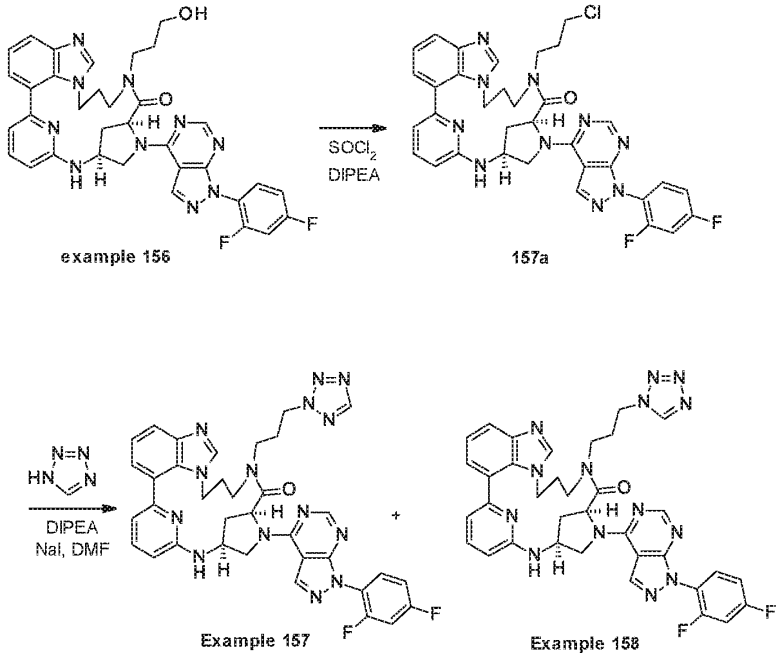
To a microwave tube was added (8*S*,11*S*)-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (**156f**, 126.15 mg, 0.300 mmol), 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (**Intermediate C2**, 103.99 mg, 0.390 mmol), DIPEA (77.55 mg, 104.79 μL, 0.600 mmol), acetonitrile (5 mL), a yellow solution formed. The mixture was heated to 86 °C and stirred for about 2 hrs. The mixture was concentrated to give an oil and then purified via flash column (EA/PE=0~100% & MeOH/EA=10% & MeOH/DCM=20%), the elution was concentrated to give **Example 156** (6.6 mg). LCMS ($M+H^+$): 651. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.61 (s, 1H), 8.53 - 8.42 (m, 1H), 8.23 (s, 1H), 7.81 - 7.68 (m, 3H), 7.60 (ddd, *J* = 2.8, 9.1, 10.3 Hz, 1H), 7.39 - 7.26 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 5.58 (br d, *J* = 8.4 Hz, 1H), 5.44 (d, *J* = 8.6 Hz, 1H), 4.91 (dt, *J* = 4.6, 12.6 Hz, 1H), 4.73 - 4.65 (m, 1H), 4.64 - 4.44 (m, 2H), 4.22 (br d, *J* = 11.7 Hz, 1H), 4.18 - 4.03 (m, 2H), 3.85 - 3.72 (m, 2H), 3.49 - 3.45 (m, 2H), 2.94 - 2.83 (m, 1H), 2.40 - 2.34 (m, 1H), 2.11 - 2.00 (m, 1H), 1.84 - 1.64 (m, 1H), 1.63 - 1.42 (m, 1H), 1.40 - 1.27 (m, 1H), 1.27 - 1.10 (m, 1H).

Example 157 and Example 158

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-2-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*)-13-(3-chloropropyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 157a)

To a tube was added (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example **156**, 169 mg, 0.260 mmol), DIPEA (67.14 mg, 90.73 μL, 0.519 mmol) and DCM (2 mL). Then $SOCl_2$ (308.97 mg, 189.55 μL, 2.6 mmol) was added and the mixture kept stirring at r.t. for 5 hrs. The mixture was quenched with water and then it was adjusted pH to about 7, the mixture was extracted with 10 mL DCM twice, the organic layer was dried and concentrated to give compound **157a** (65 mg). LCMS ($M+H^+$): 669.

Step 2: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-2-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 157 & 158)

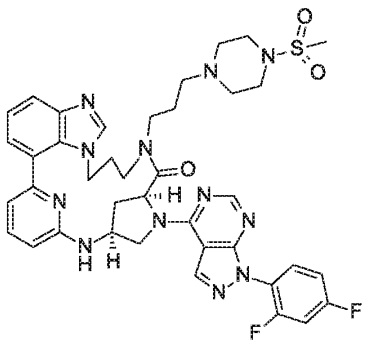
To a tube was added (8*S*,11*S*)-13-(3-chloropropyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (**157a**, 33. mg, 0.049 mmol), 2*H*-tetrazole (6.91 mg, 0.099 mmol), DIEA (19.12 mg, 25.84 µL, 0.148 mmol), sodium iodide (14.78 mg, 0.099 mmol), and DMF (0.262 mL). The mixture was heated to 70 °C for 16 hrs and then the reaction mixture was purified by prep-HPLC to give Example **157** (faster eluted) and Example **158** (slower eluted).

Example 157 (5.6 mg), LCMS (M+H$^+$): 703. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.45 (s, 1H), 8.60 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 7.76 - 7.66 (m, 3H), 7.64 - 7.54 (m, 1H), 7.36 - 7.29 (m, 1H), 7.29 - 7.20 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 8.4 Hz, 1H), 5.35 (d, *J* = 8.8 Hz, 1H), 4.92 - 4.80 (m, 1H), 4.71 - 4.63 (m, 1H), 4.62 - 4.46 (m, 3H), 4.45 - 4.35 (m, 1H), 4.22 (br d, *J* = 11.5 Hz, 1H), 4.11 - 3.98 (m, 1H), 3.78 (br dd, *J* = 10.2, 13.1 Hz, 1H), 2.87 (br dd, *J* = 7.9, 13.0 Hz, 1H), 2.40 - 2.34 (m, 1H), 2.22 - 2.13 (m, 2H), 2.05 - 1.93 (m, 1H), 1.91 - 1.80 (m, 1H), 1.38 - 1.22 (m, 1H).

Example 158 (10.6 mg), LCMS (M+H$^+$): 703. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.01 (s, 1H), 8.60 (s, 1H), 8.28 (s, 1H), 8.21 (s, 1H), 7.77 - 7.66 (m, 3H), 7.59 (ddd, *J* = 2.8, 9.1, 10.4 Hz, 1H), 7.37 - 7.29 (m, 1H), 7.29 - 7.20 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.57 (br d, *J* = 8.8 Hz, 1H), 5.35 (br d, *J* = 8.9 Hz, 1H), 4.89 - 4.74 (m, 3H), 4.70 - 4.62 (m, 1H), 4.52 - 4.44 (m, 1H), 4.22 (br d, *J* = 11.5 Hz, 1H), 4.16 - 4.09 (m, 1H), 4.08 - 4.02 (m, 1H), 3.87 - 3.80 (m, 1H), 2.91 (br dd, *J* = 7.6, 13.4 Hz, 1H), 2.44 - 2.36 (m, 1H), 2.30 - 2.22 (m, 1H), 2.19 (br d, *J* = 13.3 Hz, 1H), 2.06 - 1.90 (m, 2H), 1.39 - 1.24 (m, 1H).

Example 159

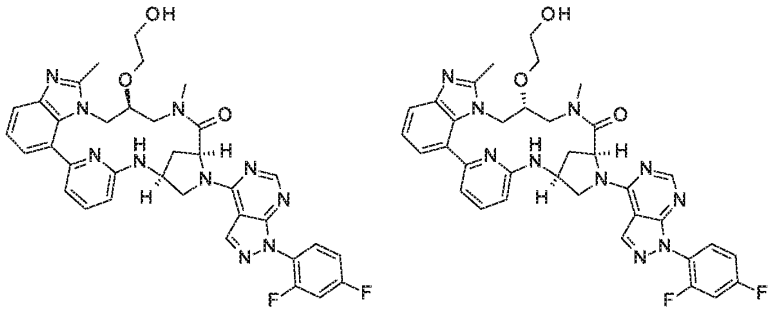
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(4-methylsulfonylpiperazin-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



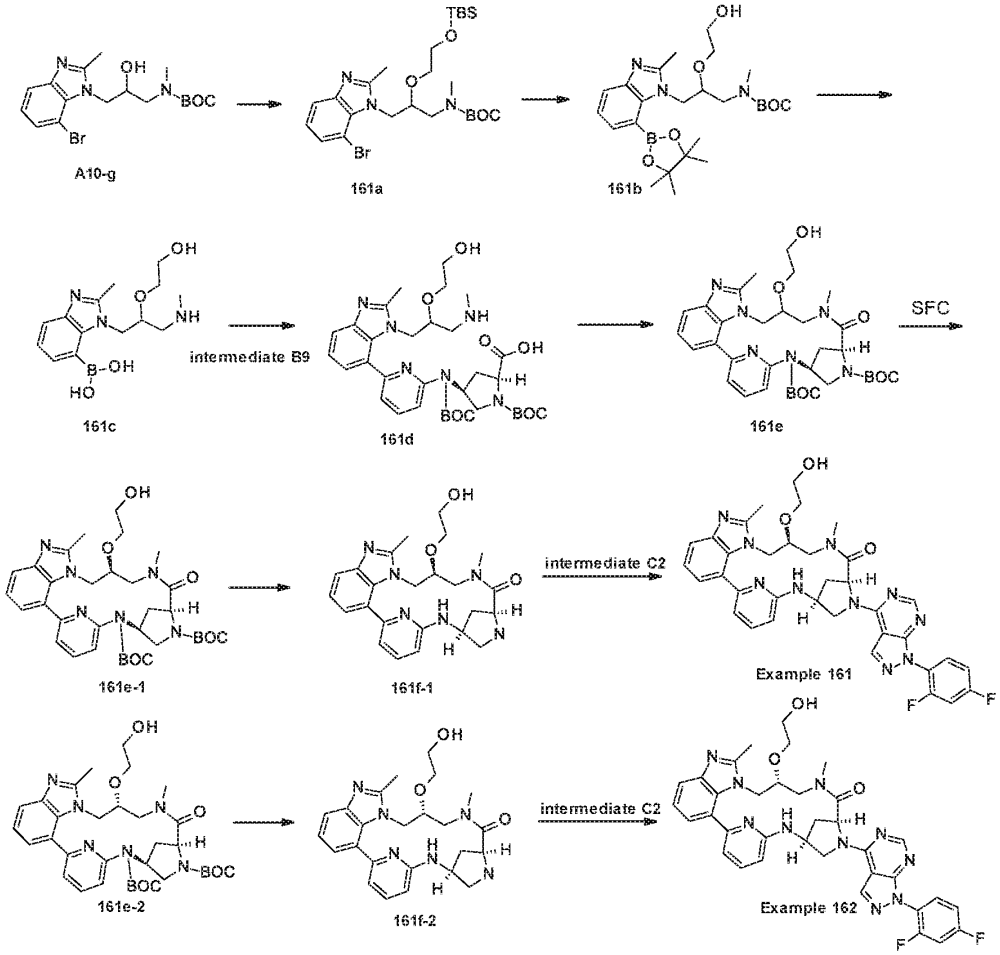
The title compound was prepared in analogy to the preparation of **Example 157** by using 1-methylsulfonylpiperazine instead of 2*H*-tetrazole in step 2. LCMS ($M+H^+$): 797, ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.24 (s, 1H), 8.22 (s, 1H), 7.83 - 7.75 (m, 1H), 7.71 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.66 (dt, *J* = 5.8, 8.6 Hz, 1H), 7.37 - 7.34 (m, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.23 - 7.16 (m, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.61 (br d, *J* = 7.9 Hz, 1H), 4.77 - 4.71 (m, 1H), 4.64 - 4.49 (m, 6H), 4.31 (d, *J* = 11.4 Hz, 1H), 4.19 - 4.07 (m, 1H), 3.95 (dd, *J* = 8.9, 14.2 Hz, 1H), 3.52 - 3.41 (m, 1H), 3.28 - 3.17 (m, 4H), 3.01 (br dd, *J* = 7.3, 13.9 Hz, 1H), 2.83 (s, 3H), 2.65 - 2.48 (m, 6H), 2.48 - 2.38 (m, 1H), 2.24 - 1.78 (m, 1H), 1.70 - 1.39 (m, 1H).

Example 161 and Example 162

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]propyl]-*N*-methyl-carbamate (compound 161a)

To a mixture of **intermediate A10-g** (2.5 g, 6.28 mmol, the synthesis refer to **intermediate A7-g**) and (2-bromoethoxy)-*tert*-butyldimethylsilane (3 g, 12.55 mmol) in dry DMF(20 mL) was added NaH (502 mg, 12.55 mmol) at 0 °C in portions. The mixture was stirred at rt for 1 hour. The mixture was poured into 100 mL water and extracted with 100 mL EA. The organic layer was dried and concentrated; the crude oil was purified by silica gel to give compound **161a** (1.5 g). LCMS ($M+H^+$): 556.

Step 2: preparation of *tert*-butyl *N*-[2-(2-hydroxyethoxy)-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 161b)

A mixture of compound **161a** (1.5 g, 1.35 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.05 g, 8.08 mmol), potassium acetate (397 mg, 4 mmol) in DMSO (35

mL) was bubbled with N_2 for 5 mins. Then $Pd(PPh_3)_2Cl_2$ (94.6 mg, 0.135 mmol) and Butyl di-1-adamantylphosphine (96.6 mg, 0.269 mmol) were added and stirred at 130 °C for about 4 hours. The mixture was diluted with water and extracted with EA. The organic layer was dried and concentrated to give crude compound **161b** (1.72 g). LCMS ($M+H^+$): 490.

Step 3: preparation of [3-[2-(2-hydroxyethoxy)-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]boronic acid (compound 161c)

A mixture of compound **161b** (1.72 g, 1.53 mmol) in HCl in Dioxane (4 M, 7.66 mL, 30.65 mmol) and DCM (15 mL) was stirred at rt for 2 hours. Then the reaction was concentrated, 1 M HCl (10 mL) was added, the aqueous phase was washed with EA and then lyophilized to give compound **161c** (1 g). LCMS ($M+H^+$): 308.

Step 4: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[*tert*-butoxycarbonyl-[6-[3-[2-(2-hydroxyethoxy)-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 161d)

A mixture of K_2CO_3 (6.56 g, 47.49 mmol), compound **161c** (1.17 g, 3.8 mmol), **intermediate B8** (4.75 g, 9.5 mmol) and $PdCl_2$(DPPF)DCM (775.7 mg, 0.950 mmol) in Dioxane/ H_2O (10:1, 50 mL) was stirred at 90 °C for 2 hours. Then mixture was filtered and concentrated, the residue was dissolved in THF/MeOH (2:1, 10 mL), 2 M LiOH (2.93 mL, 5.86 mmol) was added and stirred at rt for 4 hours. The reaction was adjusted to pH=5, and then the mixture was concentrated to remove most organic solvent, the residue was purified by flash preparation (MeCN/ TFA in water) to give compound **161d** (1 g). LCMS ($M+H^+$): 569.

Step 5: preparation of ditert-butyl (8*S*,11*S*,15*R*)-15-(2-hydroxyethoxy)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate and ditert-butyl (8*S*,11*S*,15*S*)-15-(2-hydroxyethoxy)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound 161e-1 & 161e-2)

To a mixture of DIPEA (1.16 g, 1.57 mL, 8.97 mmol) and HATU (1.36 g, 3.59 mmol) in acetonitrile (90 mL) was added a solution of compound **161d** (1.2 g, 0.897 mmol) in acetonitrile (90 mL) dropwise in 2 hours. Then the reaction was stirred at rt for 1 hour. The reaction was concentrated; the residue was purified by silica gel and SFC to give compound **161e-1** (40 mg, faster eluted) and **161e-2** (40 mg, slower eluted). LCMS ($M+H^+$): 551

SFC condition: instrument: SFC 80. Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O). Gradient: B 25%. Flow rate: 60 mL /min. Backpressure: 100bar.

Step 6: preparation of (8*S*,11*S*,15*R*)-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 161f-1 & 161f-2)

A mixture of compound **161e-1** (40 mg, 0.061 mmol) and 4 M HCl in dioxane (1 mL) in DCM (2 mL) was stirred at rt for 4 hours, then the reaction was concentrated to give compound **161f-1** (40 mg). LCMS (M+H$^+$): 451.

A mixture of compound **161e-2** (40 mg, 0.061 mmol) and 4 M HCl in dioxane (1 mL) in DCM (2 mL) was stirred at rt for 4 hours, then the reaction was concentrated to give compound **161f-2** (40 mg). LCMS (M+H$^+$): 451.

Step 7: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 161 & 162)

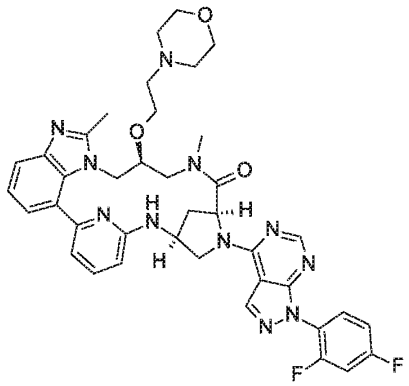
A mixture of compound **161f-1** (40 mg, 0.09 mmol), **intermediate C2** (24 mg, 0.09 mmol) and DIPEA (57 mg, 0.44 mmol) in acetonitrile (2 mL) was stirred at 80 °C for 2 hours, then the reaction was concentrated, the residue was purified by HPLC to give Example **161** (15 mg). LCMS (M+H$^+$): 681. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.59 - 8.36 (m, 1H), 8.27 - 7.80 (m, 2H), 7.75 - 7.61 (m, 2H), 7.44 - 7.18 (m, 4H), 7.18 - 7.08 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.86 - 5.68 (m, 1H), 5.54 - 5.38 (m, 1H), 4.72 - 4.52 (m, 2H), 4.39 - 4.29 (m, 1H), 4.25 - 4.14 (m, 1H), 4.05 - 3.99 (m, 2H), 3.06 (s, 6H), 3.00 - 2.93 (m, 1H), 2.79 - 2.59 (m, 6H).

A mixture of compound **161f-2** (40 mg, 0.09 mmol), **intermediate C2** (24 mg, 0.09 mmol) and DIPEA (57 mg, 0.44 mmol) in acetonitrile (2 mL) was stirred at 80 °C for 2 hours, then the reaction was concentrated, the residue was purified by HPLC to give Example **162** (15 mg). LCMS (M+H$^+$): 681. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.50 - 8.23 (m, 1H), 8.17 - 7.64 (m, 2H), 7.62 - 7.42 (m, 2H), 7.26 - 7.04 (m, 4H), 6.80 (br s, 1H), 6.65 - 6.54 (m, 1H), 5.48 -

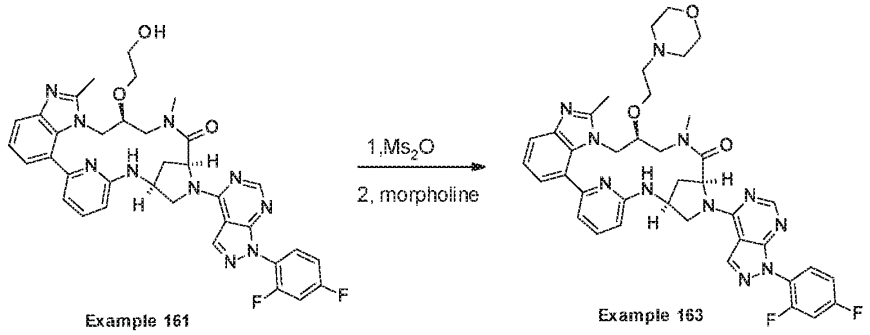
5.31 (m, 1H), 4.68 - 4.62 (m, 1H), 4.53 - 4.44 (m, 1H), 4.31 - 4.17 (m, 1H), 4.15 - 3.98 (m, 1H), 3.96 - 3.75 (m, 2H), 3.11 - 2.98 (m, 7H), 2.94 - 2.84 (m, 1H), 2.76 - 2.58 (m, 2H), 2.56 - 2.44 (m, 4H).

Example 163

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

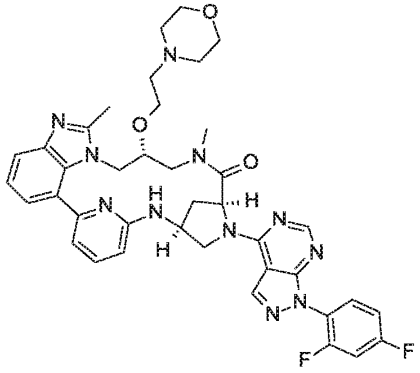


To a mixture of Example **161** (15 mg, 0.022 mmol) and DIPEA (14 mg, 0.110 mmol) in DCM (2 mL) was added methanesulfonic anhydride (7.7 mg, 0.044 mmol) and stirred at rt for 1 hour. Then the reaction was concentrated, the residue was dissolved in acetonitrile (2 mL), DIPEA (14 mg, 0.11 mmol), sodium iodide (3 mg, 0.02 mmol) and morpholine (19 mg, 0.220 mmol) was added and stirred at 80 °C for 30 mins. The reaction was concentrated and the residue was purified by HPLC to Example **163** (4 mg). LCMS (M+H$^+$): 750. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 - 8.23 (m, 1H), 8.18 - 7.67 (m, 2H), 7.62 - 7.47 (m, 2H), 7.33 - 7.06 (m, 4H), 7.04 - 6.95 (m, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.76 - 5.51 (m, 1H), 5.44 - 5.23 (m, 1H), 4.63 - 4.51 (m, 1H), 4.46 - 4.36 (m, 1H), 4.28 - 4.02 (m, 2H), 3.86 (br dd, J = 9.2, 14.3 Hz, 1H),

3.51 - 3.23 (m, 5H), 3.09 - 2.78 (m, 5H), 2.73 - 2.64 (m, 1H), 2.60 - 2.35 (m, 5H), 2.10 - 1.98 (m, 1H), 1.97 - 1.82 (m, 3H), 1.80 - 1.70 (m, 2H).

Example 164

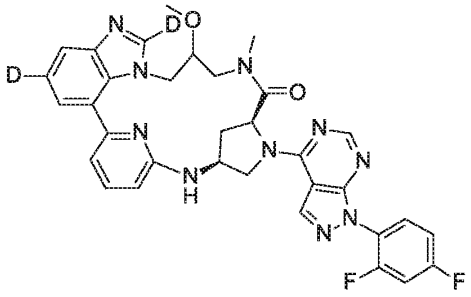
(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



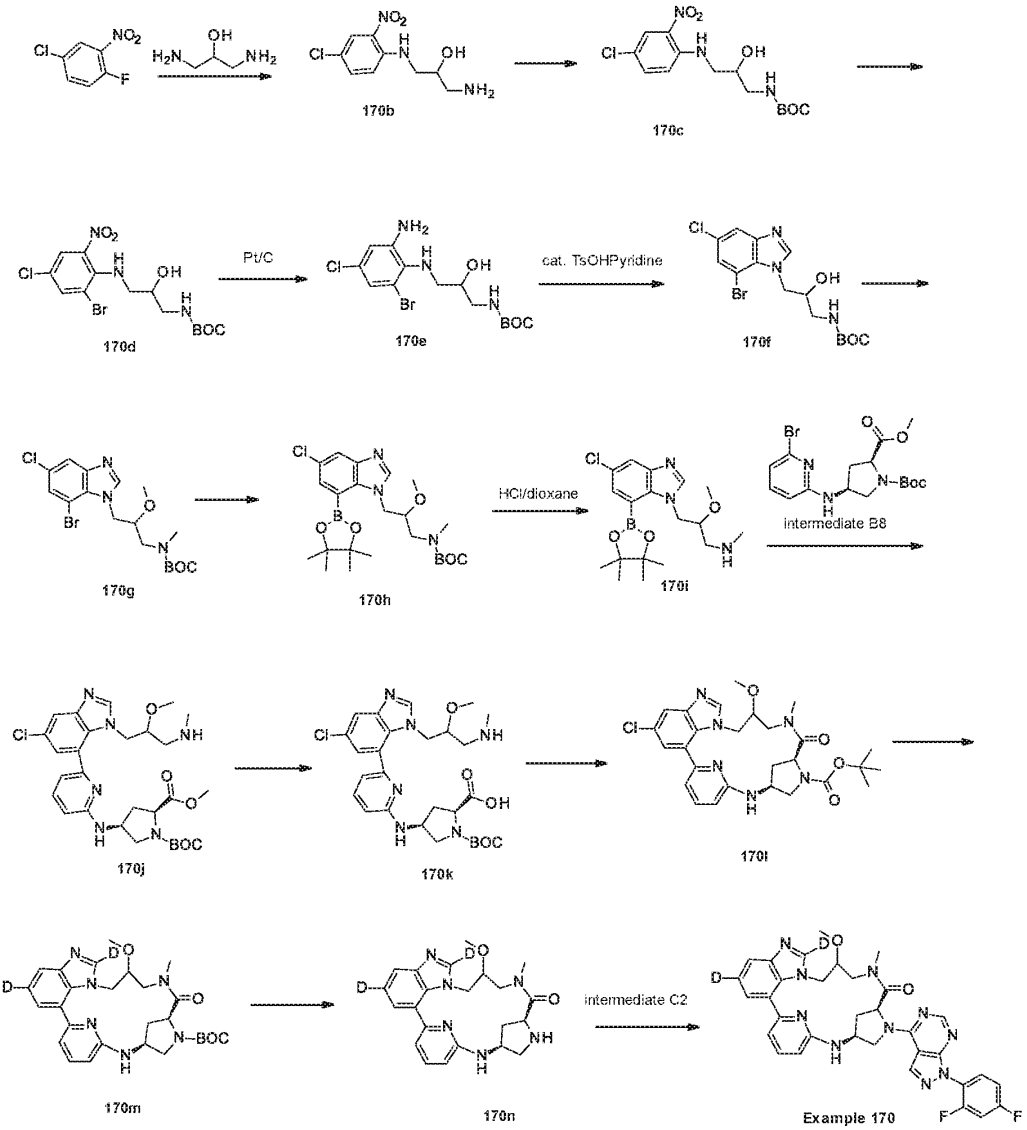
The title compound was prepared in analogy to the preparation of example **163** by using example **162** instead of example **161**. LCMS (M+H$^+$): 750. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 - 8.22 (m, 1H), 8.18 - 7.62 (m, 2H), 7.50 (br d, *J* = 9.0 Hz, 2H), 7.27 - 7.04 (m, 4H), 6.82 (br s, 1H), 6.61 (br d, *J* = 8.4 Hz, 1H), 5.53 - 5.26 (m, 1H), 4.68 - 4.60 (m, 1H), 4.52 - 4.42 (m, 1H), 4.29 - 4.17 (m, 1H), 4.01 (br d, *J* = 14.5 Hz, 3H), 3.38 - 3.25 (m, 5H), 3.13 - 2.82 (m, 6H), 2.66 - 2.41 (m, 5H), 2.03 - 1.80 (m, 6H).

Example 170

(8*S*,11*S*)-18,22-dideuterio-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-amino-3-(4-chloro-2-nitro-anilino)propan-2-ol (compound 170b)

To a mixture of 5-chloro-2-fluoronitrobenzene (10.0 g, 56.97 mmol) and in acetonitrile (200 mL) was added 1,3-diamino-2-propanol (20.54 g, 227.87 mmol) slowly at 25 °C. After being stirred at 70 °C for 0.5 h, the mixture was filtered and concentrated to afford compound **170b** (14 g). LCMS $(M+H)^+$: 246.

Step 2: preparation of *tert*-butyl *N*-[3-(4-chloro-2-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 170c)

To a mixture of compound **170b** (14 g, 57 mmol) and DIPEA (11 g, 85 mmol) in methanol (150 mL) was added di-t-butyldicarbonate (15 g, 69 mmol) slowly at 25 °C. After being stirred

at 20 °C for 1 h, *tert*-butyl (2-methylpropan-2-yl)oxycarbonyl carbonate (60.0 mL, 284.95 mmol) was added and the mixture was stirred at 20 °C for another 1 h. Then the mixture was concentrated and the residue was purified by silica gel to give compound **170c** (27 g). LCMS $(M+H)^+$: 368.

Step 3: preparation of *tert*-butyl *N*-[3-(2-bromo-4-chloro-6-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 170d)

A mixture of compound **170c** (27.0 g, 78.08 mmol) and NBS (15.29 g, 85.89 mmol) in acetonitrile (270 mL) was stirred at 85 °C for 12 h. Then the mixture was diluted with EA, washed with water and brine. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **170d** (7.5 g), LCMS $(M+H)^+$: 448.

Step 4: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-4-chloro-anilino)-2-hydroxy-propyl]carbamate (compound 170e)

A mixture of compound **170d** (7.0 g, 16.48 mmol) and Pt/C (1.4 g, 25 mmol) in EA (82.42 mL) was stirred for 2 h at 20 °C under H_2 balloon. The mixture was filtered and the filtrate was concentrated to give compound **170e** (7 g) LCMS $(M+H)^+$: 396.

Step 5-7: preparation of *tert*-butyl *N*-[3-[5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (compound 170h)

Compound **170h** was prepared in analogy to the preparation of Intermediate **A1** by using compound **170e** instead of compound **A1-c** and trimethoxymethane instead of trimethyl orthoacetate. LCMS $(M+H)^+$: 480.

Step 8-11: preparation of *tert*-butyl (8*S*,11*S*)-22-chloro-15-methoxy-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 170l)

Compound **170l** was prepared in analogy to the preparation of compound **289c** by using compound **170h** instead of intermediate **A12** and intermediate **B8** instead of intermediate **B1**. LCMS $(M+H)^+$: 541.

Step 12: preparation of *tert*-butyl (8*S*,11*S*)-18,22-dideuterio-15-methoxy-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 170m)

To a mixture of triethylamine (0.01 mL, 0.06 mmol) and compound **170l** (20.0 mg, 0.04 mmol) in trideuterio(deuteriooxy)methane (2 mL) was added Pd/C (2 mg, washed with deuterium oxide) under N_2. The mixture was stirred at 20 °C for 4 h under deuterium balloon.

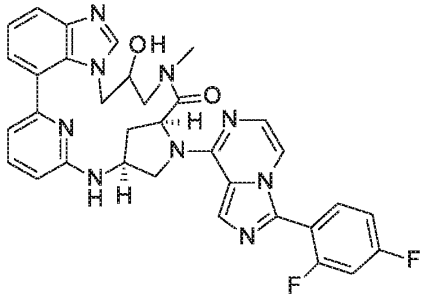
Then the reaction mixture was filtered, the filtrate was concentrated to give compound **170m** (14 mg). LCMS $(M+H)^+$: 509.

Step 13-14: preparation of (8*S*,11*S*)-18,22-dideuterio-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 170)

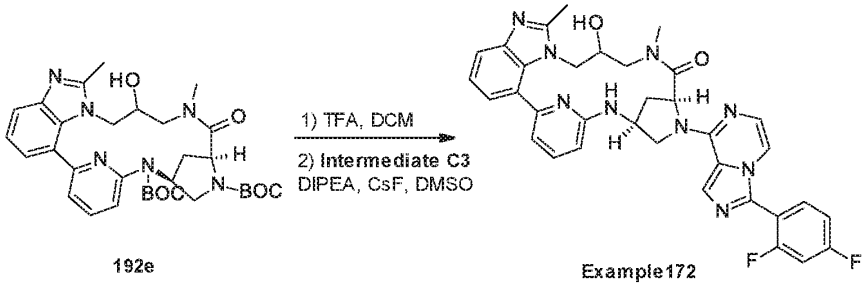
Example **170** was prepared in analogy to the preparation of Example **289** by using compound **170m** instead of compound **289c**. LCMS $(M+H)^+$: 639. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.45 - 9.28 (m, 0.5H), 8.60 - 8.22 (m, 2H), 7.94 - 7.60 (m, 4H), 7.35 - 7.27 (m, 1H), 7.24 - 7.04 (m, 2H), 6.79 (t, J = 8.4 Hz, 1H), 6.14 - 5.99 (m, 1H), 5.58 - 5.37 (m, 1H), 4.79 - 4.70 (m, 1H), 4.60 - 4.06 (m, 4H), 3.99 - 3.79 (m, 1H), 3.23 - 2.94 (m, 8H), 2.76 - 2.51 (m, 2H).

Example 172

(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-hydroxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

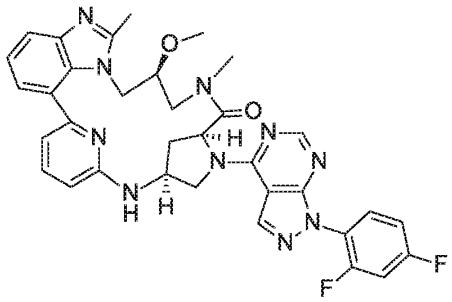


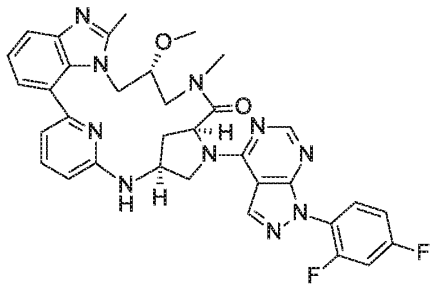
To a flask was added *ditert*-butyl (8*S*,11*S*)-15-hydroxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound **192e**, 30.0 mg, 0.05 mmol), DCM (1 mL) and TFA

(1.48 g, 1 mL, 12.98 mmol), the mixture was stirred at r.t. for 1 hr. The mixture was concentrated to give an oil. The oil was dissolved in dimethyl sulfoxide (1 mL), and then 8-chloro-3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazine (**Intermediate C3**, 19.9 mg, 0.075 mmol), DIPEA (25. mg, 35 µL, 0.200 mmol) and cesium fluoride (15.19 mg, 0.100 mmol) were added. The mixture was heated to 90 °C and stirred for about 16 hrs. The mixture was purified via prep-HPLC to give Example **172** (4.8 mg). LCMS ($M+H^+$): 622, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.26 (s, 1H), 8.02 (s, 1H), 7.79 - 7.71 (m, 2H), 7.68 (dt, *J* = 1.5, 6.7 Hz, 1H), 7.58 - 7.49 (m, 1H), 7.44 - 7.27 (m, 2H), 7.27 - 7.21 (m, 2H), 7.20 - 7.07 (m, 1H), 7.07 - 6.86 (m, 1H), 6.75 - 6.58 (m, 1H), 5.60 - 5.46 (m, 1H), 5.45 - 5.24 (m, 1H), 4.88 - 4.75 (m, 1H), 4.73 - 4.51 (m, 1H), 4.32 - 4.20 (m, 1H), 4.13 (br d, *J* = 14.9 Hz, 1H), 4.07 - 3.94 (m, 1H), 3.25 - 3.02 (m, 4H), 3.00 - 2.84 (m, 2H), 2.83 - 2.69 (m, 1H), 2.46 - 2.35 (m, 1H), 2.29 - 2.10 (m, 1H).

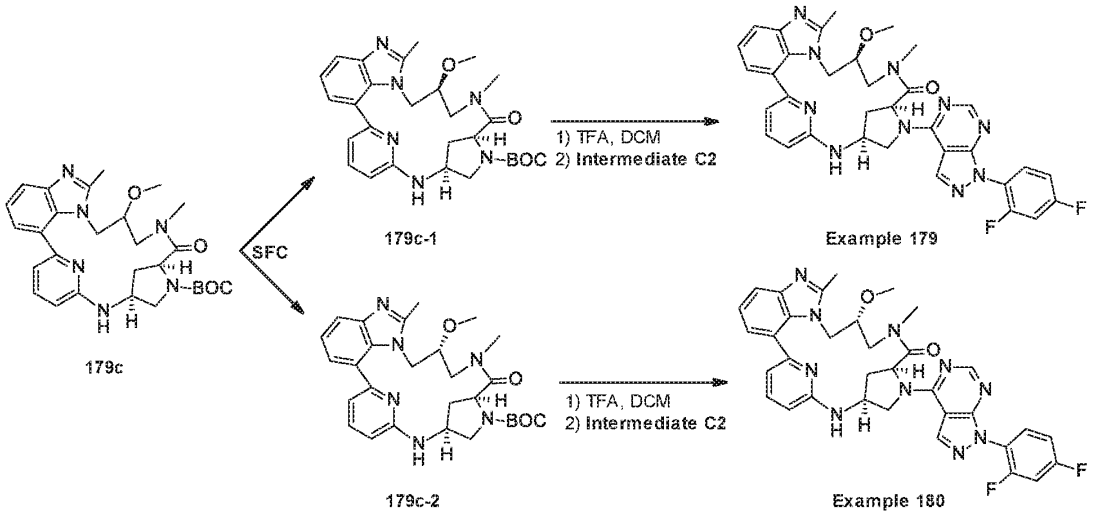
Example 179 and Example 180

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared according to the following scheme:



Compound **179c** (The compound was prepared in analogy to the preparation of compound **189c** by using **Intermediate B8** instead of **Intermediate B1** in step 2)) was separated via SFC to give the compound **179c-1** and **179c-2**. (SFC condition: Instrument: SFC 80; Column: IA, 250×30 mm I.D., 5μm; Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O); Gradient: B 35%; Flow rate: 60 mL /min; Back pressure: 100 bar; Column temperature: 35°C)

Step 1: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 179 and Example 180)

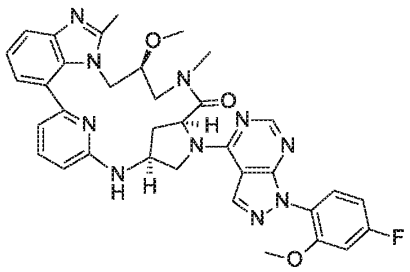
To a flask was added *tert*-butyl (8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1$^{2.6}$.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (**179c-1**, 120 mg, 0.230 mmol), dichloromethane (1 mL) and TFA (1.48 g, 1 mL, 12.98 mmol), the yellow solution was stirred at r.t. for 1 hr. The mixture was concentrated to give an oil, some of the oil (32 mg, 0.060 mmol) was dissolved in acetonitrile (0.8 mL), and then 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (**Intermediate C2**, 16 mg, 0.060 mmol), DIEA (46 mg, 63 μL, 0.36 mmol) was added. The mixture was heated to 85 °C for 1 hr, then the mixture was concentrated and purified via prep-HPLC, Example **179** (27.4 mg) was obtained. LCMS ($M+H^+$): 651, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.57 (s, 1H), 8.25 (s, 1H), 7.90 - 7.84 (m, 1H), 7.81 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.76 - 7.71 (m, 1H), 7.70 -

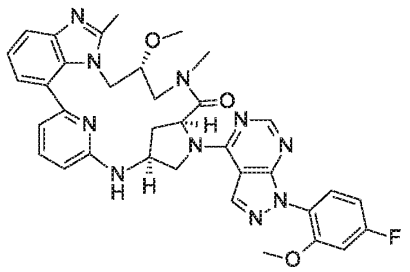
7.61 (m, 2H), 7.30 (ddd, *J* = 2.6, 8.8, 10.1 Hz, 1H), 7.24 - 7.19 (m, 1H), 7.18 - 7.14 (m, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.17 (dd, *J* = 4.6, 15.4 Hz, 1H), 5.49 (d, *J* = 9.0 Hz, 1H), 4.73 - 4.67 (m, 1H), 4.57 - 4.50 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.33 - 4.27 (m, 1H), 4.00 - 3.91 (m, 1H), 3.17 - 3.06 (m, 3H), 2.98 (dd, *J* = 1.5, 14.3 Hz, 1H), 2.96 (s, 3H), 2.92 (br d, *J* = 13.6 Hz, 1H), 2.86 - 2.79 (m, 3H), 2.64 - 2.51 (m, 2H).

To a flask was added *tert*-butyl (8*S*,11*S*,15*S*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (**179c-2**, 120 mg, 0.230 mmol), dichloromethane (1 mL) and TFA (1.48 g, 1.0 mL, 12.98 mmol), the yellow solution was stirred at r.t. for 1 hr. The mixture was concentrated to give an oil, some of the oil (32 mg, 0.06 mmol) was dissolved in acetonitrile (0.800 mL), and then 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (Intermediate **C2**, 16. mg, 0.060 mmol), DIEA (46 mg, 63 µL, 0.360 mmol) was added. The mixture was heated to 85 °C for 1 hr, then the mixture was concentrated and purified via prep-HPLC, Example **180** (34.4 mg) was obtained. LCMS (M+H$^+$): 651, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.57 (s, 1H), 8.24 (s, 1H), 7.85 - 7.81 (m, 1H), 7.80 - 7.76 (m, 1H), 7.70 - 7.66 (m, 1H), 7.65 - 7.59 (m, 2H), 7.30 (ddd, *J* = 2.7, 8.9, 10.1 Hz, 1H), 7.25 - 7.16 (m, 1H), 6.99 (br d, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 5.94 - 5.58 (m, 1H), 5.55 - 5.46 (m, 1H), 4.77 - 4.73 (m, 1H), 4.58 (dd, *J* = 6.4, 11.6 Hz, 1H), 4.37 - 4.31 (m, 1H), 4.28 - 4.16 (m, 1H), 4.15 - 4.06 (m, 1H), 3.88 - 3.72 (m, 1H), 3.22 - 3.19 (m, 1H), 3.10 (s, 3H), 2.97 - 2.92 (m, 3H), 2.88 - 2.82 (m, 3H), 2.78 (br d, *J* = 13.6 Hz, 1H), 2.62 - 2.55 (m, 1H).

Example 183 and Example 184

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





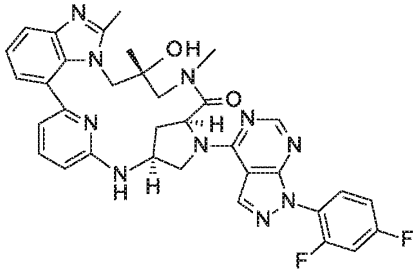
The compounds were prepared analogy to the preparation of Example **179** and Example **180** by using intermediate **C11** instead of intermediate **C2** in step 1.

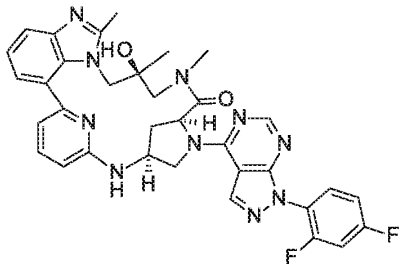
Example 183, LCMS (M+H$^+$): 663, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.24 (s, 1H), 7.88 (t, *J* = 7.9 Hz, 1H), 7.83 - 7.80 (m, 1H), 7.76 - 7.72 (m, 1H), 7.69 - 7.63 (m, 1H), 7.47 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.20 - 7.14 (m, 1H), 7.08 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.94 - 6.85 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.16 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.49 (d, *J* = 8.9 Hz, 1H), 4.73 - 4.67 (m, 1H), 4.55 (dd, *J* = 5.9, 11.5 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.35 - 4.28 (m, 1H), 4.01 - 3.90 (m, 1H), 3.80 - 3.74 (m, 3H), 3.19 - 3.14 (m, 1H), 3.14 - 3.03 (m, 3H), 3.00 (br d, *J* = 1.4 Hz, 1H), 2.96 (s, 3H), 2.85 (s, 3H), 2.64 - 2.53 (m, 2H).

Example 184, LCMS (M+H$^+$): 663, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.23 (s, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.81 - 7.76 (m, 1H), 7.68 - 7.58 (m, 2H), 7.47 (dd, *J* = 6.0, 8.7 Hz, 1H), 7.08 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.99 (br d, *J* = 6.9 Hz, 1H), 6.93 - 6.85 (m, 1H), 6.81 - 6.72 (m, 1H), 6.06 - 5.57 (m, 1H), 5.53 (d, *J* = 9.0 Hz, 1H), 4.78 - 4.74 (m, 1H), 4.59 (dd, *J* = 6.3, 11.6 Hz, 1H), 4.36 (br d, *J* = 11.4 Hz, 1H), 4.28 - 4.15 (m, 1H), 4.14 - 4.07 (m, 1H), 3.88 - 3.78 (m, 1H), 3.78 - 3.73 (m, 3H), 3.22 - 3.08 (m, 4H), 2.98 - 2.94 (m, 3H), 2.87 (s, 3H), 2.80 (br d, *J* = 13.4 Hz, 1H), 2.64 - 2.56 (m, 1H).

Example 187 and Example 188

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



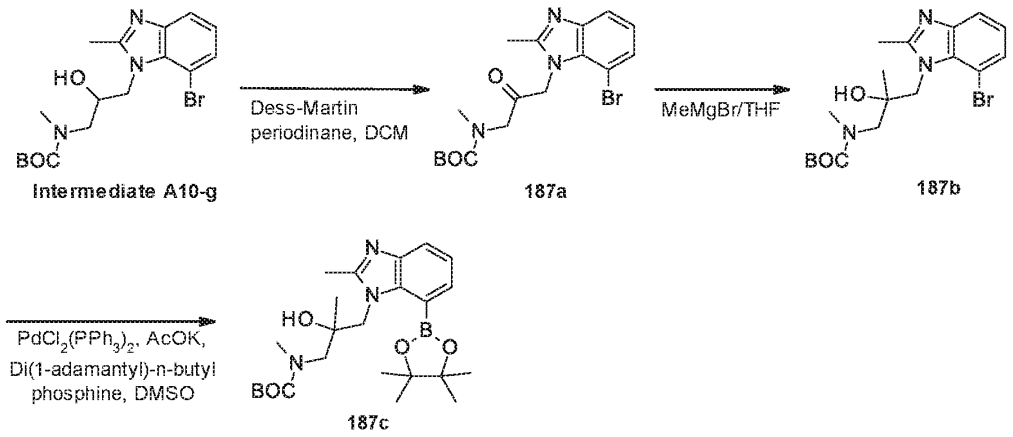


The compounds were prepared analogy to the preparation of Example **12** by using compound **187f** instead of intermediate **A11** in step 1. The mixture of Example 187 (faster eluted) and Example 188 (slower eluted) was separated via prep-HPLC.

Example 187, LCMS (M+H$^+$): 651, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.22 (s, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.67 (dt, *J* = 6.0, 8.6 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.45 - 7.40 (m, 1H), 7.32 - 7.24 (m, 2H), 7.23 - 7.17 (m, 1H), 7.15 - 7.10 (m, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.84 - 5.72 (m, 1H), 5.52 - 5.39 (m, 1H), 4.68 (br t, *J* = 5.1 Hz, 1H), 4.55 - 4.49 (m, 1H), 4.31 (br d, *J* = 11.1 Hz, 1H), 4.23 - 4.12 (m, 1H), 4.08 (br d, *J* = 14.2 Hz, 1H), 3.17 - 3.04 (m, 3H), 2.99 (br d, *J* = 13.6 Hz, 1H), 2.65 (br d, *J* = 14.0 Hz, 1H), 2.60 - 2.56 (m, 3H), 2.55 - 2.48 (m, 1H), 0.79 (s, 3H).

Example 188, LCMS (M+H$^+$): 651, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.24 (s, 1H), 7.81 - 7.74 (m, 1H), 7.67 (dt, *J* = 5.8, 8.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.30 - 7.25 (m, 2H), 7.23 - 7.17 (m, 1H), 7.15 - 7.10 (m, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.68 - 5.58 (m, 1H), 5.49 (d, *J* = 9.0 Hz, 1H), 4.72 - 4.68 (m, 1H), 4.54 (dd, *J* = 6.3, 11.3 Hz, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.25 (br d, *J* = 15.3 Hz, 1H), 4.16 - 4.10 (m, 1H), 3.23 - 3.09 (m, 3H), 2.77 - 2.71 (m, 1H), 2.70 - 2.66 (m, 3H), 2.65 (br d, *J* = 13.9 Hz, 1H), 2.58 (ddd, *J* = 4.4, 9.1, 13.6 Hz, 1H), 0.48 - 0.39 (m, 3H).

The compound **187f** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-oxo-propyl]-*N*-methyl-carbamate (compound 187a)

To a microwave tube was added *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]-*N*-methyl-carbamate (**Intermediate A10-g**, 1.9 g, 4.77 mmol), 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benzodioxol-3-(1*H*)-one (2.63 g, 6.2 mmol) and DCM(19 mL). The mixture was stirred at r.t. for 2 hrs and then quenched with aqueous solution of $NaHSO_3$. The mixture was neutralized with aqueous solution of $NaHCO_3$ and separated, the water layer was extracted with another 30 mL DCM. The organic layer was dried over Na_2SO_4 and concentrated to give compound **187a** (2.2 g). LCMS (M+H$^+$): 396.

Step 2: preparation of *tert*-butyl N-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-hydroxy-2-methyl-propyl]-N-methyl-carbamate (compound 187b)

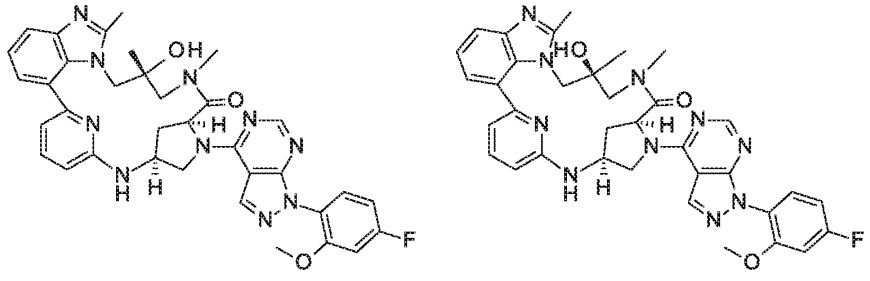
To a flask which contain *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-oxo-propyl]-*N*-methyl-carbamate (**187a**, 1.78 g, 4.5 mmol) was added 1 M methylmagnesium bromide (11.25 mL, 11.25 mmol). The mixture was stirred at r.t. for about 2 hrs. The mixture was quenched with 50 mL sat. NH_4Cl and then extracted with 20 mL EA twice, the organic layer was dried over Na_2SO_4 and concentrated, a yellow oil was obtained. The final oil was purified by silica gel to give compound **187b** (830 mg).LCMS ($M+H^+$): 412.

Step 3: preparation of *tert*-butyl N-[2-hydroxy-2-methyl-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-N-methyl-carbamate (compound 187c)

To a microwave tube was added compound **187b** (830 mg, 2.01 mmol), potassium acetate (395 mg, 4.03 mmol) and DMSO (12 mL), the solution was bubbled with N_2 for 5 mins and then bis(triphenylphosphine)palladium(ii) dichloride (141 mg, 0.201 mmol) & bis(1-adamantyl)-butyl-phosphine (144 mg, 0.403 mmol) were added. The tube was heated to 130 °C and stirred for about 5hrs. The mixture was diluted with 100mL water and then extracted with 25 mL EA for 3 times. The organic layer was dried over Na_2SO_4 and concentrated, the residue was purified by silica gel to give compound **187c** (830 mg). LCMS ($M+H^+$): 460.

Example 189 and Example 190

(8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The compounds were prepared analogy to the preparation of Example **12** by using compound **187f** instead of intermediate **A11** in step 1 and using intermediate **C11** instead of

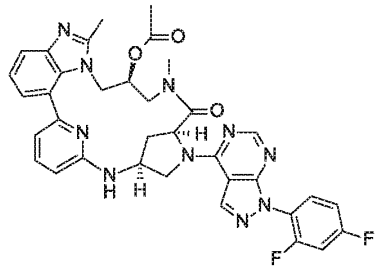
intermediate **C2** in step 5. The mixture of Example **189** (faster eluted) and Example **190** (Slower eluted) was separated via prep-HPLC.

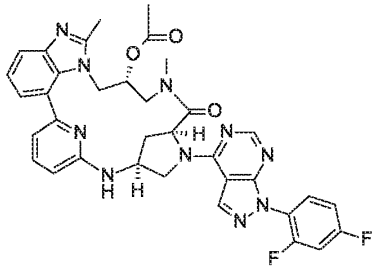
Example 189, LCMS ($M+H^+$): 663, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.20 - 8.15 (m, 1H), 7.76 - 7.69 (m, 1H), 7.61 (br d, *J* = 7.8 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.26 (br t, *J* = 7.7 Hz, 1H), 7.16 - 7.09 (m, 1H), 7.08 - 7.01 (m, 1H), 6.92 - 6.82 (m, 1H), 6.58 (br d, *J* = 8.2 Hz, 1H), 5.80 (br d, *J* = 15.7 Hz, 1H), 5.49 (br d, *J* = 9.2 Hz, 1H), 4.68 (br t, *J* = 4.9 Hz, 1H), 4.56 - 4.49 (m, 1H), 4.31 (br d, *J* = 11.1 Hz, 1H), 4.21 - 4.05 (m, 2H), 3.79 - 3.72 (m, 4H), 3.16 - 3.03 (m, 3H), 2.67 - 2.62 (m, 1H), 2.61 - 2.56 (m, 3H), 2.55 - 2.48 (m, 1H), 0.79 (s, 3H).

Example 190, LCMS ($M+H^+$): 663, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.18 (s, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.06 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.88 (dt, *J* = 2.7, 8.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.66 (d, *J* = 15.4 Hz, 1H), 5.48 (d, *J* = 9.0 Hz, 1H), 4.70 (t, *J* = 5.2 Hz, 1H), 4.54 (dd, *J* = 6.2, 11.4 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.26 (br d, *J* = 15.4 Hz, 1H), 4.14 (d, *J* = 13.9 Hz, 1H), 3.78 - 3.74 (m, 3H), 3.11 (s, 3H), 2.76 - 2.71 (m, 1H), 2.70 - 2.67 (m, 3H), 2.65 (d, *J* = 13.9 Hz, 1H), 2.61 - 2.53 (m, 1H), 0.47 - 0.40 (m, 3H).

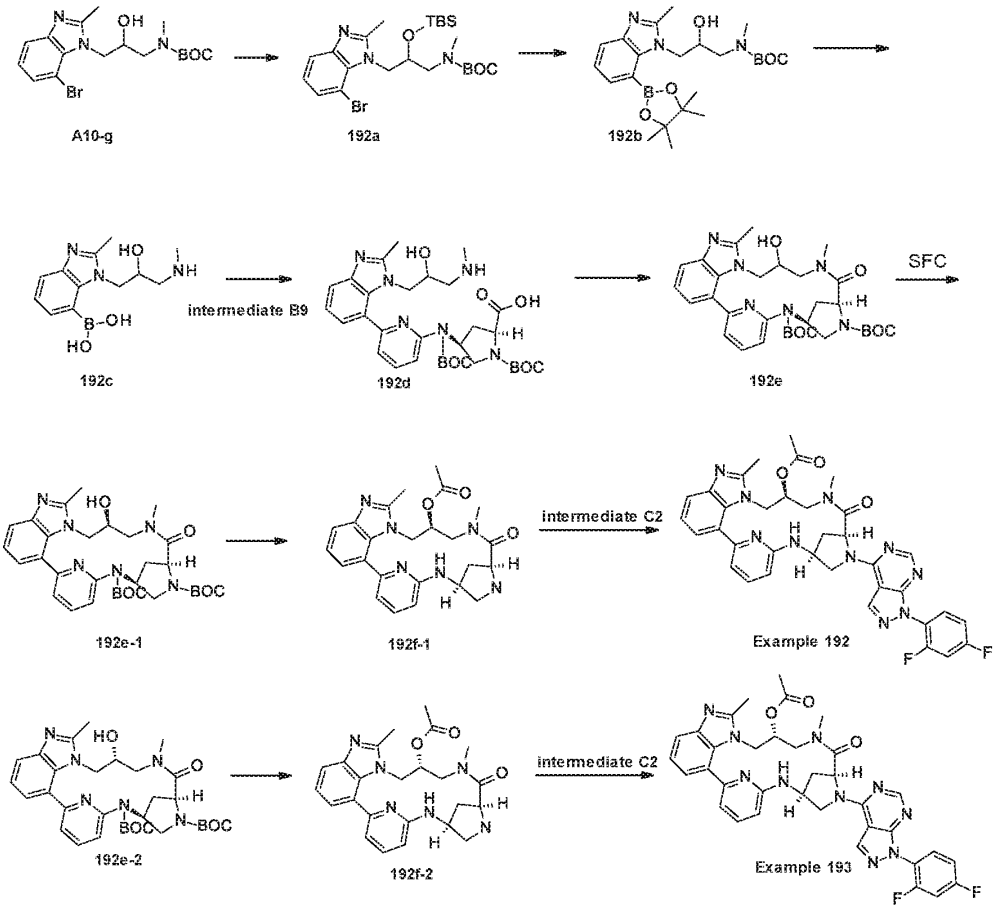
Example 192 and Example 193

[(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate





The title compounds were prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]-*N*-methyl-carbamate (compound 192a)

A mixture of intermediate **A10-g**, (3 g, 7.53 mmol), imidazole (5.12 g, 75.3 mmol) and TBDMS-Cl (5.67 g, 37.6 mmol) in DMF (95 mL) was stirred at r.t. for 16 hrs, then the reaction was diluted with EA, washed with water and brine. The organic layer was concentrated and the residue was purified by silica gel to give compound **192a**. LCMS ($M+H^+$): 512.

Step 2~5: preparation of di*tert*-butyl (8*S*,11*S*,15*R*)-15-hydroxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate and ditert-butyl (8*S*,11*S*,15*S*)-15-hydroxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound 192e-1 and 192e-2)

The preparation of compound **192e** was in analogy to the preparation of compound **161e** by using compound **192a** instead of compound **161a**. LCMS: LCMS ($M+H^+$): 607. Compound **192e** was separated by SFC to give compound **192e-1** (faster eluted) and **192e-2** (slower eluted).

SFC condition: Instrument: SFC 80. Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O). Gradient: B 25%. Flow rate: 60 mL /min. Backpressure: 100bar.

Step 6: preparation of [(8*S*,11*S*,15*R*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (compound 192f-1) and [(8*S*,11*S*,15*S*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (compound 192f-2)

To a tube was added *ditert*-butyl (8*S*,11*S*,15*R*)-15-hydroxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound **192e-1**, 130 mg, 0.214 mmol) and Ac_2O (1.08 g, 1 mL, 10.6 mmol), the solution was heated to 80 °C and stirred for about 16 hrs. The mixture was concentrated directly to give an oil (140 mg). Then it was dissolved in dichloromethane (1 mL) and TFA (1.48 g, 1 mL, 12.98 mmol), the solution was stirred at r.t. for 1 hr. The mixture was concentrated directly to give compound **192f-1** (160 mg). LCMS ($M+H^+$): 449.

To a tube was added *ditert*-butyl (8*S*,11*S*,15*S*)-15-hydroxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-7,10-dicarboxylate (compound **192e-2**, 130 mg, 0.214 mmol) and Ac_2O (1.08 g, 1 mL, 10.6 mmol), the solution was heated to 80 °C and stirred for about 16 hrs. The mixture was concentrated directly to give an oil (135 mg). Then it was dissolved in dichloromethane (1 mL) and TFA (1.48 g, 1.0 mL, 12.98 mmol), the solution was stirred at r.t. for 1 hr. The mixture was concentrated directly to give compound **192f-2** (150 mg). LCMS ($M+H^+$): 449.

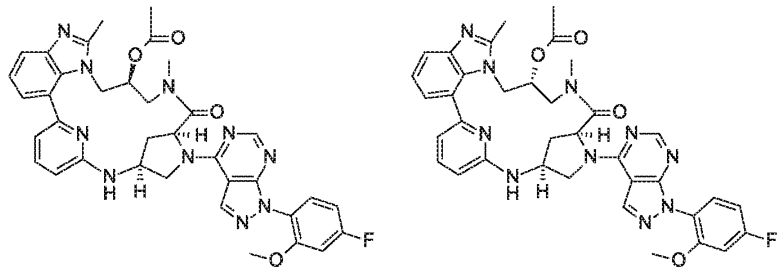
Step 7: preparation of [(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (Example 192 and Example 193)

To a microwave tube was added [(8*S*,11*S*,15*R*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (compound **192f-1**, 28.13 mg, 0.050 mmol), 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (intermediate **C2**, 13.3 mg, 0.050 mmol), DIEA (38.8 mg, 52.4 µL, 0.300 mmol) and acetonitrile (0.667 mL), a yellow solution formed. The mixture was heated to 85 °C and stirred for about 1 hr. The mixture was concentrated to give an oil and then it was purified via prep-HPLC to give Example **192**. LCMS (M+H$^+$): 679. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.22 (s, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.67 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.59 - 7.55 (m, 1H), 7.54 - 7.48 (m, 1H), 7.32 - 7.25 (m, 1H), 7.24 - 7.17 (m, 1H), 7.13 - 7.08 (m, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.20 (dd, *J* = 4.0, 15.3 Hz, 1H), 5.47 (d, *J* = 8.9 Hz, 1H), 4.69 (t, *J* = 4.9 Hz, 1H), 4.57 - 4.49 (m, 1H), 4.49 - 4.40 (m, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.23 - 4.12 (m, 2H), 3.04 (s, 3H), 2.98 - 2.92 (m, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 2.83 (s, 3H), 2.58 - 2.48 (m, 1H), 1.73 (s, 3H).

To a microwave tube was added [(8*S*,11*S*,15*S*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate (28.1 mg, 0.050 mmol), 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (intermediate **C2**, 13.3 mg, 0.050 mmol), DIEA (64.6 mg, 87.3 µL, 0.500 mmol) and acetonitrile (0.667 mL), a yellow solution formed. The mixture was heated to 85 °C and stirred for about 1 hr. The mixture was concentrated to give an oil and then it was purified via prep-HPLC to give Example **193**. LCMS (M+H$^+$): 679. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.22 (s, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.68 - 7.62 (m, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.32 - 7.26 (m, 1H), 7.23 - 7.17 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.51 - 6.34 (m, 1H), 5.51 (d, *J* = 9.2 Hz, 1H), 5.23 (br dd, *J* = 5.0, 10.9 Hz, 1H), 4.77 - 4.74 (m, 1H), 4.62 - 4.54 (m, 1H), 4.46 (br d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.30 - 4.22 (m, 1H), 3.19 (dd, *J* = 5.4, 14.9 Hz, 1H), 3.05 (s, 3H), 2.79 (s, 3H), 2.76 - 2.72 (m, 1H), 2.65 - 2.57 (m, 1H), 1.57 (s, 3H).

Example 194 and Example 195

[(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate and [(8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate



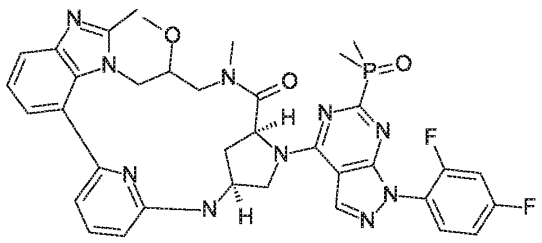
The title compounds were preparation in analogy to the preparation of Example **192** and Example **193** by using Intermediate **C11** instead of Intermediate **C2** in step 7.

Example 194, LCMS (M+H$^+$): 691, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 8.16 (s, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.12 - 7.09 (m, 1H), 7.06 (dd, *J* = 2.5, 10.6 Hz, 1H), 6.92 - 6.85 (m, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.16 (dd, *J* = 3.8, 15.3 Hz, 1H), 5.46 (d, *J* = 8.9 Hz, 1H), 4.68 (t, *J* = 4.9 Hz, 1H), 4.55 - 4.49 (m, 1H), 4.47 - 4.40 (m, 1H), 4.37 - 4.26 (m, 1H), 4.23 - 4.11 (m, 2H), 3.79 - 3.74 (m, 3H), 3.14 - 3.02 (m, 3H), 2.93 (br d, *J* = 13.9 Hz, 1H), 2.85 (d, *J* = 12.5 Hz, 1H), 2.81 - 2.75 (m, 3H), 2.57 - 2.49 (m, 1H), 1.73 - 1.67 (m, 3H).

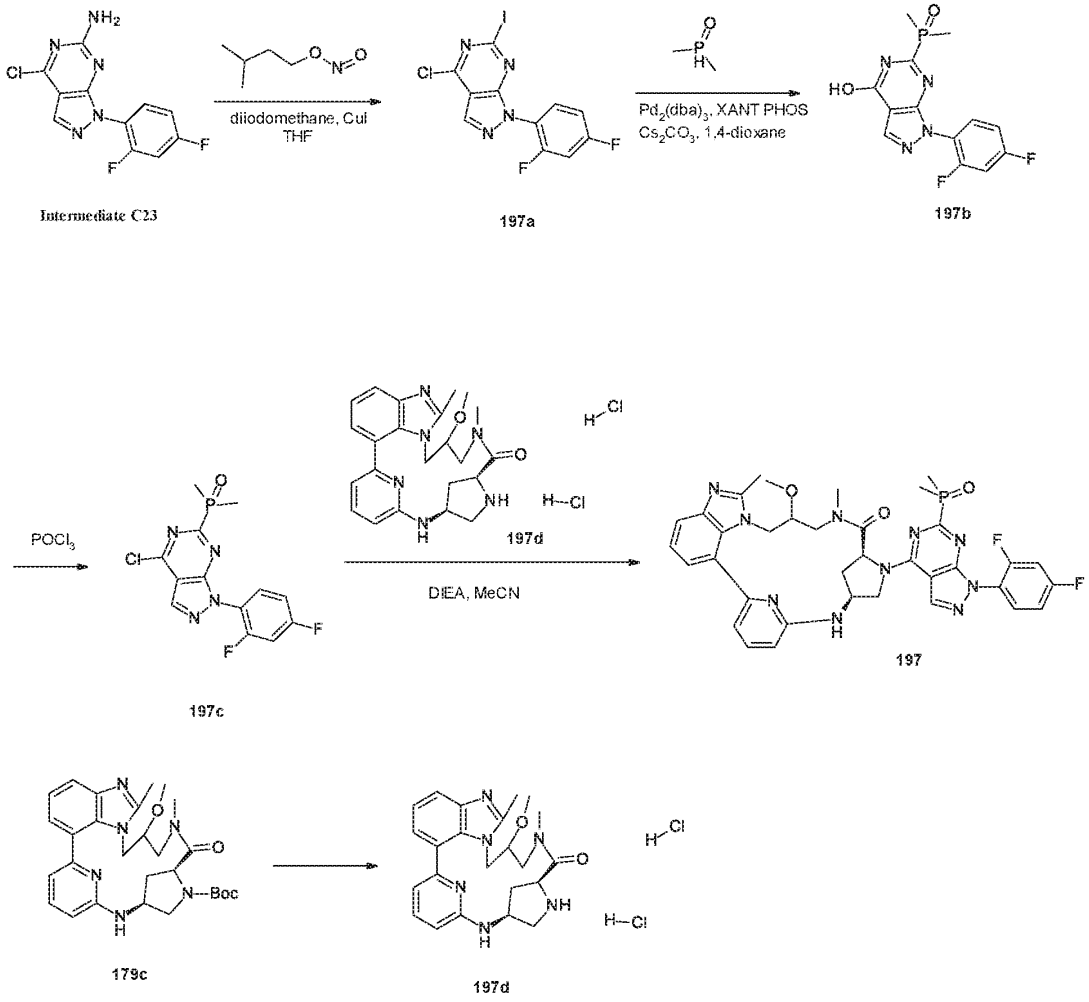
Example 195, LCMS (M+H$^+$): 691, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.22 (s, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.68 - 7.62 (m, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.32 - 7.26 (m, 1H), 7.23 - 7.17 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.51 - 6.34 (m, 1H), 5.51 (d, *J* = 9.2 Hz, 1H), 5.23 (br dd, *J* = 5.0, 10.9 Hz, 1H), 4.77 - 4.74 (m, 1H), 4.62 - 4.54 (m, 1H), 4.46 (br d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.30 - 4.22 (m, 1H), 3.19 (dd, *J* = 5.4, 14.9 Hz, 1H), 3.16 - 3.04 (m, 3H), 2.81 - 2.77 (m, 3H), 2.76 (s, 1H), 2.65 - 2.57 (m, 1H), 1.60 - 1.54 (m, 3H).

Example 197

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-chloro-1-(2,4-difluorophenyl)-6-iodo-pyrazolo[3,4-d]pyrimidine (compound 197a)

To a suspension of **Intermediate C23** (700 mg, 2.49 mmol), diiodomethane (3.33 g, 1.0 mL, 12.43 mmol) and copper (I) iodide (946 mg, 4.97 mmol) in extra dry tetrahydrofuran (40 mL) was added isoamyl nitrite (998 µL, 7.46 mmol) dropwise under nitrogen atmosphere. After the addition, the reaction mixture was stirred at 90°C for 3 hours. The mixture was cooled to the room temperature, EtOAc (60 mL) was added to dilute the solution, $Na_2S_2O_3$ (saturated solution, 30 mL) was added and the organic layer was washed with water (twice, 50 mL). The organic layer was dried and concentrated, the crude product was purified by silica gel to afford compound **197a** (420 mg). LCMS ($M+H^+$): 393.

Step 2: preparation of 1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-d]pyrimidin-4-ol (compound 197b)

To a mixture of compound **197a** (120 mg, 0.284 mmol) in extra dry 1,4-dioxane (6 mL) was added methylphosphonoylmethane (24 mg, 0.313 mmol), $Pd_2(dba)_3$ (26 mg, 0.028 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (33 mg, 0.057 mmol), cesium carbonate (185 mg, 0.569 mmol). The resulting mixture was stirred at 90 °C overnight. The mixture was concentrated and the residue was purified by silica gel to afford compound **197b** (80 mg). LCMS ($M+H^+$): 325.

Step 3: preparation of 4-chloro-1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-*d*]pyrimidine (compound 197c)

A suspension of compound **197c** (80 mg, 0.247 mmol) in phosphorus oxychloride (1 mL, 10.73 mmol) was stirred at 90 °C for 2 hours. The reaction mixture was cooled to room temperature and then removed the solvent. The resulting residue was purified by silica gel to afford compound **197c** (64 mg). LCMS ($M+H^+$): 343.

Step 4: preparation of (8*S*,11*S*)-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 197d)

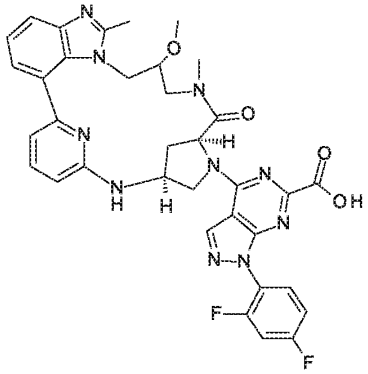
A solution of compound **179c** (972 mg, 1.49 mmol) in dichloromethane (10 mL) was added a HCl solution(4M in dioxane, 5 mL, 20 mmol) at 0 °C and then stirred at room temperature for 4 hours. The solvent was removed to afford crude product compound **197d** (954 mg). LCMS ($M+H^+$): 421.

Step 5: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 197)

A solution of compound **197c** (22 mg, 0.064 mmol), compound **197d** (45 mg, 0.064 mmol) and DIEA (33 μL, 0.193 mmol) in 1,4-dioxane (2 mL) was stirred at 70 °C for 1 hour. The solvent was removed and purified by prep-HPLC to afford Example **197** (12.6 mg). LCMS ($M+H^+$): 727. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.51 - 8.45 (m, 1H), 7.79 - 7.66 (m, 1H), 7.64 - 7.53 (m, 2H), 7.41 - 7.16 (m, 3H), 7.14 - 7.00 (m, 2H), 6.85 - 6.58 (m, 1H), 5.87 - 5.68 (m, 1H), 5.53 - 5.21 (m, 1H), 4.68 - 4.58 (m, 1H), 4.52 - 4.42 (m, 1H), 4.29 - 4.16 (m, 1H), 4.13 - 4.05 (m, 1H), 4.00 - 3.89 (m, 1H), 3.87 - 3.76 (m, 1H), 3.10 - 2.94 (m, 3H), 2.89 - 2.81 (m, 1H), 2.79 - 2.75 (m, 3H), 2.64 - 2.52 (m, 4H), 2.50 - 2.41 (m, 1H), 1.81 - 1.62 (m, 6H).

Example 198

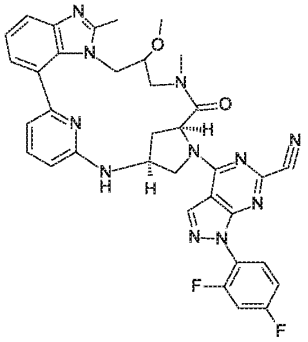
1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid



The title compound was prepared in analogy to the preparation of Example **37** by using Example **214** instead of compound **37a**. Example **198** (13 mg) was obtained. LCMS (M+H$^+$): 695. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.54 - 8.46 (m, 1H), 7.81 - 7.53 (m, 5H), 7.24 - 7.14 (m, 1H), 7.13 - 7.02 (m, 2H), 6.71 - 6.63 (m, 1H), 6.09 - 5.95 (m, 1H), 5.68 - 5.34 (m, 1H), 4.67 - 4.57 (m, 1H), 4.53 - 4.42 (m, 1H), 4.32 - 4.17 (m, 2H), 4.11 - 3.96 (m, 1H), 3.90 - 3.81 (m, 1H), 3.12 - 2.95 (m, 4H), 2.91 - 2.80 (m, 4H), 2.77 - 2.67 (m, 3H), 2.52 - 2.40 (m, 2H).

Example 199

1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile

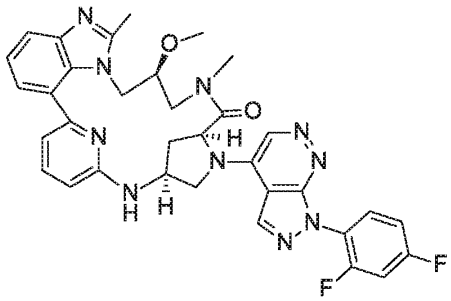


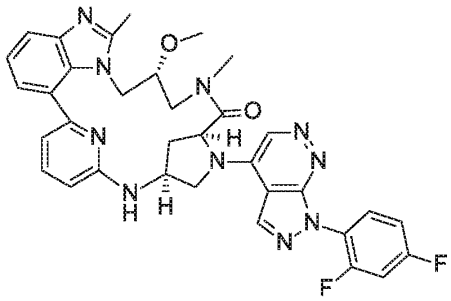
The title compound was prepared in analogy to the preparation of Example **214** by using 4-intermediate **C27** instead of compound **214c**. Example **199** (7 mg) was obtained. LCMS (M+H$^+$): 676. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.70 - 8.50 (m, 1H), 7.93 - 7.59 (m, 3H), 7.47 - 7.08 (m, 5H), 6.97 - 6.59 (m, 1H), 5.86 - 5.68 (m, 1H), 5.54 - 5.41 (m, 1H), 4.69 - 4.47 (m, 3H),

4.39 - 3.86 (m, 4H), 3.17 - 3.04 (m, 3H), 3.00 - 2.91 (m, 1H), 2.88 - 2.80 (m, 3H), 2.65 - 2.58 (m, 3H), 2.56 - 2.48 (m, 1H).

Example 200 and Example 201

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The compounds were prepared analogy to the preparation of Example **179** and Example **180** by using intermediate **C6** instead of intermediate **C2**.

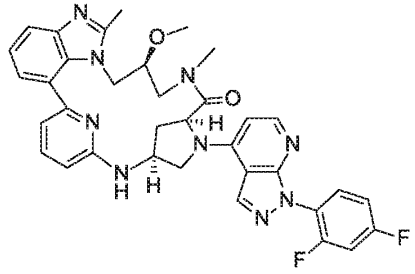
Example 200, LCMS (M+H$^+$): 651. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.70 - 8.50 (m, 1H), 8.21 - 7.91 (m, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.78 - 7.69 (m, 1H), 7.67 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.41 - 7.36 (m, 1H), 7.32 - 7.26 (m, 1H), 7.21 (br t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.78 (br d, *J* = 15.0 Hz, 1H), 5.47 - 5.22 (m, 1H), 4.67 - 4.45 (m, 2H), 4.36 (br d, *J* = 10.8 Hz, 1H), 4.28 - 4.07 (m, 2H), 4.05 - 3.85 (m, 1H), 3.16 - 3.12 (m, 1H), 3.12 - 3.02 (m, 3H), 2.85 (s, 3H), 2.63 (br s, 3H), 2.61 - 2.49 (m, 2H).

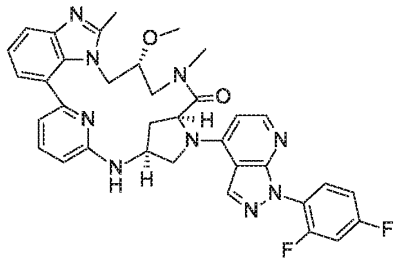
Example 201, LCMS (M+H$^+$): 651. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.72 - 8.51 (m, 1H), 8.16 - 7.88 (m, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.71 (br s, 1H), 7.67 - 7.62 (m, 1H), 7.39 - 7.33 (m, 2H), 7.30 (ddd, *J* = 2.7, 8.8, 10.3 Hz, 1H), 7.23 - 7.16 (m, 1H), 6.95 (br d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.57 - 5.39 (m, 1H), 5.36 - 5.17 (m, 1H), 4.73 - 4.63 (m, 1H), 4.41 - 4.25 (m, 1H), 4.21 - 3.99 (m, 3H), 3.76 - 3.64 (m, 1H), 3.23 - 3.18 (m, 1H), 3.17 - 3.05 (m, 3H), 3.01 - 2.88 (m, 1H), 2.87 (s, 3H), 2.65 (br s, 3H), 2.64 - 2.58 (m, 1H).

Example 202 and Example 203

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-

difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





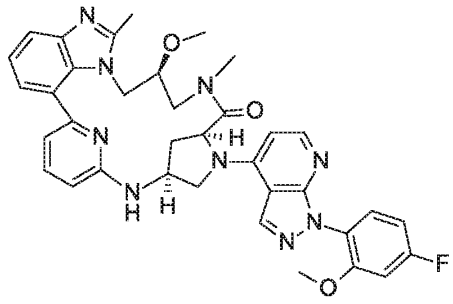
The compounds were prepared analogy to the preparation of Example **179** and Example **180** by using Intermediate **C8** instead of Intermediate **C2** (Reaction condition: using $Pd_2(dba)_3$, BINAP, Cs_2CO_3, dioxane 100°C instead of DIPEA, CAN 85°C).

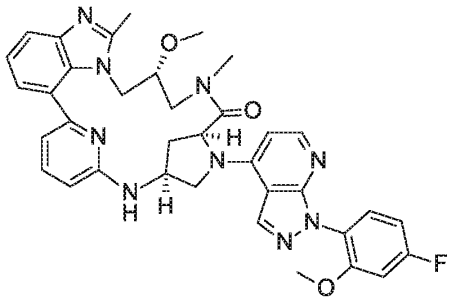
Example 202, LCMS (M+H$^+$): 650, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.71 - 8.34 (m, 1H), 8.15 - 7.95 (m, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.64 (br d, *J* = 7.5 Hz, 2H), 7.58 - 7.53 (m, 1H), 7.31 - 7.24 (m, 1H), 7.20 (br t, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.57 - 6.08 (m, 1H), 6.02 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.55 - 5.02 (m, 1H), 4.66 - 4.38 (m, 2H), 4.33 - 4.06 (m, 2H), 3.97 (br dd, *J* = 9.4, 14.1 Hz, 1H), 3.11 (br s, 3H), 3.06 - 2.96 (m, 2H), 2.92 (s, 3H), 2.76 (s, 3H), 2.67 - 2.51 (m, 2H).

Example 203, LCMS (M+H$^+$): 650, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.83 - 8.68 (m, 1H), 8.18 - 7.87 (m, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.80 - 7.77 (m, 1H), 7.76 - 7.68 (m, 1H), 7.63 (br d, *J* = 4.7 Hz, 2H), 7.42 - 7.33 (m, 1H), 7.27 (br t, *J* = 7.6 Hz, 1H), 7.06 - 6.96 (m, 1H), 6.76 (br d, *J* = 8.4 Hz, 1H), 6.73 - 6.29 (m, 1H), 5.72 - 5.51 (m, 1H), 5.42 - 5.23 (m, 1H), 4.77 - 4.63 (m, 1H), 4.53 - 4.27 (m, 1H), 4.24 - 4.04 (m, 2H), 3.87 - 3.73 (m, 1H), 3.29 - 3.25 (m, 1H), 3.23 - 3.07 (m, 4H), 3.03 - 2.96 (m, 1H), 2.95 (s, 3H), 2.85 (s, 3H), 2.77 - 2.64 (m, 1H).

Example 204 and Example 205

(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





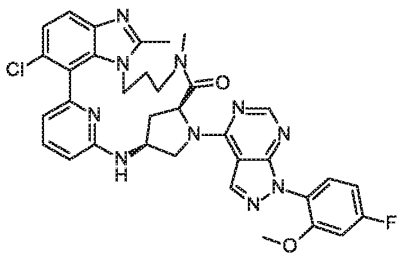
The compounds were prepared analogy to the preparation of Example **179** and Example **180** by using Intermediate **C9** instead of Intermediate **C2** (Reaction condition: using $Pd_2(dba)_3$, BINAP, Cs_2CO_3, dioxane 100°C instead of DIPEA, CAN 85°C).

Example 204, LCMS ($M+H^+$): 662, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.76 - 8.35 (m, 1H), 8.14 - 7.90 (m, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.46 (br t, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 2.4, 10.6 Hz, 1H), 6.89 (dt, *J* = 2.4, 8.2 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.56 - 6.06 (m, 1H), 5.91 (br dd, *J* = 4.0, 15.3 Hz, 1H), 5.58 - 5.07 (m, 1H), 4.67 - 4.48 (m, 2H), 4.23 (br dd, *J* = 11.1, 15.3 Hz, 2H), 3.97 (br dd, *J* = 9.5, 14.0 Hz, 1H), 3.77 (s, 3H), 3.18 - 2.93 (m, 5H), 2.88 (s, 3H), 2.69 (s, 3H), 2.65 - 2.48 (m, 2H).

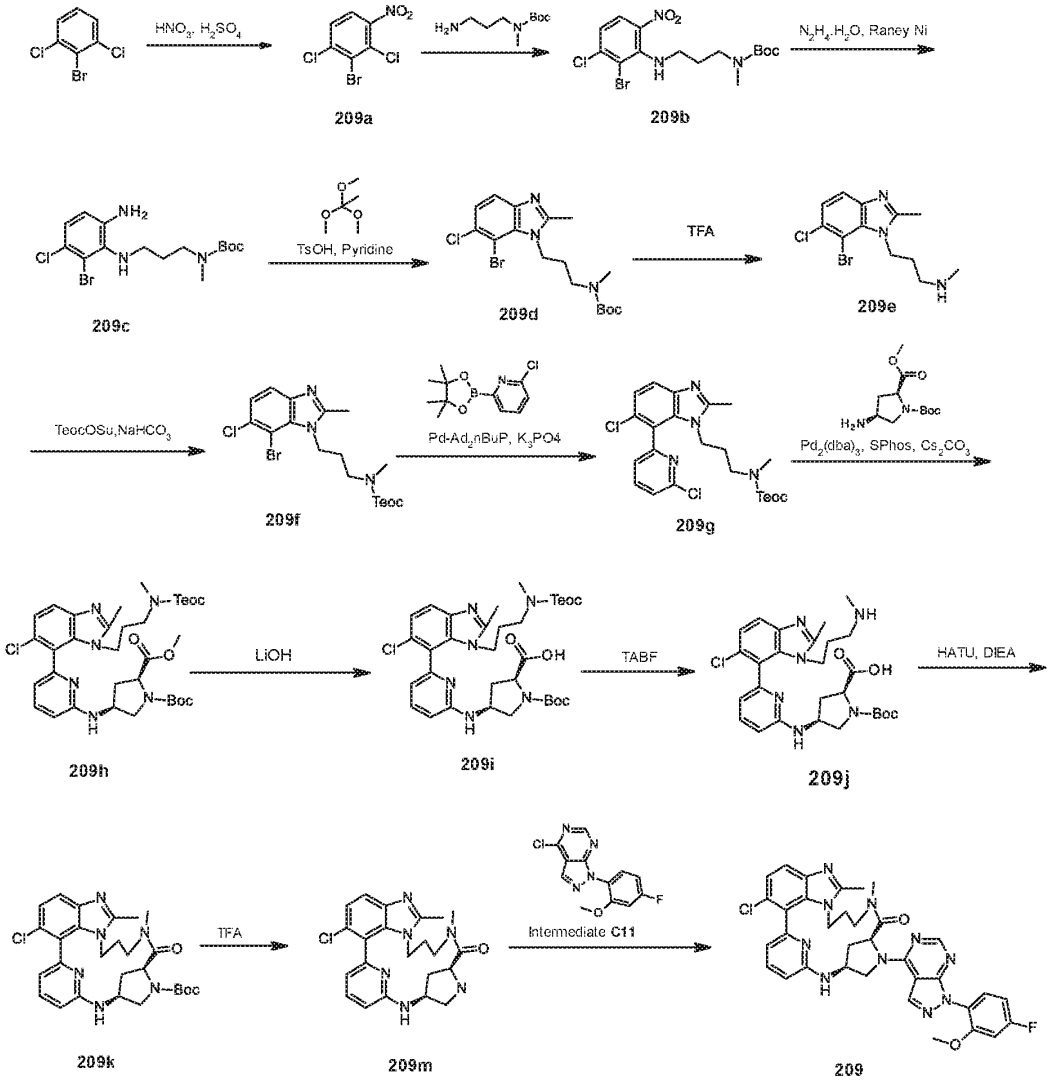
Example 205, LCMS ($M+H^+$): 662, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.74 - 8.46 (m, 1H), 8.07 - 7.86 (m, 1H), 7.79 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.51 - 7.36 (m, 3H), 7.07 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.95 (br d, *J* = 7.2 Hz, 1H), 6.89 (dt, *J* = 2.6, 8.3 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.59 - 6.02 (m, 1H), 5.68 - 5.10 (m, 2H), 4.73 - 4.55 (m, 2H), 4.17 - 4.03 (m, 2H), 3.76 (s, 3H), 3.75 (br s, 1H), 3.23 - 3.06 (m, 4H), 2.94 - 2.90 (m, 1H), 2.89 (s, 3H), 2.88 - 2.83 (m, 1H), 2.71 (s, 3H), 2.67 (br d, *J* = 15.1 Hz, 1H).

Example 209

(8*S*,11*S*)-23-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-bromo-1,3-dichloro-4-nitro-benzene (compound 209a)

In a 100.0 mL round-bottom flask was added H_2SO_4 (20.0 mL) and to the mixture was added HNO_3 (6.0 g, 66.67 mmol) dropwise over 15 minutes. Then a solution of 1-bromo-2,6-dichlorobenzene (10.0 g, 44.27 mmol) in dichloromethane (10.0 mL) was added to the mixture dropwise and the mixture was stirred at 20 °C for 12 h. The mixture was poured into ice (100.0 g) and extracted with EtOAc (50.0 mL twice). The combined organic layer was washed with $NaHCO_3$ aqueous solution and brine (50.0 mL), dried and concentrated to give compound **209a** (10.0 g). LCMS ($M+H^+$): 271.

Step 2: preparation of *tert*-butyl *N*-[3-(2-bromo-3-chloro-6-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 209b)

To a mixture of 2-bromo-1,3-dichloro-4-nitro-benzene (**209a**, 10.0 g, 36.91 mmol) in DMF (100.0 mL) was added a solution of N-(3-aminopropyl)-N-methylcarbamic acid tert-butylester (10.4 g, 55.37 mmol) in DMF (100.0 mL). The mixture was stirred at 20 °C for 16 h. To the mixture was added 2-bromo-1,3-dichloro-4-nitro-benzene (10.0 g, 36.91 mmol) and the resulting mixture was stirred at 20 °C for 2 h. The mixture was poured into water (200.0 mL) and extracted with EtOAc (200.0 mL for 3 times). The combined organic layer was washed with water (200.0 mL for 5 times), dried and concentrated. The residue was purified by flash chromatography column to give compound **209b** (13.0 g). LCMS ($M+H^+$): 422.

Step 3: preparation of *tert*-butyl *N*-[3-(6-amino-2-bromo-3-chloro-anilino)propyl]-*N*-methyl-carbamate (compound 209c)

To a mixture of *tert*-butyl *N*-[3-(2-bromo-3-chloro-6-nitro-anilino)propyl]-*N*-methyl-carbamate (**209b**, 13.0 g, 30.75 mmol) in methanol (100.0 mL) was added Raney Ni (15.0 g) under N_2. Then $N_2H_4 \cdot H_2O$ (15.0 g, 312.50 mmol) was added dropwise at 20 °C over 0.5 h. The resulting mixture was stirred at 20 °C for 0.5 h, and then filtered. The filtrate was concentrated and the residue was taken in DCM (300.0 mL) and washed with water (100.0 mL for 3 times). The organic layer was dried and concentrated to give compound **209c** (10.0 g). LCMS ($M+H^+$): 394.

Step 4: preparation of *tert*-butyl *N*-[3-(7-bromo-4-fluoro-2-oxo-3H-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 209d)

To a solution of *tert*-butyl *N*-[3-(6-amino-2-bromo-3-chloro-anilino)propyl]-*N*-methyl-carbamate (**209c**, 10.0 g, 7.64 mmol) in THF (100 mL) was added trimethyl orthoacetate (2.8 g, 22.92 mmol). The mixture was stirred at 20 °C for 12 h under N_2 and then concentrated. The residue was taken in EtOAc (200.0 mL) and washed with brine (100.0 mL twice). The organic layer was dried and concentrated, the residue was purified by flash chromatography column to give compound **209d** (2.5 g). LCMS ($M+H^+$): 420.

Step 5: preparation of 3-(7-bromo-6-chloro-2-methyl-benzimidazol-1-yl)-*N*-methyl-propan-1-amine (compound 209e)

To a solution of *tert*-butyl *N*-[3-(7-bromo-6-chloro-2-methyl-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (**209d**, 2.5 g, 6.00 mmol) in DCM (10.0 mL) was added TFA (3.0 mL) and the mixture was stirred at 20 °C for 12 h under N_2. The mixture was concentrated to give compound **209e** (1.8 g). LCMS ($M+H^+$): 320.

Step 6: preparation of 2-trimethylsilylethyl *N*-[3-(7-bromo-6-chloro-2-methyl-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 209f)

To a solution of 3-(7-bromo-6-chloro-2-methyl-benzimidazol-1-yl)-*N*-methyl-propan-1-amine (**209e**, 1.2 g, 3.79 mmol) and 2,5-dioxopyrrolidin-1-yl (2-(trimethylsilyl)ethyl) carbonate (1.5 g, 5.69 mmol) in THF (50.0 mL) was added saturated aqueous solution of $NaHCO_3$ (50.0 mL) dropwise. The reaction mixture was stirred at 25 °C for 1 h, and then adjusted to pH=7 by saturated aq. NH_4Cl. The mixture was extracted with EtOAc (100.0 mL twice) and the combined organic layer was washed with brine (100.0 mL twice), dried and concentrated. The residue was purified by reversed phase flash chromatography to give compound **209f** (1400 mg). LCMS ($M+H^+$): 462.

Step 7: preparation of 2-trimethylsilylethyl *N*-[3-[6-chloro-7-(6-chloro-2-pyridyl)-2-methyl-benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 209g)

To a solution of compound **209f** (1.7 g, 3.82 mmol) in 1,4-dioxane (40.0 mL) and water (4.0 mL) was added 6-chloropyridine-2-boronic acid pinacol ester (1.4 g, 5.73 mmol), chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (200.0 mg), phosphoric acid and potassium salt (0.6 mL, 7.64 mmol) under Ar, and the mixture was stirred at 80 °C for 4 h. The mixture was diluted with EtOAc (100.0 mL) and then washed with brine (100.0 mL twice), dried and concentrated. The residue was purified by reversed phase flash chromatography to give compound **209g** (1.5 g). LCMS ($M+H^+$): 493.

Step 8: Preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[5-chloro-2-methyl-3-[3-[methyl(2-trimethylsilylethoxycarbonyl)amino]propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 209h)

To a solution of compound **209g**, (1.3 g, 2.63 mmol) in 1,4-dioxane (20.0 mL) was added *O*1-tert-butyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (1.5 g, 5.27 mmol), cesium carbonate (2.6 g, 7.90 mmol), SPhos (200.0 mg) and $Pd_2(dba)_3$ (200.0 mg) under Ar. The mixture was stirred at 90 °C for 12 h. After cooled to r.t., the reaction mixture was diluted with EtOAc (200.0 mL) and poured into water (200.0 mL). The aqueous layer was extracted with EtOAc (200.0 mL twice). The combined organic layer was washed with brine (200.0 mL twice), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give compound **209h** (800.0 mg). LCMS ($M+H^+$): 701.

Step 9: preparation of *tert*-butyl (2*S*,4*S*)-1-tert-butoxycarbonyl-4-[[6-[5-chloro-2-methyl-3-[3-[methyl(2-trimethylsilylethoxycarbonyl)amino]propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 209i)

A solution of compound **209h** (400.0 mg, 0.57 mmol) and lithium hydroxide hydrate (136.6 mg, 5.70 mmol) in methanol (5.0 mL) and water (1.0 mL) was stirred at 25 °C for 12 h.

The reaction mixture was diluted with EtOAc (100.0 mL) and poured into water (100.0 mL). The resulting mixture was extracted with EtOAc (100.0 mL twice). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by reversed phase flash chromatography to give compound **209i** (250.0 mg). LCMS ($M+H^+$): 687.

Step 10: preparation of (2*S*,4*S*)-1-tert-butoxycarbonyl-4-[[6-[5-chloro-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 209j)

To a solution of TBAF in THF (5.0 mL, 5.00 mmol) was added of compound **209i** (250.0 mg, 0.36 mmol). The mixture was stirred at 25 °C for 12 h and then partitioned between EtOAc (100.0 mL) and water (100.0 mL). The aqueous layer was extracted with EtOAc (100.0 mL twice). The combined organic layer was washed with brine (100.0 mL twice), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by reversed phase flash chromatography to give compound **209j** (200.0 mg). LCMS ($M+H^+$): 543.

Step 11: preparation of *tert*-butyl (8*S*,11*S*)-23-chloro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaene-10-carboxylate (compound 209k)

A solution of HATU (93.6 mg, 0.40 mmol), DIEA (64.3 mg, 0.50 mmol) in DMF (250.0 mL) was stirred at 0 °C for 0.5 h. Then compound **209j** (180.0 mg, 0.33 mmol) in DMF (250.0 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, and then concentrated. The residue was purified by reversed phase flash chromatography to give compound **209k** (160.0 mg). LCMS ($M+H^+$): 525.

Step 12 : preparation of (8*S*,11*S*)-23-chloro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (compound 209m)

A solution of compound **209k** (160.0 mg, 0.3 mmol) in trifluoroacetic acid (3.0 mL, 38.94 mmol) was stirred at 25°C for 1h. The mixture was concentrated under reduced pressure to give compound **209m** (150.0 mg) as a light yellow solid, which was used in next step directly. LCMS ($M+H^+$): 425.

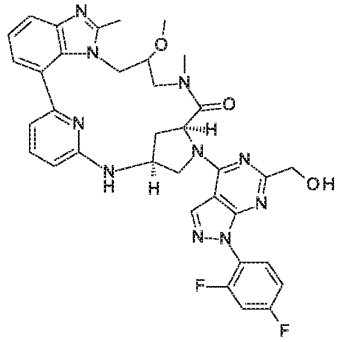
Step 13: preparation of (8*S*,11*S*)-23-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 209)

To a solution of compound **209m** (91.5 mg, 0.22 mmol) and DIEA (34.7 mg, 0.27 mmol)

in NMP (3.0 mL) was added 4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (50.0 mg, 0.18 mmol). The reaction mixture was stirred at 80 °C for 1 h, and then purified by prep-HPLC to give Example **209** (43.1 mg). LCMS ($M+H^+$): 667. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.51 - 8.46 (m, 1H), 8.12 (m, 1H), 7.80 (m, 1H), 7.54 (m, 1H), 7.47 - 7.41 (m, 1H), 7.29 (s, 1H), 7.07 - 7.03 (m, 1H), 6.89 - 6.81 (m, 2H), 6.65 (m, 1H), 5.52 - 5.46 (m, 1H), 4.80 - 4.72 (m, 1H), 4.63 - 4.57 (m, 2H), 4.27 (m, 1H), 4.07 - 3.98 (m, 2H), 3.76 - 3.74 (m, 3H), 3.43 - 3.37 (m, 1H), 3.19 (s, 1H), 3.09 (s, 3H), 2.82 (m, 1H), 2.69 - 2.62 (m, 1H), 2.58 (s, 3H), 1.19 - 1.11 (m, 1H).

Example 211

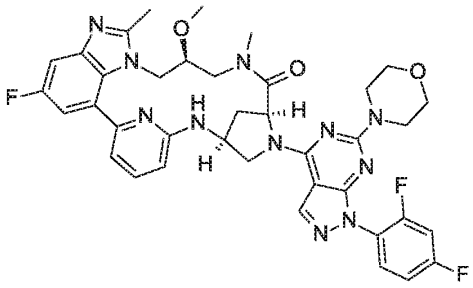
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



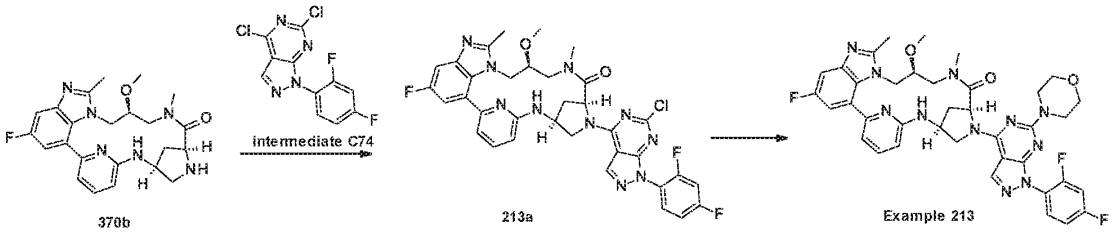
The title compound was prepared in analogy to the preparation of Example **34** by using Example **214** instead of compound **36j.** LCMS ($M+H^+$): 681. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 7.84 - 7.72 (m, 1H), 7.70 - 7.58 (m, 2H), 7.38 - 7.34 (m, 1H), 7.29 - 7.23 (m, 2H), 7.18 (br t, J = 7.7 Hz, 1H), 7.13 - 7.08 (m, 1H), 6.71 - 6.62 (m, 1H), 5.82 - 5.68 (m, 1H), 5.67 - 5.58 (m, 1H), 5.45 - 5.32 (m, 1H), 4.68 - 4.47 (m, 4H), 4.35 - 4.22 (m, 1H), 4.18 - 4.06 (m, 1H), 4.00 - 3.90 (m, 1H), 3.19 - 3.08 (m, 2H), 3.04 (s, 1H), 2.98 - 2.88 (m, 1H), 2.86 - 2.79 (m, 3H), 2.74 - 2.60 (m, 1H), 2.59 - 2.54 (m, 3H), 2.51 (dt, J = 4.4, 9.5 Hz, 1H).

Example 213

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-morpholino-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 213a)

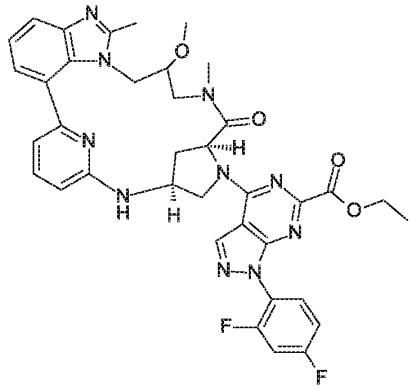
A mixture of compound **370b** (0.90 g, 2.05 mmol), intermediate **C74** (618.0 mg, 2.05 mmol) and DIPEA (1.33 g, 10.26 mmol) in acetonitrile (60 mL) was stirred at 45 °C for 3 hours, then the reaction was concentrated and the residue was purified by silica gel to give compound **213a** (1 g), LCMS (M+H$^+$): 703.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-morpholino-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 213)

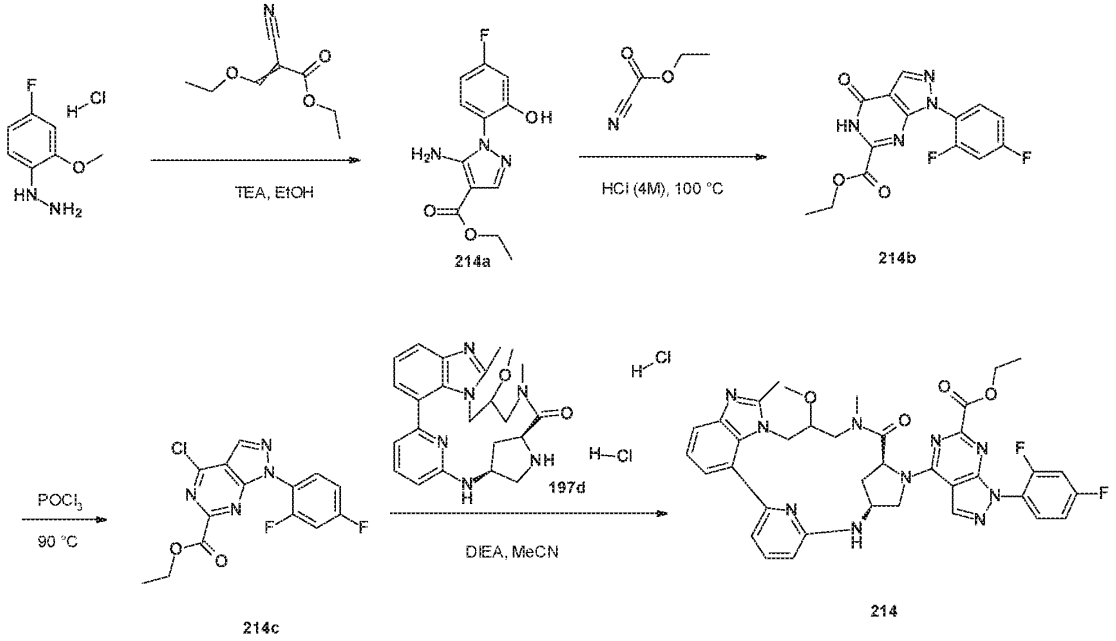
A mixture of compound **213a** (15 mg, 0.021 mmol), morpholine (9.3 mg, 9.3 μL, 0.107 mmol) and DIPEA (27.6 mg, 0.213 mmol) in acetonitrile (1 mL) was stirred at 80 °C for 3 hours, then the reaction was purified by prep-HPLC to give example **213** (15 mg). LCMS (M+H$^+$): 754. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.14 (s, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.58 - 7.48 (m, 1H), 7.48 - 7.42 (m, 1H), 7.39 (dd, J = 2.3, 10.2 Hz, 1H), 7.20 - 6.95 (m, 3H), 6.67 (d, J = 8.3 Hz, 1H), 6.15 - 5.89 (m, 1H), 5.36 - 5.13 (m, 1H), 4.59 - 4.09 (m, 4H), 3.89 - 3.74 (m, 1H), 3.74 - 3.48 (m, 8H), 3.17 - 3.09 (m, 1H), 3.06 - 2.95 (m, 3H), 2.93 - 2.82 (m, 4H), 2.74 - 2.59 (m, 3H), 2.58 - 2.35 (m, 2H).

Example 214

Ethyl 1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carboxylate



The title compound was prepared according to the following scheme:



Step 1: preparation of 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxylic acid ethyl ester (compound 214a)

A solution of 2-cyano-3-ethoxy-acrylic acid ethyl ester (507 mg, 3 mmol), (2,4-difluorophenyl)hydrazine;hydrochloride (54 mg, 3 mmol) and Et_3N (836 µL, 6 mmol) in ethanol

(10 mL) was stirred at 90 °C for 12 hours. The mixture was concentrated and the residue was purified by silica gel to afford compound **198a** (635 mg), LCMS ($M+H^+$): 268.

Step 2: preparation of 1-(2,4-difluorophenyl)-4-keto-5*H*-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid ethyl ester (compound 214b)

To a suspension of compound **214a** (635 mg, 2.38 mmol) and a HCl solution (4 M in dioxane, 12 mL, 48 mmol) at room temperature was added cyanoformic acid ethyl ester (470 mg, 469 μL, 4.75 mmol). The mixture was stirred at 100 °C for 14 hours and then was cooled to room temperature. After 1,4-dioxane was removed in *vacuo*, the residue was partitioned between methylene chloride and water. The organic layer was separated, dried and concentrated, the residue was purified by silica gel to afford compound **214b** (700 mg), LCMS ($M+H^+$): 321.

Step 3: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carboxylic acid ethyl ester (compound 214c)

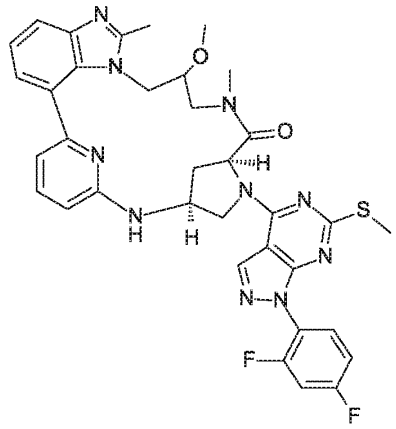
A solution of compound **214b** (120 mg, 0.375 mmol) in phosphorus oxychloride (2.0 mL, 21.46 mmol) was stirred at 90 °C for 4 hours. The cooled solution was poured into cooled saturated $NaHCO_3$ solution and then extracted with EtOAc (10 mL, three times). The combined organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel o afford compound **214c** (80 mg), LCMS ($M+H^+$): 339.

Step 4: preparation of Ethyl 1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidine-6-carboxylate (Example 214)

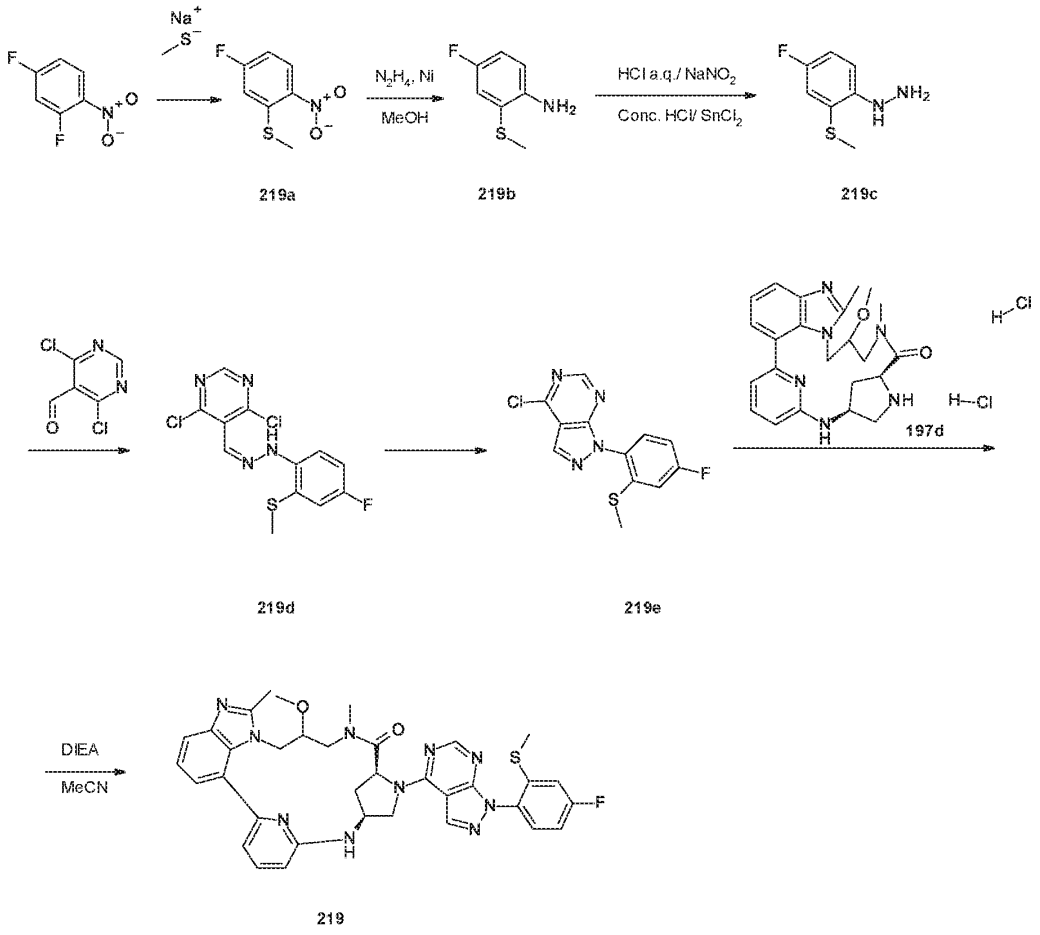
A suspension of compound **214c** (50 mg, 0.140 mmol), compound **197d** (98 mg, 0.140 mmol) and DIEA (74 μL, 0.421 mmol) in acetonitrile (1 mL) was stirred at 70 °C for 0.5 hour. The solvent was removed by reduce pressure and then purified by prep-HPLC to afford Example **214** (33.8 mg), LCMS ($M+H^+$): 723. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 7.80 - 7.66 (m, 1H), 7.65 - 7.45 (m, 3H), 7.43 - 7.32 (m, 1H), 7.23 - 7.14 (m, 1H), 7.13 - 6.81 (m, 2H), 6.66 - 6.57 (m, 1H), 5.98 - 5.76 (m, 1H), 5.58 - 5.34 (m, 1H), 4.66 - 4.56 (m, 1H), 4.50 - 4.18 (m, 5H), 4.18 - 4.08 (m, 1H), 4.05 - 3.93 (m, 1H), 3.89 - 3.80 (m, 1H), 3.09 - 2.90 (m, 4H), 2.86 - 2.76 (m, 4H), 2.66 - 2.57 (m, 3H), 2.51 - 2.40 (m, 1H), 1.33 - 1.20 (m, 3H).

Example 219

(8*S*,11*S*)-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-fluoro-2-(methylthio)-1-nitro-benzene (compound 219a)

To a mixture of 2,4-difluoro-1-nitro-benzene (4.0 g, 25.1 mmol), pyridine (4 mL, 49.5 mmol) in methanol (20 mL) was added the solution of sodium thiomethoxide (1.76 g, 25.1 mmol) in methanol (20 mL) dropwise at 0 °C. The mixture was stirred for 1 hour and then diluted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was recrystallized from EA/PE to afford compound **219a** (2.3 g), LCMS ($M+H^+$): 188.

Step 2: preparation of [4-fluoro-2-(methylthio)phenyl]amine (compound 219b)

To a flask was added nickel (721 mg, 12.29 mmol), methanol (40 mL), compound **219a** (2.3 g, 12.29 mmol), the suspension was stirred vigorously and hydrazine;hydrate (615.09 mg, 12.29 mmol) was added. After being stirred at room temperature for 1 hr, the mixture was filtered through celite, the filtrate was concentrated to give an oil. The oil was dissolved in 40 mL DCM and washed with 20 mL water for three times. The organic layer was dried over Na_2SO_4 and concentrated to afford compound **219b** (731 mg), LCMS ($M+H^+$): 158.

Step 3: preparation of [4-fluoro-2-(methylthio)phenyl]hydrazine (compound 219c)

To a stirring solution of compound **219b** (731 mg, 4.65 mmol) in 5 M HCl (6.7 mL, 33.5 mmol) at 0 °C was added a solution of sodium nitrite (481 mg, 6.97 mmol) in water (4 mL) below 0 °C. The reaction mixture was stirred at 0 °C for another 30 mins and a solution of tin (II) chloride (1.32 g, 6.97 mmol) dissolved in conc. HCl (2 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. Then the mixture was adjusted to pH 12-14 with 20% aqueous sodium hydroxide and extracted with EA. The organic layer was dried and concentrated to afford **compound 219c** (499 mg), LCMS ($M-NH_3+H^+$): 156.

Step 4: preparation of [(*Z*)-(4,6-dichloropyrimidin-5-yl)methyleneamino]-[4-fluoro-2-(methylthio)phenyl]amine (compound 219d)

A suspension of compound **219c** (499 mg, 2.9 mmol) and 4,6-dichloropyrimidine-5-carbaldehyde (513 mg, 2.9 mmol) in acetonitrile (15 mL) was stirred at room temperature for 12 hours. The mixture was concentrated and the residue was purified by silica gel to afford compound **219d** (900 mg). LCMS ($M+H^+$): 331.

Step 5: preparation of [(*Z*)-(4,6-dichloropyrimidin-5-yl)methyleneamino]-[4-fluoro-2-(methylthio)phenyl]amine (compound 219e)

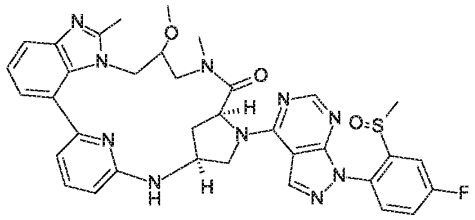
A suspension of compound **219d** (900 mg, 2.72 mmol) in extra dry acetonitrile (20 mL) was microwaved at 180 °C for 1 hour. Then the solvent was removed and the resulting residue was purified by silica gel to afford compound **219e,** (430 mg), LCMS ($M+H^+$): 295.

Step 6: preparation of (8*S*,11*S*)-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 219)

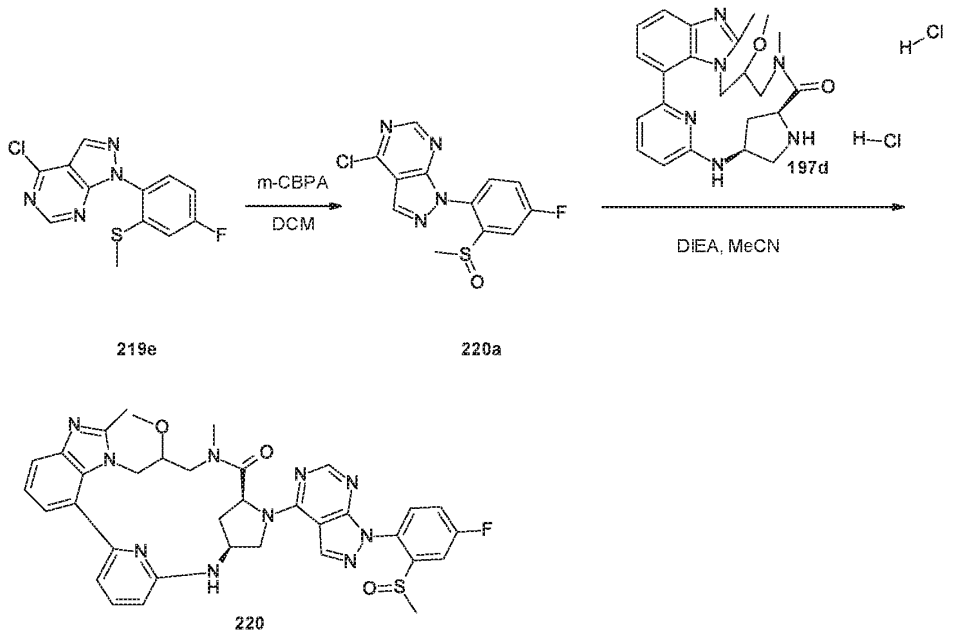
A solution of compound **197d** (50 mg, 0.071 mmol), compound **219e** (23. mg, 0.078 mmol) and DIEA (49 µL, 0.284 mmol) in acetonitrile (2 mL) was stirred at 70 °C for 1 hour. The solvent was removed and the resulting residue was purified by prep-HPLC to afford Example **219** (6 mg), LCMS (M+H$^+$): 679. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.54 - 8.49 (m, 1H), 8.33 - 8.13 (m, 1H), 7.84 - 7.74 (m, 1H), 7.67 - 7.60 (m, 1H), 7.45 - 7.24 (m, 4H), 7.13 - 7.05 (m, 2H), 6.95 - 6.88 (m, 1H), 6.72 - 6.65 (m, 1H), 5.86 - 5.74 (m, 1H), 5.52 - 5.40 (m, 1H), 4.75 - 4.65 (m, 1H), 4.61 - 4.50 (m, 2H), 4.37 - 4.27 (m, 1H), 4.25 - 4.14 (m, 1H), 4.11 - 3.90 (m, 1H), 3.19 - 3.01 (m, 3H), 2.94 - 2.88 (m, 1H), 2.86 - 2.82 (m, 3H), 2.64 - 2.59 (m, 3H), 2.56 - 2.49 (m, 1H), 2.43 - 2.38 (m, 3H).

Example 220

(8*S*,11*S*)-10-[1-(4-fluoro-2-methylsulfinyl-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



219e 220a

220

Step 1: preparation of 4-chloro-1-(4-fluoro-2-methylsulfinyl-phenyl)pyrazolo[3,4-d]pyrimidine (compound 220a)

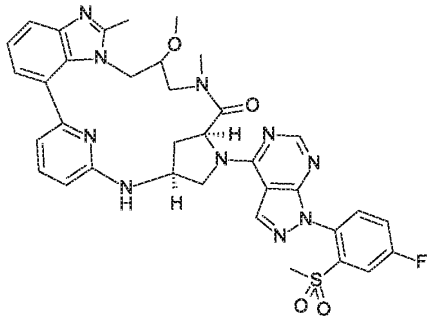
To a solution of compound **219e** (300 mg, 1.02 mmol) in dichloromethane (30 mL) was added 3-chloroperoxybenzoic acid (175 mg, 1.02 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for another 2 hours. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and then extracted with DCM (three times, 40 mL). The combined organic layer was washed with brine (30 mL) and then concentrated. The residue was purified by silica gel to afford compound **220a** (230 mg), LCMS ($M+H^+$): 311.

Step 2: preparation of (8*S*,11*S*)-10-[1-(4-fluoro-2-methylsulfinyl-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 220)

A solution of compound **197d** (50 mg, 0.071 mmol), compound **220a** (22 mg, 0.071 mmol) and DIEA (49 µL, 0.284 mmol) in 1,4-dioxane (1 mL) was stirred at 70°C for 1 hour. The solvent was removed and the residue was purified by prep-HPLC to afford Example **220** (16.1 mg), LCMS ($M+H^+$): 695. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.57 - 8.50 (m, 1H), 8.43 - 8.24 (m, 1H), 8.03 - 7.94 (m, 1H), 7.92 - 7.86 (m, 1H), 7.83 - 7.73 (m, 1H), 7.68 - 7.60 (m, 1H), 7.54 - 7.47 (m, 1H), 7.44 - 7.39 (m, 1H), 7.37 - 7.28 (m, 1H), 7.14 - 6.88 (m, 1H), 6.71 - 6.61 (m, 1H), 5.87 - 5.64 (m, 1H), 5.53 - 5.41 (m, 1H), 4.74 - 4.45 (m, 3H), 4.36 - 4.26 (m, 1H), 4.23 - 3.90 (m, 2H), 3.18 - 3.01 (m, 4H), 2.95 - 2.87 (m, 4H), 2.86 - 2.81 (m, 3H), 2.65 - 2.57 (m, 3H), 2.55 - 2.47 (m, 1H).

Example 221

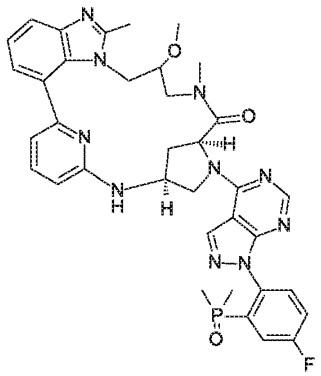
(8*S*,11*S*)-10-[1-(4-fluoro-2-methylsulfonyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **219** by using (4-fluoro-2-mesyl-phenyl)amine instead of [4-fluoro-2-(methylthio)phenyl]amine (compound **219b**). LCMS (M+H$^+$): 711. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.19 (s, 1H), 8.04 - 7.96 (m, 1H), 7.84 - 7.58 (m, 5H), 7.41 - 7.36 (m, 1H), 7.32 - 7.23 (m, 1H), 7.14 - 6.88 (m, 1H), 6.72 - 6.63 (m, 1H), 5.82 - 5.69 (m, 1H), 5.53 - 5.38 (m, 1H), 4.73 - 4.64 (m, 1H), 4.62 - 4.51 (m, 4H), 4.38 - 3.91 (m, 4H), 3.15 - 3.01 (m, 3H), 2.95 - 2.87 (m, 1H), 2.85 - 2.80 (m, 3H), 2.61 - 2.57 (m, 3H), 2.54 - 2.48 (m, 1H).

Example 222

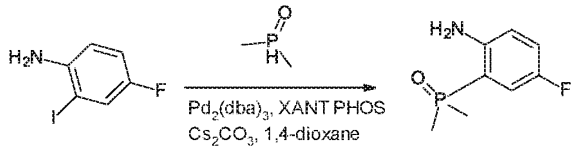
(8*S*,11*S*)-10-[1-(2-dimethylphosphoryl-4-fluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **219** by using compound **222a** instead of compound **219b** in step 3. LCMS (M+H$^+$): 709. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.62 - 8.56 (m, 1H), 8.37 - 8.21 (m, 1H), 7.91 - 7.70 (m, 3H), 7.67 - 7.58 (m, 1H),

7.57 - 7.40 (m, 3H), 7.14 - 6.93 (m, 1H), 6.76 - 6.65 (m, 1H), 5.90 - 5.71 (m, 1H), 5.51 - 5.38 (m, 1H), 4.71 - 4.56 (m, 1H), 4.52 - 4.41 (m, 1H), 4.35 - 4.09 (m, 2H), 4.00 - 3.82 (m, 1H), 3.11 - 2.97 (m, 2H), 2.96 - 2.88 (m, 2H), 2.81 - 2.76 (m, 3H), 2.74 - 2.62 (m, 4H), 2.03 - 1.94 (m, 1H), 1.58 - 1.49 (m, 1H), 1.48 - 1.39 (m, 4H), 1.29 - 1.20 (m, 3H).

The compound **222a** was prepared according to the following scheme:

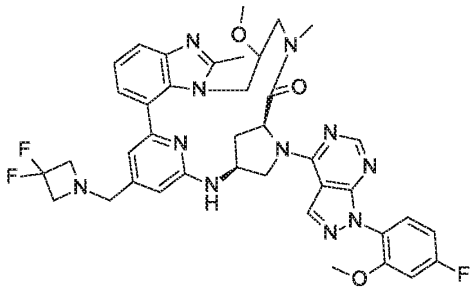


222a

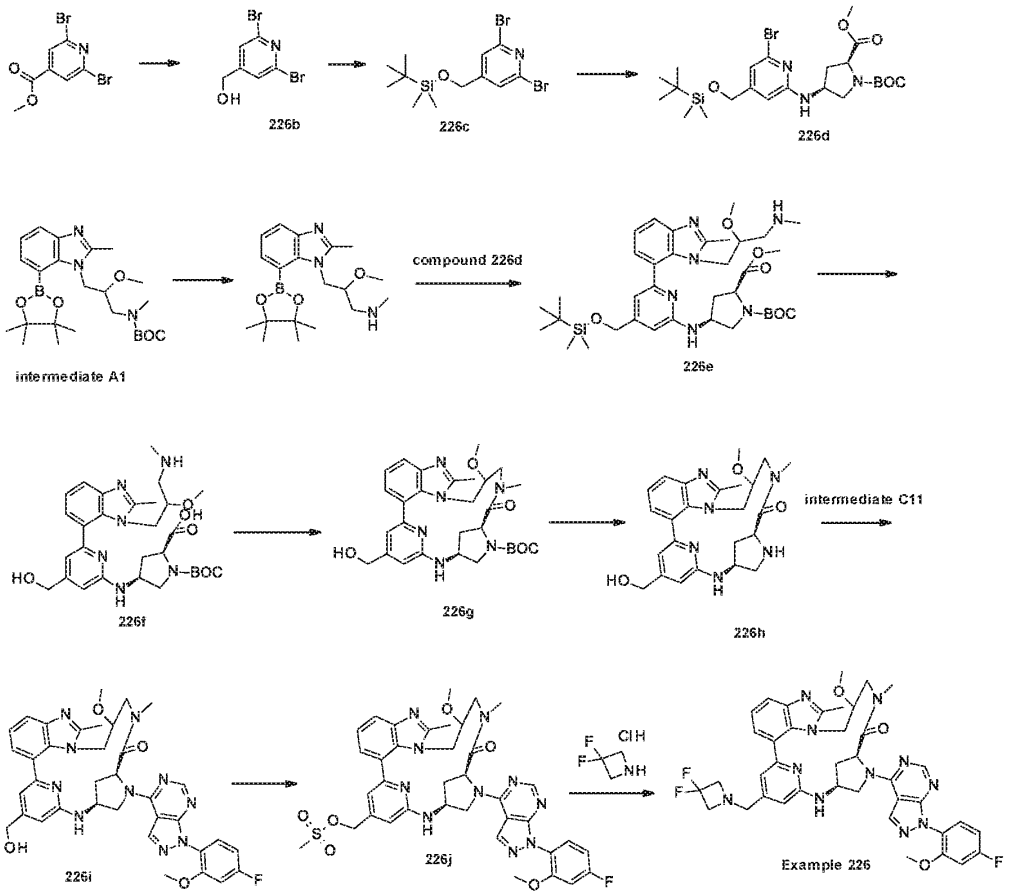
A suspension of 4-fluoro-2-iodoaniline (1.19 g, 5.0 mmol), methylphosphonoylmethane (429 mg, 5.5 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (578 mg, 1.0 mmol), tris(dibenzylideneacetone)dipalladium (457 mg, 0.50 mmol) and cesium carbonate (3.26 g, 10.0 mmol) in 1,4-dioxane (2.5 mL) was stirred at 100 °C for 12 hour. The solvent was removed and the residue was purified by reversed-phase chromatography to afford compound **222a** (690 mg), LCMS ($M+H^+$): 188.

Example 226

(8*S*,11*S*)-4-[(3,3-difluoroazetidin-1-yl)methyl]-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (2,6-dibromo-4-pyridyl)methanol (compound 226b)

To a solution of methyl 2,6-dibromopyridine-4-carboxylate (10. g, 33.91 mmol) in methanol (100 mL) was added sodium borohydride (5.13 g, 135.63 mmol) at 0 °C. After being heated to 65 °C for 3 h, the reaction mixture was cooled and poured into ice water. Then the mixture was adjusted to pH around 7 and extracted with EA, the organic layer was dried and concentrated to give the crude compound **226b** (8.5 g)

LCMS $(M+H)^+$: 268.

Step 2: preparation of *tert*-butyl-[(2,6-dibromo-4-pyridyl)methoxy]-dimethyl-silane (compound 226c)

To a mixture of triethylamine (1.31 mL, 9.37 mmol) and compound **226b** (1 g, 3.75 mmol) in DCM (10 mL) was added *tert*-butyldimethylsiyl triflate (1.3 g, 4.9 mmol) dropwise at 0 °C. After being stirred at 0 °C for 2 h, the reaction was quenched with water and then extracted with DCM, the organic layer was dried and concentrated to give compound **226c** (1.3 g). LCMS $(M+H)^+$: 379.

Step 3: preparation of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[[6-bromo-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 226d)

A mixture of compound **226c** (3.93 g, 10.3 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate;hydrochloride (2.5 g, 8.9 mmol), Cs_2CO_3 (8.7 g, 26.71 mmol), $Pd(OAc)_2$ (0.33 g, 1.48 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.86 g, 1.48 mmol) in 1,4-dioxane (60 mL) was stirred at 85 °C for 12 h under N_2. The reaction mixture was concentrated and the residue was purified by silica gel to give compound **226d** (2.3 g). LCMS $(M+H)^+$: 544.

Step 4-9: preparation of (8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4-(hydroxymethyl)-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 226i)

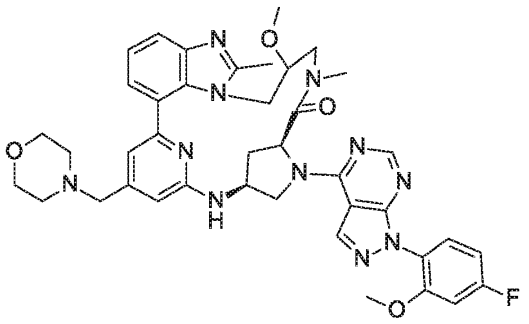
Compound **226i** was prepared in analogy to the preparation of compound **289** by using compound **226d** instead of intermediate **B1**, intermediate **A1** instead of intermediate **A12**. LCMS $(M+H)^+$: 693.

Step 10-11: preparation of (8*S*,11*S*)-4-[(3,3-difluoroazetidin-1-yl)methyl]-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (Example 226)

To a mixture of compound **226i** (25.0 mg, 0.03 mmol) and DIPEA (17.5 μL, 0.110 mmol) in DCM (1 mL) was added Ms_2O (18.86 mg, 0.11 mmol) at 0 °C. After being stirred at rt for 1 h, 3,3-difluoroazetidine hydrochloride (21.01 mg, 0.160 mmol) was added and the mixture was stirred at rt for 12 h. Then the mixture was concentrated, the residue was purified by prep-HPLC to give Example **226** (2.3 mg). LCMS $(M+H)^+$: 768. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.37 - 8.18 (m, 1H), 7.92 - 7.63 (m, 3H), 7.52 - 7.37 (m, 1H), 7.25 - 7.02 (m, 2H), 6.96 - 6.68 (m, 2H), 6.27 - 6.04 (m, 1H), 5.57 - 5.37 (m, 1H), 4.79 - 4.70 (m, 1H), 4.60 - 4.52 (m, 1H), 4.47 - 4.15 (m, 7H), 4.04 - 3.73 (m, 5H), 3.23 - 2.94 (m, 8H), 2.88 - 2.82 (m, 3H), 2.72 - 2.53 (m, 2H).

Example 230

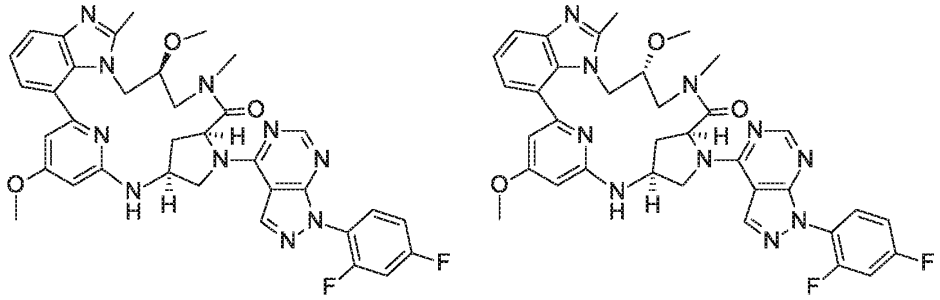
(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(morpholinomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **226** by using morpholine instead of 3,3-difluoroazetidine hydrochloride. LCMS $(M+H)^+$: 762. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.39 - 8.21 (m, 1H), 7.88 - 7.73 (m, 2H), 7.71 - 7.62 (m, 1H), 7.50 - 7.38 (m, 1H), 7.35 - 7.14 (m, 1H), 7.08 (dd, J = 2.4, 10.4 Hz, 1H), 6.93 - 6.84 (m, 2H), 6.19 - 5.45 (m, 2H), 4.80 - 4.69 (m, 1H), 4.64 - 4.55 (m, 1H), 4.51 - 4.22 (m, 5H), 4.13 - 3.87 (m, 5H), 3.77 (s, 3H), 3.46 - 3.36 (m, 3H), 3.23 - 3.03 (m, 4H), 3.01 - 2.75 (m, 8H), 2.67 - 2.58 (m, 1H).

Example 231 and Example 232

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



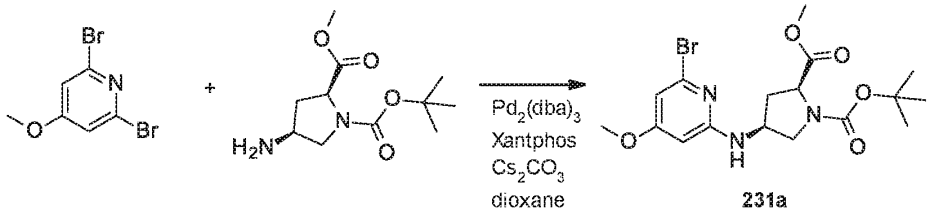
The title compounds were prepared in analogy to the preparation of Example **129** by using Intermediate **A1** instead of compound **129c** in step 2 and compound **231a** instead of Intermediate **B9** in step 3.

The mixture Example **231** (Faster eluted) and Example **232** (Slower eluted) was separated via prep-HPLC.

Example 231, LCMS (M+H$^+$): 681, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.22 (s, 1H), 7.69 - 7.61 (m, 1H), 7.61 - 7.57 (m, 1H), 7.31 - 7.16 (m, 4H), 6.53 - 6.45 (m, 1H), 6.21 - 6.15 (m, 1H), 5.50 (d, *J* = 9.0 Hz, 1H), 5.13 - 4.96 (m, 1H), 4.71 (t, *J* = 5.3 Hz, 1H), 4.56 (dd, *J* = 6.5, 11.5 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.13 - 4.05 (m, 1H), 4.02 - 3.94 (m, 1H), 3.94 - 3.91 (m, 3H), 3.86 - 3.74 (m, 1H), 3.12 (s, 3H), 3.02 - 2.93 (m, 1H), 2.86 (s, 3H), 2.76 (d, *J* = 13.4 Hz, 1H), 2.60 - 2.57 (m, 3H), 2.54 (td, *J* = 4.5, 9.1 Hz, 1H).

Example 232, LCMS (M+H$^+$): 681, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.22 (s, 1H), 7.67 (dt, *J* = 6.0, 8.5 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.32 - 7.25 (m, 2H), 7.20 (br t, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 1.7 Hz, 1H), 6.14 (s, 1H), 5.85 - 5.70 (m, 1H), 5.50 - 5.39 (m, 1H), 4.67 - 4.57 (m, 1H), 4.53 - 4.46 (m, 1H), 4.31 (br d, *J* = 11.3 Hz, 1H), 4.27 - 4.20 (m, 1H), 4.18 - 4.09 (m, 1H), 3.98 (s, 3H), 3.96 - 3.91 (m, 1H), 3.08 (s, 3H), 2.98 - 2.87 (m, 2H), 2.85 (s, 3H), 2.67 - 2.59 (m, 1H), 2.59 - 2.55 (m, 3H).

The compound **231a** was prepared according to the following scheme:

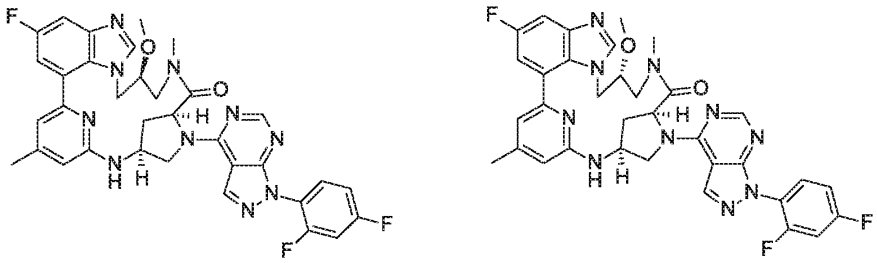


231a

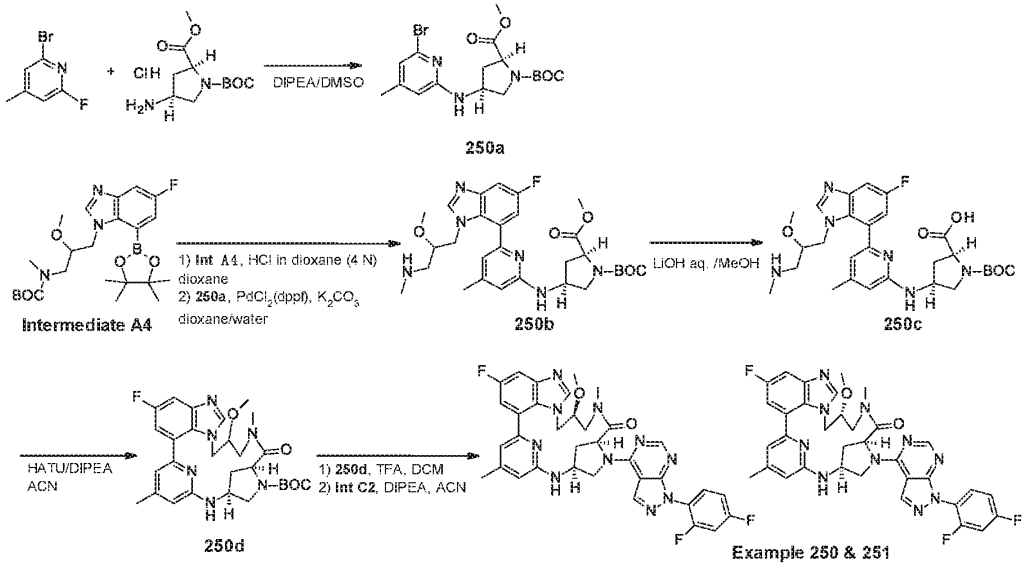
To a solution of 2,6-dibromo-4-methoxy-pyridine (1000 mg, 3.74 mmol) in 1,4-dioxane (20 mL) was added *O*1-tert-butyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (1052 mg, 3.74 mmol), cesium carbonate (3652 mg, 11.24 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (343 mg, 0.75 mmol) and tris(dibenzylideneacetone) dipalladium (0) (400.0 mg, 0.375 mmol). The reaction was stirred at 85 °C for 12 hrs under N_2. The reaction mixture was filtered and concentrated, the residue was purified by flash-HPLC to give compound **231a** (600 mg), LCMS (M+H)$^+$: 431.

Example 250 & 251

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[(6-bromo-4-methyl-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate (compound 250a)

To a flask was added 2-bromo-6-fluoro-4-methyl-pyridine (372 mg, 1.96 mmol), O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (500 mg, 1.78 mmol), DIPEA (690 mg, 933 μL, 5.34 mmol), DMSO (10mL). The mixture was heated to 110 °C for 12 hrs. The mixture was diluted with 40 mL EA and then it was washed with water 25 mL for three times, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel to give compound **250a** (390 mg), LCMS ($M+H^+$): 414.

Step 2: preparation of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[[6-[6-fluoro-3-[2-methoxy-3-(methylamino)propyl]benzimidazol-4-yl]-4-methyl-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 250b)

To a flask was added *tert*-butyl *N*-[3-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (Intermediate **A4**, 800 mg, 1.38 mmol), 1,4-dioxane (3 mL). Then HCl in dioxane (4 N, 3 mL) was added to the suspension

dropwise. The suspension was stirred at room temperature for 1 hr. Then the mixture was concentrated and the residue was dissolved in 1,4-dioxane (5 mL), compound **250a** (390 mg, 0.94 mmol), K_2CO_3 (650 mg, 4.71 mmol) and water (1mL) were added. The suspension was bubbled with N_2 for 5 mins and $PdCl_2$(DPPF)-CH_2Cl_2 adduct (69 mg, 94 μmol) was added. The mixture was heated to 90 °C for 1 hr, then filtered, the filtrate was diluted with water and then it was extracted with EA for three times, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel to give compound **250b** (270 mg), LCMS ($M+H^+$): 571.

Step 3: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[6-[6-fluoro-3-[2-methoxy-3-(methylamino)propyl]benzimidazol-4-yl]-4-methyl-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 250c)

To the flask containing O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[[6-[6-fluoro-3-[2-methoxy-3-(methylamino)propyl]benzimidazol-4-yl]-4-methyl-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound **250b**, 177 mg, 0.31 mmol) was added MeOH (2 mL) and 2 N aqueous solution of LiOH (2 mL, 4 mmol). The mixture was stirred at room temperature for 30 mins, then the mixture was acidified to pH = 5 with 1 N HCl. The mixture was concentrated, the residue was purified by flash preparation to give compound **250c** (220 mg), LCMS ($M+H^+$): 557.

Step 4: preparation of *tert*-butyl (8*S*,11*S*)-22-fluoro-15-methoxy-4,13-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 250d)

To a 250 mL flask was added 2-(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (451 mg, 1.19 mmol), DIPEA (511 mg, 690 μL, 3.95 mmol) and acetonitrile (60 mL). Then a solution of compound **250c** (220 mg, 0.39 mmol) in acetonitrile (60 mL) was added dropwise in 20 mins. The mixture was concentrated, the residue was purified via flash preparation to give compound **250d** (200 mg), LCMS ($M+H^+$): 539.

Step 5: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (example 250 & 251)

To a microwave tube was added *tert*-butyl (8*S*,11*S*)-22-fluoro-15-methoxy-4,13-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound **250d**, 200 mg, 0.362 mmol), 4-chloro-1-(2,4-difluorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidine (Intermediate **C2**, 116 mg, 0.434 mmol), DIPEA (468 mg, 632 µL, 3.62 mmol) and acetonitrile (4 mL). The mixture was heated to 80 °C and stirred for about 30 mins. The mixture was filtered and concentrated, then it was purified via prep-HPLC and SFC to obtain example **250** and example **251**.

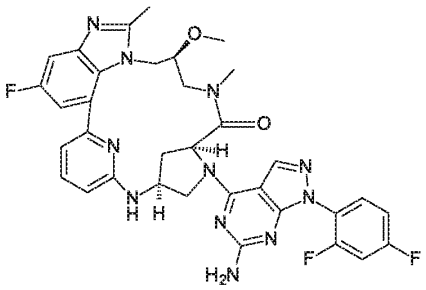
SFC conditions: Instrument: SFC 80; Column: TCI Chiral MB-S 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 20%. Flow rate: 60 mL /min. Back pressure: 100 bar. Column temperature: 35°C.

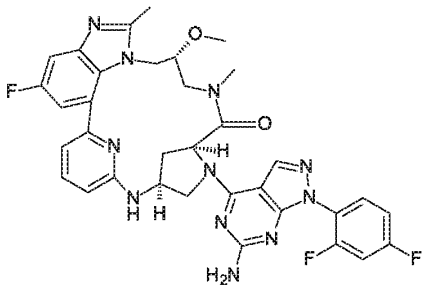
Example 250 (faster eluted, 44 mg), LCMS ($M+H^+$): 669. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.59 - 8.34 (m, 1H), 8.27 - 7.81 (m, 2H), 7.79 - 7.70 (m, 1H), 7.60 (ddd, *J* = 2.8, 9.1, 10.4 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.37 - 7.30 (m, 1H), 7.29 - 7.23 (m, 1H), 7.04 - 6.96 (m, 1H), 6.56 - 6.46 (m, 1H), 5.73 - 5.60 (m, 1H), 5.60 - 5.43 (m, 2H), 4.64 - 4.56 (m, 1H), 4.50 - 4.38 (m, 1H), 4.28 (br d, *J* = 11.5 Hz, 1H), 4.19 - 4.05 (m, 2H), 3.85 - 3.70 (m, 1H), 3.04 (s, 1H), 2.95 (s, 2H), 2.92 - 2.85 (m, 1H), 2.82 (br d, *J* = 12.8 Hz, 1H), 2.75 (s, 2H), 2.73 (s, 1H), 2.63 (br d, *J* = 13.4 Hz, 1H), 2.40 (s, 3H).

Example 251 (slower eluted, 96 mg), LCMS ($M+H^+$): 669. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.62 (s, 1H), 8.55 - 8.47 (m, 1H), 8.39 - 8.25 (m, 1H), 7.77 - 7.69 (m, 1H), 7.60 (ddd, *J* = 2.8, 9.1, 10.4 Hz, 1H), 7.53 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.22 (dd, *J* = 2.4, 10.4 Hz, 1H), 6.89 - 6.82 (m, 1H), 6.69 - 6.56 (m, 1H), 5.56 - 5.44 (m, 1H), 5.41 - 5.31 (m, 1H), 4.99 - 4.83 (m, 1H), 4.77 - 4.69 (m, 1H), 4.57 - 4.49 (m, 1H), 4.26 - 4.16 (m, 2H), 4.05 - 3.96 (m, 1H), 3.91 (br dd, *J* = 5.0, 10.5 Hz, 1H), 3.24 - 3.15 (m, 1H), 3.13 (s, 1H), 3.03 (s, 2H), 2.92 (s, 2H), 2.88 (s, 1H), 2.59 - 2.53 (m, 1H), 2.38 (s, 3H), 2.34 - 2.27 (m, 1H).

Example 269 and Example 270

(8*S*,11*S*,15*R*)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared in analogy to the preparation of Example **12** by using intermediate **A2** and instead of Intermediate **A11** andIntermediate **C23** instead of Intermediate **C2.** The example **269** and **270** were separated via SFC.

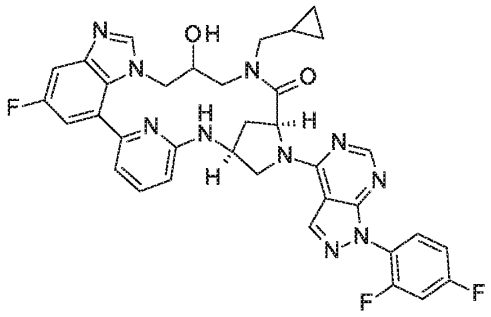
SFC conditions: Instrument: SFC 80; Column: OD, 250×20 mm I.D., 5μm.; Mobile phase: A for CO_2 and B for ethanol (0.1% $NH_3{\cdot}H_2O$); Gradient: B 35%; Flow rate: 40 mL /min; Back pressure: 100bar; Column temperature: 35°C

Example 269, faster eluted, LCMS ($M+H^+$): 684. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.21 - 8.10 (m, 1H), 7.79 - 7.67 (m, 1H), 7.55 - 7.32 (m, 2H), 7.30 - 7.21 (m, 1H), 7.19 - 7.11 (m, 2H), 7.10 - 7.04 (m, 1H), 7.03 - 6.97 (m, 1H), 6.65 - 6.55 (m, 1H), 5.82 - 5.64 (m, 1H), 5.36 - 5.20 (m, 1H), 4.57 - 4.49 (m, 1H), 4.40 - 4.30 (m, 1H), 4.18 - 3.96 (m, 3H), 3.88 - 3.78 (m, 1H), 3.07 - 2.98 (m, 1H), 2.93 (s, 2H), 2.79 - 2.75 (m, 3H), 2.57 - 2.51 (m, 3H), 2.45 - 2.32 (m, 2H).

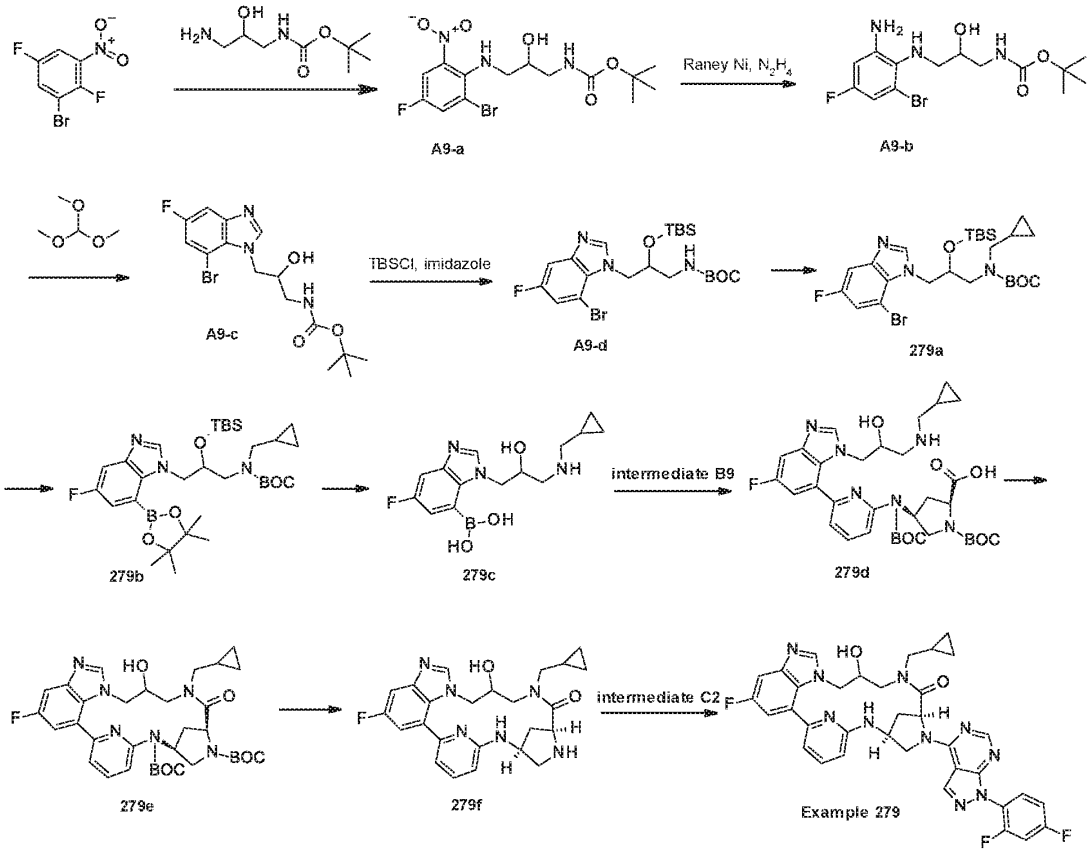
Example 270, slower eluted, LCMS ($M+H^+$): 684. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.20 - 8.11 (m, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.24 (dd, J = 2.5, 8.3 Hz, 1H), 7.18 - 7.11 (m, 1H), 7.09 - 6.99 (m, 2H), 6.86 - 6.79 (m, 1H), 6.61 (br d, J = 8.4 Hz, 1H), 5.36 (d, J = 9.0 Hz, 1H), 5.28 - 5.16 (m, 1H), 4.61 - 4.54 (m, 1H), 4.44 - 4.34 (m, 1H), 4.17 - 4.09 (m, 1H), 4.03 - 3.90 (m, 2H), 3.68 - 3.54 (m, 1H), 3.09 - 3.04 (m, 1H), 2.96 (s, 2H), 2.93 - 2.87 (m, 1H), 2.77 (s, 3H), 2.61 - 2.48 (m, 4H), 2.39 (ddd, J = 4.6, 9.0, 13.5 Hz, 1H).

Example 279

(8*S*,11*S*)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-hydroxy-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1~5: preparation of *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl)-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]-*N*-(cyclopropylmethyl)carbamate (compound 279a)

The compound **279a** was prepared in analogy to the preparation of intermediate **A7-f** by using *tert*-butyl *N*-[(3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate, trimethoxymethane instead of 1,1,1-trimethoxyethane and bromomethylcyclopropane instead of methyl iodide. LCMS $(M+H)^+$: 556.

Step 6: preparation of *tert*-butyl *N*-[2-[*tert*-butyl(dimethyl)silyl]oxy-3-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-(cyclopropylmethyl)carbamate (compound 279b)

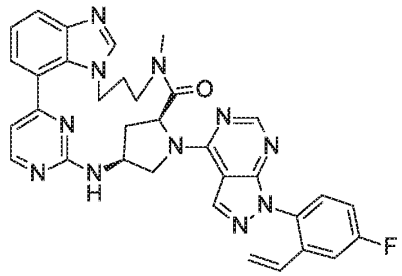
The compound **279b** was prepared in analogy to the preparation of intermediate **A7** by using compound **279a** instead of intermediate **A7-h**. LCMS $(M+H)^+$: 604.

Step 7~11: preparation of (8*S*,11*S*)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-hydroxy-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 279)

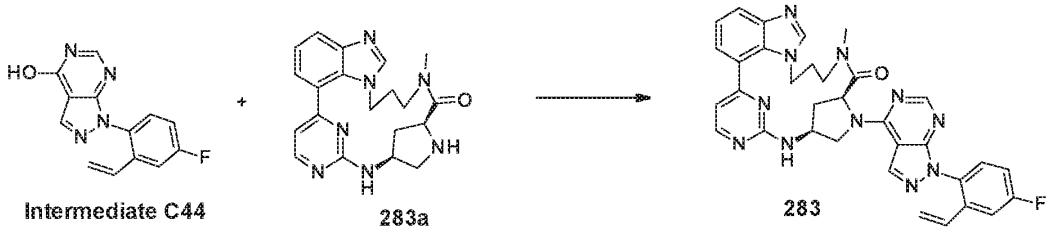
The title compound was prepared in analogy to the preparation of Example **289** by using compound **279b** instead of intermediate **A12**, intermediate **B9** instead of intermediate **B1** and intermediate **C2** instead of intermediate **C11**. LCMS $(M+H)^+$: 681. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.59 - 8.33 (m, 1H), 8.33 - 7.84 (m, 2H), 7.80 - 7.54 (m, 2H), 7.46 - 7.01 (m, 4H), 6.94 - 6.63 (m, 1H), 5.82 - 5.41 (m, 1H), 4.79 - 4.67 (m, 1H), 4.62 - 3.88 (m, 7H), 3.57 - 3.44 (m, 1H), 3.26 - 3.08 (m, 2H), 3.00 - 2.76 (m, 1H), 2.69 - 2.56 (m, 1H), 1.10 - 0.96 (m, 1H), 0.74 - 0.11 (m, 4H).

Example 283

(8*S*,11*S*)-10-[1-(4-fluoro-2-vinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



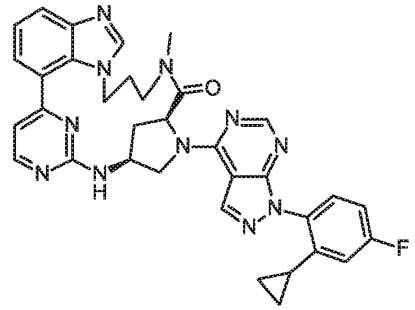
The title compound was prepared according to the following scheme:



To the solution of Intermediate **C44** (15.0 mg, 0.06 mmol) in DMF (1.0 mL) was added PyBOP (28.5 mg, 0.06 mmol) and DIEA (15.1 mg, 0.12 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. Then compound **283a** (22.1 mg, 0.06 mmol, the preparation was refer to compound **289d** by using Intermediate **A11** instead of Intermediate **A12**) was added and the mixture was stirred at 20 °C for additional 2 h. The mixture was purified by prep-HPLC to give Example **283** (5.2 mg). LCMS $(M+H)^+$: 616. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.15 - 9.22 (m, 1H), 8.64 (d, *J*=5.26 Hz, 1H), 8.56 (s, 1H), 8.20 - 8.35 (m, 1H), 7.95 (d, *J*=7.46 Hz, 1H), 7.60 - 7.85 (m, 3H), 7.47 (dd, *J*=8.68, 5.14 Hz, 1H), 7.23 - 7.30 (m, 1H), 7.15 (d, *J*=5.26 Hz, 1H), 6.17 - 6.27 (m, 1H), 5.81 - 5.89 (m, 1H), 5.38 - 5.54 (m, 2H), 5.29 (d, *J*=11.25 Hz, 1H), 4.49 - 4.57 (m, 1H), 4.38 - 4.47 (m, 2H), 4.08 - 4.18 (m, 1H), 3.05 - 3.22 (m, 4H), 2.89 - 2.97 (m, 2H), 2.57 - 2.66 (m, 1H), 1.89 - 2.01 (m, 1H), 1.45 - 1.57 (m, 1H).

Example 284

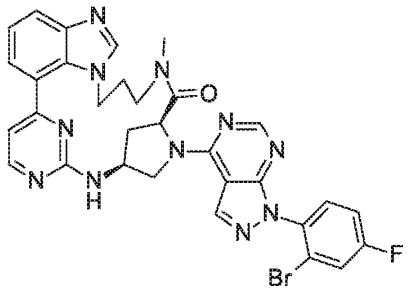
(8*S*,11*S*)-10-[1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **283** by using Intermediate **C45** instead of Intermediate **C44**. LCMS $(M+H)^+$: 630. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 - 8.65 (m, 2H), 8.18 - 8.35 (m, 2H), 7.82 (d, *J*=8.44 Hz, 1H), 7.52 (br d, *J*=7.46 Hz, 1H), 7.35 - 7.44 (m, 2H), 7.05 - 7.17 (m, 2H), 6.94 (dd, *J*=9.96, 2.87 Hz, 1H), 5.49 (d, *J*=8.68 Hz, 1H), 5.16 - 5.31 (m, 1H), 4.51 (s, 1H), 4.25 - 4.39 (m, 2H), 4.12 (br d, *J*=4.16 Hz, 1H), 2.77 - 3.27 (m, 6H), 2.52 - 2.73 (m, 1H), 1.75 - 1.95 (m, 1H), 1.39 - 1.58 (m, 2H), 0.63 - 0.77 (m, 4H).

Example 286

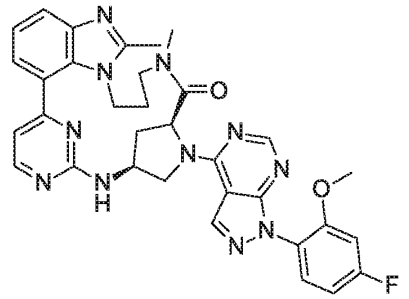
(8*S*,11*S*)-10-[1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



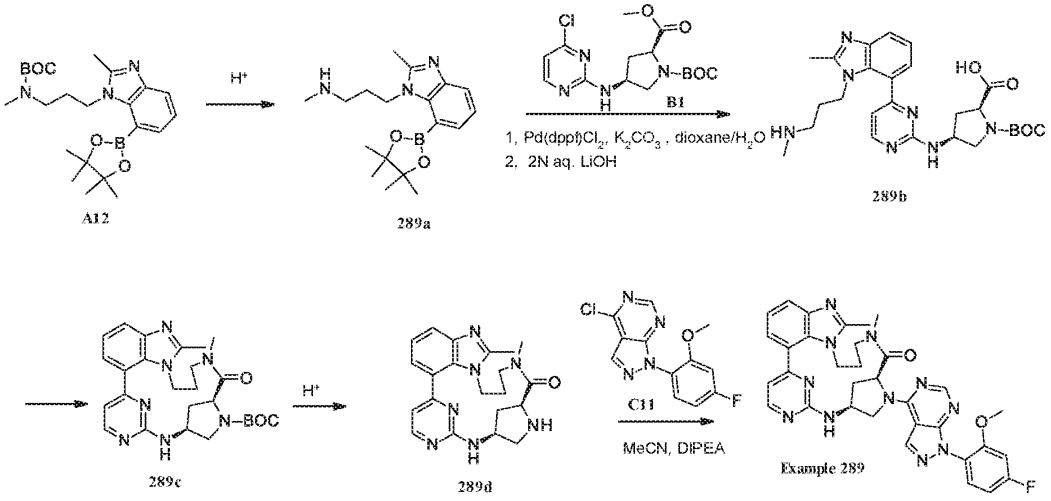
The title compound was prepared in analogy to the preparation of Example **283** by using Intermediate **C43** instead of Intermediate **C44**. LCMS $(M+H)^+$: 668. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.78 - 8.87 (m, 1H), 8.61 (d, *J*=5.14 Hz, 1H), 8.56 (s, 1H), 8.21 - 8.38 (m, 1H), 7.90 (d, *J*=8.44 Hz, 1H), 7.66 - 7.74 (m, 2H), 7.54 - 7.64 (m, 2H), 7.40 (td, *J*=8.41, 2.87 Hz, 1H), 7.13 (d, *J*=5.14 Hz, 1H), 5.51 (d, *J*=8.93 Hz, 1H), 5.31 - 5.39 (m, 1H), 4.47 - 4.58 (m, 1H), 4.31 - 4.43 (m, 2H), 4.05 - 4.19 (m, 1H), 3.04 - 3.18 (m, 4H), 2.83 - 2.97 (m, 2H), 2.60 (s, 1H), 1.94 - 2.07 (m, 1H), 1.50 - 1.67 (m, 1H).

Example 289

(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *N*-methyl-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propan-1-amine (compound 289a)

A mixture of *N*-methyl-*N*-[3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamic acid *tert*-butyl ester (compound **A12**, 500 mg, 1.16 mmol, as the "**BORONIC REAGENT**" in table 6) in DCM (5 mL) and HCl in Dioxane (4 M, 2 mL,) was stirred at rt for 4 hours, then the reaction was filtered to give compound **289a** (400 mg). LCMS ($M+H^+$): 330.

Step 2: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[4-[2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-2-carboxylic acid (compound 289b)

A mixture of K_2CO_3 (968.36 mg, 7.01 mmol), *N*-methyl-3-[2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propan-1-amine (compound **289a**, 580 mg, 1.68 mmol), intermediate **B1** (500 mg, 1.4 mmol, as the "**HALIDE 1**" in table 6) and $PdDCl_2(DPPF)$ (114.4 mg, 0.14 mmol) in Dioxane/ H_2O (10:1, 20 mL) was stirred at 90 °C for 2 hours. Then the reaction mixture was concentrated, the residue was dissolved in THF/MeOH (15 mL, 2:1), 2 M LiOH (3.87 mL, 7.73 mmol) was added and stirred at rt for 4 hours. The reaction was adjusted to pH=5, then the reaction was concentrated to remove most organic solvent, the residue was purified by flash preparation (MeCN/ TFA in water) to give compound **289b** (600mg). LCMS ($M+H^+$): 510.

Step 3~4: preparation of (8*S*,11*S*)-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 289d)

To a mixture of HATU (1.23 g, 3.23 mmol) and DIPEA (1.04 g, 8.07 mmol) in acetonitrile (150 mL) was added (2*S*,4*S*)-1-tert-butoxycarbonyl-4-[[4-[2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-2-carboxylic acid (**289b**, 800 mg, 1.61 mmol) in acetonitrile (150 mL) dropwise in 2 hours. Then the reaction was concentrated, the residue was purified by flash preparation (MeCN/ TFA in water) to give a light yellow solid, which was dissolved in dichloromethane (10 mL) and 4 M HCl in dioxane (4.04 mL, 16.14 mmol) and stirred at rt for 4 hours. The reaction was concentrated to give compound **289d** (400 mg). LCMS ($M+H^+$): 392.

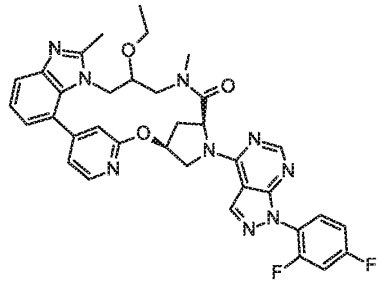
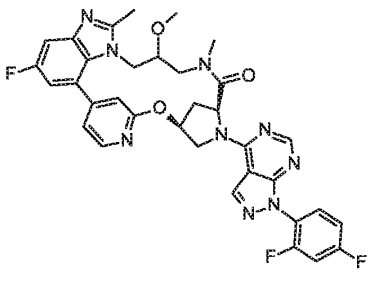
Step 5: preparation of (8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 289)

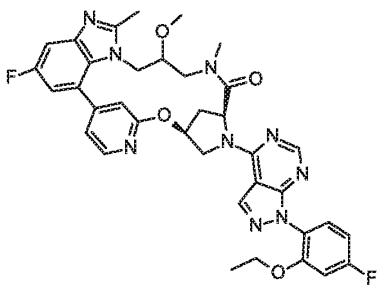
A mixture of ((8*S*,11*S*)-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound **289d**, 100 mg, 0.255 mmol), 4-chloro-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (intermediate **C11**, 71 mg, 0.255 mmol, as the "**HALIDE 2**" in table 6) and DIPEA (165 mg, 1.28 mmol) in acetonitrile (5 mL) was stirred at 80 °C for 2 hours. Then the reaction was concentrated, the residue was purified by HPLC to give Example **289** (70 mg). LCMS ($M+H^+$): 634. ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.55 (d, *J* = 5.2 Hz, 1H), 8.49 - 8.24 (m, 1H), 8.20 - 7.65 (m, 2H), 7.50 - 7.32 (m, 3H), 7.12 - 6.95 (m, 2H), 6.87 (dt, *J* = 2.7, 8.4 Hz, 1H), 5.54 - 5.19 (m, 2H), 4.66 (br d, *J* = 3.5 Hz, 1H), 4.47 (dd, *J* = 6.3, 11.4 Hz, 1H), 4.36 - 4.19 (m, 1H), 4.13 - 3.99 (m, 2H), 3.84 - 3.69 (m, 3H), 3.11 (s, 1H), 3.03 (s, 2H), 2.99 - 2.82 (m, 2H), 2.72 - 2.49 (m, 3H), 2.55 (ddd, *J* = 4.6, 9.0, 13.6 Hz, 1H), 2.04 - 1.75 (m, 1H), 1.44 - 1.24 (m, 1H).

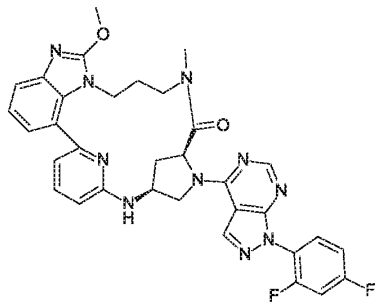
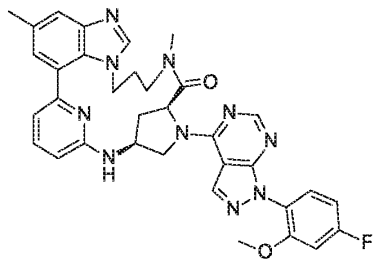
The following examples in Table 6 were prepared in analogy to Example **289**, replacing **Intermediate A12** with the "**BORONIC REAGENT**" in step 1, **Intermediate B1** with the "**HALIDE 1**" in step 2, **Intermediate C11** with the "**HALIDE 2**" in step 5 by the reagents indicated in Table 6.

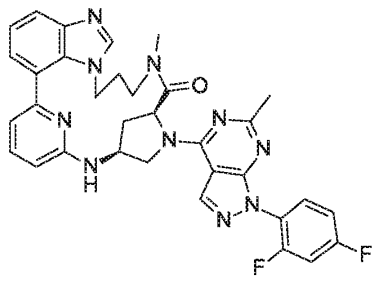
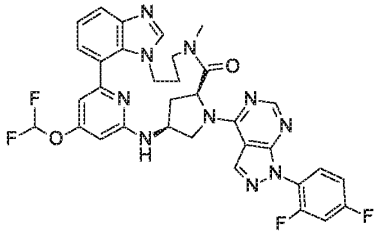
Table 6. Compound synthesis and characterization

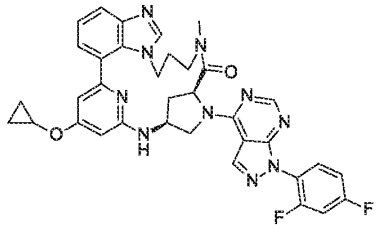
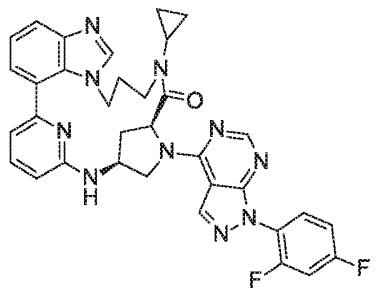
No.	Compound Name and Structure	BORONIC REAGENT, HALIDE 1, HALIDE 2	^{1}H NMR and MS (ESI)

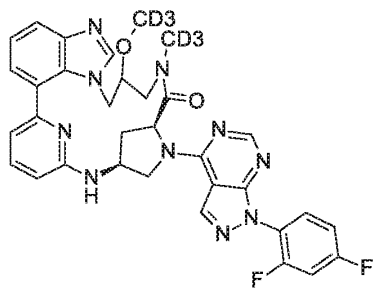
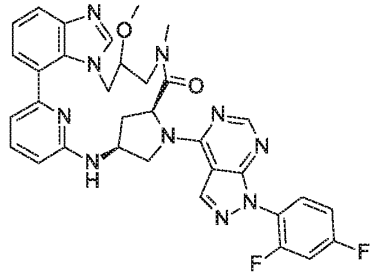
46	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A10** **HALIDE 1**: Intermediate **B20** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.59 (s, 1H), 8.32 (d, *J*=5.14 Hz, 1H), 8.24 (s, 1H), 7.70 - 7.62 (m, 1H), 7.70 - 7.60 (m, 2H), 7.40 - 7.35 (m, 1H), 7.30 - 7.25 (m, 1H) 7.25 - 7.20 (m, 1H), 6.93 - 6.89 (m, 2H), 5.90 (t, *J*=3.79 Hz, 1H), 5.54 - 5.41 (m, 1H), 4.60 - 4.43 (m, 2H), 4.17 - 4.10 (m, 2H), 3.79 - 3.60 (m, 1H), 3.57 - 3.48 (m, 1H), 3.32 - 3.26 (m, 2H), 3.03 (s, 3H), 2.98 - 2.95 (m, 1H), 2.85 (s, 3H), 2.73 - 2.64 (m, 2H), 0.63 (t, *J*=7.03 Hz, 3H). LCMS(M+H)$^+$: 666.
47	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B20** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.59 (s, 1H), 8.35 - 8.44 (m, 1H), 8.24 (s, 1H), 7.73 - 7. 58 (m, 2H), 7.34 - 7.16 (m, 3H), 7.04 - 6.94 (m, 2H), 5.94 - 5.73 (m, 1H), 5.49 - 5.40 (m, 1H), 4.59 - 4.38 (m, 2H), 4.37 - 4.19 (m, 2H), 3.79 - 3.62 (m, 2H), 3.46 - 3.36 (m, 1H), 3.13 - 3.04 (m, 3H), 3.04 - 3.00 (m, 3H), 2.97 (br d, *J*=14.88 Hz, 1H), 2.86 - 2.81 (m, 3H), 2.79 - 2.68 (m, 1H). LCMS (M+H)$^+$: 670.

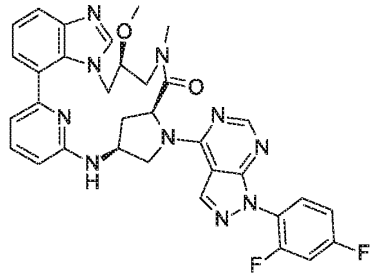
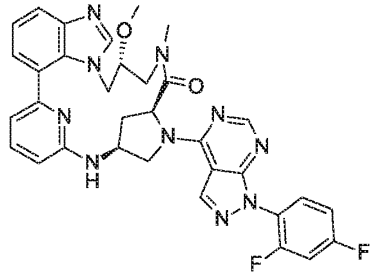
48	**(8*S*,11*S*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B20** **HALIDE 2**: Intermediate **C18**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.42 - 8.35 (m, 1H), 8.23 (s, 1H), 7.65 - 7.58 (m, 1H), 7.50 - 7.39 (m, 1H), 7.25 (br dd, *J*=9.63, 2.00 Hz, 1H), 7.09 – 6.95 (m, 3H), 6.92 - 6.83 (m, 1H), 5.95 - 5.73 (m, 1H), 5.46 (br d, *J*=9.51 Hz, 1H), 4.92 - 4.40 (m, 2H), 4.37 - 4.19 (m, 2H), 4.11 - 4.01 (m, 2H), 3.78 - 3.62 (m, 2H), 3.46 - 3.37 (m, 1H), 3.13 - 3.04 (m, 3H), 3.04 – 2.99 (m, 3H), 2.97 (br s, 1H), 2.87 - 2.80 (m, 3H), 2.78 - 2.71 (m, 1H), 1.20 - 1.09 (m, 3H). LCMS(M+H)$^+$: 696.
134	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A26** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.18 - 8.60 (m, 2H), 7.77 - 7.83 (m, 1H), 7.69 (td, *J*=8.65, 5.81 Hz, 1H), 7.51 (d, *J*=7.70 Hz, 1H), 7.26 - 7.35 (m, 1H), 7.13 - 7.25 (m, 3H), 6.92 (d, *J*=7.21 Hz, 1H), 6.72 - 6.78 (m, 1H), 5.53 (d, *J*=8.31 Hz, 1H), 4.71 - 4.76 (m, 1H), 4.57 - 4.65 (m, 1H), 4.28 (br d, *J*=11.49 Hz, 1H), 4.17 - 4.22 (m, 3H), 4.06 (br dd, *J*=14.00, 8.13 Hz, 1H), 3.77 -

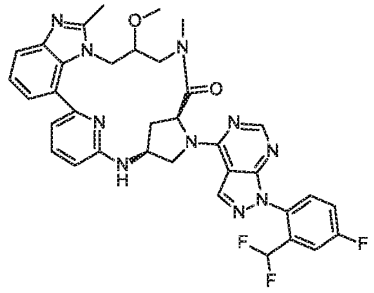
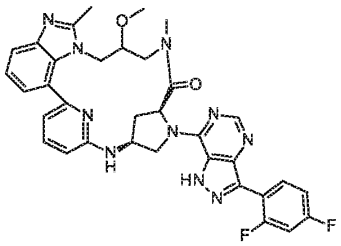
			3.91 (m, 1H), 2.78 - 3.16 (m, 4H), 2.53 - 2.73 (m, 2H), 2.07 - 2.25 (m, 1H), 1.30 - 1.42 (m, 1H). LCMS ($M+H^+$): 637.
138	**(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,22-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A19** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C11**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 8.17 (d, J = 4.9 Hz, 2H), 7.83 - 7.73 (m, 1H), 7.51 (s, 1H), 7.44 (dd, J = 6.1, 8.6 Hz, 1H), 7.21 - 7.17 (m, 1H), 7.05 (dd, J = 2.4, 10.7 Hz, 1H), 6.98 (br d, J = 7.4 Hz, 1H), 6.88 (dt, J = 2.5, 8.3 Hz, 1H), 6.76 - 6.69 (m, 1H), 5.52 - 5.39 (m, 1H), 4.57 - 4.51 (m, 2H), 4.49 - 4.15 (m, 2H), 4.14 - 3.98 (m, 2H), 3.77 (s, 3H), 3.13 - 3.02 (m, 3H), 2.87 (br dd, J = 6.7, 13.4 Hz, 1 H), 2.72 - 2.53 (m, 2H), 2.48 (s, 3H), 2.04 (s, 2H). LCMS($M+H)^+$: 633.
140	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-**	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C15**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.43 - 9.54 (m, 1H), 8.49 - 8.58 (m, 1H), 7.87 - 7.96 (m, 2H), 7.61 - 7.78 (m, 3H), 7.28 - 7.38 (m, 1H), 7.19 - 7.27 (m, 1H), 7.11 - 7.18 (m, 1H),

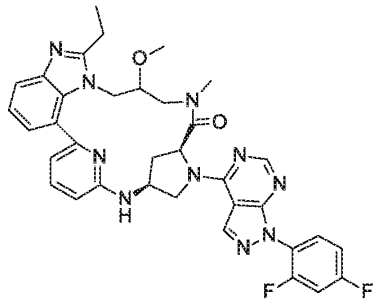
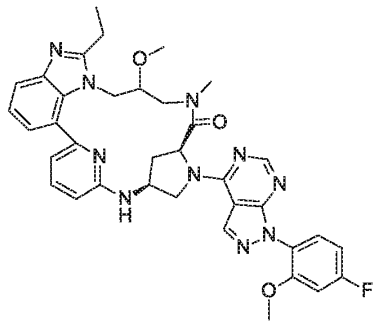
	heptaen-12-one 		6.81 - 6.92 (m, 1H), 5.47 - 5.64 (m, 1H), 5.03 - 5.18 (m, 1H), 4.72 - 4.82 (m, 1H), 4.50 - 4.65 (m, 1H), 4.20 - 4.46 (m, 3H), 3.07 - 3.21 (m, 3H), 2.88 - 3.00 (m, 1H), 2.43 - 2.83 (m, 5H), 1.92 - 2.24 (m, 1H), 1.51 - 1.80 (m, 1H). LCMS $(M+H)^+$: 621.
143	**(8*S*,11*S*)-4-(difluoromethoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B21** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.45 (s, 1H), 8.56 (s, 1H), 8.27 (s, 1H), 7.95 – 7.80 (m, 1H), 7.78 – 7.65 (m, 3H), 7.45 - 7.25 (m, 3H), 6.83 (s, 1H), 6.55 (m, 1H), 5.65 – 5.45 (m, 1H), 5.20 - 5.11 (m, 1H), 4.65 – 4.50 (m, 1H), 4.45 - 4.31 (m, 3H), 4.20 - 4.15 (m, 1H), 3.21 (s, 3H), 3.0 – 2.85 (m, 1H), 2.80 – 2.62 (m, 2H), 2.21 – 2.15 (m, 1H), 1.85 - 1.59 (m, 1H). LCMS $(M+H)^+$: 673.
144	**(8*S*,11*S*)-4-(cyclopropoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B22** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 - 8.55 (m, 1H), 8.21 - 8.29 (m, 2H), 7.61 - 7.74 (m, 2H), 7.16 - 7.37 (m, 4H), 6.67 - 6.71 (m, 1H), 6.33 - 6.39 (m, 1H), 5.43 - 5.56 (m, 1H), 4.68 - 4.76 (m, 1H), 4.59 (s, 3H), 4.53 - 4.57 (m, 1H),

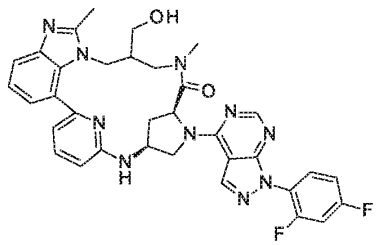
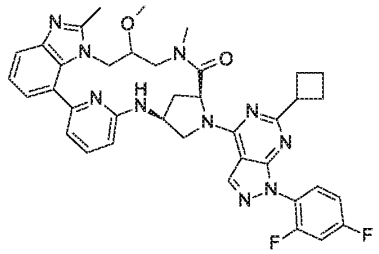
			4.25 - 4.31 (m, 1H), 4.06 - 4.23 (m, 2H), 3.97 - 4.05 (m, 1H), 3.10 (s, 3H), 2.85 – 2.91 (m, 1H), 2.65 - 2.75 (m, 1H), 2.50 - 2.64 (m, 1H), 0.87 - 0.94 (m, 2H), 0.78 - 0.86 (m, 2H). LCMS $(M+H)^+$: 663.
149	**(8*S*,11*S*)-13-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A20** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.52 (s, 1H), 8.60 (s, 1H), 8.28 (s, 1H), 7.88 - 7.98 (m, 2H), 7.65 - 7.80 (m, 3H), 7.14 - 7.35 (m, 3H), 6.95 – 6.96 (m, 1H), 5.79 (m, 1H), 4.77 - 4.88 (m, 1H), 4.54 (m, 1H), 4.44 (m, 1H), 4.26 - 4.36 (m, 1H), 4.15 (m, 1H), 3.14 - 3.31 (m, 1H), 2.92 - 3.02 (m, 1H), 2.60 - 2.75 (m, 2H), 2.10 - 2.22 (m, 1H), 1.78 (m, 1H), 1.28 - 1.40 (m, 2H), 1.12 - 1.25 (m, 1H), 0.77 - 1.00 (m, 2H). LCMS $(M+H)^+$: 633.
169	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-**	**BORONIC REAGENT:** Intermediate **A21** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.45 - 9.26 (m, 1H), 8.56 (d, *J* = 1.5 Hz, 1H), 8.40 - 8.18 (m, 1H), 7.94 - 7.79 (m, 3H), 7.74 - 7.63 (m, 2H), 7.34 - 7.25 (m, 1H), 7.25 - 7.05 (m, 2H), 6.83 - 6.72 (m, 1H), 6.16 - 5.93 (m, 1H), 5.66 - 5.37 (m,

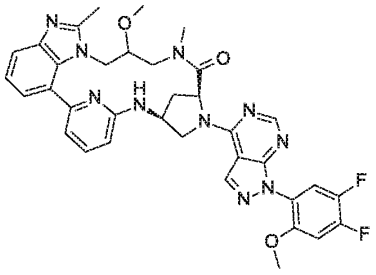
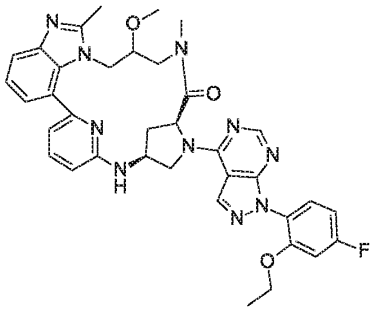
	heptaen-12-one 		2H), 4.81 - 4.66 (m, 1H), 4.63 - 4.08 (m, 3H), 3.99 - 3.76 (m, 1H), 3.12 - 2.88 (m, 1H), 2.75 - 2.50 (m, 2H). LCMS(M+H)$^+$: 643.
173	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C2**	LCMS(M+H)$^+$: 637.
173A & 173B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-**	Example **173** was separated by SFC to give Example **173A** (Faster eluted) and Example **173B** **SFC condition:** Instrument: ACS WH-PREP-SFC-B	**Example 173A**: ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.50 - 8.43 (m, 1H), 8.22 (s, 1H), 7.86 - 7.76 (m, 2 H), 7.70 - 7.61 (m, 1H), 7.58 (br d, J = 7.8 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.29 (br t, J = 9.3 Hz, 1H), 7.24 - 7.12 (m, 2H), 6.70 (br d, J = 7.9 Hz, 1H), 5.90 -

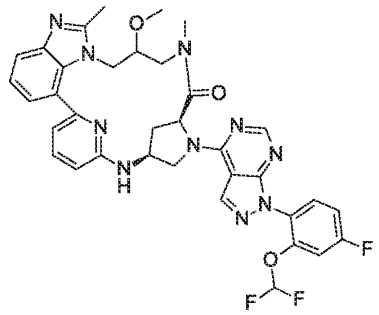
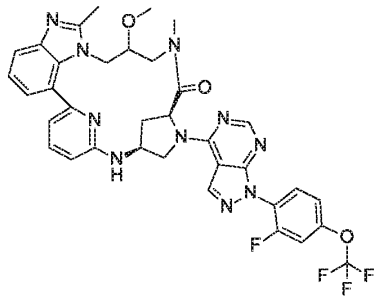
	d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one  	Column: DAICEL CHIRALPAK AD(250mm×30mm,10μm) Mobile phase: A for CO_2 and B for 0.1%NH3H2O IPA Gradient: B 70% Flow rate: 80 mL/min Back pressure: 100bar Column temperature: 35°C	5.73 (m, 1H), 5.54 - 5.38 (m, 1H), 4.68 (br d, *J* = 4.9 Hz, 1H), 4.58 - 4.45 (m, 1H), 4.62 - 4.14 (m, 2H), 3.99 - 3.89 (m, 1H), 3.14 (s, 1H), 3.06 (s, 2H), 3.02 - 2.91 (m, 1H), 2.91 - 2.87 (m, 3H), 2.86 (br s, 1H), 2.69 - 2.48 (m, 2H). LCMS(M+H)$^+$: 637. **Example 173B**: ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.40 - 8.19 (m, 2H), 7.81 - 7.63 (m, 3H), 7.39 - 7.24 (m, 3H), 7.20 (br t, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.73 - 6.68 (m, 1H), 5.56 - 5.43 (m, 1H), 5.19 - 4.97 (m, 1H), 4.75 (br s, 1H), 4.62 - 4.54 (m, 1H), 4.46 - 3.97 (m, 3H), 3.92 - 3.76 (m, 1H), 3.20 (s, 1H), 3.13 - 3.04 (m, 3H), 2.97 - 2.90 (m, 3H), 2.76 - 2.52 (m, 2H). LCMS(M+H)$^+$: 637.
196	**(8*S*,11*S*)-10-[1-[2-(difluoromethyl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C47**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.21 - 8.60 (m, 2H), 7.75 - 7.86 (m, 1H), 7.25 - 7.73 (m, 6H), 6.61 - 7.17 (m, 3H), 4.97 - 5.94 (m, 2H), 4.65 - 4.78 (m, 1H), 4.46 - 4.64 (m, 1H), 3.66 - 4.40 (m, 4H), 3.00 - 3.21 (m, 4H), 2.85 (d, *J*=4.52

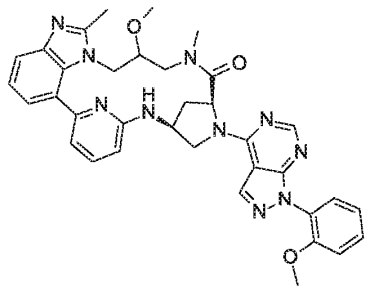
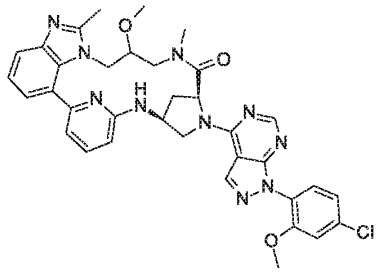
			Hz, 4H), 2.51 - 2.64 (m, 4H). LCMS (M+H$^+$): 683.
206	**(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C41**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.08 - 8.48 (m, 3H), 7.58 - 7.86 (m, 2H), 7.11 - 7.40 (m, 4H), 6.89 (br d, *J*=6.36 Hz, 1H), 6.63 - 6.77 (m, 1H), 5.99 - 6.15 (m, 1H), 4.93 - 5.85 (m, 1H), 3.71 - 4.76 (m, 6H), 2.99 - 3.20 (m, 4H), 2.78 - 2.90 (m, 4H), 2.46 - 2.69 (m, 5H). LCMS (M+H$^+$): 651.
207	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-ethyl-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A22** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.40 - 8.21 (m, 1H), 7.90 - 7.61 (m, 5H), 7.34 - 7.26 (m, 1H), 7.25 - 7.15 (m, 1H), 7.05 - 6.96 (m, 1H), 6.79 - 6.73 (m, 1H), 5.55 - 5.41 (m, 1H), 4.84 - 4.80 (m, 1H), 4.80 - 4.66 (m, 1H), 4.62 - 4.49 (m, 1H), 4.40 -

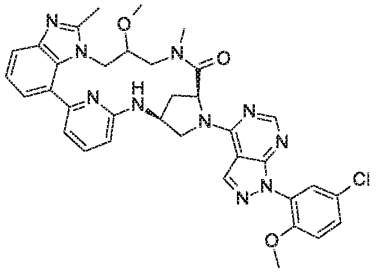
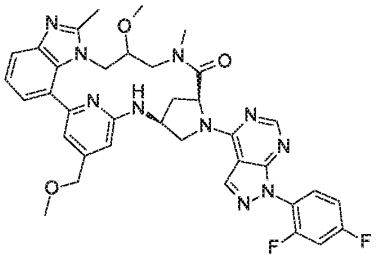
			4.21 (m, 2H), 4.15 - 3.91 (m, 1H), 3.85 - 3.36 (m, 1H), 3.28 - 3.15 (m, 3H), 3.14 - 2.99 (m, 3H), 2.94 (d, *J* = 1.1 Hz, 3H), 2.91 - 2.65 (m, 1H), 2.63 - 2.51 (m, 1H), 1.57 - 1.45 (m, 3H). LCMS(M+H)$^+$: 665.
208	**(8*S*,11*S*)-18-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A22** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C11**	^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.53 (s, 1H), 8.35 - 8.20 (m, 1H), 7.91 - 7.62 (m, 4H), 7.50 - 7.37 (m, 1H), 7.18 - 6.95 (m, 2H), 6.94 - 6.85 (m, 1H), 6.80 - 6.73 (m, 1H), 5.55 - 5.43 (m, 1H), 4.85 - 4.78 (m, 1H), 4.78 - 4.67 (m, 1H), 4.63 - 4.50 (m, 1H), 4.42 - 3.87 (m, 4H), 3.79 - 3.75 (m, 3H), 3.28 - 3.15 (m, 3H), 3.11 - 2.98 (m, 3H), 2.95 (d, *J* = 2.5 Hz, 3H), 2.80 (br d, *J* = 14.3 Hz, 1H), 2.64 - 2.51 (m, 1H), 1.58 - 1.45 (m, 3H). LCMS(M+H)$^+$: 677.
210	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(hydroxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-**	**BORONIC REAGENT:** Intermediate **A23** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.55 (s, 1H), 8.40 - 8.21 (m, 1H), 7.91 - 7.61 (m, 5H), 7.33 - 7.26 (m, 1H), 7.25 - 7.08 (m, 2H), 6.83 - 6.71 (m, 1H), 6.16 - 5.97 (m, 1H), 5.52 - 5.41 (m, 1H), 4.71 - 4.50 (m,

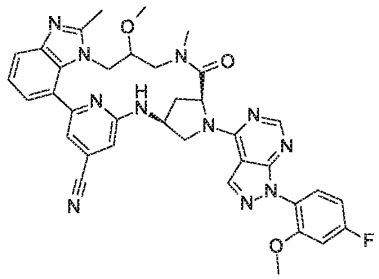
	heptaen-12-one 		2H), 4.49 - 4.27 (m, 2H), 4.21 - 4.04 (m, 1H), 3.27 - 3.15 (m, 3H), 3.14 - 2.98 (m, 2H), 2.97 - 2.85 (m, 3H), 2.83 - 2.58 (m, 2H), 2.53 - 2.42 (m, 1H), 2.30 - 2.15 (m, 1H). LCMS ($M+H^+$) :651
212	**(8S,11S)-10-[6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C30**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (s, 1H), 7.90 - 7.71 (m, 3H), 7.70 - 7.59 (m, 3H), 7.28 (td, *J*=9.44, 2.38 Hz, 1H), 7.23 - 7.18 (m, 1H), 6.82 - 6.75 (m, 1H), 5.67 - 5.55 (m, 1H), 4.79 - 4.51 (m, 1H), 4.40 - 4.19 (m, 2H), 4.06 (br d, *J*=14.13 Hz, 1H), 3.96 - 3.79 (m, 1H), 3.74 - 3.46 (m, 2H), 3.19 - 3.11 (m, 3H), 3.04 - 2.92 (m, 4H), 2.87 - 2.84 (m, 3H), 2.79 - 2.67 (m, 1H), 2.66 - 2.18 (m, 6H), 2.11 - 1.86 (m, 2H). LCMS $(M+H)^+$: 705.
215	**(8*S*,11*S*)-10-[1-(4,5-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C31**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, *J* =1.83 Hz, 1H), 8.39 - 8.24 (m, 1H), 7.90 - 7.62 (m, 4H), 7.53 - 7.39 (m, 1H), 7.28 (ddd, *J* =12.23, 7.21, 2.57 Hz, 1H), 7.19 - 6.96 (m, 1H), 6.80 - 6.74 (m, 1H), 6.25 - 6.02 (m, 1H), 5.54 -

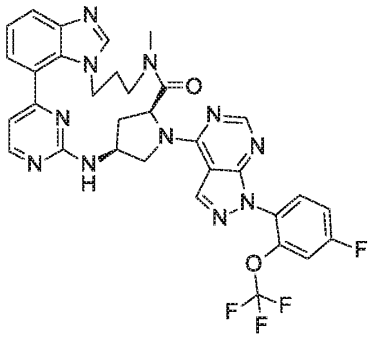
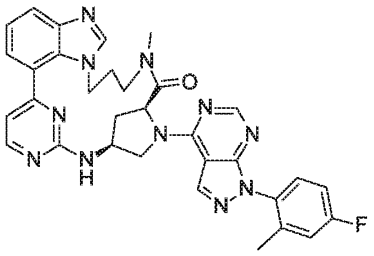
			5.45 (m, 1H), 4.77 - 4.67 (m, 1H), 4.55 (ddd, *J*=15.07, 11.65, 6.05 Hz, 1H), 4.43 - 4.07 (m, 3H), 4.01 - 3.80 (m, 1H), 3.78 - 3.73 (m, 3H), 3.18 (d, *J* =16.26 Hz, 1H), 3.08 (d, *J* =14.79 Hz, 3H), 2.96 (s, 3H), 2.88 - 2.82 (m, 3H), 2.76 - 2.52 (m, 2H). LCMS $(M+H)^+$: 681.
216	**(8*S*,11*S*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C18**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.18 - 8.52 (m, 2H), 7.74 - 7.85 (m, 1H), 7.59 - 7.66 (m, 1H), 7.24 - 7.49 (m, 3H), 6.83 - 7.16 (m, 3H), 6.69 (dd, *J*=14.00, 8.38 Hz, 1H), 5.50 (t, *J*=9.35 Hz, 1H), 4.66 - 4.77 (m, 1H), 4.58 (br dd, *J*=11.74, 6.24 Hz, 1H), 4.34 (br t, *J*=12.17 Hz, 1H), 3.72 - 4.27 (m, 5H), 2.98 - 3.24 (m, 4H), 2.85 (d, *J*=5.26 Hz, 4H), 2.48 - 2.74 (m, 5H), 1.12 - 1.23 (m, 3H). LCMS $(M+H^+)$: 677.
217	**(8*S*,11*S*)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-**	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C19**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.17 - 8.60 (m, 2H), 7.75 - 7.85 (m, 1H), 7.59 - 7.69 (m, 2H), 7.21 - 7.43 (m, 4H), 6.64 - 7.16 (m, 3H), 5.55 (m, 1H), 4.49 - 4.77 (m, 2H), 4.29 -

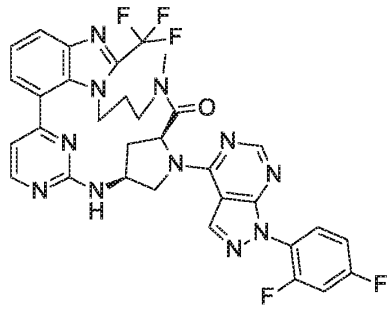
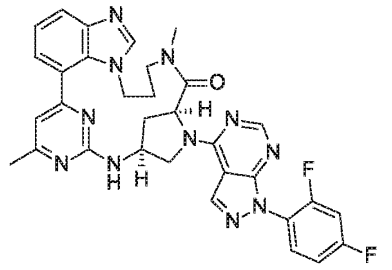
	1(24),2,4,6(26),18,20,22-heptaen-12-one 		4.39 (m, 1H), 3.71 - 4.27 (m, 3H), 2.98 - 3.22 (m, 4H), 2.71 - 2.93 (m, 4H), 2.49 - 2.62 (m, 4H). LCMS $(M+H)^+$: 699.
218	**(8*S*,11*S*)-10-[1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C46B**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.11 - 8.50 (m, 2H), 7.49 - 7.77 (m, 4H), 7.12 - 7.39 (m, 4H), 6.53 - 7.04 (m, 1H), 5.03 - 5.77 (m, 2H), 4.79 - 4.88 (m, 1H), 4.55 - 4.75 (m, 2H), 3.61 - 4.53 (m, 3H), 2.93 - 3.10 (m, 4H), 2.71 - 2.86 (m, 4H), 2.43 - 2.50 (m, 4H). LCMS $(M+H)^+$: 717.
223	**(8*S*,11*S*)-15-methoxy-10-[1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-**	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C10**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.38 - 8.19 (m, 1H), 7.91 - 7.82 (m, 1H), 7.82 - 7.77 (m, 1H), 7.76 - 7.61 (m, 2H), 7.60 - 7.53 (m, 1H), 7.48 - 7.36 (m, 1H), 7.26 (br d, J = 8.3 Hz, 1H), 7.20 –

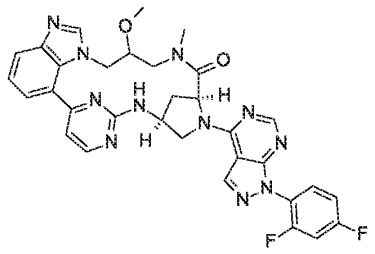
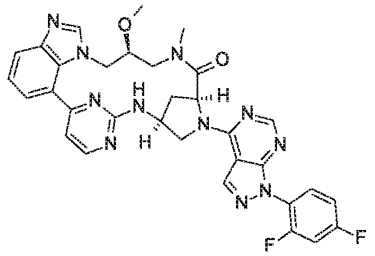
	heptaen-12-one 		6.96 (m, 2H), 6.77 (dd, *J* = 3.5, 8.3 Hz, 1H), 6.22 - 6.04 (m, 1H), 5.58 - 5.43 (m, 1H), 4.79 - 4.67 (m, 1H), 4.64 - 4.51 (m, 1H), 4.45 - 4.08 (m, 3H), 4.02 - 3.81 (m, 1H), 3.77 (d, *J* = 2.0 Hz, 3H), 3.19 (d, *J* = 15.7 Hz, 1H), 3.15 - 3.04 (m, 3H), 2.96 (s, 3H), 2.90 - 2.72 (m, 4H), 2.65 - 2.53 (m, 1H). LCMS(M+H)$^+$: 645.
224	**(8*S*,11*S*)-10-[1-(4-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C32**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.38 - 8.20 (m, 1H), 7.91 - 7.77 (m, 2H), 7.76 - 7.59 (m, 2H), 7.47 - 7.36 (m, 1H), 7.31 (s, 1H), 7.17 (br d, *J* = 7.8 Hz, 1H), 6.99 (br d, *J* = 7.8 Hz, 1H), 6.81 - 6.72 (m, 1H), 6.21 - 6.03 (m, 1H), 5.50 (br dd, *J* = 8.8, 14.3 Hz, 1H), 4.78 - 4.66 (m, 1H), 4.63 - 4.48 (m, 1H), 4.43 - 4.05 (m, 3H), 4.02 - 3.81 (m, 1H), 3.78 (d, *J* = 2.1 Hz, 3H), 3.18 (br d, *J* = 16.3 Hz, 1H), 3.14 - 3.03 (m, 3H), 3.01 (s, 3H), 2.91 - 2.74 (m, 4H), 2.65 - 2.52 (m, 1H). LCMS(M+H)$^+$: 679.
225	**(8S,11S)-10-[1-(5-chloro-2-methoxy-phenyl)pyrazolo[3,4-**	**BORONIC REAGENT:**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s,

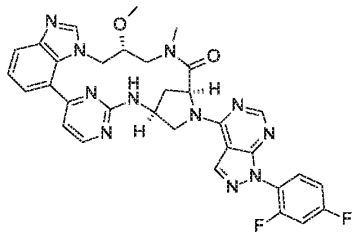
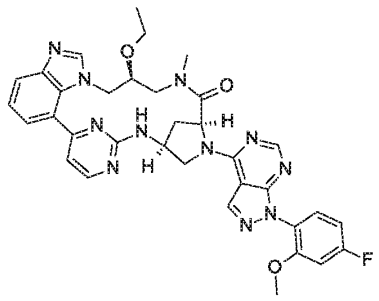
	d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C33**	1H), 8.37 - 8.17 (m, 1H), 7.90 - 7.78 (m, 2H), 7.78 - 7.72 (m, 1H), 7.67 - 7.62 (m, 1H), 7.59 - 7.53 (m, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.26 (dd, *J* = 2.0, 8.9 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.04 - 6.72 (m, 1H), 6.26 - 6.03 (m, 1H), 5.56 - 5.40 (m, 1H), 4.78 - 4.68 (m, 1H), 4.61 - 4.50 (m, 1H), 4.40 - 4.06 (m, 3H), 4.02 - 3.81 (m, 1H), 3.79 - 3.75 (m, 3H), 3.23 - 3.15 (m, 1H), 3.08 (d, *J* = 14.2 Hz, 3H), 2.96 (s, 3H), 2.88 - 2.74 (m, 4H), 2.59 (ddd, *J* = 4.6, 8.6, 13.1 Hz, 1H). LCMS(M+H)$^+$: 679.
239	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-4-(methoxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B23** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.56 (s, 1H), 8.40 - 8.22 (m, 1H), 7.84 - 7.61 (m, 4H), 7.34 - 7.26 (m, 1H), 7.21 (br t, *J* = 7.9 Hz, 1H), 7.13 - 6.90 (m, 1H), 6.73 (d, *J* = 6.8 Hz, 1H), 6.24 - 5.40 (m, 1H), 4.79 - 4.68 (m, 1H), 4.65 - 4.49 (m, 3H), 4.40 - 4.05 (m, 3H), 4.01 - 3.68 (m, 1H), 3.53 (s, 1H), 3.50 (s, 2H), 3.24 - 3.15 (m, 1H), 3.13 - 3.05 (m, 3H), 3.02 - 2.88 (m, 4H), 2.85 (d, *J* = 7.1 Hz, 3H), 2.83 - 2.72

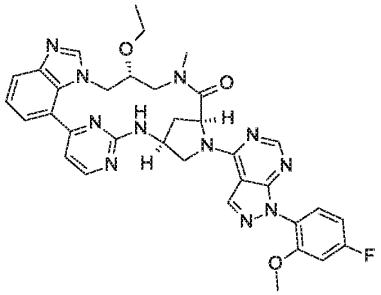
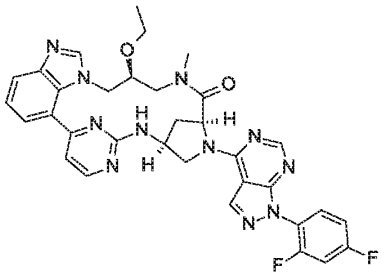
			(m, 1H), 2.60 (ddd, *J* = 4.3, 8.9, 13.1 Hz, 1H). LCMS $(M+H)^+$: 695.
241	**(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B24** **HALIDE 2**: Intermediate **C11**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.52 (s, 1H), 8.22 (s, 1H), 7.89 - 7.77 (m, 2H), 7.73 - 7.62 (m, 2H), 7.48 - 7.44 (m, 1H), 7.12 - 7.06 (m, 2H), 6.89 (td, *J* = 8.34, 2.51 Hz, 1H), 5.56 - 5.49 (m, 1H), 4.78 - 4.71 (m, 1H), 4.60 - 4.53 (m, 1H), 4.46 - 4.27 (m, 3H), 4.08 (br d, *J* = 14.79 Hz, 1H), 3.77 (s, 3H), 3.26 - 3.17 (m, 2H), 3.14 - 3.09 (m, 3H), 2.96 (d, *J* = 11.00 Hz, 3H), 2.86 (d, *J* = 6.48 Hz, 3H), 2.76 - 2.61 (m, 2H). LCMS $(M+H)^+$: 688.
285	**(8*S*,11*S*)-10-[1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C46A**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 - 8.64 (m, 2H), 8.23 - 8.38 (m, 2H), 7.79 - 7.87 (m, 1H), 7.68 - 7.77 (m, 1H), 7.36 - 7.54 (m, 4H), 7.09 (d, *J*=5.26 Hz, 1H), 5.42 - 5.53 (m, 1H), 5.19 - 5.28 (m, 1H), 4.51 (br dd, *J*=11.74, 5.99 Hz, 1H), 4.37 (br d, *J*=11.37 Hz, 1H), 4.22 - 4.31 (m, 1H), 4.12 (br dd, *J*=14.18, 9.90 Hz, 1H), 2.84 - 3.17 (m, 6H), 2.55 -

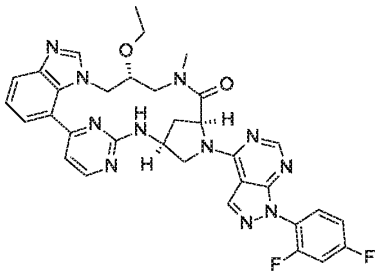
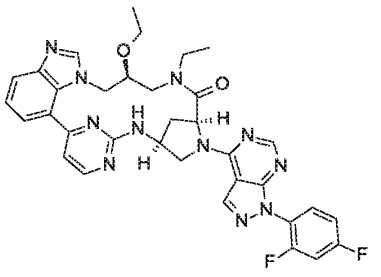
			2.75 (m, 1H), 1.86 - 2.07 (m, 1H), 1.42 - 1.52 (m, 1H). LCMS $(M+H)^+$: 674.
287	**(8*S*,11*S*)-10-[1-(4-fluoro-2-methyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C42**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (br d, *J*=11.49 Hz, 2H), 8.30 (s, 1H), 8.22 (s, 1H), 7.82 (d, *J*=7.95 Hz, 1H), 7.52 (br d, *J*=7.46 Hz, 1H), 7.40 (br d, *J*=7.82 Hz, 2H), 7.24 (br d, *J*=9.05 Hz, 1H), 7.16 (br s, 1H), 7.10 (d, *J*=5.14 Hz, 1H), 5.43 - 5.54 (m, 1H), 5.18 - 5.32 (m, 1H), 4.48 - 4.67 (m, 1H), 4.25 - 4.40 (m, 2H), 4.08 - 4.16 (m, 1H), 2.77 - 3.21 (m, 6H), 2.53 - 2.70 (m, 1H), 2.08 - 2.12 (m, 3H), 1.82 - 1.97 (m, 1H), 1.35 - 1.51 (m, 1H). LCMS $(M+H)^+$: 604.
298	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(trifluoromethyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-**	**BORONIC REAGENT:** Intermediate **A25** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2**	1H NMR (400 MHz, METHANOL-d_4) δ = 8.63 (s, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 8.41 – 8.29 (m, 1H), 7.97 - 7.89 (m, 1H), 7.75 - 7.64 (m, 2H), 7.55 - 7.48 (m, 1H), 7.35 - 7.27 (m, 1H), 7.26 -

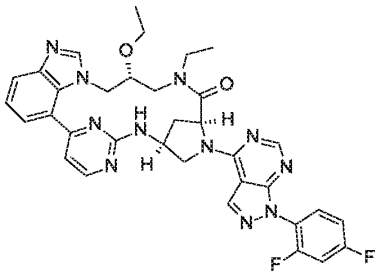
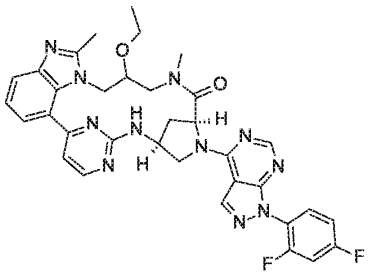
	1(23),2(26),3,5,18,20(24),21-heptaen-12-one 		7.18 (m, 1H), 7.11 (d, *J* = 5.3 Hz, 1H), 5.71 - 5.55 (m, 1H), 5.52 - 5.37 (m, 1H), 4.82 (br t, *J* = 4.5 Hz, 1H), 4.53 - 4.42 (m, 1H), 4.38 - 4.21 (m, 1H), 4.06 - 3.93 (m, 1H), 3.14 (br d, *J* = 13.7 Hz, 1H), 3.11 - 2.97 (m, 3H), 2.97 - 2.83 (m, 1H), 2.76 - 2.52 (m, 1H), 1.77 - 1.58 (m, 1H), 1.49 - 1.11 (m, 2H). LCMS(M+H)$^+$: 676.
299	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B3** **HALIDE 2**: Intermediate **C2**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.55 - 9.38 (m, 1H), 8.65 - 8.36 (m, 1H), 8.30 - 7.92 (m, 2H), 7.90 - 7.79 (m, 1H), 7.78 - 7.53 (m, 2H), 7.36 - 7.25 (m, 1H), 7.21 (br d, *J* = 1.2 Hz, 1H), 7.04 (s, 1H), 5.46 (d, *J* = 8.8 Hz, 2H), 4.73 - 4.20 (m, 3H), 4.12 (br dd, *J* = 9.8, 14.2 Hz, 1H), 3.28 - 2.84 (m, 6H), 2.76 - 2.36 (m, 4H), 2.00 - 1.78 (m, 1H), 1.59 - 1.36 (m, 1H). LCMS (M+H$^+$): 622.
301	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-**	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B1** **HALIDE 2**:	LCMS (M+H$^+$): 638

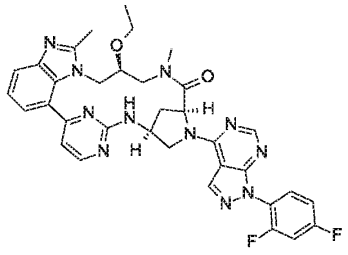
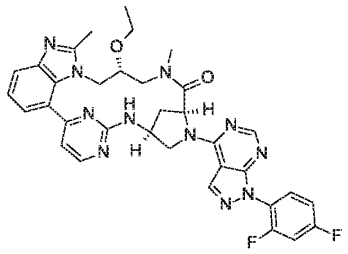
	1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **C2**	
301A & 301B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	Example **301** was separated by SFC to give Example **301A** (Faster eluted) and Example **301B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: Pyridine, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 20% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	Example **301A** ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.61 - 8.33 (m, 3H), 8.26 - 7.76 (m, 2H), 7.73 - 7.63 (m, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.50 - 7.36 (m, 1H), 7.32 - 7.16 (m, 2H), 7.06 (d, *J* = 5.3 Hz, 1H), 5.62 - 5.34 (m, 2H), 4.56 - 4.22 (m, 3H), 4.18 - 3.99 (m, 2H), 3.72 - 3.57 (m, 1H), 3.25 - 3.04 (m, 4H), 2.94 - 2.76 (m, 4H), 2.76 - 2.51 (m, 1H). LCMS (M+H$^+$): 638. Example **301B** ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.71 - 8.30 (m, 3H), 8.24 - 7.78 (m, 2H), 7.78 - 7.49 (m, 3H), 7.34 - 7.05 (m, 3H), 5.73 (br dd, *J* = 3.5, 14.9 Hz, 1H), 5.52 - 5.36 (m, 1H), 4.37 (s, 3H), 4.14 - 4.06 (m, 1H), 4.02 - 3.86 (m, 1H), 3.15 -

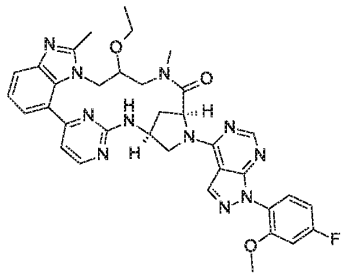
			2.95 (m, 4H), 2.93 - 2.80 (m, 4H), 2.66 - 2.47 (m, 2H). LCMS ($M+H^+$): 638
303 & 304	**(8*S*,11*S*,15*R*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A17** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C11** Reaction mixture separated by prep-HPLC to give Example **303** and **304**.	Example **303** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.30 - 9.21 (m, 1H), 8.63 - 8.24 (m, 2H), 8.21 - 7.72 (m, 3H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.44 - 7.27 (m, 1H), 7.17 - 7.06 (m, 1H), 7.03 - 6.93 (m, 1H), 6.79 (dt, *J* = 2.6, 8.3 Hz, 1H), 5.84 - 5.59 (m, 1H), 5.37 (d, *J* = 8.7 Hz, 1H), 4.70 (t, *J* = 4.7 Hz, 1H), 4.46 - 4.10 (m, 3H), 3.88 (dd, *J* = 9.8, 14.2 Hz, 1H), 3.74 - 3.59 (m, 3H), 3.39 - 3.26 (m, 1H), 3.11 - 2.92 (m, 4H), 2.92 - 2.76 (m, 1H), 2.72 - 2.59 (m, 2H), 2.49 (ddd, *J* = 4.2, 9.0, 13.7 Hz, 1H), 0.50 (t, *J* = 6.9 Hz, 3H). LCMS $(M+H)^+$: 664. Example **304** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.41 - 9.29 (m, 1H), 8.53 - 8.22 (m, 2H), 8.18 - 7.68 (m, 3H), 7.67 - 7.57 (m, 1H), 7.37 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.11 - 6.93 (m, 2H), 6.80 (dt, *J* =

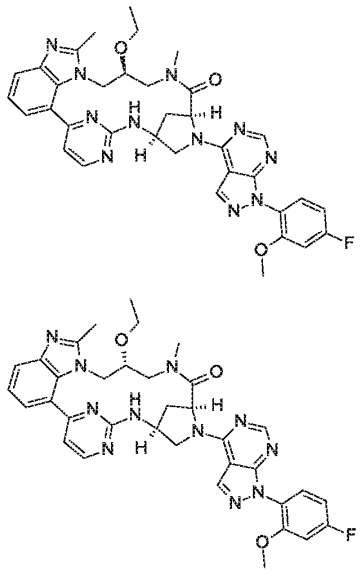
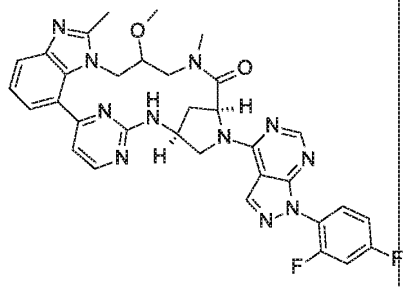
			2.5, 8.4 Hz, 1H), 5.81 - 5.57 (m, 1H), 5.42 (d, *J* = 9.0 Hz, 1H), 4.52 - 4.15 (m, 3H), 4.01 (d, *J* = 14.6 Hz, 1H), 3.77 - 3.61 (m, 4H), 3.40 - 3.27 (m, 1H), 3.19 - 2.92 (m, 5H), 2.91 - 2.74 (m, 2H), 2.72 - 2.46 (m, 1H), 0.63 - 0.46 (m, 3H). LCMS $(M+H)^+$: 664.
305 and 306	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A17** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2** Reaction mixture separated by prep-HPLC to give Example **305** and **306**.	Example **305** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.31 - 9.11 (m, 1H), 8.64 - 8.22 (m, 2H), 8.18 - 7.71 (m, 3H), 7.70 - 7.46 (m, 2H), 7.28 - 7.01 (m, 3H), 5.86 - 5.60 (m, 1H), 5.41 - 5.28 (m, 1H), 4.72 - 4.42 (m, 1H), 4.41 - 4.05 (m, 3H), 3.87 (dd, *J* = 9.6, 14.2 Hz, 1H), 3.41 - 3.27 (m, 1H), 3.11 - 2.92 (m, 4H), 2.90 - 2.78 (m, 1H), 2.73 - 2.60 (m, 2H), 2.59 - 2.41 (m, 1H), 0.59 - 0.39 (m, 3H). LCMS $(M+H)^+$: 652. Example **306** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.36 - 9.22 (m, 1H), 8.54 - 8.22 (m, 2H), 8.18 - 7.70 (m, 3H), 7.68 - 7.45 (m, 2H), 7.30 - 6.97 (m, 3H), 5.82 - 5.56 (m,

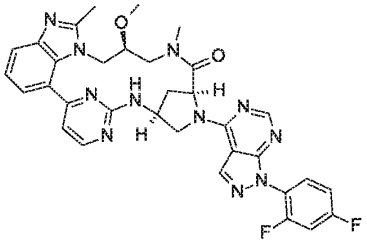
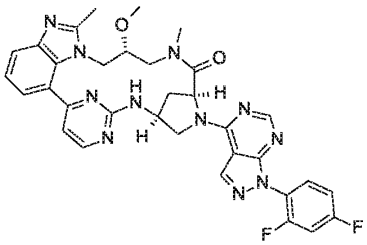
			1H), 5.49 - 5.28 (m, 1H), 4.72 - 4.11 (m, 4H), 4.01 (d, *J* = 14.6 Hz, 1H), 3.75 - 3.56 (m, 1H), 3.29 (dd, *J* = 7.0, 9.5 Hz, 1H), 3.15 - 2.94 (m, 4H), 2.86 - 2.72 (m, 2H), 2.68 - 2.44 (m, 1H), 0.62 - 0.41 (m, 3H). LCMS $(M+H)^+$: 652.
307 and 308	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A5** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2** Reaction mixture separated by prep-HPLC to give Example **307** and **308**.	Example **307** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.39 - 9.25 (m, 1H), 8.65 (d, *J* = 5.2 Hz, 1H), 8.59 - 8.32 (m, 1H), 8.27 - 7.89 (m, 3H), 7.83 - 7.73 (m, 1H), 7.67 (dt, *J* = 5.8, 8.6 Hz, 1H), 7.37 - 7.11 (m, 3H), 5.92 (dd, *J* = 3.5, 14.6 Hz, 1H), 5.58 - 5.33 (m, 1H), 4.50 - 4.17 (m, 4H), 3.89 - 3.76 (m, 1H), 3.67 - 3.56 (m, 1H), 3.52 - 3.44 (m, 1H), 3.43 - 3.32 (m, 1H), 3.12 - 2.92 (m, 2H), 2.73 (br dd, *J* = 7.0, 9.6 Hz, 2H), 2.58 (s, 1H), 1.12 - 0.94 (m, 3H), 0.68 - 0.52 (m, 3H). LCMS $(M+H)^+$: 666. Example **308** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 9.27 (s, 1H), 8.63 - 8.33 (m, 2H), 8.30 - 7.90 (m, 2H), 7.85 -

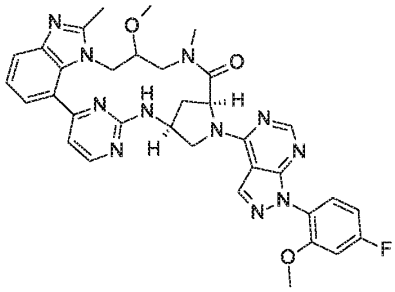
			7.61 (m, 3H), 7.35 - 7.01 (m, 3H), 5.59 - 5.34 (m, 2H), 4.58 - 4.21 (m, 3H), 4.01 - 3.77 (m, 2H), 3.60 (br dd, *J* = 7.3, 14.8 Hz, 1H), 3.47 - 3.36 (m, 2H), 3.26 - 3.13 (m, 2H), 2.92 (br dd, *J* = 7.0, 9.6 Hz, 1H), 2.74 - 2.56 (m, 2H), 1.34 - 1.15 (m, 3H), 0.72 - 0.56 (m, 3H). LCMS $(M+H)^+$: 666.
309	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A10** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2**	LCMS $(M+H)^+$: 666
309A & 309B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-**	Example **309** was separated by SFC to give Example **309A** (Faster eluted) and	Example **309A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 - 8.30 (m, 2H), 8.22 - 7.78 (m, 1H), 7.72 - 7.54 (m, 2H),

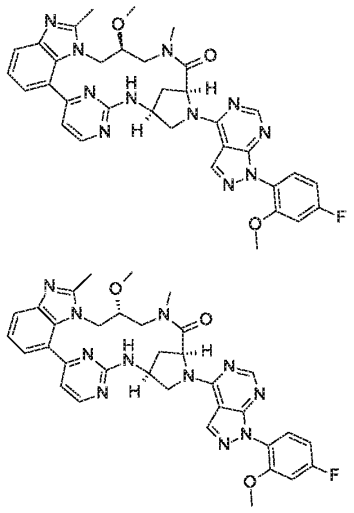
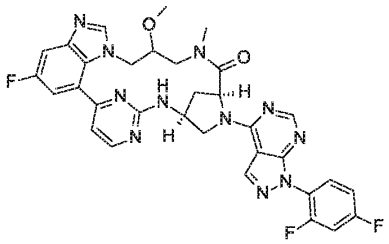
	heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	Example **309B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	7.51 - 7.43 (m, 1H), 7.36 - 7.14 (m, 3H), 7.14 - 7.04 (m, 1H), 5.65 - 5.48 (m, 1H), 5.47 - 5.30 (m, 1H), 4.79 - 4.70 (m, 1H), 4.48 - 4.29 (m, 2H), 4.24 - 4.09 (m, 1H), 4.07 - 3.87 (m, 1H), 3.29 - 3.20 (m, 1H), 3.13 - 2.96 (m, 4H), 2.93 - 2.78 (m, 1H), 2.70 - 2.44 (m, 6H), 0.59 - 0.42 (m, 3H). LCMS $(M+H)^+$: 666. Example **309B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 - 8.33 (m, 2H), 8.25 - 7.74 (m, 1H), 7.72 - 7.56 (m, 2H), 7.50 - 7.36 (m, 1H), 7.34 - 7.23 (m, 2H), 7.22 - 7.13 (m, 1H), 7.07 - 6.94 (m, 1H), 5.74 - 5.53 (m, 1H), 5.52 - 5.37 (m, 1H), 4.84 - 4.64 (m, 1H), 4.61 - 4.39 (m, 1H), 4.38 - 4.21 (m, 1H), 4.17 - 4.00 (m, 2H), 3.73 - 3.55 (m, 1H), 3.28 - 3.20 (m, 1H), 3.20 - 3.02 (m, 4H), 2.95 - 2.74 (m, 2H), 2.73 - 2.50 (m, 4H), 0.61 - 0.46 (m, 3H). LCMS $(M+H)^+$: 666.
311	**(8*S*,11*S*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-**	**BORONIC REAGENT:** Intermediate **A10**	LCMS $(M+H)^+$: 678.

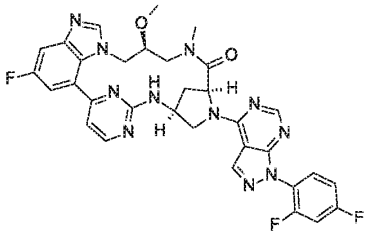
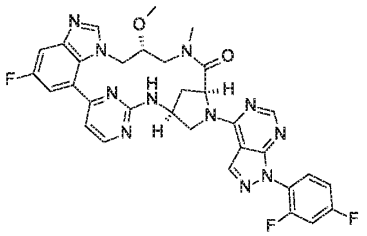
	d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	**HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C11**	
311A & 311B	**(8*S*,11*S*,15*R*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	Example **311** was separated by SFC to give Example **311A** (Faster eluted) and Example **311B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 50% Flow rate: 60 mL /min	Example **311A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.58 - 8.23 (m, 2H), 8.17 - 7.65 (m, 2H), 7.52 - 7.25 (m, 3H), 7.19 - 6.98 (m, 2H), 6.94 - 6.73 (m, 1H), 5.65 - 5.49 (m, 1H), 5.47 - 5.30 (m, 1H), 4.80 - 4.65 (m, 1H), 4.50 - 4.38 (m, 1H), 4.37 - 4.27 (m, 1H), 4.24 - 4.11 (m, 1H), 4.06 - 3.92 (m, 1H), 3.82 - 3.70 (m, 3H), 3.27 - 3.20 (m, 1H), 3.13 - 2.95 (m, 4H), 2.93 - 2.76 (m, 1H), 2.70 - 2.41 (m, 6H), 0.61 - 0.41 (m, 3H). LCMS $(M+H)^+$: 678. Example **311B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 -

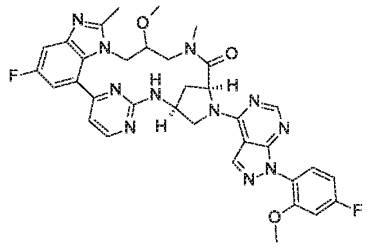
		Back pressure: 100bar Column temperature: 35°C	8.25 (m, 2H), 8.19 - 7.62 (m, 2H), 7.48 - 7.33 (m, 2H), 7.33 - 7.25 (m, 1H), 7.10 - 6.96 (m, 2H), 6.92 - 6.79 (m, 1H), 5.81 - 5.50 (m, 1H), 5.48 - 5.29 (m, 1H), 4.84 - 4.80 (m, 1H), 4.49 - 4.39 (m, 1H), 4.36 - 4.21 (m, 1H), 4.17 - 4.00 (m, 2H), 3.79 - 3.69 (m, 3H), 3.69 - 3.57 (m, 1H), 3.28 - 3.19 (m, 1H), 3.19 - 3.00 (m, 4H), 2.86 - 2.70 (m, 2H), 2.69 - 2.47 (m, 4H), 0.60 - 0.49 (m, 3H). LCMS $(M+H)^+$: 678.
313	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2**	LCMS $(M+H)^+$: 652
313A	**(8*S*,11*S*,15*R*)-10-[1-(2,4-**	Example **313** was	Example **313A**

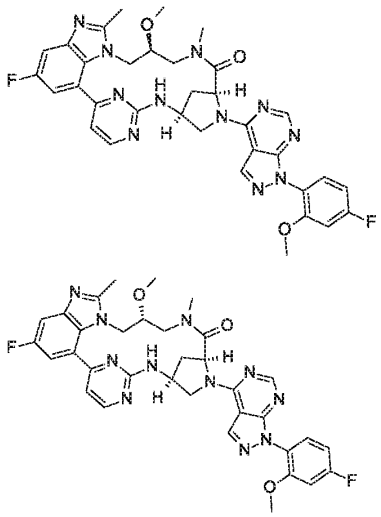
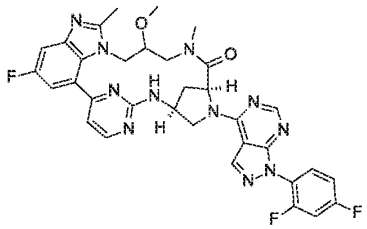
& 313B	**difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**  	separated by SFC to give Example **313A** (Faster eluted) and Example **313B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: OD, 250×20 mm I.D., 5µm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 30% Flow rate: 50 mL /min Back pressure: 100bar Column temperature: 35°C	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 - 8.29 (m, 2H), 8.22 - 7.75 (m, 1H), 7.72 - 7.53 (m, 2H), 7.51 - 7.43 (m, 1H), 7.35 - 7.23 (m, 2H), 7.21 - 7.05 (m, 2H), 5.62 - 5.45 (m, 1H), 5.44 - 5.27 (m, 1H), 4.76 - 4.67 (m, 1H), 4.43 - 4.28 (m, 2H), 4.26 - 4.10 (m, 1H), 4.05 - 3.85 (m, 1H), 3.17 - 2.97 (m, 4H), 2.96 - 2.74 (m, 4H), 2.60 - 2.35 (m, 5H). LCMS (M+H)$^+$: 652. Example **313B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 - 8.29 (m, 2H), 8.25 - 7.74 (m, 1H), 7.71 - 7.55 (m, 2H), 7.46 - 7.34 (m, 1H), 7.34 - 7.13 (m, 3H), 7.06 - 6.93 (m, 1H), 5.68 - 5.51 (m, 1H), 5.50 - 5.34 (m, 1H), 4.84 - 4.80 (m, 1H), 4.70 - 4.43 (m, 1H), 4.40 - 4.22 (m, 1H), 4.19 - 3.99 (m, 2H), 3.60 - 3.47 (m, 1H), 3.23 - 3.04 (m, 4H), 2.94 - 2.75 (m, 4H), 2.75 - 2.47 (m, 4H). LCMS (M+H)$^+$: 652.
315	**(8*S*,11*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-**	**BORONIC REAGENT:** Intermediate **A1**	LCMS (M+H)$^+$: 664.

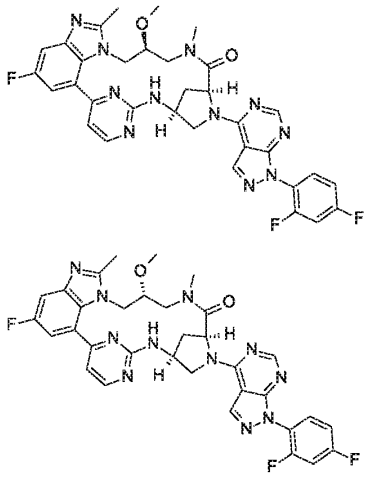
	13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	**HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C11**	
315A & 315B	**(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	Example **315** was separated by SFC to give Example **315A** (Faster eluted) and Example **315B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: OD, 250×20 mm I.D., 5μm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 30% Flow rate: 50 mL	Example **315A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.60 - 8.50 (m, 1H), 8.48 - 8.23 (m, 1H), 8.20 - 7.73 (m, 1H), 7.73 - 7.65 (m, 1H), 7.51 - 7.27 (m, 3H), 7.16 - 6.95 (m, 2H), 6.94 - 6.77 (m, 1H), 5.68 - 5.49 (m, 1H), 5.49 - 5.32 (m, 1H), 4.78 - 4.50 (m, 1H), 4.48 - 4.11 (m, 3H), 4.04 - 3.91 (m, 1H), 3.82 - 3.70 (m, 3H), 3.18 - 2.99 (m, 4H), 2.99 - 2.75 (m, 4H), 2.66 - 2.45 (m, 5H). LCMS (M+H)$^+$: 664. Example **315B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 -

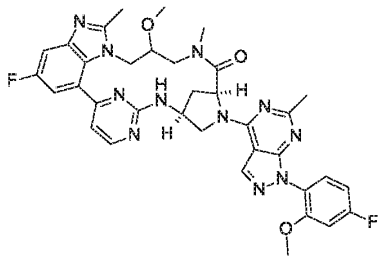
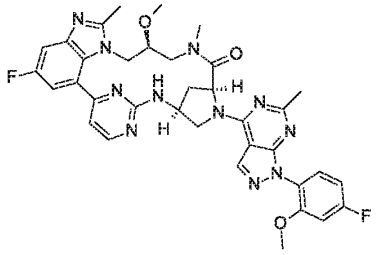
		/min Back pressure: 100bar Column temperature: 35°C	8.27 (m, 2H), 8.22 - 7.69 (m, 1H), 7.69 - 7.64 (m, 1H), 7.49 - 7.33 (m, 2H), 7.33 - 7.24 (m, 1H), 7.12 - 6.93 (m, 2H), 6.93 - 6.77 (m, 1H), 5.68 - 5.51 (m, 1H), 5.51 - 5.33 (m, 1H), 4.82 - 4.56 (m, 1H), 4.55 - 4.18 (m, 2H), 4.18 - 3.96 (m, 2H), 3.81 - 3.68 (m, 3H), 3.59 - 3.45 (m, 1H), 3.25 - 3.03 (m, 4H), 2.93 - 2.76 (m, 4H), 2.73 - 2.50 (m, 4H). LCMS $(M+H)^+$: 664.
317	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A4** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2**	LCMS $(M+H)^+$: 656.
317A & 317B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-**	Example **317** was separated by SFC to give Example	Example **317A** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.64 -

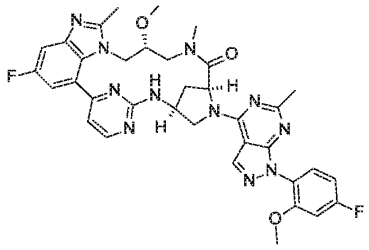
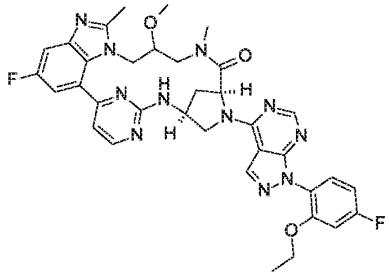
	methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	**317A** (Faster eluted) and Example **317B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: AS, 250×20 mm I.D., 5µm. Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O) Gradient: B 20% Flow rate: 50 mL /min Back pressure: 100bar Column temperature: 35°C	8.31 (m, 2H), 8.25 - 7.76 (m, 2H), 7.74 - 7.60 (m, 1H), 7.57 - 7.47 (m, 1H), 7.46 - 7.35 (m, 1H), 7.32 - 7.11 (m, 3H), 5.65 - 5.31 (m, 2H), 4.80 - 4.57 (m, 1H), 4.50 - 4.32 (m, 2H), 4.32 - 4.13 (m, 1H), 4.07 - 3.88 (m, 1H), 3.16 - 2.98 (m, 4H), 2.94 - 2.78 (m, 4H), 2.69 - 2.44 (m, 2H). LCMS (M+H)$^+$: 656. Example **317B** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.48 - 8.17 (m, 3H), 8.16 - 7.65 (m, 1H), 7.61 - 7.49 (m, 1H), 7.38 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.27 - 7.03 (m, 3H), 6.99 - 6.89 (m, 1H), 5.45 - 5.20 (m, 2H), 4.60 - 4.45 (m, 1H), 4.42 - 4.12 (m, 3H), 4.10 - 3.92 (m, 1H), 3.57 - 3.40 (m, 1H), 3.16 - 2.93 (m, 4H), 2.83 - 2.65 (m, 4H), 2.65 - 2.41 (m, 1H). LCMS (M+H)$^+$: 656.
319	**(8*S*,11*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,}**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C11**	LCMS (M+H)$^+$: 682.

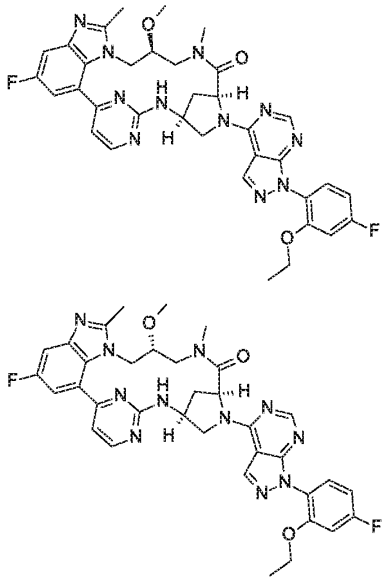
	^{11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 		
319A & 319B	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	Example **319** was separated by SFC to give Example **319A** (Faster eluted) and Example **319B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 45% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	Example **319A** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.56 - 8.43 (m, 1H), 8.40 - 8.14 (m, 1H), 8.08 - 7.58 (m, 1H), 7.42 - 7.25 (m, 2H), 7.25 - 7.15 (m, 1H), 7.06 - 6.90 (m, 2H), 6.84 - 6.65 (m, 1H), 5.53 - 5.38 (m, 1H), 5.37 - 5.23 (m, 1H), 4.70 - 4.61 (m, 1H), 4.38 - 4.16 (m, 2H), 4.15 - 3.99 (m, 1H), 3.95 - 3.84 (m, 1H), 3.68 - 3.57 (m, 3H), 3.06 - 2.89 (m, 4H), 2.81 - 2.67 (m, 4H), 2.55 - 2.34 (m, 5H). LCMS $(M+H)^+$: 682. Example **319B** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 8.45 - 8.16 (m, 2H), 8.11 - 7.57 (m, 1H), 7.39 - 7.23 (m, 2H), 7.15 - 7.08 (m, 1H), 6.99 - 6.86 (m, 2H), 6.84 - 6.71 (m,

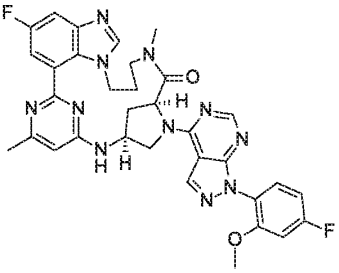
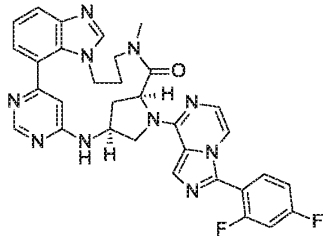
			1H), 5.53 - 5.40 (m, 1H), 5.40 - 5.25 (m, 1H), 4.74 - 4.52 (m, 1H), 4.40 - 4.32 (m, 1H), 4.29 - 4.10 (m, 1H), 4.06 - 3.88 (m, 2H), 3.71 - 3.62 (m, 3H), 3.53 - 3.31 (m, 1H), 3.13 - 2.96 (m, 4H), 2.83 - 2.70 (m, 4H), 2.62 - 2.40 (m, 4H). LCMS $(M+H)^+$: 682.
322	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C2**	LCMS $(M+H)^+$: 670.
322A & 322B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,}**	Example **322** was separated by SFC to give Example **322A** (Faster eluted) and Example **322B**	Example **322A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.65 - 8.29 (m, 2H), 8.26 - 7.76 (m, 1H), 7.74 - 7.59 (m, 1H), 7.45 - 7.16 (m, 4H), 7.15 -

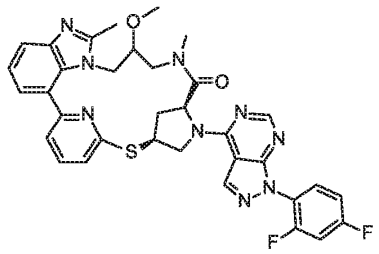
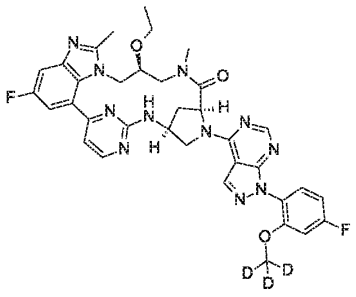
	^{11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	(Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 40% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	7.05 (m, 1H), 5.67 - 5.34 (m, 2H), 4.79 - 4.52 (m, 1H), 4.49 - 4.41 (m, 1H), 4.39 - 4.26 (m, 1H), 4.25 - 4.10 (m, 2H), 4.07 - 3.92 (m, 1H), 3.17 - 2.92 (m, 4H), 2.92 - 2.74 (m, 4H), 2.61 - 2.49 (m, 4H). LCMS (M+H)$^+$: 670. Example **322B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.58 - 8.33 (m, 2H), 8.26 - 7.75 (m, 1H), 7.71 - 7.57 (m, 1H), 7.39 - 7.16 (m, 4H), 7.04 - 6.95 (m, 1H), 5.63 - 5.40 (m, 2H), 4.53 - 4.42 (m, 1H), 4.41 - 4.20 (m, 2H), 4.19 - 3.97 (m, 3H), 3.23 - 3.03 (m, 4H), 2.92 - 2.77 (m, 4H), 2.64 - 2.51 (m, 4H) LCMS (M+H)$^+$: 670.
324	**(8*S*,11*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C12**	LCMS (M+H)$^+$: 696

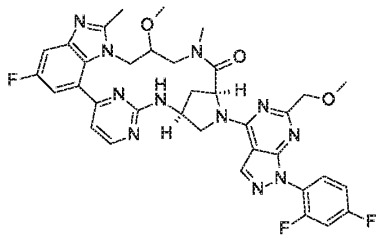
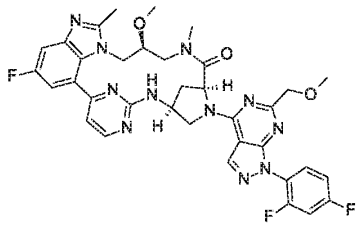
			
324A & 324B	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	Example **324** was separated by SFC to give Example **324A** (Faster eluted) and Example **324B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 40% Flow rate: 60 mL /min Back pressure: 100bar Column temperature: 35°C	Example **324A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.57 (d, *J* = 5.2 Hz, 1H), 8.43 - 7.63 (m, 1H), 7.52 - 7.34 (m, 2H), 7.34 - 7.23 (m, 1H), 7.17 - 6.97 (m, 2H), 6.86 (dt, *J* = 2.6, 8.3 Hz, 1H), 5.71 - 5.26 (m, 2H), 4.78 - 4.53 (m, 1H), 4.48 - 4.12 (m, 3H), 4.07 - 3.89 (m, 1H), 3.76 (s, 3H), 3.18 - 3.01 (m, 4H), 2.98 - 2.78 (m, 4H), 2.67 - 2.37 (m, 8H). LCMS (M+H)$^+$: 696 Example **324B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.55 - 8.46 (m, 1H), 8.43 - 7.59 (m, 1H), 7.49 - 7.32 (m, 2H), 7.21 (br d, *J* = 10.1 Hz, 1H), 7.15 - 6.93 (m, 2H), 6.86 (dt, *J* = 2.5, 8.4 Hz, 1H), 5.63 - 5.28 (m, 2H), 4.83 - 4.61 (m, 1H), 4.60 - 4.39 (m, 1H), 4.36 - 3.99 (m, 3H), 3.83 -

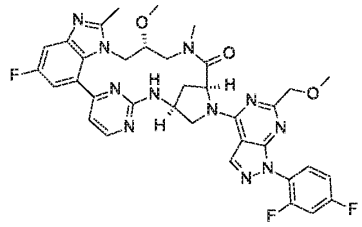
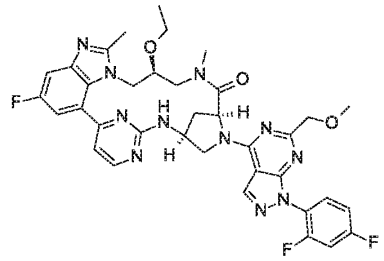
			3.70 (m, 3H), 3.22 - 3.04 (m, 4H), 2.93 - 2.82 (m, 4H), 2.77 - 2.37 (m, 8H) LCMS $(M+H)^+$: 696
328	**(8*S*,11*S*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A2** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C18**	LCMS $(M+H)^+$: 696
328A & 328B	**(8*S*,11*S*,15*R*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-**	Example **328** was separated by SFC to give Example **328A** (Faster eluted) and Example **328B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: OD,	Example **328A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (d, J = 5.3 Hz, 1H), 8.51 - 8.24 (m, 1H), 8.21 - 7.69 (m, 1H), 7.54 - 7.34 (m, 2H), 7.29 (dd, J = 2.4, 10.2 Hz, 1H), 7.17 - 6.95 (m, 2H), 6.85 (dt, J = 2.6, 8.3 Hz, 1H), 5.64 - 5.31 (m, 2H), 4.75 (br t, J = 4.6 Hz, 1H), 4.51 - 4.28

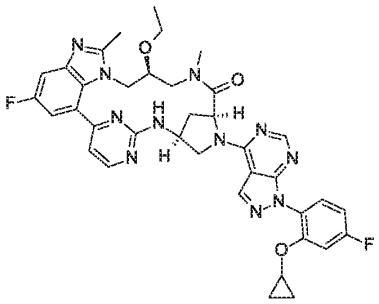
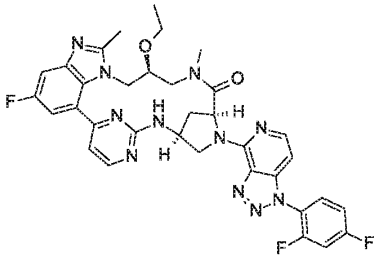
	d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	250×20 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 35% Flow rate: 40 mL /min Back pressure: 100bar Column temperature: 35°C	(m, 2H), 4.24 - 3.88 (m, 5H), 3.16 - 2.90 (m, 4H), 2.90 - 2.77 (m, 3H), 2.64 - 2.43 (m, 5H), 1.18 - 1.13 (m, 3H). LCMS $(M+H)^+$: 696. Example **328B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.59 - 8.27 (m, 2H), 8.24 - 7.69 (m, 1H), 7.53 - 7.34 (m, 2H), 7.23 (br d, J = 9.8 Hz, 1H), 7.08 - 6.97 (m, 2H), 6.93 - 6.77 (m, 1H), 5.68 - 5.36 (m, 2H), 4.80 - 4.62 (m, 1H), 4.52 - 4.23 (m, 2H), 4.18 - 3.99 (m, 4H), 3.58 - 3.45 (m, 1H), 3.22 - 3.04 (m, 4H), 2.93 - 2.80 (m, 4H), 2.73 - 2.52 (m, 4H), 1.14 (t, J = 6.1 Hz, 3H). LCMS $(M+H)^+$: 696
336	**(8*S*,11*S*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-3,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A13** **HALIDE 1**: Intermediate **B4** **HALIDE 2**: Intermediate **C11**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.39 - 8.17 (m, 2H), 8.14 - 7.59 (m, 1H), 7.52 - 7.24 (m, 3H), 6.96 (dd, J = 2.6, 10.7 Hz, 1H), 6.78 (dt, J = 2.4, 8.3 Hz, 1H), 6.68 - 6.55 (m, 1H), 5.47 - 5.33 (m, 1H), 5.24 - 5.13 (m, 1H), 4.53 - 4.39 (m, 1H), 4.34 - 4.17 (m, 1H), 4.15 - 3.92 (m, 2H), 3.71 -

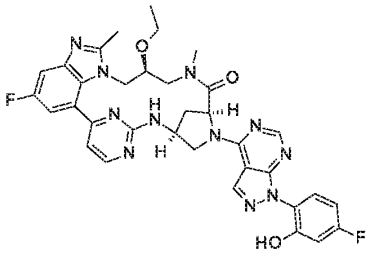
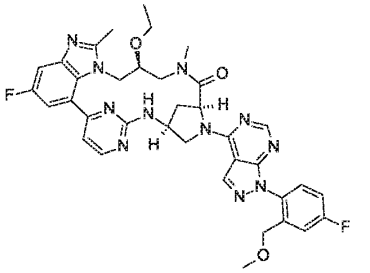
			3.55 (m, 3H), 3.41 - 3.28 (m, 1H), 3.08 - 2.92 (m, 4H), 2.89 - 2.72 (m, 1H), 2.69 - 2.40 (m, 4H), 1.88 - 1.68 (m, 1H), 1.47 - 1.28 (m, 1H) LCMS $(M+H)^+$: 652.
337	**(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-3,5,7,10,13,17,19-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A11** **HALIDE 1**: Intermediate **B5** **HALIDE 2**: Intermediate **C3**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.63 (d, *J* = 1.0 Hz, 1H), 8.25 (s, 1H), 7.88 - 7.60 (m, 2H), 7.49 - 7.17 (m, 6H), 7.08 (br d, *J* = 4.9 Hz, 1H), 6.75 (d, *J* = 1.0 Hz, 1H), 5.45 - 5.31 (m, 1H), 4.69 - 4.54 (m, 2H), 4.41 - 4.20 (m, 2H), 4.14 - 3.96 (m, 1H), 3.81 - 3.67 (m, 1H), 3.19 - 2.96 (m, 4H), 2.93 - 2.75 (m, 1H), 2.62 - 2.43 (m, 1H), 2.36 - 2.16 (m, 1H), 1.58 - 1.40 (m, 1H). LCMS $(M+H)^+$: 607.
349	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-thia-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B25** **HALIDE 2**: Intermediate **C21**	^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.62 - 8.38 (m, 1H), 8.25 (s, 1H), 8.12 - 7.98 (m, 1H), 7.87 - 7.82 (m, 1H), 7.80 - 7.63 (m, 4H), 7.61 - 7.50 (m, 1H), 7.37 - 7.17 (m, 2H), 5.54 - 5.43 (m, 1H), 4.77 - 4.59 (m, 2H), 4.44 - 4.22 (m, 3H), 3.66 - 3.55 (m, 1H), 3.20 - 3.14 (m, 1H), 3.12 - 2.99 (m, 4H), 2.97 - 2.86 (m, 7H),

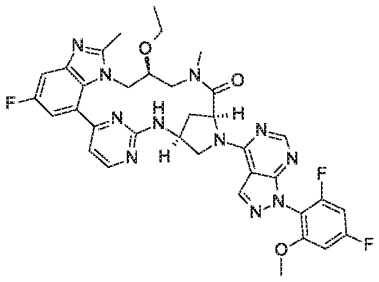
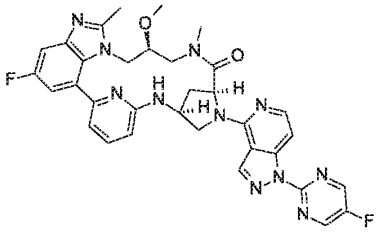
			2.76 - 2.67 (m, 1H). LCMS $(M+H)^+$: 668.
372	**(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C62**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (d, J = 5.2 Hz, 1H), 8.47 - 8.20 (m, 1H), 8.15 - 7.65 (m, 1H), 7.64 - 7.49 (m, 2H), 7.43 - 7.23 (m, 1H), 7.15 - 7.05 (m, 1H), 6.97 (dd, J = 2.5, 10.6 Hz, 1H), 6.87 - 6.73 (m, 1H), 5.86 - 5.64 (m, 1H), 5.43 - 5.22 (m, 1H), 4.72 - 4.51 (m, 1H), 4.45 - 4.09 (m, 3H), 3.95 - 3.87 (m, 1H), 3.43 - 3.28 (m, 1H), 3.09 - 2.89 (m, 4H), 2.87 - 2.59 (m, 6H), 2.58 - 2.36 (m, 1H), 0.63 - 0.40 (m, 3H). LCMS $(M+H)^+$: 699.
373	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C28**	LCMS $(M+H)^+$: 714

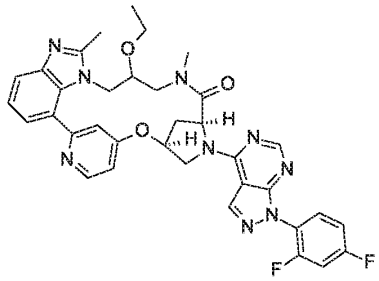
			
373A & 373B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	Example **373** was separated by SFC to give Example **373A** (Faster eluted) and Example **373B** (Slower eluted) **SFC condition:** Instrument: SFC 80 Column: OD, 250×20 mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O) Gradient: B 35% Flow rate: 40 mL /min Back pressure: 100bar Column temperature: 35°C	**Example 373A** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.59 (d, J = 5.2 Hz, 1H), 8.53 - 7.77 (m, 1H), 7.74 - 7.58 (m, 1H), 7.45 - 7.37 (m, 1H), 7.35 - 7.25 (m, 2H), 7.25 - 7.05 (m, 2H), 5.70 - 5.58 (m, 1H), 5.55 - 5.40 (m, 1H), 4.84 - 4.58 (m, 1H), 4.57 - 4.24 (m, 4H), 4.23 - 4.13 (m, 1H), 4.04 - 3.88 (m, 1H), 3.56 - 3.40 (m, 3H), 3.25 - 3.06 (m, 4H), 3.04 - 2.80 (m, 4H), 2.70 - 2.47 (m, 5H). LCMS $(M+H)^+$: 714. **Example 373B** ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.44 - 7.61 (m, 2H), 7.59 - 7.48 (m, 1H), 7.32 - 7.21 (m, 1H), 7.20 - 7.03 (m, 3H), 6.94 - 6.85 (m, 1H), 5.49 -5.29 (m, 2H), 4.73 - 4.51 (m, 1H), 4.47 - 4.10 (m, 4H), 4.10 - 3.85 (m, 2H), 3.49 - 3.26 (m, 4H), 3.12 - 2.95 (m, 4H),

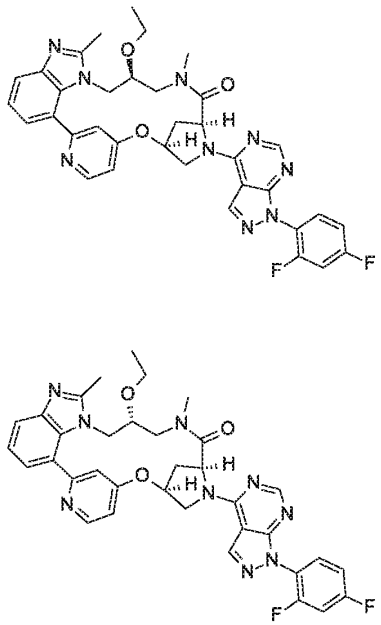
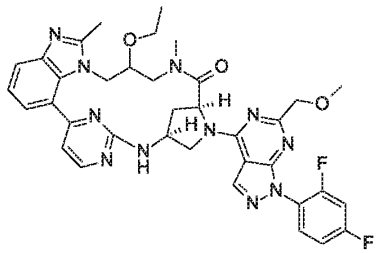
			2.81 - 2.68 (m, 4H), 2.63 - 2.40 (m, 4H). LCMS $(M+H)^+$: 714.
375	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C28**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (d, J = 5.0 Hz, 1H), 8.44 - 7.66 (m, 1H), 7.64 - 7.43 (m, 3H), 7.25 - 7.04 (m, 3H), 5.94 - 5.59 (m, 1H), 5.53 - 5.24 (m, 1H), 4.70 - 4.46 (m, 1H), 4.44 - 4.09 (m, 5H), 3.95 - 3.80 (m, 1H), 3.45 - 3.26 (m, 4H), 3.11 - 2.95 (m, 4H), 2.95 - 2.81 (m, 1H), 2.78 - 2.59 (m, 5H), 2.59 - 2.37 (m, 1H), 0.61 - 0.40 (m, 3H). LCMS $(M+H)^+$: 728.
376	**(8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C17**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (d, J = 5.2 Hz, 1H), 8.48 - 8.21 (m, 1H), 8.16 - 7.67 (m, 1H), 7.63 - 7.49 (m, 2H), 7.41 - 7.16 (m, 2H), 7.12 - 6.99 (m, 1H), 6.91 - 6.73 (m, 1H), 5.85 - 5.66 (m, 1H), 5.34 (d, J = 8.7 Hz, 1H), 4.70 - 4.65 (m, 1H), 4.41 - 4.17

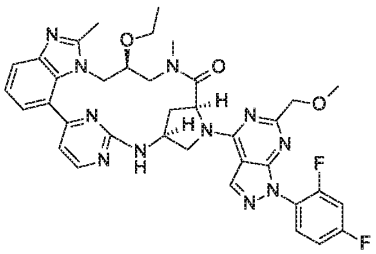
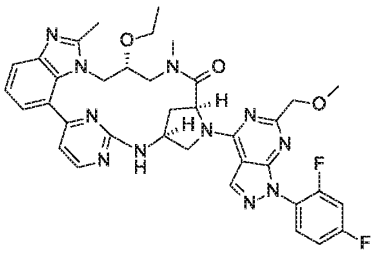
			(m, 3H), 3.96 - 3.85 (m, 1H), 3.81 - 3.71 (m, 1H), 3.42 - 3.28 (m, 1H), 3.12 - 2.94 (m, 4H), 2.93 - 2.61 (m, 6H), 2.59 - 2.43 (m, 1H), 0.72 - 0.61 (m, 2H), 0.58 - 0.40 (m, 5H). LCMS $(M+H)^+$: 722
377	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)triazolo[4,5-c]pyridin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C63**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.65 (d, J = 5.2 Hz, 1H), 7.89 - 7.74 (m, 1H), 7.71 - 7.57 (m, 2H), 7.54 - 7.43 (m, 2H), 7.40 - 7.22 (m, 2H), 7.17 (d, J = 5.0 Hz, 1H), 6.26 (d, J = 8.7 Hz, 1H), 5.86 (br dd, J = 4.0, 15.4 Hz, 1H), 4.66 (br t, J = 4.3 Hz, 1H), 4.39 - 4.15 (m, 3H), 3.88 (dd, J = 9.4, 14.1 Hz, 1H), 3.52 - 3.38 (m, 1H), 3.25 - 3.01 (m, 4H), 2.93 (br d, J = 13.9 Hz, 1H), 2.83 - 2.59 (m, 6H), 0.64 (t, J = 6.9 Hz, 3H). LCMS $(M+H)^+$: 684
378	**(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-**	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C50**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.66 (d, J = 5.2 Hz, 1H), 8.59 - 8.33 (m, 1H), 8.28 - 7.78 (m, 1H), 7.74 - 7.60 (m, 2H), 7.51 (dd, J = 6.1, 8.5 Hz, 1H), 7.27 - 7.09 (m, 1H), 6.92 - 6.69 (m, 2H), 5.98 -

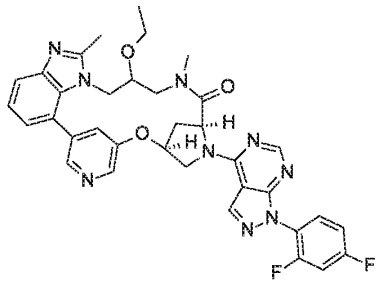
	heptaen-12-one 		5.68 (m, 1H), 5.57 - 5.41 (m, 1H), 4.83 - 4.57 (m, 1H), 4.54 - 4.22 (m, 3H), 4.02 (br dd, *J* = 9.4, 14.3 Hz, 1H), 3.48 - 3.36 (m, 2H), 3.24 - 3.07 (m, 3H), 3.05 - 2.88 (m, 1H), 2.87 - 2.70 (m, 5H), 2.69 - 2.53 (m, 1H), 0.76 - 0.51 (m, 3H). LCMS $(M+H)^+$: 682
379	**(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(methoxymethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C52**	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.66 (d, *J* = 5.2 Hz, 1H), 8.59 - 8.31 (m, 1H), 8.26 - 7.77 (m, 1H), 7.70 - 7.57 (m, 2H), 7.56 - 7.38 (m, 2H), 7.34 - 7.22 (m, 1H), 7.22 - 7.10 (m, 1H), 5.95 - 5.68 (m, 1H), 5.55 - 5.36 (m, 1H), 4.84 - 4.60 (m, 1H), 4.55 - 4.46 (m, 1H), 4.45 - 4.38 (m, 1H), 4.35 - 4.24 (m, 3H), 4.02 (dd, *J* = 9.5, 14.3 Hz, 1H), 3.51 - 3.40 (m, 1H), 3.28 - 3.20 (m, 3H), 3.20 - 3.05 (m, 4H), 3.05 - 2.89 (m, 1H), 2.83 - 2.65 (m, 5H), 2.60 - 2.51 (m, 1H), 0.71 - 0.58 (m, 3H) LCMS $(M+H)^+$: 710
380	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-**	**BORONIC REAGENT:** Intermediate **A7** **HALIDE 1**:	^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.56 (d, *J* = 5.2 Hz, 1H), 8.51 - 8.20 (m, 1H), 8.14 - 7.70 (m,

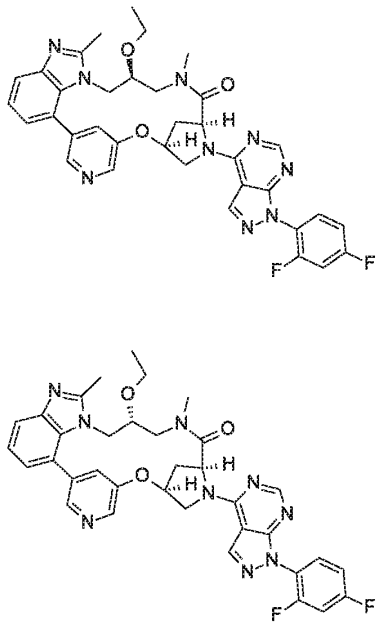
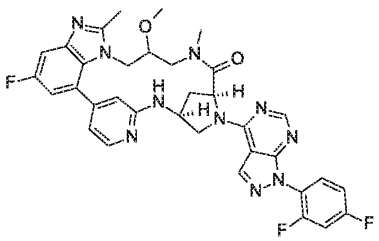
	fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **B1** **HALIDE 2**: Intermediate **C52**	1H), 7.66 - 7.49 (m, 2H), 7.17 - 7.01 (m, 1H), 6.96 - 6.59 (m, 2H), 5.78 (td, *J* = 4.7, 15.6 Hz, 1H), 5.47 - 5.25 (m, 1H), 4.72 - 4.48 (m, 1H), 4.42 - 4.08 (m, 3H), 4.02 - 3.84 (m, 1H), 3.77 - 3.60 (m, 3H), 3.40 - 3.27 (m, 1H), 3.10 - 2.88 (m, 4H), 2.87 - 2.58 (m, 6H), 2.58 - 2.38 (m, 1H), 0.64 - 0.35 (m, 3H). LCMS (M+H)$^+$: 714
381	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[4,3-c]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C53**	LCMS (M+H)$^+$: 652 ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.83 (s, 2H), 8.67 - 8.29 (m, 1H), 7.98 (d, *J* = 6.2 Hz, 1H), 7.85 (d, *J* = 6.2 Hz, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.18 - 7.01 (m, 2H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.78 - 5.62 (m, 1H), 5.36 (d, *J* = 8.8 Hz, 1H), 4.72 - 4.52 (m, 2H), 4.41 (dd, *J* = 6.0, 10.1 Hz, 1H), 4.31 - 4.24 (m, 1H), 4.15 - 4.04 (m, 1H), 3.92 (dd, *J* = 9.4, 14.2 Hz, 1H), 3.04 (s, 3H), 2.91 - 2.79 (m, 5H), 2.56 - 2.40 (m, 5H).
382	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-**	**BORONIC REAGENT:**	LCMS (M+H)$^+$: 666

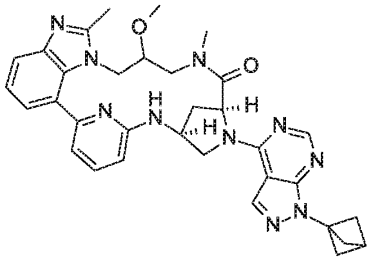
	d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **A10** **HALIDE 1**: Intermediate **B30** **HALIDE 2**: Intermediate **C2**	
382A & 382B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	Example **382** was separated by SFC to give Example **382A** (Faster eluted) and Example **382B** (Slower eluted) **SFC condition:** Instrument: Waters 80Q Column: DAICEL CHIRALPAK AD(250 mm×30 mm,10 μm) Mobile phase: Phase A for Supercritical CO_2, and Phase B for	Example **382A** LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ=8.74 (d, J = 3.2 Hz, 1H), 8.58 (s, 1H), 8.43 - 8.20 (m, 1H), 7.94 - 7.85 (m, 1H), 7.74 - 7.51 (m, 5H), 7.34 - 7.19 (m, 2H), 5.84 - 5.47 (m, 2H), 4.66 - 4.54 (m, 1H), 4.37 - 4.05 (m, 3H), 3.19 - 3.07 (m, 3H), 3.03 - 2.69 (m, 10H), 1.26 - 1.19 (m, 3H) Example **382B** LCMS $(M+H)^+$: 666 ^{1}H NMR (400 MHz, METHANOL-d_4) δ=8.66 - 8.60 (m, 1H), 8.41 - 8.37 (m, 1H), 8.30 - 8.25 (m, 1H),

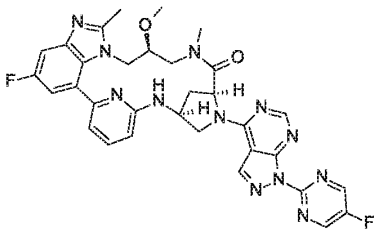
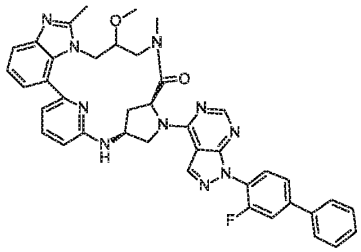
		IPA+ACN (0.05% DEA) Gradient elution: 55% Phase B (45% Phase A) Flow rate: 80 mL/min Back Pressure: 100 bar Column Temp: 30 °C	7.76 - 7.71 (m, 1H), 7.61 - 7.54 (m, 1H), 7.29 - 7.28 (m, 1H), 7.17 - 6.99 (m, 4H), 6.89 (dd, *J* = 2.4, 5.7 Hz, 1H), 5.62 - 5.39 (m, 2H), 4.72 - 4.61 (m, 1H), 4.47 - 4.22 (m, 2H), 3.94 - 3.81 (m, 1H), 3.68 - 3.57 (m, 1H), 3.53 - 3.43 (m, 1H), 3.27 - 3.05 (m, 2H), 3.01 - 2.92 (m, 3H), 2.71 - 2.64 (m, 1H), 2.60 - 2.58 (m, 3H), 2.58 - 2.44 (m, 2H), 0.65 - 0.59 (m, 3H).
384	**(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A10** **HALIDE 1**: Intermediate **B1** **HALIDE 2**: Intermediate **C28**	LCMS (M+H)$^+$: 710.
384A & 384B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-**	Example **384** was separated by SFC to give Example	Example **384A** LCMS (M+H)$^+$: 710. ^{1}H NMR (400 MHz, DMSO-

	d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one  	**384A** (Faster eluted) and Example **384B** (Slower eluted) **SFC condition:** Instrument: Waters 80Q Column: DAICEL CHIRALPAK AD(250 mm×30 mm,10 μm) Mobile phase: Phase A for Supercritical CO_2, and Phase B for EtOH (0.05% DEA) Gradient elution: 60% Phase B (40% Phase A) Flow rate: 80 mL/min Back Pressure: 100 bar Column Temp: 30 °C	*d*$_6$) δ = 8.56 (dd, *J* = 2.3, 5.2 Hz, 1H), 7.76 - 7.59 (m, 3H), 7.42 - 7.31 (m, 2H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.10 (dd, *J* = 5.1, 11.5 Hz, 1H), 6.87 - 6.58 (m, 1H), 5.51 - 5.31 (m, 2H), 4.63 - 4.43 (m, 1H), 4.43 - 4.18 (m, 4H), 4.14 - 3.73 (m, 3H), 3.42 - 3.34 (m, 3H), 3.33 - 3.31 (m, 3H), 3.31 - 3.11 (m, 2H), 3.06 - 2.89 (m, 4H), 2.86 - 2.61 (m, 2H), 0.42 (q, *J* = 6.8 Hz, 3H). Example **384B** LCMS (M+H)$^+$: 710. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.63 - 8.53 (m, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.81 - 7.57 (m, 4H), 7.40 - 7.26 (m, 1H), 7.08 (d, *J* = 0.8 Hz 1H), 6.45 - 6.23 (m, 1H), 5.46 (t, *J* = 7.8 Hz, 1H), 4.80 - 4.45 (m, 2H), 4.43 - 4.20 (m, 6H), 4.14 - 4.07 (m, 2H), 3.41 - 3.30 (m, 4H), 3.29 - 3.18 (m, 2H), 3.12 - 2.97 (m, 4H), 2.83 (d, *J* = 2.0 Hz, 3H), 0.52 (dt, *J* = 3.9, 6.9 Hz, 3H)
386	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-**	**BORONIC REAGENT:** Intermediate **A10** **HALIDE 1**:	LCMS (M+H)$^+$: 666.

	4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one 	Intermediate **B21** **HALIDE 2**: Intermediate **C2**	
386A & 386B	**(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	Example **386** was separated by SFC to give Example **386A** (Faster eluted) and Example **386B** (Slower eluted) **SFC condition:** Instrument: ACSWH-PREP-SFC-B Column: DAICEL CHIRALPAK IC(250 mm×30 mm,10 μm) Mobile phase: Phase A for CO_2, and Phase B for 0.1% NH_3H_2O in MEOH;	Example **386A** LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.59 (s, 1H), 8.53 (d, *J* = 2.4 Hz, 1H), 8.29 - 8.19 (m, 2H), 7.88 (s, 1H), 7.75 - 7.64 (m, 2H), 7.37 - 7.28 (m, 2H), 7.26 - 7.18 (m, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 5.78 (d, *J* = 2.9 Hz, 1H), 5.58 - 5.45 (m, 1H), 4.55 - 4.44 (m, 2H), 4.21 - 3.93 (m, 2H), 3.63 (q, *J* = 7.0 Hz, 1H), 3.58 - 3.46 (m, 1H), 3.16 (s, 1H), 3.07 (s, 2H), 2.96 - 2.91 (m, 1H), 2.86 - 2.71 (m, 3H), 2.70 - 2.59 (m, 4H), 0.64 (s, 3H). Example **386B** LCMS $(M+H)^+$: 666 ^{1}H NMR (400 MHz,

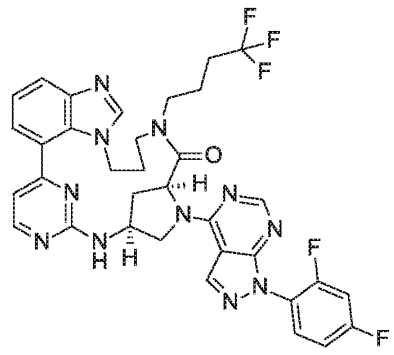
		Gradient elution: 60% B in A Flow rate: 80 mL/min Back pressure: 100 bar Column temperature: 35 °C	METHANOL-d_4) δ = 8.53 - 8.38 (m, 2H), 8.12 (s, 1H), 8.06 - 7.89 (m, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.32 (s, 1H), 7.26 - 7.07 (m, 3H), 6.89 – 6.87 (d, J = 7.0 Hz, 1H), 5.66 (d, J = 3.3 Hz, 1H), 5.34 (d, J = 9.4 Hz, 1H), 4.54 - 4.30 (m, 2H), 4.08 - 3.87 (m, 2H), 3.67 - 3.51 (m, 1H), 3.44 - 3.34 (m, 1H), 3.17 - 3.08 (m, 1H), 3.05 - 2.96 (m, 1H), 2.93 (s, 2H), 2.75 - 2.68 (m, 1H), 2.66 - 2.51 (m, 3H), 2.49 (s, 3H), 0.51 (t, J = 7.1 Hz, 3H).
388	**(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A12** **HALIDE 1**: Intermediate **B32** **HALIDE 2**: Intermediate **C2**	LCMS (M+H)$^+$: 669 ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.60 (s, 1H), 8.25 – 8.20 (m, 2H), 7.69 – 7.68 (dd, J = 5.6, 8.6 Hz, 1H), 7.61 - 7.60 (dd, J = 2.4, 7.8 Hz, 1H), 7.29 - 7.23 (m, 3H), 6.83 (s, 1H), 6.72 – 6.71 (d, J = 6.4 Hz, 1H), 5.44 – 5.42 (d, J = 8.9 Hz, 1H), 4.53 - 4.48 (m, 1H), 4.44 - 4.32 (m, 3H), 4.26 - 4.07 (m, 2H), 3.83 – 3.82 (dd, J = 3.6, 15.2 Hz, 1H), 3.73 - 3.58 (m, 2H), 3.09 (s, 3H), 3.01 (s, 3H), 2.81 (s, 3H), 2.64 - 2.56 (m, 1H)

389	**(8*S*,11*S*)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A1** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C56**	LCMS (M+H)$^+$: 605 ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.40 - 8.32 (m, 1H), 8.27 (d, J = 2.8 Hz, 1H), 7.90 - 7.76 (m, 2H), 7.75 - 7.60 (m, 2H), 7.18 - 6.95 (m, 1H), 6.74 (br d, J = 8.4 Hz, 1H), 6.14 - 6.01 (m, 1H), 5.42 (dd, J = 9.0, 15.1 Hz, 1H), 4.69 (td, J = 4.7, 18.4 Hz, 1H), 4.57 - 4.44 (m, 1H), 4.40 - 4.08 (m, 3H), 4.06 - 3.85 (m, 1H), 3.85 - 3.69 (m, 1H), 3.15 (d, J = 15.5 Hz, 1H), 3.06 (d, J = 14.1 Hz, 3H), 2.96 - 2.93 (m, 3H), 2.88 - 2.80 (m, 3H) 2.71 - 2.68 (m, 1H), 2.62 - 2.54 (m, 1H), 2.53 - 2.47 (m, 6H).
390	**(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**	**BORONIC REAGENT:** Intermediate **A6** **HALIDE 1**: Intermediate **B8** **HALIDE 2**: Intermediate **C54**	LCMS (M+H)$^+$: 653 ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.92 (s, 2H), 8.71 - 8.63 (m, 1H), 8.43 (s, 1H), 7.91 - 7.84 (m, 1H), 7.63 - 7.49 (m, 2H), 7.22 - 7.11 (m, 1H), 6.82 - 6.73 (m, 1H), 6.18 - 5.97 (m, 1H), 5.58 - 5.45 (m, 1H), 4.74 - 4.68 (m, 1H), 4.59 - 4.49 (m, 1H), 4.43 - 4.25 (m, 2H), 3.94 (dd, *J* = 9.4, 14.4 Hz, 1H), 3.22 - 3.04 (m, 3H), 3.04 - 2.99 (m, 1H), 2.98 -

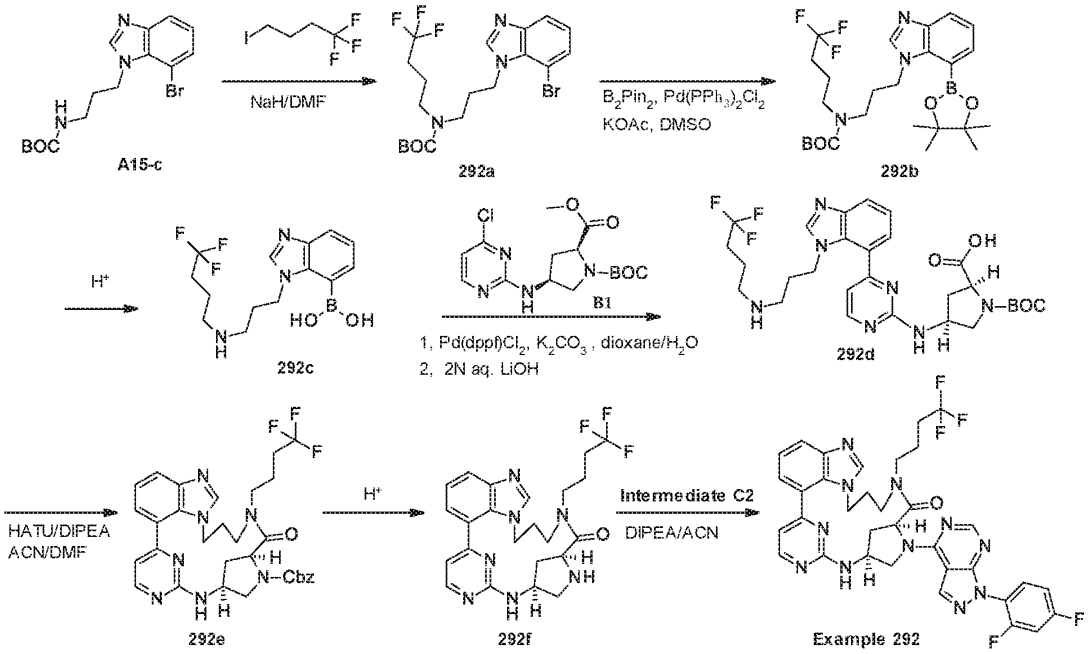
			2.95 (m, 3H), 2.90 (br d, *J* = 13.8 Hz, 1H), 2.83 - 2.76 (m, 3H), 2.62 - 2.51 (m, 2H)
423	**(8*S*,11*S*)-10-[1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one** 	**BORONIC REAGENT:** Intermediate **A3** **HALIDE 1**: Intermediate **B9** **HALIDE 2**: Intermediate **C71**	LCMS (M+H$^+$): 709. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.19 - 8.61 (m, 2H), 7.41 - 7.88 (m, 11H), 7.28 - 7.32 (m, 1H), 6.88 - 7.16 (m, 1H), 6.71 (dd, *J* = 12.10, 8.19 Hz, 1H), 5.52 (t, *J* = 9.54 Hz, 1H), 4.68 - 4.77 (m, 1H), 4.51 - 4.66 (m, 2H), 4.12 - 4.41 (m, 2H), 3.73 - 4.10 (m, 2H), 3.01 - 3.24 (m, 4H), 2.86 (m, 4H), 2.49 - 2.65 (m, 4H).

Example 292

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(4,4,4-trifluorobutyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1~2: preparation of *tert*-butyl *N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-(4,4,4-trifluorobutyl)carbamate (compound 292b)

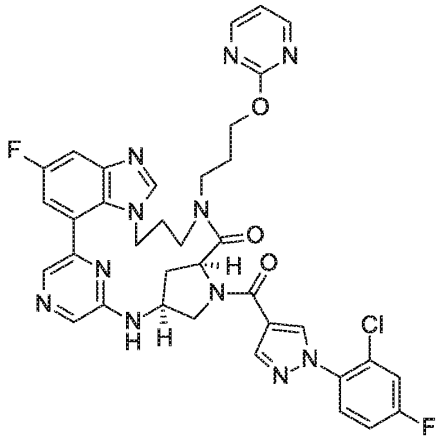
Compound **292b** was prepared in analogy to the preparation of compound **340b** and by using 1,1,1-trifluoro-4-iodo-butane instead of 1-bromo-3-methoxy-propane. LCMS $(M+H)^+$: 512.

Step 3~7: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(4,4,4-trifluorobutyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 292)

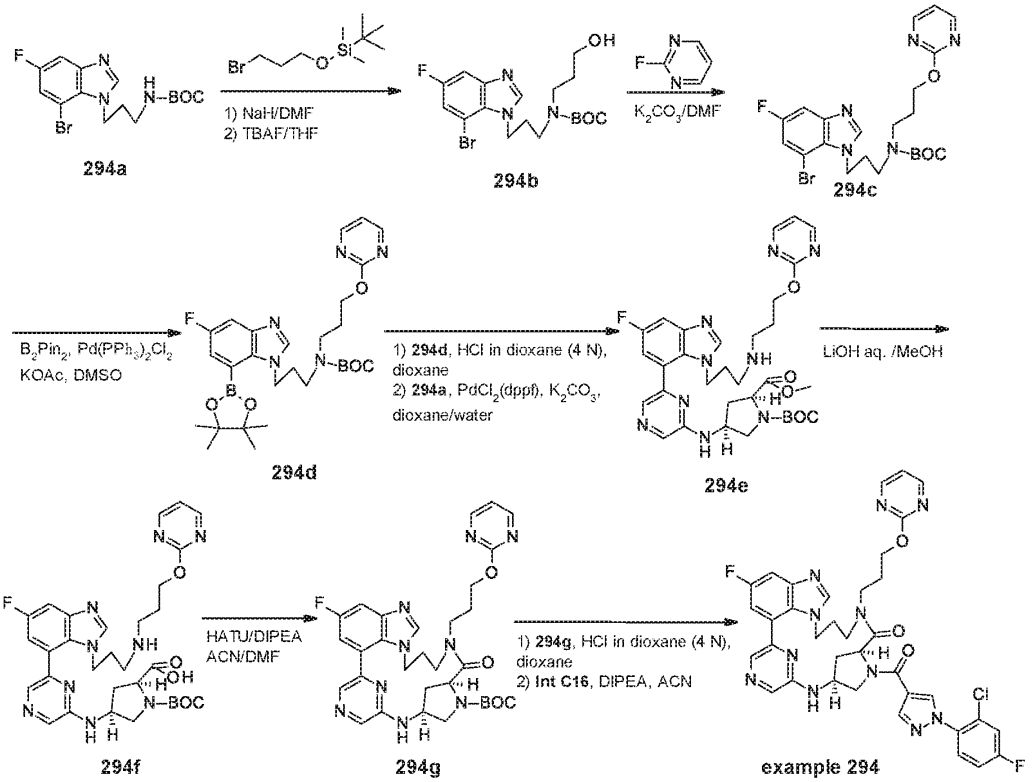
The title compounds were prepared in analogy to the preparation of Example **289** by using compound **292b** instead of **Intermediate A12** and **Intermediate C2** instead of **Intermediate C11**. LCMS $(M+H)^+$: 704. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.58 - 9.33 (m, 1H), 8.69 - 8.34 (m, 2H), 8.29 - 7.92 (m, 2H), 7.88 - 7.54 (m, 3H), 7.40 - 7.09 (m, 3H), 5.66 - 5.39 (m, 2H), 4.99 - 4.91 (m, 1H), 4.58 - 4.16 (m, 3H), 3.95 (br dd, *J* = 10.0, 14.4 Hz, 1H), 3.57 - 3.33 (m, 2H), 3.15 - 2.96 (m, 1H), 2.86 - 2.75 (m, 1H), 2.74 - 2.56 (m, 1H), 2.43 - 2.10 (m, 2H), 2.06 - 1.71 (m, 2H), 1.63 - 1.21 (m, 2H).

Example 294

(8*S*,11*S*)-10-[1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carbonyl]-22-fluoro-13-(3-pyrimidin-2-yloxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl) propyl] carbamate (compound 294a)

Compound **294a** was prepared in analogy to the preparation of **Intermediate A15-c** by using 1-bromo-2,5-difluoro-3-nitro-benzene instead of 1-bromo-2-fluoro-3-nitro-benzene. LCMS ($M+H^+$): 372.

Step 2: preparation of *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl)propyl]-*N*-(3-hydroxypropyl]carbamate (compound 294b)

To a flask was added 3-bromopropoxy-*tert*-butyl-dimethyl-silane (2.04 g, 8.06 mmol), DMF (30mL), NaH (60% purity, 645 mg, 16.12 mmol). The solution was stirred at room temperature for 10 mins, then *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl) propyl] carbamate (compound **294a,** 3 g, 8.06 mmol) was added. The mixture was stirred at room temperature for 2 hrs, then NaH (60% purity, 645 mg, 16.12 mmol) and *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl) propyl] carbamate (compound **294a,** 3 g, 8.06 mmol) were added again. The mixture was stirred at room temperature for 12 hrs, and then it was quenched with water. The mixture was poured into 150 mL EA, and then washed with 50 mL water for three times. The organic layer was dried and concentrated, the residue was dissolved in THF (40 mL), then TBAF (1 M, 33.4 mL, 33.4 mmol) was added. After being stirred at room temperature for 1 hr, the mixture was concentrated and the residue was purified by silica gel to give compound **294b** (3.34 g), LCMS ($M+H^+$): 430.

Step 3: preparation of *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl)propyl]-*N*-(3-pyrimidin-2-yloxypropyl]carbamate (compound 294c)

A mixture of *tert*-butyl *N*-[3-(7-bromo-5-fluoro-benzimidazol-1-yl)propyl]-*N*-(3-hydroxypropyl]carbamate (compound **294b**, 3.34 g, 7.76 mmol), 2-fluoropyrimidine (1.52 g, 15.52 mmol), and Cs_2CO_3 (7.59 g, 23.29 mmol) in DMF (60 mL) was heated to 100 °C for 12 hrs. The mixture was poured into 150 mL EA, and then washed with 50 mL water for three times. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **294c** (3.2 g), LCMS ($M+H^+$): 508.

Step 4: preparation of *tert*-butyl *N*-[3-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-(3-pyrimidin-2-yloxypropyl)carbamate (compound 294d)

To a flask was added compound **294c** (3.2 g, 6.29 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.2 g, 12.59 mmol), KOAc (1.24 g, 12.59 mmol) and DMSO (30mL), the suspension was bubbled with N_2 for 5 mins, then $Pd(PPh_3)_2Cl_2$ (441.8 mg, 629 μmol) and bis(1-adamantyl)-butylphosphane (451.4 mg, 1.26 mmol) were added. The mixture was heated to 130 °C for 12 hrs. The mixture was poured into 150 mL EA, and then washed with 50 mL water for three times. The organic layer was dried and concentrated; the residue was purified by silica gel to give compound **294d** (1.6 g), LCMS ($M+H^+$): 556.

Step 5~7: preparation of *tert*-butyl (8*S*,11*S*)-22-fluoro-12-oxo-13-(3-pyrimidin-2-yloxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaene-10-carboxylate (compound 294g)

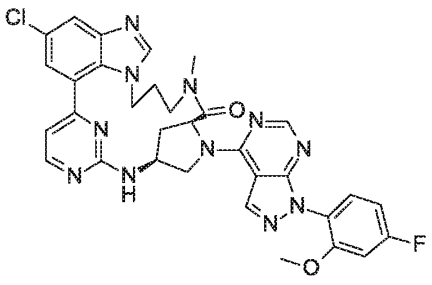
Compound **294g** was prepared in analogy to the preparation of compound **289c** by using compound **294d** instead of **intermediate A12** and **Intermediate B13** instead of **intermediate B2**. LCMS (M+H$^+$): 618.

Step 8: preparation of (8*S*,11*S*)-10-[1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carbonyl]-22-fluoro-13-(3-pyrimidin-2-yloxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 294)

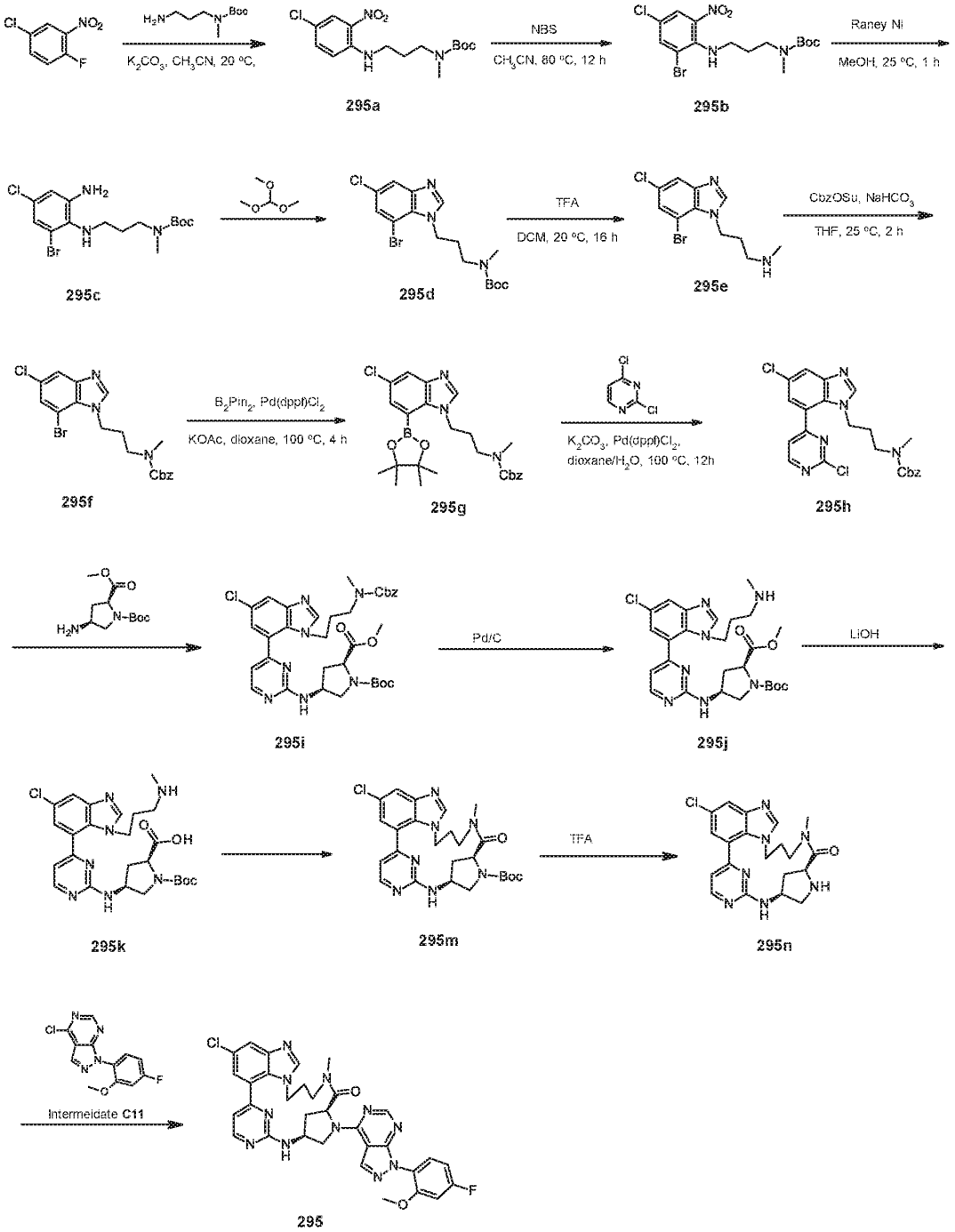
To a mixture of **294g** (200 mg, 0.324 mmol) in 1,4-dioxane (2 mL) was added HCl in dioxane (4 N, 2 mL) dropwise. The suspension was stirred at room temperature for 2 hrs. Then the mixture was concentrated, and 30 mg of the crude was dissolved in DMF (2mL), to the mixture was added intermediate **C16** (16.7 mg, 70 μmol), HATU (66.1 mg, 174 μmol) and DIPEA (74.9 mg, 101 μL, 0.58 mmol). The mixture was stirred at room temperature for 2 hrs. The mixture was filtered and the filtrated was purified by prep-HPLC to give Example **294** (2 mg), LCMS (M+H$^+$): 740. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.65 (s, 1H), 8.60 (d, *J* = 4.8 Hz, 2H), 8.58 (d, *J* = 4.8 Hz, 1H), 8.26 - 8.11 (m, 3H), 7.81 - 7.71 (m, 2H), 7.61 - 7.54 (m, 1H), 7.49 - 7.36 (m, 1H), 7.33 - 7.24 (m, 1H), 7.16 - 7.11 (m, 1H), 5.21 – 5.04 (m, 1H), 4.86 - 4.64 (m, 1H), 4.36 - 4.27 (m, 3H), 4.20 - 3.96 (m, 4H), 3.88 - 3.71 (m, 1H), 2.97 - 2.78 (m, 1H), 2.46 - 2.38 (m, 2H), 2.23 – 2.20 (m, 1H), 2.11 - 1.90 (m, 2H), 1.85 - 1.64 (m, 2H), 1.50 - 1.21 (m, 1H).

Example 295

(8*S*,11*S*)-22-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



295a 295b 295c 295d 295e 295f 295g 295h 295i 295j 295k 295m 295n 295

Step 1: preparation of *tert*-butyl *N*-[3-(4-chloro-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 295a)

To a solution of 4-chloro-1-fluoro-2-nitro-benzene (5.0 g, 28.4 mmol) and *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate (3.56 mL, 28.4 mmol) in ACN (50.0 mL) was added

potassium carbonate (11.8 g, 85.4 mmol), and the mixture was stirred at 20 °C for 12 h under N_2. The reaction mixture was filtered and the filtrate was concentrated to give compound **295a** (9.7 g) which was used in next step directly. LCMS $(M+H)^+$: 244.

Step 2: preparation of *tert*-butyl *N*-[3-(2-bromo-4-chloro-6-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 295b)

To a solution of *tert*-butyl *N*-[3-(4-chloro-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound **295a**, 9.5 g, 27.63 mmol) in ACN (50.0 mL) was added NBS (9.7 g, 55.26 mmol), and the mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated the residue was purified by column chromatography to give compound **295b** (1.5 g). LCMS $(M+H)^+$: 321.

Step 3: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-4-chloro-anilino)propyl]-*N*-methyl-carbamate (compound 295c)

To a mixture of Raney Ni (2.0 g) and compound **295b** (1.5 g, 3.55 mmol) in methanol (20.0 mL) was added $NH_2NH_2{\cdot}H_2O$ (0.96 g) dropwise below 20 °C over 0.5 h. After being stirred at 20 °C for 0.5 h, the mixture was filtered and the filtrate was concentrated, the residue was dissolved in DCM (0.5 L) and washed with brine (0.2 L for 3 times). The organic layer was dried and concentrated to give compound **295c** (1.0 g). LCMS $(M+H)^+$: 392.

Step 4: preparation of *tert*-butyl *N*-[3-(7-bromo-5-chloro-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 295d)

To a solution of compound **295c** (1.0 g, 2.55 mmol) in anhydrous THF (20.0 mL) was added trimethoxymethane (0.84 mL, 7.64 mmol) and pyridinium p-toluenesulfonate (0.32 g, 1.27 mmol). The mixture was stirred at 20 °C for 16 h, and then partitioned between EtOAc (0.5 L) and water (0.1 L). The organic layer was washed with brine (0.1 L), dried over anhydrous Na_2SO_4 and concentrated to give compound **295d** (0.9 g). LCMS $(M+H)^+$: 368.

Step 5: preparation of 3-(7-bromo-5-chloro-benzimidazol-1-yl)-*N*-methyl-propan-1-amine (compound 295e)

To a mixture of compound **295d** (0.85 g, 2.12 mmol) in anhydrous DCM (2.0 mL) was added TFA (0.2 mL). The mixture was stirred at 20 °C for 16 h, and then concentrated to give compound **295e** (0.5 g). LCMS $(M+H)^+$: 301.

Step 6: preparation of benzyl *N*-[3-(7-bromo-5-chloro-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 295f)

To a solution of compound **295e** (0.5 g, 1.65 mmol) in THF (10.0 mL) and was added sodium hydrogen carbonate (0.7 g, 8.26 mmol) and benzyl carbonochloridate (1.1 g, 6.61 mmol). After being stirred 25 °C for 2 h, the mixture was concentrated; the residue was dissolved in

EtOAc (0.1 L) and washed with water and brine. The organic layer was dried and concentrated, the residue was purified by flash column chromatography to give compound **295f** (0.7 g). LCMS $(M+H)^+$: 436.

Step 7: preparation of benzyl *N*-[3-[5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 295g)

To a mixture of compound **295f** (0.4 g, 0.92 mmol) in 1,4-dioxane (5.0 mL) was added potassium acetate (179.8 mg, 1.83 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (67.0 mg, 0.09 mmol). The mixture was stirred at 100 °C for 4 h under N_2, and then the mixture was used directly in next step without purification. LCMS $(M+H)^+$: 484.

Step 8: preparation of benzyl *N*-[3-[5-chloro-7-(2-chloropyrimidin-4-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound 295h)

To a mixture of 2,4-dichloropyrimidine (138.6 mg, 0.93 mmol) and benzyl *N*-[3-[5-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]-*N*-methyl-carbamate (compound **295g**, 0.5 g, 0.62 mmol) in 1,4-dioxane (5.0 mL) and H_2O (0.5 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (453.7 mg, 0.62 mmol) and potassium carbonate (85.7 mg, 0.62 mmol). The mixture was stirred at 130 °C for 4 h under N_2. After cooled to room temperature, the mixture was poured into water (0.1 L) and extracted with EtOAc (0.1 L twice). The combined organic layer was concentrated and the residue was purified by prep-HPLC to give compound **295h** (200.0 mg). LCMS $(M+H)^+$: 470.

Step 9: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[4-[3-[3-[benzyloxycarbonyl(methyl)amino]propyl]-6-chloro-benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-1,2-dicarboxylate (compound 295i)

A mixture of compound **295h** (190.0 mg, 0.40 mmol), DIEA (260.5 mg, 2.02 mmol) and *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (170.1 mg, 0.61 mmol) in NMP (5.0 mL) was stirred at 110 °C for 16 h. The mixture was purified by prep-HPLC to give compound **295i** (150.0 mg). LCMS $(M+H)^+$: 678.

Step 10: preparation of O1-*tert*-butyl O2-methyl (2*S*,4*S*)-4-[[4-[6-chloro-3-[3-(methylamino)propyl]benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-1,2-dicarboxylate (compound 295j)

A mixture of compound **295i** (120.0 mg, 0.18 mmol) in formic acid (10.0 mL) and methanol (10.0 mL) was added Pd/C (240.0 mg). The mixture was stirred at 20 °C for 0.25 h.

The mixture was filtered and concentrated to give compound **295j** (85.0 mg) as a yellow oil. LCMS $(M+H)^+$: 544.

Step 11: preparation of (2*S*,4*S*)-1-tert-butoxycarbonyl-4-[[4-[6-chloro-3-[3-(methylamino)propyl]benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-2-carboxylic acid (compound 295k)

A mixture of compound **295j** (85.0 mg, 0.16 mmol) and LiOH (32.0 mg, 0.78 mmol) in methanol (5.0 mL) and water (0.5 mL) was stirred at 20 °C for 12 h. The mixture was adjusted to pH=5, and then concentrated under reduced pressure. The residue was purified by prep-HPLC to give compound **295k** (60.0 mg). LCMS $(M+H)^+$: 530.

Step 12: preparation of *tert*-butyl (8*S*,11*S*)-22-chloro-13-methyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaene-10-carboxylate (compound 295m)

To a mixture of HATU (35.8 mg, 0.09 mmol) and DIPEA (0.03 mL, 0.19 mmol) in DMF (20.0 mL) was added compound **295k** (50.0 mg, 0.09 mmol). The mixture was stirred at 20 °C for 1 h under N_2, and then concentrated under reduced pressure. The residue was purified by prep-HPLC to give compound **295m** (30.0 mg). LCMS $(M+H)^+$: 512.

Step 13: preparation of (8*S*,11*S*)-22-chloro-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (compound 295n)

To a mixture of compound **295m** (30.0 mg, 0.06 mmol) in DCM (1.0 mL) was added TFA (0.5 mL). The mixture was stirred at 20 °C for 4 h and then concentrated to give compound **295n** (20.0 mg). LCMS $(M+H)^+$: 412.

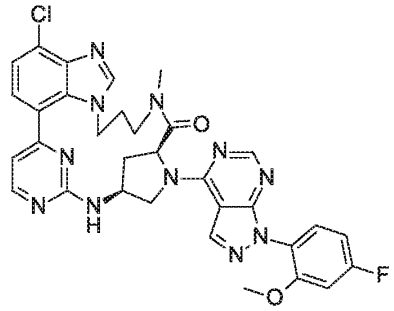
Step 14: preparation (8*S*,11*S*)-22-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 295)

A mixture of compound **295n** (20.0 mg, 0.04 mmol), intermediate **C11** (20.3 mg, 0.06 mmol) and DIPEA (0.02 mL, 0.08 mmol) in NMP (1.0 mL) was stirred at 100 °C for 2 h. The mixture was concentrated and the residue was purified by prep-HPLC to give example **295** (14 mg). LCMS $(M+H)^+$: 654. ^{1}H NMR (DMSO-d_6) δ = 8.58-8.64 (m, 1H), 8.37-8.49 (m, 2H), 8.15-8.31 (m, 1H), 7.86 (d, *J*=2.0 Hz, 1H), 7.38-7.49 (m, 2H), 7.20 (dd, *J*=11.3, 2.8 Hz, 1H), 7.08-7.12 (m, 1H), 6.92-7.00 (m, 1H), 6.50-6.66 (m, 1H), 5.36-5.45 (m, 1H), 4.86-5.02 (m, 1H), 4.52-4.81 (m, 1H), 4.05-4.46 (m, 3H), 3.87-4.00 (m, 1H), 3.74 (s, 3H), 2.93-3.06 (m, 3H), 2.73-2.91

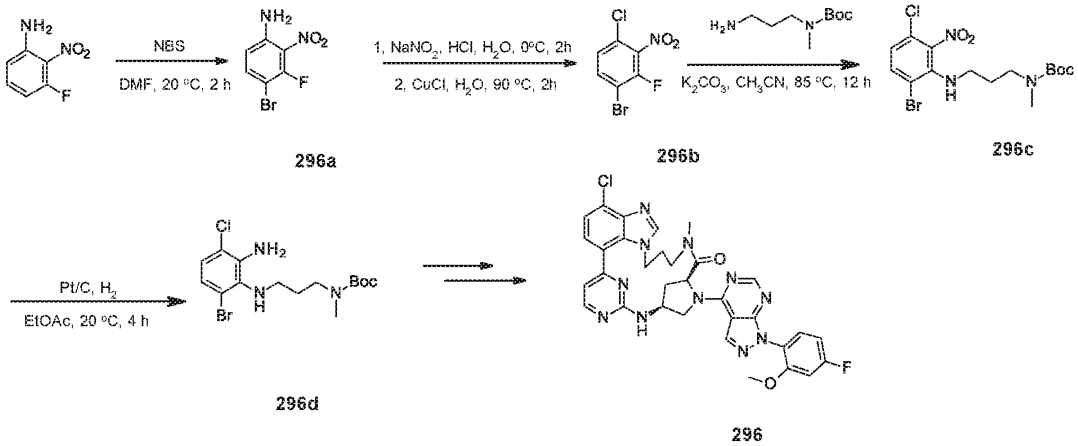
(m, 1H), 2.59-2.70 (m, 1H), 2.53-2.58 (m, 1H), 1.68-1.90 (m, 1H), 1.24 (br s, 1H).

Example 296

(8*S*,11*S*)-21-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-bromo-3-fluoro-2-nitro-aniline (compound 296a)

To a mixture of 3-fluoro-2-nitro-aniline (10.0 g, 64.06 mmol) in DMF (10.1L) was added NBS (11.4 g, 64.1 mmol) at 0°C. The mixture was stirred at 20 °C for 2 h and then concentrated. The residue was dissolved in EtOAc (0.5 L). The resulting organic solution was washed with water and brine, dried over anhydrous Na_2SO_4 and concentration to give compound **296a** (11.0 g). LCMS $(M+H)^+$: 235.

Step 2: preparation of 1-bromo-4-chloro-2-fluoro-3-nitro-benzene (compound 296b)

To a mixture of compound **296a** (5.0 g, 21.3 mmol) in hydrochloric acid (2 M) (122.3 mL, 244.73 mmol) was added a solution of sodium nitrite (1.6 g, 23.4 mmol) in water (50.0 mL) dropwise at 0 °C. After addition, the mixture was stirred at 0 °C for 2 h. Then a solution of copper (I) chloride (2.1 g, 21.3 mmol) in water (10.0 mL) was added into this mixture at 0 °C.

The resulting mixture was stirred at 90 °C for 2 h. This mixture was extracted by EtOAc (0.1 L twice). The combined organic layer was dried over Na_2SO_4 and concentrated to give compound **296b** (4.5 g).

Step 3: preparation of *tert*-butyl *N*-[3-(6-bromo-3-chloro-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 296c)

A mixture of *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate (3.7 g, 19.45 mmol), compound **296b** (4.5 g, 17.69 mmol) and potassium carbonate (4.9 g, 35.37 mmol) in MeCN (0.1 L) was stirred at 85 °C for 12 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (0.2 L). The organic solution washed with water and brine, dried over anhydrous $MgSO_4$ and concentration. The residue was purified by flash column chromatography to give compound **296c** (3.5 g). LCMS $(M+H)^+$: 322.

Step 4: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-3-chloro-anilino)propyl]-*N*-methyl-carbamate (compound 296d)

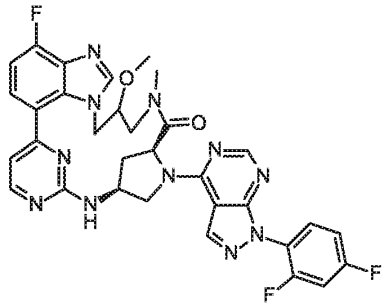
A mixture of compound **296c** (3.5 g, 8.56 mmol) and Pt/C (1.04 g, 18.56 mmol) in EA (80.0 mL) was stirred at 20 °C for 4 h under H_2 ballnoon. The mixture was filtered through celite and the filtrate was concentrated to compound **296d** (2.8 g) as a colorless oil. LCMS $(M+H)^+$: 392.

Step 5~15: preparation of (8*S*,11*S*)-21-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 296)

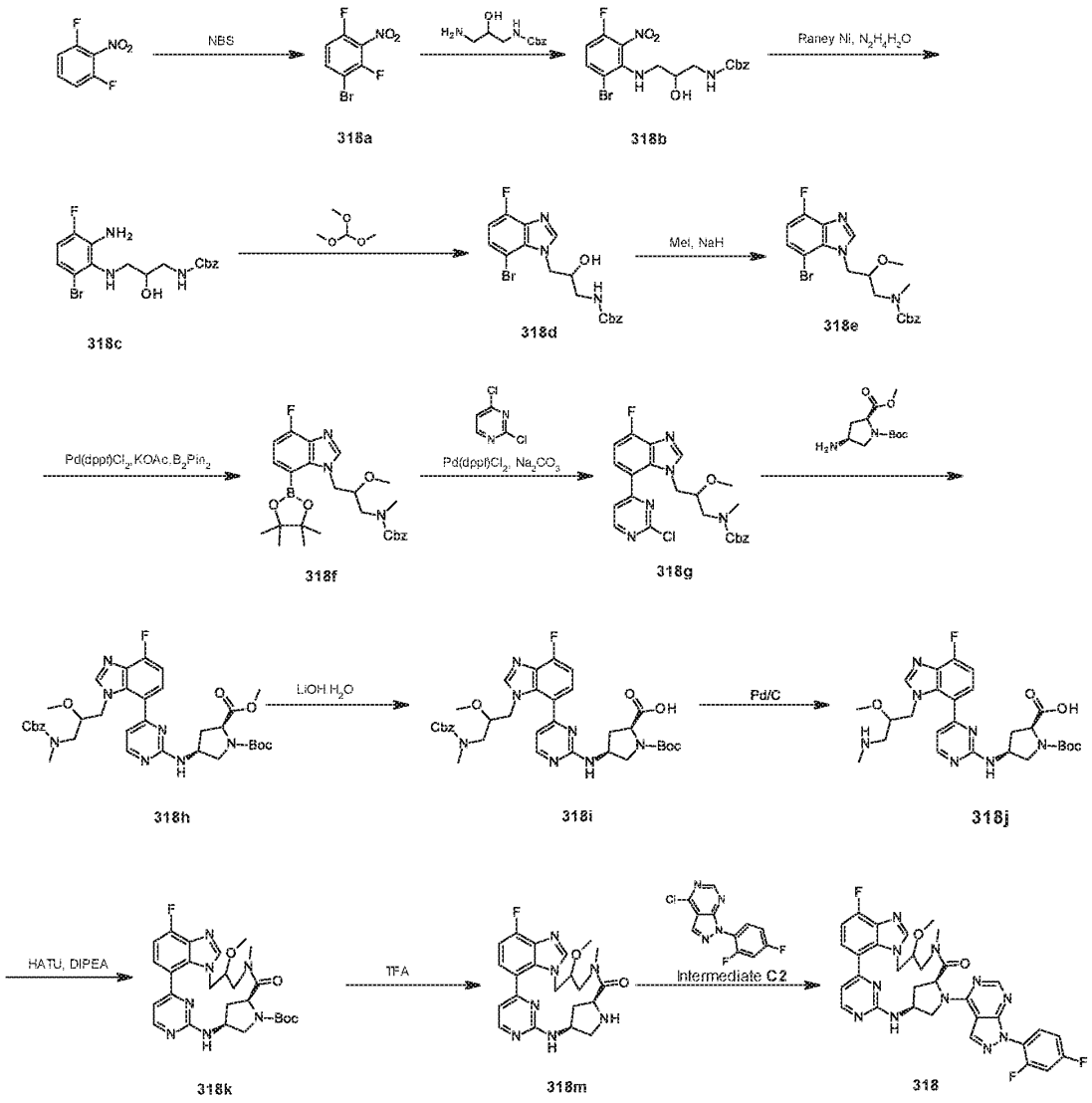
The title compound was prepared in analogy to the preparation of **Example 295** (Step 4~14) by using compound **296d** instead of compound **295c**. LCMS $(M+H)^+$: 654. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.57-8.65 (m, 1H), 8.39-8.49 (m, 2H), 8.15-8.31 (m, 1H), 7.40-7.47 (m, 3H), 7.20 (dd, *J*=11.3, 2.8 Hz, 1H), 7.03-7.09 (m, 1H), 6.90-7.00 (m, 1H), 6.46-6.66 (m, 1H), 5.33-5.48 (m, 1H), 4.92-5.08 (m, 1H), 4.51-4.81 (m, 1H), 4.36-4.45 (m, 1H), 4.14-4.34 (m, 2H), 3.94 (br dd, *J*=14.3, 9.3 Hz, 1H), 3.75 (s, 3H), 2.93-3.05 (m, 3H), 2.76-2.86 (m, 1H), 2.61-2.66 (m, 1H), 2.40-2.46 (m, 1H), 1.71-1.88 (m, 1H), 1.25-1.33 (m, 1H).

Example 318

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-bromo-2,4-difluoro-3-nitro-benzene (compound 318a)

To a mixture of 1,3-difluoro-2-nitro-benzene (20.0 g, 0.12 mol) in sulfuric acid (40.0 mL)

and trifluoroacetic acid (80.0 mL) was added NBS (26.8 g, 0.15 mol). The mixture was stirred at 80 °C for 12 hrs. The mixture was poured into ice water (0.1 L) and extracted with EtOAc (0.1 L twice). The combined organic layer was washed with $NaHCO_3$ aq. (0.1 L) and brine (0.1 L), and then the organic layer was dried and concentrated, the residue was purified by flash chromatography to give compound **318a** (22.0 g).

Step 2: preparation of benzyl *N*-[3-(6-bromo-3-fluoro-2-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 318b)

To a mixture of compound **318a** (22.0 g, 0.1 mol) and DIEA (23.8 g, 0.2 mol, 2.0 eq) in DMF (0.1 L) was added a solution of benzyl *N*-(3-amino-2-hydroxy-propyl)carbamate (20.7 g, 0.1 mol) in DMF (0.2 L) dropwise over 0.5 h. The mixture was stirred at 20 °C for 1 h and then poured into ice water (0.5 L). The resulting mixture was extracted with EtOAc (0.5 L twice). The combined organic layer was washed with $NaHCO_3$ aq. (0.1 L) followed by brine (0.1 L), dried and concentrated. The residue was purified by flash chromatography to give compound **318b** (20.0 g).

Step 3: preparation of benzyl *N*-[3-(2-amino-6-bromo-3-fluoro-anilino)-2-hydroxy-propyl]carbamate (compound 318c)

To a mixture of Raney Ni (11.0 g) and compound **318b** (10.0 g, 22.61 mmol) in methanol (0.3 L) was added $N_2H_4 \cdot H_2O$ (11.0 g) dropwise and the mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in DCM (0.3 L) and the solution was washed with brine (0.1 L twice). The organic layer was dried and concentrated to give compound **318c** (8.0 g). LCMS $(M+H)^+$: 412.

Step 4: preparation of benzyl *N*-[3-(7-bromo-4-fluoro-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (compound 318d)

To a solution of compound **318c** (8.0 g) in anhydrous THF (0.1 L) was added trimethyl orthoformate (6.37 mL, 58.2 mmol) and pyridinium p-toluenesulfonate (1.0 g, 3.9 mmol). The mixture was stirred at 20 °C for 2 h, and then diluted with EtOAc (0.1 L). The resulting mixture was partitioned between water (0.1L) and EtOAc (0.1 L). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give compound **318d** (5.0 g). LCMS $(M+H)^+$: 422.

Step 5: preparation of benzyl *N*-[3-(7-bromo-4-fluoro-benzimidazol-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (compound 318e)

To a mixture of compound **318d** (3.0 g, 7.1 mmol) and iodomethane (5.0 g, 35.5 mmol) in DMF (20.0 mL) was added sodium hydride (60% in oil, 1.4 g, 35.5 mmol) at -10 °C. The

mixture was stirred at -10 °C for 2 h, and then poured into a.q. NH_4Cl (30.0 mL). The resulting mixture was extracted with EtOAc (30.0 mL twice). Then the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give compound **318e** (1.5 g). LCMS $(M+H)^+$: 450.

Step 6~8: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[4-[3-[3-[benzyloxycarbonyl(methyl)amino]-2-methoxy-propyl]-7-fluoro-benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-1,2-dicarboxylate (compound 318h)

The title compound was prepared in analogy to the preparation of **Example 295** (Step 7~9) by using compound **318e** instead of compound **295f**. Compound **318h** (0.2g) was obtained. LCMS $(M+H)^+$: 692.

Step 9: preparation of (2*S*,4*S*)-4-[[4-[3-[3-[benzyloxycarbonyl(methyl)amino]-2-methoxy-propyl]-7-fluoro-benzimidazol-4-yl]pyrimidin-2-yl]amino]-1-tert-butoxycarbonyl-pyrrolidine-2-carboxylic acid (compound 318i)

To a mixture of compound **318h** (180.0 mg, 0.26 mmol) in water (5.0 mL) was added $LiOH•H_2O$ (32.8 mg, 0.78 mmol) and the mixture was stirred at 20 °C for 12 h. The mixture was acidified with HCl (1M) to pH=4~5, and then extracted with EtOAc (20 mL twice). The combined organic layer was washed with brine, dried and concentrated to give compound **318i** (150.0 mg). LCMS $(M+H)^+$: 678.

Step 10: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[4-[7-fluoro-3-[2-methoxy-3-(methylamino)propyl]benzimidazol-4-yl]pyrimidin-2-yl]amino]pyrrolidine-2-carboxylic acid (compound 318j)

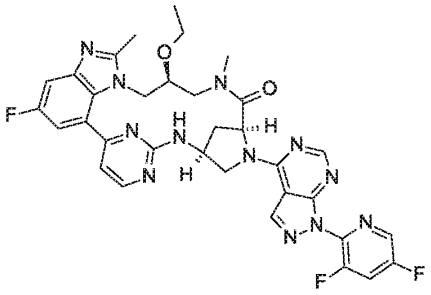
To the solution of compound **318i** (150.0 mg, 0.22 mmol) in IPA (10.0 mL) was added Pd/C (150.0 mg) and the mixture was stirred at 80 °C for 12 h under H_2. The mixture was filtered and the filtrate was concentrated to give compound **318j** (70.0 mg). LCMS $(M+H)^+$: 544.

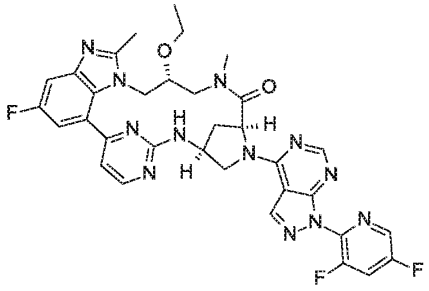
Step 11~13: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 318)

The title compound was prepared in analogy to the preparation of Example **295** (Step 12~14) by using compound **318j** instead of compound **295k**, and intermediate **C2** instead of intermediate **C11**. LCMS $(M+H)^+$: 656. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.42 - 8.60 (m, 2H), 8.08 - 8.37 (m, 2H), 7.48 - 7.87 (m, 2H), 7.00 - 7.36 (m, 4H), 5.36 - 5.69 (m, 2H), 3.86 - 4.70 (m, 5H), 2.97 - 3.30 (m, 5H), 2.80 - 2.93 (m, 4H), 2.52 - 2.65 (m, 1H).

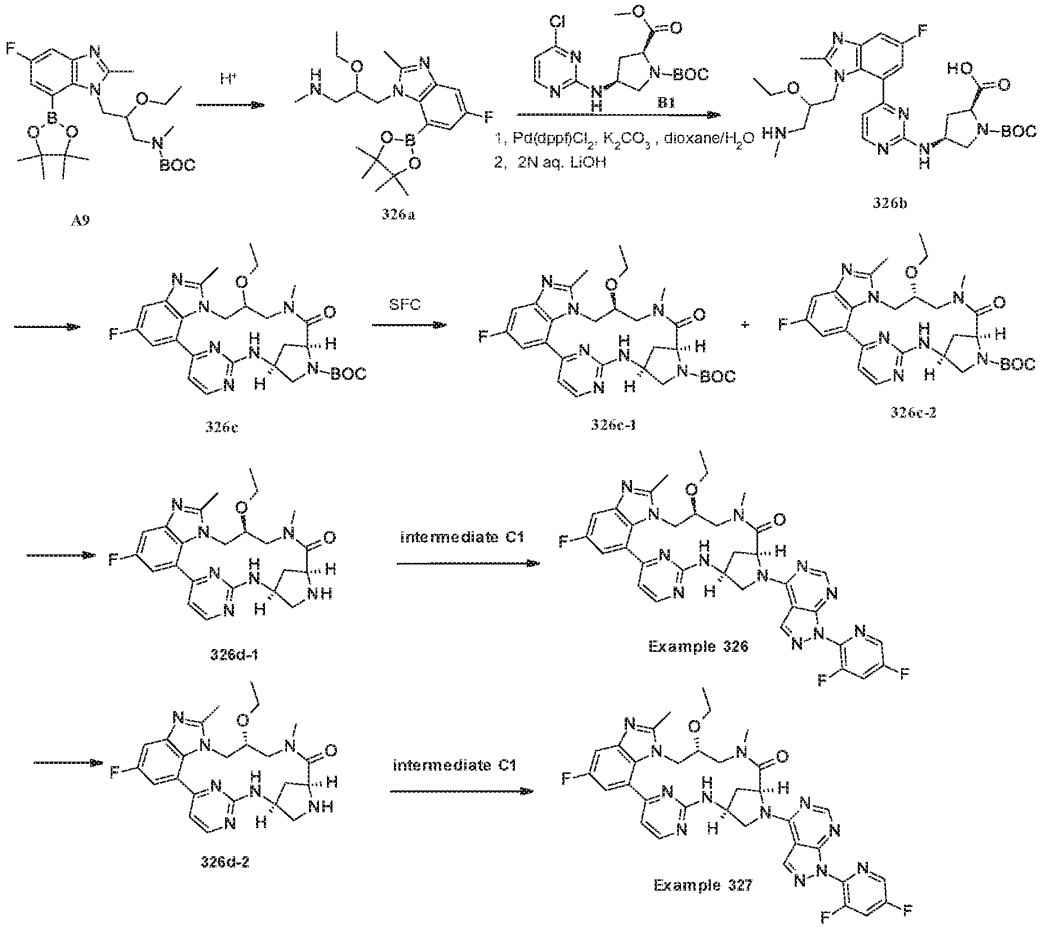
Example 326 and Example 327

(8*S*,11*S*,15*R*)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compounds were prepared according to the following scheme:



The title compounds were prepared in analogy to the preparation of Example **161** and Example **162** by using **Intermediate A9** instead of compound **161b** and **Intermediate C1** instead of **Intermediate C2**.

SFC condition of compound **326c**: Instrument SFC 80. Column: IA, 250×30 mm I.D., 5µm. Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O). Gradient: B 40%. Flow rate: 60 mL /min. Backpressure: 100 bar. Column temperature: 35 °C. Compound **326c-1** (faster eluted), compound **326c-2** (slower eluted).

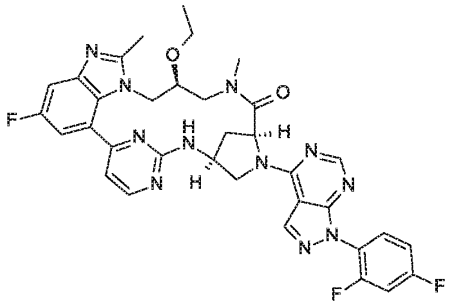
Example **326**, LCMS $(M+H)^+$: 685. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.73 - 8.33 (m, 3H), 8.31 - 7.82 (m, 2H), 7.75 - 7.62 (m, 2H), 7.25 - 7.08 (m, 1H), 5.95 - 5.73 (m, 1H), 5.55 - 5.35 (m, 1H), 4.81 - 4.55 (m, 1H), 4.52 - 4.16 (m, 3H), 4.07 - 3.90 (m, 1H), 3.55 - 3.38 (m, 1H), 3.19 - 2.98 (m, 4H), 2.95 - 2.75 (m, 5H), 2.75 - 2.63 (m, 1H), 2.55 (ddd, J = 4.3, 9.1, 13.7 Hz, 1H), 0.73 - 0.54 (m, 3H).

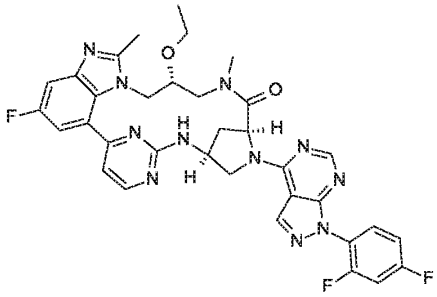
Example **327**, LCMS $(M+H)^+$: 685. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.67 - 8.35 (m, 3H), 8.30 - 7.79 (m, 2H), 7.72 - 7.55 (m, 2H), 7.09 (br s, 1H), 6.21 - 5.85 (m, 1H), 5.57 -

5.37 (m, 1H), 4.70 (br s, 1H), 4.50 (dd, *J* = 6.1, 11.6 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.31 - 4.23 (m, 1H), 4.07 (br d, *J* = 14.8 Hz, 1H), 3.82 - 3.66 (m, 1H), 3.45 - 3.36 (m, 1H), 3.21 - 3.04 (m, 4H), 2.98 - 2.80 (m, 5H), 2.74 - 2.50 (m, 1H), 0.73 - 0.54 (m, 3H).

Example 330 and Example 331

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





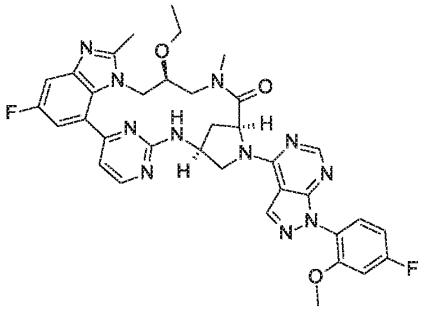
The title compounds were prepared in analogy to the preparation of Example **161** and Example **162** by using compound **326d-1** instead of compound **161e-1** and compound **326d-2** instead of compound **161e-2**.

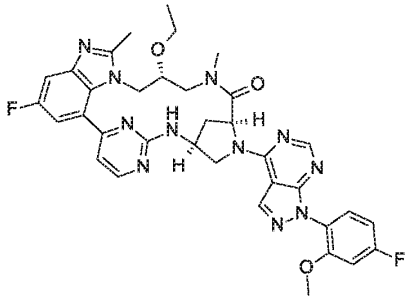
Example **330**, LCMS (M+H)$^+$: 684. ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.64 (d, *J* = 5.2 Hz, 1H), 8.57 - 8.32 (m, 1H), 8.27 - 7.79 (m, 1H), 7.74 - 7.58 (m, 3H), 7.39 - 7.05 (m, 3H), 5.94 - 5.67 (m, 1H), 5.53 - 5.33 (m, 1H), 4.81 - 4.58 (m, 1H), 4.51 - 4.16 (m, 3H), 3.99 (dd, *J* = 9.5, 14.3 Hz, 1H), 3.49 - 3.38 (m, 1H), 3.20 - 3.00 (m, 4H), 2.97 - 2.64 (m, 6H), 2.59 - 2.45 (m, 1H), 0.69 - 0.56 (m, 3H).

Example **331**, LCMS (M+H)$^+$: 684. ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.53 - 8.24 (m, 2H), 8.18 - 7.67 (m, 1H), 7.65 - 7.39 (m, 3H), 7.28 - 6.92 (m, 3H), 6.12 - 5.73 (m, 1H), 5.49 - 5.26 (m, 1H), 4.71 - 4.55 (m, 1H), 4.46 - 4.13 (m, 3H), 4.03 - 3.86 (m, 1H), 3.75 - 3.57 (m, 1H), 3.39 - 3.27 (m, 1H), 3.15 - 2.97 (m, 4H), 2.89 - 2.70 (m, 5H), 2.68 - 2.46 (m, 1H), 0.62 - 0.47 (m, 3H).

Example 332 and Example 333

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





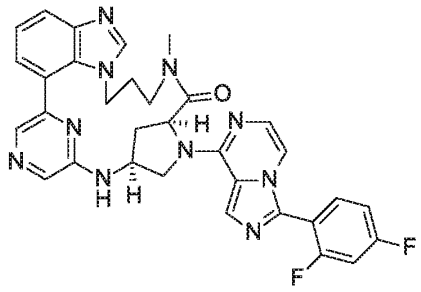
The title compounds were prepared in analogy to the preparation of Example **161** and Example **162** by using compound **326d-1** instead of compound **161e-1**; compound **326d-2** instead of compound **161e-2** and **Intermediate C11** instead of **Intermediate C2**.

Example **332**, LCMS (M+H)$^+$: 696. ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.65 (d, *J* = 5.2 Hz, 1H), 8.59 - 8.29 (m, 1H), 8.25 - 7.76 (m, 1H), 7.74 - 7.64 (m, 2H), 7.51 - 7.35 (m, 1H), 7.24 - 7.12 (m, 1H), 7.08 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.96 - 6.81 (m, 1H), 5.95 - 5.70 (m, 1H), 5.53 - 5.37 (m, 1H), 4.81 - 4.59 (m, 1H), 4.53 - 4.18 (m, 3H), 4.05 - 3.94 (m, 1H), 3.83 - 3.70 (m, 3H), 3.51 - 3.36 (m, 1H), 3.19 - 3.01 (m, 4H), 2.95 - 2.64 (m, 6H), 2.62 - 2.42 (m, 1H), 0.69 - 0.53 (m, 3H).

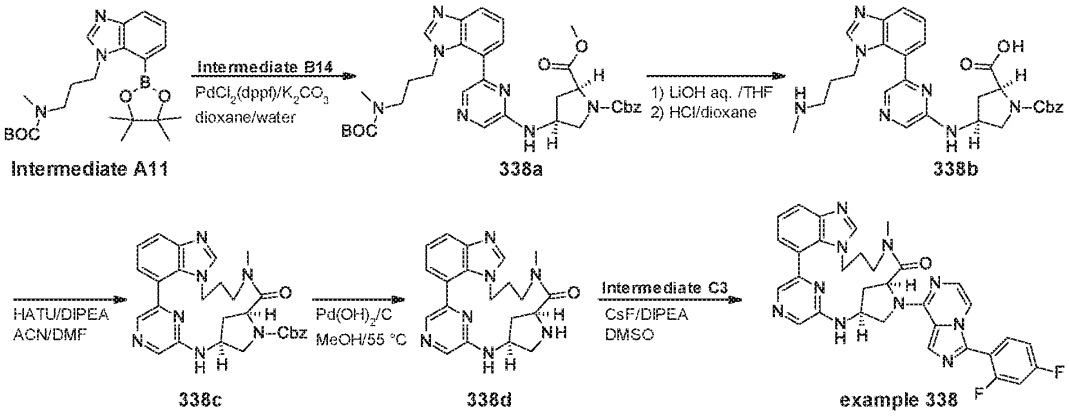
Example **333**, LCMS (M+H)$^+$: 696. ^{1}H NMR (500 MHz, METHANOL-d$_4$) δ = 8.64 - 8.29 (m, 2H), 8.25 - 7.71 (m, 1H), 7.64 (br dd, *J* = 2.4, 7.5 Hz, 2H), 7.51 - 7.33 (m, 1H), 7.07 (dd, *J* = 2.6, 10.7 Hz, 2H), 6.96 - 6.77 (m, 1H), 6.19 - 5.79 (m, 1H), 5.58 - 5.40 (m, 1H), 4.81 - 4.68 (m, 1H), 4.57 - 4.18 (m, 3H), 4.14 - 4.01 (m, 1H), 3.83 - 3.65 (m, 4H), 3.48 - 3.35 (m, 1H), 3.23 - 3.04 (m, 4H), 2.97 - 2.78 (m, 5H), 2.76 - 2.52 (m, 1H), 0.71 - 0.58 (m, 3H).

Example 338

(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1~4: preparation of (8*S*,11*S*)-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 338d)

Compound **338d** was prepared in analogy to the preparation of compound **1d** in Example **1** by using **intermediate A11** instead of **Intermediate B12** and **intermediate B14** instead of intermediate **A15-c**. LCMS (M+H$^+$): 378.

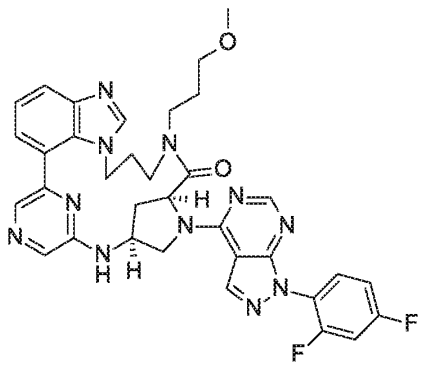
Step 5: preparation of (8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 338)

To a microwave tube was added (8*S*,11*S*)-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (**338d**, 50 mg, 132 μmol), 8-chloro-3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazine (**Intermediate C3**, 70.4 mg, 265 μmol), CsF (100.6 mg, 662 μmol), DIPEA (51.4 mg, 69.4 μL, 397 μmol) and DMSO (4mL). After being stirred at 90 °C for 12 hrs, the mixture was filtered and the filtrate was purified via prep-HPLC to give Example **338** (21 mg), LCMS (M+H$^+$): 607. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.26 (s, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.77 (dd, *J* = 1.3, 7.9 Hz,

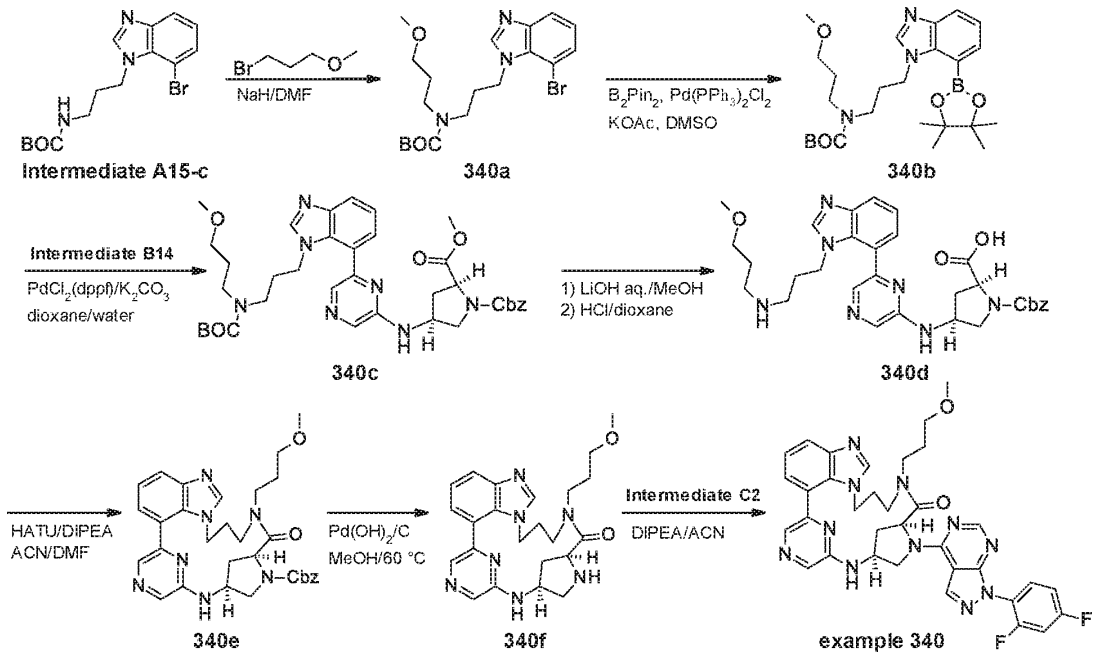
1H), 7.73 - 7.65 (m, 1H), 7.44 - 7.33 (m, 2H), 7.29 - 7.16 (m, 4H), 7.09 (t, *J* = 4.6 Hz, 1H), 5.51 - 5.37 (m, 1H), 5.10 - 4.96 (m, 1H), 4.80 - 4.75 (m, 1H), 4.68 - 4.51 (m, 1H), 4.48 - 4.30 (m, 1H), 4.22 - 4.05 (m, 2H), 3.07 (s, 3H), 2.93 – 2.88 (m, 1H), 2.69 - 2.54 (m, 2H), 2.15 - 2.01 (m, 1H), 1.54 - 1.39 (m, 1H).

Example 340

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-methoxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]-*N*-(3-

methoxypropyl)carbamate (compound 340a)

To a flask was added *tert*-butyl *N*-[3-(7-bromobenzimidazol-1-yl)propyl]carbamate (compound **A15-c,** 2.5 g, 3.53 mmol), 1-bromo-3-methoxy-propane (1.08 g, 7.06 mmol), DMF (15mL). Then NaH (60% purity, 423.4 mg, 10.59 mmol) was added. The mixture was stirred at room temperature for 12 hrs, then it was quenched with water. The mixture was poured into 150 mL EA, and then washed with 50 mL water for three times. The organic layer was dried and concentrated, the residue was purified by silica gel to give compound **340a** (1.5 g), LCMS ($M+H^+$): 427.

Step 2: preparation of *tert*-butyl *N*-(3-methoxypropyl)-*N*-[3-[7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]propyl]carbamate (compound 340b)

Compound **340b** was prepared in analogy to the preparation of compound **294d** by using compound **340a** instead of compound **294c**. LCMS ($M+H^+$): 474.

Step 3: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[*tert*-butoxycarbonyl(3-methoxypropyl)amino]propyl]benzimidazol-4-yl]pyrazin-2-yl]amino]pyrrolidine-1,2-dicarboxylate (compound 340c)

Compound **340c** was prepared in analogy to the preparation of compound **338a** by using compound **340b** instead of **intermediate A11**. LCMS ($M+H^+$): 702.

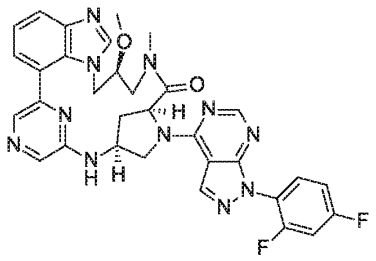
Step 4~7: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-methoxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 340)

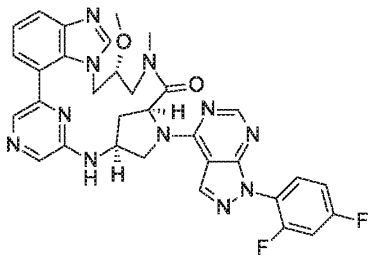
Example **340** was prepared in analogy to the preparation of Example **1** by using compound **340c** instead of compound **1a**. LCMS ($M+H^+$): 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (s, 1H), 8.26 - 8.19 (m, 3H), 8.15 - 8.08 (m, 1H), 7.77 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.68 - 7.59 (m, 1H), 7.48 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 7.28 (ddd, *J* = 2.8, 8.8, 10.2 Hz, 1H), 7.23 - 7.14 (m, 1H), 5.57 - 5.45 (m, 1H), 5.27 - 4.99 (m, 1H), 4.61 - 4.49 (m, 1H), 4.42 - 4.29 (m, 1H), 4.23 - 4.12 (m, 1H), 3.94 – 3.88 (m, 1H), 3.56 - 3.43 (m, 2H), 3.42 - 3.35 (m, 2H), 3.35 (s, 3H), 3.02 – 2.96 (m, 1H), 2.71 - 2.62 (m, 1H), 2.63 - 2.54 (m, 1H), 2.13 - 1.99 (m, 1H), 1.96 - 1.74 (m, 2H), 1.70 - 1.57 (m, 1H), 1.43 - 1.26 (m, 1H).

Example 344 and Example 345

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-

difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one





Example **344** and **345** were prepared in analogy to the preparation of Example **250** and **251** by using **intermediate A3** instead of **intermediate A4** and **intermediate B13** instead of compound **250a**.

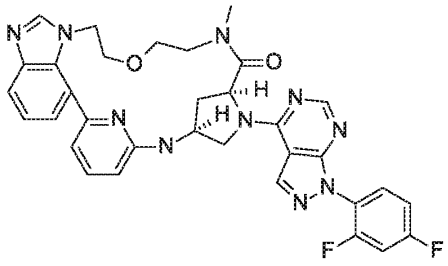
SFC conditions: Instrument: SFC 80; Column: AS, 250×20 mm I.D., 5µm; Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O); Gradient: B 25%; Flow rate: 50 mL /min; Back pressure: 100 bar. Column temperature: 35°C

Example 344, faster eluted, LCMS ($M+H^+$): 638. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.61 (s, 1H), 8.39 - 8.25 (m, 2H), 8.22 - 8.10 (m, 2H), 7.79 - 7.70 (m, 2H), 7.60 (ddd, *J* = 2.8, 9.1, 10.4 Hz, 1H), 7.40 - 7.24 (m, 3H), 5.94 - 5.80 (m, 1H), 5.53 - 5.44 (m, 1H), 5.00 - 4.81 (m, 2H), 4.53 - 4.45 (m, 1H), 4.34 - 4.31 (m, 1H), 4.27 - 4.17 (m, 2H), 4.02 - 3.92 (m, 1H), 3.80 - 3.60 (m, 1H), 3.23 - 3.13 (m, 1H), 3.12 (s, 1H), 3.02 (s, 2H), 2.84 (s, 2H), 2.80 (s, 1H), 2.62 - 2.53 (m, 1H).

Example 345, slower eluted, LCMS ($M+H^+$): 638. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.59 (s, 1H), 8.43 - 8.26 (m, 3H), 8.20 - 8.14 (m, 1H), 7.85 - 7.80 (m, 1H), 7.78 - 7.70 (m, 1H), 7.64 - 7.57 (m, 1H), 7.43 - 7.29 (m, 2H), 7.37 - 7.30 (m, 1H), 6.41 - 6.24 (m, 1H), 5.50 - 5.29 (m, 2H), 4.81 - 4.72 (m, 2H), 4.48 - 4.10 (m, 4H), 3.86 - 3.75 (m, 1H), 3.06 (s, 1H), 2.97 (s, 2H), 2.90 - 2.81 (m, 1H), 2.79 (s, 2H), 2.76 (s, 1H), 2.66 - 2.56 (m, 1H).

Example 350

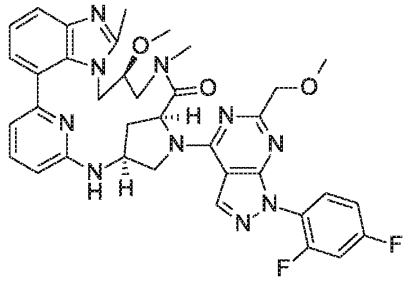
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-16-oxa-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **12** by using Intermediate **A28** instead of Intermediate **A12**. Example **350** was obtained. LCMS ($M+H^+$): 637. ^1H NMR (500 MHz, METHANOL-d_4) δ = 9.60 - 9.13 (m, 1H), 8.54 - 8.15 (m, 2H), 8.02 - 7.86 (m, 2H), 7.74 - 7.52 (m, 3H), 7.32 - 7.14 (m, 2H), 7.11 - 6.71 (m, 2H), 5.57 - 5.25 (m, 1H), 4.60 - 4.26 (m, 4H), 4.25 - 3.59 (m, 5H), 3.27 - 2.95 (m, 3H), 2.83 - 2.62 (m, 3H), 2.34 - 2.15 (m, 1H).

Example 363

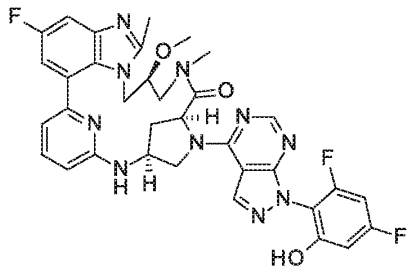
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



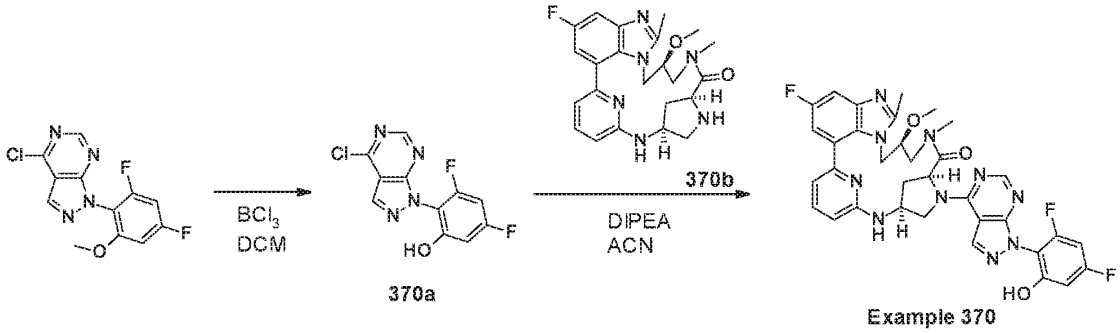
The title compound was prepared analogy to the preparation of Example **179** by using intermediate **C28** instead of intermediate **C2**. LCMS ($M+H^+$): 695, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.52 - 7.46 (m, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.24 (m, 1H), 7.22 - 7.16 (m, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.92 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 4.70 - 4.65 (m, 1H), 4.54 - 4.51 (m, 1H), 4.51 - 4.38 (m, 2H), 4.34 - 4.26 (m, 1H), 4.24 - 4.16 (m, 1H), 3.98 - 3.86 (m, 1H), 3.43 (s, 3H), 3.06 (s, 3H), 2.95 - 2.87 (m, 2H), 2.87 (s, 3H), 2.66 (s, 3H), 2.58 - 2.47 (m, 2H).

Example 370

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-3,5-difluoro-phenol (370a)

To a tube was added 4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (120 mg, 0.405 mmol) and dichloromethane (1 mL), the solution was cooled with ice bath and 1 M boron trichloride (solution in DCM) (1.62 mL, 1.62 mmol) was added. The mixture was warmed to r.t. and stirred for 16 hrs. The mixture was quenched with water and extracted with 15 mL DCM for 3 times. The organic layer was concentrated to give an oil, and then it was purified via prep-HPLC to give compound **370a** (38 mg). LCMS (M+H$^+$): 397.

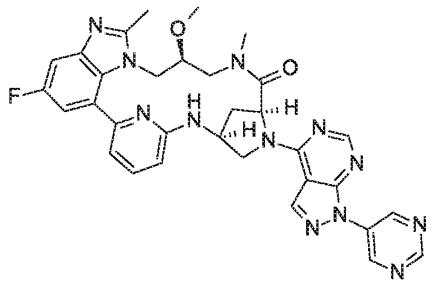
Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 370)

To a flask was added (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **370b**, 60.78 mg, 0.110 mmol, prepared analogy to compound **12d** by

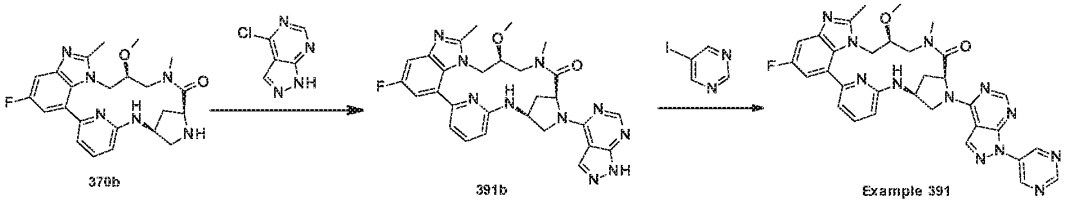
using intermediate **A6** instead of intermediate **A11** in step 1), 2-(4-chloropyrazolo[3,4-d]pyrimidin-1-yl)-3,5-difluoro-phenol (compound **370a**, 31.09 mg, 0.110 mmol), DIEA (56.87 mg, 76.85 µL, 0.440 mmol) and acetonitrile (3 mL). The mixture was heated to 85 °C and stirred for about 1 hr. The mixture was concentrated and the residue was purified by prep-HPLC to give Example **370** (58 mg). LCMS ($M+H^+$): 685, ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.20 (s, 1H), 7.85 (t, J = 7.9 Hz, 1H), 7.44 (dd, J = 2.1, 7.7 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.17 - 7.09 (m, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.71 - 6.60 (m, 2H), 5.96 (br dd, J = 4.1, 15.4 Hz, 1H), 5.49 (br d, J = 8.9 Hz, 1H), 4.68 (br t, J = 4.7 Hz, 1H), 4.55 - 4.48 (m, 1H), 4.39 - 4.31 (m, 1H), 4.27 - 4.17 (m, 1H), 4.01 - 3.88 (m, 1H), 3.05 (s, 3H), 2.96 - 2.91 (m, 1H), 2.90 (s, 3H), 2.90 - 2.85 (m, 1H), 2.70 (s, 3H), 2.58 - 2.48 (m, 2H).

Example 391

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(1-pyrimidin-5-ylpyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound 391b)

The mixture of compound **370b** (30 mg, 0.06 mmol), DIEA (0.03 mL, 0.19 mmol) and 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (10.25 mg, 0.070 mmol) in ACN (2 mL) was stirred at 85

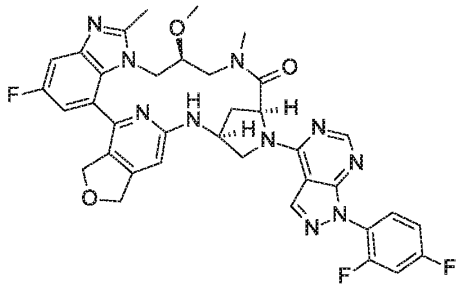
°C for 1 h. The mixture was purified by prep-HPLC to give compound **391b** (20 mg). LCMS $(M+H)^+$: 557.

Step 2: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(1-pyrimidin-5-ylpyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (Example 391)

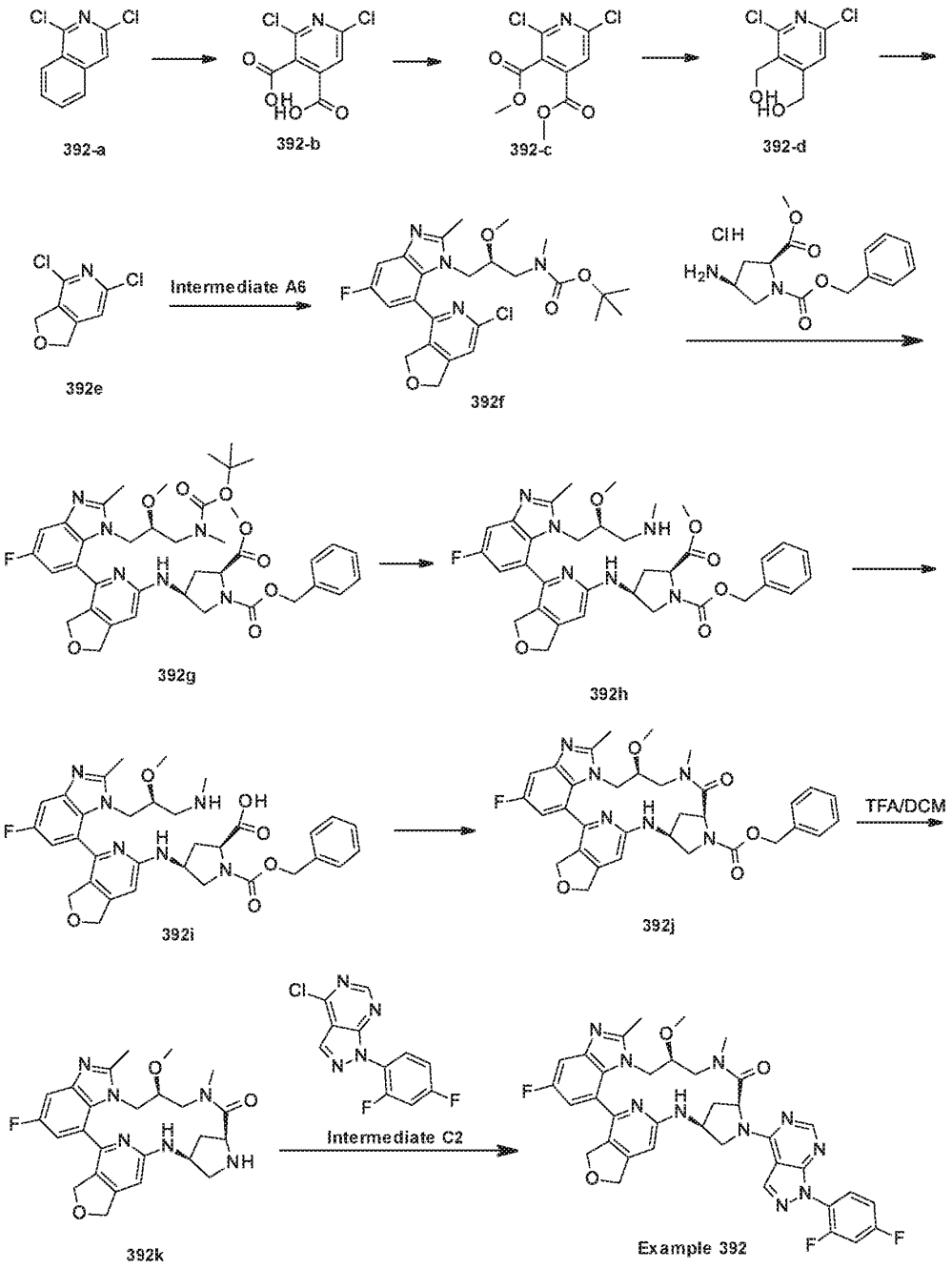
To a solution of compound **391b** (17.0 mg, 0.03 mmol), 5-iodopyrimidine (7.55 mg, 0.04 mmol) and CuI (0.58 mg, 0.004 mmol) in NMP (1 mL) was added (1*R*,2*R*)-N_1,N_2-dimethylcyclohexane-1,2-diamine (1.12 mg, 0.006 mmol) and K_3PO_4 (19.45 mg, 0.09 mmol) under N_2, and the reaction mixture was stirred for 2 h at 110 °C. The mixture was purified by prep-HPLC to give Example **391** (6.91 mg). LCMS $(M+H)^+$: 635. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.78 - 9.68 (m, 2H), 9.12 (s, 1H), 8.64 - 8.53 (m, 1H), 8.39 (s, 1H), 7.91 - 7.83 (m, 1H), 7.59 - 7.47 (m, 2H), 7.19 - 7.11 (m, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.16 - 5.93 (m, 1H), 5.52 - 5.40 (m, 1H), 4.67 (br d, *J* = 3.1 Hz, 1H), 4.55 - 4.47 (m, 1H), 4.38 - 4.24 (m, 2H), 3.99 - 3.90 (m, 1H), 3.17 - 3.04 (m, 3H), 3.04 - 2.98 (m, 1H), 2.97 - 2.95 (m, 3H), 2.87 (br d, *J* = 13.0 Hz, 1H), 2.82 - 2.75 (m, 3H), 2.63 - 2.49 (m, 2H).

Example 392

(11*S*,14*S*,18*R*)-13-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-25-fluoro-18-methoxy-16,21-dimethyl-5-oxa-10,13,16,20,22,29-hexazahexacyclo[18.6.1.1^{2,9}.1^{11,14}.0^{3,7}.0^{23,27}]nonacosa-1(26),2(29),3(7),8,21,23(27),24-heptaen-15-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 2,6-dichloropyridine-3,4-dicarboxylic acid (compound 392-b)

To a solution of $NaIO_4$ (129.54 g, 605.91 mmol) in DCM (40 mL), ACN (40 mL) and water (80 mL) was added $RuCl_3$ (0.1 g, 0.5 mmol) at 0 °C, then 1,3-dichloroisoquinoline (compound **A392-a**, 10 g, 50.49 mmol) was added portion wise over 30 min at 0 °C. After being stirred at 50 °C for 16 hours, the mixture was diluted with water and extracted with EtOAc. The organic layer was dried and concentrated to give compound **392-b** (9.7 g). LCMS $(M+H)^+$: 236.

Step 2: preparation of dimethyl 2,6-dichloropyridine-3,4-dicarboxylate (compound 392-c)

To a solution of 2,6-dichloropyridine-3,4-dicarboxylic acid (compound **392-b**, 9.7 g, 41.1 mmol) in DMF (100 mL) was added cesium carbonate (20.09 g, 61.65 mmol) and iodomethane (7.68 mL, 123.3 mmol) at 0 °C. After stirring at 50 °C for 16 hours, the reaction mixture was poured into water and extracted with EA, the organic layer was dried and concentrated to give the crude product, which was purified by flash chromatography to give compound **392-c** (5 g). LCMS $(M+H)^+$: 264.

Step 3: preparation of [2,6-dichloro-3-(hydroxymethyl)-4-pyridyl]methanol (compound 392-d)

To a solution of dimethyl dimethyl 2,6-dichloropyridine-3,4-dicarboxylate (compound **392-c,** 5.0 g, 18.94 mmol) in THF (73 mL) was added calcium chloride (8.41 g, 75.74 mmol) and $NaBH_4$ (6.45 g, 170.42 mmol) at 0 °C. Then the mixture was stirred at 25 °C for 16 hours. The mixture was quenched with H_2O and adjusted pH to 2 with HCl (1 M), the resulting aqueous phase was extracted with EtOAc. The organic layer was dried and concentrated to give compound **392-d** (4 g). LCMS $(M+H)^+$: 208.

Step 4: preparation of 4,6-dichloro-1,3-dihydrofuro[3,4-c]pyridine (compound 392e)

To a stirred solution of [2,6-dichloro-3-(hydroxymethyl)-4-pyridyl]methanol (compound **392-d,** 3.4 g, 16.34 mmol) in DCM (170 mL) was added manganese(IV) oxide (7.1 g, 81.72 mmol). The reaction mixture was cooled to 0 °C and triethylsilane (15.62 mL, 98.04 mmol) was added dropwise over a period of 10 mins, maintaining the reaction temperature at -5 °C. Then TFA (18.81 mL, 187.67 mmol) was added dropwise over a period of 15 mins. After stirring at 0 °C for 1 h, the mixture was stirred at 35 °C for 16 hours. The reaction was quenched with water and the mixture was filtered, the filtrate was extracted with EA. The organic layer was concentrated and the residue was purified by flash chromatography to give compound **392e** (760 mg), LCMS $(M+H)^+$: 190.

Step 5: preparation of *tert*-butyl *N*-[(2*R*)-3-[7-(6-chloro-1,3-dihydrofuro[3,4-c]pyridin-4-yl)-5-fluoro-2-methyl-benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate;2,2,2-trifluoroacetic acid (compound 392f)

A solution of intermediate **A6** (2.52 g, 5.28 mmol), 4,6-dichloro-1,3-dihydrofuro[3,4-c]pyridine (compound **392e,** 1.0 g, 5.28 mmol), $Pd(dppf)_2Cl_2$ (0.77 g, 1.06 mmol) and K_2CO_3 (2.19 g, 15.85 mmol) in water (2.28 mL) and 1,4-dioxane (20 mL) was stirred 85 °C for 2 h. The

mixture was filtered and concentrated, the residue was purified by column chromatography to give compound **392f** (1000 mg). LCMS $(M+H)^+$: 505.

Step 6: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[4-[3-[(2*R*)-3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-1,3-dihydrofuro[3,4-c]pyridin-6-yl]amino]pyrrolidine-1,2-dicarboxylate (compound 392g)

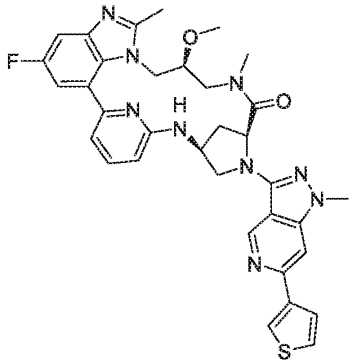
To a solution of compound **392f** (1000.0 mg, 1.98 mmol), O1-benzyl O2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate hydrochloride (934.97 mg, 2.97 mmol), cesium carbonate (1935.64 mg, 5.94 mmol) and S-Phos (162.59 mg, 0.400 mmol) in 1,4-dioxane (15 mL) was added $Pd_2(dba)_3$ (181.34 mg, 0.200 mmol) in one portion under N_2. The mixture was stirred at 90 °C for 16 hours under N_2. The reaction mixture was filtered and the filtrate was concentrated to afford compound **392g** (2000 mg). LCMS $(M+H)^+$: 747.

Step 7~11: preparation of (11*S*,14*S*,18*R*)-13-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-25-fluoro-18-methoxy-16,21-dimethyl-5-oxa-10,13,16,20,22,29-hexazahexacyclo[18.6.1.1^{2,9}.1^{11,14}.0^{3,7}.0^{23,27}]nonacosa-1(26),2(29),3(7),8,21,23(27),24-heptaen-15-one (Example 392)

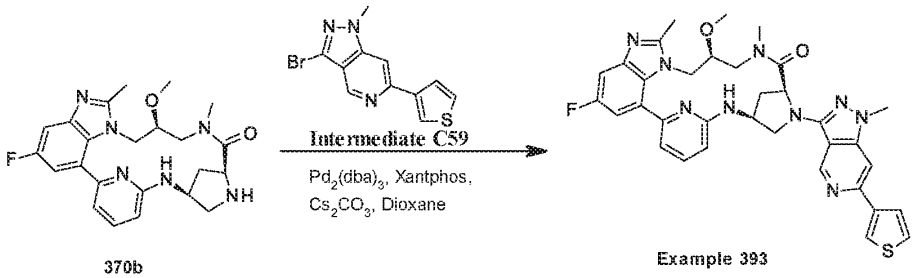
The title compound was prepared in the analogy to the preparation of Example **12** by using compound **392g** instead of compound **12a**. LCMS $(M+H)^+$: 711, ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 (s, 1H), 8.39 - 8.20 (m, 1H), 7.70 - 7.62 (m, 1H), 7.60 (dd, *J* = 2.5, 7.3 Hz, 1H), 7.45 (dd, *J* = 2.4, 10.1 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.24 - 7.18 (m, 1H), 6.89 - 6.72 (m, 1H), 6.04 - 5.85 (m, 1H), 5.53 - 5.36 (m, 2H), 5.26 - 5.07 (m, 2H), 4.69 - 4.66 (m, 1H), 4.57 - 4.46 (m, 2H), 4.38 (br d, *J* = 12.0 Hz, 1H), 4.33 - 4.23 (m, 2H), 3.98 - 3.91 (m, 1H), 3.70 - 3.57 (m, 1H), 3.19 (s, 1H), 3.10 (s, 2H), 3.00 (s, 3H), 2.84 - 2.78 (m, 3H), 2.62 - 2.45 (m, 2H).

Example 393

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-methyl-6-(3-thienyl)pyrazolo[4,3-c]pyridin-3-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

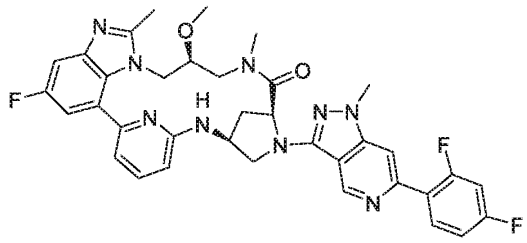


370b Example 393

To a solution of intermediate **C59** (20 mg, 0.07 mmol), compound **370b** (48 mg, 0.1 mmol), cesium carbonate (77 mg, 0.240 mmol) and xantphos (7.87 mg, 0.01 mmol) in 1,4-dioxane (1 mL) was added bis(dibenzylideneacetone)palladium (3.91 mg, 0.010 mmol) under N_2. The mixture was degassed with N_2 for 5 mins, then the mixture was stirred at 115 °C for 24 hours. The reaction mixture was filtered and the filtrate was concentrated, the residue was purified by prep-HPLC to give Example **393** (1.4 mg). LCMS(M+H)$^+$: 652. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.94 (s, 1H), 8.27 (t, *J* = 2.1 Hz, 1H), 8.08 (s, 1H), 7.91 - 7.87 (m, 1H), 7.78 (d, *J* = 2.2 Hz, 2H), 7.55 (dd, *J* = 2.4, 7.6 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.18 - 7.15 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.05 - 6.00 (m, 1H), 5.15 - 5.13 (m, 1H), 4.64 (br s, 1H), 4.34 - 4.30 (m, 2H), 4.16 (m, 1H), 4.03 (s, 3H), 3.98 (br d, *J* = 5.4 Hz, 1H), 3.10 (s, 3H), 3.02 (s, 1H), 2.96 (s, 3H), 2.93 - 2.90 (m, 1H), 2.78 (s, 3H), 2.72 (s, 2H).

Example 394

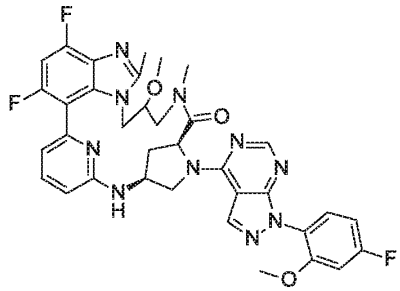
(8*S*,11*S*,15*R*)-10-[6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridin-3-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



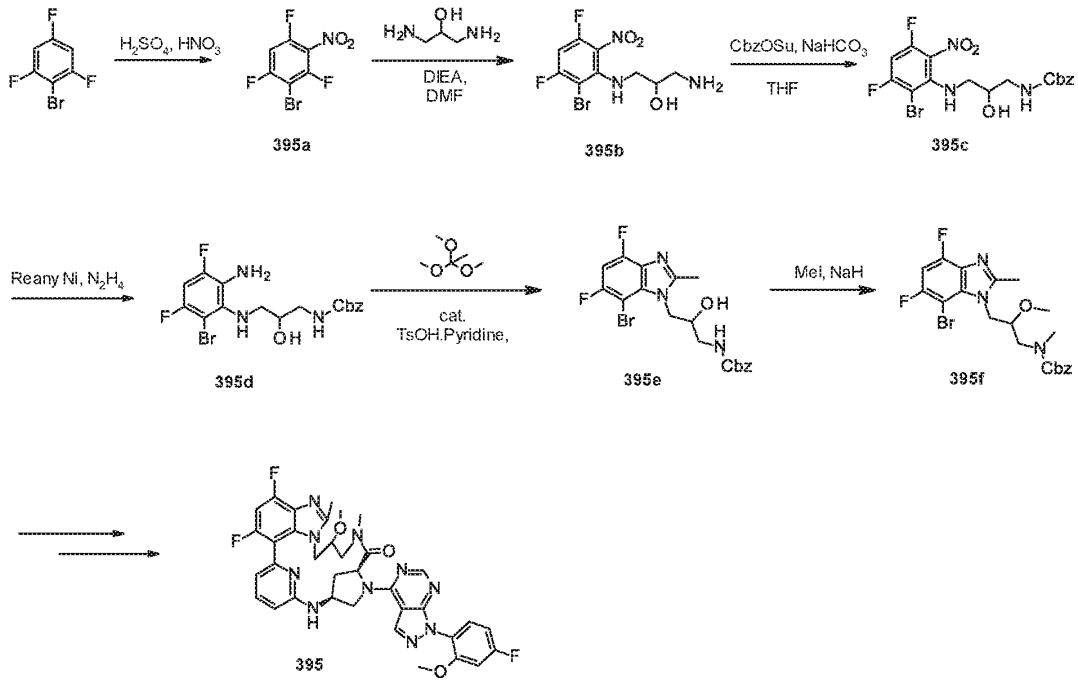
The title compound was prepared in the analogy to the preparation of Example **393** by using intermediate **C60** instead of intermediate **C59**. LCMS $(M+H)^+$: 682, ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.10 (s, 1H), 7.96 (s, 1H), 7.92 - 7.81 (m, 2H), 7.59 (dd, *J* = 2.7, 7.6 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.35 - 7.25 (m, 2H), 7.16 (d, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.08 (dd, *J* = 4.4, 15.2 Hz, 1H), 5.14 (d, *J* = 8.8 Hz, 1H), 4.63 (t, *J* = 4.6 Hz, 1H), 4.34 - 4.25 (m, 2H), 4.17 (d, *J* = 10.8 Hz, 1H), 4.02 (s, 3H), 3.99 - 3.92 (m, 1H), 3.08 (s, 3H), 3.00 (br d, *J* = 15.2 Hz, 1H), 2.97 (s, 3H), 2.93 (br d, *J* = 13.7 Hz, 1H), 2.81 (s, 3H), 2.65 - 2.55 (m, 2H).

Example 395

(8*S*,11*S*)-21,23-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-bromo-1,3,5-trifluoro-4-nitro-benzene (compound 395a)

To a solution of 2-bromo-1,3,5-trifluoro-benzene (13.0 g, 61.6 mmol) in H_2SO_4 (80 mL) was added HNO_3 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then poured into ice water (0.2 L). The mixture was extracted with EtOAc (0.5 L), and the organic layer was washed with water (0.2 L twice) and brine (0.2 L), dried and concentrated to give compound **395a** (15.1 g). LCMS ($M+H^+$): 256.

Step 2: preparation of 1-amino-3-(2-bromo-3,5-difluoro-6-nitro-anilino)propan-2-ol (compound 395b)

To a solution of compound **395a** (1.9 g, 21.1 mmol) in MeCN (0.1 L) was added 1,3-diaminopropan-2-ol (2.6 g, 10.2 mmol) dropwise. The reaction mixture was stirred at 20 °C for 1 h, and then concentrated. The residue was diluted with a mixture solvent of petroleum ether: EtOAc (10/1, v/v, 50 mL), and stirred for 0.5 h. Then the mixture was filtered, and filter cake was collected to give compound **395b** (3.1 g) as a yellow solid. LCMS ($M+H^+$): 326.

Step 3: preparation of benzyl *N*-[3-(2-bromo-3,5-difluoro-6-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 395c)

A mixture of compound **395b** (2.7 g, 8.3 mmol), *N*-(benzyloxycarbonyloxy)succinimide (2.2 g, 8.8 mmol) and $NaHCO_3$ in water (24 mL) and THF (24 mL) was stirred for 12 hours at 20 °C. The mixture was partitioned between EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-HPLC to give

compound **395c** (3.5 g). LCMS ($M+H^+$): 460.

Step 4: preparation of benzyl *N*-[3-(2-amino-6-bromo-3,5-difluoro-anilino)-2-hydroxy-propyl]carbamate (compound 395d)

To a solution of compound **395c** (3.5 g, 7.6 mmol) and Raney Ni (3.5 g) in methanol (50 mL) was added $N_2H_4 \cdot H_2O$ (3 mL) dropwise at 20 °C and stirred for 2 hours. Then the mixture was filtered and concentrated, the residue was partitioned between EtOAc and water. The organic layer was separated, dried and concentrated to give compound **395d** (3.2 g), which was used in next step directly. LCMS ($M+H^+$): 430.

Step 5: preparation of benzyl *N*-[3-(7-bromo-4,6-difluoro-2-methyl-benzimidazol-1-yl)-2-hydroxy-propyl]carbamate (compound 395e)

A mixture of pyridinium p-toluenesulfonate (130.0 mg, 0.5 mmol), trimethyl orthoacetate (3.0 g, 25.0 mmol) and compound **395d** (3.1 g, 7.2 mmol) in anhydrous THF (60 mL) was stirred for 12 hours at 20 °C. The mixture was poured into water (0.1 L) and extracted with EtOAc (0.1 L twice). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **395e** (1.3 g). LCMS ($M+H^+$): 454.

Step 6: preparation of benzyl *N*-[3-(7-bromo-4,6-difluoro-2-methyl-benzimidazol-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (compound 395f)

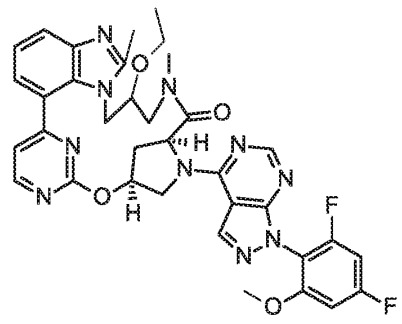
To a mixture of compound **395e** (1.3 g, 2.9 mmol) and iodomethane (1.3 g, 9.2 mmol) in anhydrous DMF (15 mL) was added sodium hydride (60% in oil, 0.5 g, 20.8 mmol) in portions at 0 °C, and the reaction mixture was stirred for 1 h. The mixture was poured into NH_4Cl aq. (0.1 L) and extracted with EtOAc (0.1 L twice). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to give compound **395f** (1.1 g). LCMS ($M+H^+$): 484.

Step 7~13: preparation of (8*S*,11*S*)-21,23-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

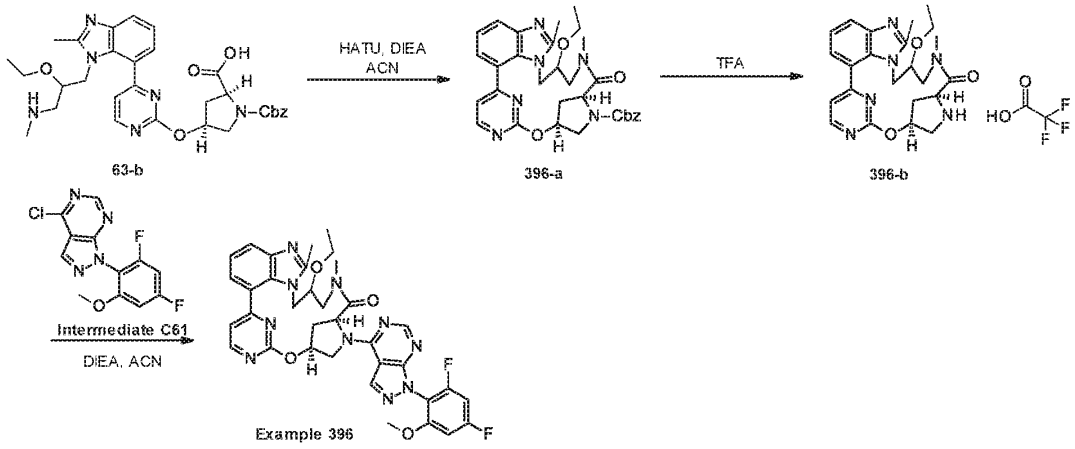
The title compound was prepared in analogy to the preparation of Example **209** (Step 7~13) by using compound **395f** instead of compound **209f**. LCMS ($M+H^+$): 699. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.49 - 8.52 (m, 1H), 8.16 - 8.20 (m, 1H), 7.68 - 7.82 (m, 1H), 7.39 - 7.52 (m, 1H), 6.86 - 7.10 (m, 3H), 6.79 (m, 2H), 5.39 - 5.57 (m, 1H), 4.71 - 4.84 (m, 1H), 4.55 - 4.69 (m, 2H), 4.27 - 4.52 (m, 2H), 4.09 - 4.23 (m, 1H), 3.74 - 3.97 (m, 4H), 3.68 (m, 1H), 3.12 - 3.21 (m, 1H), 3.05 - 3.11 (m, 3H), 2.79 - 3.02 (m, 4H), 2.52 - 2.74 (m, 3H).

Example 396

(8*S*,11*S*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaene-10-carboxylate (compound 396-a)

To a mixture of HATU (4.13 g, 10.9 mmol) and *N*,*N*-diisopropylethylamine (3.51 g, 27.2 mmol) in acetonitrile (400 mL) was added (2*S*,4*S*)-1-benzyloxycarbonyl-4-[4-[3-[2-ethoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]pyrimidin-2-yl]oxy-pyrrolidine-2-carboxylic acid (compound **63-b**, 3.2 g, 5.4 mmol) in acetonitrile (1400 mL) dropwise at room temperature. The mixture was stirred at room temperature for 1 hour, then the reaction mixture was concentrated, the residue was partitioned between water and EtOAc. The organic layer was separated, dried and concentrated to afford compound **396-a** (4.0 g). LCMS (M+H)$^+$: 571.

Step 2: preparation of (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound 396-b)

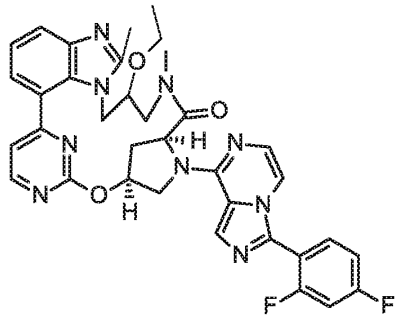
A solution of benzyl (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaene-10-carboxylate (compound **396-a**, 610 mg, 1.1 mmol) in TFA (5 mL, 64.9 mmol) was heated at 90 °C for 10 mins under microwave irritation. Then the reaction was concentrated to give compound **396-b** (720 mg). LCMS (M+H)$^+$: 437.

Step 3: preparation of (8*S*,11*S*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 396)

A mixture of (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **396-b**, 40 mg, 0.06 mmol), 4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine (21 mg, 0.07 mmol) and *N*,*N*-diisopropylethylamine (22 mg, 0.17 mmol) in acetonitrile (1 mL) was heated at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was directly purified by prep-HPLC to afford Example **396** (9 mg). LCMS (M+H)$^+$: 697. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.83 - 8.11 (m, 3H), 7.87 - 7.44 (m, 3H), 7.32 - 7.22 (m, 1H), 7.21 - 7.09 (m, 2H), 5.86 - 5.27 (m, 3H), 4.53 - 4.35 (m, 1H), 4.25 - 3.88 (m, 2H), 3.85 - 3.70 (m, 3H), 3.52 - 3.40 (m, 1H), 3.20 - 3.10 (m, 1H), 3.05 - 2.58 (m, 6H), 2.56 - 2.52 (m, 3H), 2.47 - 2.39 (m, 2H), 0.48 - 0.34 (m, 3H).

Example 397

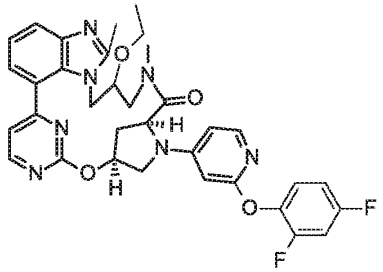
(8*S*,11*S*)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **396** by using Intermediate **C3** instead of Intermediate **C61**. Example **397** was obtained. LCMS ($M+H^+$): 666. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.89 - 8.11 (m, 2H), 7.85 - 7.65 (m, 3H), 7.62 - 7.42 (m, 3H), 7.38 - 7.22 (m, 3H), 5.82 - 5.39 (m, 3H), 4.68 - 4.13 (m, 3H), 4.09 - 3.80 (m, 4H), 3.17 - 3.10 (m, 1H), 3.05 - 2.68 (m, 4H), 2.62 - 2.57 (m, 1H), 2.56 - 2.52 (m, 3H), 0.46 - 0.37 (m, 3H).

Example 398

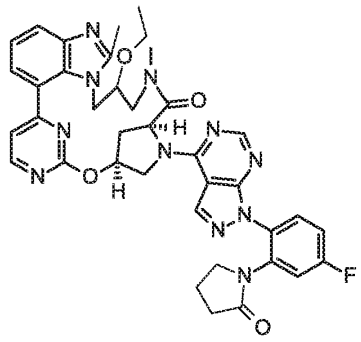
(8*S*,11*S*)-10-[2-(2,4-difluorophenoxy)-4-pyridyl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **396** by using Intermediate **C67** instead of Intermediate **C61**. Example **398** was obtained. LCMS ($M+H^+$): 642. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.85 - 8.71 (m, 1H), 7.81 (br t, J = 9.2 Hz, 1H), 7.75 - 7.52 (m, 3H), 7.48 - 7.25 (m, 3H), 7.10 (br t, J = 8.3 Hz, 1H), 6.49 - 5.94 (m, 2H), 5.85 - 4.89 (m, 3H), 4.21 - 3.73 (m, 5H), 3.21 - 3.13 (m, 1H), 3.05 - 2.82 (m, 4H), 2.78 - 2.57 (m, 6H), 0.49 - 0.36 (m, 3H).

Example 399

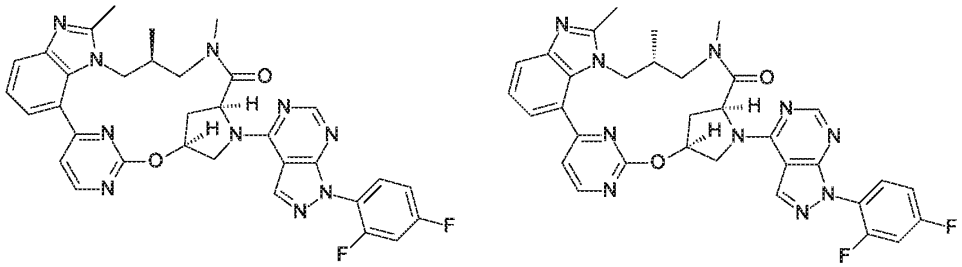
(8*S*,11*S*)-15-ethoxy-10-[1-[4-fluoro-2-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



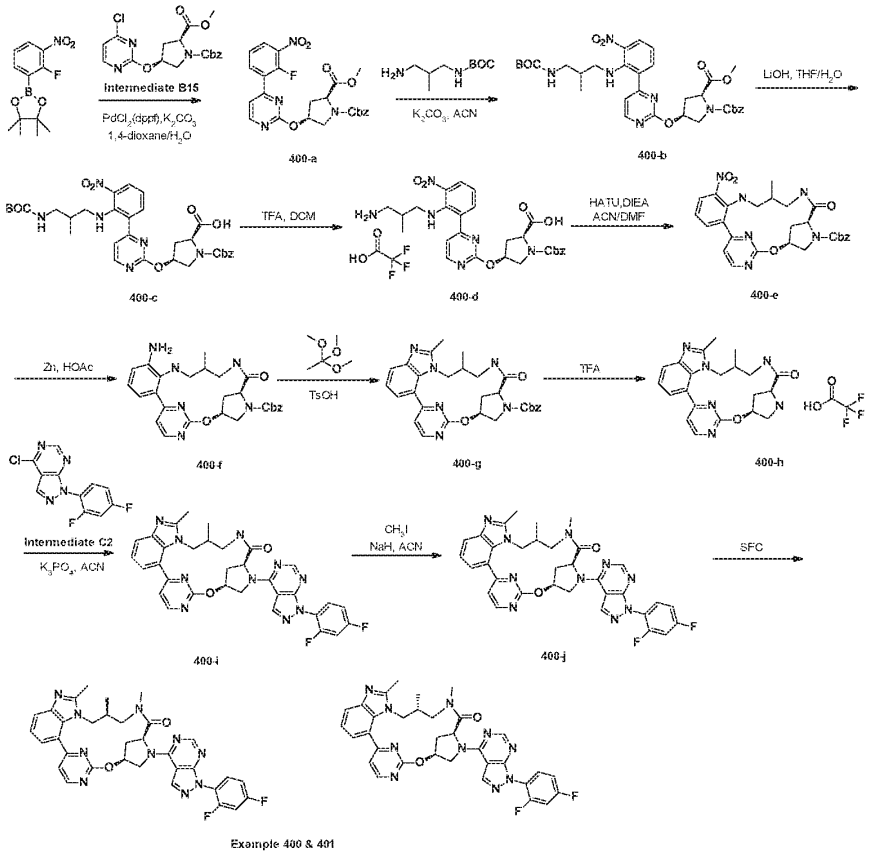
The title compound was prepared in analogy to the preparation of Example **396** by using Intermediate **C68** instead of Intermediate **C61**. Example **399** was obtained. LCMS ($M+H^+$): 732. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.84 - 8.70 (m, 1H), 8.59 - 7.77 (m, 2H), 7.76 - 7.44 (m, 5H), 7.40 - 7.34 (m, 1H), 7.29 (td, J = 7.7, 15.5 Hz, 1H), 5.82 - 5.43 (m, 3H), 4.50 - 4.16 (m, 2H), 4.12 - 3.77 (m, 2H), 3.58 - 3.41 (m, 2H), 3.19 - 3.12 (m, 1H), 3.06 - 2.85 (m, 4H), 2.82 - 2.58 (m, 3H), 2.57 - 2.53 (m, 3H), 2.48 - 2.40 (m, 1H), 2.19 - 2.06 (m, 2H), 1.98 - 1.84 (m, 2H), 0.48 - 0.37 (m, 3H).

Example 400 and Example 401

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[4-(2-fluoro-3-nitro-phenyl)pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 400-a)

A mixture of 2-(2-fluoro-3-nitro-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.36 g, 5.1 mmol), *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-(4-chloropyrimidin-2-yl)oxypyrrolidine-1,2-dicarboxylate (2 g, 5.1 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (187 mg, 0.26 mmol) and potassium carbonate (2.12 g, 15.3 mmol) in 1,4-dioxane (15 mL) and water (1.5 mL) was heated to 100 °C for 1 h with microwave irritation under nitrogen. The reaction mixture was diluted with water and extracted two times with EtOAc, the combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to give compound **400-a** (2.9 g). LCMS $(M+H)^+$: 497.

Step 2: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[4-[2-[[3-(*tert*-butoxycarbonylamino)-2-methyl-propyl]amino]-3-nitro-phenyl]pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 400-b)

To a mixture of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[4-(2-fluoro-3-nitro-phenyl)pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (**400-a** 2.9 g, 4.97 mmol) and potassium carbonate (2.06 g, 14.9 mmol) in acetonitrile (30 mL) was added *tert*-butyl *N*-(3-amino-2-methyl-propyl)carbamate

(1.03 g, 5.46 mmol), the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered; the filtrate was concentrated to give compound **400-b** (3.25 g). LCMS $(M+H)^+$: 665.

Step 3: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[4-[2-[[3-(*tert*-butoxycarbonylamino)-2-methyl-propyl]amino]-3-nitro-phenyl]pyrimidin-2-yl]oxy-pyrrolidine-2-carboxylic acid (compound 400-c)

A mixture of O1-benzyl O2-methyl (2*S*,4*S*)-4-[4-[2-[[3-(*tert*-butoxycarbonylamino)-2-methyl-propyl]amino]-3-nitro-phenyl]pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (3.25 g, 4.4 mmol) and lithium hydroxide monohydrate (compound **400-b**, 923 mg, 22mmol) in tetrahydrofuran (30 mL) and water (10 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water, acidified to pH = 5 with 1 M aq. HCl, and then extracted with DCM. The organic layer was dried and concentrated to afford compound **400-c** (3.55 g). LCMS $(M+H)^+$: 651.

Step 4: preparation of (2*S*,4*S*)-4-[4-[2-[(3-amino-2-methyl-propyl)amino]-3-nitro-phenyl]pyrimidin-2-yl]oxy-1-benzyloxycarbonyl-pyrrolidine-2-carboxylic acid;2,2,2-trifluoroacetic acid (compound 400-d)

A mixture of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[4-[2-[[3-(*tert*-butoxycarbonylamino)-2-methyl-propyl]amino]-3-nitro-phenyl]pyrimidin-2-yl]oxy-pyrrolidine-2-carboxylic acid (compound **400-c**, 3.55 g, 4.4 mmol) and TFA (10 mL) in dichloromethane (30 mL) was stirred at room temperature for 2 h. Then the mixture was concentrated to give compound **400-d** (3.43 g. LCMS $(M+H)^+$: 551.

Step 5: preparation of benzyl (14*S*,17*S*)-10-methyl-6-nitro-13-oxo-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.1^{14,17}.0^{2,7}]tetracosa-1(23),2,4,6,19,21-hexaene-15-carboxylate (compound 400-e)

To a mixture of HATU (3.14 g, 8.3 mmol) and *N*,*N*-diisopropylethylamine (2.67 g, 20.6 mmol) in *N*,*N*-dimethylformamide (20 mL) was added (2*S*,4*S*)-4-[4-[2-[(3-amino-2-methyl-propyl)amino]-3-nitro-phenyl]pyrimidin-2-yl]oxy-1-benzyloxycarbonyl-pyrrolidine-2-carboxylic acid 2,2,2-trifluoroacetic acid (compound **400-d**, 3.43 g, 4.1 mmol) in acetonitrile (2000 mL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C to room temperature for 1 h. After removing ACN under reduced pressure, the mixture was diluted with water and EtOAc, then extracted with EtOAc. The combined organic layer was dried and concentrated to afford compound **400-e** (2.97 g). LCMS $(M+H)^+$: 533.

Step 6: preparation of benzyl (14*S*,17*S*)-6-amino-10-methyl-13-oxo-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.1^{14,17}.0^{2,7}]tetracosa-1(23),2,4,6,19,21-hexaene-15-carboxylate (compound 400-f)

A mixture of (14*S*,17*S*)-10-methyl-6-nitro-13-oxo-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.114,17.02,7]tetracosa-1(23),2,4,6,19,21-hexaene-15-carboxylate (compound **400-e,** 2.97 g, 3.9 mmol) and zinc (2.55 g, 39 mmol) in acetic acid (30 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered, the filtrate was concentrated and the residue was then dissolved in *N*,*N*-dimethylformamide and diluted with water, the resulted precipitation was filtered, the filter cake was collected and dried to afford compound **400-f** (1.60 g). LCMS (M+H)$^+$: 503.

Step 7: preparation of benzyl (8*S*,11*S*)-15,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 400-g)

A mixture of benzyl (14*S*,17*S*)-6-amino-10-methyl-13-oxo-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.114,17.02,7]tetracosa-1(23),2,4,6,19,21-hexaene-15-carboxylate (compound **400-f**, 1.6 g, 3.2 mmol) and 1,1,1-trimethoxyethane (9.4 g, 78.2 mmol) in *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) was heated at 70 °C for 1 h. After cooling to room temperature, the mixture was concentrated and the residue was purified by flash chromatography to afford compound **400-g** (585 mg). LCMS (M+H)$^+$: 527.

Step 8: preparation of (8*S*,11*S*)-15,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound 400-h)

A solution of benzyl (8*S*,11*S*)-15,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound **400-g**, 585 mg, 1.0 mmol) in TFA (5 mL) was heated at 90 °C for 10 mins under microwave irritation. Then the mixture was concentrated to give compound **400-h** (1.02 g). LCMS (M+H)$^+$: 393.

Step 9: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 400-i)

A mixture of (8*S*,11*S*)-15,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **400-h**, 510 mg, 0.45 mmol), intermediate **C2** (121 mg,

0.45 mmol) and potassium phosphate (385 mg, 1.81 mmol) in anhydrous acetonitrile (2 mL) was heated at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was partitioned between water and DCM. The separated aqueous layer was extracted with DCM, and then the combined organic layer was washed with brine, dried and concentrated to afford compound **400-i** (308 mg) as a brown foam. LCMS $(M+H)^+$: 623.

Step 10: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 400-j)

To a mixture of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **400-i**, 308 mg, 0.42 mmol) and NaH (50 mg, 1.3 mmol) in anhydrous DMF (2 mL) was added iodomethane (179 mg, 1.3 mmol), the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between water and DCM, the separated aqueous layer was extracted with DCM, and then the combined organic layer was washed with brine, dried and concentrated, the residue was purified by prep-HPLC to afford compound **400-j** (130 mg). LCMS $(M+H)^+$: 637.

Step 11: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 400 and Example 401)

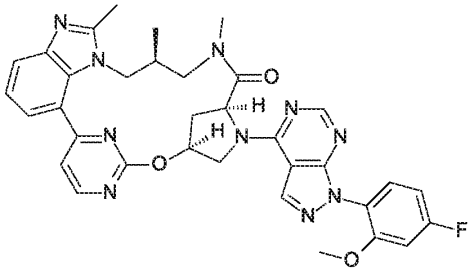
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **400-j**, 120 mg, 0.18 mmol) was separated by SFC (Instrument: SFC 80, Column: IA, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 50%, Flow rate: 50 mL /min, Back pressure: 100 bar, Column temperature: 35°C) to afford Example **400** and Example **401**.

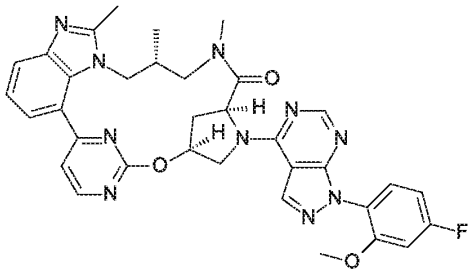
Example **400** (33 mg, faster eluted) was obtained. LCMS $(M+H)^+$: 637. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.84 - 8.61 (m, 2H), 8.42 - 8.23 (m, 1H), 7.80 - 7.69 (m, 3H), 7.65 - 7.55 (m, 2H), 7.37 - 7.27 (m, 2H), 5.72 - 5.35 (m, 3H), 4.53 - 4.15 (m, 2H), 3.95 - 3.75 (m, 2H), 3.14 - 2.75 (m, 5H), 2.70 - 2.60 (m, 1H), 2.60 - 2.52 (m, 3H), 2.48 - 2.38 (m, 1H), 0.22 - 0.08 (m, 3H).

Example **401** (53 mg, slower eluted) was obtained. LCMS $(M+H)^+$: 637. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.83 - 8.75 (m, 1H), 8.68 - 8.20 (m, 2H), 7.81 - 7.70 (m, 2H), 7.64 - 7.55 (m, 2H), 7.52 - 7.46 (m, 1H), 7.37 - 7.26 (m, 2H), 5.86 - 5.28 (m, 3H), 4.51 - 4.40 (m, 1H), 4.33 - 4.05 (m, 3H), 3.13 - 2.95 (m, 3H), 2.94 - 2.63 (m, 3H), 2.56 - 2.52 (m, 3H), 2.48 (s, 1H), 0.17 - 0.06 (m, 3H).

Example 402 and Example 403

(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





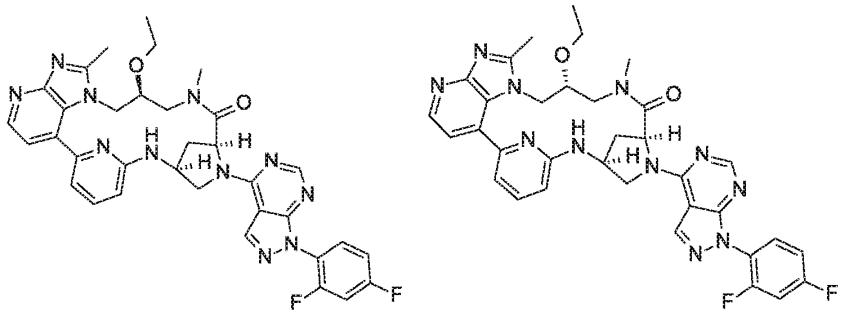
The title compound was prepared in analogy to the preparation of Example **400** and Example **401** by using Intermediate **C11** instead of Intermediate **C2** and SFC separation (Instrument: SFC 80, Column: MB-S, 250×30 mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA (0.1% NH_3H_2O), Gradient: B 30%, Flow rate: 50 mL /min, Back pressure: 100 bar, Column temperature: 35°C) to afford Example **402** and Example **403**.

Example **402** (26 mg, faster eluted) was obtained. LCMS $(M+H)^+$: 649. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.81 (dd, *J* = 1.2, 5.3 Hz, 1H), 7.81 - 7.72 (m, 2H), 8.57 - 7.71 (m, 2H), 7.64 - 7.57 (m, 1H), 7.49 - 7.38 (m, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 2.7, 11.1 Hz, 1H), 6.99 - 6.91 (m, 1H), 5.73 - 5.36 (m, 3H), 4.49 - 4.12 (m, 2H), 3.93 - 3.77 (m, 2H), 3.75 (s, 3H), 3.11 - 2.74 (m, 5H), 2.71 - 2.55 (m, 4H), 2.52 - 2.38 (m, 1H), 0.20 - 0.13 (m, 3H).

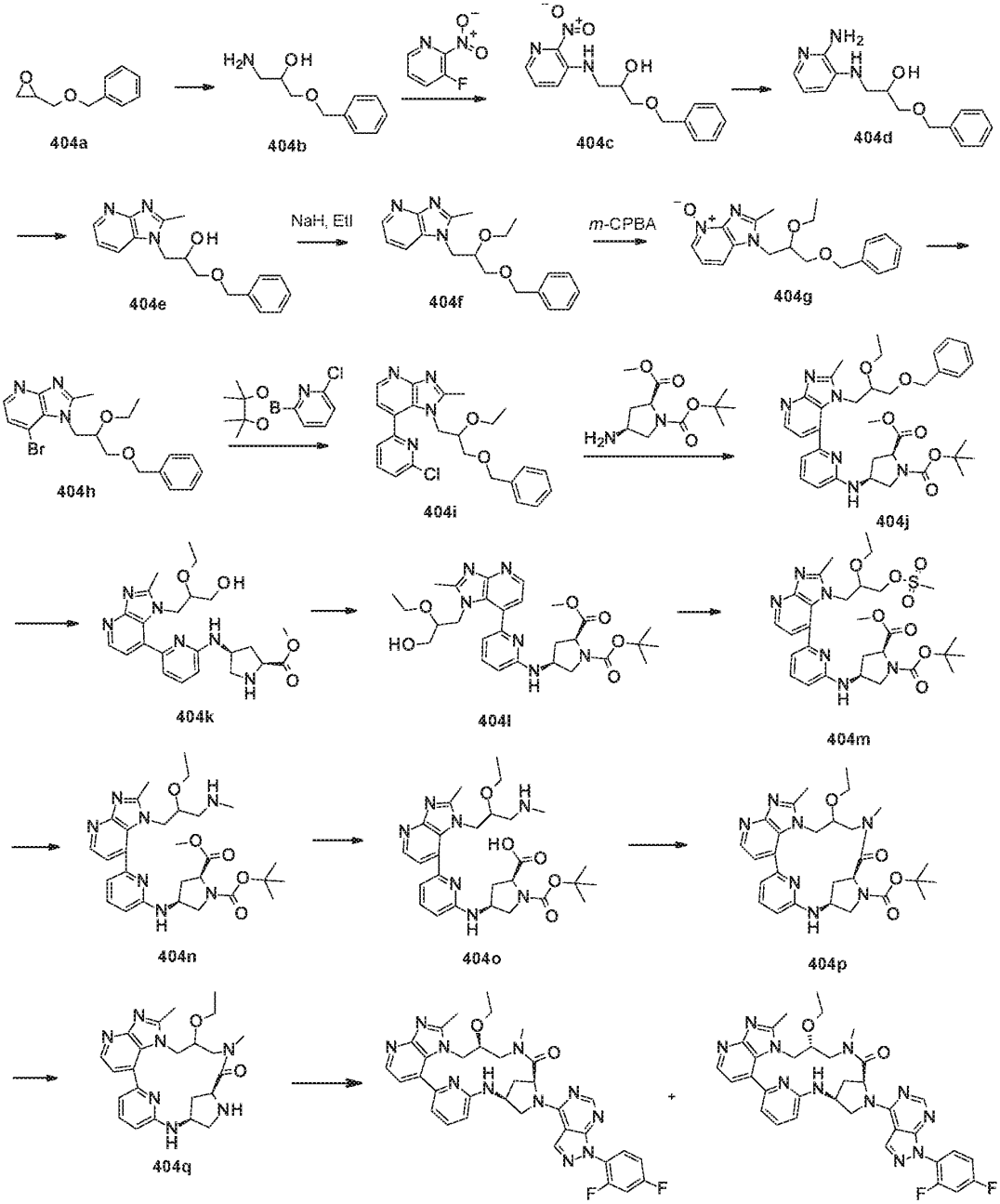
Example **403** (50 mg, slower eluted) was obtained. LCMS $(M+H)^+$: 649. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.81 (d, *J* = 5.3 Hz, 1H), 8.57 - 7.66 (m, 3H), 7.64 - 7.49 (m, 2H), 7.48 - 7.39 (m, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.20 (td, *J* = 3.0, 11.0 Hz, 1H), 6.99 - 6.91 (m, 1H), 5.87 - 5.33 (m, 3H), 4.52 - 4.07 (m, 4H), 3.78 - 3.69 (m, 3H), 3.16 - 2.87 (m, 4H), 2.85 - 2.62 (m, 2H), 2.60 - 2.45 (m, 4H), 0.16 - 0.08 (m, 3H).

Example 404 and 405

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of 1-amino-3-benzyloxy-propan-2-ol (compound 404b)

To benzyl glycidyl ether (compound **404a**, 20.0 g, 121.8 mmol) was added NH_3/H_2O (300.0 mL) dropwise at 20 °C, and the reaction was stirred at 20 °C for 16 hours. The reaction mixture was concentrated to afford compound **404b** (24 g). LCMS $(M+H)^+$: 182.

Step 2: preparation of 1-benzyloxy-3-[(2-nitro-3-pyridyl)amino]propan-2-ol (compound 404c)

To a solution of 3-fluoro-2-nitropyridine (compound **404b**, 5.0 g, 35.19 mmol) and N,N-diisopropylethylamine (6.82 g, 52.78 mmol) in DMSO (70 mL) was added 1-amino-3-benzyloxy-propan-2-ol (10.0 g, 44.69 mmol) at 20 °C. The mixture was stirred at 60 °C for 6 hours and then the reaction mixture was poured into water, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to afford compound **404c** (10.5 g). LCMS $(M+H)^+$: 304.

Step 3: preparation of 1-[(2-amino-3-pyridyl)amino]-3-benzyloxy-propan-2-ol (compound 404d)

To a solution of 1-benzyloxy-3-[(2-nitro-3-pyridyl)amino]propan-2-ol (compound **404c**, 10.5 g, 34.62 mmol) and Raney Ni (8.13 g, 138.47 mmol) in methanol (100 mL) was added hydrazine hydrate (16.83 mL, 346.18 mmol) dropwise at 20 °C, and the mixture was stirred at 20 °C for 1 h. The reaction was filtered and the filtrate was concentrated to afford compound **404d** (10 g). LCMS $(M+H)^+$: 274.

Step 4: preparation of 1-benzyloxy-3-(2-methylimidazo[4,5-b]pyridin-1-yl)propan-2-ol (compound 404e)

To a stirred solution of 1-[(2-amino-3-pyridyl)amino]-3-benzyloxy-propan-2-ol (compound **404d**, 9 g, 32.93 mmol) in trimethyl orthoacetate (90 mL) was added HCl/H_2O (0.9 mL, 10.8 mmol) at 0 °C, and the reaction mixture was stirred at 20 °C for 16 hours. The reaction was concentrated and the residue was poured into sat.aq.$NaHCO_3$, extracted with ethyl acetate. The organic phase was dried and concentrated to afford compound **404e** (11 g). LCMS $(M+H)^+$: 298.

Step 5: preparation of 1-(3-benzyloxy-2-ethoxy-propyl)-2-methyl-imidazo[4,5-b]pyridine (compound 404f)

To a solution of 1-benzyloxy-3-(2-methylimidazo[4,5-b]pyridin-1-yl)propan-2-ol (compound **404e**, 5.5 g, 14.98 mmol) in DMF (70 mL) was added sodium hydride (0.76 g, 18.96 mmol) at 0 °C, and the reaction was stirred at 0 °C for 0.5 hours. Then iodoethane (1.8 mL, 22.49 mmol) was added and the reaction was stirred at 0 °C for 1.5 hours. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate, the organic phase was dried and concentrated to afford compound **404f** (6 g). LCMS $(M+H)^+$: 326.

Step 6: preparation of 1-(3-benzyloxy-2-ethoxy-propyl)-2-methyl-4-oxido-imidazo[4,5-b]pyridin-4-ium (compound 404g)

To a solution of 1-(3-benzyloxy-2-ethoxy-propyl)-2-methyl-imidazo[4,5-b]pyridine (compound **404f**, 5.0 g, 15.37 mmol) in DCM (60 mL) was added *mCPBA* (4.0 g, 19.7 mmol) at 0 °C, and the reaction was stirred at 20 °C for 5 hours. The reaction was poured into sat.aq.$NaHCO_3$ and extracted with DCM. The organic phase was dried and concentrated to afford compound **404g** (5.7 g). LCMS $(M+H)^+$: 342.

Step 7: preparation of 1-(3-benzyloxy-2-ethoxy-propyl)-7-bromo-2-methyl-imidazo[4,5-b]pyridine (compound 404h)

To a solution of 1-(3-benzyloxy-2-ethoxy-propyl)-2-methyl-4-oxido-imidazo[4,5-b]pyridin-4-ium (compound **404g**, 4.5 g, 13.18 mmol) in DCM (50 mL) was added Phosphorus Oxybromide (5670.0 mg, 19.78 mmol) at 0 °C, and the reaction was stirred at 20 °C for 16 hrs. The reaction mixture was concentrated, the residue was poured into sat.aq.$NaHCO_3$ and extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by prep-HPLC to afford compound **404h** (600 mg). LCMS $(M+H)^+$: 406.

Step 8: preparation of 1-(3-benzyloxy-2-ethoxy-propyl)-7-(6-chloro-2-pyridyl)-2-methyl-imidazo[4,5-b]pyridine (compound 404i)

To a solution of 1-(3-benzyloxy-2-ethoxy-propyl)-7-bromo-2-methyl-imidazo[4,5-b]pyridine (compound **404h**, 600.0 mg, 1.48 mmol), 6-chloropyridine-2-boronic acid pinacol ester (450.0 mg, 1.88 mmol) and K_3PO_4 (450.0 mg, 2.12 mmol) in 1,4-dioxane (10 mL) and Water (1 mL) was added chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (60.0 mg) in one portion under N_2 at 25°C. The reaction mixture was stirred at 55 °C for 24 hours under N_2, then the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed, dried and concentrated, the residue was purified by silica gel to afford compound **404i** (645 mg). LCMS $(M+H)^+$: 437.

Step 9: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[1-(3-benzyloxy-2-ethoxy-propyl)-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 404j)

To a solution of 1-(3-benzyloxy-2-ethoxy-propyl)-7-(6-chloro-2-pyridyl)-2-methyl-imidazo[4,5-b]pyridine (compound **404i**, 645.0 mg, 1.48 mmol) , *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate;hydrochloride (580.0 mg, 2.07 mmol), Cesium carbonate (1300.0 mg, 3.99 mmol) and S-Phos (121.0 mg, 0.290 mmol) in 1,4-dioxane (10 mL) was added $Pd_2(dba)_3$ (121.0 mg, 0.130 mmol) in one portion under N_2. The mixture was stirred at 90 °C for 16 hours under N_2, then the reaction mixture was poured into water and extracted

with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by prep-TLC to afford compound **404j** (550 mg). LCMS $(M+H)^+$: 645.

Step 10: preparation of methyl (4S)-4-[[6-[1-(2-ethoxy-3-hydroxy-propyl)-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylate (compound 404k)

To a solution of compound **404j** (450 mg, 0.7 mmol) in DCM (10 mL) was added BCl_3 (1.8 mL, 1.8 mmol) at 0 °C, and the mixture was stirred at 20 °C for 24 hours under N_2. To the reaction mixture was added 5 mL MeOH, and the mixture was stirred at 20 °C for 0.25 hours. Then the reaction mixture was concentrated to afford compound **404k** (317 mg). LCMS $(M+H)^+$: 455.

Step 11: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[1-(2-ethoxy-3-hydroxy-propyl)-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 404l)

To a solution of compound **404k** (317 mg, 0.7 mmol) and DIEA (0.36 mL, 2.09 mmol) in DCM (10 mL) was added Boc_2O (400.0 mg, 1.83 mmol) at 0 °C, and the mixture was stirred at 20 °C for 4 hours under N_2. The reaction mixture was concentrated and the residue was purified by prep-TLC to afford compound **404l** (300 mg). LCMS $(M+H)^+$: 555.

Step 12: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[1-(2-ethoxy-3-methylsulfonyloxy-propyl)-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 404m)

To a solution of compound **404l** (600 mg, 1.08 mmol) and DIEA (0.54 mL, 3.1 mmol) in DCM (10 mL) was added methanesulfonyl chloride (0.39 mL, 5.06 mmol) dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into aq.$NaHCO_3$ (20 mL, 5%) and extracted with ethyl acetate. The organic phase was dried and concentrated to afford compound **404m** (684 mg). LCMS $(M+H)^+$: 633.

Step 13: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[1-[2-ethoxy-3-(methylamino)propyl]-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 404n)

To a solution of compound **404m** (684.0 mg, 1.08 mmol) in acetonitrile (8 mL) was added methylamine/THF (2.5 mL, 5 mmol) at 20 °C, and the reaction mixture was stirred at 80 °C for 16 hrs. The reaction was concentrated and the residue was purified by prep-TLC to afford compound **404n** (200 mg). LCMS $(M+H)^+$: 568.

Step 14: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[6-[1-[2-ethoxy-3-(methylamino)propyl]-2-methyl-imidazo[4,5-b]pyridin-7-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 404o)

To a solution of compound **404n** (200.0 mg, 0.350 mmol) in methanol (2 mL) and THF (2 mL) was added $LiOH•H_2O$ (60.0 mg, 1.43 mmol) in water (1.5 mL) at 0 °C, and the reaction mixture was stirred at 20 °C for 16 hrs. The reaction was concentrated and the residue was purified by prep-HPLC to afford compound **404o** (210 mg). LCMS $(M+H)^+$: 554.

Step 15: preparation of *tert*-butyl (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 404p)

To a mixture of HATU (190.0 mg, 0.500 mmol) and DIEA (114.0 mg, 0.880 mmol) in DMF (75 mL) was added compound **404o** (190.0 mg, 0.280 mmol) in DMF (225 mL) dropwise at 0 °C for 0.5 hours, then the mixture was stirred for 2 hrs at 0 °C. The reaction was concentrated and the residue was purified by prep-HPLC to afford compound **404p** (55 mg) as. LCMS $(M+H)^+$:536.

Step 16: preparation of (8*S*,11*S*)-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;hydrochloride (compound 404q)

To a solution of compound **404p** (56 mg, 0.07 mmol) in 1,4-dioxane (0.5 mL) was added HCl/1,4-dioxane (0.5 mL, 4 mol/L) dropwise at 0 °C, then the mixture was stirred for 1 hr at 0 °C. The reaction was concentrated and the residue was purified by prep-HPLC to afford compound **404q** (40 mg). LCMS $(M+H)^+$: 436.

Step 17: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 404 and 405)

To a solution of compound **404q** (40 mg, 0.07 mmol) and 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (20.0 mg, 0.080 mmol) in acetonitrile (1 mL) was added DIEA (40.0 mg, 0.310 mmol) at 25 °C, and the mixture was stirred at 80 °C for 1 h. The reaction mixture was purified by prep-HPLC and SFC to give Example **404** (4.4 mg) and **405** (10.9 mg). SFC condition: Instrument: waters 80Q; Column: DAICEL CHIRALCEL OD

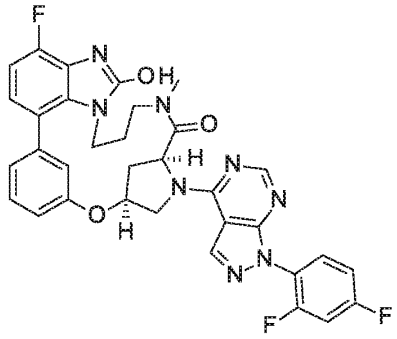
(250mm×30mm, 10μm); Mobile phase: Phase A for Supercritical CO_2, and Phase B for IPA+ACN(0.1%NH_3H_2O); Gradient: 60%Phase B (40% Phase A); Flow rate: 70g/min; Back pressure: 100 bar to keep the CO_2 in Supercritical flow; Column temperature: 30°C.

Example **404**, faster eluted, LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.64 (d, J = 5.4 Hz, 1H), 8.59 (s, 1H), 8.40 - 8.24 (m, 1H), 7.93 (t, J = 7.9 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.72 - 7.60 (m, 1H), 7.36 - 7.19 (m, 3H), 6.90 - 6.84 (m, 1H), 6.15 - 5.99 (m, 1H), 5.57 - 5.41 (m, 1H), 4.74 - 4.72 (m, 1H), 4.59 - 4.54 (m, 1H), 4.40 - 4.30 (m, 2H), 4.00 (dd, J = 9.5, 14.4 Hz, 1H), 3.47 - 3.40 (m, 1H), 3.16 - 3.11 (m, 1H), 3.06 - 2.98 (m, 3H), 2.97 - 2.90 (m, 1H), 2.87 - 2.84 (m, 3H), 2.82 - 2.69 (m, 3H), 2.64 - 2.52 (m, 1H), 0.68 - 0.60 (m, 3H).

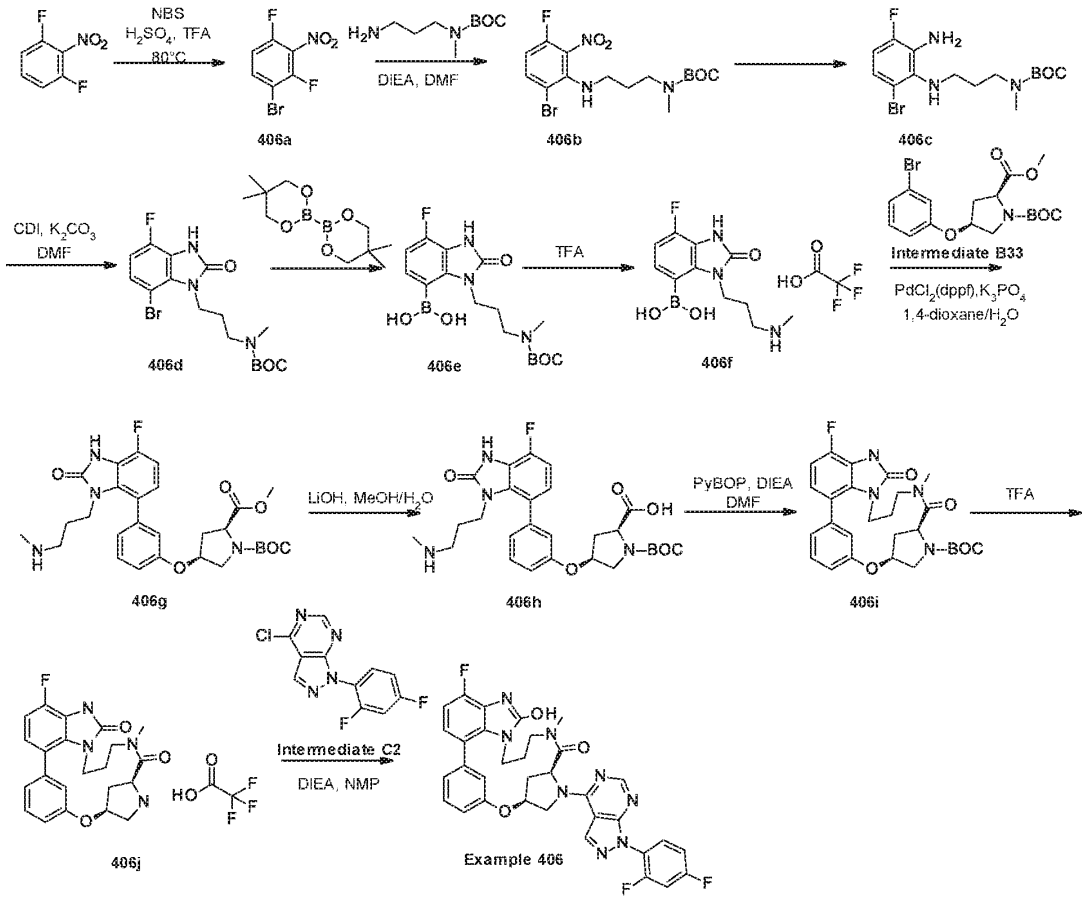
Example **405**, slower eluted, LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL- d_4) δ = 8.67 - 8.53 (m, 2H), 8.41 - 8.20 (m, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.82 - 7.60 (m, 2H), 7.35 - 7.27 (m, 1H), 7.26 - 7.17 (m, 2H), 6.91 - 6.80 (m, 1H), 6.29 - 5.90 (m, 1H), 5.59 - 5.46 (m, 1H), 4.79 - 4.74 (m, 1H), 4.64 - 4.54 (m, 1H), 4.41 - 4.23 (m, 3H), 4.08 (d, J = 14.7 Hz, 1H), 3.77 (dd, J = 2.6, 4.5 Hz, 1H), 3.41 - 3.33 (m, 2H), 3.20 - 3.09 (m, 3H), 2.91 - 2.87 (m, 1H), 2.86 - 2.83 (m, 3H), 2.79 - 2.57 (m, 2H), 0.64 - 0.58 (m, 3H).

Example 406

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-18-hydroxy-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of 1-bromo-2,4-difluoro-3-nitro-benzene (compound 406a)

To a mixture of 1,3-difluoro-2-nitro-benzene (5.0 g, 31.4 mmol) in sulfuric acid (10 mL) and trifluoroacetic acid (20 mL) was added *N*-bromosuccinimide (6.7 g, 37.7 mmol) and the mixture was stirred at 80 °C for 12 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with saturated aq.$NaHCO_3$ and brine, then dried and concentrated. The residue was purified by flash chromatography to afford compound **406a** (7.3 g).

Step 2: preparation of *tert*-butyl *N*-[3-(6-bromo-3-fluoro-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 406b)

To a solution of 1-bromo-2,4-difluoro-3-nitro-benzene (compound **406a**, 7.3 g, 30.6 mmol) and *tert*-butyl *N*-(3-aminopropyl)-*N*-methyl-carbamate (5.8 g, 30.6 mmol) in *N,N*-dimethylformamide (100 mL) was added *N,N*-diisopropylethylamine (11 mL, 61.3 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water, extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous

Na_2SO_4. After filtration, the solvent was removed in *vacuo*, the residue was purified by column chromatography to give compound **406b** (9.0 g). LCMS $(M-100+H)^+$: 306.

Step 3: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-3-fluoro-anilino)propyl]-*N*-methyl-carbamate (compound 406c)

To a solution of *tert*-butyl *N*-[3-(6-bromo-3-fluoro-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound **406b**, 7.0 g, 17.2 mmol) in methanol (250 mL) was added Raney Ni (7.0 g), followed by hydrazine hydrate (4 mL) added dropwise, meanwhile keeping the temperature below 25 °C. The reaction mixture was stirred at room temperature for 1 h, then filtered and the filtrate was concentrated in *vacuo* to give compound **406c** (4.0 g). LCMS $(M+H)^+$: 376.

Step 4: preparation of *tert*-butyl *N*-[3-(7-bromo-4-fluoro-2-oxo-3H-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 406d)

To a solution of *tert*-butyl *N*-[3-(2-amino-6-bromo-3-fluoro-anilino)propyl]-*N*-methyl-carbamate (compound **406c**, 4.0 g, 10.6 mmol) and *N*, *N*'-carbonyldiimidazole (2.2 g, 13.8 mmol) in *N*,*N*-dimethylformamide (100 mL) was added potassium carbonate (4.4 g, 31.9 mmol), the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was poured into water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in *vacuo*, the residue was purified by column chromatography to give compound **406d** (2.0 g). LCMS $(M-100+H)^+$: 302.

Step 5: preparation of [3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-7-fluoro-2-oxo-1H-benzimidazol-4-yl]boronic acid (compound 406e)

To a solution of bis(neopentyl glycolato)diboron (1.4 g, 6.2 mmol), *tert*-butyl *N*-[3-(7-bromo-4-fluoro-2-oxo-3H-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound **406d**, 1.0 g, 2.5 mmol), XPhos (240 mg, 0.3 mmol) and $Pd_2(dba)_3$ (240 mg, 0.4 mmol) in 1,4-dioxane (20 mL) was added sodium acetate (0.4 g, 5.0 mmol), and the reaction mixture was stirred at 100 °C for 12 h under argon. After cooling to room temperature, the reaction mixture was poured into water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a crude product, which was purified by prep-HPLC to give compound **406e** (0.8 g). LCMS $(M+H)^+$: 368.

Step 6: preparation of [7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1H-benzimidazol-4-yl]boronic acid 2,2,2-trifluoroacetic acid (compound 406f)

A solution of [3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-7-fluoro-2-oxo-1H-benzimidazol-4-yl]boronic acid (compound **406e**, 0.8 g, 2.2 mmol) in TFA (10 mL) was stirred

at room temperature for 1 h. Then the reaction mixture was concentrated to give compound **406f** (0.5 g). LCMS $(M+H)^+$: 268.

Step 7: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[3-[7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1*H*-benzimidazol-4-yl]phenoxy]pyrrolidine-1,2-dicarboxylate (compound 406g)

To a solution of [7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1H-benzimidazol-4-yl]boronic acid;2,2,2-trifluoroacetic acid (compound **406f**, 0.5 g, 3.0 mmol), **Intermediate B33** (1.4 g, 3.6 mmol), $Pd(dppf)Cl_2$ (0.2 g, 0.40 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was added potassium phosphate (1.6 g, 7.5 mmol), and the reaction mixture was stirred at 100 °C for 12 h under argon. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to get a crude product, which was purified by prep-HPLC to give compound **406g** (250 mg). LCMS $(M+H)^+$: 543.

Step 8: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[3-[7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1*H*-benzimidazol-4-yl]phenoxy]pyrrolidine-2-carboxylic acid (compound 406h)

To a solution of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[3-[7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1H-benzimidazol-4-yl]phenoxy]pyrrolidine-1,2-dicarboxylate (compound **406g**, 250 mg, 0.5 mmol) in methanol (5 mL) and water (1 mL) was added lithium hydroxide hydrate (110 mg, 4.6 mmol), then the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was acidified with 1 M HCl to pH = 6, then purified by reversed flash column to give compound **406h** (0.2 g). LCMS $(M+H)^+$: 529.

Step 9: preparation of *tert*-butyl (8*S*,11*S*)-21-fluoro-13-methyl-12,18-dioxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,20,22-hexaene-10-carboxylate (compound 406i)

To a solution of PyBOP (236 mg, 0.45 mmol), DIEA (97 mg, 0.8 mmol) in DMF (150 mL) was added a solution of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[3-[7-fluoro-3-[3-(methylamino)propyl]-2-oxo-1H-benzimidazol-4-yl]phenoxy]pyrrolidine-2-carboxylic acid (compound **406h**, 0.2 g, 0.4 mmol) in *N*,*N*-dimethylformamide (150 mL). The resulting mixture was stirred at 0 °C for 1 h, then the reaction mixture was concentrated in *vacuo* to get a crude product, which was purified by reversed flash to give compound **406i** (150 mg, 0.3 mmol). LCMS $(M+H)^+$: 511.

Step 10: preparation of (8*S*,11*S*)-21-fluoro-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,20,22-hexaene-12,18-dione;2,2,2-trifluoroacetic acid (compound 406j)

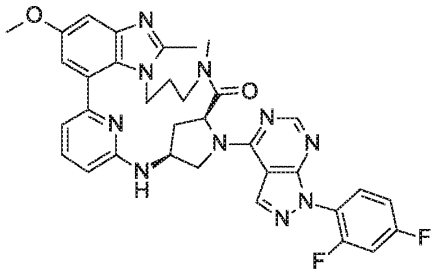
A solution of *tert*-butyl (8*S*,11*S*)-21-fluoro-13-methyl-12,18-dioxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,20,22-hexaene-10-carboxylate (compound **406i**, 150 mg, 0.3 mmol) in TFA (5.0 mL) was stirred at room temperature for 1 h. Then the reaction mixture was concentrated in *vacuo* to give compound **406j** (0.1 g). LCMS (M+H)$^+$: 411.

Step 11: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-18-hydroxy-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 406)

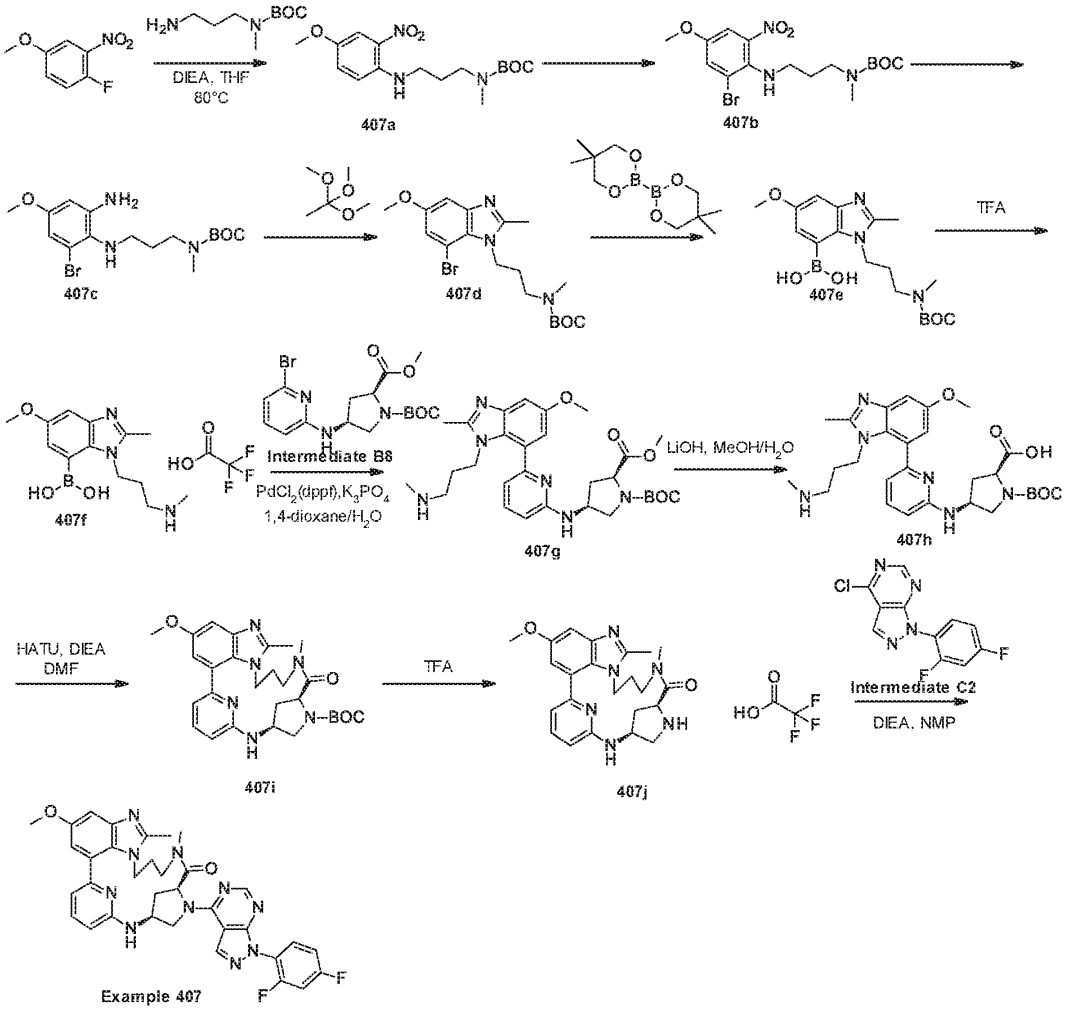
To a solution of (8*S*,11*S*)-21-fluoro-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,20,22-hexaene-12,18-dione;2,2,2-trifluoroacetic acid (compound **406j**, 62 mg, 0.15 mmol) and Intermediate **C2** (40 mg, 0.15 mmol) in NMP (3 mL) was added *N*,*N*-diisopropylethylamine (0.5 mL), and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was directly purified by prep-HPLC to give Example **406** (11 mg). LCMS (M+H)$^+$: 641. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.21 (s, 1H), 7.70 - 7.59 (m, 1H), 7.48 (m, 1H), 7.30 - 7.25 (m, 1H), 7.23 - 7.18 (m, 2H), 7.00 - 6.96 (m, 1H), 6.89 - 6.85 (m, 2H), 6.82 - 6.77 (m, 1H), 5.59 (m, 1H), 5.51 - 5.43 (m, 1H), 4.60 (s, 1H), 4.52 - 4.31 (m, 2H), 4.11 - 4.04 (m, 1H), 3.72 - 3.64 (m, 1H), 3.08 (s, 1H), 2.98 (s, 3H), 2.79 - 2.66 (m, 2H), 2.39 - 2.29 (m, 1H), 1.58 - 1.49 (m, 1H).

Example 407

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(4-methoxy-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 407a)

A mixture of 1-fluoro-4-methoxy-2-nitro-benzene (7.0 g, 40.9 mmol), *tert*-butyl *N*-(3-amino-2-methyl-propyl)carbamate (8.0 g, 42.5 mmol) and *N,N*-diisopropylethylamine (6.0 g, 46.4 mmol) in anhydrous THF (150 mL) was stirred at 80 °C for 12 h. The reaction mixture was diluted with EtOAc (100 mL), washed with water and brine, the separated organic layer was dried over and concentrated to give the crude product, which was purified by flash chromatography to afford compound **407a** (12 g). LCMS ($M+H^+$): 340.

Step 2: preparation of *tert*-butyl *N*-[3-(2-bromo-4-methoxy-6-nitro-anilino)propyl]-*N*-methyl-carbamate (compound 407b)

To a mixture of *tert*-butyl *N*-[3-(4-methoxy-2-nitro-anilino)propyl]-*N*-methyl-carbamate (compound **407-a**, 5.0 g, 14.7 mmol) and *N*-bromosuccinimide (6.6 g, 36.8 mmol) in anhydrous THF (100 mL) was added *p*-toluenesulfonic acid monohydrate (0.4 g, 0.3 mmol), the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in *vacuo* to get a crude product, which was purified by column chromatography to give compound **407b** (1.0 g). LCMS ($M+H^+$): 418.

Step 3: preparation of *tert*-butyl *N*-[3-(2-amino-6-bromo-4-methoxy-anilino)propyl]-*N*-methyl-carbamate (compound 407c)

To a solution of *tert*-butyl *N*-[3-(2-bromo-4-methoxy-6-nitro-anilino)propyl]-*N*-methyl-carbamate (compound **407b**, 1.0 g, 2.4 mmol) and Raney Ni (1.0 g) in methanol (50 mL) was added hydrazine hydrate (1.0 g) dropwise. The reaction mixture was stirred at room temperature for 1 h, then the reaction mixture was filtered and filtrate was concentrated. The residue was dissolved in EtOAc and then washed with brine, The organic layer was dried and concentrated to give compound **407c** (0.8 g). LCMS ($M+H^+$): 388.

Step 4: preparation of *tert*-butyl *N*-[3-(7-bromo-5-methoxy-2-methyl-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 407d)

To a solution of *tert*-butyl *N*-[3-(2-amino-6-bromo-4-methoxy-anilino)propyl]-*N*-methyl-carbamate (compound **407c**, 0.8 g, 2.1 mmol), trimethyl orthoacetate (371 mg, 3.1 mmol) in THF (10 mL) was added pyridinium p-toluenesulfonate (0.2 g). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in *vacuo* to get a crude product, which was purified by column chromatography to give compound **407-d** (0.8 g). LCMS ($M+H^+$): 412.

Step 5: preparation of [3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-6-methoxy-2-methyl-benzimidazol-4-yl]boronic acid (compound 407e)

To a solution of *tert*-butyl *N*-[3-(7-bromo-5-methoxy-2-methyl-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound **407d**, 0.8 g, 1.33 mmol), bis(neopentyl glycolato)diboron (0.6 g, 2.7 mmol), XPhos (150 mg, 0.3 mmol) and sodium acetate (1.5 g, 4.0 mmol) in 1,4-dioxane (20 mL) was added $Pd_2(dba)_3$ (150 mg, 0.4 mmol), the resulting mixture was stirred at 100 °C for 12 h under argon. Then the reaction mixture was diluted with water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4. After filtration, the solvent

was removed in *vacuo* to get a crude product, which was purified by column chromatography to give compound **407e** (0.3 g). LCMS ($M+H^+$): 378.

Step 6: preparation of [6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]boronic acid;2,2,2-trifluoroacetic acid (compound 407f)

A solution of [3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-6-methoxy-2-methyl-benzimidazol-4-yl]boronic acid (compound **407e**, 0.2 g, 0.5 mmol) in TFA (5 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated to give compound **407f** (140 mg). LCMS ($M+H^+$): 278.

Step 7: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 407-g)

To a solution of [6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]boronic acid;2,2,2-trifluoroacetic acid (compound **407f**, 0.1 g, 0.4 mmol), Intermediate **B8** (0.2 g, 0.5 mmol), potassium phosphate (153 mg, 0.72 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was added $Pd(dppf)Cl_2$ (40 mg, 0.4 mmol), the reaction mixture was stirred at 100 °C for 12 h under argon. The reaction mixture was filtered and the filtrate was purified by reversed flash to give compound **407g** (80 mg). LCMS ($M+H^+$): 553.

Step 8: preparation of (2*S*,4*S*)-1-tert-butoxycarbonyl-4-[[6-[6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 407h)

To a solution of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound **407g**, 80 mg, 0.14 mmol) in methanol (2 mL) and water (0.5 mL) was added lithium hydroxide hydrate (61 mg, 1.5 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate was purified by reversed flash to give compound **407-h** (30 mg). LCMS ($M+H^+$): 539.

Step 9: preparation of *tert*-butyl (8*S*,11*S*)-22-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 407i)

To a solution of HATU (20 mg, 0.08 mmol) and *N*,*N*-diisopropylethylamine (14 mg, 0.11 mmol) in *N*,*N*-dimethylformamide (15 mL) was added a solution of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[6-[6-methoxy-2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound **407h**, 30 mg, 0.06 mmol) in *N*,*N*-

dimethylformamide (15 mL) dropwise and then the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated and the residue was purified by reversed flash to give compound **407-i** (15 mg). LCMS ($M+H^+$): 521.

Step 10: preparation of (8*S*,11*S*)-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound 407j)

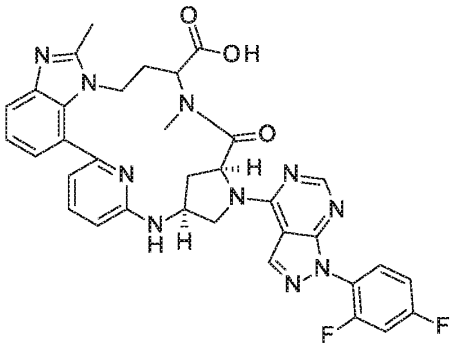
A solution of *tert*-butyl (8*S*,11*S*)-22-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound **407i**, 15 mg, 0.03 mmol) in TFA (1 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated to give compound **407j** (5.0 mg). LCMS ($M+H^+$): 421.

Step 11: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 407)

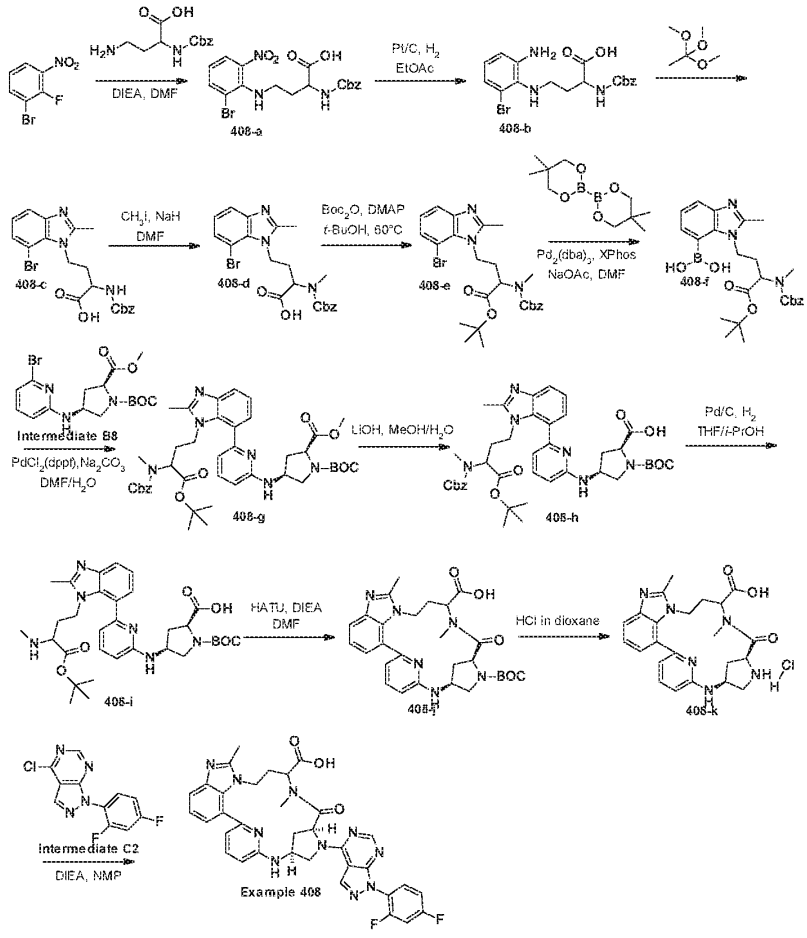
To a solution of (8*S*,11*S*)-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **407j**, 5.0 mg, 0.01 mmol) and Intermediate **C2** (3.0 mg, 0.01 mmol) in NMP (0.5 mL) was added *N*,*N*-diisopropylethylamine (0.1 mL, 0.02 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered, the filtrate was purified by reversed flash to give Example **407** (1.4 mg). LCMS ($M+H^+$): 651. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (s, 1H), 8.51 (br s, 1H), 7.81 - 7.76 (m, 1H), 7.70 - 7.60 (m, 1H), 7.32 - 7.26 (m, 1H), 7.24 - 7.17 (m, 1H), 7.12 (m,1H), 6.92 - 6.87 (m, 1H), 6.85 - 6.81 (m, 1H), 6.77 - 6.72 (m, 1H), 5.54 - 5.42 (m, 1H), 4.75 (s, 1H), 4.31 - 4.21 (m, 1H), 4.06 (m, 1H), 3.84 (s, 3H), 3.66 - 3.61 (m, 1H), 3.59 - 3.49 (m, 1H), 3.14 (s, 1H), 3.05 (s, 2H), 3.01 - 2.84 (m, 2H), 2.73 - 2.58 (m, 2H), 2.58 - 2.55 (m, 3H), 2.24 - 2.06 (m, 1H), 1.43 (m, 1H).

Example 408

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid



The title compounds were prepared according to the following scheme:



Step 1: preparation of 2-(benzyloxycarbonylamino)-4-(2-bromo-6-nitro-anilino)butanoic acid (compound 408-a)

A mixture of 1-bromo-2-fluoro-3-nitro-benzene (8.0 g, 36.4 mmol), 4-amino-2-(benzyloxycarbonylamino)butanoic acid (9.6 g, 38.0 mmol) and *N*,*N*-diisopropylethylamine (8.0 g, 61.9 mmol) in anhydrous THF (100 mL) was stirred at room temperature for 12 h. The

mixture was concentrated to give the crude product, which was purified by prep-HPLC to give compound **408-a** (12 g). LCMS ($M+H^+$): 454.

Step 2: preparation of 4-(2-amino-6-bromo-anilino)-2-(benzyloxycarbonylamino)butanoic acid (compound 408-b)

A mixture of 2-(benzyloxycarbonylamino)-4-(2-bromo-6-nitro-anilino)butanoic acid (compound **408-a**, 1.0 g, 2.21 mmol) and Pt/C (200 mg) in anhydrous EtOAc (10 mL) was stirred at room temperature for 4 h under hydrogen. The mixture was filtered and the filtrate was concentrated to give compound **408-b** (675 mg). LCMS ($M+H^+$): 422.

Step 3: preparation of 2-(benzyloxycarbonylamino)-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoic acid (compound 408-c)

A mixture of 4-(2-amino-6-bromo-anilino)-2-(benzyloxycarbonylamino)butanoic acid (compound **408-b**, 9.0 g, 21.3 mmol), trimethyl orthoacetate (6.0 g, 49.9 mmol) and pyridinium p-toluenesulfonate (0.4 g, 1.59 mmol) in anhydrous THF (100 mL) was stirred at room temperature for 12 h. The mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried and concentrated to give compound **408-c** (8.0 g). LCMS ($M+H^+$): 446.

Step 4: preparation of 2-[benzyloxycarbonyl(methyl)amino]-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoic acid (compound 408-d)

To a solution of 2-(benzyloxycarbonylamino)-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoic acid (compound **408-c**, 1.0 g, 2.2 mmol) and iodomethane (1.0 g, 7.0 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) was added NaH (300 mg, 7.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 11 h. The mixture was poured into water, then adjusted to pH=3 with 1 M HCl, and extracted with EtOAc. The organic layer was dried and concentrated to give the crude product, which was purified by prep-HPLC to give compound **408-d** (0.9 g). LCMS ($M+H^+$): 462.

Step 5: preparation of *tert*-butyl 2-[benzyloxycarbonyl(methyl)amino]-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoate (compound 408-e)

A solution of 2-[benzyloxycarbonyl(methyl)amino]-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoic acid (compound **408-d**, 4.0 g, 8.7 mmol), Boc_2O (2.3 g, 10.4 mmol), DMAP (318 mg, 2.6 mmol) in *tert*-butanol (50 mL) was stirred at 60 °C for 2 h. The reaction mixture was poured into water, then the resulting mixture was filtered, the filter cake was collected and dried to give compound **408-e** (4.0 g). LCMS ($M+H^+$): 516.

Step 6: preparation of [3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]boronic acid (compound 408-f)

A solution of *tert*-butyl 2-[benzyloxycarbonyl(methyl)amino]-4-(7-bromo-2-methyl-benzimidazol-1-yl)butanoate (compound **408-e**, 4.0 g, 7.8 mmol), bis(neopentyl glycolato)diboron (2.2 g, 9.3 mmol), $Pd_2(dba)_3$ (1.2 g, 0.04 mmol), X-phos (1.2 g, 2.5 mmol) and sodium acetate (1.3 g, 15.5 mmol) in *N*,*N*-dimethylformamide (90 mL) was stirred at 100 °C for 12 h. The reaction mixture was poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried and concentrated to get a crude product, which was purified by prep-HPLC to give compound **408-f** (2.2 g). LCMS ($M+H^+$): 482.

Step 7: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 408-g)

To a solution of Intermediate **B8** (2.2 g, 5.5 mmol), $Pd(dppf)Cl_2$ (600 mg, 0.04 mmol) and sodium carbonate (969 mg, 9.1 mmol) in *N*,*N*-dimethylformamide (80 mL) and water (1.5 mL) were added [3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]boronic acid (compound **408-f**, 2.2 g, 4.6 mmol), and the reaction mixture was stirred at 80 °C for 12 h under nitrogen. After cooling to room temperature, the reaction mixture was poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried and then concentrated to get a crude product, which was purified by column chromatography to give compound **408-g** (2.8 g, 3.7 mmol). LCMS ($M+H^+$): 757.

Step 8: preparation of (2*S*,4*S*)-4-[[6-[3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]-1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylic acid (compound 408-h)

To a solution of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound **408-g**, 2.8 g, 3.7 mmol) in methanol (20 mL) and water (1 mL) were added lithium hydroxide hydrate (310 mg, 7.4 mmol), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was adjusted with saturated aq.NH_4Cl to pH=6, then the mixture was poured into water (0.1 L), and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to get a crude product, which was purified by reversed flash to give compound **408-h** (600 mg). LCMS ($M+H^+$): 743.

Step 9: preparation of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[6-[3-[4-*tert*-butoxy-3-(methylamino)-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 408-i)

A suspension of (2*S*,4*S*)-4-[[6-[3-[3-[benzyloxycarbonyl(methyl)amino]-4-*tert*-butoxy-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]-1-tert-butoxycarbonyl-pyrrolidine-2-carboxylic acid (compound **408-h**, 600 mg, 0.81 mmol) and Pd/C (100 mg) in THF (3 mL) and *i*-PrOH (3 mL) was stirred at 50 °C for 1 h under hydrogen. The reaction mixture was filtered and the filtrate was concentrated to get a crude product, which was purified by prep-HPLC to afford compound **408-i** (260 mg). LCMS ($M+H^+$): 609.

Step 10: preparation of (8*S*,11*S*)-10-*tert*-butoxycarbonyl-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid (compound 408-j)

To a solution of HATU (145 mg, 0.62 mmol) in DMF (100 mL) was added *N*,*N*-diisopropylethylamine (159 mg, 1.2 mmol) at 0 °C. And then (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[[6-[3-[4-*tert*-butoxy-3-(methylamino)-4-oxo-butyl]-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound **408-i**, 250 mg, 0.4 mmol) in *N*,*N*-dimethylformamide (100 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then concentrated to get a crude product, which was purified by reversed flash to give compound **408-j** (150 mg). LCMS ($M+H^+$): 591.

Step 11: preparation of (8*S*,11*S*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid;hydrochloride (compound 408-k)

A solution of (8*S*,11*S*)-10-*tert*-butoxycarbonyl-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid (compound **408-j**, 150 mg, 0.25 mmol) in TFA (1.0 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated to get a crude product, which was purified by reversed flash column to give compound **408-k** (100 mg). LCMS ($M+H^+$): 435.

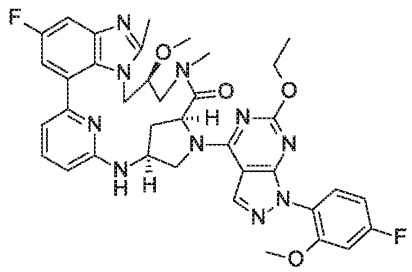
Step 12: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid (Example 408)

A solution of (8*S*,11*S*)-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid;hydrochloride (compound **408-k**, 36 mg, 0.08 mmol), Intermediate **C2** (20 mg, 0.08 mmol) and *N*,*N*-diisopropylethylamine (97 mg, 0.8 mmol) in NMP (1 mL) was stirred at 80 °C for 2 h. The reaction mixture was directly purified by prep-HPLC to give Example **408** (3.5

mg). LCMS (M+H$^+$): 665. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.40 - 8.26 (m, 2H), 8.22 - 8.12 (m, 1H), 7.94 (m, 1H), 7.68 (m, 1H), 7.64 - 7.58 (m, 1H), 7.50 - 7.40 (m, 1H), 7.37 - 7.31 (m, 1H), 7.30 - 7.23 (m, 2H), 7.21 - 7.14 (m, 1H), 5.81 - 5.58 (m, 1H), 4.61 - 4.48 (m, 2H), 4.45 - 4.33 (m, 1H), 4.23 (m, 1H), 3.98 - 3.83 (m, 1H), 3.04 - 2.76 (m, 1H), 2.72 - 2.61 (m, 4H), 2.40 - 2.28 (m, 3H), 2.27 - 2.02 (m, 1H), 1.73 - 1.50 (m, 2H).

Example 409

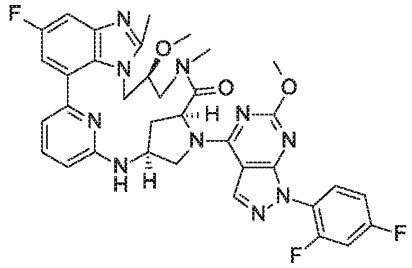
(8*S*,11*S*,15*R*)-10-[6-ethoxy-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



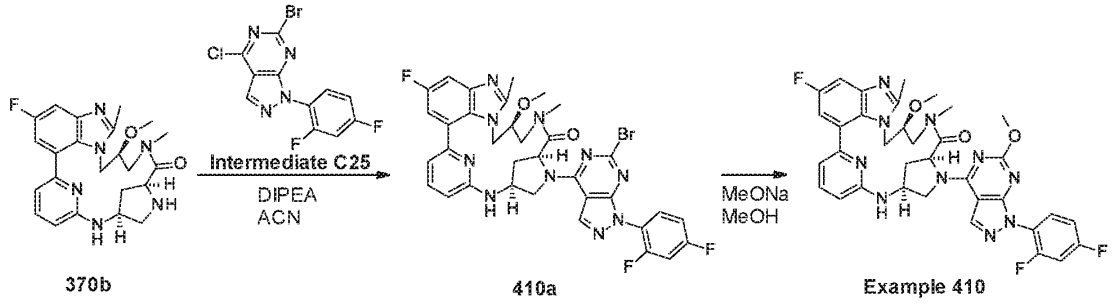
The title compound was prepared in analogy to the preparation of Example **410** by using intermediate **C26** instead of intermediate **C25** in step 1 and using 3M NaOEt solution in EtOH instead of 5 M NaOMe solution in MeOH in step 2. LCMS (M+H$^+$): 725, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.32 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.40 (dd, *J* = 6.1, 8.5 Hz, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.16 (dd, *J* = 2.5, 10.5 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.02 (dd, *J* = 2.6, 10.7 Hz, 1H), 6.83 (dt, *J* = 2.6, 8.3 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.79 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.67 - 4.56 (m, 1H), 4.50 - 4.39 (m, 2H), 4.34 - 4.11 (m, 4H), 3.92 (dd, *J* = 9.2, 14.1 Hz, 1H), 3.77 (s, 3H), 3.03 (s, 3H), 2.90 - 2.85 (m, 1H), 2.84 (s, 3H), 2.57 (s, 3H), 2.49 (tt, *J* = 4.4, 9.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

Example 410

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 410a)

To a flask was added (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **370b**, 96.14 mg, 0.174 mmol), 6-bromo-4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (Intermediate **C25**, 81.4 mg, 0.209 mmol), DIEA (151.5 mg, 204 μL, 1.17 mmol) and ethanol (3 mL). The mixture was stirred at 40 °C for about 4 hrs. The mixture was concentrated and the residue was purified by prep-HPLC to give compound **410a** (130 mg). LCMS (M+H$^+$): 747.

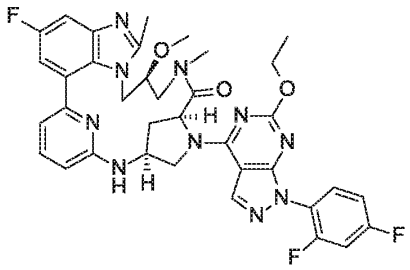
Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 410)

To a microwave tube was added (8*S*,11*S*,15*R*)-10-[6-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-

heptaen-12-one (compound **410a**, 65 mg, 0.075 mmol), 5 M NaOMe solution in MeOH (105.62 µL, 0.528 mmol) and MeOH (1 mL). The solution was stirred at 60 °C for 24 hrs. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **410** (30 mg). LCMS ($M+H^+$): 699, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.39 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.33 (dd, J = 2.6, 8.4 Hz, 1H), 7.25 (ddd, J = 2.7, 8.8, 10.2 Hz, 1H), 7.20 (dd, J = 2.4, 10.4 Hz, 1H), 7.19 - 7.14 (m, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.82 (dd, J = 4.3, 15.5 Hz, 1H), 5.42 (d, J = 8.9 Hz, 1H), 4.67 - 4.61 (m, 1H), 4.47 (dd, J = 6.0, 11.3 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.17 (dd, J = 10.8, 15.4 Hz, 1H), 4.00 - 3.92 (m, 2H), 3.84 (s, 3H), 3.03 (s, 3H), 2.91 - 2.86 (m, 1H), 2.85 (s, 3H), 2.60 (s, 3H), 2.53 - 2.46 (m, 2H).

Example 411

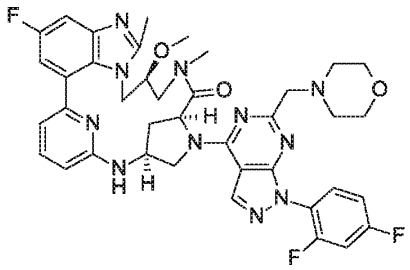
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



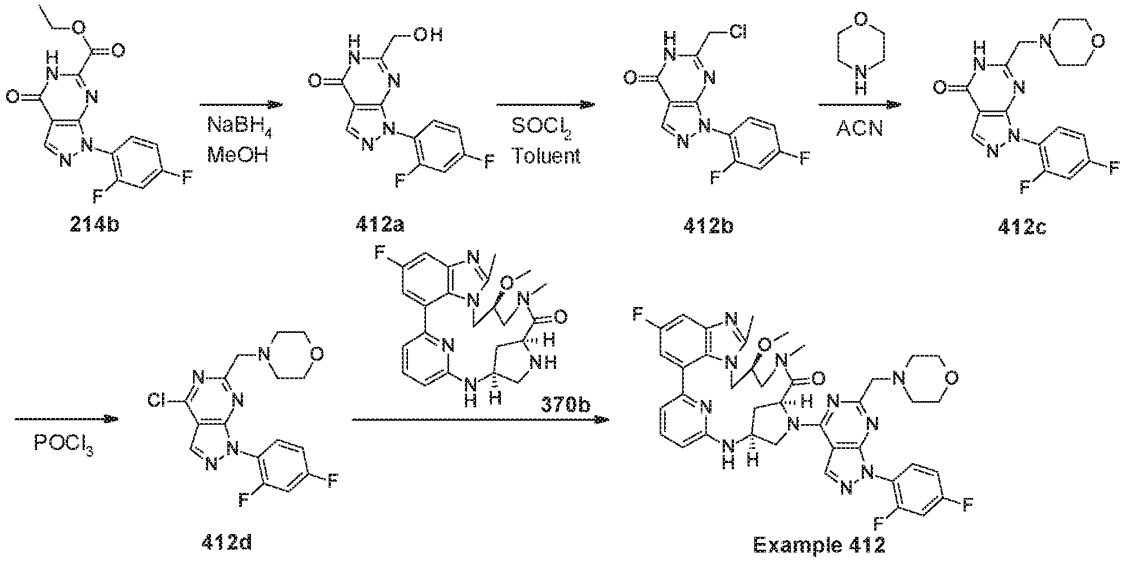
The title compound was prepared in analogy to the preparation of Example **410** by using 3M NaOEt in solution EtOH instead of 5 M NaOMe solution in MeOH. LCMS ($M+H^+$): 713, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.38 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.32 (dd, J = 2.6, 8.4 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.21 - 7.18 (m, 1H), 7.18 - 7.13 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.81 (dd, J = 4.3, 15.5 Hz, 1H), 5.42 (d, J = 9.0 Hz, 1H), 4.66 - 4.62 (m, 1H), 4.50 - 4.40 (m, 2H), 4.35 - 4.11 (m, 4H), 3.92 (dd, J = 9.2, 14.2 Hz, 1H), 3.03 (s, 3H), 2.91 - 2.86 (m, 1H), 2.85 (s, 3H), 2.59 (s, 3H), 2.53 - 2.44 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

Example 412

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(morpholinomethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-(2,4-difluorophenyl)-6-(hydroxymethyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound 412a)

$NaBH_4$ (56.7 mg, 1.5 mmol) was added to a solution of ethyl 1-(2,4-difluorophenyl)-4-oxo-5*H*-pyrazolo[3,4-d]pyrimidine-6-carboxylate (compound **214b**, 160 mg, 0.500 mmol) in methanol (5 mL) at room temperature. The reaction mixture was stirred at r.t. for 1 h and then heated to 70 °C for 6 hrs. The mixture was concentrated and the residue was purified by reversed-phase HPLC to give compound **412a** (50 mg). LCMS ($M+H^+$): 279.

Step 2: preparation of 6-(chloromethyl)-1-(2,4-difluorophenyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound 412b)

To a tube was added 1-(2,4-difluorophenyl)-6-(hydroxymethyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound **412a**, 47 mg, 0.169 mmol), toluene (2 mL) and $SOCl_2$ (80.4 mg, 49 µL, 0.676 mmol). The suspension was heated to 100 °C and stirred for 2 hrs. The mixture was diluted with EA and then the organic layer was washed with water, then concentrated to give compound **412b** (52 mg). LCMS ($M+H^+$): 297.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-(morpholinomethyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound 412c)

To a tube was added 6-(chloromethyl)-1-(2,4-difluorophenyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound **412b**, 52 mg, 0.175 mmol), morpholine (45.8 mg, 46 µL, 0.526 mmol) and acetonitrile (1 mL). The solution was heated to 70 °C and stirred for 2 hrs. The mixture was concentrated to give compound **412c** (60 mg). LCMS ($M+H^+$): 348.

Step 4: preparation of 4-[[4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methyl]morpholine (compound 412d)

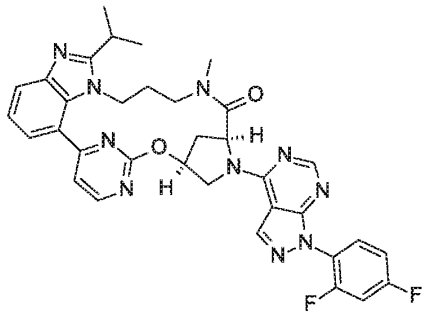
A solution of 1-(2,4-difluorophenyl)-6-(morpholinomethyl)-5*H*-pyrazolo[3,4-d]pyrimidin-4-one (compound **412c**, 60 mg, 0.173 mmol) in phosphorus oxychloride (830.5 mg, 505 µL, 5.42 mmol) was stirred at 90 °C for 16 hrs. The mixture was concentrated directly to give an oil, which was purified by prep-HPLC to give compound **412d** (50 mg). LCMS ($M+H^+$): 366.

Step 5: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(morpholinomethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 412)

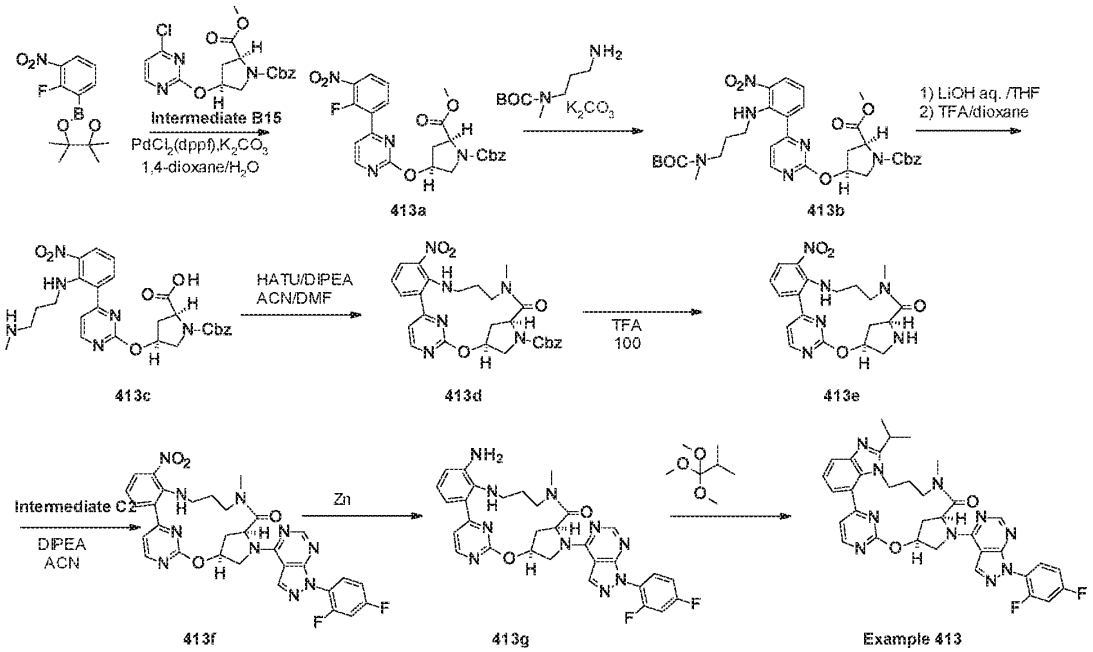
To a flask was added (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **370b**, 70 mg, 0.105 mmol), 4-[[4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methyl]morpholine;2,2,2-trifluoroacetic acid (compound **412d**, 50.4 mg, 0.105 mmol), DIEA (121 mg, 163 µL, 0.935 mmol) and acetonitrile (2 mL). The mixture was heated to 85 °C and stirred for about 1 hr, then concentrated to give an oil, which was purified prep-HPLC to give Example **412** (59.7 mg). LCMS ($M+H^+$): 768, ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.69 - 7.61 (m, 1H), 7.32 - 7.26 (m, 2H), 7.22 - 7.14 (m, 2H), 7.12 - 7.08 (m, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.74 (dd, *J* = 4.3, 15.6 Hz, 1H), 5.62 (d, *J* = 8.9 Hz, 1H), 4.70 - 4.64 (m, 1H), 4.54 - 4.45 (m, 1H), 4.36 - 4.27 (m, 1H), 4.11 (dd, *J* = 10.9, 15.5 Hz, 1H), 4.05 - 3.94 (m, 1H), 3.94 - 3.84 (m, 2H), 3.84 - 3.69 (m, 5H), 3.14 - 3.08 (m, 1H), 3.05 (s, 3H), 2.95 - 2.84 (m, 4H), 2.83 (s, 3H), 2.56 (s, 3H), 2.53 - 2.44 (m, 2H).

Example 413

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-isopropyl-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *O*1-benzyl *O*2-methyl (2*S*,4S)-4-[4-(2-fluoro-3-nitro-phenyl)pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 413a)

A mixture of K_2CO_3 (3.17 g, 22.97 mmol), 2-(2-fluoro-3-nitro-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.04 g, 7.66 mmol), intermediate **B15** (3 g, 7.66 mmol) and $PdCl_2(dppf)$ (280 mg, 0.38 mmol) in 1,4-dioxane (50 mL) and water (5 mL) was heated to 100 °C for 12 hours under N_2. The reaction mixture was diluted with water and extracted two times with EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel to give compound **413a** (2.94 g). LCMS ($M+H^+$): 497.

Step 2: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[4-[2-[3-[*tert*-butoxycarbonyl(methyl)amino]propylamino]-3-nitro-phenyl]pyrimidin-2-yl]oxypyrrolidine-1,2-dicarboxylate (compound 413b)

Compound **413a** (2.94 g, 5.03 mmol) and K_2CO_3 (2.09 g, 15.1 mmol) were dissolved in acetonitrile (20 mL) and *N*-(3-aminopropyl)-*N*-methyl-carbamic acid *tert*-butyl ester (0.94 g, 5.03 mmol) was added at rt. The mixture was stirred at 25 °C for 12hours. The reaction mixture was diluted with water and extracted two times with EtOAc. The organic layer was washed with brine, dried and concentrated. The crude material was purified by silica gel to give compound **413b** (2.8 g). LCMS ($M+H^+$): 665.

Step 3-6: preparation of (14*S*,17*S*)-15-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-methyl-6-nitro-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.1^{14,17}.0^{2,7}]tetracosa-1(23),2,4,6,19,21-hexaen-13-one (compound 413f)

Compound **413f** was prepared in analogy to the preparation of Example **12** by using compound **413b** instead of compound **12a**. LCMS ($M+H^+$): 629.

Step 7: preparation of (14*S*,17*S*)-6-amino-15-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-methyl-18-oxa-8,12,15,20,23-pentazatetracyclo[17.3.1.1^{14,17}.0^{2,7}]tetracosa-1(23),2,4,6,19,21-hexaen-13-one (compound 413g)

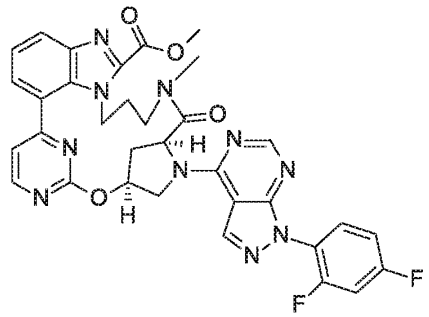
A mixture of compound **413f** (1.0 g, 1.59 mmol), zinc (1.0 g, 15.91 mmol) and NH_4Cl (170.19 mg, 3.18 mmol) in ethanol (10 mL) and water (1 mL) was stirred at 25 °C for 12 hours. The reaction mixture was filtered and the filtrate was concentrated to give compound **413g**(500 mg). LCMS ($M+H^+$): 599.

Step 8: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-isopropyl-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 413)

Compound **413g** (50.0 mg, 0.084 mmol) and 1,1,1-trimethoxy-2-methyl-propane (123.0 mg, 0.835 mmol) were dissolved in methanol (1 mL), and then 1-mesyl-4-methyl-benzene (1 mg, 0.004 mmol) was added at rt. The mixture was stirred for 12 hours at 25 °C and then purified by prep-HPLC to give Example **413**(7.6 mg). LCMS ($M+H^+$): 651. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.86 - 8.81 (m, 1H), 8.61 - 8.06 (m, 2H), 7.92 - 7.86 (m, 1H), 7.75 - 7.70 (m, 2H), 7.58 (d, *J* = 5.3 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.26 - 7.22 (m, 2H), 5.97 - 5.41 (m, 3H), 4.59 - 4.33 (m, 2H), 4.33 - 4.21 (m, 1H), 4.19 - 4.09 (m, 1H), 3.60 - 3.51 (m, 1H), 3.11 - 2.99 (m, 3H), 2.98 - 2.85 (m, 2H), 2.83 - 2.75 (m, 1H), 2.21 (s, 1H), 1.91 - 1.78 (m, 1H), 1.54 - 1.48 (m, 6H).

Example 414

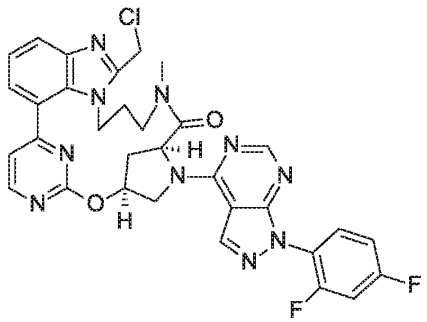
Methyl (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxylate



The title compound was prepared in analogy to the preparation of Example **413** by using the reaction condition with 2,2,2-trimethoxyacetic acid methyl ester instead of 1,1,1-trimethoxy-2-methyl-propane. Example **414**. LCMS (M+H$^+$): 667. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.86 - 8.82 (m, 1H), 8.75 - 8.04 (m, 2H), 8.00 - 7.95 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.63 - 7.57 (m, 1H), 7.38 - 7.32 (m, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.07 - 5.34 (m, 3H), 4.69 - 4.59 (m, 2H), 4.28 - 4.16 (m, 1H), 4.08 - 4.02 (m, 2H), 3.13 - 2.99 (m, 3H), 2.99 - 2.93 (m, 1H), 2.91 - 2.86 (m, 1H), 2.38 - 2.35 (m, 3H), 2.08 - 1.99 (m, 1H), 1.65 - 1.48 (m, 1H).

Example 415

(8*S*,11*S*)-18-(chloromethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

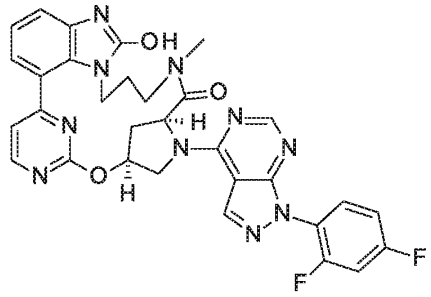


The title compound was prepared in analogy to the preparation of Example **413** by using the reaction condition with 2-chloro-1,1,1-trimethoxy-ethane instead of 1,1,1-trimethoxy-2-methyl-propane. LCMS (M+H$^+$): 658. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.83 - 8.76 (m, 1H), 8.62 - 7.89 (m, 2H), 7.87 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.72 - 7.68 (m, 2H), 7.61 - 7.56 (m, 1H),

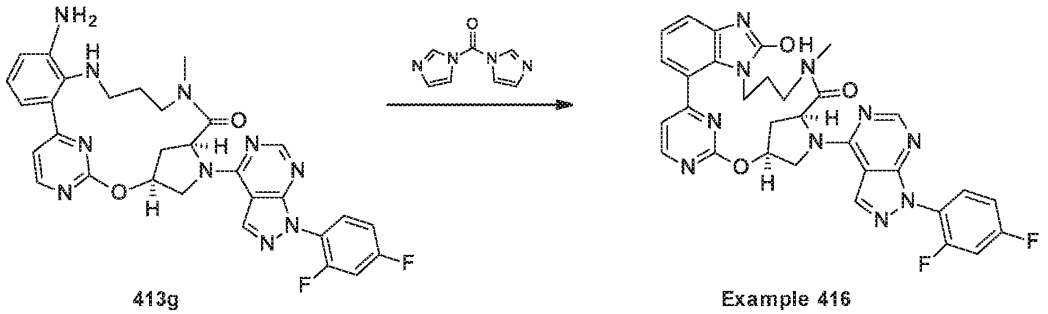
7.51 (t, *J* = 7.9 Hz, 1H), 7.33 - 7.27 (m, 1H), 7.22 (br d, *J* = 8.1 Hz, 1H), 5.94 - 5.76 (m, 1H), 5.73 - 5.63 (m, 1H), 5.60 - 5.33 (m, 1H), 5.13 - 5.02 (m, 2H), 4.61 - 4.09 (m, 4H), 3.09 - 2.97 (m, 3H), 2.92 - 2.74 (m, 2H), 2.36 (s, 1H), 2.24 - 1.99 (m, 1H), 1.91 - 1.75 (m, 1H).

Example 416

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-hydroxy-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



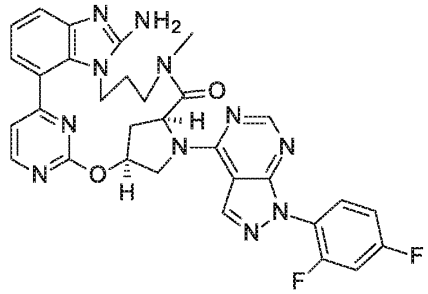
413g Example 416

Compound **413g** (80 mg, 0.134 mmol) and CDI (32.51 mg, 0.200 mmol) were dissolved in tetrahydrofuran (2 mL) and DIEA (34.54 mg, 0.267 mmol) was added at rt. The mixture was stirred for 12 hours at 25 °C. The reaction mixture was added MeOH and purified by prep-HPLC to give Example **416**(5.3 mg). LCMS (M+H$^+$): 625. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.71 - 8.65 (m, 1H), 8.57 - 8.24 (m, 2H), 8.23 - 8.17 (m, 1H), 7.70 - 7.62 (m, 1H), 7.43 - 7.34 (m, 1H), 7.32 - 7.25 (m, 2H), 7.25 - 7.15 (m, 3H), 6.19 - 5.94 (m, 1H), 5.63 - 5.52 (m, 1H), 5.40 - 5.32 (m, 1H), 4.59 - 4.55 (m, 1H), 4.53 - 4.40 (m, 1H), 3.12 - 2.98 (m, 3H), 2.42 - 2.36 (m, 1H), 2.21 - 2.18 (m, 1H), 2.17 - 2.08 (m, 1H), 2.07 - 2.01 (m, 2H), 1.76 - 1.64 (m, 1H), 1.62 - 1.57 (m, 1H).

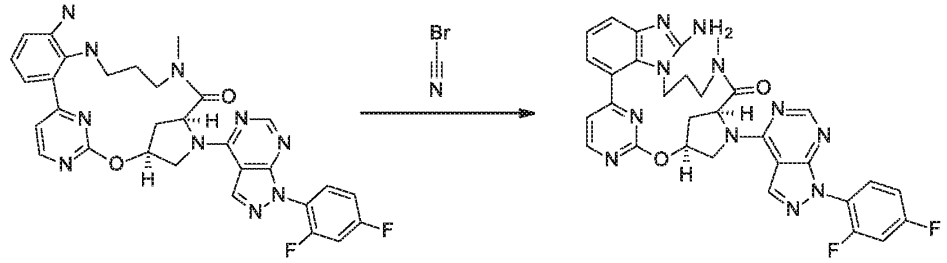
Example 417

(8*S*,11*S*)-18-amino-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-

oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

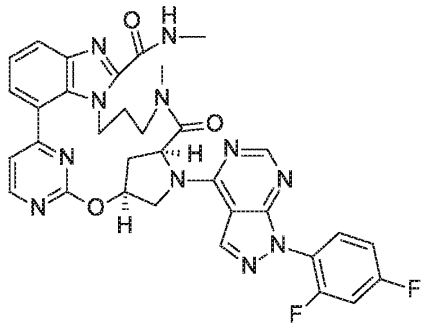


413g Example 417

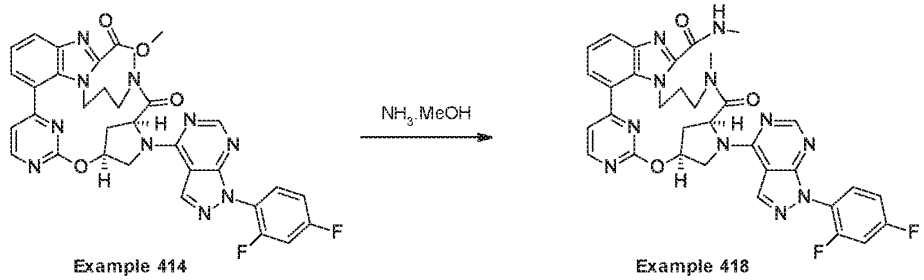
Compound **413g** (50 mg, 0.084 mmol) and cyanogen bromide (11.5 mg, 0.109 mmol) were dissolved in acetonitrile (5 mL) and water(5 mL). The mixture was stirred for 12 hours at 25 °C. The reaction mixture was added MeOH and purified by prep-HPLC to give Example **417**(4.4 mg). LCMS (M+H$^+$): 624. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.76 - 8.72 (m, 1H), 8.58 - 7.85 (m, 2H), 7.74 - 7.62 (m, 1H), 7.46 - 7.38 (m, 2H), 7.35 - 7.28 (m, 1H), 7.25 - 7.17 (m, 3H), 6.00 - 5.82 (m, 1H), 5.62 - 5.47 (m, 1H), 5.39 - 5.32 (m, 1H), 5.20 - 5.10 (m, 1H), 4.86 - 4.84 (m, 2H), 4.56 (s, 1H), 4.27 - 4.17 (m, 1H), 3.90 - 3.81 (m, 1H), 3.12 - 2.99 (m, 3H), 2.84 - 2.73 (m, 2H), 2.05 (br d, J = 5.3 Hz, 1H), 1.99 - 1.88 (m, 1H), 1.70 - 1.55 (m, 1H).

Example 418

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-N,13-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxamide



The title compound was prepared according to the following scheme:

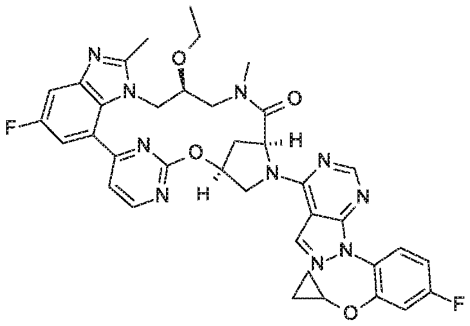


Example 414 Example 418

Example **414** (60 mg, 0.090 mmol) was dissolved in methanol (1 mL) and then methylamine/MeOH (28 mg, 0.90 mmol) was added at rt. The mixture was stirred at 80 °C for 12 hours, then the reaction mixture was purified by prep-HPLC to give Example **418** (4.9 mg). LCMS ($M+H^+$): 666. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.87 - 8.80 (m, 1H), 8.66 - 7.90 (m, 2H), 7.89 (d, J = 2.0 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.63 - 7.57 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 - 7.41 (m, 1H), 7.36 - 7.30 (m, 1H), 7.22 - 7.15 (m, 1H), 5.94 - 5.46 (m, 2H), 5.38 - 5.26 (m, 2H), 4.55 - 4.44 (m, 1H), 4.33 - 4.12 (m, 1H), 3.99 - 3.90 (m, 1H), 3.01 - 2.87 (m, 3H), 2.84 - 2.79 (m, 3H), 2.77 - 2.64 (m, 2H), 2.58 - 2.51 (m, 1H), 2.17 - 2.07 (m, 1H), 1.46 (br d, J = 7.2 Hz, 1H).

Example 419

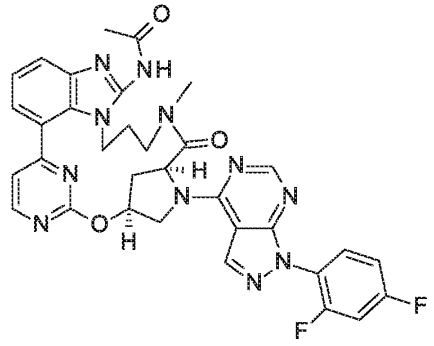
(8*S*,11*S*,15*R*)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



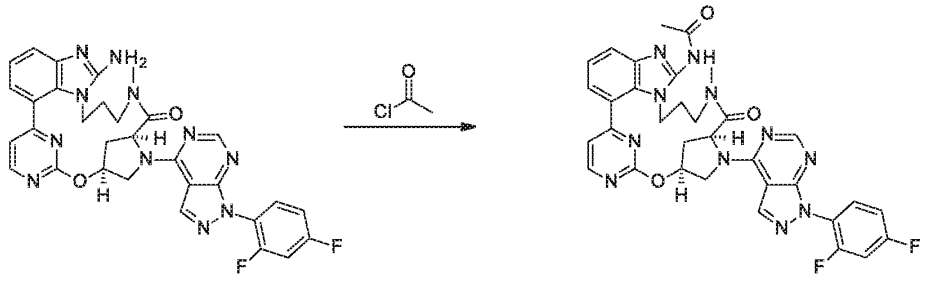
The title compound was prepared in analogy to the preparation of Example **81** by using intermediate **C17** instead of intermediate **C2**. Example **419**, LCMS ($M+H^+$): 723. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.84 - 8.71 (m, 1H), 8.50 - 7.74 (m, 2H), 7.69 - 7.59 (m, 1H), 7.50 - 7.37 (m, 3H), 7.35 - 7.26 (m, 1H), 6.97 - 6.82 (m, 1H), 5.90 - 5.65 (m, 2H), 5.60 - 5.27 (m, 1H), 4.54 - 4.25 (m, 2H), 4.21 - 4.12 (m, 1H), 4.05 - 3.95 (m, 1H), 3.89 - 3.78 (m, 1H), 3.29 - 3.24 (m, 1H), 3.17 - 2.97 (m, 3H), 2.96 - 2.77 (m, 2H), 2.77 - 2.68 (m, 1H), 2.63 (s, 3H), 2.61 (s, 1H), 2.57 (dd, J = 7.0, 9.2 Hz, 1H), 0.77 - 0.69 (m, 2H), 0.64 - 0.52 (m, 5H).

Example 420

***N*-[(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-18-yl]acetamide**



The title compound was prepared according to the following scheme:

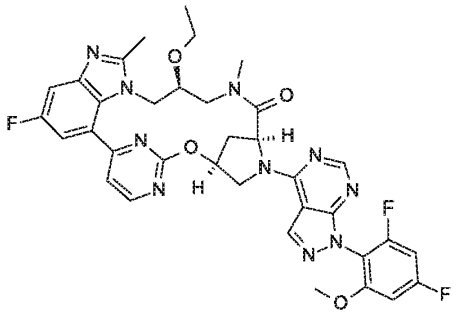


Example 417 Example 420

Example **417** (30 mg, 0.048 mmol) and Et_3N (9.74 mg, 0.096 mmol) were dissolved in tetrahydrofuran (3 mL) and then AcCl (3.78 mg, 0.048 mmol) was added at 0 °C. After being stirred at 0 °C for 2 hours, the reaction mixture was diluted with water and extracted two times with EtOAc. The organic layer was dried and concentrated, the crude material was purified by prep-HPLC to give Example **420**(4.3 mg). LCMS ($M+H^+$): 666. ^1H NMR (500 MHz, DMSO-d_6) δ = 10.43 - 10.29 (m, 1H), 8.86 - 8.77 (m, 1H), 8.68 - 7.85 (m, 2H), 7.79 - 7.68 (m, 2H), 7.65 - 7.57 (m, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.38 - 7.29 (m, 2H), 5.83 - 5.45 (m, 2H), 5.14 - 4.96 (m, 1H), 4.52 - 4.12 (m, 2H), 3.97 - 3.79 (m, 2H), 2.97 - 2.83 (m, 3H), 2.83 - 2.70 (m, 1H), 2.69 - 2.59 (m, 2H), 2.14 - 2.03 (m, 3H), 1.68 - 1.44 (m, 1H), 1.12 - 0.94 (m, 1H).

Example 421

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

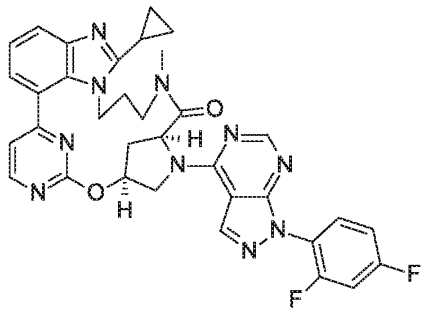


The title compound was prepared in analogy to the preparation of Example **81** by using intermediate **C61** instead of intermediate **C2**. Example **421**, LCMS ($M+H^+$): 715. ^1H NMR (500 MHz, DMSO- d_6) δ = 8.86 - 8.80 (m, 1H), 8.62 - 7.81 (m, 2H), 7.80 - 7.75 (m, 1H), 7.61 - 7.54 (m, 1H), 7.52 - 7.44 (m, 1H), 7.20 - 7.09 (m, 2H), 5.77 - 5.42 (m, 3H), 4.51 - 3.97 (m, 3H), 3.93 - 3.82 (m, 1H), 3.81 - 3.71 (m, 3H), 3.30 - 3.23 (m, 1H), 3.22 - 3.08 (m, 1H), 2.98 - 2.87 (m, 3H), 2.86 - 2.75 (m, 1H), 2.73 - 2.65 (m, 2H), 2.55 - 2.52 (m, 3H), 2.47 - 2.44 (m, 1H), 0.44 - 0.37 (m,

3H).

Example 422

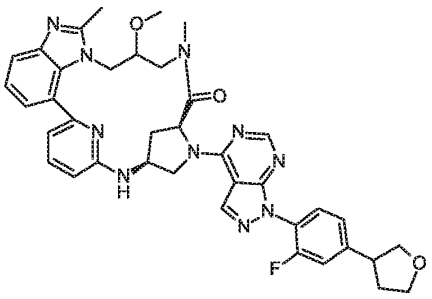
(8*S*,11*S*)-18-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of Example **413** by using cyclopropanecarboxaldehyde instead of 1,1,1-trimethoxy-2-methyl-propane. LCMS (M+H$^+$): 649. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.86 - 8.81 (m, 1H), 8.67 - 7.88 (m, 2H), 7.79 - 7.67 (m, 2H), 7.64 - 7.52 (m, 2H), 7.48 - 7.39 (m, 1H), 7.37 - 7.26 (m, 2H), 5.89 - 5.66 (m, 1H), 5.59 - 5.46 (m, 1H), 5.37 - 5.14 (m, 1H), 4.54 - 3.97 (m, 4H), 3.00 - 2.88 (m, 3H), 2.82 - 2.67 (m, 2H), 2.59 (br d, *J* = 14.5 Hz, 1H), 2.26 (br d, *J* = 3.7 Hz, 1H), 2.05 - 1.95 (m, 1H), 1.94 - 1.72 (m, 1H), 1.18 - 0.98 (m, 4H).

Example 424

(8*S*,11*S*)-10-[1-(2-fluoro-4-tetrahydrofuran-3-yl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

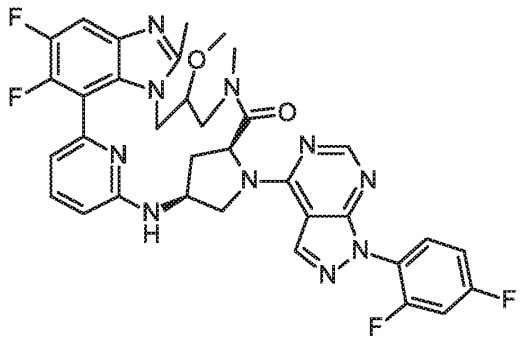


The title compound was prepared in analogy to the preparation of Example **283** by using compound **197d** instead of compound **283a** and intermediate **C72** instead of intermediate **C44**. LCMS (M+H$^+$): 703. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.20 - 8.60 (m, 2H), 7.77 - 7.85

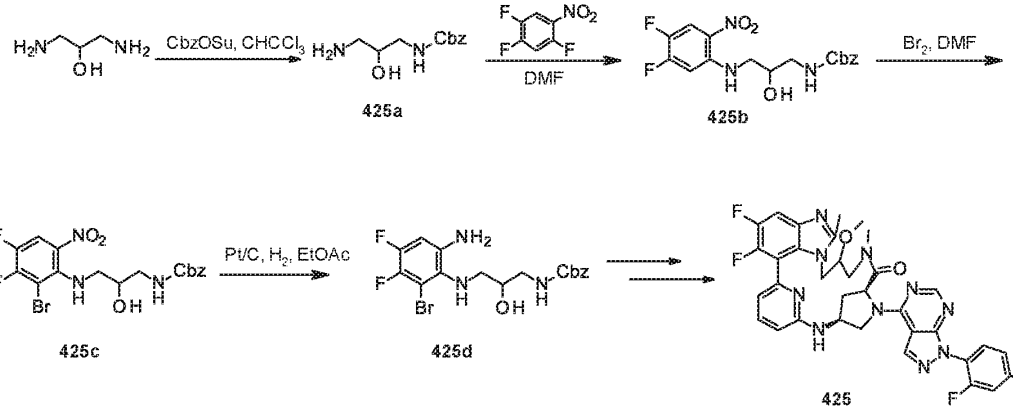
(m, 1H), 7.52 - 7.65 (m, 2H), 7.25 - 7.39 (m, 4H), 6.89 - 7.14 (m, 1H), 6.69 (dd, *J* = 14.55, 8.44 Hz, 1H), 5.40 - 5.57 (m, 1H), 4.50 - 4.58 (m, 1H), 4.28 - 4.37 (m, 1H), 4.06 - 4.22 (m, 4H), 3.91 - 4.01 (m, 2H), 3.78 - 3.84 (m, 1H), 3.56 - 3.64 (m, 1H), 3.03 - 3.21 (m, 4H), 2.76 - 2.89 (m, 4H), 2.45 - 2.65 (m, 6H), 2.05 - 2.14 (m, 1H), 1.37 (d, *J* = 6.60 Hz, 1H).

Example 425

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22,23-difluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl *N*-(3-amino-2-hydroxy-propyl)carbamate (compound 425a)

To a solution of 1,3-diamino-2-propanol (250.0 g, 2.8 mol) in chloroform (2 L) was added a solution of *N*-(benzyloxycarbonyloxy)succinimide (34.6 g, 0.12 mol) in chloroform (0.7 L) dropwise over 6 hours at 0 °C. The mixture was stirred at 20 °C for 18 hours, and then washed with brine (0.5 L for three times). The organic layer was dried and concentrated to give compound **425a** (15.0 g). LCMS (M+H$^+$): 225.

Step 2: preparation of benzyl *N*-[3-(4,5-difluoro-2-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 425b)

To a solution of 1,2,4-trifluoro-5-nitro-benzene (10.0 g, 0.05 mol) and DIEA (14.6 g, 0.1 mol) in DMF (0.1 L) was added a solution of compound **425a** (12.7 g, 0.05 mol) in DMF (0.1 L). The mixture was stirred at 20 °C for 12 hours, and then concentrated. The residue was purified by flash column to give compound **425b** (4.0 g). LCMS ($M+H^+$): 382.

Step 3: preparation of benzyl *N*-[3-(2-bromo-3,4-difluoro-6-nitro-anilino)-2-hydroxy-propyl]carbamate (compound 425c)

A mixture of compound **425b** (2.7 g, 7.1 mmol) and bromine (2.3 g, 14.2 mmol) in DMF (20 mL) was stirred at 60 °C for 1 h. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mL twice). The combined organic layer was washed with brine (20 mL twice), dried and concentrated. The residue was purified by flash column to give compound **425c** (2.3 g). LCMS ($M+H^+$): 460.

Step 4: preparation of benzyl *N*-[3-(6-amino-2-bromo-3,4-difluoro-anilino)-2-hydroxy-propyl]carbamate (compound 425d)

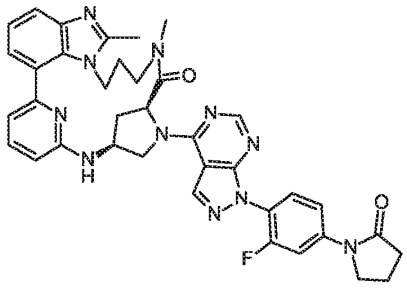
To a solution of compound **425c** (2.0 g, 4.3 mmol) in ethyl acetate (10 mL) was added Pt/C (0.1 g) and the mixture stirred at 20 °C for 1 h under H_2. The mixture was filtered and the filtrate was concentrated to give compound **425d** (1.5 g). LCMS ($M+H^+$): 430.

Step 5~13: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22,23-difluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

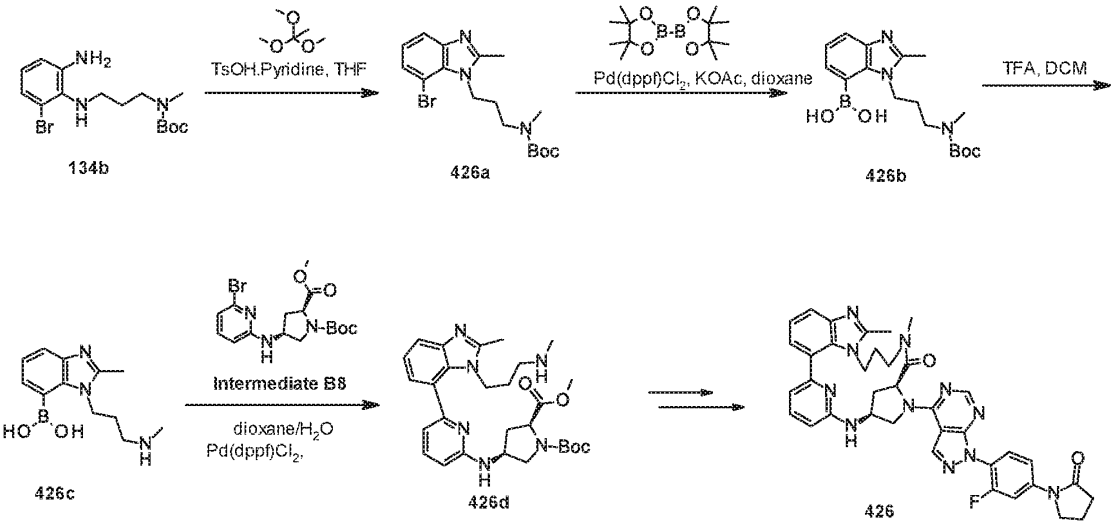
The title compound was prepared in analogy to the preparation of Example **395** (Step 5~13) by using compound **425d** instead of compound **395d**, and intermediate **C1** instead of intermediate **C11**. LCMS ($M+H^+$): 687. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.21 - 8.59 (m, 2H), 6.71 - 7.87 (m, 7H), 5.34 - 5.59 (m, 2H), 4.05 - 4.55 (m, 3H), 3.78 - 4.02 (m, 1H), 3.03 - 3.22 (m, 4H), 2.78 - 2.96 (m, 5H), 2.50 - 2.66 (m, 5H).

Example 426

(8*S*,11*S*)-10-[1-[2-fluoro-4-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[3-(7-bromo-2-methyl-benzimidazol-1-yl)propyl]-*N*-methyl-carbamate (compound 426a)

To a mixture of compound **134b** (10.0 g, 29.0 mmol) in THF (0.2 L) was added 1,1,1-trimethoxyethane (7.0 g, 58.1 mmol) and TsOH•pyridine (1.5 g, 5.8 mmol). The mixture was stirred at 25 °C for 12 hours, and then concentrated. The residue was purified by pre-HPLC to give compound **426a** (4.0 g). LCMS ($M+H^+$): 368.

Step 2: preparation of [3-[3-[*tert*-butoxycarbonyl(methyl)amino]propyl]-2-methyl-benzimidazol-4-yl]boronic acid (compound 426b)

To a mixture of compound **426a** (3.0 g, 7.8 mmol) and bis(pinacolato)diboron (3.0 g, 11.7 mmol) in 1,4-dioxane (30 mL) was added 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride toluene (0.6 g, 0.7 mmol) and potassium acetate (2.3 g, 23.4 mmol). Then the mixture was stirred at 100 °C for 12 hours under N_2, and then filtered. The filtrate was concentrated and the residue was purified by pre-HPLC to compound **426b** (1.2 g). LCMS ($M+H^+$): 348.

Step 3: preparation of [2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-

yl]boronic acid (compound 426c)

A mixture of compound **426b** (1.2 g, 3.5 mmol) in DCM (10 mL) and TFA (3 mL) was stirred at 20 °C for 2 hours. The mixture was concentrated to give compound **426c** (0.8 g). LCMS ($M+H^+$): 248.

Step 4: preparation of *O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[[6-[2-methyl-3-[3-(methylamino)propyl]benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 426d)

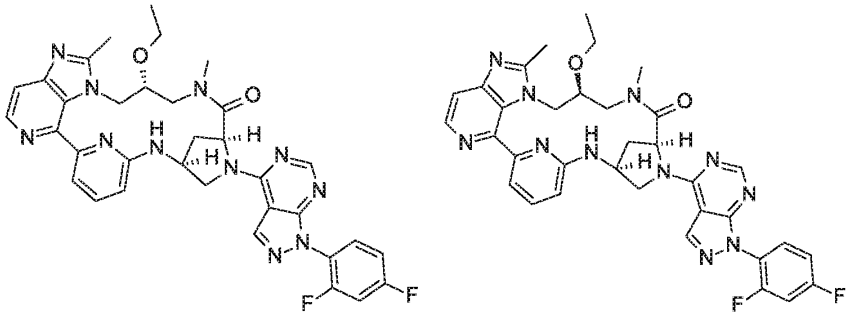
To the mixture of compound **426c** (0.8 g, 3.2 mmol) and intermediate **B8** (1.5 g, 3.9 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added Na_2CO_3 (1.0 g, 9.7 mmol) and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride toluene (0.2 g, 0.3 mmol) under N_2. After stirring at 80 °C for 12 hours, the mixture was poured into water (50 mL) and extracted with EtOAc (50 mL twice). The organic layer was dried and concentrated, the residue was purified by pre-HPLC to give compound **426d** (0.2 g). LCMS ($M+H^+$): 523.

Step 5~8: preparation of (8*S*,11*S*)-10-[1-[2-fluoro-4-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (Example 426)

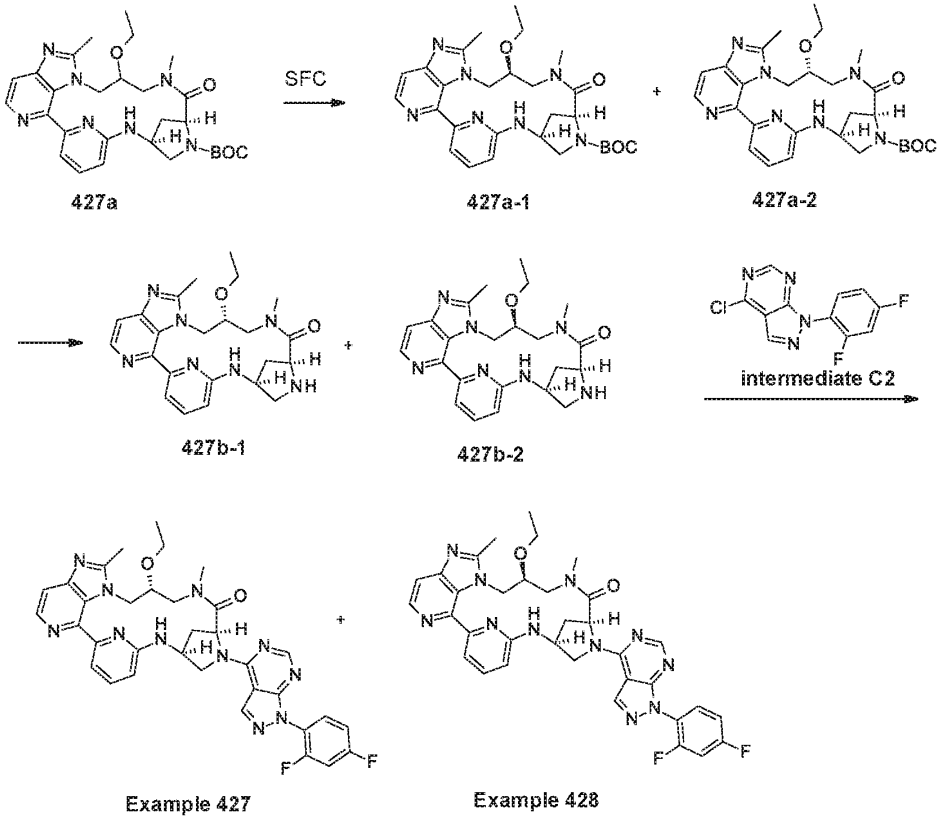
The title compound was prepared in analogy to the preparation of Example **295** (step 11~14) by using compound **426d** instead of compound **295j**, and intermediate **C73** instead of intermediate **C11**. LCMS ($M+H^+$): 686. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.21 - 8.58 (m, 2H), 7.92 - 8.05 (m, 1H), 7.79 - 7.83 (m, 1H), 7.59 - 7.65 (m, 3H), 7.25 (dt, *J*=14.95, 7.38 Hz, 2H), 6.91 (d, *J*=7.58 Hz, 1H), 6.77 (br d, *J*=8.19 Hz, 1H), 5.53 (br d, *J*=8.56 Hz, 1H), 5.05 - 5.16 (m, 2H), 3.90 - 4.35 (m, 4H), 3.05 - 3.18 (m, 3H), 2.85 - 3.01 (m, 1H), 2.54 - 2.75 (m, 8H), 2.24 (br t, *J*=7.58 Hz, 3H), 1.22 - 1.43 (m, 2H).

Example 427 and 428

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compounds were prepared according to the following scheme:



Step 1: preparation of *tert*-butyl (8*S*,11*S*,15*S*)-15-ethoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,23,26- heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate and *tert*-butyl (8*S*,11*S*,15*R*)-15-ethoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-10-carboxylate (compound 427b-1 & 427b-2)

SFC preparation of compound **427a** (the synthesis was refer to compound **404p** by using 3-fluoro-4-nitropyridine instead of 3-fluoro-2-nitropyridine) to give compound **427a-1** (slower

eluted) and compound **427a-2** (faster eluted). SFC condition: Instrument: SHIMADZU LC-30ADsf); Column: (S,S)Whelk-O1 100×4.6mm I.D., 3.5um; Mobile phase: Phase A for Supercritical CO_2, and Phase B for MeOH+ACN(0.05%DEA); Gradient: 40% Phase B (60% Phase A); Flow rate: 3mL/min; Back pressure: 100Bar; Column temperature: 35 °C. LCMS $(M+H)^+$: 536.

Step 2~3: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 427 & 428)

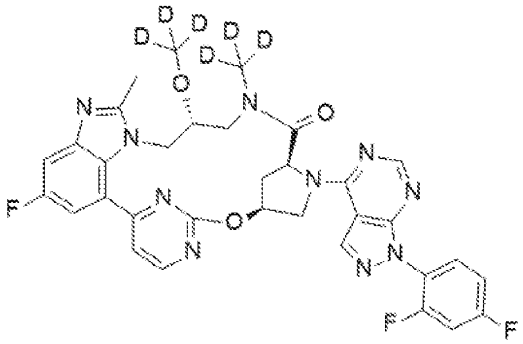
The title compounds were prepared in analogy to the preparation of Example **289** by using compound **427a-1** instead of compound **289c** and compound **427a-2** instead of compound **289c** respectively.

Example **427**, LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.60 (s, 1H), 8.49 (d, *J* = 6.4 Hz, 1H), 8.41 - 8.25 (m, 1H), 8.11 (d, *J* = 6.4 Hz, 1H), 7.97 (t, *J* = 8.0 Hz, 1H), 7.73 - 7.61 (m, 1H), 7.35 - 7.18 (m, 3H), 7.03 - 6.95 (m, 1H), 5.54 (d, *J* = 8.8 Hz, 1H), 4.82 - 4.77 (m, 1H), 4.67 - 4.56 (m, 1H), 4.44 - 4.33 (m, 1H), 4.32 - 4.22 (m, 1H), 4.15 - 4.03 (m, 1H), 3.83 - 3.73 (m, 1H), 3.40 - 3.33 (m, 1H), 3.20 (s, 1H), 3.09 (s, 2H), 2.89 - 2.81 (m, 3H), 2.71 - 2.63 (s, 1H), 2.71 - 2.61 (m, 1H), 1.40 - 1.35 (m, 3H), 0.59 (t, *J* = 6.8 Hz, 3H).

Example **428**, LCMS $(M+H)^+$: 666. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 - 8.52 (m, 1H), 8.50 (d, *J* = 6.4 Hz, 1H), 8.38 - 8.20 (m, 1H), 8.08 - 8.04 (m, 1H), 8.00 (t, *J* = 8.0 Hz, 1H), 7.71 - 7.63 (m, 1H), 7.43 - 7.36 (m, 1H), 7.33 - 7.26 (m, 1H), 7.25 - 7.18 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.97 (dd, *J* = 15.2, 4.0 Hz, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 4.58 - 4.52 (m, 1H), 4.41 - 4.32 (m, 2H), 4.05 - 3.95 (m, 1H), 3.41 - 3.35 (m, 1H), 3.16 - 3.02 (m, 4H), 3.00 - 2.89 (m, 1H), 2.86 - 2.76 (m, 4H), 2.74 - 2.69 (m, 1H), 2.67 - 2.54 (m, 2H), 0.69 - 0.55 (m, 3H).

Example 430

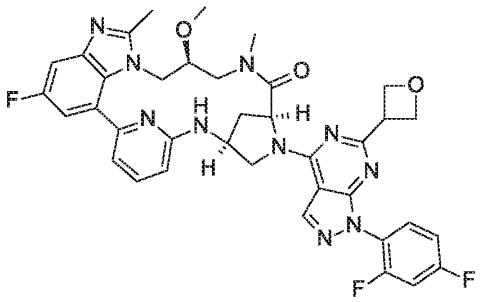
(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



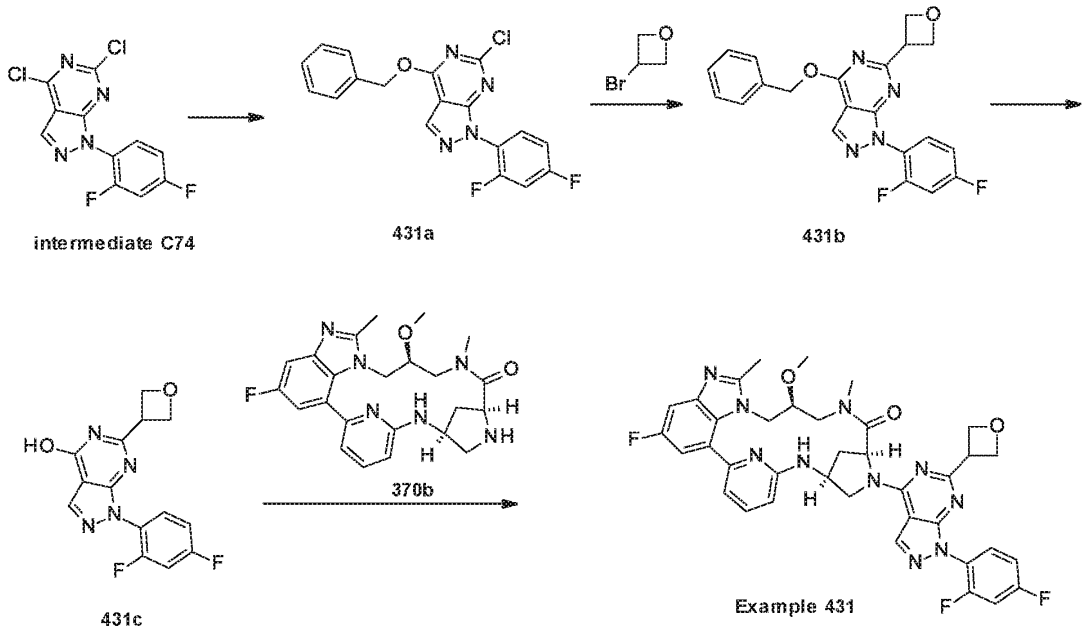
The title compound was prepared in analogy to the preparation of **Example 12** by using **Intermediate A30** instead of **Intermediate A11** and **Intermediate B15** instead of **Intermediate B10**. LCMS $(M+H)^+$: 677. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.76 (dd, J = 3.4, 5.2 Hz, 1H), 8.69 - 8.34 (m, 1H), 8.30 - 7.82 (m, 1H), 7.75 (dtd, J = 6.1, 8.7, 11.6 Hz, 1H), 7.66 - 7.45 (m, 3H), 7.40 - 7.27 (m, 2H), 5.76 (s, 2H), 5.58 - 5.41 (m, 2H), 4.55 - 4.13 (m, 2H), 4.10 - 3.82 (m, 2H), 3.20 - 2.96 (m, 1H), 2.93 - 2.62 (m, 2H), 2.53 (d, J = 2.7 Hz, 3H).

Example 431

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-benzyloxy-6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (compound 431a)

A mixture of 4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (**intermediate C47**, 1 g, 3.3 mmol), KOtBu (447 mg, 4 mmol) and benzyl alcohol (395 mg, 3.6 mmol) in tetrahydrofuran (15 mL) was stirred at rt for 2 hours. Then the reaction was diluted with EA, washed with water and brine, the organic layer was dried and concentrated, the residue was purified by silica gel to give to give compound **431a** (400 mg). LCMS ($M+H^+$): 373.

Step 2: preparation of 4-benzyloxy-1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidine (compound 431b)

To an 8 mL vial equipped with a stir bar was added photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (15 mg, 0.013 mmol), tris(trimethylsilyl)silane (67 mg, 0.27 mmol), compound **431a** (100 mg, 0.27 mmol), 3-bromooxetane (73.5 mg, 0.54 mmol), $NiCl_2(dtbbpy)$ (10.68 mg, 0.027 mmol) and Na_2CO_3 (85 mg, 0.8 mmol). The vial was sealed and placed under nitrogen before 4 mL of DME was added. The reaction was stirred and irradiated with a 34 W blue LED lamp (450-455 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hours. The reaction was quenched by exposure to air and concentrated in *vacuo*, the residue was purified by silica gel to give compound **431b** (60 mg). LCMS ($M+H^+$): 395.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 431c)

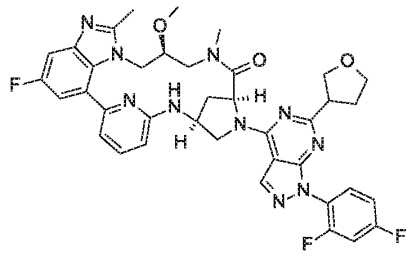
A mixture of compound **431b** (60 mg, 0.15 mmol) and $Pd(OH)_2$ (21 mg, 0.15 mmol) in methanol (12 mL) was stirred at rt 2 hours under H_2 atmosphere. Then the reaction mixture was filtered and the filtrate was concentrated to give compound **431c** (40 mg). LCMS ($M+H^+$): 305.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 431)

A mixture of compound **431c** (17 mg, 0.055 mmol), (1-hydroxy-1*H*-benzotriazolato-o)tri-1-pyrrolidinylphosphorus hexafluorophosphate (36 mg, 0.068 mmol) and DIPEA (30 mg, 0.23 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at rt for 1 hour, then compound **370b** (20 mg, 0.046 mmol) was added. The reaction was stirred at 50 °C for 16 hours and then the reaction mixture was purified by prep-HPLC to give Example **431** (7 mg). LCMS ($M+H^+$): 725. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.43 - 8.29 (m, 1H), 7.83 - 7.71 (m, 1H), 7.61 - 7.35 (m, 3H), 7.25 - 7.00 (m, 3H), 6.74 - 6.65 (m, 1H), 6.16 - 5.91 (m, 1H), 5.55 - 5.28 (m, 1H), 5.03 - 4.79 (m, 4H), 4.66 - 4.57 (m, 1H), 4.50 - 4.40 (m, 1H), 4.29 - 4.13 (m, 3H), 3.90 - 3.72 (m, 1H), 3.07 - 2.99 (m, 3H), 2.98 - 2.89 (m, 1H), 2.89 - 2.84 (m, 3H), 2.76 - 2.67 (m, 4H), 2.63 - 2.41 (m, 2H).

Example 432

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydrofuran-3-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

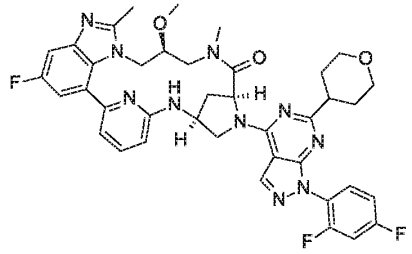


To an 8 mL vial equipped with a stir bar was added photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (3 mg, 0.003 mmol), tris(trimethylsilyl)silane (14 mg, 0.057 mmol), compound **213a** (40 mg, 0.057 mmol), 3-iodotetrahydrofuran (23 mg, 0.114 mmol), $NiCl_2$(dtbbpy) (2.3 mg, 0.006 mmol) and Na_2CO_3 (18 mg, 0.17 mmol). The vial was sealed and placed under nitrogen before 4 mL of DME was added. The reaction was stirred and irradiated with a 34 W blue LED lamp (450-455 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hours. The reaction was quenched by exposure to air and concentrated in *vacuo*,

the residue was purified by HPLC to give compound **432** (9 mg). LCMS ($M+H^+$): 739. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.50 - 7.59 (m, 3H), 7.57 - 7.46 (m, 1H), 7.36 - 7.18 (m, 2H), 7.11 - 6.95 (m, 2H), 6.64 - 6.50 (m, 1H), 5.78 - 5.56 (m, 1H), 5.52 - 5.40 (m, 1H), 5.38 - 5.22 (m, 1H), 4.57 - 4.05 (m, 3H), 4.01 - 3.89 (m, 2H), 3.87 - 3.77 (m, 1H), 3.75 - 3.61 (m, 3H), 3.01 - 2.74 (m, 5H), 2.69 - 2.61 (m, 3H), 2.54 - 2.47 (m, 1H), 2.41 - 2.37 (m, 3H), 2.33 - 2.20 (m, 2H), 2.15 - 1.93 (m, 2H).

Example 433

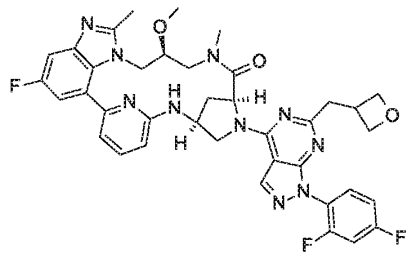
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydropyran-4-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **433** was prepared in analogy to the preparation of Example **432** by using 4-iodotetrahydropyran instead of 3-iodotetrahydrofuran. Example **433** (15 mg). LCMS ($M+H^+$): 753. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.58 - 7.69 (m, 3H), 7.65 - 7.55 (m, 1H), 7.41 - 7.27 (m, 2H), 7.18 - 7.04 (m, 2H), 6.74 - 6.58 (m, 1H), 5.84 - 5.65 (m, 1H), 5.61 - 5.50 (m, 1H), 5.46 - 5.33 (m, 1H), 4.68 - 4.15 (m, 3H), 4.12 - 3.97 (m, 1H), 3.95 - 3.70 (m, 4H), 3.05 - 2.95 (m, 3H), 2.94 - 2.85 (m, 2H), 2.82 - 2.68 (m, 4H), 2.65 - 2.58 (m, 1H), 2.49 - 2.45 (m, 3H), 2.42 - 2.33 (m, 1H), 1.95 - 1.65 (m, 5H).

Example 434

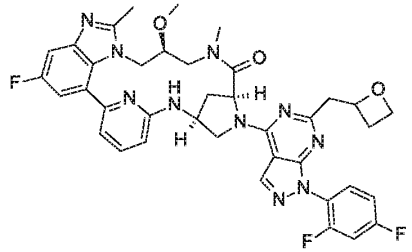
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **434** was prepared in analogy to the preparation of Example **432** by using 3-(iodomethyl)oxetane instead of 3-iodotetrahydrofuran. Example **434** (7 mg). LCMS ($M+H^+$): 739. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.35 - 7.58 (m, 2H), 7.56 - 7.40 (m, 1H), 7.22 - 6.88 (m, 5H), 6.61 - 6.49 (m, 1H), 5.70 - 5.50 (m, 1H), 5.36 - 5.18 (m, 1H), 4.56 - 4.31 (m, 5H), 4.17 - 3.97 (m, 2H), 3.88 - 3.69 (m, 1H), 3.47 - 3.26 (m, 1H), 3.07 - 2.86 (m, 6H), 2.82 - 2.68 (m, 5H), 2.50 - 2.32 (m, 5H).

Example 435

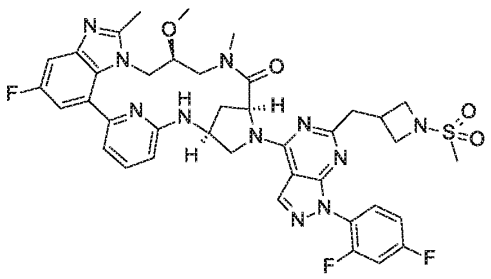
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-2-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



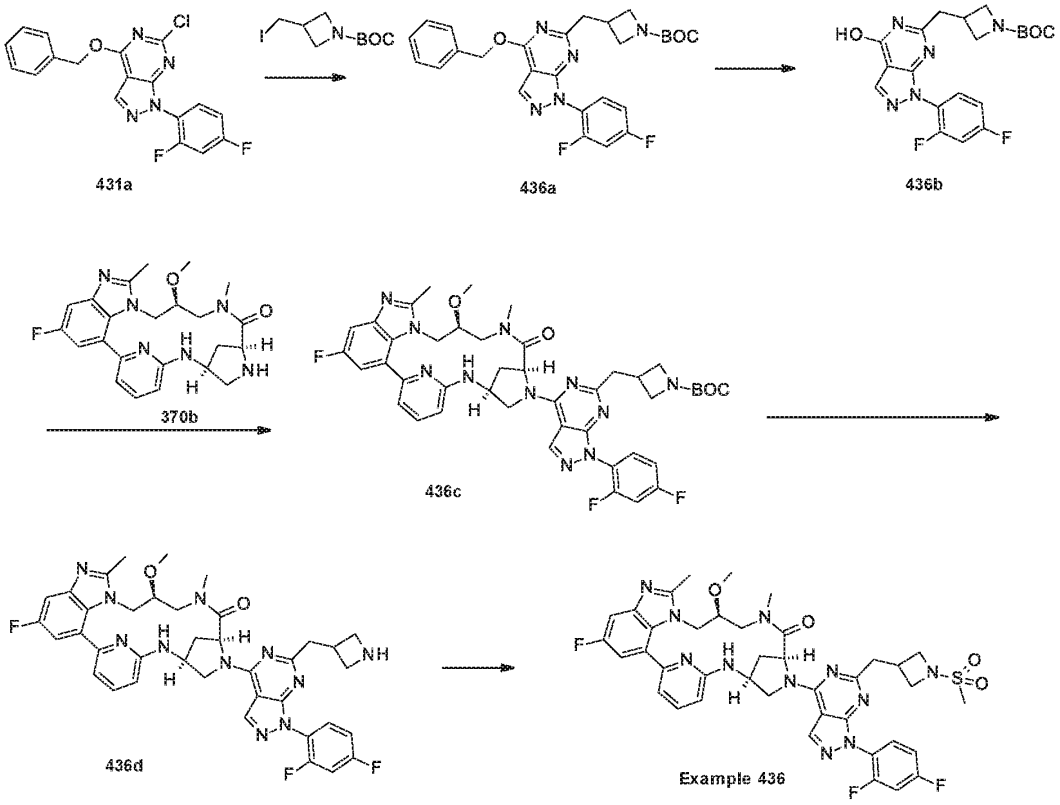
Example **435** was prepared in analogy to the preparation of Example **432** by using 2-(iodomethyl)oxetane instead of 3-iodotetrahydrofuran. Example **435** (10 mg). LCMS ($M+H^+$): 739. ^1H NMR (400 MHz, METHANOL-d_4) δ= 8.36 - 7.60 (m, 2H), 7.59 - 7.44 (m, 1H), 7.23 - 6.95 (m, 5H), 6.63 - 6.50 (m, 1H), 5.74 - 5.55 (m, 1H), 5.43 - 5.07 (m, 2H), 4.61 - 4.33 (m, 4H), 4.22 - 4.12 (m, 1H), 4.10 - 3.96 (m, 1H), 3.88 - 3.77 (m, 1H), 3.08 - 2.92 (m, 5H), 2.87 - 2.69 (m, 5H), 2.64 - 2.33 (m, 7H).

Example 436

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1~3: preparation of *tert*-butyl 3-[[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]methyl]azetidine-1-carboxylate (compound 436c)

Compound **436c** was prepared in analogy to the preparation of Examples **431** by using *tert*-butyl 3-(iodomethyl)azetidine-1-carboxylate instead of 3-bromooxetane. LCMS (M+H$^+$): 507.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-ylmethyl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 436d)

A mixture of compound **436c** (35 mg, 0.042 mmol) in TFA (0.5 mL) and DCM (0.5 mL) was stirred at rt for 1 h, then the reaction was concentrated to give compound **436d** (30 mg). LCMS (M+H$^+$): 738.

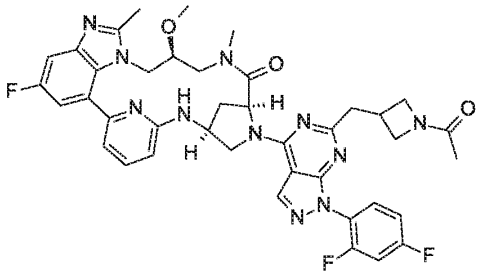
Step 5: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-

13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 436)

To a solution of compound **436d** (30 mg, 0.04 mmol) and DIPEA (26 mg, 0.2 mmol, 5.0) in dichloromethane (2 mL) was added methanesulfonic anhydride (14 mg, 0.08 mmol) at rt. Then the mixture was stirred at rt for 1 hour, the reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **436** (7 mg). LCMS (M+H$^+$): 816. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 - 8.45 (m, 1H), 7.95 - 7.84 (m, 1H), 7.72 - 7.48 (m, 3H), 7.35 - 7.10 (m, 3H), 6.84 - 6.73 (m, 1H), 6.21 - 6.01 (m, 1H), 5.54 - 5.33 (m, 1H), 4.73 - 4.66 (m, 1H), 4.57 - 4.47 (m, 1H), 4.43 - 4.26 (m, 2H), 4.02 - 3.82 (m, 5H), 3.11 - 3.08 (m, 3H), 3.03 - 2.89 (m, 7H), 2.88 - 2.76 (m, 7H), 2.63 - 2.51 (m, 2H).

Example 437

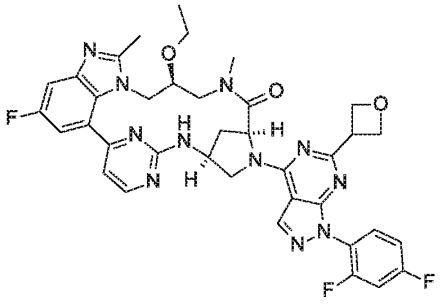
(8*S*,11*S*,15*R*)-10-[6-[(1-acetylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **437** was prepared in analogy to the preparation of Example **436** by using acetyl acetate instead of methanesulfonic anhydride. Example **437** (17 mg). LCMS (M+H$^+$): 780. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.46 (m, 1H), 7.96 - 7.85 (m, 1H), 7.73 - 7.53 (m, 3H), 7.38 - 7.14 (m, 3H), 6.84 - 6.76 (m, 1H), 6.23 - 6.03 (m, 1H), 5.56 - 5.40 (m, 1H), 4.75 - 4.68 (m, 1H), 4.58 - 4.49 (m, 1H), 4.42 - 4.27 (m, 3H), 4.19 - 3.86 (m, 4H), 3.19 - 3.11 (m, 4H), 3.09 - 3.03 (m, 3H), 3.01 - 2.98 (m, 3H), 2.94 - 2.79 (m, 4H), 2.74 - 2.52 (m, 2H), 1.93 - 1.78 (m, 3H).

Example 438

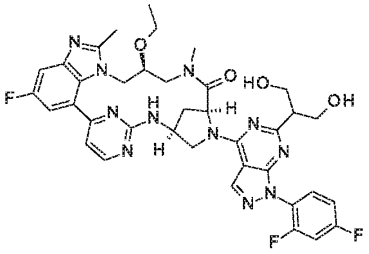
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



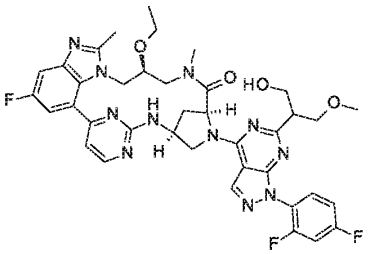
Example **438** as prepared in analogy to the preparation of Example **431** by using compound **326d-1** instead of compound **370b**. Example **438** (22 mg). LCMS ($M+H^+$): 740. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.78 - 8.62 (m, 1H), 8.58 - 7.75 (m, 1H), 7.73 - 7.58 (m, 3H), 7.35 - 7.13 (m, 3H), 6.04 - 5.77 (m, 1H), 5.66 - 5.37 (m, 1H), 5.16 - 5.10 (m, 1H), 5.06 - 5.01 (m, 1H), 4.98 - 4.93 (m, 5H), 4.55 - 4.21 (m, 3H), 4.05 - 3.93 (m, 1H), 3.52 - 3.42 (m, 1H), 3.21 - 3.09 (m, 3H), 3.08 - 2.99 (m, 1H), 2.89 - 2.50 (m, 6H), 0.72 - 0.53 (m, 3H).

Example 439 and 440

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-hydroxy-1-(hydroxymethyl)ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and **(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(hydroxymethyl)-2-methoxy-ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**

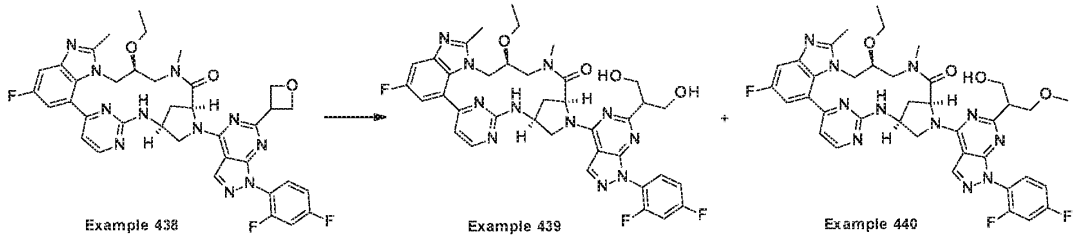


(Example 439)



(Example 440)

The title compound was prepared according to the following scheme:



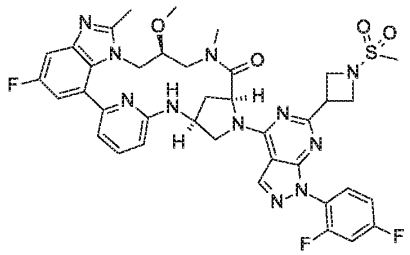
A mixture of Example **438** (10 mg, 13 umol) and TFA (0.5 mL, 6.5 mmol) in methanol (0.5 mL) and water (0.5 mL) was stirred at 50 °C for 16 hours, then the reaction was concentrated and the residue was purified by prep-HPLC to give Example **439** and Example **440**.

Example **439**, 5 mg, LCMS ($M+H^+$): 758. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.60 - 8.48 (m, 1H), 8.43 - 7.66 (m, 1H), 7.65 - 7.46 (m, 3H), 7.22 - 6.97 (m, 3H), 5.83 - 5.61 (m, 1H), 5.39 - 5.23 (m, 1H), 4.55 - 4.32 (m, 1H), 4.29 - 4.07 (m, 2H), 3.98 - 3.67 (m, 5H), 3.40 - 3.30 (m, 2H), 3.08 - 3.02 (m, 1H), 3.00 - 2.90 (m, 4H), 2.90 - 2.81 (m, 1H), 2.73 - 2.58 (m, 5H), 2.57 - 2.40 (m, 1H), 0.59 - 0.45 (m, 3H).

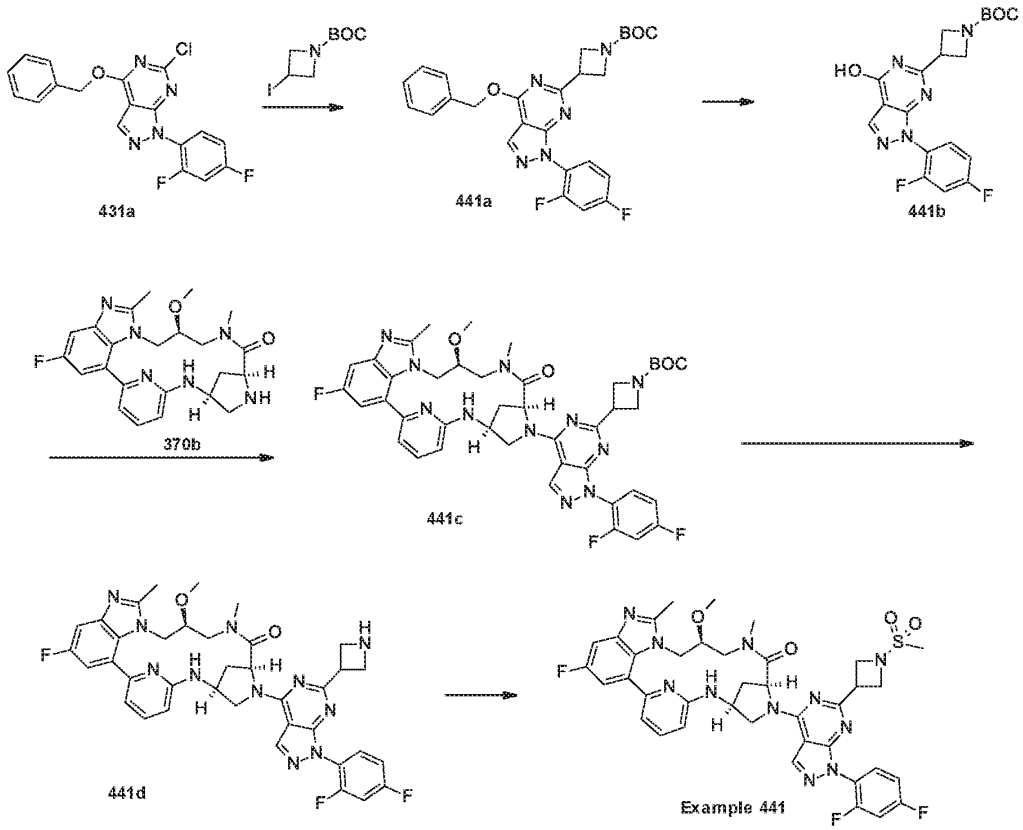
Example **440**, 2 mg, LCMS ($M+H^+$): 772. ^1H NMR (400 MHz, METHANOL-d_4)δ = 8.57 - 8.47 (m, 1H), 8.42 - 7.64 (m, 1H), 7.63 - 7.51 (m, 1H), 7.46 - 7.30 (m, 2H), 7.23 - 6.96 (m, 3H), 5.71 - 5.49 (m, 1H), 5.42 - 5.23 (m, 1H), 4.57 - 4.31 (m, 1H), 4.30 - 4.06 (m, 2H), 3.95 - 3.57 (m, 5H), 3.56 - 3.35 (m, 1H), 3.32 - 3.25 (m, 1H), 3.19 (br s, 3H), 3.09 - 2.80 (m, 6H), 2.65 - 2.54 (m, 5H), 2.50 - 2.39 (m, 1H), 0.57 - 0.43 (m, 3H).

Example 441

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylazetidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



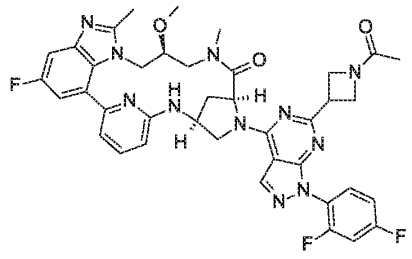
The title compound was prepared according to the following scheme:



Example **441** was prepared in analogy to the preparation of Example **436** by using *tert*-butyl 3-iodoazetidine-1-carboxylate instead of *tert*-butyl 3-(iodomethyl)azetidine-1-carboxylate. Example **441** (6 mg). LCMS ($M+H^+$): 802. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.45 - 7.67 (m, 2H), 7.59 - 7.38 (m, 3H), 7.22 - 7.04 (m, 3H), 6.73 - 6.67 (m, 1H), 6.11 - 5.91 (m, 1H), 5.54 - 5.39 (m, 1H), 4.49 - 4.42 (m, 1H), 4.28 - 3.96 (m, 6H), 3.88 - 3.79 (m, 1H), 3.72 - 3.64 (m, 1H), 3.07 - 2.96 (m, 4H), 2.91 - 2.81 (m, 7H), 2.79 - 2.63 (m, 4H), 2.54 - 2.42 (m, 2H).

Example 442

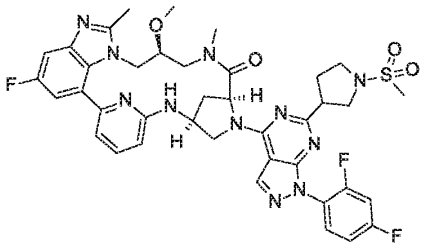
(8*S*,11*S*,15*R*)-10-[6-(1-acetylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



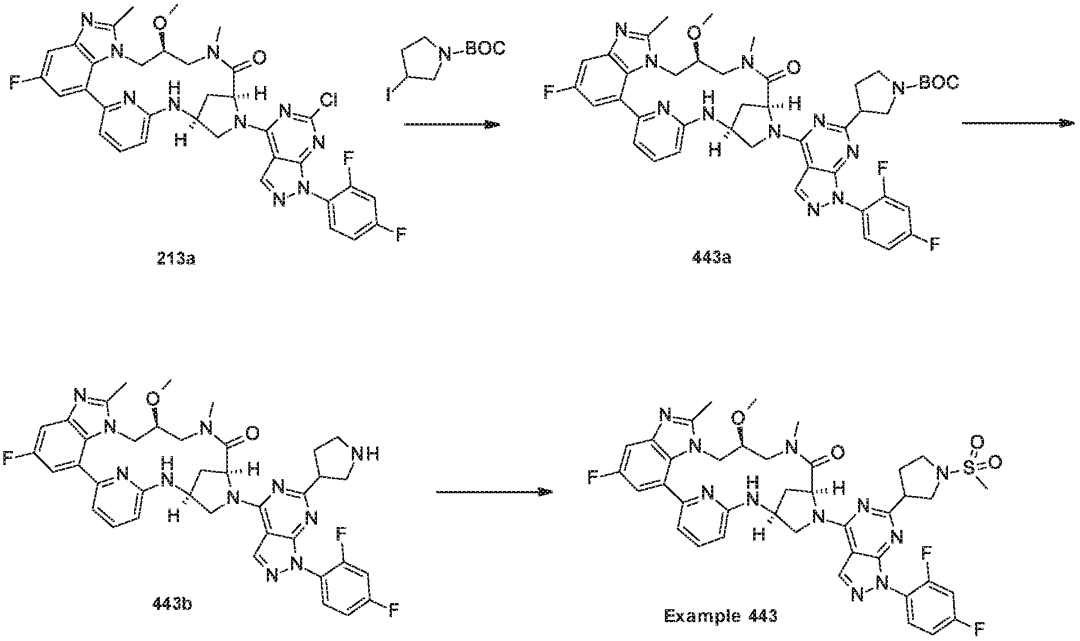
Example **442** was prepared in analogy to the preparation of Example **436** by using *tert*-butyl 3-iodoazetidine-1-carboxylate instead of *tert*-butyl 3-(iodomethyl)azetidine-1-carboxylate and acetyl acetate instead of methanesulfonic anhydride. Example **441** (22 mg). LCMS ($M+H^+$): 766. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.45 - 7.65 (m, 2H), 7.61 - 7.36 (m, 3H), 7.23 - 7.00 (m, 3H), 6.75 - 6.65 (m, 1H), 6.12 - 5.91 (m, 1H), 5.48 - 5.29 (m, 1H), 4.48 - 4.40 (m, 2H), 4.31 - 4.09 (m, 5H), 3.86 - 3.76 (m, 1H), 3.68 - 3.60 (m, 1H), 3.07 - 2.84 (m, 8H), 2.74 - 2.66 (m, 4H), 2.59 - 2.42 (m, 2H), 1.84 - 1.71 (m, 3H).

Example 443

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylpyrrolidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidine-1-carboxylate (compound 443a)

To an 8 mL vial equipped with a stir bar was added Na_2CO_3 (45 mg, 0.42 mmol), photocatalyst(Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (8 mg, 0.007 mmol), $NiCl_2$(dtbbpy) (6 mg, 0.014 mmol), tris(trimethylsilyl)silane (35 mg, 0.14 mmol), *tert*-butyl 3-iodopyrrolidine-1-carboxylate (85 mg, 0.28 mmol) and compound **213a** (100 mg, 0.14 mmol) in 1,4-dioxane (6 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (450-450 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hours. Then the reaction was filtered and the filtrate was concentrated to give compound **443a** (120 mg). LCMS (M+H$^+$): 838.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-pyrrolidin-3-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 443b)

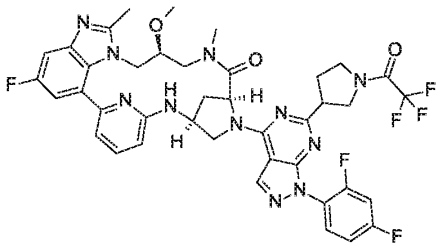
A mixture of compound **443a** (100 mg, 0.12 mmol) in 4 M 4 M HCl in dioxane (2 mL, 8 mmol) and dichloromethane (2 mL) was stirred at rt for 2 hours, then the solid was collected by filtration to give compound **443b** (60 mg). LCMS (M+H$^+$): 738.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylpyrrolidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 443)

A mixture of compound **443b** (30 mg, 0.04 mmol), DIPEA (53 mg, 0.41 mmol) and methanesulfonic anhydride (35 mg, 0.20 mmol) in dichloromethane (2 mL) was stirred at rt for 30 mins, then the reaction was concentrated and the residue was purified by HPLC to give Examples **443** (14 mg). LCMS (M+H$^+$): 816. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.37 (m, 1H), 7.98 - 7.83 (m, 1H), 7.74 - 7.50 (m, 3H), 7.36 - 7.12 (m, 3H), 6.89 - 6.76 (m, 1H), 6.29 - 6.03 (m, 1H), 5.59 - 5.37 (m, 1H), 4.77 - 4.66 (m, 1H), 4.59 - 4.48 (m, 1H), 4.45 - 4.25 (m, 2H), 4.09 - 3.93 (m, 1H), 3.86 - 3.71 (m, 1H), 3.67 - 3.39 (m, 4H), 3.21 - 3.09 (m, 3H), 3.08 - 2.96 (m, 4H), 2.90 - 2.70 (m, 7H), 2.66 - 2.50 (m, 2H), 2.43 - 2.19 (m, 2H).

Example 444

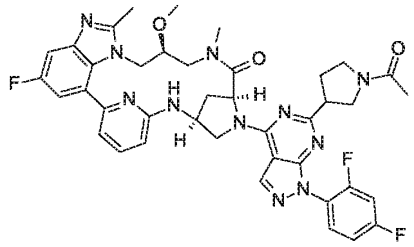
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **444** was prepared in analogy to the preparation of Example **443** by using (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate instead of methanesulfonic anhydride. Example **444** (7 mg). LCMS ($M+H^+$): 834. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.44 (m, 1H), 7.93 - 7.85 (m, 1H), 7.73 - 7.49 (m, 3H), 7.37 - 7.11 (m, 3H), 6.88 - 6.74 (m, 1H), 6.27 - 6.02 (m, 1H), 5.57 - 5.31 (m, 1H), 4.74 - 4.65 (m, 1H), 4.60 - 4.45 (m, 1H), 4.40 - 4.23 (m, 2H), 4.18 - 3.86 (m, 3H), 3.85 - 3.54 (m, 3H), 3.20 - 3.03 (m, 3H), 3.02 - 2.95 (m, 4H), 2.90 - 2.76 (m, 4H), 2.74 - 2.51 (m, 2H), 2.48 - 2.07 (m, 2H).

Example 445

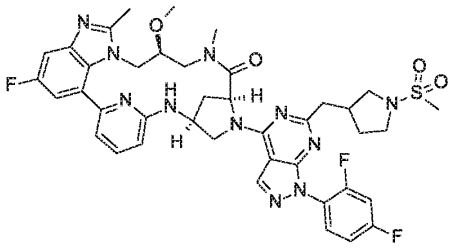
(8*S*,11*S*,15*R*)-10-[6-(1-acetylpyrrolidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **445** was prepared in analogy to the preparation of Example **443** by using acetyl acetate instead of methanesulfonic anhydride. Example **445** (11 mg). LCMS ($M+H^+$): 780. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.54 - 7.75 (m, 2H), 7.73 - 7.52 (m, 3H), 7.37 - 7.10 (m, 3H), 6.81 (br d, J = 8.5 Hz, 1H), 6.27 - 5.98 (m, 1H), 5.58 - 5.34 (m, 1H), 4.74 - 4.66 (m, 1H), 4.61 - 4.48 (m, 1H), 4.38 - 4.25 (m, 2H), 4.08 - 3.72 (m, 3H), 3.71 - 3.46 (m, 3H), 3.22 - 2.98 (m, 7H), 2.92 - 2.76 (m, 4H), 2.74 - 2.49 (m, 2H), 2.46 - 2.17 (m, 2H), 2.16 - 2.00 (m, 3H).

Example 446

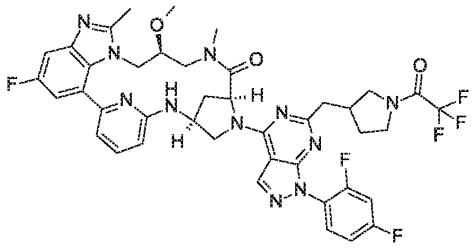
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylpyrrolidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **446** was prepared in analogy to the preparation of Example **443** by using *tert*-butyl 3-(iodomethyl)pyrrolidine-1-carboxylate instead of *tert*-butyl 3-iodopyrrolidine-1-carboxylate. Example **446** (14 mg). LCMS ($M+H^+$): 830. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (d, J = 3.1 Hz, 1H), 7.90 (t, J = 7.9 Hz, 1H), 7.75 - 7.46 (m, 3H), 7.38 - 7.12 (m, 3H), 6.81 (d, J = 8.5 Hz, 1H), 6.15 (td, J = 4.7, 15.3 Hz, 1H), 5.59 - 5.31 (m, 1H), 4.71 (br t, J = 4.6 Hz, 1H), 4.61 - 4.49 (m, 1H), 4.48 - 4.25 (m, 2H), 4.20 - 3.90 (m, 1H), 3.61 - 3.39 (m, 3H), 3.22 - 3.07 (m, 4H), 3.06 - 2.96 (m, 5H), 2.93 - 2.78 (m, 8H), 2.76 - 2.64 (m, 1H), 2.63 - 2.50 (m, 2H), 2.28 - 2.07 (m, 1H), 1.88 - 1.66 (m, 1H).

Example 447

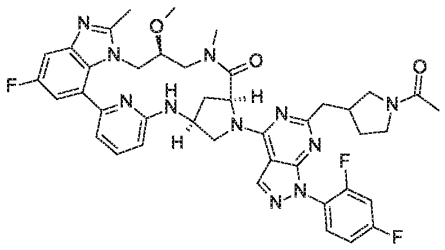
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **447** was prepared in analogy to the preparation of Example **443** by using *tert*-butyl 3-(iodomethyl)pyrrolidine-1-carboxylate instead of *tert*-butyl 3-iodopyrrolidine-1-carboxylate and (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate instead of methanesulfonic anhydride. Example **447** (9 mg). LCMS ($M+H^+$): 848. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (s, 1H), 7.90 (t, J = 7.9 Hz, 1H), 7.75 - 7.47 (m, 3H), 7.36 - 7.10 (m, 3H), 6.87 - 6.75 (m, 1H), 6.25 - 6.02 (m, 1H), 5.61 - 5.36 (m, 1H), 4.75 - 4.66 (m, 1H), 4.60 - 4.48 (m, 1H), 4.42 - 4.24 (m, 2H), 4.09 - 3.79 (m, 2H), 3.77 - 3.46 (m, 2H), 3.20 - 3.03 (m, 4H), 3.02 - 2.91 (m, 5H), 2.90 - 2.78 (m, 5H), 2.76 - 2.67 (m, 1H), 2.66 - 2.49 (m, 2H), 2.30 - 2.07 (m, 1H), 1.94 - 1.66 (m, 1H).

Example 448

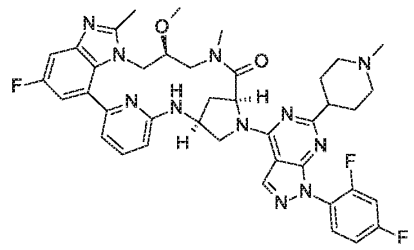
(8*S*,11*S*,15*R*)-10-[6-[(1-acetylpyrrolidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



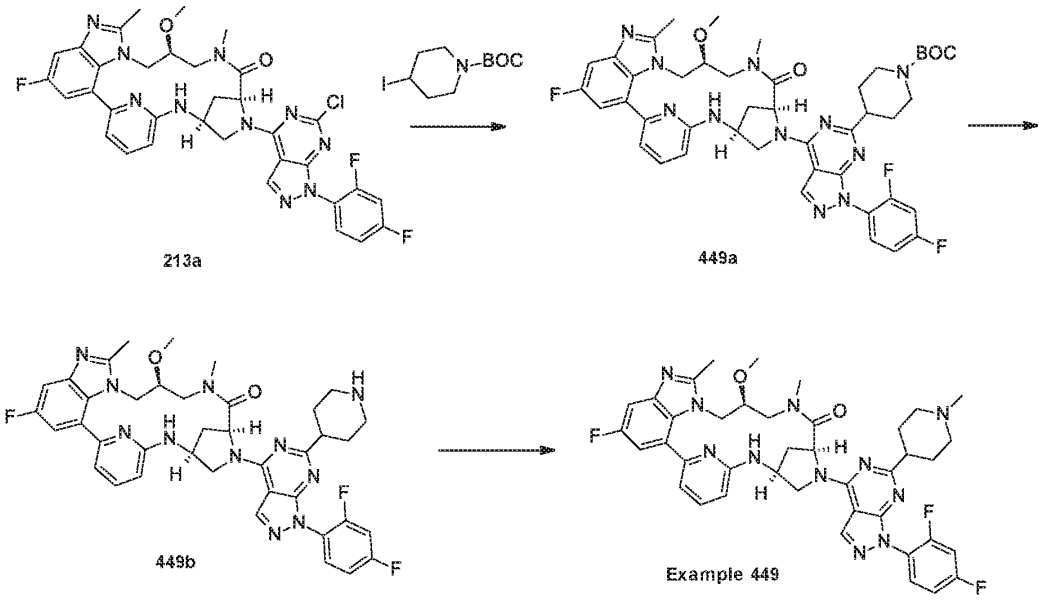
Examples **448** was prepared in analogy to the preparation of Example **443** by using *tert*-butyl 3-(iodomethyl)pyrrolidine-1-carboxylate instead of *tert*-butyl 3-iodopyrrolidine-1-carboxylate and acetyl acetate instead of methanesulfonic anhydride. Example **448** (12 mg). LCMS (M+H$^+$): 794. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.45 (m, 1H), 7.96 - 7.79 (m, 1H), 7.73 - 7.48 (m, 3H), 7.35 - 7.14 (m, 3H), 6.88 - 6.76 (m, 1H), 6.22 - 6.01 (m, 1H), 5.60 - 5.36 (m, 1H), 4.73 - 4.68 (m, 1H), 4.59 - 4.49 (m, 1H), 4.40 - 4.23 (m, 2H), 4.04 - 3.82 (m, 1H), 3.74 - 3.55 (m, 2H), 3.54 - 3.43 (m, 1H), 3.21 - 3.06 (m, 4H), 3.03 - 2.94 (m, 5H), 2.91 - 2.80 (m, 5H), 2.74 - 2.49 (m, 3H), 2.21 - 1.99 (m, 4H), 1.90 - 1.63 (m, 1H).

Example 449

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methyl-4-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1-2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 449b)

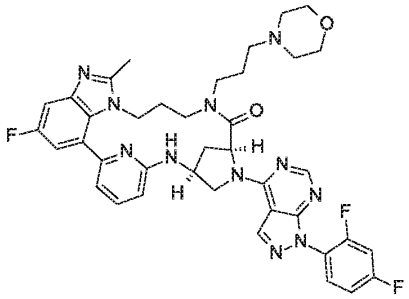
Compound **449b** was prepared in analogy to the preparation of compound **443b** by using *tert*-butyl 3-(iodomethyl)pyrrolidine-1-carboxylate instead of *tert*-butyl 3-iodopyrrolidine-1-carboxylate. LCMS (M+H$^+$): 752.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methyl-4-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 449)

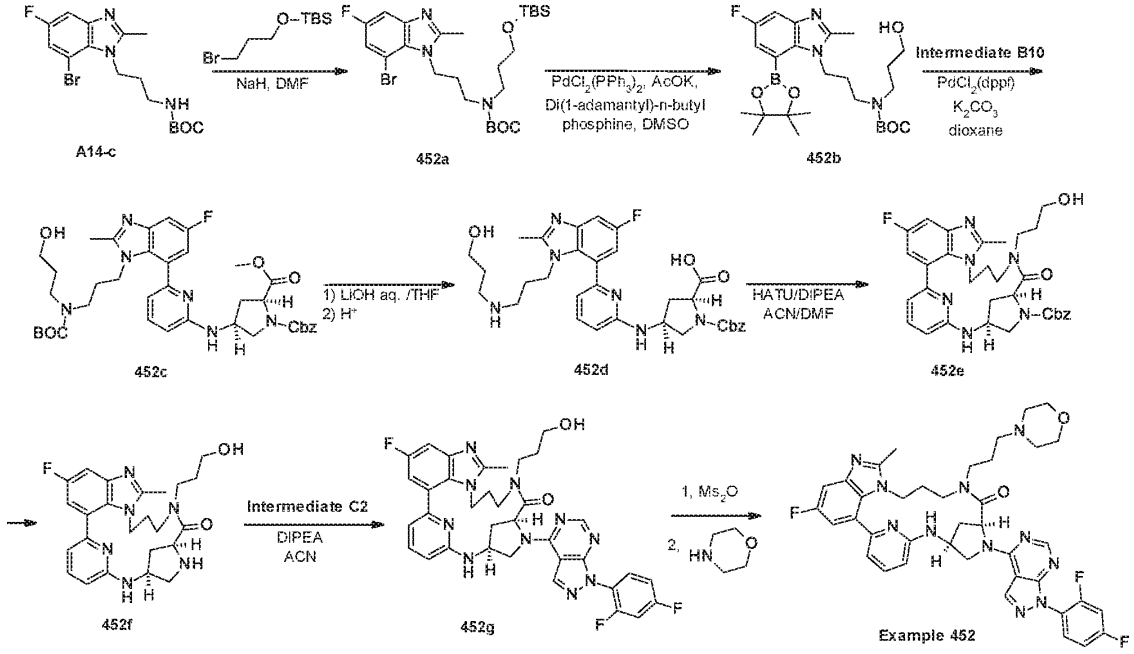
A mixture of compound **449b** (30 mg, 0.04 mmol), formaldehyde (12 mg, 0.4 mmol) and $NaBH_3CN$ (25 mg, 0.4 mmol) was stirred at 40 °C for 6 hours, then the solid was fitered off, the filtrate was concentrated and the residue was purified by prep-HPLC to give Example **449** (5 mg). LCMS (M+H$^+$): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.42 - 7.60 (m, 2H), 7.59 - 7.49 (m, 1H), 7.25 - 6.94 (m, 5H), 6.65 - 6.49 (m, 1H), 5.79 - 5.50 (m, 1H), 5.47 - 5.21 (m, 1H), 4.62 - 4.35 (m, 2H), 4.28 - 4.13 (m, 1H), 4.09 - 3.97 (m, 1H), 3.90 - 3.70 (m, 1H), 3.08 - 2.93 (m, 3H), 2.92 - 2.60 (m, 7H), 2.58 - 2.35 (m, 6H), 2.29 - 2.16 (m, 3H), 2.14 - 1.86 (m, 3H), 1.85 - 1.70 (m, 3H).

Example 452

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-(3-morpholinopropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1-7: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13-(3-hydroxypropyl)-18-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 452g)

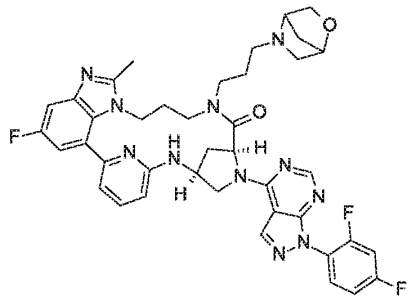
Examples **452g** was prepared in analogy to the preparation of Examples **156** by using intermediate **A14-c** (the synthesis was refer to intermediate **A15-c**) instead of intermediate **A15-c**. LCMS (M+H$^+$): 683.

Step 8: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-(3-morpholinopropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 452)

To a mixture of compound **452g** (200 mg, 0.26 mmol) and DIPEA (340 mg, 2.64 mmol) in dichloromethane (10 mL) was added methanesulfonic anhydride (184 mg, 1.05 mmol) and then stirred at rt for 30 mins. The reaction mixture was diluted with EA, washed with water and brine, the organic layer was concentrated to a residue. Then the residue was dissolved in acetonitrile (2 mL), morpholine (34 mg, 0.4 mmol) and DIPEA (51 mg, 0.4 mmol) was added, the reaction mixture stirred at 80 °C for 2 hours. The reaction mixture was concentrated and the residue was purified by HPLC to Example 452 (3 mg). LCMS (M+H$^+$): 752. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (s, 1H), 8.28 - 7.75 (m, 2H), 7.75 - 7.56 (m, 1H), 7.39 - 7.16 (m, 3H), 7.13 - 6.96 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.85 - 6.68 (m, 1H), 5.65 (br d, J = 4.0 Hz, 1H), 5.04 (br s, 1H), 4.80 - 4.74 (m, 1H), 4.64 - 4.49 (m, 1H), 4.39 - 4.23 (m, 1H), 4.03 - 3.80 (m, 2H), 3.77 - 3.67 (m, 4H), 3.58 - 3.45 (m, 1H), 3.13 - 2.98 (m, 1H), 2.70 - 2.35 (m, 11H), 2.31 - 2.16 (m, 1H), 1.96 - 1.59 (m, 2H), 1.46 - 1.21 (m, 2H).

Example 453

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

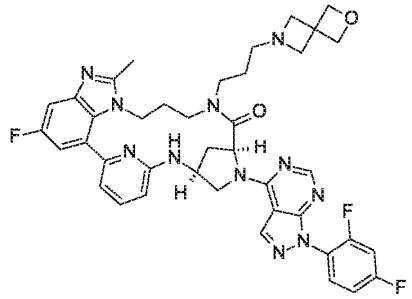


Examples **453** was prepared in analogy to the preparation of Examples **452** by using 2-oxa-5-azabicyclo[2.2.1]heptane instead of morpholine. Example **453** (5 mg). LCMS (M+H$^+$): 764. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.63 - 8.34 (m, 1H), 8.31 - 7.76 (m, 2H), 7.73 - 7.52 (m, 2H), 7.40 - 7.15 (m, 3H), 7.12 - 6.86 (m, 2H), 6.84 - 6.69 (m, 1H), 5.71 - 5.45 (m, 1H), 5.12 - 4.97 (m, 1H), 4.80 - 4.69 (m, 1H), 4.68 - 4.51 (m, 1H), 4.49 - 4.39 (m, 1H), 4.38 - 4.20 (m, 1H), 4.07 - 3.82 (m, 3H), 3.68 - 3.58 (m, 2H), 3.58 - 3.48 (m, 1H), 3.10 - 2.99 (m, 1H), 2.95 - 2.84 (m,

1H), 2.81 - 2.65 (m, 2H), 2.64 - 2.56 (m, 6H), 2.35 - 2.15 (m, 1H), 1.94 - 1.72 (m, 3H), 1.66 - 1.49 (m, 1H), 1.38 - 1.31 (m, 1H).

Example 454

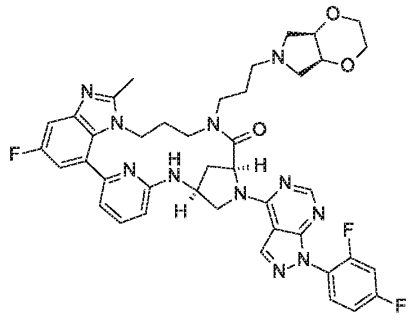
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **454** was prepared in analogy to the preparation of Examples **452** by using 2-oxa-6-azaspiro[3.3]heptane instead of morpholine. Example **454** (6 mg). LCMS (M+H$^+$): 764. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.68 - 8.35 (m, 1H), 8.30 - 7.73 (m, 2H), 7.73 - 7.55 (m, 1H), 7.37 - 7.17 (m, 3H), 7.11 - 6.90 (m, 2H), 6.79 (d, J = 8.3 Hz, 1H), 5.58 (br d, J = 7.3 Hz, 1H), 5.12 - 4.96 (m, 1H), 4.75 (s, 5H), 4.68 - 4.51 (m, 1H), 4.42 - 4.12 (m, 1H), 4.01 - 3.79 (m, 2H), 3.48 - 3.38 (m, 5H), 3.04 - 2.89 (m, 1H), 2.67 - 2.32 (m, 7H), 2.28 - 2.04 (m, 1H), 1.83 - 1.38 (m, 2H), 1.31 (br s, 2H).

Example 455

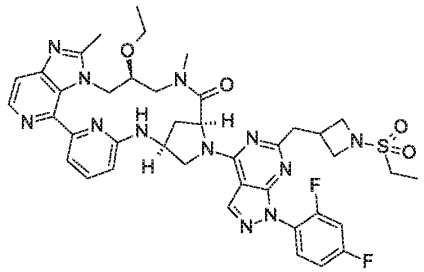
(8*S*,11*S*)-13-[3-[(4a*R*,7a*S*)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]propyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **454** was prepared in analogy to the preparation of Examples **452** by using (4a*S*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole instead of morpholine. Example **455** (8 mg). LCMS ($M+H^+$): 794. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.66 - 8.35 (m, 1H), 8.25 (s, 1H), 7.89 - 7.57 (m, 2H), 7.42 - 7.14 (m, 3H), 7.12 - 6.87 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.73 - 5.47 (m, 1H), 5.14 - 4.97 (m, 1H), 4.79 - 4.70 (m, 1H), 4.63 - 4.51 (m, 1H), 4.40 - 4.22 (m, 1H), 4.17 - 4.03 (m, 2H), 4.00 - 3.72 (m, 4H), 3.69 - 3.44 (m, 3H), 3.30 - 3.21 (m, 1H), 3.09 - 2.85 (m, 3H), 2.85 - 2.74 (m, 2H), 2.71 - 2.48 (m, 6H), 2.30 - 2.13 (m, 1H), 2.02 - 1.79 (m, 1H), 1.79 - 1.53 (m, 1H), 1.42 - 1.18 (m, 2H).

Example 456

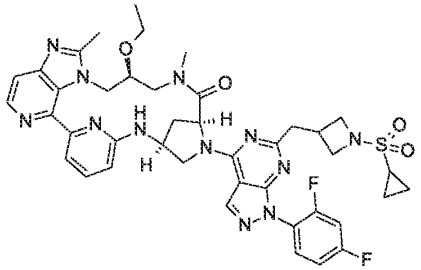
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-ethylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **456** was prepared in analogy to the preparation of Examples **436** by using compound **427b-2** instead of compound **370b** and ethanesulfonyl chloride instead of methylsulfonyl methanesulfonate. Example **456** (9 mg). LCMS ($M+H^+$): 827. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.43 - 8.35 (m, 1H), 8.32 - 8.22 (m, 1H), 7.83 - 7.70 (m, 1H), 7.61 - 7.49 (m, 2H), 7.44 - 7.25 (m, 1H), 7.23 - 7.01 (m, 2H), 6.74 - 6.62 (m, 1H), 5.95 - 5.76 (m, 1H), 5.48 - 5.26 (m, 1H), 4.64 - 4.54 (m, 1H), 4.48 - 4.41 (m, 1H), 4.27 - 4.09 (m, 2H), 4.00 - 3.64 (m, 5H), 3.05 - 2.76 (m, 10H), 2.75 - 2.65 (m, 1H), 2.65 - 2.29 (m, 7H), 1.25 - 1.09 (m, 3H), 0.55 - 0.39 (m, 3H).

Example 457

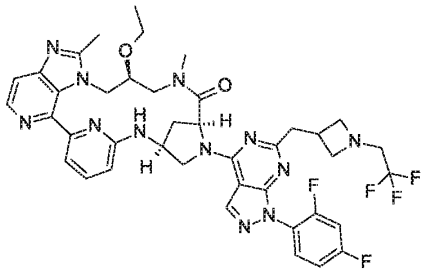
(8*S*,11*S*,15*R*)-10-[6-[(1-cyclopropylsulfonylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Examples **457** was prepared in analogy to the preparation of Examples **436** by using compound **427b-2** instead of compound **370b** and cyclopropanesulfonyl chloride instead of methylsulfonyl methanesulfonate. Example **457** (9 mg). LCMS ($M+H^+$): 839. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.41 - 8.33 (m, 1H), 8.32 - 8.24 (m, 1H), 7.82 - 7.73 (m, 1H), 7.61 - 7.46 (m, 2H), 7.38 - 7.32 (m, 1H), 7.23 - 7.03 (m, 2H), 6.72 - 6.62 (m, 1H), 5.93 - 5.73 (m, 1H), 5.48 - 5.25 (m, 1H), 4.62 - 4.58 (m, 1H), 4.45 - 4.41 (m, 1H), 4.24 - 4.11 (m, 2H), 3.96 - 3.71 (m, 5H), 3.04 - 2.95 (m, 4H), 2.95 - 2.86 (m, 2H), 2.84 - 2.79 (m, 1H), 2.75 - 2.69 (m, 1H), 2.60 - 2.54 (m, 4H), 2.54 - 2.35 (m, 3H), 1.06 - 0.84 (m, 4H), 0.81 - 0.70 (m, 1H), 0.52 - 0.43 (m, 3H).

Example 458

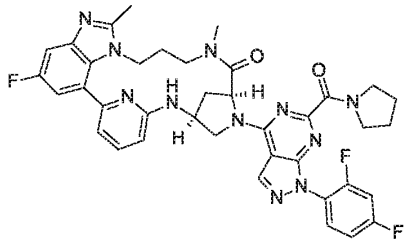
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



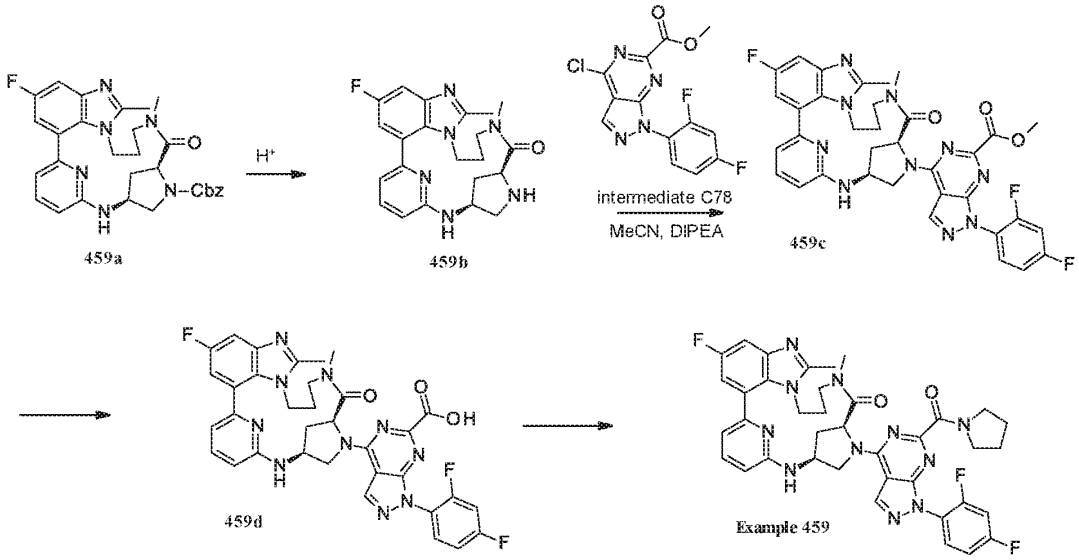
Examples **458** was prepared in analogy to the preparation of Examples **436** by using compound **427b-2** instead of compound **370b** and 2,2,2-trifluoroethyl trifluoromethanesulfonate instead of methylsulfonyl methanesulfonate. Example **458** (5 mg). LCMS ($M+H^+$): 817. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.00 - 7.92 (m, 1H), 7.90 - 7.77 (m, 1H), 7.41 - 7.30 (m, 1H), 7.20 - 7.05 (m, 2H), 6.99 - 6.91 (m, 1H), 6.80 - 6.64 (m, 2H), 6.30 - 6.23 (m, 1H), 5.56 - 5.33 (m, 1H), 5.04 - 4.83 (m, 1H), 4.26 - 4.16 (m, 1H), 4.07 - 3.94 (m, 1H), 3.84 - 3.63 (m, 2H), 3.55 - 3.39 (m, 1H), 3.22 - 3.07 (m, 2H), 2.74 - 2.53 (m, 8H), 2.49 - 1.96 (m, 11H), 0.13 - -0.01 (m, 3H).

Example 459

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(pyrrolidine-1-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*)-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one (compound 459b)

A mixture of compound **459a** (1.2 g, 2.21 mmol, prepared in analogy to compound **12c** by using intermediate **A14** instead of intermediate **A11**) in TFA (20 mL) was stirred for 4 hours at 100 ° C, then the reaction was concentrated, the residue was dissolved in EA, 4M HCl in dioxane (10 mL) was added, then off white solid was precipitated, the solid was collected by filtration to give compound **459b** (1 g) as off-white solid. LCMS (M+H$^+$): 409.

Step 2: preparation of methyl 1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-22-fluoro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylate (compound 459c)

A mixture of compound **459b** (150 mg, 0.37 mmol), intermediate **C78** (131 mg, 0.4 mmol) and DIPEA (237 mg, 1.8 mmol) in acetonitrile (10 mL) was stirred at 45 °C for 1 hour, then the reaction was diluted with EA, washed with water and brine, the organic layer was dried and concentrated to give compound **459c** (200 mg) as light yellow foam. LCMS ($M+H^+$): 697.

Step 3: preparation of 1-(2,4-difluorophenyl)-4-[(8*S*,11*S*)-22-fluoro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylic acid (compound 459d)

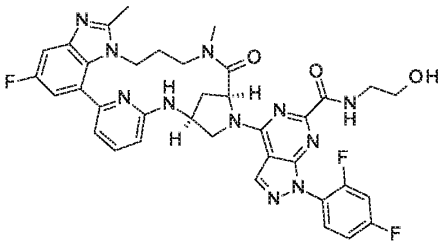
A mixture of **compound 459d** (200 mg, 0.29 mmol) and 2 M LiOH (718 μL, 1.44 mmol,) in methanol (10 mL) was stirred at rt for 2 hours, then the reaction was adjusted to pH = 6. The resulted mixture was concentrated and the residue was dissolved in MeOH, after the solid was removed by filtration, the filtrated was concentrated to give compound **459d** (150 mg) as light yellow solid. LCMS ($M+H^+$): 683.

Step 3: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(pyrrolidine-1-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 459)

A mixture of compound **459d** (50 mg, 0.07 mmol), pyrrolidine (52 mg, 0.73 mmol), HATU (55 mg, 0.14 mmol) and DIPEA (95 mg, 0.73 mmol) in N,N-dimethylformamide (3 mL) was stirred at rt for 1 hour, then the reaction mixture was purified by prep-HPLC to give Example **459** (30 mg) as white powder. LCMS ($M+H^+$): 736, ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.85 - 7.69 (m, 1H), 7.65 - 7.40 (m, 2H), 7.38 - 7.29 (m, 1H), 7.25 - 7.02 (m, 2H), 7.01 - 6.86 (m, 1H), 6.80 - 6.66 (m, 1H), 5.68 - 5.30 (m, 2H), 4.66 (s, 1H), 4.53 - 4.42 (m, 1H), 4.26 - 4.15 (m, 1H), 4.10 - 3.87 (m, 2H), 3.56 - 3.28 (m, 4H), 3.11 - 2.89 (m, 3H), 2.87 - 2.73 (m, 4H), 2.71 - 2.54 (m, 1H), 2.54 - 2.39 (m, 1H), 2.08 - 1.72 (m, 5H), 1.39 - 1.16 (m, 1H).

Example 460

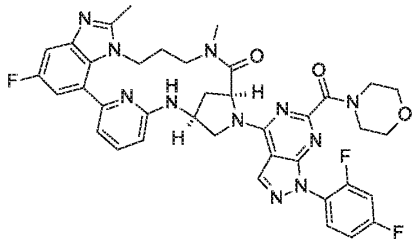
1-(2,4-difluorophenyl)-4-[(8S,11S)-22-fluoro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]-N-(2-hydroxyethyl)pyrazolo[3,4-d]pyrimidine-6-carboxamide



Examples **460** was prepared in analogy to the preparation of Examples **459** by using 2-aminoethanol instead of pyrrolidine. LCMS ($M+H^+$): 726. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 - 7.71 (m, 2H), 7.67 - 7.51 (m, 1H), 7.45 (dd, J = 2.5, 7.3 Hz, 1H), 7.40 - 7.29 (m, 1H), 7.25 - 7.03 (m, 2H), 7.02 - 6.86 (m, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.85 - 5.30 (m, 2H), 4.66 - 4.58 (m, 1H), 4.55 - 4.41 (m, 1H), 4.36 - 4.19 (m, 1H), 4.12 - 3.89 (m, 2H), 3.73 - 3.52 (m, 2H), 3.50 - 3.29 (m, 2H), 3.08 - 2.94 (m, 3H), 2.93 - 2.80 (m, 1H), 2.76 - 2.70 (m, 3H), 2.63 (s, 1H), 2.55 - 2.36 (m, 1H), 2.10 - 1.67 (m, 1H), 1.41 - 1.08 (m, 1H).

Example 461

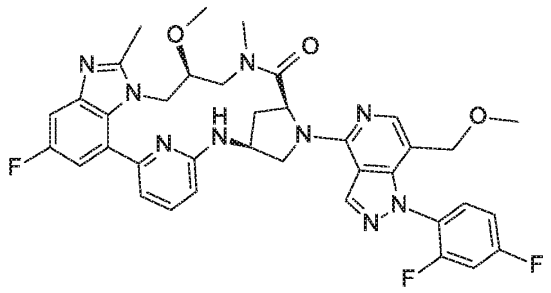
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(morpholine-4-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



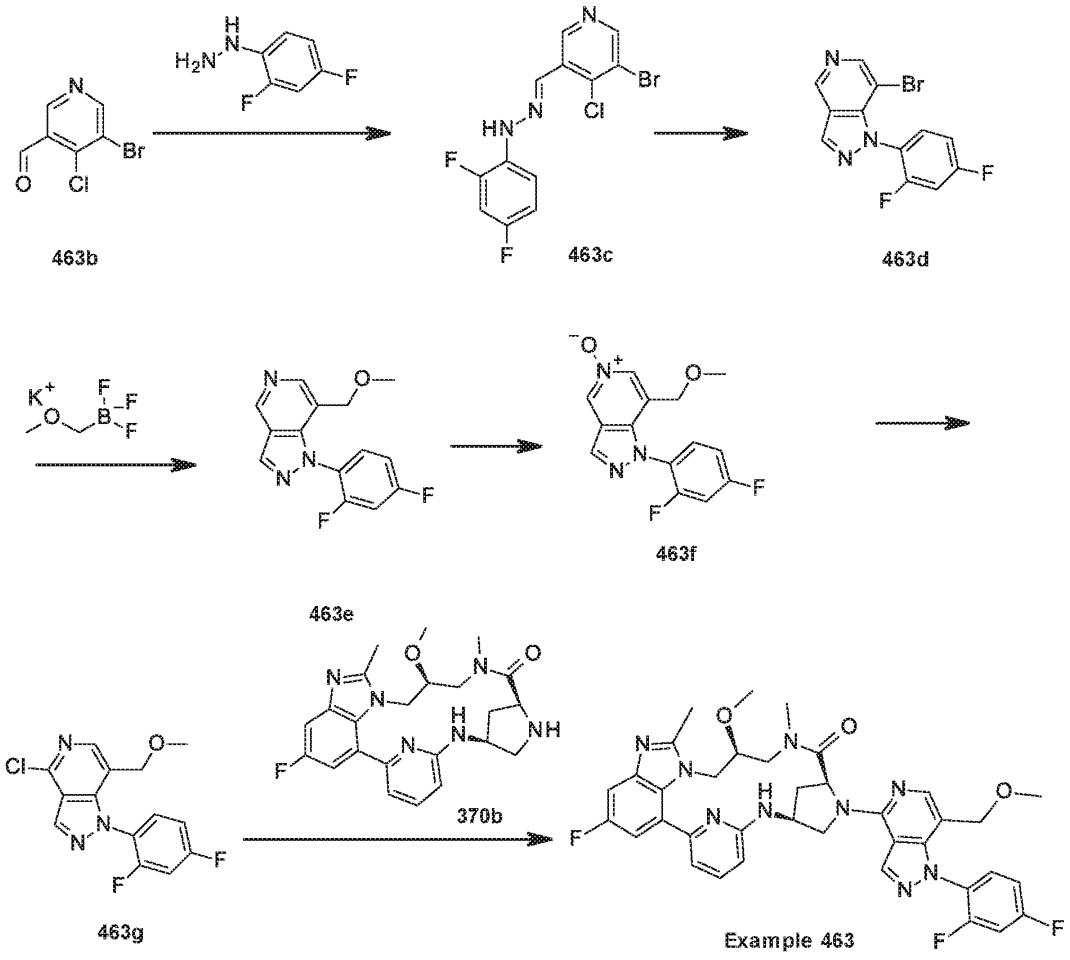
Examples **461** was prepared in analogy to the preparation of Examples **459** by using morpholine instead of pyrrolidine. LCMS ($M+H^+$): 752. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.88 - 7.69 (m, 1H), 7.57 (dq, J = 5.8, 8.7 Hz, 1H), 7.46 (dd, J = 2.4, 7.4 Hz, 1H), 7.39 - 7.29 (m, 1H), 7.25 - 7.04 (m, 2H), 6.99 - 6.89 (m, 1H), 6.80 - 6.65 (m, 1H), 5.65 - 5.31 (m, 2H), 4.64 (br t, J = 5.1 Hz, 1H), 4.55 - 4.43 (m, 1H), 4.30 - 4.11 (m, 1H), 4.11 - 3.88 (m, 2H), 3.73 - 3.40 (m, 6H), 3.38 - 3.24 (m, 2H), 3.07 - 2.90 (m, 3H), 2.89 - 2.72 (m, 4H), 2.69 - 2.57 (m, 1H), 2.53 - 2.40 (m, 1H), 2.03 - 1.76 (m, 1H), 1.34 - 1.14 (m, 1H).

Example 463

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(methoxymethyl)pyrazolo[4,3-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 3-bromo-4-chloro-5-((2-(2,4-difluorophenyl)hydrazineylidene) methyl)pyridine (compound 463c)

The mixture of 2,4-difluorophenylhydrazine hydrochloride (983 mg, 5.44 mmol,) and compound **463b** (1000 mg, 4.54 mmol) in DMF (10 mL) was stirred at 25 °C for 4 hrs. The mixture was poured into water (30 mL) to afford a solid, the resulting solid was filtered and the

filter-cake was washed with water (30 mL), then dried under reduced pressure to give compound **463c** (1300 mg). LCMS ($M+2H^+$): 348.

Step 2: preparation of 7-bromo-1-(2, 4-difluorophenyl)-1*H*-pyrazolo [4, 3-c] pyridine (compound 463d)

A suspension of compound **463c** (3000 mg, 8.66 mmol), DBU (2649 mg, 17 mmol,) and molecular sieve (200 mg) in NMP (100 mL) was stirred at 100 °C for 16 hrs. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to give compound **463d** (710 mg). LCMS ($M+2H^+$): 312.

Step 3: preparation of 1-(2,4-difluorophenyl)-7-(methoxymethyl)-1*H*-pyrazolo[4,3-c]pyridine(compound 463e)

To a mixture of compound **463d** (500 mg, 1.29 mmol), potassium methoxymethyl trifluoroborate (392 mg, 2.58 mmol) and Cs_2CO_3 (2102 mg, 6.45 mmol) in 1,4-Dioxane (7 mL) and water (3 mL) was added $Pd(dppf)Cl_2$ (168 mg, 0.26 mmol), then the mixture was stirred at 100 °C for 16 hrs. The reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (50 mL×3). The combined organic layer was concentrated under reduced pressure to obtained a residue, the residue was purified by prep-HPLC to give compound **463e** (190 mg). LCMS ($M+H^+$): 276.

Step 4: preparation of 1-(2,4-difluorophenyl)-7-(methoxymethyl)-1*H*-pyrazolo[4,3-c]pyridine 5-oxide (compound 463f)

To a solution of compound **463e** (150 mg, 0.54 mmol) in DCM (5 mL) was added mCPBA (140.6 mg, 0.82 mmol), then the mixture was stirred at 25 °C for 5 hrs. The reaction mixture was quenched with sat. aq. Na_2SO_3 (10 mL×2), and extracted with EtOAc (5 mL×3). The combined organic layer was washed with brine (20 mL×2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC to give the compound **463f** (60 mg). LCMS ($M+H^+$): 292.

Step 5: preparation of 4-chloro-1-(2,4-difluorophenyl)-7-(methoxymethyl)-1*H*-pyrazolo[4,3-c]pyridine (compound 463g)

A solution of compound **463f** (60 mg, 0.21 mmol) in $POCl_3$ (1 ml) was stirred at 90 °C for 5 hrs. The reaction mixture was quenched with sat.aq. $NaHCO_3$ (5 mL) at 0 °C, then extracted with DCM(10 mL×3), the combined organic layer was concentrated under reduced pressure to

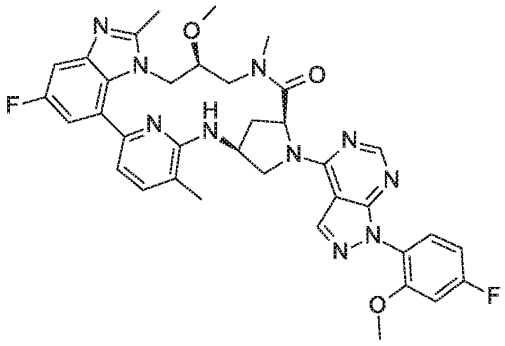
give a residue, the residue was purified by prep-HPLC to give compound **463g** (50 mg). LCMS ($M+H^+$): 310.

Step 6: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(methoxymethyl)pyrazolo[4,3-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 463)

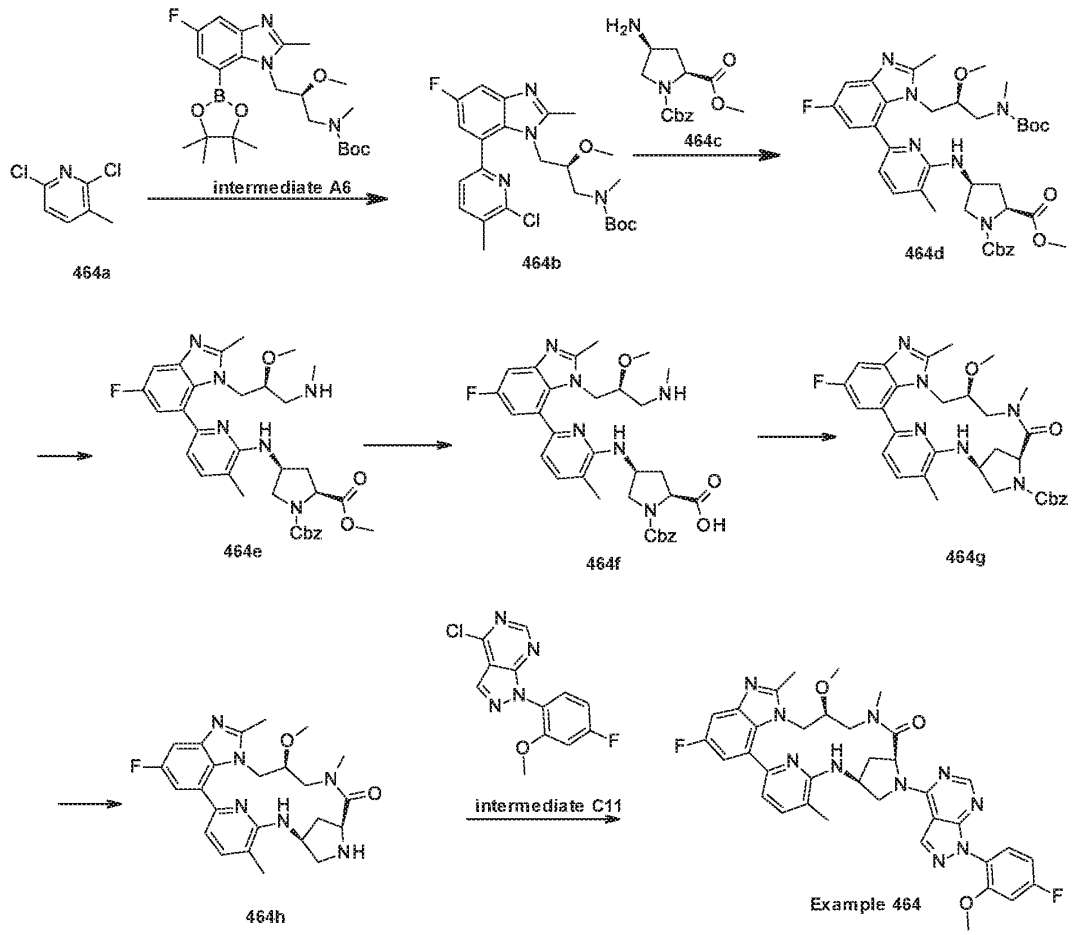
A mixture of compound **370b** (142 mg, 0.32 mmol), CsF (25 mg, 0.16 mmol), compound **463g** (50 mg, 0.16 mmol) and DIEA (63 mg, 0.48 mmol) in *N,N*-dimethylacetamide (2 mL) was stirred at 130 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (DCM/MeOH=10/1) to give Example **463** (7.0 mg). LCMS ($M+H^+$): 712. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.68 - 8.47 (m, 1H), 7.84 - 7.64 (m, 3H), 7.62 - 7.53 (m, 1H), 7.39 - 7.26 (m, 2H), 7.22 (s, 1H), 7.16 - 7.07 (m, 2H), 6.65 (br d, *J* = 8.8 Hz, 1H), 5.73 - 5.51 (m, 2H), 5.47 - 5.27 (m, 2H), 4.67 - 4.41 (m, 2H), 4.07 - 3.99 (m, 2H), 3.98 - 3.92 (m, 1H), 3.82 - 3.72 (m, 1H), 3.50 (s, 2H), 3.01 - 2.89 (m, 3H), 2.72 (d, *J* = 1.6 Hz, 6H), 2.34 - 2.32 (m, 1H), 2.03 - 1.94 (m, 3H).

Example 464

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-5,13,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl *N*-[(2*R*)-3-[7-(6-chloro-5-methyl-2-pyridyl)-5-fluoro-2-methyl-benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (compound 464b)

To a suspension of compound **464a** (2036 mg, 12.57 mmol), intermediate **A6** (1000 mg, 2.09 mmol) and K_2CO_3 (867 mg, 6.28 mmol) in 1,4-Dioxane (10 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (342 mg, 0.42 mmol), then the mixture was stirred at 70 °C for 8 hrs under nitrogen atmosphere. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give compound **464b** (450 mg). LCMS ($M+H^+$): 477.

Step 2: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[6-[3-[(2*R*)-3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-3-methyl-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 464d)

To a suspension of **464c**(439 mg, 1.58 mmol), **464b** (400.0 mg, 0.79 mmol) and Cs_2CO_3 (1028 mg, 3.15 mmol) in 1,4-Dioxane (5 mL) was added *t*-Bu_3P-Pd-G2 (80.72 mg, 0.16 mmol) under nitrogen atmosphere, then the mixture was stirred at 90 °C for 16 hrs. The reaction mixture was concentrated to give compound **464d** (600 mg). LCMS ($M+H^+$): 719.

Step 3: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[[6-[6-fluoro-3-[(2*S*)-2-methoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]-3-methyl-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound 464e)

To a solution of compound **464d** (600 mg, 0.83 mmol) in 1,4-Dioxane (10 mL) was added HCl/Dioxane (4 M, 10 mL), then the mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give compound **464e** (500 mg). LCMS ($M+H^+$): 619.

Step 4: preparation of (2*S*,4*S*)-1-benzyloxycarbonyl-4-[[6-[6-fluoro-3-[(2*S*)-2-methoxy-3-(methylamino)propyl]-2-methyl-benzimidazol-4-yl]-3-methyl-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound 464f)

To a solution of compound **464e** (500 mg, 0.81 mmol) in methanol (3 mL) was added a solution of LiOH (372 mg, 16.16 mmol) in water (1 mL), then the mixture was stirred at 25 °C for 0.5 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give compound **464f** (480 mg). LCMS ($M+H^+$): 605.

Step 5: benzyl (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-5,13,18-trimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-10-carboxylate (compound 464g)

To a solution of HATU (560 mg, 1.47 mmol) and DIPEA (253 mg, 1.96 mmol) in DMF (120 mL) was added a solution of compound **464f** (297 mg, 0.49 mmol) in DMF (360 mL) slowly, then the mixture was stirred at 25 °C for 0.5 hrs. The reaction was concentrated and the residue was purified by prep-HPLC (0.1%TFA) to give compound **464g** (50 mg). LCMS ($M+H^+$): 587.

Step 6: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-5,13,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (compound 464h)

A solution of compound **464g** (50 mg, 0.09 mmol) in TFA (2 mL) was stirred at 90 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give compound **464h** (50 mg). LCMS ($M+H^+$): 453.

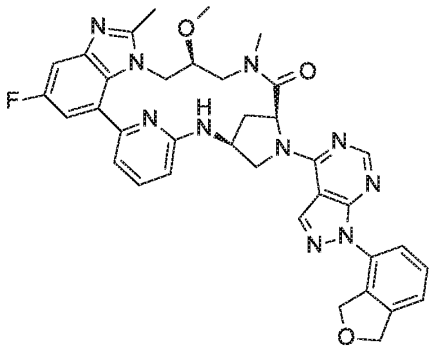
Step 7: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-5,13,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 464)

A mixture of compound **464h** (50 mg, 0.11 mmol), DIEA (57 mg, 0.44 mmol) and intermediate **C11** (31 mg, 0.11 mmol) in ACN (2 mL) was stirred at 85 °C for 1 hr. The reaction

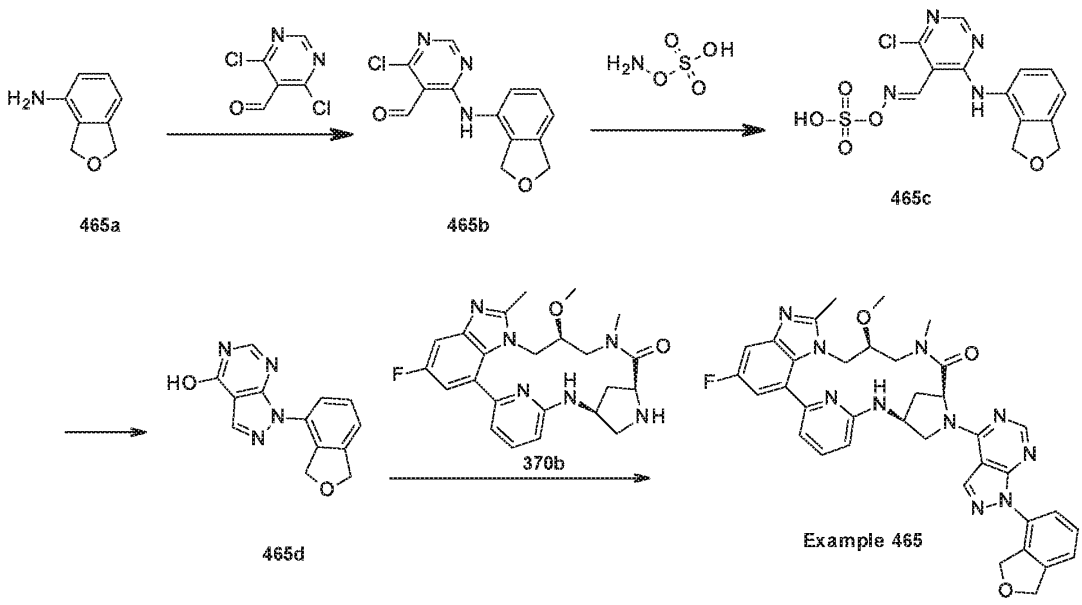
mixture was concentrated and the residue was purified by prep-HPLC to give **Example 464** (14 mg). LCMS ($M+H^+$): 695. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.12 (s, 1H), 8.49 (s, 1H), 8.19 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.50 - 7.40 (m, 1H), 7.39 - 7.37 (m, 1H), 7.24 - 7.16 (m, 2H), 6.98 - 6.90 (m, 1H), 6.48 (d, J = 7.2 Hz, 1H), 5.64 - 5.51 (m, 1H), 5.19 - 5.05 (m, 1H), 4.67 (d, J = 10.9 Hz, 1H), 4.45 (s, 2H), 4.32 (s, 1H), 4.20 (dd, J = 4.0, 10.8 Hz, 1H), 4.07 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.87 - 2.81 (m, 3H), 2.75 - 2.70 (m, 3H), 2.47 (s, 1H), 2.41 (s, 2H), 2.11 (s, 3H).

Example 465

(8*S*,11*S*,15*R*)-10-[1-(1,3-dihydroisobenzofuran-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1~3: preparation of 1-(1,3-dihydroisobenzofuran-4-yl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 465d)

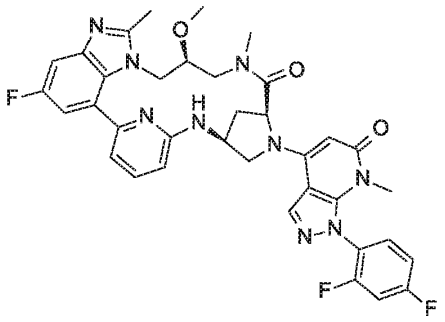
Compound **465d** was prepared in analogy to the preparation of intermediate **C10** by using compound **465a** instead of O-anisidine, LCMS ($M+H^+$): 255.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(1,3-dihydroisobenzofuran-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 465)

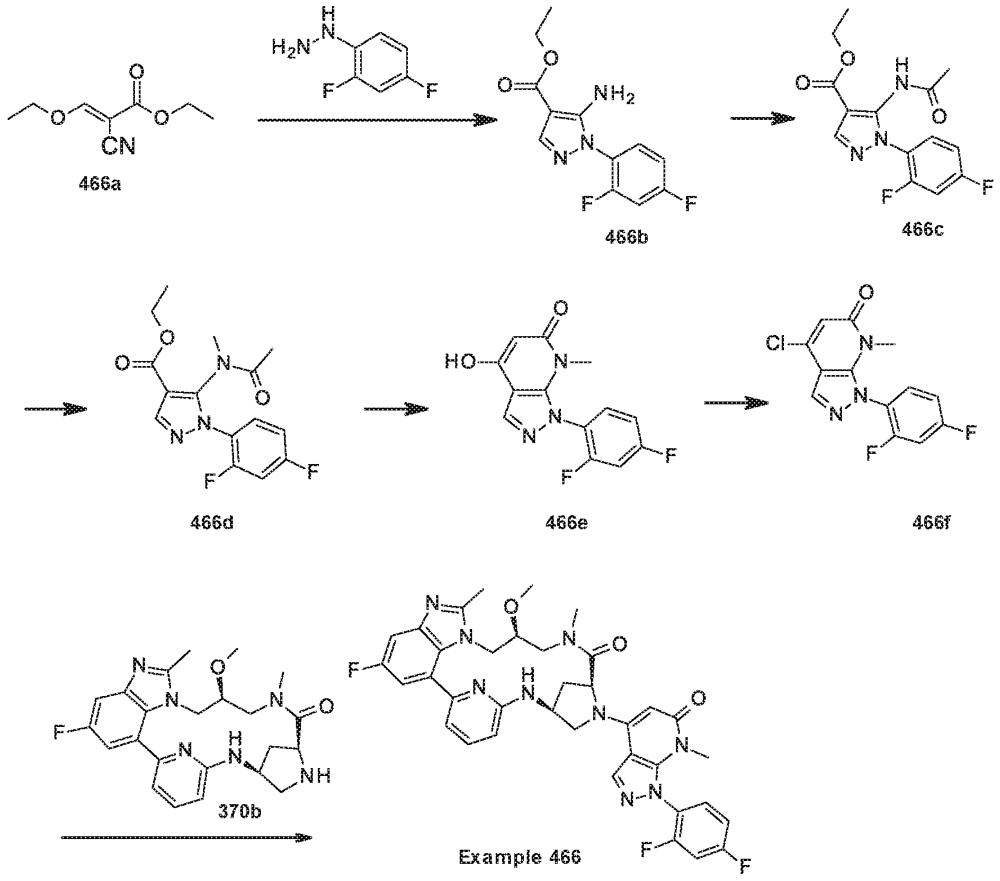
A mixture of compound **465d** (10.4 mg, 0.04 mmol), PyBOP (27.8 mg, 0.05 mmol) and DIEA (13.3 mg, 0.1 mmol) in DMF (0.5 mL) was stirred at 20 °C for 0.5 hrs, then the compound **370b** (18.0 mg, 0.04 mmol) was added and the mixture was stirred at 20 °C for 12 hrs. The reaction mixture was purified by prep-HPLC to give Example **465** (1.9 mg). LCMS ($M+H^+$): 675. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.51 (s, 1H), 8.45 - 8.27 (m, 1H), 8.04 - 7.95 (m, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.61 - 7.45 (m, 3H), 7.40 - 7.33 (m, 1H), 7.20 - 7.13 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.19 - 6.01 (m, 1H), 5.51 - 5.41 (m, 1H), 5.28 - 5.22 (m, 2H), 5.18 (s, 2H), 4.71 - 4.67 (m, 1H), 4.57 - 4.50 (m, 1H), 4.41 - 4.23 (m, 2H), 4.00 - 3.87 (m, 1H), 3.35 (s, 1H), 3.16 (s, 1H), 3.06 (s, 2H), 2.97 (s, 3H), 2.90 - 2.80 (m, 1H), 2.82 (s, 3H), 2.67 - 2.49 (m, 2H).

Example 466

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methyl-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 466b)

To a solution of 2,4-difluorophenylhydrazine hydrochloride (5.0 g, 28 mmol) in ethanol (50 mL) was added compound **466a** (5.62 g, 33 mmol) and DIPEA (9.81 mL, 55 mmol) at 25 °C, then the mixture was stirred at 90 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford a residue. The residue was purified by flash chromatography to afford compound **466b** (6.4 g). LCMS ($M+H^+$): 268.

Step 2: preparation of ethyl 5-acetamido-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 466c)

To a solution of compound **466b** (2.0 g, 7.5 mmol) in chloroform (10 mL) was added acetyl chloride (1 mL, 15 mmol) at 25 °C, and the mixture was stirred at 65 °C for 16 hrs. The reaction was concentrated in *vacuo*. The residue was purified by flash chromatography to afford compound **466c** (2.13 g). LCMS ($M+H^+$): 310.

Step 3: preparation of ethyl 5-[acetyl(methyl)amino]-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 466d)

To a solution of NaH (327 mg, 8.2 mmol) in DMF (20 mL) was added compound **466c** (2.1 g, 6.79 mmol) in DMF (10 mL) dropwise at 0 °C under N_2 atmosphere, after being stirred at 0 °C for 0.5 hrs, iodomethane (0.85 mL, 13.6 mmol) was added. The reaction mixture was stirred at 20 °C for 1.5 hrs, then the reaction was poured into sat.NH_4Cl (50 mL) and extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by flash chromatography to afford compound **466d** (1.93 g). LCMS ($M+H^+$): 324.

Step 4: preparation of 1-(2,4-difluorophenyl)-4-hydroxy-7-methyl-pyrazolo[3,4-b]pyridin-6-one (compound 466e)

To a stirred solution of compound **466d** (1.8 g, 5.57 mmol) in THF (20 mL) was added LDA (6.96 mL, 13.92 mmol) dropwise at -78°C under N_2 atmosphere, and the mixture was stirred at 20 °C for 2 hrs. The reaction was poured into water (50 mL) and extracted with ethyl acetate. The aqueous phase was adjusted pH to 4-5, and extracted with ethyl acetate, the organic phase was dried and concentrated to afford compound **466e** (0.9 g). LCMS ($M+H^+$): 278.

Step 5: preparation of 4-chloro-1-(2,4-difluorophenyl)-7-methyl-pyrazolo[3,4-b]pyridin-6-one (compound 466f)

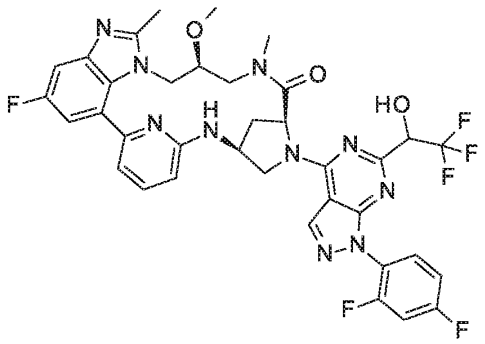
To a solution of compound **466e** (100 mg, 0.36 mmol) in MeCN (1 mL) was added phosphorus oxychloride (0.04 mL, 0.39 mmol) dropwise at 25 °C, and the reaction mixture was stirred at 80 °C for 3 hrs. The reaction was poured into sat.$NaHCO_3$ (15 mL) at 0 °C, and extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by flash chromatography to afford compound **466f** (60.0 mg). LCMS (M+H+): 296.

Step 6: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methyl-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 466)

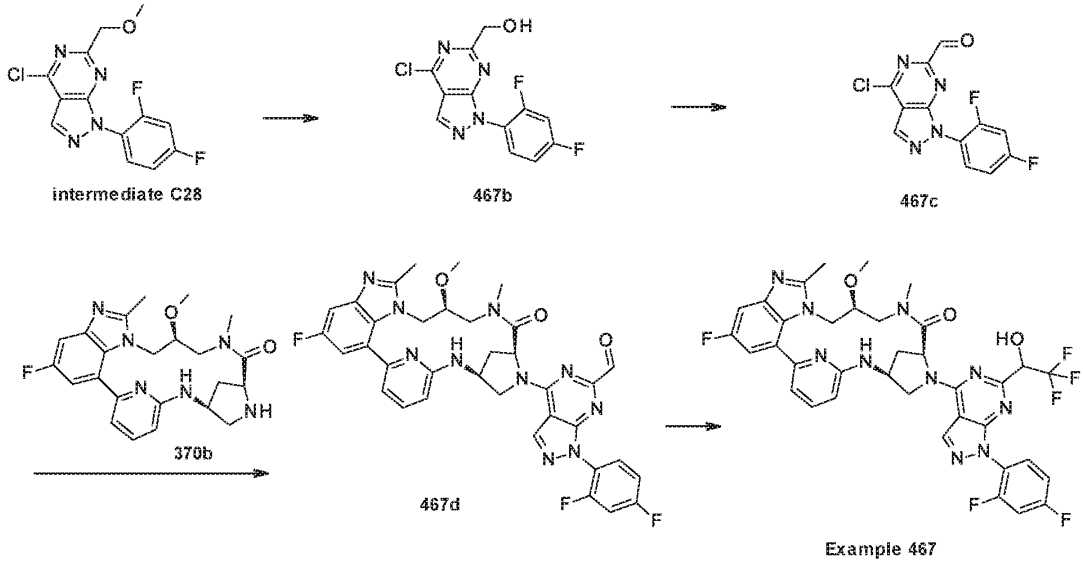
To a solution of compound **466f** (7 mg, 0.02 mmol) and compound **370b** (11 mg, 0.02 mmol) in DMSO (1 mL) was added N,N-diisopropylethylamine (0.01 mL, 0.03 mmol) and cesium fluoride (6.0 mg, 0.04 mmol), the reaction mixture was stirred at 130 °C for 6 hrs. Then the reaction mixture was purified by prep-HPLC to afford Example **466** (4.03 mg). LCMS ($M+H^+$): 698. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.33 (s, 1H), 7.92 - 7.81 (m, 2H), 7.65 - 7.58 (m, 2H), 7.59 - 7.43 (m, 2H), 7.37 - 7.34 (m, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.84 - 5.67 (m, 2H), 5.41 - 5.18 (m, 1H), 4.94 - 4.85 (m, 1H), 4.50 - 4.43 (m, 1H), 4.28 - 4.17 (m, 2H), 3.91 - 3.82 (m, 2H), 3.01 (s, 3H), 2.98 (s, 2H), 2.81 (s, 3H), 2.69 (s, J = 1.5 Hz, 3H), 2.67 (s, 1H), 2.33 (s, 3H).

Example 467

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoro-1-hydroxy-ethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of [4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methanol (compound 467b)

To a solution of intermediate **C28** (500 mg, 1.6 mmol) in DCM (20 mL) was added BCl_3/DCM (8.05 mL, 8.05 mmol) slowly at -78 °C, then the mixture was stirred at -78 °C for 1 h and stirred at 25 °C for 16 hrs. The reaction mixture was quenched with ice-water, and then extracted with DCM. The organic layer was dried and concentrated to give the compound **467b** (450 mg) as a light yellow solid. LCMS ($M+H^+$): 297.

Step 2: preparation of 4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine-6-carbaldehyde (compound 467c)

To a solution of compound **467b** (190 mg, 0.64 mmol) in toluene (10 mL) was added Manganese (IV) oxide (1.1 g, 12.8 mmol). After addition, the mixture was stirred at 110 °C for 8 hrs. Then the mixture was filtered and concentrated to give compound **467c** (110 mg) as a yellow solid. LCMS ($M+H^+$): 295.

Step 3: preparation of 1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5, 18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carbaldehyde (compound 467d)

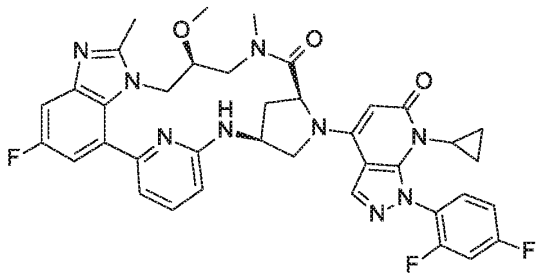
A suspension of compound **370b** (36 mg, 0.07 mmol), DIPEA (0.03 mL, 0.2 mmol) and compound **467c** (20 mg, 0.07 mmol) in ACN (1 mL) was stirred at 85 °C for 1 h. The reaction mixture was cooled to room temperature, EtOAc (40 mL) and water (40 mL) were added and layers were separated. The organic layer was dried and concentrated to give compound **467d** (60 mg) as a yellow solid. LCMS ($M+H^+$): 697.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoro-1-hydroxy-ethyl)pyrazolo [3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 467)

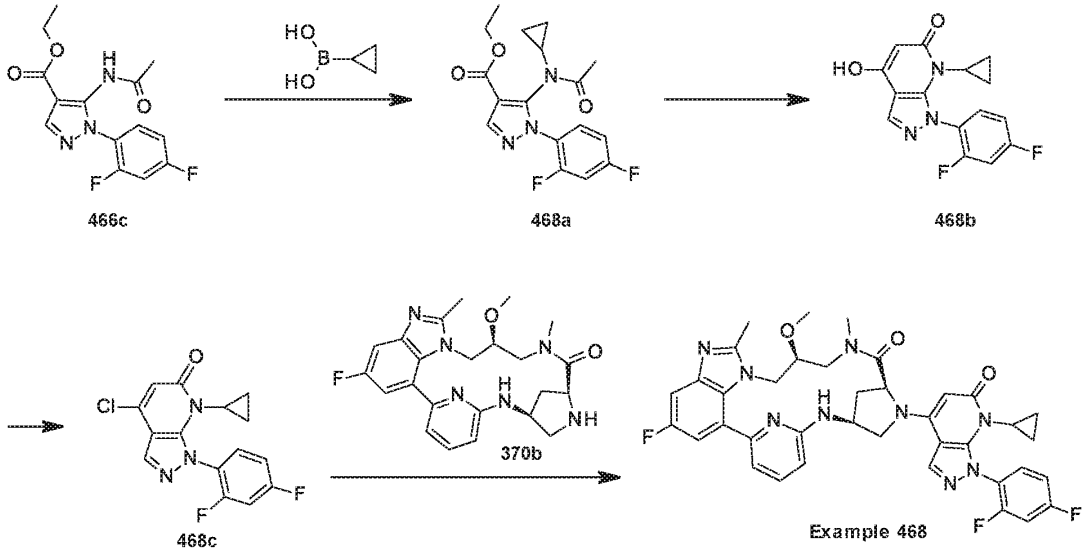
To an ice-water cooled solution of compound **467d** (10.0 mg, 0.01 mmol) in DMF (1 mL) was added K_2CO_3 (5.9 mg, 0.04 mmol), then trifluoromethyltrimethylsilane (20.0 mg, 0.14 mmol) was added dropwise to the solution at 0 °C. Then the reaction was stirred at 20 °C for 2 hrs, the solid was filtered off and the filtrate was purified by preparative HPLC to give Example **467** (2.2 mg). LCMS ($M+H^+$): 767. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 - 8.49 (m, 1H), 7.92 - 7.80 (m, 1H), 7.76 - 7.60 (m, 1H), 7.57 - 7.44 (m, 2H), 7.37 - 7.26 (m, 1H), 7.24 - 7.13 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.20 - 5.94 (m, 1H), 5.70 - 5.39 (m, 1H), 4.90 (s, 1H), 4.71 (br s, 1H), 4.59 - 4.49 (m, 1H), 4.39 - 4.20 (m, 2H), 4.01 - 3.80 (m, 1H), 3.16 - 3.05 (m, 3H), 3.05 - 2.98 (m, 1H), 2.98 - 2.93 (m, 3H), 2.85 (br d, *J* = 13.2 Hz, 1H), 2.81 - 2.74 (m, 3H), 2.71 - 2.48 (m, 2H).

Example 468

(8*S*,11*S*,15*R*)-10-[7-cyclopropyl-1-(2,4-difluorophenyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 5-[acetyl(cyclopropyl)amino]-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 468a)

A suspension of cyclopropylboronic acid (560 mg, 6.5 mmol), compound **466c** (1.0 g, 3.3 mmol), 2,2'-bipyridine (510 mg, 3.3 mmol), sodium carbonate (690 mg, 6.5 mmol) and $Cu(OAc)_2$ (590 mg, 3.3 mmol) in DCE (15 mL) was stirred at 80 °C for 16 hrs under O_2 atmosphere. Then the reaction mixture was filtered and the filtrate was concentrated, the residue was purified by flash chromatography to afford compound **468a** (900 mg). LCMS ($M+H^+$): 350.

Step 2: preparation of 7-cyclopropyl-1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-b]pyridin-6-one (compound 468b)

To a solution of compound **468a** (500.0 mg, 1.43 mmol) in THF (5 mL) was added LDA (1.43 mL, 2.86 mmol) dropwise at -78 °C under N_2 atmosphere, then the mixture was stirred at 20 °C for 1 h. The reaction was poured into water (15 mL) and extracted with ethyl acetate.

The aqueous phase was adjusted pH to 4~5, and extracted with ethyl acetate. The organic phase was dried and concentrated to afford compound **468b** (90 mg). LCMS ($M+H^+$): 304.

Step 3: preparation of 4-chloro-7-cyclopropyl-1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-6-one (compound 468c)

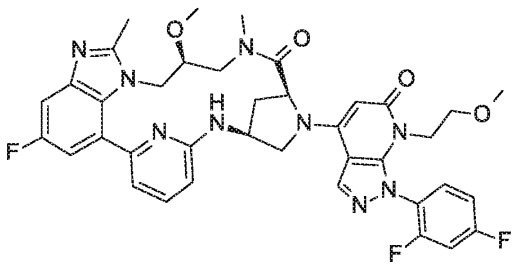
To a solution of compound **468b** (50.0 mg, 0.16 mmol) in MeCN (1 mL) was added phosphorus oxychloride (0.02 mL, 0.18 mmol) dropwise at 25 °C, and the reaction mixture was stirred at 80 °C for 3 hrs. The reaction mixture was poured into sat.$NaHCO_3$ (8 mL) at 0 °C slowly, and then extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by prep-TLC to afford compound **468c** (15 mg). LCMS ($M+H^+$): 322.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[7-cyclopropyl-1-(2,4-difluorophenyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 468)

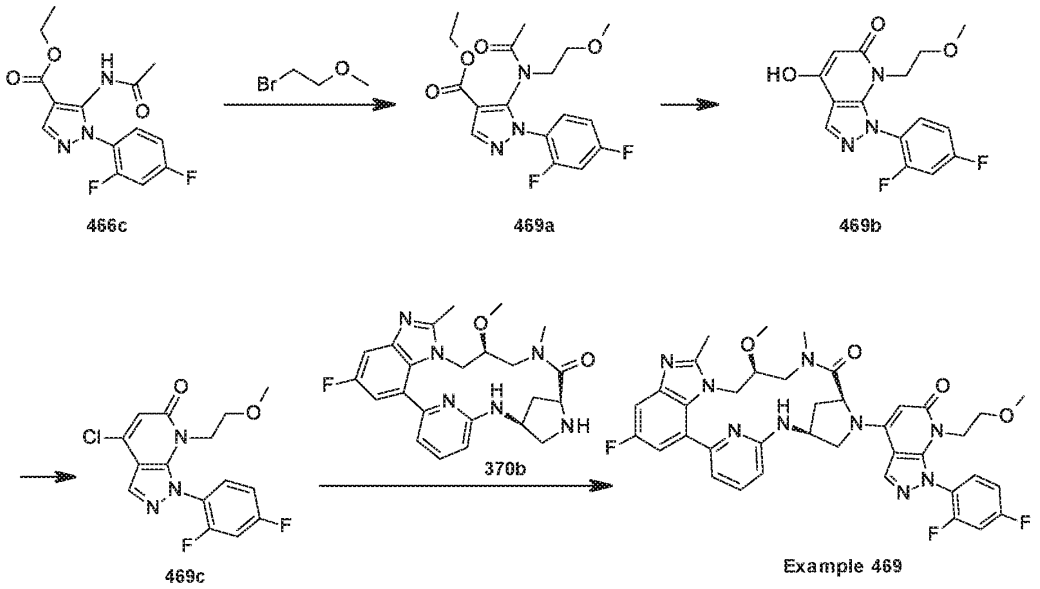
To a solution of compound **370b** (15.0 mg, 0.03 mmol) and compound **468c** (10.0 mg, 0.03 mmol) in DMSO (1 mL) was added N,N-diisopropylethylamine (0.01 mL, 0.05 mmol) and cesium fluoride (8.0 mg, 0.05 mmol, 1.54 eq), then the reaction mixture was stirred at 130 °C for 6 hrs. The reaction mixture was purified by prep-HPLC to give Example **468** (1.8 mg). LCMS ($M+H^+$): 724. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.51 - 8.18 (m, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.60 - 7.53 (m, 2H), 7.32 - 7.17 (m, 3H), 7.15 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.14 - 6.09 (m, 1H), 4.81 (s, 1H), 4.56 (s, 1H), 4.35 - 4.29 (m, 1H), 3.98 - 3.92 (m, 1H), 3.35 (s, 2H), 3.28 (s, 1H), 3.08 - 2.97 (m, 7H), 2.83 (s, 3H), 2.61 - 2.54 (m, 3H), 0.77 - 0.48 (m, 4H).

Example 469

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(2-methoxyethyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 5-[acetyl(2-methoxyethyl)amino]-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 469a)

To a suspension of NaH (156.0 mg, 3.9 mmol) in DMF (7 mL) was added a solution of 2-bromoethyl methyl ether (0.61 mL, 6.48 mmol) in DMF (3 mL) slowly at 0 °C under N_2, then the mixture was stirred at 0 °C for 0.5 hrs and compound **466c** (1000.0 mg, 3.2 mmol) was added to the mixture. After being stirred at 20 °C for 15 hrs, the reaction mixture was poured into sat.NH_4Cl (40 mL) and extracted with ethyl acetate (2 × 20 mL). The organic phase was dried and concentrated, the residue was purified by flash chromatography to afford compound **469a** (800 mg). LCMS ($M+H^+$): 368.

Step 2: preparation of 1-(2,4-difluorophenyl)-4-hydroxy-7-(2-methoxyethyl)pyrazolo[3,4-b]pyridin-6-one (compound 469b)

To a solution of compound **469a** (500 mg, 1.36 mmol) in THF (5 mL) was added LDA (1.36 mL, 2.72 mmol) dropwise at -78 °C under N_2, and the mixture was stirred at 20 °C for 1 h under N_2. The reaction was poured into water (15 mL) and extracted with ethyl acetate. The aqueous phase was adjusted pH to 4~5, and extracted with ethyl acetate. The organic phase was dried and concentrated to afford compound **469b** (150 mg). LCMS ($M+H^+$): 322.

Step 3: preparation of 4-chloro-1-(2,4-difluorophenyl)-7-(2-methoxyethyl)pyrazolo[3,4-b]pyridin-6-one (compound 469c)

To a solution of compound **469b** (50 mg, 0.16 mmol) in MeCN (1 mL) was added phosphorus oxychloride (0.02 mL, 0.16 mmol) dropwise at 25°C, and then reaction mixture was

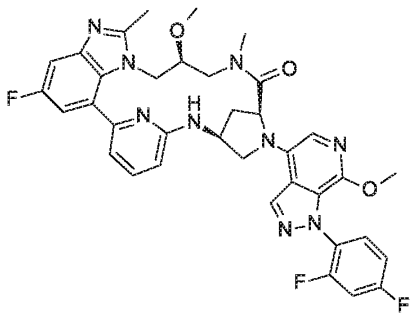
stirred at 80 °C for 3 hrs. The reaction mixture was poured into sat.$NaHCO_3$ (10 mL) at 0 °C, and then extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by prep-TLC to afford compound **469c** (15 mg). LCMS ($M+H^+$): 340.

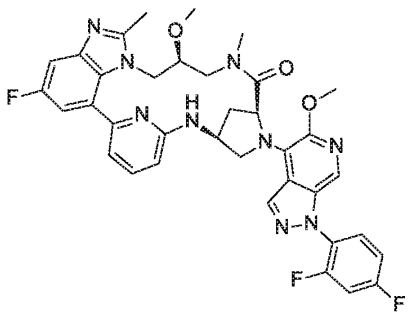
Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(2-methoxyethyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 469)

To a solution of compound **469c** (10 mg, 0.03 mmol) and compound **370b** (15 mg, 0.03 mmol) in DMSO (1 mL) was added DIPEA (0.01 mL, 0.05 mmol) and cesium fluoride (8.0 mg, 0.05 mmol), then the reaction mixture was stirred at 130 °C for 6 hrs. The reaction mixture was purified by prep-HPLC directly to give Example **469** (3.75 mg). LCMS ($M+H^+$): 742. ^1H NMR (400 MHz, METHANOL-d_4) = 8.01 - 7.97 (m, 1H), 7.87 (t, J = 7.94 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.59 - 7.58 (m, 1H), 7.57 - 7.55 (m, 1H), 7.36 - 7.19 (m, 3H), 7.15 (d, J = 7.38 Hz, 1H), 6.76 (d, J = 8.50 Hz, 1H), 6.14 - 6.09 (m, 1H), 4.98 - 4.92 (m, 1H), 4.57 (s, 1H), 4.37 - 4.28 (m, 1H), 4.13 - 4.05 (m, 1H), 4.01 - 3.85 (m, 2H), 3.38 - 3.34 (m, 3H), 3.29 - 3.25 (m, 2H), 3.14 (s, 3H), 3.12 (s, 3H), 3.04 - 3.00 (m, 1H), 2.97 (s, 3H), 2.86 - 2.83 (m, 3H), 2.66 - 2.54 (m, 2H).

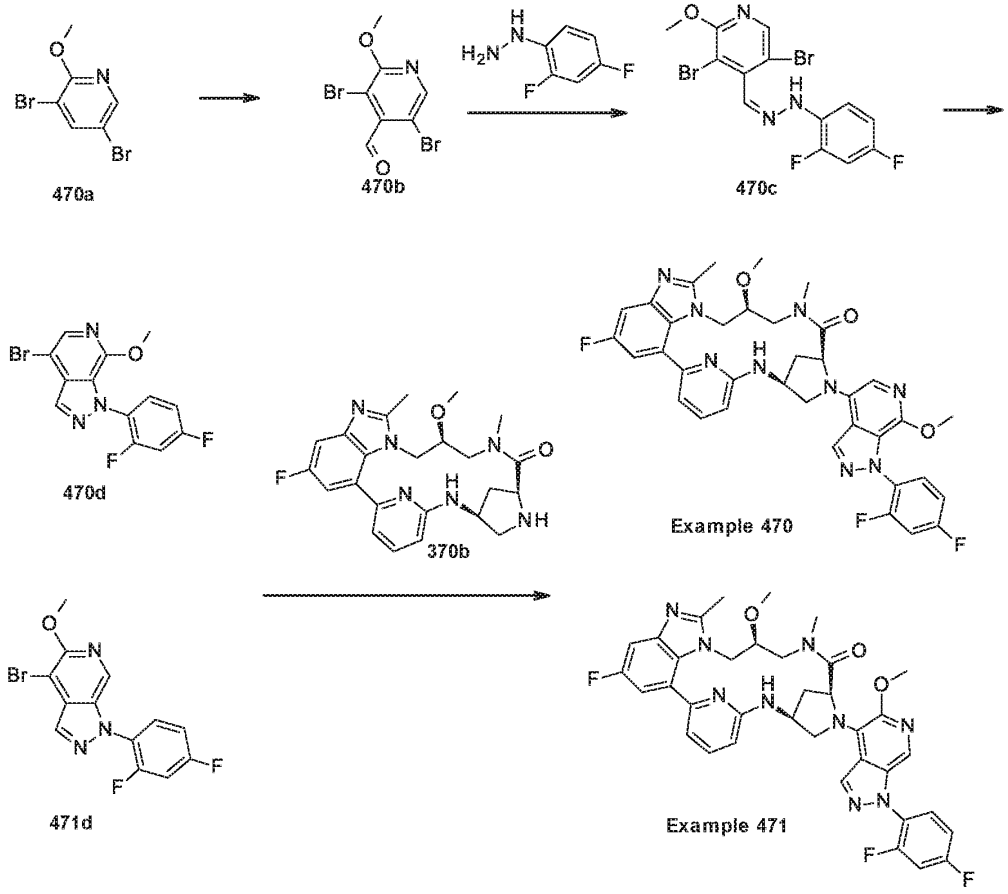
Example 470 and Example 471

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26- hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26- hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





The title compound was prepared according to the following scheme:



Step 1: preparation of 3,5-dibromo-2-methoxy-pyridine-4-carbaldehyde (compound 470b)

To a solution of compound **470a** (8.0 g, 30 mmol) in THF (80 mL) was added LDA (22.5 mL, 2 M) dropwise at -70 °C under N_2, the mixture was stirred at -70 °C for 1 h, DMF (11.6 mL, 150 mmol) was added to the mixture slowly which was then stirred at rt for 1 h. The reaction was quenched with ice water (300 mL), and the resulted mixture was extracted with EtOAc, the organic layer was dried and concentrated to give compound **470b** (7.27 g).

Step 2: preparation of *N*-[(3,5-dibromo-2-methoxy-4-pyridyl)methyleneamino]-2,4-difluoro-aniline (compound 470c)

A mixture of compound **470b** (7.27 g, 24.6 mmol) and 2,4-difluorophenylhydrazine hydrochloride (5.34 g, 29.6 mmol) in DMF (145 mL) was stirred at 20 °C for 16 hrs. Then the reaction mixture was poured into ice water (600 mL), yellow precipitate formed, the mixture was filtered and the filter-cake was dried to give compound **470c** (9.79 g) as a yellow solid. LCMS ($M+H^+$): 422.

Step 3: preparation of 4-bromo-1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridine (compound 470d) and 4-bromo-1-(2,4-difluorophenyl)-5-methoxy-pyrazolo[3,4-c]pyridine(compound 471d)

To a suspension of compound **470c** (9.79 g, 23.2 mmol) in DMF (90 mL) was added K_2CO_3 (9.64 g, 69.8 mmol) and CuI (0.44 g, 2.3 mmol). The mixture was stirred at 100 °C for 12 hrs, then the mixture was diluted with EA, washed with water and brine, the organic layer was dried and concentrated. The residue was purified by silica gel to give a crude product (1.1 g), which was purified by SFC (DAICEL CHIRALPAK IC(250mm×30mm,5um), 0.1%NH_3•H_2O MEOH, begin 15% B (MeOH) to 15% B, rate:50mL/min) to give compound **470d** (0.8 g, faster eluted) as yellow solid and compound **471d** (0.3 g, slower eluted) as yellow solid. LCMS ($M+H^+$): 340.

Step 4: (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 470 & 471)

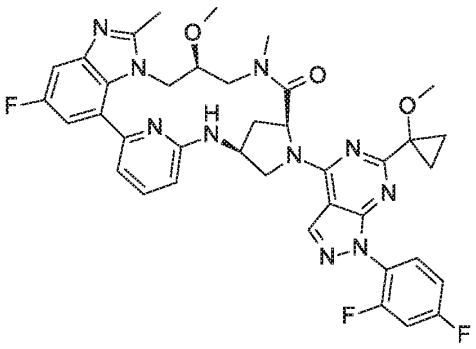
A mixture of compound **370b** (90.0 mg, 0.21 mmol), compound **470d** (40.0 mg, 0.12 mmol), BINAP (14.6 mg, 0.02 mmol), bis(dibenzylideneacetone)palladium (6.8 mg, 0.01 mmol) and cesium carbonate (153.0 mg, 0.47 mmol) in THF (1.5 mL) was stirred at 90 °C for 12 hrs under N_2. The mixture was diluted with H_2O and extracted with EA, the organic layer was dried and concentrated, the residue was purified by prep-HPLC to give Example **470** (35.0 mg). LCMS ($M+H^+$): 698. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.61 (s, 1H), 7.86 (s, 1H), 7.68 (dt, *J* = 5.6, 8.8 Hz, 1H), 7.63 - 7.60 (m, 1H), 7.60 - 7.51 (m, 2H), 7.36 - 7.29 (m, 1H), 7.25 - 7.18 (m, 1H), 7.16 - 7.13 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.27 (dd, *J* = 4.4, 15.2 Hz, 1H), 5.67 (d, *J* = 8.8 Hz, 1H), 4.73 - 4.65 (m, 1H), 4.57 (t, *J* = 4.8 Hz, 1H), 4.38 - 4.26 (m, 2H), 3.93 (dd, *J* = 9.2, 14.3 Hz, 1H), 3.81 (s, 3H), 3.07 (s, 3H), 3.03 (br d, *J* = 14.0 Hz, 1H), 3.00 - 2.97 (m, 3H), 2.82 (s, 3H), 2.74 - 2.67 (m, 1H), 2.64 - 2.55 (m, 1H), 2.49 (ddd, *J* = 4.4, 8.8, 13.2 Hz, 1H).

A mixture of compound **370b** (90 mg, 0.21 mmol), compound **471d** (40.0 mg, 0.12 mmol), BINAP (14.6 mg, 0.02 mmol), bis(dibenzylideneacetone)palladium (6.8 mg, 0.01 mmol) and cesium carbonate (153.0 mg, 0.47 mmol) in THF (1.5 mL) was stirred at 90 °C for 12 hrs under N_2. The mixture was diluted with H_2O and extracted with EA, the organic layer was dried and

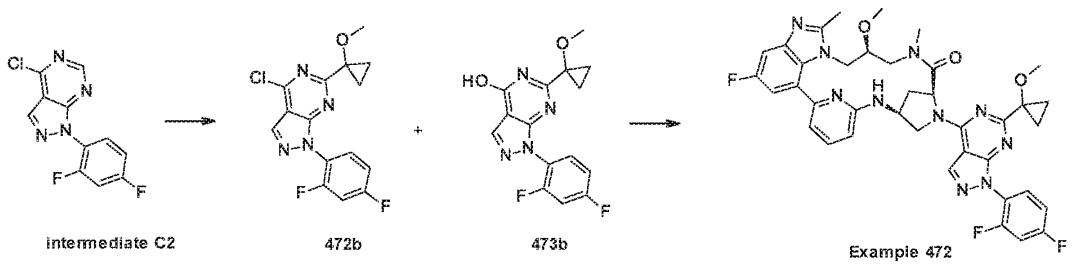
concentrated, the residue was purified by prep-HPLC to give Example **471** (7.0 mg) as a white solid. LCMS ($M+H^+$): 698. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.16 (s, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.61 - 7.55 (m, 2H), 7.52 (dd, J = 2.4, 10.0 Hz, 1H), 7.22 (ddd, J = 2.4, 8.8, 10.0 Hz, 1H), 7.18 - 7.11 (m, 2H), 6.92 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.12 (dd, J = 4.8, 15.0 Hz, 1H), 5.10 (d, J = 8.8 Hz, 1H), 4.58 (t, J = 4.4 Hz, 1H), 4.31 (dd, J = 11.2, 15.2 Hz, 1H), 4.24 (dd, J = 5.6, 10.4 Hz, 1H), 4.02 - 3.93 (m, 2H), 3.80 (s, 3H), 3.13 (s, 3H), 3.07 - 3.01 (m, 1H), 2.97 (s, 3H), 2.88 (d, J = 13.2 Hz, 1H), 2.81 (s, 3H), 2.64 - 2.52 (m, 2H).

Example 472

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methoxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-chloro-1-(2,4-difluorophenyl)-6-(1-methoxycyclopropyl)pyrazolo[3,4-d]pyrimidine (compound 472b)

To a solution of intermediate **C2** (400 mg, 1.5 mmol) in ACN (5 mL) was added 1-methoxycyclopropanecarboxylic acid (348 mg, 3.0 mmol) and silver nitrate (2032 mg, 12.0 mmol). The reaction mixture was heated at 60 °C and then a solution of ammonium persulfate (1.71 g, 7.5 mmol) in water (5 mL) was added slowly. After being stirred at 60 °C for 2 hours, the reaction mixture was diluted with H_2O (30mL) and extracted with EA. The organic layer was

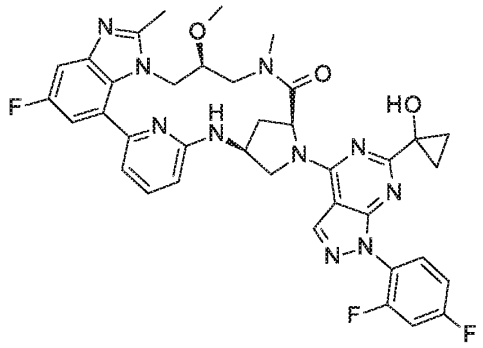
dried and concentrated, the residue was purified by column chromatography to give compound **473b** (50 mg), LCMS ($M+H^+$): 319, and compound **472b** (35 mg), LCMS ($M+H^+$): 337.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methoxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 472)

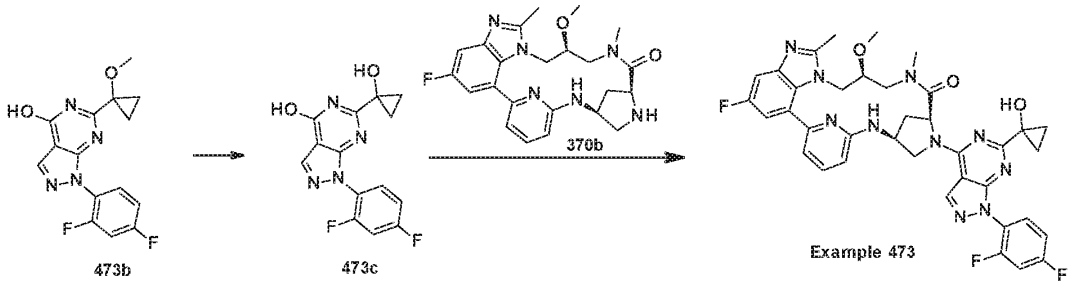
A mixture of compound **472b** (38 mg, 0.11 mmol), compound **370b** (50 mg, 0.11 mmol) and DIPEA (0.06 mL, 0.34 mmol) in ACN (1 mL) was stirred at 85 °C for 1 h. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **472** (20 mg). LCMS ($M+H^+$): 739. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.45 (s, 1H), 7.90 - 7.84 (m, 1H), 7.70 - 7.62 (m, 1H), 7.62 - 7.52 (m, 2H), 7.30 - 7.22 (m, 1H), 7.21 - 7.13 (m, 2H), 6.82 - 6.74 (m, 1H), 6.27 - 6.01 (m, 1H), 5.51 - 5.37 (m, 1H), 4.69 (t, J = 4.8 Hz, 1H), 4.54 - 4.46 (m, 1H), 4.36 - 4.19 (m, 2H), 4.00 - 3.80 (m, 1H), 3.44 (s, 3H), 3.16 - 3.07 (m, 3H), 3.05 - 3.00 (m, 1H), 3.00 - 2.96 (m, 3H), 2.85 - 2.80 (m, 3H), 2.80 - 2.74 (m, 1H), 2.64 - 2.48 (m, 2H), 1.30 - 1.15 (m, 4H).

Example 473

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-hydroxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-(2,4-difluorophenyl)-6-(1-hydroxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 473c)

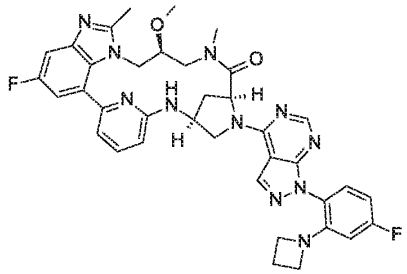
To a solution of compound **473b** (10 mg, 0.03 mmol) in DCM (1 mL) was added BCl_3/DCM (0.5 mL, 0.5 mmol, 1 M) dropwise at -70 °C and then the mixture was stirred at 30 °C for 48 hours. The reaction was quenched with ice-water and the mixture was extracted with DCM, the organic layer was dried and concentrated to give compound **473c** (9 mg). LCMS ($M+H^+$): 305.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-hydroxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 473)

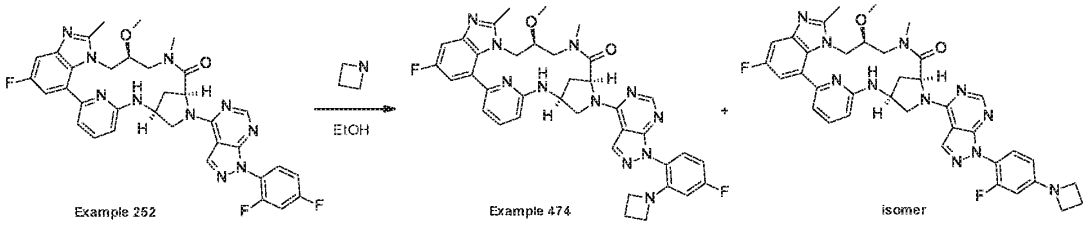
A mixture of compound **370b** (17.3 mg, 0.04 mmol), compound **473c** (12.0 mg, 0.04 mmol), PyBOP (26.7 mg, 0.05 mmol) and DIEA (12.7 mg, 0.1 mmol) in DMF (1 mL) was s stirred at 20 °C for 12 hrs. The reaction mixture was directly purified by prep-HPLC to give Example **473** (5 mg). LCMS ($M+H^+$): 725. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.43 (s, 1H), 7.85 - 7.78 (m, 1H), 7.75 - 7.64 (m, 1H), 7.33 - 7.22 (m, 2H), 7.21 - 7.07 (m, 3H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.86 - 5.60 (m, 1H), 5.47 - 5.32 (m, 1H), 4.58 (s, 1H), 4.54 - 4.45 (m, 1H), 4.30 - 4.10 (m, 2H), 3.95 - 3.85 (m, 1H), 3.61 (q, *J* = 7.0 Hz, 2H), 3.13 (s, 1H), 3.04 (s, 2H), 2.95 - 2.88 (m, 1H), 2.85 (s, 3H), 2.58 - 2.54 (m, 3H), 2.51 - 2.46 (m, 1H), 1.18 (t, *J* = 7.0 Hz, 4H).

Example 474

(8*S*,11*S*,15*R*)-10-[1-[2-(azetidin-1-yl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



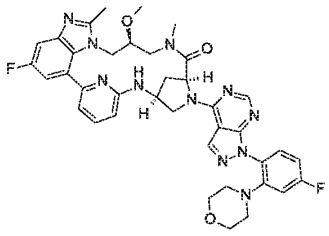
Example **474** was prepared according to the following scheme:

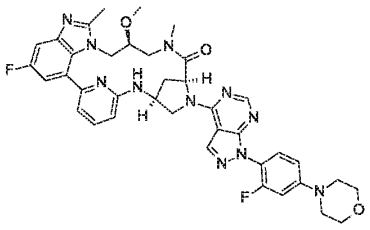


To a microwave tube was added: (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example **252**, 48 mg, 0.068 mmol), ethanol (0.5 mL) and azetidine (500 mg, 8.76 mmol). The suspension was heated to 90 °C for 24 hrs. The mixture was concentrated and purified via prep-HPLC. Example **474** (22 mg) was obtained as white powder. LCMS (M+H$^+$): 706. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.20 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.17 (dd, *J* = 2.4, 10.5 Hz, 1H), 7.14 - 7.07 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.54 (dt, *J* = 2.7, 8.3 Hz, 1H), 6.37 (dd, *J* = 2.5, 11.1 Hz, 1H), 5.76 (dd, *J* = 4.2, 15.5 Hz, 1H), 5.47 (d, *J* = 8.9 Hz, 1H), 4.70 - 4.64 (m, 1H), 4.54 - 4.48 (m, 1H), 4.34 (br d, *J* = 11.4 Hz, 1H), 4.14 (br dd, *J* = 11.0, 15.3 Hz, 1H), 3.97 - 3.89 (m, 1H), 3.43 - 3.35 (m, 4H), 3.13 - 3.02 (m, 3H), 2.89 (br t, *J* = 12.3 Hz, 2H), 2.84 (s, 3H), 2.56 (s, 3H), 2.53 - 2.45 (m, 2H), 2.09 (quin, *J* = 7.3 Hz, 2H).

Example 475 and Example 476

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(2-fluoro-4-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one





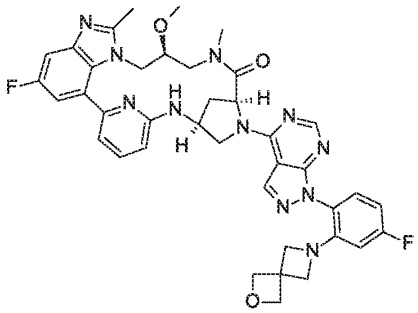
Examples **475** and Example **476** were prepared in analogy to the preparation of Examples **474** by using morpholine instead of azetidine.

Example **475**, LCMS (M+H$^+$): 736. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 (s, 1H), 8.24 (s, 1H), 7.87 (dd, *J* = 0.9, 8.6 Hz, 1H), 7.60 (dd, *J* = 2.5, 7.4 Hz, 1H), 7.53 (dd, *J* = 2.6, 10.3 Hz, 1H), 7.39 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 2.6, 10.8 Hz, 1H), 6.98 - 6.91 (m, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.14 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.50 (d, *J* = 8.9 Hz, 1H), 4.72 - 4.67 (m, 1H), 4.56 - 4.50 (m, 1H), 4.41 - 4.34 (m, 1H), 4.32 - 4.27 (m, 1H), 3.96 (dd, *J* = 9.4, 14.4 Hz, 1H), 3.37 - 3.33 (m, 4H), 3.17 - 3.13 (m, 1H), 3.06 (s, 3H), 2.98 - 2.95 (m, 3H), 2.92 - 2.86 (m, 1H), 2.83 (s, 3H), 2.75 - 2.65 (m, 4H), 2.63 - 2.52 (m, 2H).

Example **476**, LCMS (M+H$^+$): 736. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.51 (s, 1H), 8.21 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.57 (br d, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 2.4, 10.1 Hz, 1H), 7.45 - 7.35 (m, 1H), 7.18 - 7.12 (m, 1H), 6.96 - 6.87 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.10 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.48 (br d, *J* = 8.9 Hz, 1H), 4.69 (br t, *J* = 4.6 Hz, 1H), 4.56 - 4.49 (m, 1H), 4.40 - 4.31 (m, 1H), 4.30 - 4.22 (m, 1H), 3.94 (br dd, *J* = 9.4, 14.4 Hz, 1H), 3.90 - 3.81 (m, 4H), 3.30 - 3.25 (m, 4H), 3.16 - 3.11 (m, 1H), 3.06 (s, 3H), 2.95 (s, 3H), 2.91 - 2.85 (m, 1H), 2.80 (s, 3H), 2.62 - 2.50 (m, 2H).

Example 477

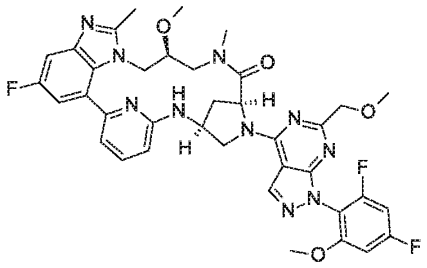
(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluor-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



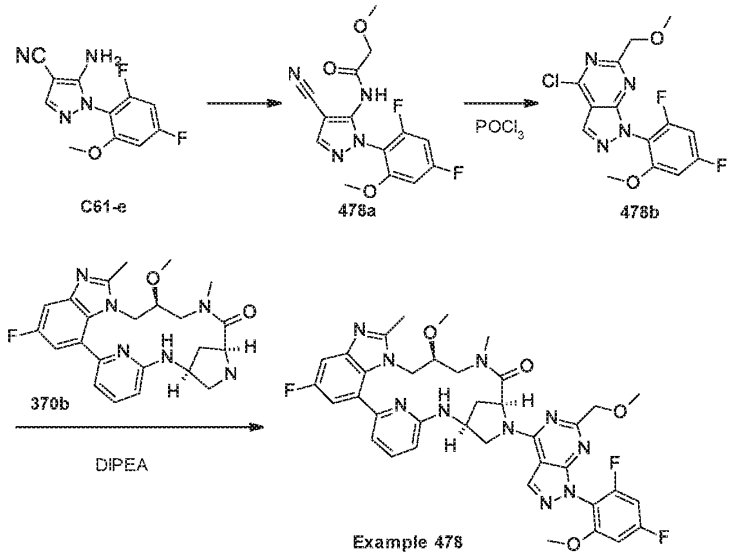
Example **477** was prepared in analogy to the preparation of Examples **474** by using 2-oxa-6-azaspiro[3.3]heptane instead of azetidine. Example **477**, LCMS ($M+H^+$): 748. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 - 8.45 (m, 1H), 8.22 - 8.15 (m, 1H), 7.86 - 7.79 (m, 1H), 7.35 - 7.29 (m, 1H), 7.22 - 7.17 (m, 1H), 7.17 - 7.08 (m, 2H), 6.69 (dd, *J* = 5.8, 8.4 Hz, 1H), 6.64 - 6.55 (m, 1H), 6.45 - 6.37 (m, 1H), 5.84 - 5.68 (m, 1H), 5.51 - 5.38 (m, 1H), 4.87 (s, 2H), 4.72 - 4.65 (m, 1H), 4.63 - 4.60 (m, 2H), 4.53 (dt, *J* = 5.9, 11.9 Hz, 1H), 4.40 - 4.25 (m, 1H), 4.21 - 4.14 (m, 1H), 4.14 - 4.09 (m, 2H), 3.94 (ddd, *J* = 5.4, 9.1, 14.3 Hz, 1H), 3.59 - 3.51 (m, 2H), 3.15 - 3.02 (m, 3H), 2.97 - 2.86 (m, 2H), 2.85 (d, *J* = 2.6 Hz, 3H), 2.58 (d, *J* = 1.6 Hz, 3H), 2.55 - 2.44 (m, 2H).

Example 478

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **478** was prepared according to the following scheme:



Step 1: preparation of *N*-[4-cyano-2-(2,4-difluoro-6-methoxy-phenyl)pyrazol-3-yl]-2-methoxy-acetamide (compound 478a)

To a tube was added compound **C61-e** (1300 mg, 5.2 mmol), methoxyacetyl chloride (1.16 g, 975 μL, 10.7 mmol) and sulfolane (16.51 g, 13 mL). After being heated to 55 °C and stirred for 16 hrs, the reaction mixture was poured into 100 mL sat. $NaHCO_3$ aq. and extracted with 20 mL EA for 3 times. The organic layer was concentrated to give an oil and purified via flash column (EA/PE=0~60%), some oil was obtained containing with some sulfolane. Then it was purified again via prep-HLC (ACN/TFA 0.05% aq.=0~25%), the elution was concentrated to remove most ACN. The residue was extracted with 80 mL EA for 4 times. The organic layer was dried and concentrated to give compound **478a** (1.1 g) as yellow solid. LCMS ($M+H^+$): 323.

Step 2: preparation of 4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidine (compound 478b)

To a microwave tube was added compound **478a** (1100 mg, 3.41 mmol) and phosphorus oxychloride (8.23 g, 5 mL, 53.64 mmol), the suspension was heated to 100 °C and further stirred for 8 hrs. The mixture was concentrated to give an oil which was purified via flash column (EA/PE=0~30%) to give compound **478b** (800 mg). LCMS ($M+H^+$): 341.

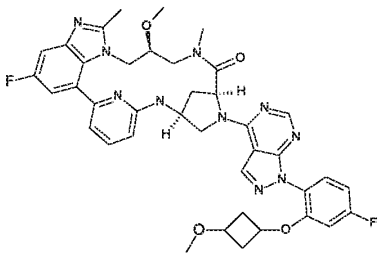
Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 478)

To a tube was added (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one; 2,2,2-trifluoroacetic acid (compound **370b**, 60 mg, 0.109 mmol), 4-chloro-1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidine (compound **478b**, 37.0 mg, 0.109 mmol), DIEA (112.3 mg, 151.7 μL, 0.869 mmol) and acetonitrile (2 mL). The mixture was heated to 85 °C and stirred for about 1 hr. The mixture was concentrated to give a light brown oil, which was purified via prep-HPLC to give Example **478** (51 mg), LCMS ($M+H^+$): 743. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.48 (d, J = 1.4 Hz, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.16 (dd, J = 2.5, 10.5 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.96 - 6.88 (m, 1H), 6.86 - 6.78 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.82 - 5.73 (m, 1H), 5.59 (d, J = 8.8 Hz, 1H), 4.68 - 4.63 (m, 1H), 4.51 - 4.48 (m, 1H), 4.47 - 4.36 (m, 2H), 4.33 - 4.24 (m, 1H), 4.19 - 4.08 (m, 1H), 3.89 (dd, J = 9.6, 14.0 Hz, 1H), 3.81 - 3.74 (m, 4H), 3.46 - 3.40 (m, 3H), 3.14 -

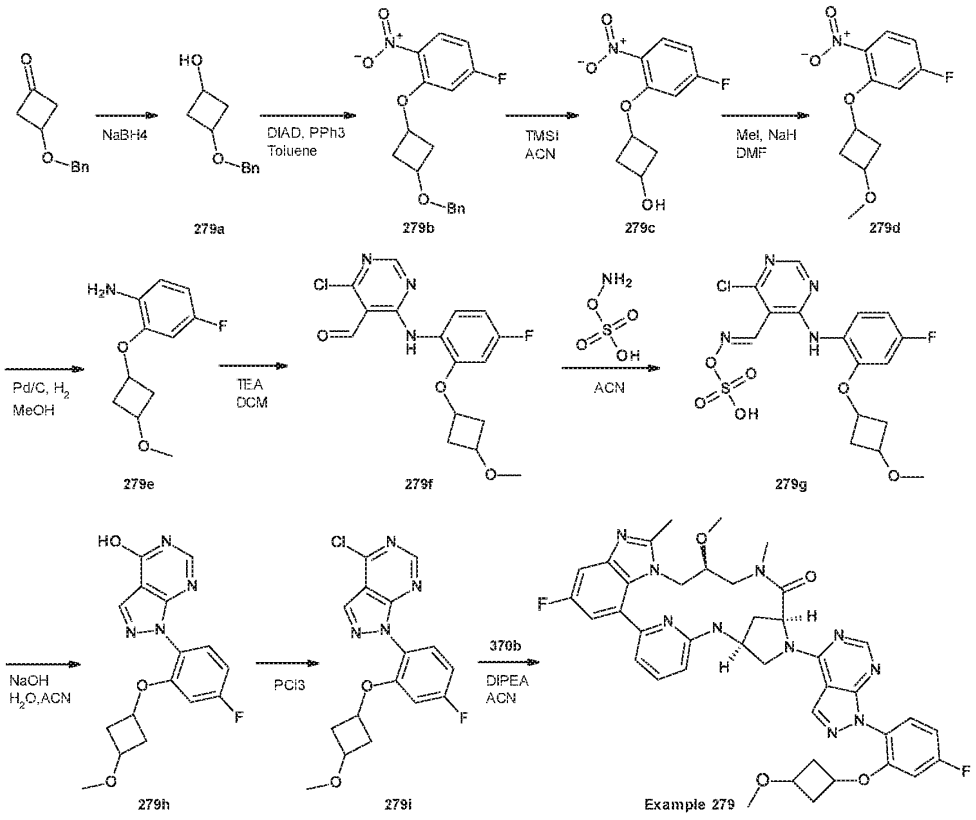
3.02 (m, 3H), 2.91 - 2.86 (m, 1H), 2.83 (d, *J* = 1.5 Hz, 3H), 2.58 - 2.54 (m, 3H), 2.49 (dt, *J* = 4.4, 9.1 Hz, 2H).

Example 479

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **479** was prepared according to the following scheme:



Step 1: preparation of 3-benzyloxycyclobutanol (compound 479a)

To a solution of 3-benzyloxycyclobutanone (5.0 g, 28.4 mmol) in ethanol (75 mL) was added $NaBH_4$ (1.08 g, 28.4 mmol) portion wise. The mixture was stirred at 0 °C for 1 h. Then it

was quenched with NH_4Cl aq. until pH=7. After concentration, the mixture was extracted with EA. The organic layer was concentrated and purified via silica gel column to give compound **479a** (4.85 g) as yellow liquid. LCMS ($M+H^+$): 179.

Step 2: preparation of 2-(3-benzyloxycyclobutoxy)-4-fluoro-1-nitro-benzene (compound 479b)

To a mixture of compound **479a** (4.45 g, 25.0 mmol), 5-fluoro-2-nitrophenol (5.88 g, 37.4 mmol) and PPh_3 (9.82 g, 37.4 mmol) in toluene (55 mL) was added DIAD (6.58 mL, 37.4 mmol) at 0 °C under N_2. Then it was stirred at 100 °C for 1 h under N_2. The mixture was concentrated and purified via silica gel column to afford compound **479b** (6.8 g) as yellow liquid. LCMS ($M+H^+$): 318.

Step 3: preparation of 3-(5-fluoro-2-nitro-phenoxy)cyclobutanol (compound 479c)

To a solution of compound **479b** (5.25 g, 16.6 mmol) in MeCN (52.5 mL) was added iodotrimethylsilane (5.89 mL, 41.4 mmol) slowly at 0°C. After being stirred at 40 °C for 12 h, the mixture was poured into water and extracted with EtOAc, the organic layer was concentrated and the residue was purified via silica gel column to give compound **479c** (3.2 g) as brown solid. LCMS ($M+H^+$): 228.

Step 4: preparation of 4-fluoro-2-(3-methoxycyclobutoxy)-1-nitro-benzene (compound 479d)

To a solution of compound **479c** (3.2 g, 14.1 mmol) in DMF (32 mL) was added iodomethane (2.63 mL, 42.3 mmol) at -10 °C under N_2, and then sodium hydride (60% in oil, 1.13 g, 28.2 mmol) was added slowly. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with cold NH_4Cl aq. and extracted with EtOAc. The organic layer was washed with NaCl aq., dried and concentrated, compound **479d** (3.0 g) was obtained as yellow liquid. LCMS ($M+H^+$): 242.

Step 5: preparation of 4-fluoro-2-(3-methoxycyclobutoxy)aniline (compound 479e)

To the mixture of compound **479d** (1.5 g, 6.22 mmol) in methanol (15 mL) was added Pd/C (300.0 mg, 18.72 mmol), and then it was stirred at 20 °C for 12 h under H_2. The mixture was filtered, the filtrate was concentrated to give compound **479e** (1.28 g) as brown liquid. LCMS ($M+H^+$): 212.

Step 6: preparation of 4-chloro-6-[4-fluoro-2-(3-methoxycyclobutoxy)anilino] pyrimidine-5-carbaldehyde (compound 479f)

To the mixture of compound **479e** (500 mg, 2.37 mmol) and TEA (478 mg, 4.73 mmol) in DCM (5 mL) was added 4,6-dichloro-5-pyrimidinecarbaldehyde (423 mg, 2.39 mmol). Then

it was stirred at 20 °C for 12 h. The mixture was poured into water, the organic layer was dried and concentrated to give compound **479f** (760 mg) as yellow solid. LCMS ($M+H^+$): 352.

Step 7: preparation of [(*E*)-[4-chloro-6-[4-fluoro-2-(3-methoxycyclobutoxy)anilino] pyrimidin-5-yl]methyleneamino] hydrogen sulfate (compound 479g)

To a solution of compound **479f** (0.76 g, 2.16 mmol) in ACN (10 mL) was added hydroxylamine-o-sulfonic acid (1.47 g, 12.96 mmol). The reaction mixture was stirred at 20 °C for 2 h under N_2. The mixture was used for next step directly. Compound **479g**, LCMS ($M+H^+$): 447.

Step 8: preparation of 1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-ol (compound 479h)

To the solution of compound **479g** (0.97 g, 2.2 mmol) in ACN (10 mL) was added NaOH aq. (12.8 mL, 38.5 mmol, 3 M). The reaction mixture was stirred at 50 °C for 2 h under N_2. The mixture was concentrated to give a solid. The solid was suspended in some MeOH and filtered. The filtrate was concentrated to give a yellow oil, which was purified via pre-HPLC to give compound **479h** (190.0 mg) as off-white solid. LCMS ($M+H^+$): 331.

Step 9: preparation of 4-chloro-1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo [3,4-d]pyrimidine (compound 479i)

A mixture of compound **479h** (0.56 g, 1.7 mmol) and $POCl_3$ (6.0 mL) was stirred at 100 °C for 2 h. The mixture was concentrated to give a solid which was dissolved in 40 mL DCM, and then the reaction was quenched with 100 mL cold $NaHCO_3$ aq. The organic layer was concentrated to give compound **479i** (170.0 mg) as yellow oil. LCMS ($M+H^+$): 349.

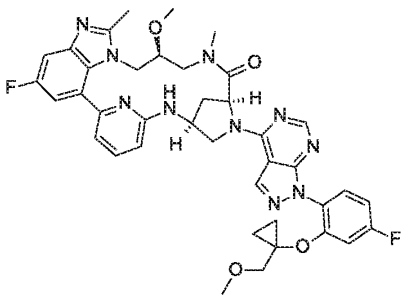
Step 10: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 479)

To a tube was added compound **370b** (50 mg, 0.090 mmol), compound **479i** (31.6 mg, 0.090 mmol), DIEA (93.6 mg, 126.4 µL, 0.724 mmol) and acetonitrile (2 mL). The mixture was heated to 85 °C and stirred for 1 hr. The mixture was concentrated to give a light brown oil, which was purified via prep-HPLC to give Example **479** (34.5 mg) as white powder. LCMS ($M+H^+$): 751. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 8.16 (s, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.37 (dd, *J* = 6.0, 8.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.83 - 6.72 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.08 - 5.95 (m, 1H), 5.39 (d, *J* = 8.9 Hz, 1H), 4.63 - 4.58 (m, 1H), 4.49 - 4.42 (m, 1H), 4.32 (br d, *J* = 11.4 Hz, 1H), 4.28 - 4.12 (m, 2H), 3.91 - 3.78 (m,

2H), 3.12 - 3.08 (m, 3H), 2.96 (s, 3H), 2.91 - 2.78 (m, 5H), 2.74 (s, 3H), 2.53 - 2.43 (m, 2H), 2.26 (dq, J = 4.8, 6.8 Hz, 2H), 2.09 (tdd, J = 3.5, 7.0, 10.5 Hz, 2H).

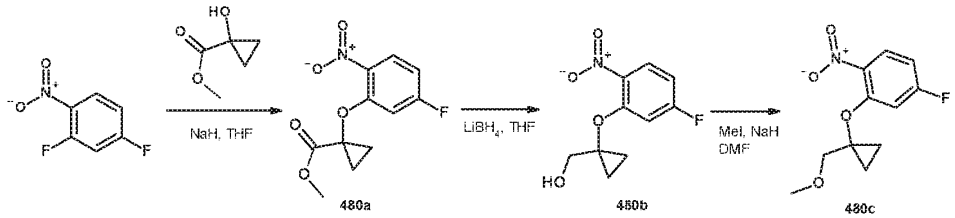
Example 480

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-[1-(methoxymethyl)cyclopropoxy]phenyl] pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **480** was prepared in analogy to the preparation of Example **479** by using compound **480c** instead of Intermediate **479d** in step 5.

Compound **480c** was prepared according to the following scheme:



Step 1: preparation of methyl 1-(5-fluoro-2-nitro-phenoxy)cyclopropanecarboxylate (compound 480a)

To a solution of 2,4-difluoro-1-nitro-benzene (6.89 mL, 62.86 mmol) in THF (150 mL) was added sodium hydride (3.02 g, 75.46 mmol) at 0 °C. After 0.5 h, to the mixture was added methyl 1-hydroxy-1-cyclopropane (7.3 g, 62.88 mmol) and 15-crown- 5 (277.0 mg, 1.26 mmol) at 0 °C under N_2. The mixture was warmed to r.t. and stirred for 14 h. The reaction was quenched with NH_4Cl (150mL), and the mixture was extracted with EtOAc. The organic layer was washed with sat. NaCl aq. and concentrated. The residue was purified by silica gel column to afford compound **480a** (13.0 g) as a light yellow solid. LCMS ($M+H^+$): 256.

Step 2: preparation of [1-(5-fluoro-2-nitro-phenoxy)cyclopropyl]methanol (compound 480b)

To a solution of lithium borohydride (4.27 g, 195.92 mmol) in THF (200 mL) was added another solution of compound **480a** (10.0 g, 39.18 mmol) in THF (50 mL) slowly at 25 °C.

And then it was stirred at 60 °C for 2 h. To the reaction was added 1N HCl aq. dropwise to pH=7, and then it was extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The residue was purified by silica gel column to afford compound **480b** (6.3 g) as a brown solid. LCMS ($M+H^+$): 228.

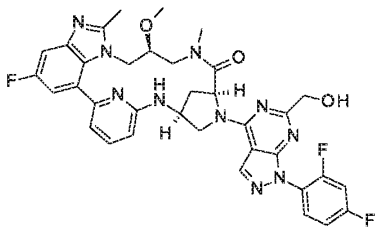
Step 3: preparation of 4-fluoro-2-[1-(methoxymethyl)cyclopropoxy]-1-nitro-benzene (compound 480c)

To a solution of sodium hydride (60% in oil, 0.76 g, 18.93 mmol) in DMF (22 mL) was added compound **480b** (2.15 g, 9.46 mmol) at -10 °C under N_2. And then iodomethane (1.77 mL, 28.39 mmol) was added slowly. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with cold NH_4Cl aq. and extracted with ethyl acetate. The organic layer was washed with brine and concentrated to give compound **480c** (2.2 g) as a brown liquid. LCMS ($M+H^+$): 242.

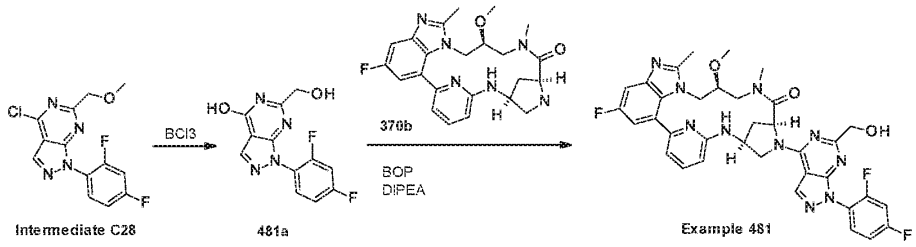
Example 480, LCMS ($M+H^+$): 751. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.49 (s, 1H), 8.18 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.32 (dd, J = 2.5, 8.4 Hz, 1H), 7.19 (dd, J = 2.5, 10.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.06 (br dd, J = 2.5, 10.6 Hz, 1H), 6.90 (dt, J = 2.6, 8.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.84 - 5.70 (m, 1H), 5.48 (d, J = 8.9 Hz, 1H), 4.67 (br t, J = 4.9 Hz, 1H), 4.54 - 4.47 (m, 1H), 4.37 - 4.30 (m, 1H), 4.29 - 4.15 (m, 1H), 4.14 - 4.11 (m, 2H), 3.99 - 3.88 (m, 1H), 3.13 - 3.03 (m, 3H), 3.02 - 2.98 (m, 3H), 2.93 - 2.85 (m, 2H), 2.85 (s, 3H), 2.60 - 2.55 (m, 3H), 2.55 - 2.45 (m, 2H), 0.72 - 0.63 (m, 2H), 0.56 - 0.50 (m, 2H).

Example 481

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **481** was prepared according to the following scheme:



Step 1: preparation of 1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 481a)

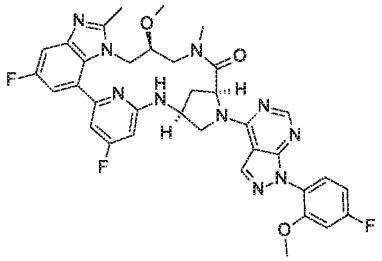
To a tube was added 4-chloro-1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidine (Intermediate **C28**, 100.0 mg, 0.322 mmol) and dichloromethane (2 mL), the solution was cooled with dry ice/EtOH bath and boron trichloride (1 M in DCM) (966 μL, 0.966 mmol) was added into. The mixture warmed to r.t. and stirred for 16 hrs. The mixture was quenched with ice water and diluted with some DCM. The mixture was separated, the organic layer was concentrated and purified via flash column chromatography (MeOH/DCM=0~30%), the elution was concentrated to give compound **481a** (63 mg) as white solid. LCMS ($M+H^+$): 279.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 481)

To a flask was added 1-(2,4-difluorophenyl)-6-methylol-pyrazolo[3,4-d]pyrimidin-4-ol (compound **481a,** 30.0 mg, 0.108 mmol), (1-hydroxy-1*H*-benzotriazolato-o)tri-1-pyrrolidinylphosphorus hexafluorophosphate (84.2 mg, 0.162 mmol), DIEA (83.6 mg, 113.0 μL, 0.647 mmol) and *N*,*N*-dimethylformamide (2 mL), the mixture was stirred at r.t. for 1 hr, and compound **370b** (100 mg, 0.150 mmol) was added. The mixture was heated to 60 °C and stirred for 16 hrs. The mixture was concentrated and purified via prep-HPLC to give Example **481** (57 mg). LCMS ($M+H^+$): 699. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.70 - 7.59 (m, 1H), 7.34 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.30 - 7.14 (m, 3H), 7.13 - 7.07 (m, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.85 - 5.70 (m, 1H), 5.63 - 5.38 (m, 1H), 4.67 - 4.63 (m, 1H), 4.62 - 4.49 (m, 2H), 4.49 - 4.45 (m, 1H), 4.30 (d, *J* = 3.8 Hz, 1H), 4.20 - 4.10 (m, 1H), 3.94 (dd, *J* = 9.3, 14.3 Hz, 1H), 3.14 - 3.02 (m, 3H), 2.99 - 2.86 (m, 2H), 2.85 (s, 3H), 2.61 - 2.56 (m, 3H), 2.54 - 2.44 (m, 2H).

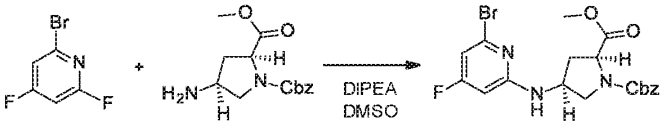
Example 482

(8*S*,11*S*,15*R*)-4,22-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **482** was prepared in analogy to the preparation of Example **12** by using Intermediate **A6** and compound **482a** instead of Intermediate **A11** and Interdiate B10 in step 1 and using Intermediate **C11** instead of Intermediate **C2** in step 5.

The compound **482a** was prepared according to the following scheme:



482a

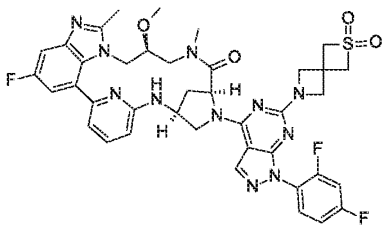
Step 1: preparation of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(6-bromo-4-fluoro-2-pyridyl)amino]pyrrolidine-1,2-dicarboxylate (compound 482a)

A mixture of 2-bromo-4,6-difluoro-pyridine (970.0 mg, 5.0 mmol), DIPEA (1.62 g, 2.18 mL, 12.5 mmol) and *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate; hydrochloride (1.57 g, 5.0 mmol) in DMSO (10 mL) was stirred at 110 °C for about 16 hrs. The reaction mixture was poured into 150 mL water and extracted with 30 mL EA for 3 times. The organic layer was dried and concentrated, the residue was purified via flash column (EA/PE= 0~30%) to give isomer A (1.6 g white solid) and isomer B (300 mg colorless oil). According to the 2 D NMR spectrum the isomer B was the desired compound **482a**. LCMS (M+H$^+$): 452.

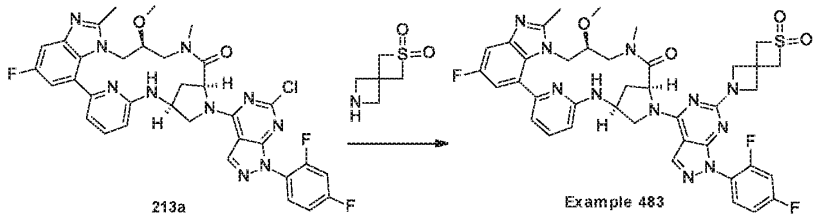
Example **482**, LCMS (M+H$^+$): 699. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.47 (s, 1H), 8.17 (s, 1H), 7.44 (dd, *J* = 6.1, 8.6 Hz, 1H), 7.33 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.21 (dd, *J* = 2.4, 10.4 Hz, 1H), 7.06 (dd, *J* = 2.4, 10.6 Hz, 1H), 6.96 - 6.82 (m, 2H), 6.52 - 6.43 (m, 1H), 5.75 (br dd, *J* = 4.3, 15.5 Hz, 1H), 5.49 (d, *J* = 8.9 Hz, 1H), 4.63 (br t, *J* = 4.9 Hz, 1H), 4.54 - 4.42 (m, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.26 (br s, 1H), 4.19 - 4.08 (m, 1H), 4.00 - 3.89 (m, 1H), 3.76 (s, 3H), 3.20 - 3.05 (m, 3H), 2.94 - 2.87 (m, 1H), 2.86 (s, 3H), 2.57 (s, 3H), 2.56 - 2.47 (m, 2H).

Example 483

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2-dioxo-2λ^6-thia-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



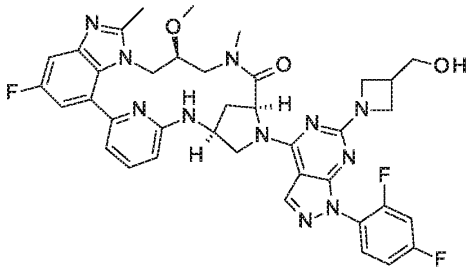
Example **483** was prepared according to the following scheme:



To a tube was added DIEA (32.2 mg, 0.249 mmol), 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide;hydrochloride (22.9 mg, 0.124 mmol), compound **213a** (35.0 mg, 0.050 mmol), and acetonitrile (2 mL). The mixture was heated to 90 °C and stirred for 4 hrs. The mixture was filtered, the filtrate was concentrated and purified via prep-HPLC to give Example **483** (30 mg) as a white powder. LCMS (M+H$^+$): 814. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.27 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.65 - 7.51 (m, 3H), 7.27 - 7.19 (m, 1H), 7.19 - 7.11 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.27 - 6.05 (m, 1H), 5.44 - 5.29 (m, 1H), 4.67 (br t, *J* = 4.7 Hz, 1H), 4.46 (br dd, *J* = 5.8, 11.3 Hz, 1H), 4.40 - 4.29 (m, 6H), 4.27 - 4.14 (m, 4H), 3.94 (dd, *J* = 9.2, 14.2 Hz, 1H), 3.15 - 3.06 (m, 3H), 3.06 - 3.00 (m, 1H), 3.00 - 2.95 (m, 3H), 2.86 - 2.80 (m, 3H), 2.75 (br d, *J* = 13.6 Hz, 1H), 2.68 - 2.45 (m, 2H).

Example 484

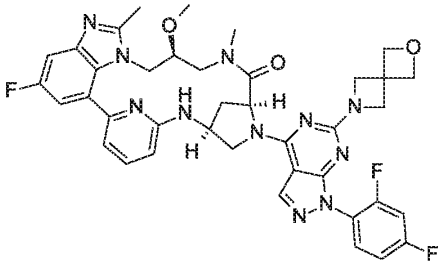
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(hydroxymethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **484** was prepared in analogy to the preparation of Example **483** by using azetidin-3-ylmethanol instead of 2λ⁶-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **484**, LCMS (M+H⁺): 754. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.30 (s, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.68 - 7.61 (m, 1H), 7.61 - 7.57 (m, 1H), 7.54 (dd, *J* = 2.3, 10.3 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.20 - 7.14 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.29 - 6.03 (m, 1H), 5.46 - 5.33 (m, 1H), 4.67 (br t, *J* = 4.8 Hz, 1H), 4.48 (br dd, *J* = 5.8, 11.2 Hz, 1H), 4.38 - 4.17 (m, 3H), 4.14 - 4.01 (m, 1H), 3.99 - 3.88 (m, 2H), 3.86 - 3.73 (m, 2H), 3.70 (br d, *J* = 6.5 Hz, 2H), 3.14 - 3.05 (m, 3H), 3.04 - 3.00 (m, 1H), 2.99 - 2.94 (m, 3H), 2.86 - 2.81 (m, 3H), 2.76 (br d, *J* = 13.8 Hz, 1H), 2.69 - 2.47 (m, 2H).

Example 485

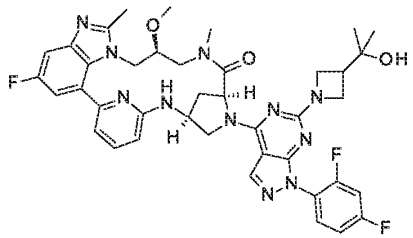
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **485** was prepared in analogy to the preparation of Example **483** by using 2-oxa-6-azaspiro[3.3]heptane instead of 2λ⁶-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **485**, LCMS (M+H⁺): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.28 (s, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.51 (m, 3H), 7.29 - 7.21 (m, 1H), 7.20 - 7.12 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.29 - 6.04 (m, 1H), 5.45 - 5.31 (m, 1H), 4.80 (s, 4H), 4.70 - 4.57 (m, 1H), 4.51 - 4.42 (m, 1H), 4.32 - 4.25 (m, 2H), 4.25 - 4.16 (m, 2H), 4.15 - 4.09 (m, 1H), 3.94 (br dd, *J* = 9.3, 14.3 Hz, 1H), 3.89 - 3.73 (m, 1H), 3.16 - 3.07 (m, 3H), 3.07 - 3.01 (m, 1H), 3.01 - 2.95 (m, 3H), 2.87 - 2.79 (m, 3H), 2.78 - 2.71 (m, 1H), 2.68 - 2.46 (m, 2H).

Example 486

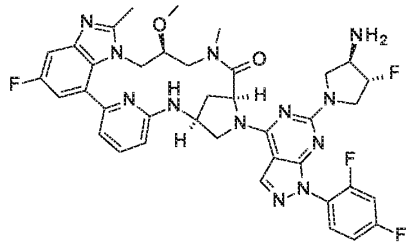
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxy-1-methyl-ethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



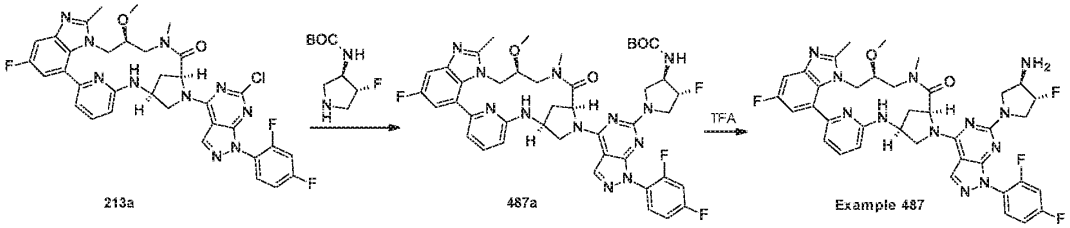
Example **486** was prepared in analogy to the preparation of Example **483** by using 2-(azetidin-3-yl)propan-2-ol;hydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **486**, LCMS (M+H$^+$): 782. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.29 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.68 - 7.57 (m, 2H), 7.54 (dd, *J* = 2.4, 10.3 Hz, 1H), 7.30 - 7.21 (m, 1H), 7.21 - 7.13 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.28 - 6.04 (m, 1H), 5.48 - 5.29 (m, 1H), 4.67 (br t, *J* = 4.8 Hz, 1H), 4.48 (br dd, *J* = 5.9, 11.4 Hz, 1H), 4.38 - 4.22 (m, 2H), 4.15 - 4.07 (m, 1H), 4.06 - 3.88 (m, 4H), 3.15 - 3.06 (m, 3H), 3.05 - 3.00 (m, 1H), 3.00 - 2.95 (m, 3H), 2.86 - 2.80 (m, 3H), 2.80 - 2.64 (m, 2H), 2.63 - 2.47 (m, 2H), 1.21 - 1.13 (m, 6H).

Example 487

(8*S*,11*S*,15*R*)-10-[6-[(3*R*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **487** was prepared according to the following scheme:



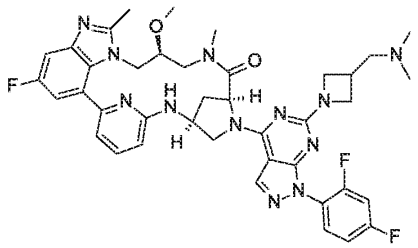
The compound **487a** was prepared in analogy to the preparation of Example **483** by using *tert*-butyl N-[(3*R*,4*R*)-4-fluoropyrrolidin-3-yl]carbamate;hydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Compound **487a**, LCMS (M+H$^+$): 871.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-[(3R,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Examples 487)

The compound **487a** was dissolved in dichloromethane (2 mL) and TFA, the solution was stirred at r.t. for 1 hr. The mixture was concentrated and purified via prep-HPLC to give Example **487**. LCMS (M+H$^+$): 771. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.29 (s, 1H), 7.92 - 7.84 (m, 1H), 7.68 - 7.51 (m, 3H), 7.27 - 7.19 (m, 1H), 7.19 - 7.12 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.29 - 6.06 (m, 1H), 5.47 - 5.36 (m, 1H), 5.36 - 5.22 (m, 1H), 4.68 (br t, *J* = 4.8 Hz, 1H), 4.53 - 4.43 (m, 1H), 4.36 - 4.18 (m, 2H), 4.15 - 3.83 (m, 5H), 3.76 - 3.65 (m, 1H), 3.17 - 3.07 (m, 3H), 3.02 (br d, *J* = 15.4 Hz, 1H), 3.00 - 2.96 (m, 3H), 2.85 - 2.81 (m, 3H), 2.78 (br d, *J* = 13.6 Hz, 1H), 2.70 - 2.48 (m, 2H).

Example 488

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(dimethylamino)methyl]azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

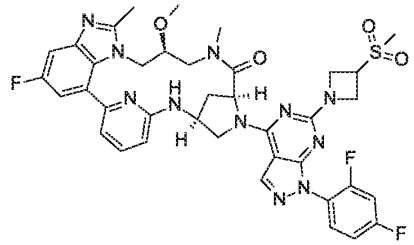


Example **488** was prepared in analogy to the preparation of Example **483** by using azetidin-3-ylmethyl(dimethyl)amine;dihydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **488**, LCMS (M+H$^+$): 781. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.28 (s,

1H), 7.92 - 7.83 (m, 1H), 7.65 - 7.51 (m, 3H), 7.27 - 7.19 (m, 1H), 7.19 - 7.12 (m, 2H), 6.81 - 6.74 (m, 1H), 6.28 - 6.04 (m, 1H), 5.43 - 5.30 (m, 1H), 4.67 (br t, J = 4.5 Hz, 1H), 4.51 - 4.43 (m, 1H), 4.38 - 4.26 (m, 2H), 4.25 - 4.13 (m, 2H), 3.99 - 3.87 (m, 2H), 3.86 - 3.72 (m, 1H), 3.53 - 3.42 (m, 2H), 3.22 - 3.14 (m, 1H), 3.06 (s, 3H), 3.04 - 2.99 (m, 1H), 2.98 (d, J = 2.6 Hz, 3H), 2.92 - 2.87 (m, 6H), 2.85 - 2.80 (m, 3H), 2.76 (br d, J = 13.6 Hz, 1H), 2.68 - 2.46 (m, 2H).

Example 489

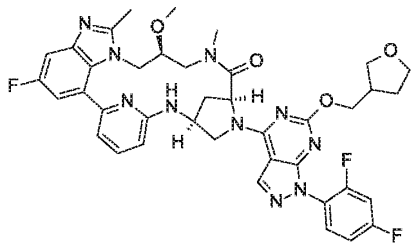
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methylsulfonylazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



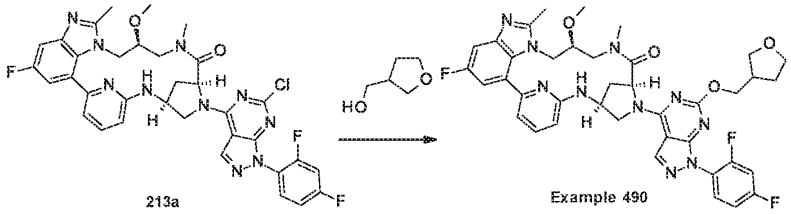
Example **489** was prepared in analogy to the preparation of Example **483** by using 3-mesylazetidine;hydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **489**, LCMS (M+H$^+$): 802. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.28 (s, 1H), 7.87 (t, J = 7.9 Hz, 1H), 7.66 - 7.50 (m, 3H), 7.26 - 7.19 (m, 1H), 7.19 - 7.11 (m, 2H), 6.78 (br d, J = 8.5 Hz, 1H), 6.28 - 6.03 (m, 1H), 5.45 - 5.30 (m, 1H), 4.66 (br t, J = 4.8 Hz, 1H), 4.46 (br dd, J = 5.8, 11.4 Hz, 1H), 4.41 - 4.36 (m, 1H), 4.35 - 4.19 (m, 6H), 3.94 (dd, J = 9.1, 14.3 Hz, 1H), 3.15 - 3.06 (m, 3H), 3.04 - 2.99 (m, 1H), 2.97 (d, J = 6.5 Hz, 6H), 2.86 - 2.79 (m, 3H), 2.78 - 2.71 (m, 1H), 2.68 - 2.45 (m, 2H).

Example 490

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(tetrahydrofuran-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



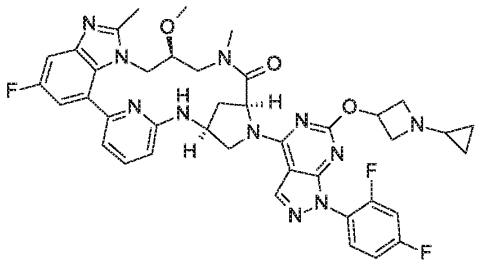
Example **490** was prepared according to the following scheme:



To a tube was added tetrahydrofuran-3-ylmethanol (15.3 mg, 0.149 mmol) and tetrahydrofuran (1.5 mL), the solution was cooled in dry ice/EtOH bath and then NaH (8.0 mg, 0.199 mmol) was added. The mixture was stirred for 30 mins and compound **213a** (35.0 mg, 0.050 mmol) was added. After being warmed to r.t. slowly and stirred for 1 hr, the mixture was quenched and filtered, the filtrate was purified via prep-HPLC to give Example **490** (6.6 mg) as white solid. LCMS ($M+H^+$): 769. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 7.87 (t, J = 7.9 Hz, 1H), 7.63 (dq, J = 6.2, 8.7 Hz, 1H), 7.54 (dd, J = 2.2, 7.4 Hz, 1H), 7.48 (dd, J = 1.6, 10.1 Hz, 1H), 7.30 - 7.23 (m, 1H), 7.21 - 7.13 (m, 2H), 6.76 (d, J = 8.5 Hz, 1H), 6.14 - 5.96 (m, 1H), 5.49 - 5.37 (m, 1H), 4.68 (br t, J = 4.7 Hz, 1H), 4.50 (dd, J = 5.7, 11.4 Hz, 1H), 4.34 - 4.28 (m, 2H), 4.28 - 4.23 (m, 1H), 4.21 (d, J = 7.3 Hz, 1H), 3.94 (br dd, J = 9.5, 13.9 Hz, 1H), 3.90 - 3.78 (m, 2H), 3.77 - 3.72 (m, 1H), 3.65 - 3.59 (m, 1H), 3.16 - 3.05 (m, 3H), 3.05 - 2.96 (m, 1H), 2.95 (s, 3H), 2.88 - 2.82 (m, 1H), 2.81 - 2.76 (m, 3H), 2.75 - 2.63 (m, 1H), 2.62 - 2.49 (m, 2H), 2.14 - 2.01 (m, 1H), 1.80 - 1.64 (m, 1H).

Example 491

(8*S*,11*S*,15*R*)-10-[6-(1-cyclopropylazetidin-3-yl)oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

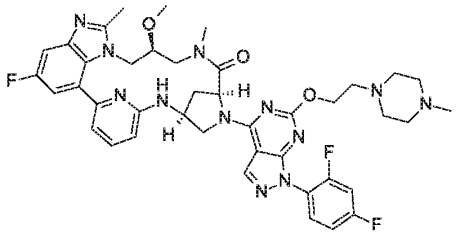


Example **491** was prepared in analogy to the preparation of Example **490** by using 1-cyclopropylazetidin-3-ol instead of tetrahydrofuran-3-ylmethanol. Example **491**, LCMS ($M+H^+$): 780. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.39 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.66 - 7.54 (m, 1H), 7.34 - 7.22 (m, 2H), 7.17 (br dd, J = 2.6, 10.4 Hz, 2H), 7.12 - 7.07 (m, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.80 - 5.65 (m, 1H), 5.41 - 5.32 (m, 1H), 5.29 - 5.01 (m, 1H), 4.63 (br t, J = 4.6 Hz,

1H), 4.48 - 4.40 (m, 1H), 4.33 - 4.25 (m, 1H), 4.23 - 4.04 (m, 2H), 3.93 (br dd, *J* = 9.4, 14.1 Hz, 2H), 3.81 (br t, *J* = 7.4 Hz, 1H), 3.58 - 3.42 (m, 2H), 3.11 - 3.03 (m, 3H), 2.90 - 2.85 (m, 1H), 2.85 - 2.81 (m, 3H), 2.58 - 2.54 (m, 3H), 2.53 - 2.44 (m, 2H), 2.25 (br s, 1H), 0.65 - 0.41 (m, 4H).

Example 492

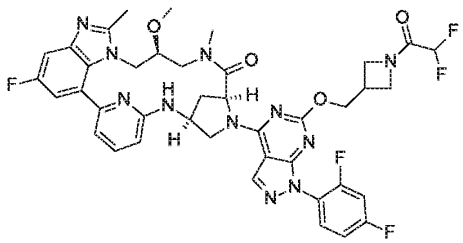
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(4-methylpiperazin-1-yl)ethoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



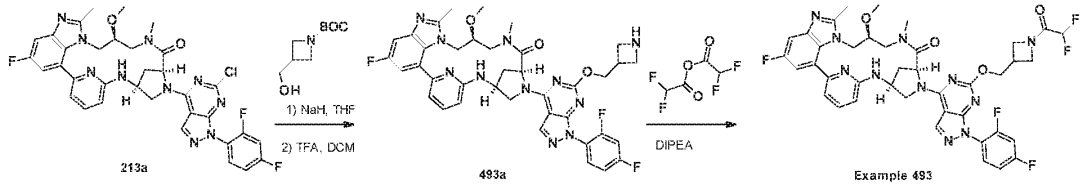
Example **492** was prepared in analogy to the preparation of Example **490** by using 2-(4-methylpiperazino)ethanol instead of tetrahydrofuran-3-ylmethanol. Example **492**, LCMS (M+H$^+$): 811. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.37 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.55 (m, 1H), 7.29 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.19 - 7.11 (m, 2H), 7.11 - 7.05 (m, 1H), 6.69 - 6.62 (m, 1H), 5.79 - 5.65 (m, 1H), 5.44 - 5.32 (m, 1H), 4.61 (br t, *J* = 4.5 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.46 - 4.29 (m, 3H), 4.25 (br d, *J* = 15.4 Hz, 1H), 4.19 - 4.08 (m, 1H), 3.94 (br dd, *J* = 9.4, 13.9 Hz, 1H), 3.12 - 3.01 (m, 3H), 2.94 (br d, *J* = 14.0 Hz, 1H), 2.87 (br s, 1H), 2.82 (s, 3H), 2.79 (br t, *J* = 6.0 Hz, 1H), 2.76 - 2.69 (m, 2H), 2.68 - 2.57 (m, 2H), 2.57 - 2.54 (m, 3H), 2.54 - 2.35 (m, 6H), 2.26 (s, 3H).

Example 493

(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroacetyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **493** was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-ylmethoxy)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 493a)

To a tube was added *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (24.0 mg, 0.128 mmol) and tetrahydrofuran (2.5 mL), the solution was cooled in dry ice/EtOH bath and then NaH (13.6 mg, 0.341 mmol) was added. The mixture was stirred for 30 mins and compound **213a** (60.0 mg, 0.085 mmol) was added, then it was warmed to r.t. slowly and stirred for 1 hr. The reaction was quenched with MeOH, and then the mixture was diluted with 20 mL water, extracted with 15 mL EA twice, the organic layer was dried and concentrated to give a residue which was purified via flash column (EA/PE=0~100%) to give a white solid.

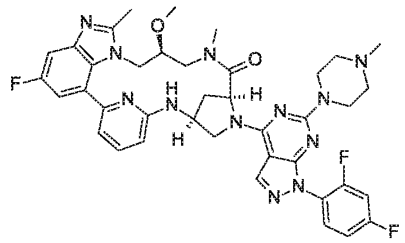
The solid was dissolved in dichloromethane (2 mL) and TFA (1 mL), the solution was stirred at r.t. for 1 hr. The mixture was concentrated to give light yellow oil which was purified via prep-HPLC (ACN/TFA 0.05% aq.=0~30%) to give compound **493a** (80 mg). LCMS (M+H$^+$): 754.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroacetyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 493)

To a tube was added compound **493a** (10.0 mg, 0.011 mmol), DIEA (8.5 mg, 11.47 μL, 0.066 mmol), dichloromethane (1 mL) and difluoroacetic anhydride (5.7 mg, 3.6 μL, 0.033 mmol). The solution was stirred at r.t. for 4 hrs, then the reaction was quenched with MeOH. The mixture was concentrated and purified via prep-HPLC to give Example **493** (5.7 mg). LCMS (M+H$^+$): 832. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.41 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.68 - 7.57 (m, 1H), 7.33 - 7.27 (m, 1H), 7.27 - 7.22 (m, 1H), 7.21 - 7.13 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.13 (dt, *J* = 1.9, 53.3 Hz, 1H), 5.82 - 5.65 (m, 1H), 5.46 - 5.35 (m, 1H), 4.63 (s, 1H), 4.60 - 4.52 (m, 2H), 4.52 - 4.39 (m, 3H), 4.34 - 4.09 (m, 4H), 4.03 - 3.89 (m, 2H), 3.13 - 3.02 (m, 3H), 2.99 - 2.85 (m, 2H), 2.84 (s, 3H), 2.59 - 2.55 (m, 3H), 2.50 (tt, *J* = 4.5, 9.0 Hz, 2H).

Example 494

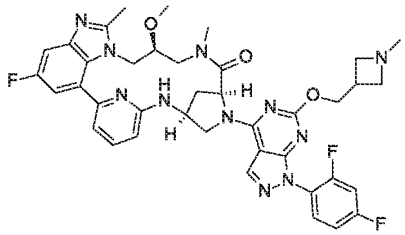
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methylpiperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **494** was prepared in analogy to the preparation of Example **483** by using 1-methylpiperazine instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **494,** LCMS (M+H$^+$): 767. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.22 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.30 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.18 - 7.11 (m, 2H), 7.09 (br d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.89 - 5.64 (m, 1H), 5.41 - 5.25 (m, 1H), 4.64 (br t, *J* = 4.9 Hz, 1H), 4.56 (s, 1H), 4.44 (br dd, *J* = 5.8, 10.8 Hz, 1H), 4.28 - 4.09 (m, 3H), 3.94 - 3.68 (m, 5H), 3.13 - 3.02 (m, 3H), 2.97 - 2.88 (m, 1H), 2.87 - 2.81 (m, 3H), 2.59 - 2.55 (m, 3H), 2.54 (br s, 1H), 2.47 (br s, 4H), 2.38 - 2.32 (m, 3H).

Example 495

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylazetidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

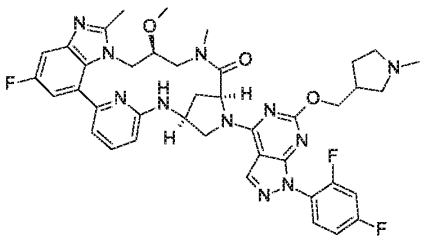


Example **495** was prepared in analogy to the preparation of Example **490** by using (1-methylazetidin-3-yl)methanol instead of tetrahydrofuran-3-ylmethanol. Example **495**, LCMS (M+H$^+$): 768. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.48 - 8.42 (m, 1H), 7.88 (dt, *J* = 4.0, 7.9 Hz, 1H), 7.71 - 7.58 (m, 1H), 7.57 - 7.53 (m, 1H), 7.49 (br d, *J* = 10.3 Hz, 1H), 7.37 - 7.27 (m, 1H), 7.22 (br d, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.78 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.16 - 5.99 (m, 1H), 5.48 - 5.39 (m, 1H), 4.69 (br d, *J* = 2.3 Hz, 1H), 4.59 - 4.45 (m, 2H), 4.43 - 4.14

(m, 7H), 4.08 - 3.87 (m, 2H), 3.17 - 3.02 (m, 4H), 2.99 - 2.93 (m, 4H), 2.93 - 2.85 (m, 3H), 2.78 (d, J = 2.4 Hz, 3H), 2.72 - 2.49 (m, 2H).

Example 496

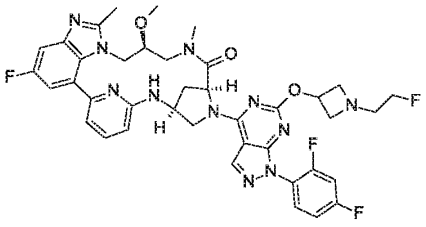
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylpyrrolidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **496** was prepared in analogy to the preparation of Example **490** by using (1-methylpyrrolidin-3-yl)methanol instead of tetrahydrofuran-3-ylmethanol. Example **496**, LCMS (M+H$^+$): 782. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.44 (br s, 1H), 7.91 - 7.84 (m, 1H), 7.69 - 7.59 (m, 1H), 7.56 (dd, J = 2.1, 7.4 Hz, 1H), 7.50 (br dd, J = 2.7, 10.2 Hz, 1H), 7.35 - 7.26 (m, 1H), 7.25 - 7.18 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 6.78 (dd, J = 3.0, 8.4 Hz, 1H), 6.16 - 5.99 (m, 1H), 5.49 - 5.39 (m, 1H), 4.72 - 4.66 (m, 1H), 4.51 (br dd, J = 5.2, 11.3 Hz, 1H), 4.43 - 4.18 (m, 4H), 4.00 - 3.87 (m, 1H), 3.84 - 3.61 (m, 2H), 3.29 - 3.21 (m, 1H), 3.18 - 3.10 (m, 2H), 3.10 - 3.02 (m, 3H), 2.95 (s, 7H), 2.92 - 2.83 (m, 1H), 2.79 (d, J = 5.4 Hz, 3H), 2.72 - 2.49 (m, 2H), 2.48 - 2.17 (m, 1H), 2.16 - 1.88 (m, 1H).

Example 497

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-fluoroethyl)azetidin-3-yl]oxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

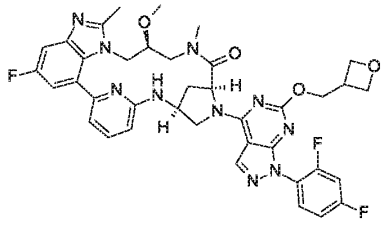


To a tube was added compound **497a** (10.0 mg, 0.012 mmol), K_2CO_3 (9.7 mg, 0.070 mmol), 1-fluoro-2-iodo-ethane (12.2 mg, 0.070 mmol) and acetonitrile (0.5 mL). The suspension stirred at r.t. for 16 hrs. Then it was filtered, the filtrate was purified via prep-HPLC to give

Example **497** (6.6 mg). LCMS (M+H$^+$): 786. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.66 - 7.55 (m, 1H), 7.32 - 7.21 (m, 2H), 7.21 - 7.13 (m, 2H), 7.12 - 7.06 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.81 - 5.65 (m, 1H), 5.45 - 5.34 (m, 1H), 5.09 (quin, J = 6.0 Hz, 1H), 4.68 - 4.64 (m, 1H), 4.55 - 4.45 (m, 2H), 4.41 (t, J = 4.5 Hz, 1H), 4.29 (d, J = 11.6 Hz, 1H), 4.22 - 4.08 (m, 1H), 3.97 - 3.87 (m, 1H), 3.86 - 3.69 (m, 2H), 3.67 - 3.46 (m, 1H), 3.22 - 3.16 (m, 1H), 3.12 - 3.03 (m, 3H), 2.94 - 2.86 (m, 3H), 2.86 - 2.82 (m, 3H), 2.82 - 2.78 (m, 1H), 2.59 - 2.55 (m, 3H), 2.54 - 2.44 (m, 2H).

Example 498

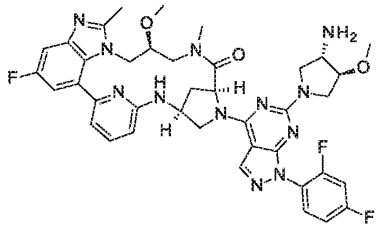
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **498** was prepared in analogy to the preparation of Example **490** by using oxetan-3-ylmethanol instead of tetrahydrofuran-3-ylmethanol. Example **498**, LCMS (M+H$^+$): 755. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.68 - 7.57 (m, 1H), 7.30 (dd, J = 2.4, 8.5 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.21 - 7.13 (m, 2H), 7.12 - 7.08 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.81 - 5.66 (m, 1H), 5.46 - 5.34 (m, 1H), 4.66 (br t, J = 4.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.60 - 4.54 (m, 1H), 4.54 - 4.43 (m, 3H), 4.33 - 4.22 (m, 1H), 4.20 - 4.09 (m, 1H), 3.94 (br dd, J = 9.4, 14.2 Hz, 1H), 3.66 - 3.57 (m, 1H), 3.51 - 3.43 (m, 1H), 3.43 - 3.34 (m, 1H), 3.13 - 3.02 (m, 3H), 2.99 - 2.85 (m, 2H), 2.84 (s, 3H), 2.60 - 2.55 (m, 3H), 2.44 (br s, 2H).

Example 499

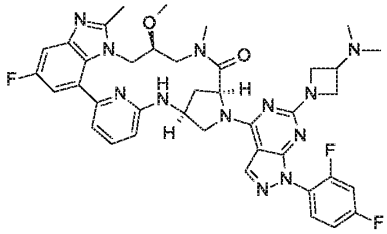
(8*S*,11*S*,15*R*)-10-[6-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **499** was prepared in analogy to the preparation of Example **487** by using *tert*-butyl *N*-[(3*S*,4*S*)-4-methoxypyrrolidin-3-yl]carbamate instead of *tert*-butyl N-[(3*R*,4*R*)-4-fluoropyrrolidin-3-yl]carbamate;hydrochloride. Example **499**, LCMS ($M+H^+$): 783. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (br s, 1H), 7.96 (br d, *J* = 6.9 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.68 - 7.61 (m, 1H), 7.58 (dd, *J* = 2.1, 10.1 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.28 - 7.21 (m, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.92 (br d, *J* = 5.5 Hz, 1H), 6.13 - 5.83 (m, 1H), 5.62 - 5.44 (m, 1H), 4.76 (br s, 1H), 4.61 - 4.52 (m, 1H), 4.42 - 4.25 (m, 2H), 4.23 - 3.83 (m, 6H), 3.75 - 3.64 (m, 1H), 3.62 - 3.56 (m, 1H), 3.50 - 3.43 (m, 3H), 3.18 - 3.12 (m, 3H), 3.09 (br dd, *J* = 6.9, 13.9 Hz, 1H), 3.04 - 2.98 (m, 3H), 2.86 (br d, *J* = 7.4 Hz, 3H), 2.78 -2.56 (m, 2H).

Example 500

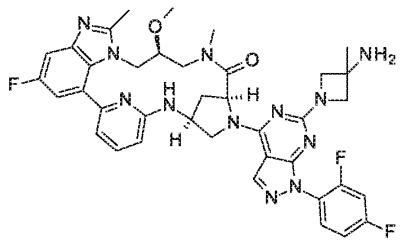
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(dimethylamino)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **500** was prepared in analogy to the preparation of Example **483** by using N,N-dimethylazetidin-3-amine;dihydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **494,** LCMS ($M+H^+$): 767. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.24 (s, 1H), 7.84 - 7.75 (m, 1H), 7.64 - 7.55 (m, 1H), 7.33 - 7.27 (m, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.87 - 5.65 (m, 1H), 5.43 - 5.25 (m, 1H), 4.64 - 4.57 (m, 1H), 4.48 - 4.36 (m, 1H), 4.27 - 4.11 (m, 3H), 4.11 - 4.02 (m, 1H), 4.02 - 3.91 (m, 2H), 3.91 - 3.75 (m, 2H), 3.12 - 3.02 (m, 3H), 2.97 - 2.87 (m, 1H), 2.85 - 2.81 (m, 3H), 2.80 - 2.72 (m, 1H), 2.59 - 2.53 (m, 3H), 2.52 - 2.39 (m, 2H), 2.28 - 2.20 (m, 6H).

Example 501

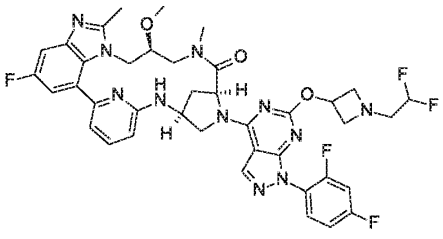
(8*S*,11*S*,15*R*)-10-[6-(3-amino-3-methyl-azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo [3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The Example **501** was prepared in analogy to the preparation of Example **487** by using *tert*-butyl *N*-(3-methylazetidin-3-yl)carbamate;hydrochloride instead of *tert*-butyl N-[(3*R*,4*R*)-4-fluoropyrrolidin-3-yl]carbamate;hydrochloride. Example **501**, LCMS (M+H$^+$): 753. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.23 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.30 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.22 (ddd, *J* = 2.8, 8.9, 10.1 Hz, 1H), 7.17 - 7.10 (m, 2H), 7.10 - 7.05 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.66 (m, 1H), 5.40 - 5.25 (m, 1H), 4.64 - 4.53 (m, 1H), 4.42 (dd, *J* = 5.9, 11.2 Hz, 1H), 4.24 - 4.11 (m, 2H), 3.97 - 3.86 (m, 2H), 3.85 - 3.72 (m, 3H), 3.11 - 3.01 (m, 3H), 2.90 (br d, *J* = 14.4 Hz, 1H), 2.86 - 2.82 (m, 3H), 2.75 (br d, *J* = 13.6 Hz, 1H), 2.59 - 2.54 (m, 3H), 2.53 - 2.41 (m, 2H), 1.47 - 1.40 (m, 3H).

Example 502

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

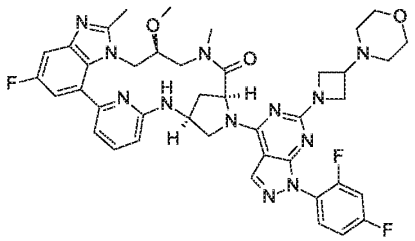


The Example **502** was prepared in analogy to the preparation of Example **497** by using 2,2-difluoroethyl trifluoromethanesulfonate instead of 1-fluoro-2-iodo-ethane and using condition (DIPEA, THF, reflux) instead of condition (K_2CO_3, ACN, r.t.) LCMS (M+H$^+$): 804. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.40 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.56 (m, 1H), 7.32 - 7.27 (m, 1H), 7.27 - 7.21 (m, 1H), 7.20 - 7.13 (m, 2H), 7.12 - 7.07 (m, 1H), 6.70 - 6.64 (m, 1H),

6.00 - 5.81 (m, 1H), 5.76 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.43 - 5.33 (m, 1H), 5.08 (quin, *J* = 6.0 Hz, 1H), 4.68 - 4.55 (m, 1H), 4.50 - 4.42 (m, 1H), 4.33 - 4.26 (m, 1H), 4.19 - 4.11 (m, 1H), 3.96 - 3.88 (m, 1H), 3.83 (br t, *J* = 7.1 Hz, 1H), 3.72 (br t, *J* = 7.3 Hz, 1H), 3.37 - 3.33 (m, 1H), 3.24 (dd, *J* = 5.9, 8.5 Hz, 1H), 3.12 - 3.03 (m, 3H), 2.97 - 2.85 (m, 4H), 2.85 - 2.81 (m, 3H), 2.59 - 2.54 (m, 3H), 2.54 - 2.45 (m, 2H).

Example 503

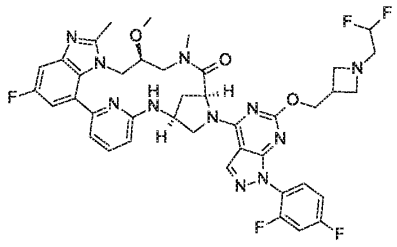
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **503** was prepared in analogy to the preparation of Example **483** by using 4-(azetidin-3-yl)morpholine;dihydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **503**, LCMS (M+H$^+$): 809. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.24 (s, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.86 - 5.65 (m, 1H), 5.42 - 5.26 (m, 1H), 4.64 - 4.59 (m, 1H), 4.46 - 4.38 (m, 1H), 4.27 - 4.12 (m, 3H), 4.08 - 3.94 (m, 2H), 3.93 - 3.79 (m, 2H), 3.76 - 3.65 (m, 4H), 3.26 - 3.15 (m, 1H), 3.12 - 3.01 (m, 3H), 2.98 - 2.87 (m, 1H), 2.85 - 2.80 (m, 3H), 2.76 (br d, *J* = 13.5 Hz, 1H), 2.60 - 2.54 (m, 3H), 2.53 - 2.37 (m, 6H).

Example 504

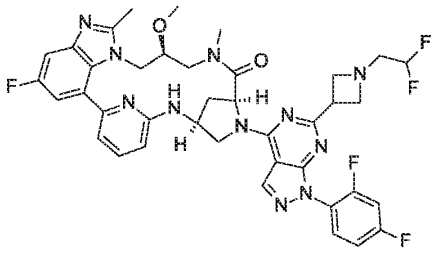
(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroethyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



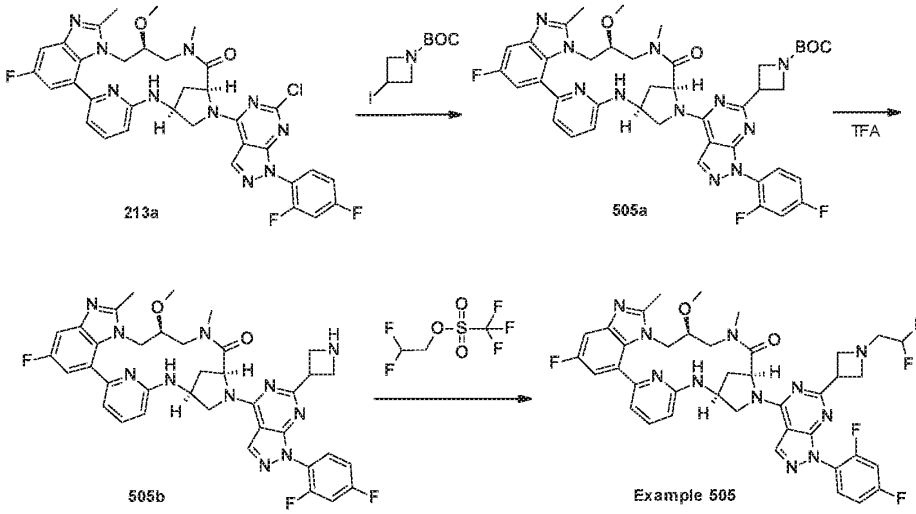
Example **504** was prepared in analogy to the preparation of Example **493** by using 2,2-difluoroethyl trifluoromethanesulfonate instead of difluoroacetic anhydride in step 2. LCMS ($M+H^+$): 818. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.49 - 8.42 (m, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.69 - 7.58 (m, 1H), 7.32 - 7.23 (m, 2H), 7.21 - 7.18 (m, 1H), 7.15 (dd, J = 2.6, 10.6 Hz, 1H), 7.12 - 7.07 (m, 1H), 6.73 - 6.65 (m, 1H), 6.00 - 5.81 (m, 1H), 5.81 - 5.65 (m, 1H), 5.63 - 5.35 (m, 1H), 4.67 (br d, J = 5.1 Hz, 1H), 4.55 - 4.48 (m, 1H), 4.34 - 4.28 (m, 1H), 4.15 (dd, J = 11.0, 15.3 Hz, 1H), 3.94 (dd, J = 9.1, 14.1 Hz, 1H), 3.89 - 3.71 (m, 4H), 3.67 - 3.62 (m, 1H), 3.54 - 3.49 (m, 1H), 3.13 - 3.07 (m, 3H), 2.94 - 2.86 (m, 3H), 2.85 - 2.82 (m, 3H), 2.56 (s, 3H), 2.54 - 2.45 (m, 2H).

Example 505

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **505** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-1-carboxylate (compound 505a)

To an 8 mL vial equipped with a stir bar was added photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (16.0 mg, 0.014 mmol), Na_2CO_3 (45.2 mg, 0.43 mmol), $NiCl_2(dtbbpy)$ (5.7 mg, 0.014 mmol), tris(trimethylsilyl)silane (35.4 mg, 43.9 μL, 0.142 mmol), *tert*-butyl 3-iodoazetidine-1-carboxylate (120.8 mg, 74.1 μL, 0.427 mmol), compound **213a** (100.0 mg, 0.142 mmol) and ethylene glycol dimethyl ether (4 mL). The vial was sealed and placed. The reaction was stirred and irradiated with a 34 W blue LED lamp (450-450 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hrs. The mixture was filtered, the filtrate was concentrated to give compound **505a** (117 mg). LCMS ($M+H^+$): 824.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 505b)

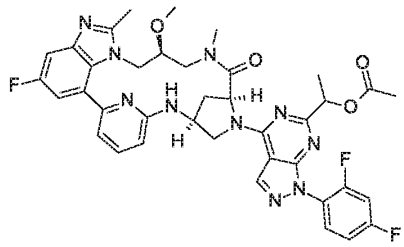
To the flask containing compound **505a** (115 mg, 0.14 mmol) was added dichloromethane (2 mL) and TFA (1 mL). The solution was stirred at r.t. for 1 hr and concentrated. The crude oil was purified via prep-HPLC (ACN/0.05%TFA aq.=0~30%) to give compound **505b** (80 mg). LCMS ($M+H^+$): 724.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 505)

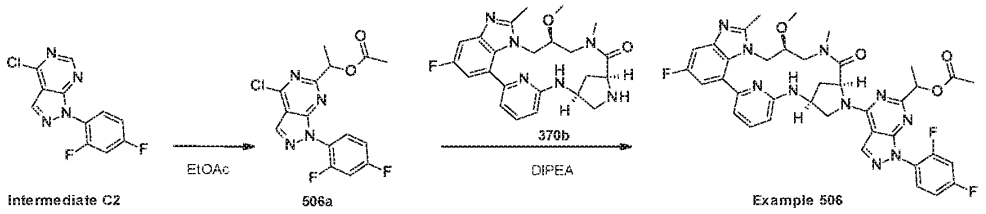
To a tube was added compound **505b** (40.0 mg, 0.048 mmol), trifluoromethanesulfonic acid 2,2-difluoroethyl ester (30.7 mg, 19 μL, 0.143 mmol), DIEA (61.7 mg, 84 μL, 0.48 mmol) and tetrahydrofuran (4 mL), the solution was heated to reflux for 2 hrs. The mixture was concentrated and purified via prep-HPLC (basic condition) to give Example **505** (9.8 mg). LCMS ($M+H^+$): 788. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.49 - 8.42 (m, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.58 (m, 1H), 7.32 - 7.23 (m, 2H), 7.21 - 7.18 (m, 1H), 7.15 (dd, *J* = 2.6, 10.6 Hz, 1H), 7.12 - 7.07 (m, 1H), 6.73 - 6.65 (m, 1H), 6.00 - 5.81 (m, 1H), 5.81 - 5.65 (m, 1H), 5.63 - 5.35 (m, 1H), 4.67 (br d, *J* = 5.1 Hz, 1H), 4.55 - 4.48 (m, 1H), 4.34 - 4.28 (m, 1H), 4.15 (dd, *J* = 11.0, 15.3 Hz, 1H), 3.94 (dd, *J* = 9.1, 14.1 Hz, 1H), 3.89 - 3.71 (m, 4H), 3.67 - 3.62 (m, 1H), 3.54 - 3.49 (m, 1H), 3.13 - 3.07 (m, 3H), 2.94 - 2.86 (m, 3H), 2.85 - 2.82 (m, 3H), 2.56 (s, 3H), 2.54 - 2.45 (m, 2H).

Example 506

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]ethyl acetate



Example **506** was prepared according to the following scheme:



Step 1: preparation of 1-[4-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]ethyl acetate (compound 506a)

To a 8 mL vial equipped with a stir bar was added photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (67.3 mg, 0.060 mmol), 4-chloro-1-(2,4-difluorophenyl)pyrazolo [3,4-d]pyrimidine (Intermediate **C2**, 400.0 mg, 1.5 mmol), ethyl acetate (10.8 g, 12 mL, 122 mmol), *tert*-butyl peroxybenzoate (2.33 g, 2.26 mL, 12 mmol), and (1*S*)-(+)-10-camphorsulfonic acid (174 mg, 0.75 mmol). The vial was sealed and placed. The reaction was stirred and irradiated with a 34 W blue LED lamp (450-450 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hours. The mixture was concentrated and purified via flash column (EA/PE=0~15%), the elution was concentrated to give compound **506a** (245 mg). LCMS (M+H$^+$): 353.

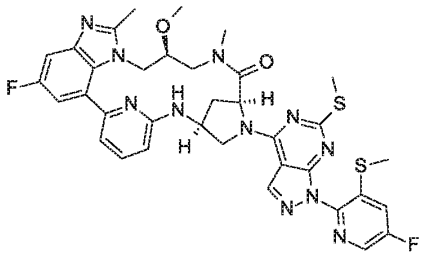
Step 2: preparation of 1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]ethyl acetate (Example 506)

To a flask was added compound **370b** (100.0 mg, 0.18 mmol), DIEA (118.0 mg, 159 μL, 0.91 mmol), compound **506a** (64.4 mg, 0.18 mmol) and acetonitrile (2 mL). The brown solution was heated to 60 °C for 1 hr. The mixture was concentrated and purified via prep-HPLC

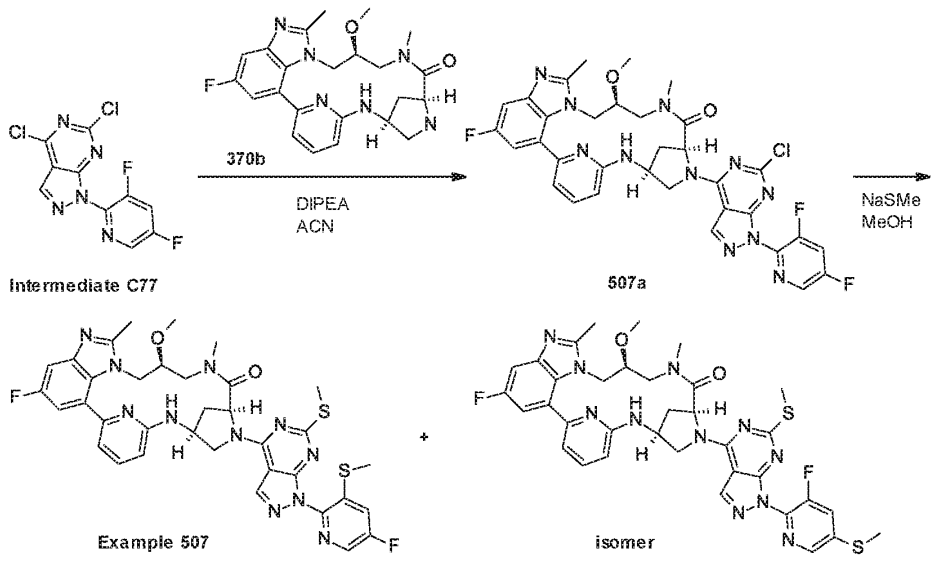
(ACN/TFA 0.05% aq.=0~50%), the elution was freeze dried to give Example **506** (105 mg). LCMS ($M+H^+$): 755. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.48 (d, J = 2.5 Hz, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.60 - 7.51 (m, 2H), 7.31 - 7.24 (m, 1H), 7.23 - 7.18 (m, 1H), 7.18 - 7.13 (m, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.22 - 6.01 (m, 1H), 5.69 - 5.57 (m, 1H), 5.57 - 5.45 (m, 1H), 4.72 - 4.67 (m, 1H), 4.55 - 4.48 (m, 1H), 4.37 - 4.23 (m, 2H), 3.99 - 3.88 (m, 1H), 3.16 - 3.08 (m, 3H), 3.07 - 3.00 (m, 1H), 2.99 - 2.95 (m, 3H), 2.88 - 2.78 (m, 4H), 2.63 - 2.49 (m, 2H), 2.10 - 2.02 (m, 3H), 1.62 - 1.48 (m, 3H).

Example 507

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoro-3-methylsulfanyl-2-pyridyl)-6-methylsulfanyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **507** was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 507a)

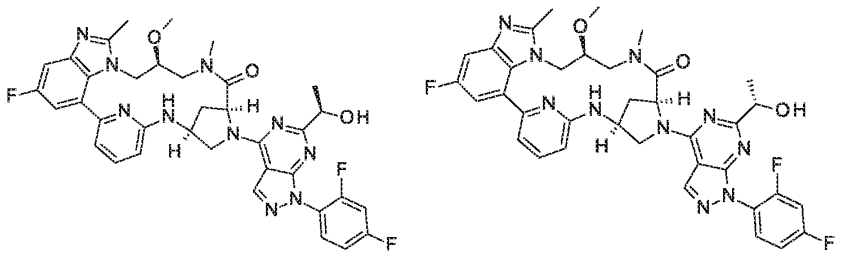
To a flask was added compound **370b**;hydrogen chloride (150 mg, 0.27 mmol), DIEA (176.9 mg, 239 µL, 1.37 mmol), 4,6-dichloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine (Intermediate **C77**, 91.0 mg, 0.30 mmol) and acetonitrile (3 mL). The brown solution was heated to 60 °C for 1 hr. The mixture was concentrated to give an oil, and then it was purified via flash column (EA/PE=0~100% & MeOH/EA=10%) to give compound **507a** (150 mg). LCMS (M+H$^+$): 704.

Step 2: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoro-3-methylsulfanyl-2-pyridyl)-6-methylsulfanyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 507)

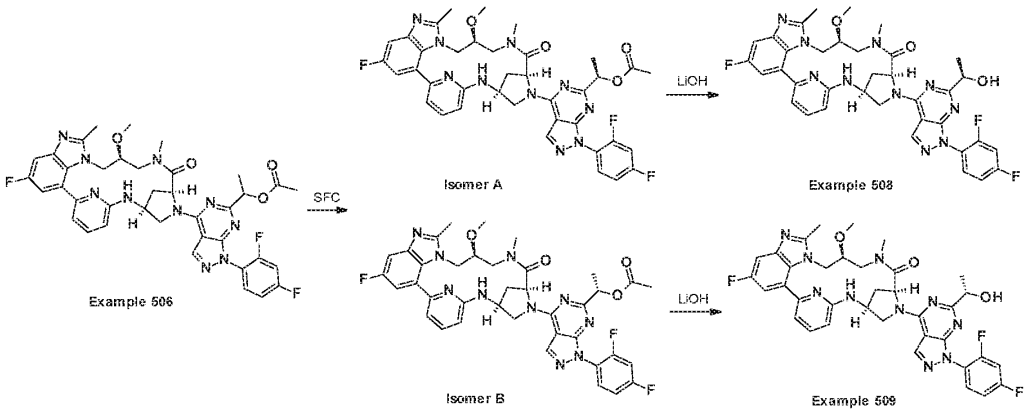
To a tube was added compound **507a** (30 mg, 0.043 mmol), NaSMe (12 mg, 0.17 mmol) and methanol (2 mL). After being heated to 60 °C and stirred at for 16 hrs, the mixture was concentrated and purified via prep-HPLC to give Example **507** (2 mg) and isomer (2.3 mg). LCMS (M+H$^+$): 744. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.41 (s, 1H), 8.27 - 8.24 (m, 1H), 7.88 - 7.85 (m, 1H), 7.84 (td, *J* = 2.8, 5.8 Hz, 1H), 7.49 (dd, *J* = 2.5, 7.6 Hz, 1H), 7.42 (dd, *J* = 2.5, 10.4 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.78 - 6.72 (m, 1H), 6.11 - 5.91 (m, 1H), 5.53 - 5.36 (m, 1H), 4.69 (t, *J* = 4.9 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.35 - 4.24 (m, 2H), 3.97 - 3.88 (m, 1H), 3.14 - 3.06 (m, 3H), 2.98 (dd, *J* = 1.2, 14.3 Hz, 1H), 2.94 - 2.91 (m, 3H), 2.86 - 2.78 (m, 1H), 2.77 - 2.73 (m, 3H), 2.59 - 2.50 (m, 3H), 2.49 - 2.44 (m, 3H), 2.40 (s, 2H).

Example 508 and Example 509

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **508** and Example **509** were prepared according to the following scheme:



Step 1: preparation of the two isomers (isomer A and isomer B)

Example **506** (105 mg) was separated via SFC (condition: Instrument: SFC 150 Mgm; Column: C-4, 250×30 mm I.D., 5μm; Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O); Gradient: B 50%; Flow rate: 80 mL /min; Back pressure: 100 bar; Column temperature: 35 °C) to give isomer **A** (30 mg, faster eluted) and isomer **B** (36 mg, slower eluted).

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 508 and Example 509)

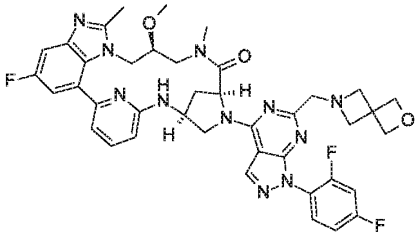
To a flask was added isomer **A** (30 mg) or isomer **B** (36 mg), 2 M LiOH (~ 2 N aq.) (2 mL, 4 mmol) and tetrahydrofuran (2 mL). The suspension was stirred at r.t. for 1 hr. The mixture was neutralized with 1N HCl aq., and the residue was concentrated to remove the THF and then it was purified via prep-HPLC to give Example **508** (11.7 mg) or Example **509** (17.2 mg).

Example **508**, LCMS (M+H$^+$): 713. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.45 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.70 - 7.60 (m, 1H), 7.32 - 7.23 (m, 2H), 7.21 - 7.13 (m, 2H), 7.11 - 7.06 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.82 - 5.64 (m, 1H), 5.63 - 5.36 (m, 1H), 4.77 - 4.59 (m, 2H), 4.51 - 4.43 (m, 1H), 4.32 - 4.25 (m, 1H), 4.18 - 4.07 (m, 1H), 3.97 - 3.86 (m, 1H), 3.13 - 3.03 (m, 3H), 2.98 - 2.84 (m, 2H), 2.84 - 2.79 (m, 3H), 2.58 - 2.53 (m, 3H), 2.53 - 2.43 (m, 2H), 1.53 - 1.39 (m, 3H).

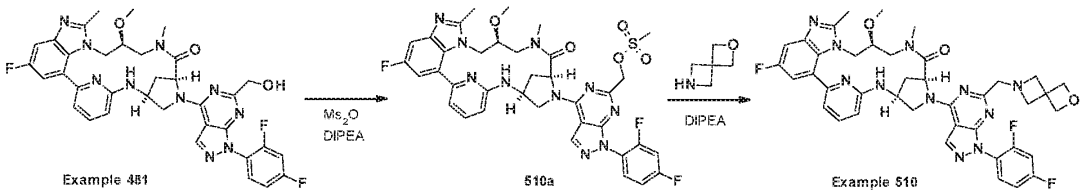
Example **509**, LCMS (M+H$^+$): 713. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.72 - 7.61 (m, 1H), 7.32 - 7.23 (m, 2H), 7.21 - 7.13 (m, 2H), 7.11 - 7.07 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.83 - 5.82 (m, 1H), 5.83 - 5.64 (m, 1H), 5.59 - 5.35 (m, 1H), 4.78 - 4.62 (m, 2H), 4.53 - 4.46 (m, 1H), 4.34 - 4.27 (m, 1H), 4.18 - 4.08 (m, 1H), 3.98 - 3.85 (m, 1H), 3.13 - 3.03 (m, 3H), 2.98 - 2.85 (m, 2H), 2.85 - 2.80 (m, 3H), 2.58 - 2.53 (m, 3H), 2.50 (ddd, J = 4.2, 9.3, 13.4 Hz, 2H), 1.54 - 1.40 (m, 3H).

Example 510

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **510** was prepared according to the following scheme:



Example 481 510a Example 510

Step 1: preparation of [1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]methyl methanesulfonate (compound 510a)

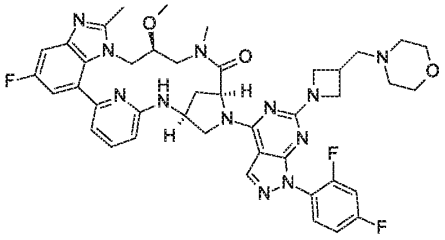
To a flask was added Example **481** (147 mg, 0.21 mmol), DIEA (54 mg, 73 µL, 0.42 mmol), dichloromethane (3 mL) and methanesulfonic anhydride (58 mg, 0.34 mmol). The solution was stirred at r.t. for 2 hrs. The mixture was diluted with 20 mL DCM and washed with 20 mL sat. NaCl aq. twice. The organic layer was dried over Na_2SO_4 and concentrated, compound **510a** (190 mg) was obtained as yellow solid. LCMS ($M+H^+$): 777.

Step 2: (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 510)

To tube was added compound **510a** (46.6 mg, 0.060 mmol), 2-oxa-6-azaspiro[3.3] heptane (8.9 mg, 0.090 mmol), DIEA (15.5 mg, 21 µL, 0.120 mmol) and acetonitrile (2.5 mL). The solution was heated to 85 °C and stirred for 2 hrs. The mixture was concentrated and purified via prep-HPLC to give Example **510**. LCMS ($M+H^+$): 780. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.86 - 7.79 (m, 1H), 7.69 - 7.59 (m, 1H), 7.32 - 7.24 (m, 2H), 7.22 - 7.13 (m, 2H), 7.11 (d, J = 7.4 Hz, 1H), 6.71 - 6.66 (m, 1H), 5.82 - 5.66 (m, 1H), 5.63 - 5.35 (m, 1H), 4.75 - 4.69 (m, 4H), 4.69 - 4.63 (m, 1H), 4.52 - 4.46 (m, 1H), 4.34 - 4.26 (m, 1H), 4.20 - 4.08 (m, 1H), 3.96 (dd, J = 9.4, 14.0 Hz, 1H), 3.74 - 3.65 (m, 2H), 3.62 - 3.49 (m, 4H), 3.13 - 3.06 (m, 3H), 2.95 - 2.88 (m, 2H), 2.86 - 2.81 (m, 3H), 2.59 - 2.54 (m, 3H), 2.54 - 2.45 (m, 2H).

Example 511

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(morpholinomethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

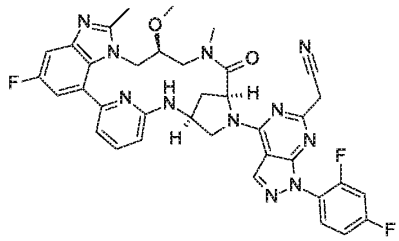


Example **511** was prepared in analogy to the preparation of Example **483** by using 4-(azetidin-3-ylmethyl)morpholine;dihydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **503**, LCMS ($M+H^+$): 823. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.20 (s, 1H), 7.82 - 7.75 (m, 1H), 7.62 - 7.54 (m, 1H), 7.33 - 7.26 (m, 1H), 7.25 - 7.17 (m, 1H), 7.14 (dd, J = 2.5, 10.5 Hz, 1H), 7.06 (d, J = 7.4 Hz, 2H), 6.66 - 6.59 (m, 1H), 5.84 - 5.65 (m, 1H), 5.36 - 5.22 (m, 1H), 4.55 - 4.37 (m, 1H), 4.34 - 4.27 (m, 1H), 4.23 - 4.13 (m, 2H), 4.13 - 4.05 (m, 1H),

4.05 - 3.98 (m, 1H), 3.92 (dd, *J* = 9.1, 14.1 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.67 (br t, *J* = 4.5 Hz, 4H), 3.62 (dt, *J* = 5.8, 8.3 Hz, 1H), 3.09 - 2.98 (m, 3H), 2.98 - 2.83 (m, 2H), 2.83 - 2.81 (m, 3H), 2.72 (br d, *J* = 13.5 Hz, 1H), 2.64 - 2.57 (m, 2H), 2.57 - 2.51 (m, 3H), 2.51 - 2.35 (m, 6H).

Example 512

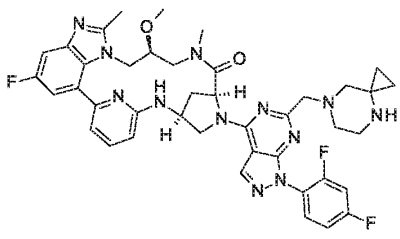
2-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile



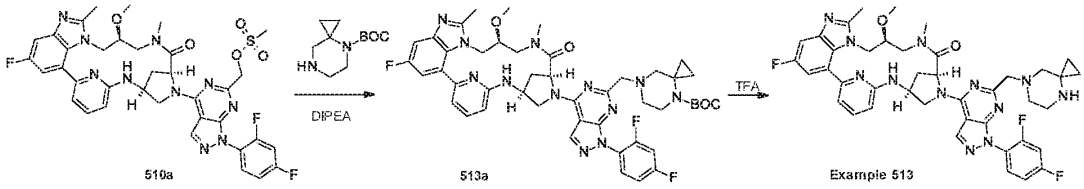
Example **512** was prepared in analogy to the preparation of Example **510** by using trimethylsilylformonitrile instead of 2-oxa-6-azaspiro[3.3] heptane and K_2CO_3 instead of DIPEA in step 2. Example **512**, LCMS (M+H+): 708. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 - 8.47 (m, 1H), 7.84 - 7.78 (m, 1H), 7.69 - 7.59 (m, 1H), 7.32 - 7.23 (m, 2H), 7.22 - 7.17 (m, 1H), 7.15 (dd, *J* = 2.6, 10.5 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.71 - 6.63 (m, 1H), 5.86 - 5.63 (m, 1H), 5.54 - 5.36 (m, 1H), 4.71 - 4.64 (m, 1H), 4.60 - 4.53 (m, 1H), 4.50 (br dd, *J* = 6.1, 11.6 Hz, 1H), 4.30 (br d, *J* = 11.0 Hz, 1H), 4.14 (dd, *J* = 11.0, 15.5 Hz, 1H), 3.99 - 3.86 (m, 1H), 3.13 - 3.02 (m, 3H), 2.98 - 2.87 (m, 1H), 2.84 (s, 3H), 2.83 - 2.79 (m, 1H), 2.68 - 2.59 (m, 1H), 2.58 - 2.54 (m, 3H), 2.54 - 2.45 (m, 2H).

Example 513

(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-ylmethyl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **513** was prepared according to the following scheme:



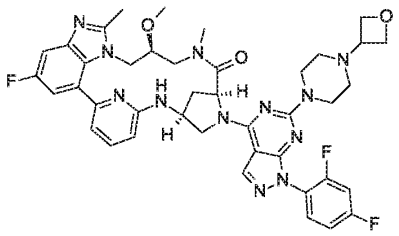
Compound **513a** was prepared in analogy to the preparation of Example **510** by using *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate instead of 2-oxa-6-azaspiro[3.3] heptane. LCMS ($M+H^+$): 893.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-ylmethyl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 513)

To a tube was added compound **513a** (71.4 mg, 0.080 mmol), TFA (1 mL) and dichloromethane (2 mL). The solution was stirred at r.t. for 1 hr, then concentrated and purified via prep-HPLC to give Example **513** (13.5 mg). LCMS ($M+H^+$): 793. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.46 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.69 - 7.57 (m, 1H), 7.32 - 7.22 (m, 2H), 7.21 - 7.13 (m, 2H), 7.12 - 7.06 (m, 1H), 6.70 - 6.63 (m, 1H), 5.79 - 5.65 (m, 1H), 5.63 - 5.33 (m, 1H), 4.67 - 4.54 (m, 1H), 4.50 - 4.42 (m, 1H), 4.32 - 4.25 (m, 1H), 4.18 - 4.07 (m, 1H), 3.92 (br dd, J = 9.4, 14.0 Hz, 1H), 3.74 - 3.58 (m, 2H), 3.13 - 3.01 (m, 3H), 2.98 - 2.84 (m, 4H), 2.82 (s, 3H), 2.76 - 2.68 (m, 1H), 2.66 - 2.57 (m, 2H), 2.57 - 2.53 (m, 3H), 2.53 - 2.43 (m, 3H), 0.63 - 0.55 (m, 2H), 0.53 - 0.44 (m, 2H).

Example 514

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

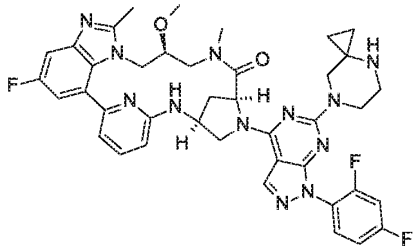


Example **514** was prepared in analogy to the preparation of Example **483** by using 1-(oxetan-3-yl)piperazine instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **514**, LCMS ($M+H^+$): 809. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.21 (s, 1H), 7.80 (t, J = 7.9 Hz,

1H), 7.65 - 7.56 (m, 1H), 7.29 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.65 (m, 1H), 5.41 - 5.25 (m, 1H), 4.72 - 4.66 (m, 2H), 4.62 (q, *J* = 5.8 Hz, 3H), 4.43 (br dd, *J* = 5.9, 11.0 Hz, 1H), 4.23 - 4.11 (m, 2H), 3.91 - 3.82 (m, 2H), 3.81 - 3.68 (m, 3H), 3.53 - 3.44 (m, 1H), 3.12 - 3.02 (m, 3H), 2.98 - 2.87 (m, 1H), 2.86 - 2.82 (m, 3H), 2.76 (br d, *J* = 13.5 Hz, 1H), 2.59 - 2.53 (m, 3H), 2.52 - 2.41 (m, 2H), 2.40 - 2.28 (m, 4H).

Example 515

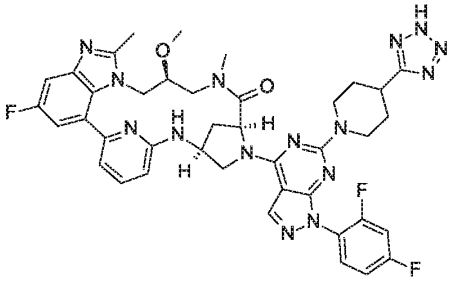
(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The Example **515** was prepared in analogy to the preparation of Example **487** by using *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate instead of *tert*-butyl *N*-[(3*R*,4*R*)-4-fluoropyrrolidin-3-yl]carbamate;hydrochloride. Example **515**, LCMS (M+H$^+$): 779. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.20 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.89 - 5.66 (m, 1H), 5.36 - 5.25 (m, 1H), 4.66 - 4.54 (m, 1H), 4.43 (dd, *J* = 6.1, 11.1 Hz, 1H), 4.24 - 4.08 (m, 2H), 3.98 - 3.83 (m, 2H), 3.76 - 3.57 (m, 2H), 3.57 - 3.51 (m, 1H), 3.11 - 2.99 (m, 3H), 2.94 - 2.86 (m, 2H), 2.86 - 2.80 (m, 4H), 2.77 - 2.69 (m, 1H), 2.59 - 2.53 (m, 3H), 2.53 - 2.42 (m, 2H), 0.66 - 0.48 (m, 4H).

Example 516

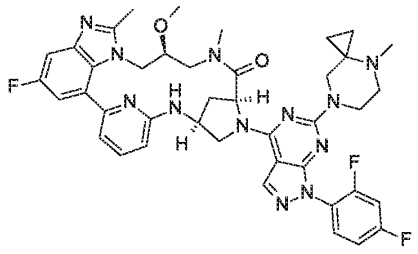
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(2H-tetrazol-5-yl)-1-piperidyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



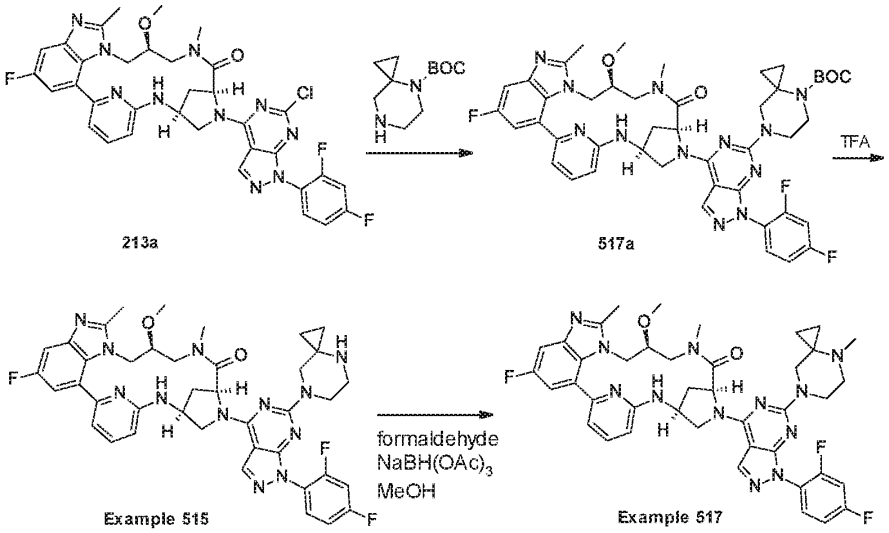
Example **516** was prepared in analogy to the preparation of Example **483** by using 4-(2*H*-tetrazol-5-yl)piperidine;hydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **516**, LCMS (M+H$^+$): 820. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.24 (s, 1H), 7.90 - 7.82 (m, 1H), 7.67 - 7.61 (m, 1H), 7.60 - 7.57 (m, 1H), 7.55 - 7.51 (m, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.11 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.28 - 6.05 (m, 1H), 5.44 - 5.30 (m, 1H), 4.70 - 4.62 (m, 2H), 4.48 (br dd, *J* = 5.9, 11.2 Hz, 1H), 4.32 - 4.19 (m, 2H), 3.99 - 3.80 (m, 1H), 3.39 - 3.33 (m, 1H), 3.17 - 3.10 (m, 2H), 3.08 (s, 3H), 3.06 - 2.98 (m, 2H), 2.97 (s, 3H), 2.84 - 2.80 (m, 3H), 2.73 (br d, *J* = 13.5 Hz, 1H), 2.62 - 2.48 (m, 2H), 2.13 - 1.95 (m, 2H), 1.85 - 1.66 (m, 2H).

Example 517

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **517** was prepared according to the following scheme:



Step 1~2: preparation of (8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 515)

To a tube was added: DIEA (14.7 mg, 20 μL, 0.114 mmol), *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate (18.1 mg, 0.085 mmol), compound **213a** (40.0 mg, 0.057 mmol) and acetonitrile (2.5 mL). The mixture was heated to 85 °C and stirred for 2 hrs. The mixture was concentrated to give an oil (compound **517a**), and then it was dissolved in TFA (0.5 mL) and dichloromethane (1 mL). The solution was stirred at r.t. for 1 hr and concentrated to give an oil. The oil was purified via prep-HPLC to give Example **515** (17.5 mg). LCMS (M+H$^+$): 779.

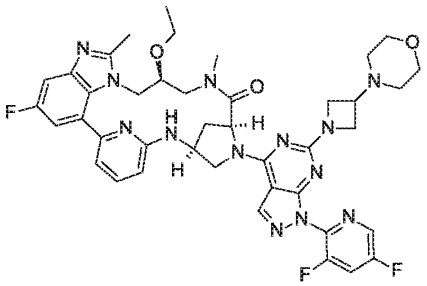
Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 517)

To a tube was added Example **515** (6 mg, 0.007 mmol), formaldehyde (22 mg, 20 μL, 0.73 mmol) and methanol (2 mL). The solution was stirred at r.t. for 30 mins and then sodium triacetoxyborohydride (15.5 mg, 0.074 mmol) was added. The mixture was stirred for another 1 hr and then concentrated to give a residue which was purified via prep-HPLC to give Example **517** (5 mg) as white powder. LCMS (M+H$^+$): 793. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.29 (s, 1H), 7.88 - 7.82 (m, 1H), 7.65 - 7.55 (m, 1H), 7.48 - 7.43 (m, 1H), 7.38 - 7.32 (m, 1H), 7.26 - 7.23 (m, 1H), 7.27 - 7.21 (m, 1H), 7.18 - 7.11 (m, 2H), 6.73 (d, *J* = 8.5 Hz, 1H), 6.05 -

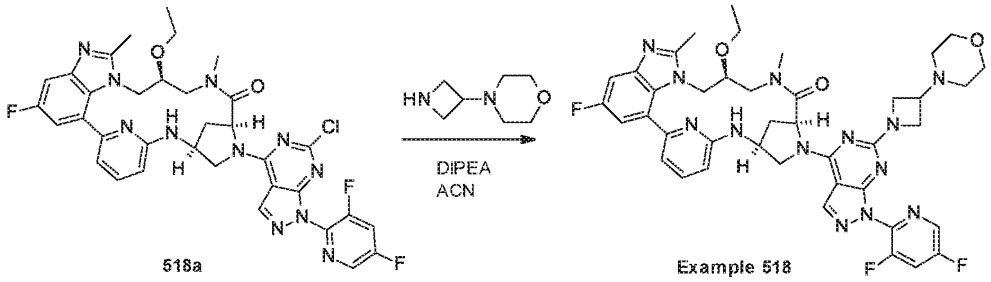
5.87 (m, 1H), 5.42 - 5.29 (m, 1H), 4.68 - 4.63 (m, 1H), 4.50 - 4.43 (m, 1H), 4.28 - 4.14 (m, 3H), 4.11 - 3.98 (m, 2H), 3.97 - 3.93 (m, 1H), 3.92 - 3.83 (m, 1H), 3.54 - 3.37 (m, 2H), 3.14 - 3.01 (m, 6H), 3.00 - 2.93 (m, 1H), 2.93 - 2.89 (m, 3H), 2.72 - 2.67 (m, 3H), 2.58 - 2.46 (m, 2H), 1.24 - 0.97 (m, 4H).

Example 518

(8*S*,11*S*,15*R*)-10-[1-(3,5-difluoro-2-pyridyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **518** was prepared according to the following scheme:



The compound **518a** was prepared in analogy to the preparation of Example **12** by using intermediate **A7** instead of intermediate **A11** in step 1 and using intermediate **C77** instead of intermediate **C2** in step 5.

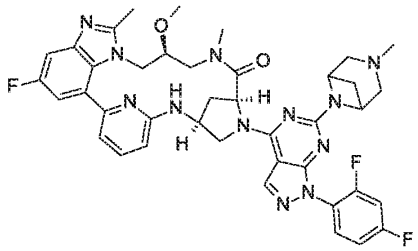
Step 1: preparation of (8*S*,11*S*,15*R*)-10-[1-(3,5-difluoro-2-pyridyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 518)

To a tube was added DIEA (32.3 mg, 44 µL, 0.25 mmol), 4-(azetidin-3-yl)morpholine;dihydrochloride (10.8 mg, 0.050 mmol), compound **518a** (30.0 mg, 0.042 mmol) and acetonitrile (1.5 mL). The mixture was heated to 90 °C and stirred for 4 hrs, then concentrated to give a residue which was purified via prep-HPLC to give example **518** (15.9 mg)

as white powder. LCMS ($M+H^+$): 824. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.45 - 8.43 (m, 1H), 8.31 (s, 1H), 7.94 - 7.88 (m, 1H), 7.84 - 7.79 (m, 1H), 7.36 (dd, J = 2.3, 8.1 Hz, 1H), 7.25 - 7.20 (m, 1H), 7.11 - 7.08 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.94 - 5.74 (m, 1H), 5.41 - 5.28 (m, 1H), 4.63 (t, J = 5.0 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.26 - 4.15 (m, 3H), 4.12 - 4.01 (m, 2H), 3.97 - 3.87 (m, 2H), 3.78 - 3.73 (m, 4H), 3.48 - 3.36 (m, 1H), 3.11 - 3.01 (m, 3H), 2.94 - 2.85 (m, 1H), 2.78 (d, J = 13.6 Hz, 1H), 2.70 - 2.53 (m, 10H), 2.47 (ddd, J = 4.3, 9.1, 13.5 Hz, 1H), 1.39 - 1.37 (m, 3H).

Example 519

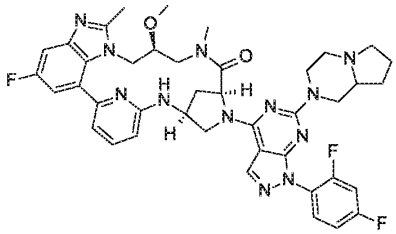
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **519** was prepared in analogy to the preparation of Example **483** by using 3-methyl-3,6-diazabicyclo[3.1.1]heptane;2,2,2-trifluoroacetic acid instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **519**, LCMS ($M+H^+$): 779. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.35 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.69 - 7.59 (m, 1H), 7.33 - 7.28 (m, 1H), 7.28 - 7.21 (m, 1H), 7.16 (td, J = 2.7, 10.4 Hz, 2H), 7.12 - 7.08 (m, 1H), 6.73 - 6.66 (m, 1H), 5.84 - 5.70 (m, 1H), 5.42 - 5.34 (m, 1H), 4.69 - 4.64 (m, 1H), 4.53 - 4.43 (m, 2H), 4.37 - 4.32 (m, 1H), 4.27 - 4.18 (m, 1H), 4.13 (br dd, J = 11.0, 15.6 Hz, 1H), 3.98 - 3.84 (m, 1H), 3.82 - 3.68 (m, 1H), 3.66 - 3.46 (m, 3H), 3.14 - 3.01 (m, 3H), 3.01 - 2.90 (m, 1H), 2.88 - 2.84 (m, 3H), 2.84 - 2.70 (m, 4H), 2.60 - 2.54 (m, 3H), 2.54 - 2.46 (m, 2H), 1.40 - 1.34 (m, 2H).

Example 520

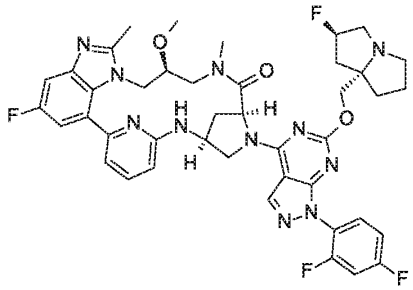
(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **520** was prepared in analogy to the preparation of Example **483** by using 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **520**, LCMS (M+H$^+$): 793. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.30 (s, 1H), 7.88 (dt, J = 3.0, 8.0 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.57 - 7.52 (m, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.13 (m, 2H), 6.79 (d, J = 8.5 Hz, 1H), 6.27 - 6.05 (m, 1H), 5.49 - 5.34 (m, 1H), 4.68 (br t, J = 4.9 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.35 - 4.17 (m, 3H), 4.14 - 3.78 (m, 3H), 3.77 - 3.52 (m, 2H), 3.51 - 3.37 (m, 1H), 3.18 - 3.08 (m, 4H), 3.07 - 3.00 (m, 2H), 3.00 - 2.94 (m, 4H), 2.83 (d, J = 7.5 Hz, 3H), 2.81 - 2.76 (m, 1H), 2.69 - 2.47 (m, 2H), 2.35 - 2.04 (m, 3H), 2.00 - 1.70 (m, 1H).

Example 521

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

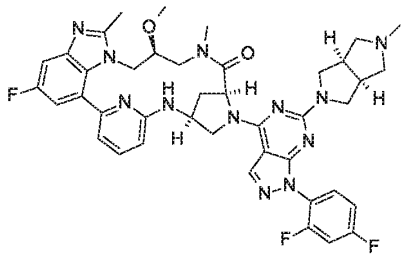


Example **521** was prepared in analogy to the preparation of Example **490** by using [(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol instead of tetrahydrofuran-3-ylmethanol. Example **521**, LCMS (M+H$^+$): 826. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.46 (s, 1H), 7.92 - 7.85 (m, 1H), 7.69 - 7.60 (m, 1H), 7.60 - 7.57 (m, 1H), 7.54 (ddd, J = 2.6, 5.1, 10.3 Hz, 1H), 7.30 (dddd, J = 2.8, 4.8, 8.6, 10.3 Hz, 1H), 7.25 - 7.20 (m, 1H), 7.18 (dd, J = 3.4, 7.4 Hz, 1H), 6.79 (dd, J = 3.3, 8.4 Hz, 1H), 6.23 - 6.03 (m, 1H), 5.63 - 5.40 (m, 2H), 4.73 - 4.63 (m, 1H), 4.59 - 4.49 (m, 2H), 4.37 (d, J = 12.3 Hz, 1H), 4.33 - 4.22 (m, 2H), 4.04 - 3.77 (m, 4H),

3.47 - 3.38 (m, 1H), 3.17 - 3.07 (m, 3H), 3.06 - 3.00 (m, 1H), 2.97 (s, 3H), 2.91 - 2.84 (m, 1H), 2.81 (d, *J* = 6.8 Hz, 3H), 2.73 - 2.49 (m, 4H), 2.40 - 2.26 (m, 3H), 2.20 - 2.02 (m, 1H).

Example 522

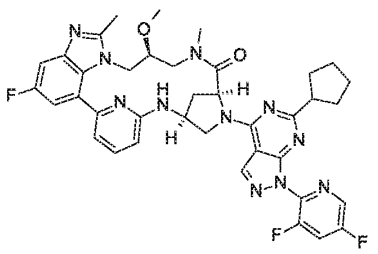
(8*S*,11*S*,15*R*)-10-[6-[(3a*R*,6a*S*)-2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **522** was prepared in analogy to the preparation of Example **483** by using (3a*R*,6a*S*)-5-methyl-2,3,3a,4,6,6a-hexahydro-1*H*-pyrrolo[3,4-c]pyrrole instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **522**, LCMS (M+H$^+$): 793. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.46 (s, 1H), 7.92 - 7.85 (m, 1H), 7.69 - 7.60 (m, 1H), 7.60 - 7.57 (m, 1H), 7.54 (ddd, *J* = 2.6, 5.1, 10.3 Hz, 1H), 7.30 (dddd, *J* = 2.8, 4.8, 8.6, 10.3 Hz, 1H), 7.25 - 7.20 (m, 1H), 7.18 (dd, *J* = 3.4, 7.4 Hz, 1H), 6.79 (dd, *J* = 3.3, 8.4 Hz, 1H), 6.23 - 6.03 (m, 1H), 5.63 - 5.40 (m, 2H), 4.73 - 4.63 (m, 1H), 4.59 - 4.49 (m, 2H), 4.37 (d, *J* = 12.3 Hz, 1H), 4.33 - 4.22 (m, 2H), 4.04 - 3.77 (m, 4H), 3.47 - 3.38 (m, 1H), 3.17 - 3.07 (m, 3H), 3.06 - 3.00 (m, 1H), 2.97 (s, 3H), 2.91 - 2.84 (m, 1H), 2.81 (d, *J* = 6.8 Hz, 3H), 2.73 - 2.49 (m, 4H), 2.40 - 2.26 (m, 3H), 2.20 - 2.02 (m, 1H).

Example 523

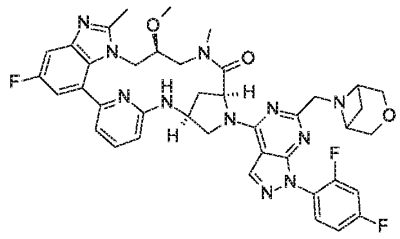
(8*S*,11*S*,15*R*)-10-[6-cyclopentyl-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **523** was prepared in analogy to the preparation of compound **505a** by using compound **507a** and iodocyclopentane instead of compound **213a** and *tert*-butyl 3-iodoazetidine-1-carboxylate. Example **523**, LCMS ($M+H^+$): 738. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.51 - 8.45 (m, 2H), 7.99 - 7.91 (m, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.29 (dd, J = 2.5, 8.5 Hz, 1H), 7.15 (dd, J = 2.6, 10.6 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.87 - 5.65 (m, 1H), 5.52 - 5.36 (m, 1H), 4.72 - 4.66 (m, 1H), 4.54 - 4.47 (m, 1H), 4.33 - 4.25 (m, 1H), 4.19 - 4.10 (m, 1H), 3.86 (dd, J = 9.2, 14.1 Hz, 1H), 3.65 - 3.63 (m, 1H), 3.13 (s, 1H), 3.12 - 3.04 (m, 3H), 2.96 - 2.87 (m, 1H), 2.86 - 2.82 (m, 3H), 2.59 - 2.55 (m, 3H), 2.51 (br dd, J = 4.3, 8.9 Hz, 2H), 2.05 - 1.62 (m, 8H).

Example 524

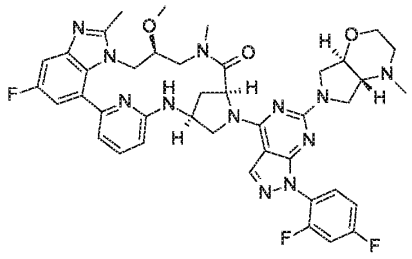
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **524** was prepared in analogy to the preparation of Example **510** by using 3-oxa-6-azabicyclo[3.1.1]heptane;hydrochloride instead of 2-oxa-6-azaspiro[3.3] heptane in step 2. LCMS ($M+H^+$): 780. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.51 - 8.45 (m, 2H), 7.99 - 7.91 (m, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.29 (dd, J = 2.5, 8.5 Hz, 1H), 7.15 (dd, J = 2.6, 10.6 Hz, 1H), 7.12 - 7.06 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.87 - 5.65 (m, 1H), 5.52 - 5.36 (m, 1H), 4.72 - 4.66 (m, 1H), 4.54 - 4.47 (m, 1H), 4.33 - 4.25 (m, 1H), 4.19 - 4.10 (m, 1H), 3.86 (dd, J = 9.2, 14.1 Hz, 1H), 3.65 - 3.63 (m, 1H), 3.13 (s, 1H), 3.12 - 3.04 (m, 3H), 2.96 - 2.87 (m, 1H), 2.86 - 2.82 (m, 3H), 2.59 - 2.55 (m, 3H), 2.51 (br dd, J = 4.3, 8.9 Hz, 2H), 2.05 - 1.62 (m, 8H).

Example 525

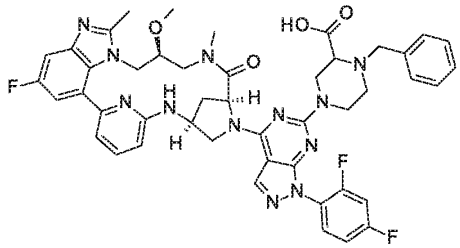
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(4a*R*,7a*R*)-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



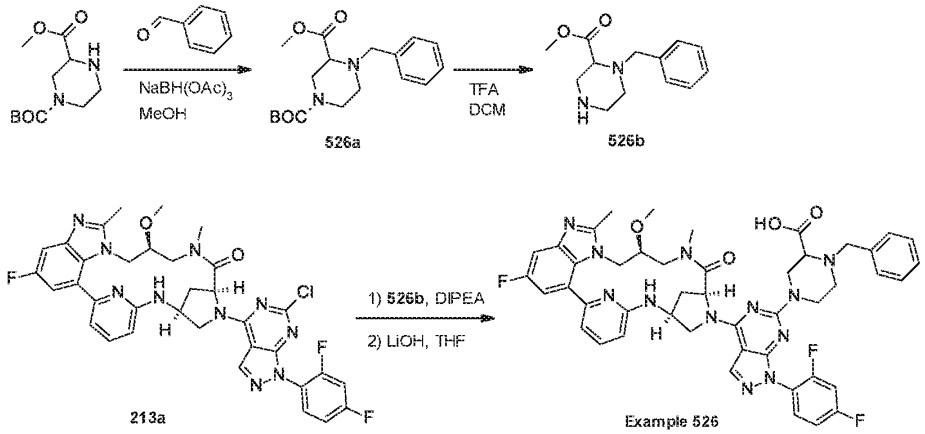
Example **525** was prepared in analogy to the preparation of Example **517** by using *tert*-butyl (4a*R*,7a*R*)-3,4a,5,6,7,7a-hexahydro-2*H*-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate instead of *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate. Example **525**, LCMS ($M+H^+$): 809. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.25 - 8.21 (m, 1H), 7.84 - 7.77 (m, 1H), 7.66 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.87 - 5.66 (m, 1H), 5.42 - 5.26 (m, 1H), 4.65 - 4.53 (m, 2H), 4.46 - 4.36 (m, 1H), 4.28 - 4.10 (m, 3H), 4.02 - 3.74 (m, 5H), 3.71 - 3.57 (m, 1H), 3.15 - 3.11 (m, 1H), 3.10 - 3.00 (m, 3H), 2.96 - 2.86 (m, 1H), 2.86 - 2.83 (m, 3H), 2.82 - 2.71 (m, 1H), 2.59 - 2.54 (m, 3H), 2.52 - 2.42 (m, 2H), 2.32 (br d, *J* = 5.6 Hz, 2H), 2.30 - 2.22 (m, 3H).

Example 526

1-benzyl-4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]piperazine-2-carboxylic acid



Example **526** was prepared according to the following scheme:



Step 1: preparation of *O*1-tert-butyl *O*3-methyl 4-benzylpiperazine-1,3-dicarboxylate (compound 526a)

To a flask was added *O*1-*tert*-butyl *O*3-methyl piperazine-1,3-dicarboxylate (500.0 mg, 2.05 mmol), benzaldehyde (260.6 mg, 2.46 mmol) and methanol (10 mL). The suspension was stirred at 60 °C for 30 mins and then sodium triacetoxyborohydride (1.08 g, 5.12 mmol) was added. The mixture was concentrated and the residue was purified via flash column (EA/PE=0~50%) to give compound **526a** (137 mg). LCMS ($M+H^+$): 335.

Step 2: preparation of methyl 1-benzylpiperazine-2-carboxylate (compound 526b)

To the flask containing the compound **526a** (137 mg, 0.41 mmol) was added dichloromethane (2 mL) and TFA (1 mL). After being stirred at r.t for 1 hr, the mixture was concentrated to give compound **526b** as an oil. LCMS ($M+H^+$): 235.

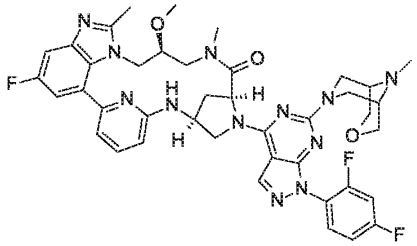
Step 3: preparation of 1-benzyl-4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]piperazine-2-carboxylic acid (Example 526)

To a tube was added methyl 1-benzylpiperazine-2-carboxylate (compound **526b**, 43.73 mg, 0.075 mmol), compound **213a** (35 mg, 0.050 mmol), DIEA (64 mg, 87 μL, 0.498 mmol), and acetonitrile (3.5 mL). After being stirred at 90 °C for 6 hrs, the mixture was concentrated to give an oil, which was dissolved in methanol (500 μL) and tetrahydrofuran (500 μL). Then LiOH (2 M, aq.) (1.0 mL, 2 mmol) was added. The mixture was stirred for 2 hrs and neutralized with 2 N HCL aq. The mixture was concentrated and the residue was purified via prep-HPLC to give Example **526**, LCMS ($M+H^+$): 887. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.27 (d, J = 2.5 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.62 (dt, J = 6.0, 8.5 Hz, 1H), 7.56 - 7.50 (m, 2H), 7.46 (br dd, J = 2.8, 3.6 Hz, 3H), 7.32 (dd, J = 2.5, 8.4 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.15 - 7.06 (m, 2H), 6.69

(dd, *J* = 3.8, 8.3 Hz, 1H), 5.88 (td, *J* = 4.7, 15.5 Hz, 1H), 5.49 - 5.41 (m, 1H), 4.70 - 4.53 (m, 3H), 4.46 (dd, *J* = 5.9, 11.2 Hz, 1H), 4.26 - 4.12 (m, 2H), 4.04 (br d, *J* = 12.5 Hz, 1H), 3.87 (ddd, *J* = 9.2, 14.4, 17.9 Hz, 1H), 3.64 - 3.50 (m, 1H), 3.28 - 3.15 (m, 2H), 3.12 - 3.07 (m, 3H), 3.06 - 3.03 (m, 1H), 3.03 - 2.91 (m, 2H), 2.91 - 2.83 (m, 3H), 2.78 (br dd, *J* = 3.7, 13.4 Hz, 1H), 2.66 - 2.59 (m, 3H), 2.59 - 2.55 (m, 1H), 2.55 - 2.44 (m, 2H).

Example 527

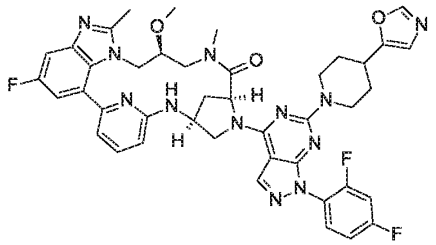
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **527** was prepared in analogy to the preparation of Example **517** by using *tert*-butyl 3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate instead of *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate. Example **527**, LCMS (M+H$^+$): 809. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.27 (d, *J* = 2.5 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.62 (dt, *J* = 6.0, 8.5 Hz, 1H), 7.56 - 7.50 (m, 2H), 7.46 (br dd, *J* = 2.8, 3.6 Hz, 3H), 7.32 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.15 - 7.06 (m, 2H), 6.69 (dd, *J* = 3.8, 8.3 Hz, 1H), 5.88 (td, *J* = 4.7, 15.5 Hz, 1H), 5.49 - 5.41 (m, 1H), 4.70 - 4.53 (m, 3H), 4.46 (dd, *J* = 5.9, 11.2 Hz, 1H), 4.26 - 4.12 (m, 2H), 4.04 (br d, *J* = 12.5 Hz, 1H), 3.87 (ddd, *J* = 9.2, 14.4, 17.9 Hz, 1H), 3.64 - 3.50 (m, 1H), 3.28 - 3.15 (m, 2H), 3.12 - 3.07 (m, 3H), 3.06 - 3.03 (m, 1H), 3.03 - 2.91 (m, 2H), 2.91 - 2.83 (m, 3H), 2.78 (br dd, *J* = 3.7, 13.4 Hz, 1H), 2.66 - 2.59 (m, 3H), 2.59 - 2.55 (m, 1H), 2.55 - 2.44 (m, 2H).

Example 528

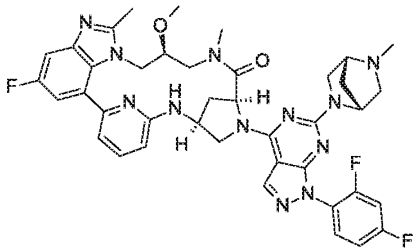
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-oxazol-5-yl-1-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **528** was prepared in analogy to the preparation of Example **483** by using 5-(4-piperidyl)oxazole instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **528**, LCMS (M+H$^+$): 819. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.21 (s, 1H), 8.07 (s, 1H), 7.80 (br t, *J* = 7.9 Hz, 1H), 7.68 - 7.57 (m, 1H), 7.32 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.25 - 7.04 (m, 4H), 6.85 (s, 1H), 6.67 (br d, *J* = 8.5 Hz, 1H), 5.91 - 5.69 (m, 1H), 5.42 - 5.25 (m, 1H), 4.68 - 4.57 (m, 2H), 4.43 (br dd, *J* = 5.9, 11.1 Hz, 1H), 4.32 - 4.06 (m, 3H), 3.97 - 3.81 (m, 1H), 3.15 - 2.89 (m, 7H), 2.88 - 2.81 (m, 3H), 2.75 (br d, *J* = 13.3 Hz, 1H), 2.66 - 2.56 (m, 3H), 2.55 - 2.43 (m, 2H), 2.07 - 1.89 (m, 2H), 1.70 - 1.50 (m, 2H).

Example 529

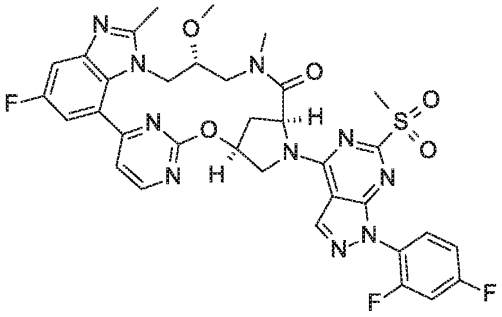
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



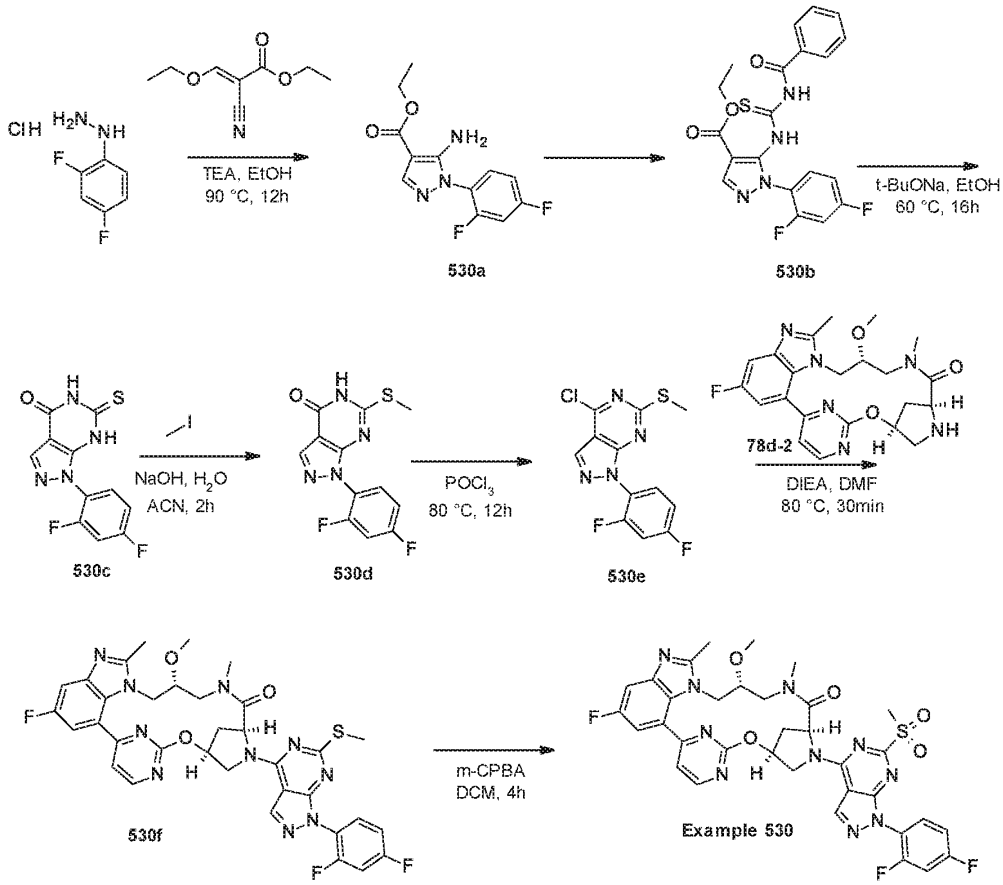
Example **529** was prepared in analogy to the preparation of Example **483** by using (3*R*)-3-ethyl-1-methyl-piperazine;dihydrochloride instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **529**, LCMS (M+H$^+$): 779. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.85 - 7.78 (m, 1H), 7.67 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.12 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.87 - 5.67 (m, 1H), 5.45 - 5.28 (m, 1H), 4.78 - 4.74 (m, 1H), 4.69 - 4.62 (m, 1H), 4.50 - 4.42 (m, 1H), 4.27 - 4.09 (m, 3H), 4.00 - 3.71 (m, 3H), 3.46 - 3.38 (m, 1H), 3.13 - 3.04 (m, 4H), 3.02 - 2.88 (m, 2H), 2.86 - 2.82 (m, 3H), 2.71 - 2.62 (m, 3H), 2.59 - 2.55 (m, 3H), 2.54 - 2.44 (m, 2H), 2.18 - 1.98 (m, 2H).

Example 530

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 530a)

A mixture of ethyl (*E*)-2-cyano-3-ethoxy-prop-2-enoate (4.68 g, 27.7 mmol), (2,4-difluorophenyl)hydrazine;hydrochloride (5 g, 27.7 mmol) and TEA (5.6 g, 55.4 mmol) in ethanol (50 mL) was heated to 90 °C for 4 hrs. The solvent was removed under reduce pressure and then the residue was purified by silica gel chromatography to afford compound **530a** (6.0 g) as a yellow powder. LCMS $(M+H)^+$: 268.

Step 2: preparation of ethyl 5-(benzoylcarbamothioylamino)-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 530b)

To a solution of ethyl 5-amino-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound **530a**, 2.3 g, 8.61 mmol) in acetonitrile (115 mL) was added isothiocyanato(phenyl)methanone (1.4 g, 8.61 mmol), the resulting mixture was stirred at room temperature for 16 hrs. The mixture was poured into water and neutralized with solid $NaHCO_3$, then extracted with DCM for three times. The combined organic layer was dried over anhydrous magnesium sulfate, evaporated *in vacuo* to give some residue. The residue was purified by silica gel chromatography to give compound **530b** (3.1 g). LCMS $(M+H)^+$: 431.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-thioxo-7H-pyrazolo[3,4-*d*]pyrimidin-4-one (compound 530c)

To a solution of ethyl 5-(benzoylcarbamothioylamino)-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound **530b**, 3.1 g, 6.97 mmol) in ethanol (40 mL) was added sodium *tert*-butoxide (1.4 g, 13.94 mmol) at room temperature, the resulting mixture was stirred at 60 °C for 16 hrs. After being cooled to room temperature, the reaction mixture was poured into water and neutralized with 1 M aq. HCl, then extracted with DCM for three times. The combined organic layer was dried over anhydrous magnesium sulfate, evaporated *in vacuo* to give some residue. The residue was purified by silica gel chromatography to give compound **530c** (2.1 g) as a yellow solid. LCMS $(M+H)^+$: 281.

Step 4: preparation of 1-(2,4-difluorophenyl)-6-methylsulfanyl-5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (compound 530d)

To a mixture of 1-(2,4-difluorophenyl)-6-thioxo-7*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (compound **530c**, 2.0 g, 7.14 mmol) and NaOH (0.57 g, 14.27 mmol) in water (5 mL) and acetonitrile (50 mL) was added iodomethane (1.01 g, 7.14 mmol) at room temperature, the resulting mixture was stirred at room temperature for 2 hrs, then diluted with water and extracted with EtOAc twice. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give crude compound **530d** (2.0 g) as a yellow solid. LCMS $(M+H)^+$: 295.

Step 5: preparation of 4-chloro-1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidine (compound 530e)

A mixture of 1-(2,4-difluorophenyl)-6-methylsulfanyl-5H-pyrazolo[3,4-*d*]pyrimidin-4-one (compound **530d**, 0.40 g, 1.36 mmol) in phosphoryl chloride (2.08 g, 13.59 mmol) was stirred at 80 °C for 12 hrs. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure, and then diluted with aq. NaOH, extracted with EtOAc twice. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give some crude. The crude was purified by flash chromatography on silica gel to give compound **530e** (0.35 g) as a white solid. LCMS $(M+H)^+$: 313.

Step 6: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa 5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa 1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 530f)

A mixture of (8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **78d-2**, 110.0 mg, 0.17 mmol), DIEA (67.1 mg, 0.52 mmol) and 4-chloro-1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidine (compound **530e**, 54.1 mg, 0.17 mmol) in anhydrous DMF (3 mL) was stirred at 80 °C for 30 minutes. After being cooled to room temperature, the reaction mixture was partitioned between water and DCM. The separated aqueous layer was extracted with DCM/MeOH, the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some crude. The crude was purified by prep-HPLC to give compound **530f** (53 mg) as a white solid. LCMS $(M+H)^+$: 717.

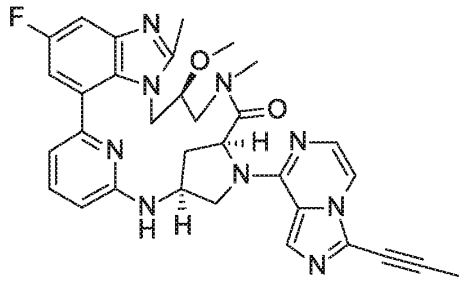
Step 7: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 530)

To a solution of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa 5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa 1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **530f**, 53 mg, 0.07 mmol) in DCM (3 mL) was added mCPBA (25.52 mg, 0.15 mmol) at room temperature, the resulting mixture was stirred at room temperature for 4 hrs. The reaction mixture was diluted with aqueous $Na_2S_2O_3$ and extracted with EtOAc twice. The

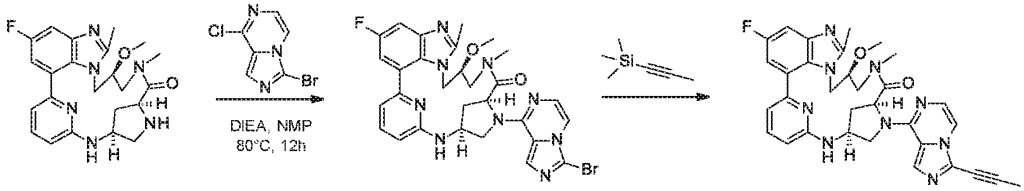
combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give some crude. The crude was purified by prep-HPLC to give Example **530** (4 mg) as a white solid. LCMS $(M+H)^+$: 749. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.84 - 7.99 (m, 2H), 7.87 - 7.73 (m, 1H), 7.72 - 7.61 (m, 1H), 7.57 (m, 1H), 7.50 (m, 1H), 7.42 - 7.29 (m, 2H), 5.83 - 5.26 (m, 3H), 4.60 - 4.43 (m, 1H), 4.39 - 4.21 (m, 1H), 4.08 - 3.85 (m, 2H), 3.40 - 3.19 (m, 5H), 3.17 - 3.06 (m, 1H), 3.05 - 2.93 (m, 3H), 2.72 - 2.66 (m, 3H), 2.55 - 2.51 (m, 3H), 2.05 - 1.94 (m, 1H).

Example 531

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(3-prop-1-ynylimidazo[1,5-*a*]pyrazin-8-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



370b 531a Example 531

Step 1: preparation of (8*S*,11*S*,15*R*)-10-(3-bromoimidazo[1,5-*a*]pyrazin-8-yl)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 531a)

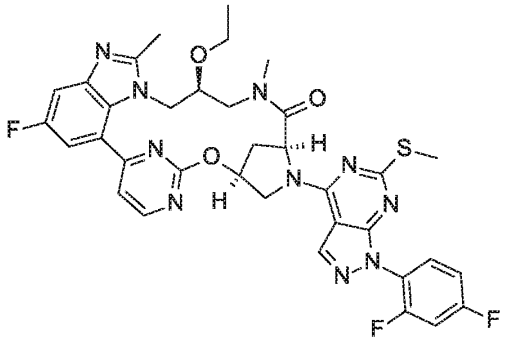
A mixture of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **370b**, 152.6 mg, 0.32 mmol), 3-bromo-8-chloro-imidazo[1,5-*a*]pyrazine (75.0 mg, 0.32 mmol) and DIEA (207.2 mg, 1.61 mmol) in NMP (2 mL) was stirred at 80 °C for 12 hrs. After being cooled to room temperature, the reaction mixture was directly purified by prep-HPLC to give compound **531a** (150 mg) as a brown oil. LCMS $(M+H)^+$: 636.

Step 2: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(3-prop-1-ynylimidazo[1,5-*a*]pyrazin-8-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (example 531)

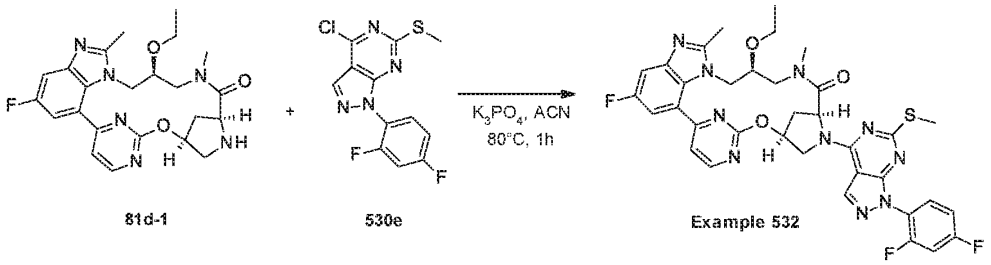
To a mixture of (8*S*,11*S*,15*R*)-10-(3-bromoimidazo[1,5-*a*]pyrazin-8-yl)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **531a**, 50 mg, 0.10 mmol), 1-(trimethylsilyl)-1-propyne (11.5 mg, 0.10 mmol), TEA (23.9 mg, 0.24 mmol) and CuI (50.0 mg, 0.10mmol) in DMF (1 mL) was added $Pd(PPh_3)_2Cl_2$ (27.7 mg, 0.04 mmol) and 1 M TBAF in THF (0.1 mL, 0.10 mmol), the resulting mixture was stirred at 60 °C for 12 hrs under nitrogen. After being cooled to room temperature, the reaction mixture was filtered, the filtrate was directly purified by prep-HPLC to give Example **531** (18.4 mg) as a white solid. LCMS $(M+H)^+$: 594. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.10 - 7.67 (m, 2H), 7.58 - 7.43 (m, 1H), 7.39 - 6.96 (m, 4H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.65 (m, 1H), 5.44 - 5.24 (m, 1H), 4.60 - 4.23 (m, 3H), 4.21 - 4.04 (m, 1H), 3.98 - 3.75 (m, 1H), 3.02 (s, 3H), 2.90 - 2.70 (m, 5H), 2.67 - 2.35 (m, 5H), 2.27 - 2.12 (m, 3H).

Example 532

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

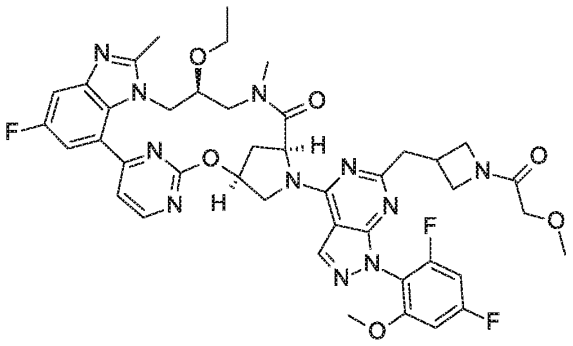


81d-1 530e Example 532

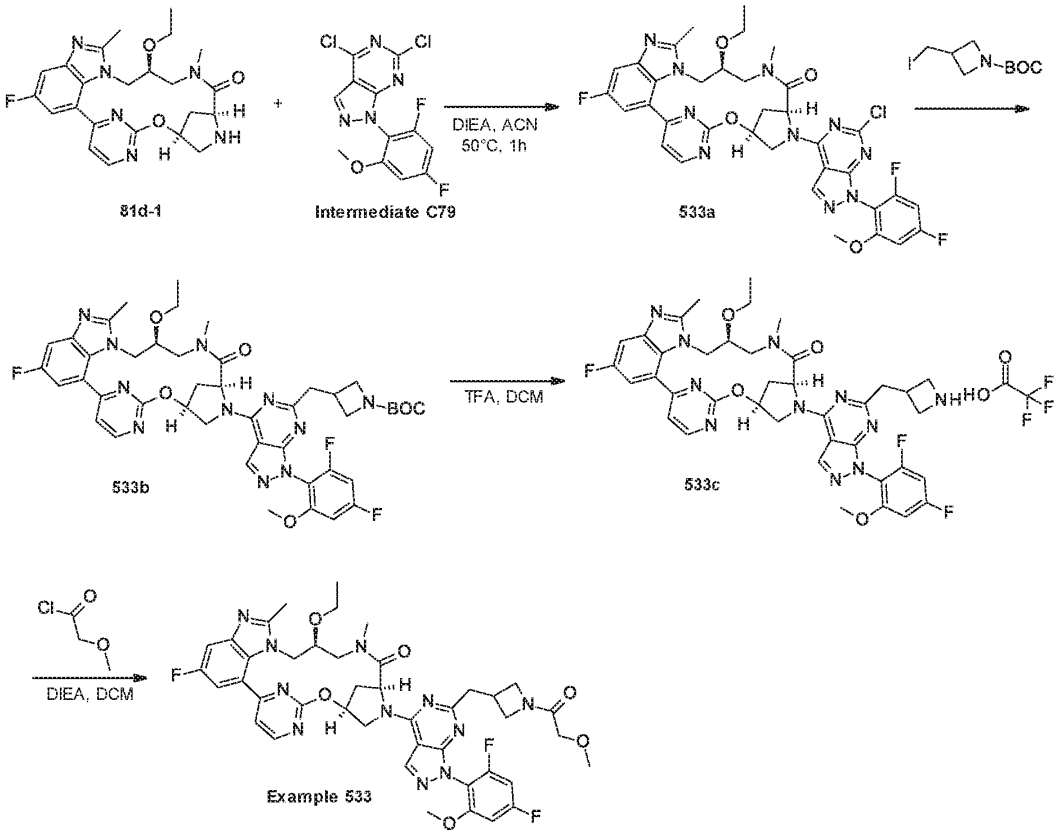
A mixture of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 31.2 mg, 0.06 mmol), 4-chloro-1-(2,4-difluorophenyl)-6-(methylthio)pyrazolo[3,4-*d*]pyrimidine (18.9 mg, 0.06 mmol) and potassium phosphate (35.0 mg, 0.16 mmol) in anhydrous acetonitrile (1 mL) was stirred at 80 °C for 1 hr. After being cooled to room temperature, the reaction mixture was directly purified by prep-HPLC to afford Example **532** (7 mg) as a white solid. LCMS (M+H)$^+$: 731. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.85 (d, *J* = 5.3 Hz, 1H), 8.57 - 7.81 (m, 1H), 7.80 - 7.68 (m, 2H), 7.65 - 7.48 (m, 3H), 7.36 - 7.28 (m, 1H), 5.77 - 5.45 (m, 3H), 4.51 - 4.32 (m, 1H), 4.23 - 4.01 (m, 2H), 3.92 - 3.79 (m, 1H), 3.22 - 3.13 (m, 2H), 3.01 - 2.86 (m, 4H), 2.83 - 2.63 (m, 3H), 2.60 - 2.52 (m, 4H), 2.38 - 2.29 (m, 2H), 0.49 - 0.36 (m, 3H).

Example 533

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-[[1-(2-methoxyacetyl)azetidin-3-yl]methyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 533a)

A mixture of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 250 mg, 0.44 mmol), 4,6-dichloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidine (**Intermediate C79**, 160.2 mg, 0.48 mmol) and DIEA (284.2 mg, 2.2 mmol) in anhydrous acetonitrile (6 mL) was stirred at 50 °C for 1 hr. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo* to give some residue. The residue was purified by flash chromatography to afford crude compound **533a** (302 mg) as a light brown solid. LCMS (M+H)$^+$: 750.

Step 2: preparation of *tert*-butyl 3-[[1-(2,4-difluoro-6-methoxy-phenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]methyl]azetidine-1-carboxylate (compound 533b)

To an 8 mL vial was added $NiCl_2$(dtbbpy) (8.0 mg, 0.02 mmol,), [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-n1,n1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-n]phenyl-c]iridium(iii) hexafluorophosphate (22.5 mg, 0.02 mmol), tris(trimethylsilyl)silane (49.8 mg, 0.20 mmol), sodium carbonate (63.7 mg, 0.60 mmol), (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **533a**, 250 mg, 0.20 mmol) and *tert*-butyl 3-(iodomethyl)azetidine-1-carboxylate (178.5 mg, 0.60 mmol) successively, followed by addition of anhydrous ethylene glycol dimethyl ether (5 mL). The vial was sealed and placed. The resulting mixture was stirred and irradiated with a 34 W blue LED lamp (450-450 nm, with cooling fan to keep the reaction temperature at 25 °C) for 16 hrs. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give an oil, which was purified by flash chromatography to afford crude compound **533b** (123 mg) as a light yellow solid. LCMS $(M+H)^+$: 885.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-ylmethyl)-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound 533c)

A mixture of *tert*-butyl 3-[[1-(2,4-difluoro-6-methoxy-phenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]methyl]azetidine-1-carboxylate (compound **533b**, 123 mg, 0.10 mmol) and TFA (1 mL) in DCM (3 mL) was stirred at room temperature for 1 hr. After removing excess TFA and DCM under reduced pressure, the crude compound **533c** (178 mg) was obtained as a light yellow oil. LCMS $(M+H)^+$: 785.

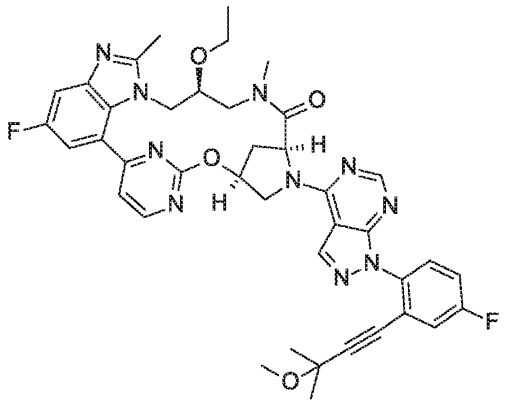
Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-[[1-(2-methoxyacetyl)azetidin-3-yl]methyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 533)

To a mixture of (8*S*,11*S*,15*R*)-10-[6-(azetidin-3-ylmethyl)-1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-

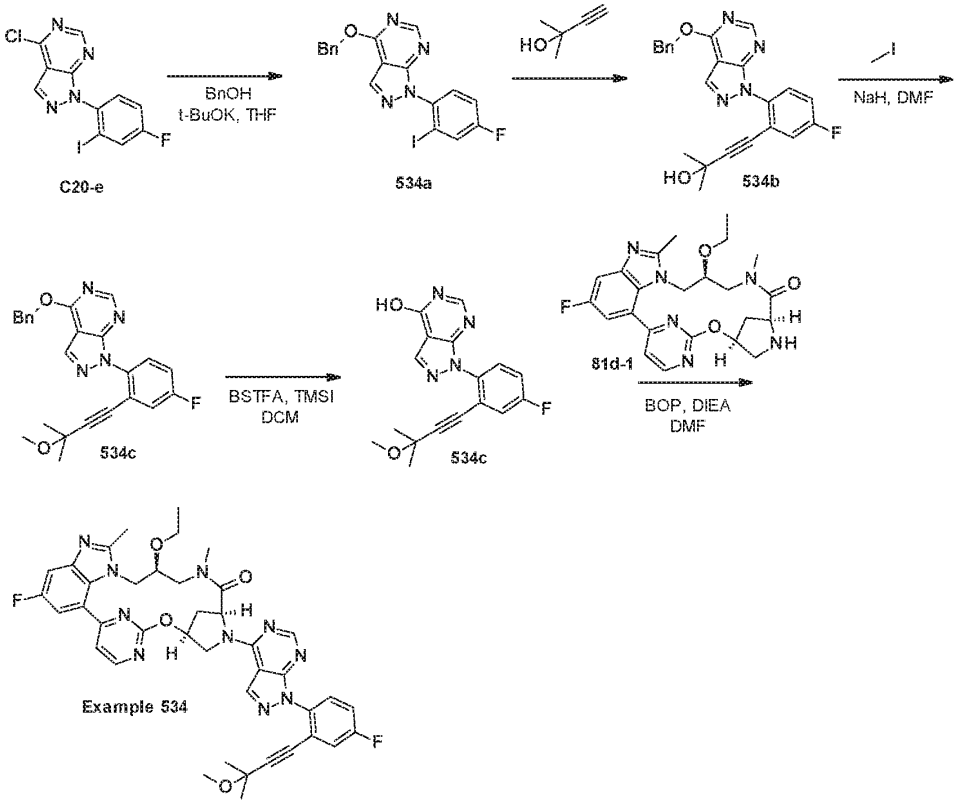
5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;2,2,2-trifluoroacetic acid (compound **533c**, 66 mg, 0.03 mmol) and DIEA (51.3 mg, 0.40 mmol,) in anhydrous DCM (0.5 mL) was added methoxyacetyl chloride (7.2 mg, 0.07 mmol,) at 0 °C, the resulting mixture was stirred at 0 °C to room temperature for 16 hrs. After removing excess DCM under reduced pressure, the resulted residue was directly purified by prep-HPLC to afford Example **533** (14 mg) as a white solid. LCMS $(M+H)^+$: 856. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.85 (d, J = 5.4 Hz, 1H), 8.55 - 7.73 (m, 2H), 7.66 - 7.47 (m, 2H), 7.20 - 7.04 (m, 2H), 5.78 - 5.38 (m, 3H), 4.50 - 4.23 (m, 2H), 4.21 - 3.94 (m, 3H), 3.93 - 3.67 (m, 8H), 3.63 - 3.48 (m, 1H), 3.26 - 3.14 (m, 5H), 3.02 - 2.85 (m, 6H), 2.83 - 2.65 (m, 3H), 2.60 - 2.52 (m, 3H), 0.47 - 0.39 (m, 3H).

Example 534

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-benzyloxy-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-*d*]pyrimidine (compound 534a)

To a mixture of 4-chloro-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-*d*]pyrimidine (**C20-e**, 14.0 g, 37.4 mmol) and benzyl alcohol (4.0 g, 37.4 mmol) in THF (150 mL) was added *t*-BuOK (74.8 mL, 74.8 mmol) at 0 °C, the resulting mixture was stirred at 0 °C and allowed to warm to room temperature in 1 hr. The reaction was quenched by water and the mixture was then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some residue. The residue was purified by flash chromatography to afford compound **534a** (10.0 g) as a colorless oil. LCMS $(M+H)^+$: 447.

Step 2: preparation of 4-[2-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-5-fluoro-phenyl]-2-methyl-but-3-yn-2-ol (compound 534b)

To a mixture of 4-benzyloxy-1-(4-fluoro-2-iodo-phenyl)pyrazolo[3,4-*d*]pyrimidine (compound **534a**, 200.0 mg, 0.45 mmol), 2-methyl-3-butyn-2-ol (37.7 mg, 0.45 mmol) and CuI (17.0 mg, 0.09 mmol) in DMF (2 mL) was added TEA (135.8 mg, 1.34 mmol) and $Pd(PPh_3)_2Cl_2$ (62.9 mg, 0.09 mmol), the resulting mixture was stirred at 80 °C for 12 hrs under nitrogen. After

being cooled to room temperature, the mixture was quenched by water and then extracted with EtOAc for three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some residue. The residue was purified by flash chromatography to give compound **534b** (150 mg) as a white solid. LCMS $(M+H)^+$: 403.

Step 3: preparation of 4-benzyloxy-1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidine (compound 534c)

To a mixture of 4-[2-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-5-fluoro-phenyl]-2-methyl-but-3-yn-2-ol (compound **534b**, 300.0 mg, 0.75 mmol) and NaH (59.6 mg, 1.49 mmol) in anhydrous DMF (2 mL) was added iodomethane (211.6 mg, 1.49 mmol), the resulting mixture was stirred at 80 °C for 12 hrs under nitrogen. After being cooled to room temperature, the mixture was quenched by water and then extracted with EtOAc for three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some residue. The residue was purified by flash chromatography to give compound **534c** (300.0 mg) as a yellow oil. LCMS $(M+H)^+$: 417.

Step 4: preparation of 1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-ol (compound 534d)

A mixture of 4-benzyloxy-1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidine (compound **534c**, 200.0 mg, 0.48 mmol), *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (494.5 mg, 1.92 mmol) and TMSI (480.5 mg, 2.4 mmol) in DCM (4 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure to get some crude, which was purified by reversed flash chromatography to afford compound **534d** (50.0 mg) as a brown solid. LCMS $(M+Na)^+$: 349.

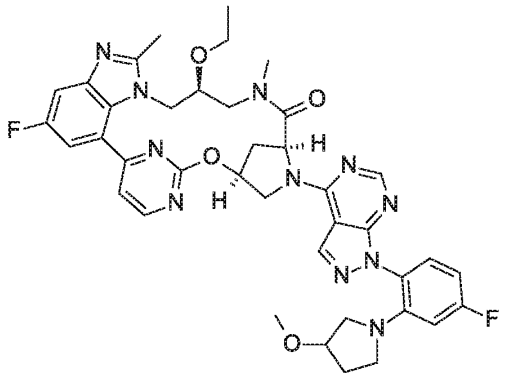
Step 5: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 534)

A mixture of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 40.0 mg, 0.09 mmol), 1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-ol (compound **534d**, 34.5 mg, 0.11 mmol), BOP (58.4 mg, 0.13 mmol) and DIEA (45.4 mg, 0.35 mmol) in DMF (1 mL) was stirred at room

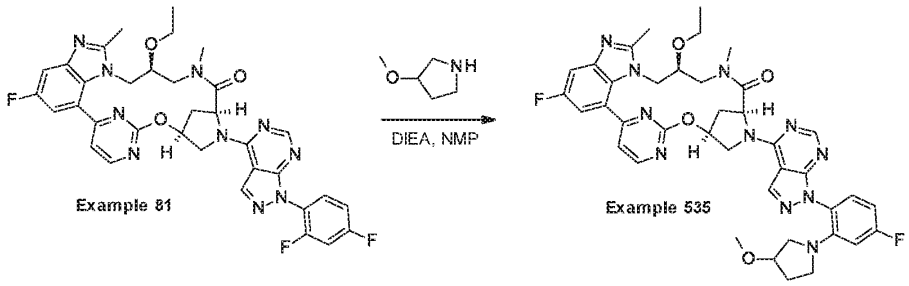
temperature for 12 hrs. The reaction mixture was filtered, the filtrate was purified by prep-HPLC to afford Example **534** (8.4 mg) as a white solid. LCMS $(M+H)^+$: 763. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.79 (d, *J*=5.14 Hz, 1H), 8.57 - 8.33 (m, 1H), 8.24 - 7.79 (m, 1H), 7.67 - 7.53 (m, 2H), 7.48 - 7.32 (m, 4H), 5.90 - 5.71 (m, 2H), 5.60 - 5.44 (m, 1H), 4.62 - 3.94 (m, 4H), 3.20 - 2.97 (m, 7H), 2.96 - 2.89 (m, 1H), 2.88 - 2.70 (m, 2H), 2.68 - 2.54 (m, 5H), 1.25 - 1.11 (m, 6H), 0.58 (t, *J*=6.97 Hz, 3H).

Example 535

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxypyrrolidin-1-yl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

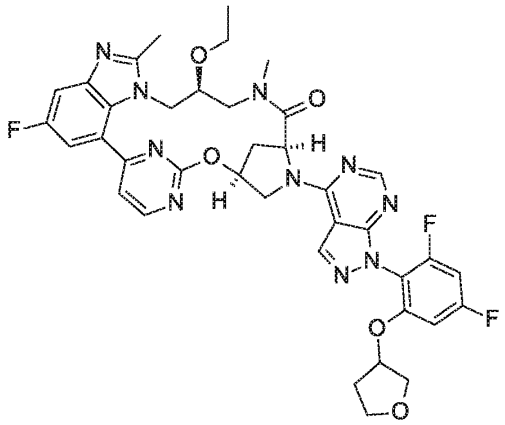


A mixture of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example **81**, 50.0 mg, 0.07 mmol), 3-methoxypyrrolidine (7.4 mg, 0.07 mmol) and DIEA (50.0 mg, 0.14 mmol) in NMP (2 mL) was stirred at 100 °C for 1 hr. After being cooled to room temperature, the reaction mixture was directly purified by prep-HPLC to afford Example **535** (17.0 mg) as a white solid. LCMS $(M+H)^+$: 766. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.79

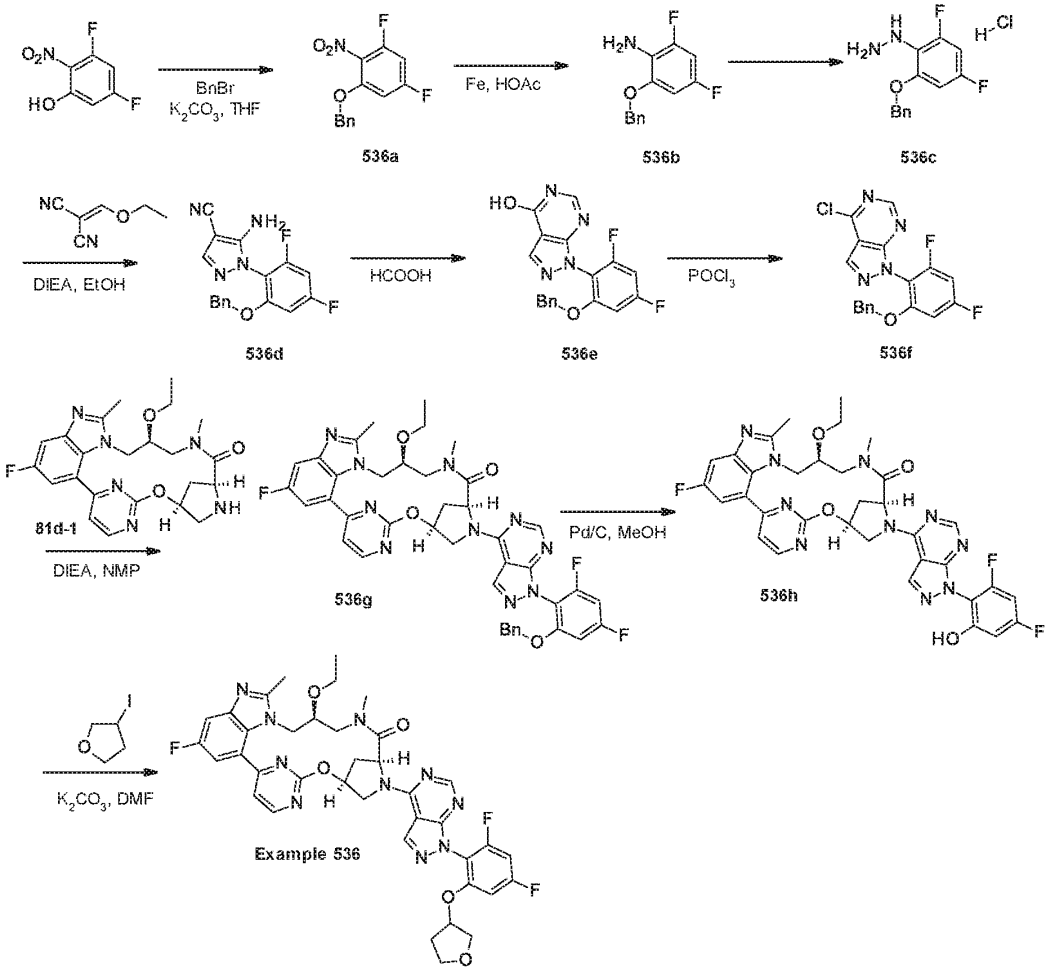
(d, J = 5.4 Hz, 1H), 8.57 - 8.31 (m, 1H), 8.25 - 7.77 (m, 1H), 7.64 (d, J = 5.3 Hz, 1H), 7.53 - 7.40 (m, 2H), 7.38 - 7.04 (m, 1H), 6.70 - 6.44 (m, 2H), 5.90 - 5.68 (m, 2H), 5.59 - 5.44 (m, 1H), 4.60 - 4.28 (m, 1H), 4.23 - 3.79 (m, 3H), 3.58 - 3.34 (m, 3H), 3.29 - 3.24 (m, 1H), 3.22 - 3.03 (m, 3H), 3.02 - 2.86 (m, 5H), 2.85 - 2.69 (m, 3H), 2.68 - 2.55 (m, 5H), 2.29 - 2.10 (m, 1H), 1.98 - 1.77 (m, 1H), 0.58 (t, J = 7.0 Hz, 3H).

Example 536

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-tetrahydrofuran-3-yloxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-benzyloxy-3,5-difluoro-2-nitro-benzene (compound 536a)

A mixture of 3,5-difluoro-2-nitro-phenol (10.0 g, 57.1 mmol), benzyl bromide (8.2 mL, 68.5 mmol) and potassium carbonate (15.8 g, 114.2 mmol) in DMF (200 mL) was stirred at room temperature for 2 hrs. The reaction mixture was poured into water, then extracted with EtOAc twice. The combined organic layer was washed with aq. $CaCl_2$, brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford compound **536a** (14.0 g) as a yellow solid, which was used for the next step directly.

Step 2: preparation of 2-benzyloxy-4,6-difluoro-aniline (compound 536b)

A mixture of 1-benzyloxy-3,5-difluoro-2-nitro-benzene (compound **536a**, 7.0 g, 26.4 mmol) and iron powder (5.9 g, 105.6 mmol) in acetic acid (15 mL) was stirred at 100 °C for 2 hrs. The reaction mixture was poured into the water, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced

pressure to give some crude. The crude was purified by flash chromatography to afford compound **536b** (4.0 g) as a light yellow oil. LCMS $(M+H)^+$: 236.

Step 3: preparation of (2-benzyloxy-4,6-difluoro-phenyl)hydrazine;hydrochloride (compound 536c)

To a mixture of 2-benzyloxy-4,6-difluoro-aniline (compound **536b**, 10.0 g, 42.5 mmol) in 6 M aq. HCl (200 mL) was added sodium nitrite (4.4 g, 63.8 mmol) slowly at -5 °C. After being stirred for 1 hr, the tin(II) chloride (4.1 mL, 85.0 mmol) in conc. HCl (50 mL) was added into the mixture, the resulting mixture was stirred at -5 °C for 1 hr. Then the reaction mixture was filtered, the filter cake was poured into the water, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound **536c** (10.0 g) as a light brown solid. LCMS $(M-NH_3+H)^+$: 234.

Step 4: preparation of 5-amino-1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazole-4-carbonitrile (compound 536d)

A mixture of (2-benzyloxy-4,6-difluoro-phenyl)hydrazine;hydrochloride (compound **536c**, 10.0 g, 40.0 mmol), ethoxymethylenemalononitrile (4.9 g, 40.0 mmol) and DIEA (10.3 g, 79.9 mmol) in ethanol (50 mL) was stirred at 60 °C for 1 hr. After being cooled to room temperature, the reaction mixture was poured into brine and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude compound **536d** (10.0 g) as a yellow oil. LCMS $(M+H)^+$: 327.

Step 5: preparation of 1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-ol (compound 536e)

A solution of 5-amino-1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazole-4-carbonitrile (compound **536d**, 10.0 g, 30.7 mmol) in formic acid (1.4 g, 30.7 mmol) was stirred at 100 °C for 1 hr. After being cooled to room temperature, the reaction mixture was poured into brine and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some residue. The residue was purified by prep-HPLC to afford compound **536e** (2.0 g) as a yellow solid. LCMS $(M+H)^+$: 355.

Step 6: preparation of 1-(2-benzyloxy-4,6-difluoro-phenyl)-4-chloro-pyrazolo[3,4-*d*]pyrimidine (compound 536f)

A mixture of 1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-ol (compound **536e**, 90.0 mg, 0.25 mmol) in phosphoryl chloride (2.0 mL) was stirred at 100 °C for 12 hrs. After being cooled to room temperature, the reaction mixture was poured into aq. NH_4Cl,

then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some crude. The crude was purified by column chromatography to afford compound **536f** (90.0 mg) as a light yellow solid. LCMS $(M+H)^+$: 373.

Step 7: preparation of (8*S*,11*S*,15*R*)-10-[1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 536g)

A mixture of 1-(2-benzyloxy-4,6-difluoro-phenyl)-4-chloro-pyrazolo[3,4-*d*]pyrimidine (compound **536f**, 90.0 mg, 0.24 mmol), (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 98.8 mg, 0.22 mmol) and DIEA (155.7 mg, 1.21 mmol) in NMP (1 mL) was stirred at 80 °C for 1 hr. After being cooled to room temperature, the reaction mixture was filtered, the filtrate was directly purified by prep-HPLC to give compound **536g** (70.0 mg) as a light yellow solid. LCMS $(M+H)^+$: 791.

Step 8: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 536h)

A mixture of (8*S*,11*S*,15*R*)-10-[1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **536g**, 65.0 mg, 0.08 mmol) and Pd/C (60.0 mg) in methanol (2 mL) was stirred at room temperature for 1 hr under hydrogen. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give crude compound **536h** (35.0 mg) as a grey solid, which was used for the next step directly. LCMS $(M+H)^+$: 701.

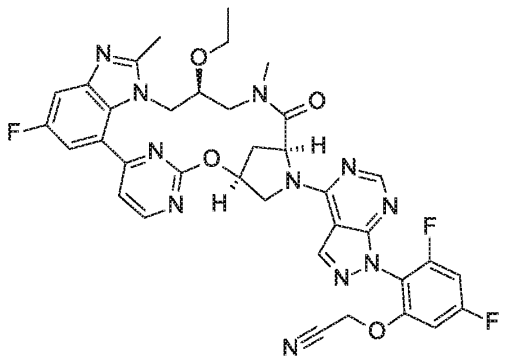
Step 9: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-tetrahydrofuran-3-yloxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 536)

A mixture of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

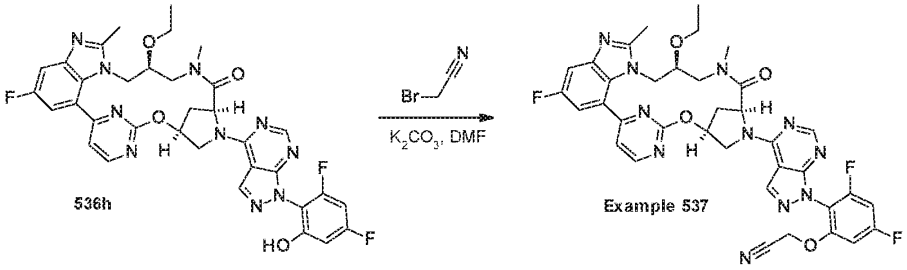
(compound **536h**, 15.0 mg, 0.02 mmol), 3-iodotetrahydrofuran (6.36 mg, 0.03 mmol) and potassium carbonate (5.9 mg, 0.04 mmol) in DMF (0.5 mL) was stirred at room temperature for 12 hrs. The reaction mixture was filtered, the filtrate was directly purified by prep-HPLC to afford Example **536** (4.0 mg) as white solid. LCMS $(M+H)^+$: 771. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.82 - 8.73 (m, 1H), 8.60 - 8.16 (m, 2H), 7.89 - 7.30 (m, 4H), 7.01 - 6.82 (m, 2H), 5.92 - 5.70 (m, 2H), 5.63 - 5.42 (m, 1H), 5.13 - 5.02 (m, 1H), 4.64 - 4.26 (m, 3H), 4.23 - 3.82 (m, 3H), 3.80 - 3.46 (m, 3H), 3.16 - 2.71 (m, 6H), 2.67 - 2.49 (m, 5H), 2.24 - 2.07 (m, 1H), 2.04 - 1.88 (m, 1H), 0.58 (br d, J = 3.2 Hz, 3H).

Example 537

2-[2-[4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-1-yl]-3,5-difluoro-phenoxy]acetonitrile



The title compound was prepared according to the following scheme:

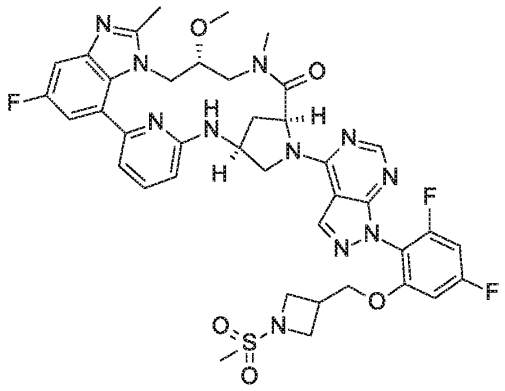


A mixture of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[**15.6.1.1^{2,6}.1^{8,11}.0^{20,24}**]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **536h**, 15.0 mg, 0.02 mmol), bromoacetonitrile (7.7 mg, 0.06 mmol) and potassium carbonate (5.9 mg, 0.04 mmol) in DMF (1 mL) was stirred at room temperature for 12 hrs. The reaction mixture was filtered, the filtrate was directly purified by prep-HPLC to afford Example

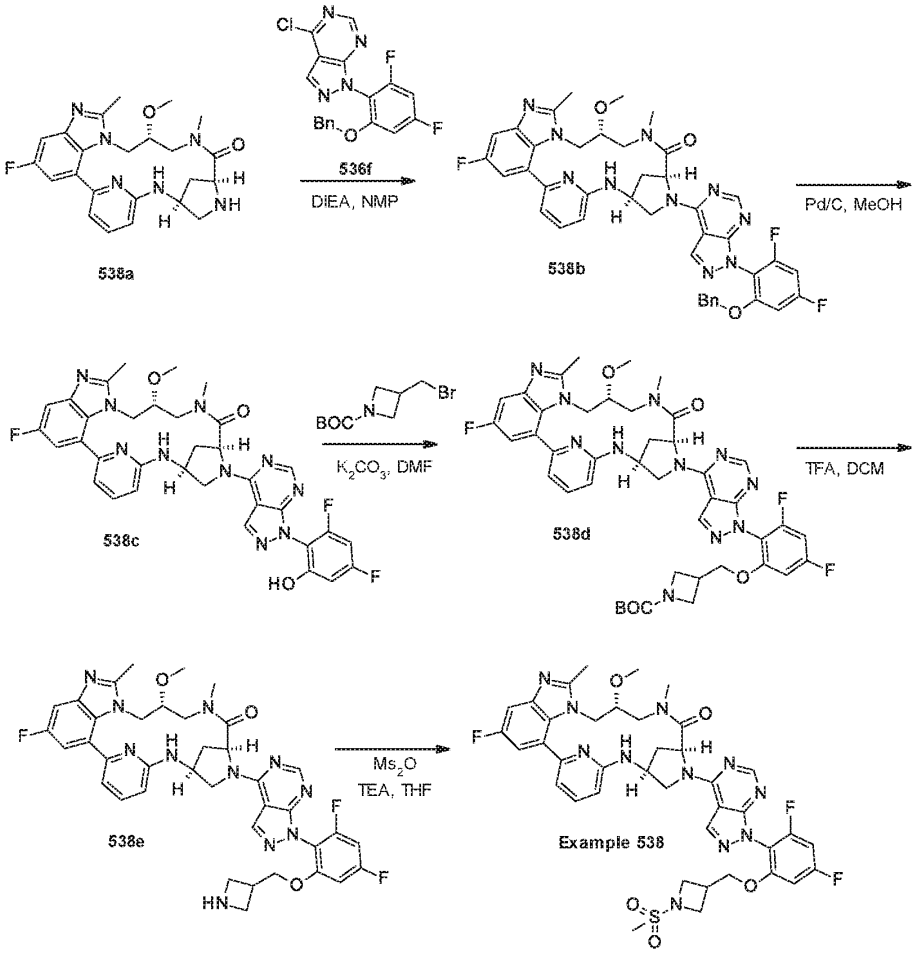
537 (6.4 mg) as a white solid. LCMS $(M+H)^+$: 740. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.78 (d, J = 5.3 Hz, 1H), 8.62 - 7.86 (m, 2H), 7.64 (d, J = 5.3 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.18 - 6.97 (m, 2H), 5.89 - 5.69 (m, 2H), 5.63 - 5.42 (m, 1H), 5.11 - 4.97 (m, 2H), 4.56 - 3.66 (m, 5H), 3.29 - 3.04 (m, 1H), 3.02 - 2.70 (m, 5H), 2.68 - 2.52 (m, 5H), 0.62 - 0.51 (m, 3H).

Example 538

(8*S*,11*S*,15*S*)-10-[1-[2,4-difluoro-6-[(1-methylsulfonylazetidin-3-yl)methoxy]phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 538a)

Compound **538a** was prepared in analogy to the preparation of **compound 12d** by using **Intermediate A30** instead of **Intermediate A11**. LCMS (M+H$^+$): 439.

Step 2: preparation of (8*S*,11*S*,15*S*)-10-[1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 538b)

A mixture of 1-(2-benzyloxy-4,6-difluoro-phenyl)-4-chloro-pyrazolo[3,4-*d*]pyrimidine (compound **536f**, 150.0 mg, 0.4 mmol), (8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **538a**, 176.4 mg, 0.4 mmol) and DIEA (103.8 mg, 0.8 mmol)

in anhydrous NMP (2 mL) was stirred at 80 °C for 1 hr. After being cooled to room temperature, the reaction mixture was poured into water, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give some crude. The crude was purified by reversed flash chromatography to afford compound **538b** (200 mg) as a brown oil. LCMS $(M+H)^+$: 775.

Step 3: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 538c)

A mixture of (8*S*,11*S*,15*S*)-10-[1-(2-benzyloxy-4,6-difluoro-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **538b**, 200.0 mg, 0.26 mmol) and Pd/C (200.0 mg) in methanol (5 mL) was stirred at room temperature for 2 hrs under hydrogen. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give crude compound **538c** (150.0 mg) as a light yellow solid. LCMS $(M+H)^+$: 685.

Step 4: preparation of *tert*-butyl 3-[[3,5-difluoro-2-[4-[(8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-1-yl]phenoxy]methyl]azetidine-1-carboxylate (compound 538d)

A mixture of *tert*-butyl 3-(bromomethyl)azetidine-1-carboxylate (54.8 mg, 0.22 mmol), (8*S*,11*S*,15*S*)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **538c**, 100.0 mg, 0.15 mmol) and potassium carbonate (40.4 mg, 0.29 mmol) in anhydrous DMF (2 mL) was stirred at 80 °C for 12 hrs. After being cooled to room temperature, the reaction mixture was filtered, and the filtrate was purified by reversed flash chromatography to give compound **538d** (120.0 mg) as a light yellow oil. LCMS $(M+H)^+$: 854.

Step 5: preparation of (8*S*,11*S*,15*S*)-10-[1-[2-(azetidin-3-ylmethoxy)-4,6-difluoro-phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 538e)

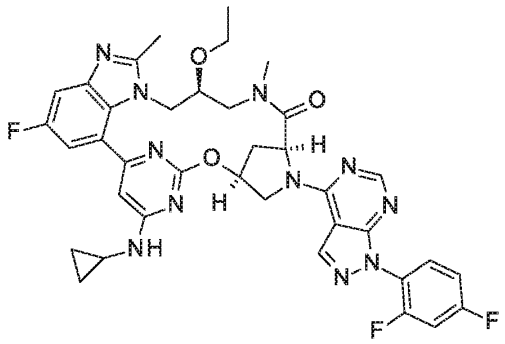
A mixture of *tert*-butyl 3-[[3,5-difluoro-2-[4-[(8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-1-yl]phenoxy]methyl]azetidine-1-carboxylate (compound **538d**, 120.0 mg, 0.14 mmol) in TFA (2.0 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure to give crude compound **538e** (65.0 mg) as a light yellow oil, which was used for the next step directly. LCMS (M+H)$^+$: 754.

Step 6: preparation of (8*S*,11*S*,15*S*)-10-[1-[2,4-difluoro-6-[(1-methylsulfonylazetidin-3-yl)methoxy]phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 538)

A mixture of (8*S*,11*S*,15*S*)-10-[1-[2-(azetidin-3-ylmethoxy)-4,6-difluoro-phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **538e**, 60.0 mg, 0.08 mmol), methanesulfonic anhydride (27.7 mg, 0.16 mmol) and TEA (24.2 mg, 0.24 mmol) in anhydrous THF (2 mL) was stirred at room temperature for 12 hrs. The reaction mixture was poured into water, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC to afford Example **538** (33.3 mg) as a white solid. LCMS (M+H)$^+$: 832. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.58 - 8.28 (m, 1H), 8.24 - 7.72 (m, 2H), 7.28 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.12 - 6.84 (m, 4H), 6.75 - 6.63 (m, 1H), 5.57 - 5.11 (m, 2H), 4.74 - 4.48 (m, 2H), 4.37 - 3.47 (m, 10H), 3.29 - 3.12 (m, 2H), 3.09 - 2.95 (m, 3H), 2.94 - 2.82 (m, 4H), 2.81 - 2.73 (m, 2H), 2.73 - 2.64 (m, 2H), 2.60 - 2.56 (m, 3H).

Example 539

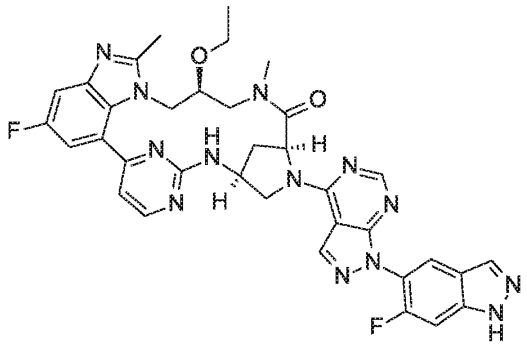
(8*S*,11*S*,15*R*)-4-(cyclopropylamino)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



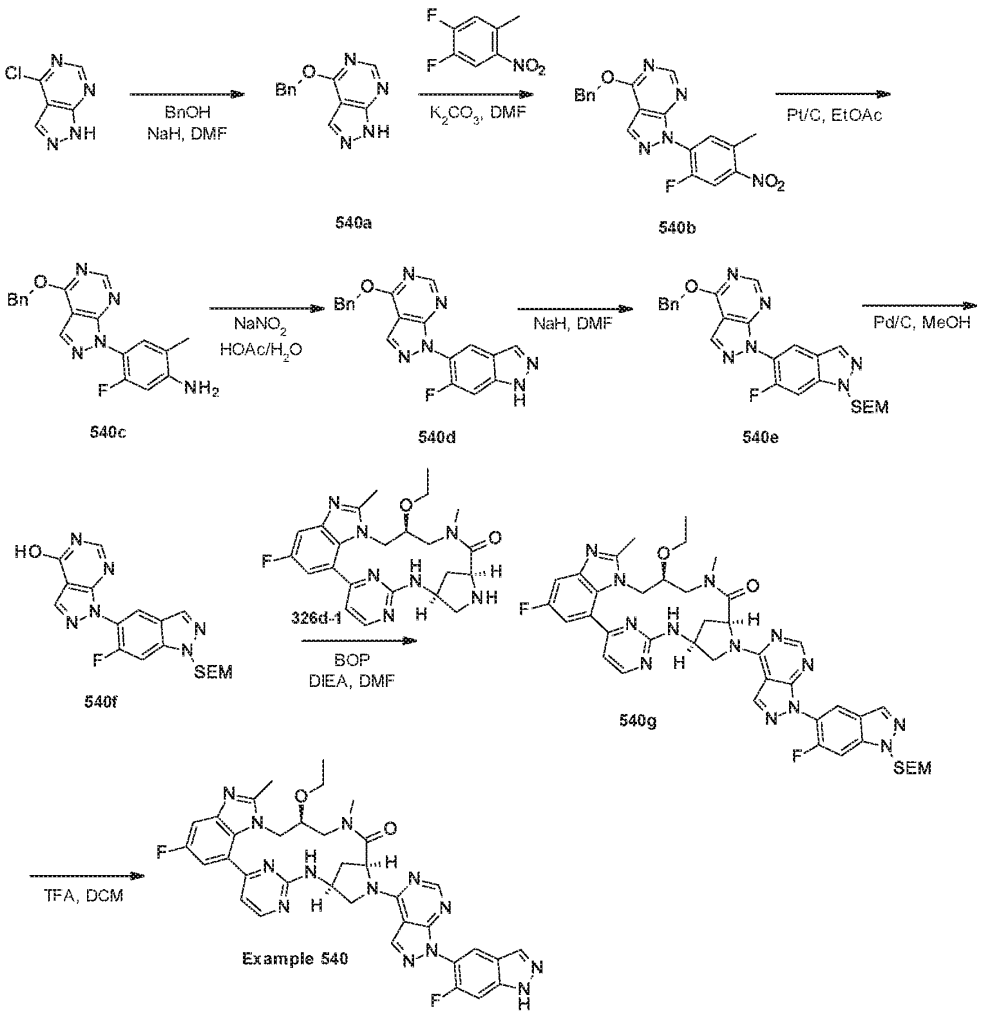
The title compound was prepared in analogy to the preparation of Example **289** by using Intermediate **A7** instead of Intermediate **A12**, Intermediate **B34** instead of Intermediate **B11**, Intermediate **C2** instead of Intermediate **C11**. LCMS $(M+H)^+$: 740. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 - 8.31 (m, 1H), 8.27 - 7.82 (m, 1H), 7.72 - 7.58 (m, 1H), 7.48 - 7.26 (m, 3H), 7.25 - 7.16 (m, 1H), 6.93 - 6.28 (m, 1H), 5.98 - 5.79 (m, 1H), 5.76 - 5.34 (m, 2H), 4.54 - 4.19 (m, 2H), 4.18 - 3.95 (m, 2H), 3.40 - 3.33 (m, 1H), 3.20 - 3.04 (m, 3H), 2.99 - 2.75 (m, 2H), 2.73 - 2.61 (m, 7H), 1.00 - 0.82 (m, 2H), 0.74 - 0.53 (m, 5H).

Example 540

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-benzyloxy-1H-pyrazolo[3,4-*d*]pyrimidine (compound 540a)

To a mixture of 4-chloro-1H-pyrazole[3,4-*d*]pyrimidine (8.0 g, 51.8 mmol) and benzyl alcohol (5.6 g, 51.8 mmol) in anhydrous DMF (100 mL) was added NaH (6.2 g, 155.3 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into saturated aq. NH_4Cl and then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to dryness to give compound **540a** (11.0 g) as a yellow solid. LCMS $(M+H)^+$: 227.

Step 2: preparation of 4-benzyloxy-1-(2-fluoro-5-methyl-4-nitro-phenyl)pyrazolo[3,4-*d*]pyrimidine (compound 540b)

To a mixture of 4,5-difluoro-2-nitrotoluene (5.0 g, 28.9 mmol) and 4-benzyloxy-1H-pyrazolo[3,4-*d*]pyrimidine (compound **540a**, 7.2 g, 31.8 mmol) in anhydrous DMF (50 mL) was added potassium carbonate (8.0 g, 57.78 mmol, 2.0 eq), the resulting mixture was stirred at 30

°C for 1 hr. The reaction mixture was quenched by water, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give some residue. The residue was purified by reversed-phase chromatography to afford compound **540b** (1.0 g) as a light yellow solid. LCMS $(M+H)^+$: 380.

Step 3: preparation of 4-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-5-fluoro-2-methyl-aniline (compound 540c)

To a solution of 4-benzyloxy-1-(2-fluoro-5-methyl-4-nitro-phenyl)pyrazolo[3,4-*d*]pyrimidine (compound **540b**, 1.00 g, 2.64 mmol) in EtOAc (10 mL) was added Pt/C (500.0 mg), the resulting mixture degassed and purged with nitrogen for four times, then stirred at room temperature for 1 hr under hydrogen. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give compound **540c** (800 mg) as a white solid. LCMS $(M+H)^+$: 350.

Step 4: preparation of 4-benzyloxy-1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-d]pyrimidine (compound 540d)

A solution of sodium nitrite (90.0 mg, 1.3 mmol) in water (1.5 mL) was added dropwise to a solution of 4-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-5-fluoro-2-methyl-aniline (compound **540c**, 300.0 mg, 0.86 mmol) in acetic acid (5 mL), the resulting mixture was stirred at room temperature for 12 hrs. The reaction was quenched by aq. $NaHCO_3$, then the mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give some crude product. The crude was purified by reversed-phase chromatography to afford compound **540d** (203.0 mg) as a brown solid, which was used for the next step directly. LCMS $(M+H)^+$: 361.

Step 5: preparation of 2-[[5-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-6-fluoro-indazol-1-yl]methoxy]ethyl-trimethyl-silane (compound 540e)

To a mixture of 4-benzyloxy-1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-d]pyrimidine (compound **540d**, 64.0 mg, 0.18 mmol) in anhydrous DMF (1 mL) was added NaH (36.7 mg, 0.92 mmol), the resulting mixture was stirred at 0 °C for 1 hr. Then 2-(trimethylsilyl)ethoxymethyl chloride (0.03 mL, 0.18 mmol) was added into the mixture, and the resulting mixture was stirred at room temperature for 1 hr. The reaction was quenched by water, then the mixture was directly purified by reversed-phase chromatography to give compound **540e** (60.0 mg, 0.12 mmol) as an off-white solid, which was used for the next step directly. LCMS $(M+H)^+$: 491.

Step 6: preparation of 1-[6-fluoro-1-(2-trimethylsilylethoxymethyl)indazol-5-yl]pyrazolo[3,4-*d*]pyrimidin-4-ol (compound 540f)

A mixture of 2-[[5-(4-benzyloxypyrazolo[3,4-*d*]pyrimidin-1-yl)-6-fluoro-indazol-1-yl]methoxy]ethyl-trimethyl-silane (compound **540e**, 60.0 mg, 0.12 mmol) and Pd/C (10.0 mg) in methanol (1 mL) was stirred at room temperature for 2 hrs under hydrogen. The reaction mixture was filtered, the filtrate was concentrated to give compound **540f** (50.0 mg) as a white solid, which was used for the next step directly. LCMS $(M+H)^+$: 401.

Step 7: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[6-fluoro-1-(2-trimethylsilylethoxymethyl)indazol-5-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 540g)

A mixture of 1-[6-fluoro-1-(2-trimethylsilylethoxymethyl)indazol-5-yl]pyrazolo[3,4-*d*]pyrimidin-4-ol (compound **540f**, 40.0 mg, 0.1 mmol), (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **326d-1**, 45.3 mg, 0.1 mmol), BOP (66.3 mg, 0.15 mmol) and DIEA (0.1 mL, 0.5 mmol) in anhydrous DMF (2 mL) was stirred at 10 °C for 4 hrs. The reaction mixture was directly purified by reversed-phase chromatography to give compound **540g** (5.0 mg) as a white powder, which was used for the next step directly. LCMS $(M+H)^+$: 836.

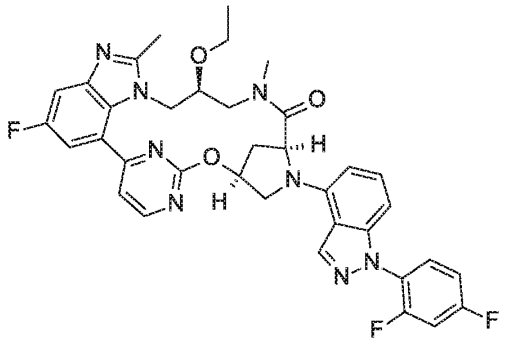
Step 8: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 540)

A mixture of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[6-fluoro-1-(2-trimethylsilylethoxymethyl)indazol-5-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **540g**, 2.0 mg, 0.01 mmol) and TFA (0.2 mL) in DCM (1 mL) was stirred at room temperature for 2 hrs. The reaction mixture was adjusted with 1 M NH_3H_2O to pH = 7, then purified by prep-HPLC to afford Example **540** (1.2 mg) as a white powder. LCMS $(M+H)^+$: 706. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.62 - 8.49 (m, 2H), 8.37 - 8.16 (m, 2H), 8.11 - 7.81 (m, 1H), 7.55 - 7.48 (m, 1H), 7.40 (br dd, J = 1.3, 8.1 Hz, 1H), 7.34 - 7.26 (m, 1H), 7.16 - 7.09 (m, 1H), 5.64 - 5.33 (m, 3H), 4.64 - 4.35 (m, 3H),

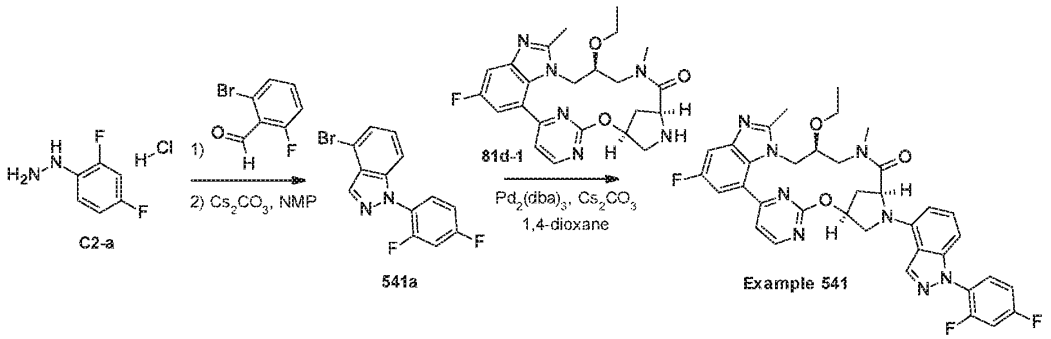
4.27 - 4.12 (m, 1H), 4.07 - 3.92 (m, 1H), 3.18 - 2.80 (m, 5H), 2.72 - 2.46 (m, 6H), 0.58 (br t, J = 6.8 Hz, 3H).

Example 541

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)indazol-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-bromo-1-(2,4-difluorophenyl)indazole (compound 541a)

A mixture of (2,4-difluorophenyl)hydrazine;hydrochloride (compound **C2-a**, 1.0 g, 5.54 mmol) and 2-bromo-6-fluorobenzaldehyde (1.35 g, 6.65 mmol) in NMP (30 mL) was stirred at room temperature for 1 hr. Then cesium carbonate (2.0 g, 6.14 mmol) was added, the resulting mixture was stirred at 140 °C for 16 hrs. After being cooled to room temperature, the reaction mixture was poured into brine, then extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give some residue. The residue was purified by flash chromatography to afford compound **541a** (650.0 mg) as a yellow solid. LCMS $(M+H)^+$: 309.

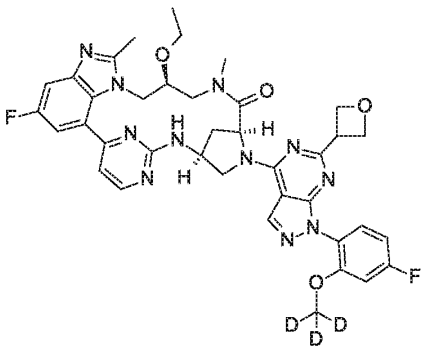
Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)indazol-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 541)

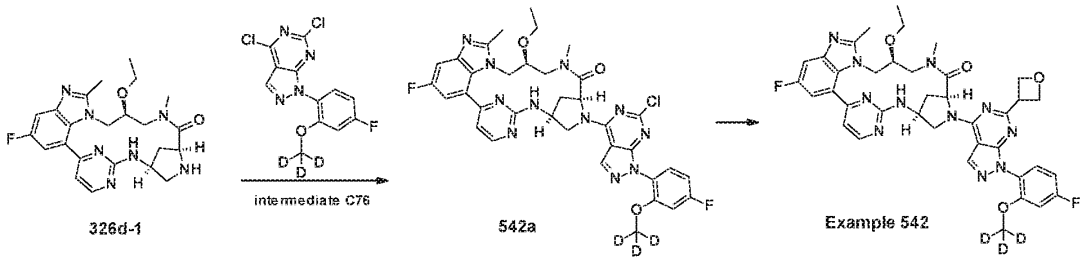
A mixture of 4-bromo-1-(2,4-difluorophenyl)indazole (compound **541a**, 31.3 mg, 0.10 mmol), (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 46.0 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium (0) (9.3 mg, 0.01 mmol), cesium carbonate (33.0 mg, 0.10 mmol) and 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (4.7 mg, 0.01 mmol) in 1,4-dioxane (0.5 mL) was stirred at 100 °C for 12 hrs under nitrogen. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure to give some crude product. The crude was purified by reversed-phase chromatography to afford Example **541** (2.3 mg) as a white solid. LCMS (M+H)$^+$: 683. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.85 - 8.70 (m, 1H), 8.61 - 8.44 (m, 1H), 7.67 - 7.60 (m, 2H), 7.50 - 7.42 (m, 2H), 7.34 - 7.27 (m, 2H), 7.24 - 7.18 (m, 1H), 6.57 - 6.50 (m, 1H), 6.30 - 6.20 (m, 1H), 5.87 - 5.77 (m, 2H), 5.23 (m, 1H), 4.36 - 4.13 (m, 3H), 4.05 (m, 1H), 3.30 - 3.20 (m, 2H), 3.08 (s, 3H), 3.00 - 2.83 (m, 2H), 2.76 - 2.55 (m, 6H), 0.60 (m, 3H).

Example 542

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 542a)

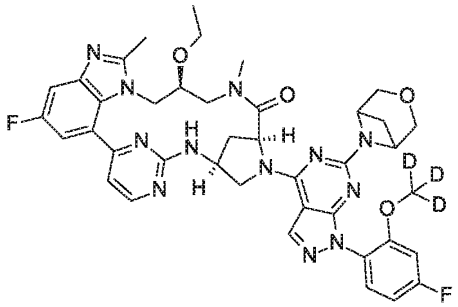
Compound **542a** was prepared in analogy to the preparation of compound **213a** by using compound **326d-1** instead of compound **370b** and intermediate **C76** instead of intermediate **C74**. LCMS (M+H$^+$): 733.

Step 2: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 542)

Example **542** was prepared in analogy to the preparation of Example **432** by using 3-iodooxetane instead of 3-iodotetrahydrofuran and compound **542a** instead of compound **213a**. LCMS (M+H$^+$): 755. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 8.66 - 8.53 (m, 1H), 8.46 - 7.65 (m, 1H), 7.48 - 7.34 (m, 2H), 7.33 - 7.23 (m, 1H), 7.15 - 7.07 (m, 1H), 7.06 - 7.00 (m, 1H), 6.93 - 6.81 (m, 1H), 5.71 - 5.27 (m, 2H), 5.11 - 4.91 (m, 4H), 4.79 - 4.49 (m, 1H), 4.48 - 4.07 (m, 4H), 4.03 - 3.88 (m, 1H), 3.30 - 3.26 (m, 1H), 3.19 - 2.78 (m, 5H), 2.70 - 2.46 (m, 6H), 0.65 - 0.48 (m, 3H).

Example 543

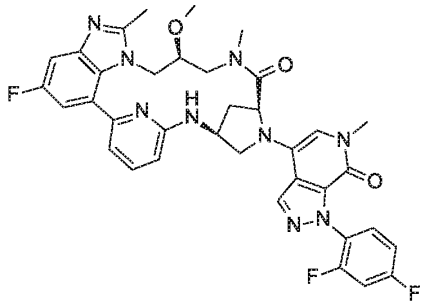
(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



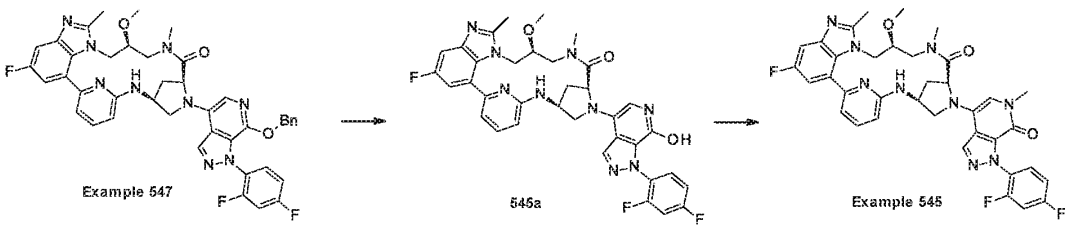
Example **543** was prepared in analogy to the preparation of Example **213** by using compound **542a** instead of compound **213a** and 3-oxa-6-azabicyclo[3.1.1]heptane instead of morpholine. LCMS ($M+H^+$): 796. ^1H NMR (500 MHz, METHANOL-d_4) δ = 8.50 - 8.38 (m, 1H), 8.20 - 7.39 (m, 1H), 7.34 - 7.15 (m, 3H), 7.07 - 6.97 (m, 1H), 6.94 - 6.86 (m, 1H), 6.77 - 6.67 (m, 1H), 5.61 - 5.34 (m, 1H), 5.30 - 5.13 (m, 1H), 4.68 - 4.50 (m, 1H), 4.35 - 4.01 (m, 7H), 3.94 - 3.75 (m, 1H), 3.68 - 3.51 (m, 2H), 3.19 - 3.12 (m, 1H), 3.04 - 2.86 (m, 3H), 2.84 - 2.70 (m, 2H), 2.61 - 2.31 (m, 7H), 1.76 - 1.69 (m, 1H), 0.55 - 0.41 (m, 3H).

Example 545

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methyl-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-hydroxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-

hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 545a)

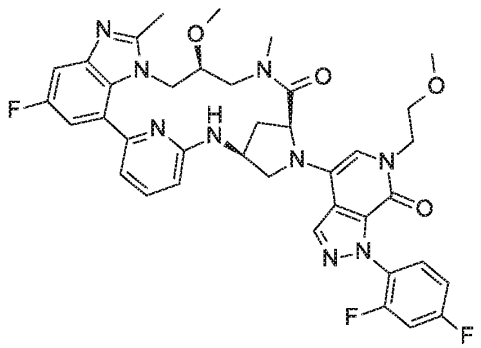
A mixture of Example **547** (100 mg, 0.11 mmol) in TFA (1 mL) was stirred at 50 °C for 2 hrs. The mixture was concentrated under reduced pressure to give a residue, which was diluted with ice sat. $NaHCO_3$ solution (10 mL) and extracted with EA. The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give compound **545a** (70 mg). LCMS ($M+H^+$): 684.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methyl-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 545)

To a solution of compound **545a** (20.0 mg, 0.03 mmol) and Cs_2CO_3 (28.6 mg, 0.09 mmol) in DMF (1 mL) was added MeI (8.5 mg, 0.06 mmol) slowly at 20 °C under N_2, then the mixture the mixture was stirred at 20 °C for 2 hrs. The reaction was quenched with 10 mL of NH_4Cl solution and then extracted with ethyl acetate, the organic layer was dried and concentrated, the residue was purified by prep-HPLC to give Example **545** (13 mg). LCMS ($M+H^+$): 698. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.01 (s, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.66 - 7.52 (m, 4H), 7.22 - 7.05 (m, 3H), 6.80 - 6.69 (m, 1H), 6.12 (dd, J = 4.4, 15.2 Hz, 1H), 5.03 (br d, J = 8.8 Hz, 1H), 4.57 - 4.47 (m, 1H), 4.34 (dd, J = 11.2, 15.2 Hz, 1H), 4.02 - 3.96 (m, 1H), 3.74 (br d, J = 10.4 Hz, 1H), 3.57 (s, 3H), 3.12 - 3.05 (m, 3H), 3.01 - 2.95 (m, 4H), 2.93 (d, J = 4.8 Hz, 1H), 2.89 - 2.86 (m, 1H), 2.84 (s, 3H), 2.62 - 2.50 (m, 2H).

Example 546

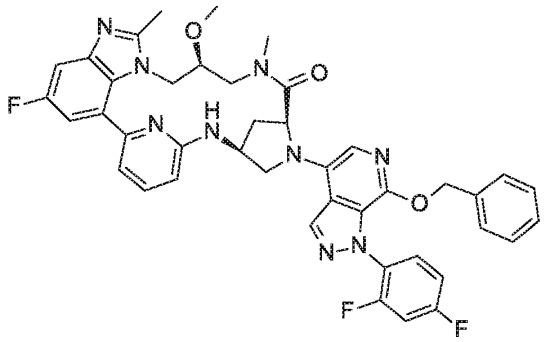
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



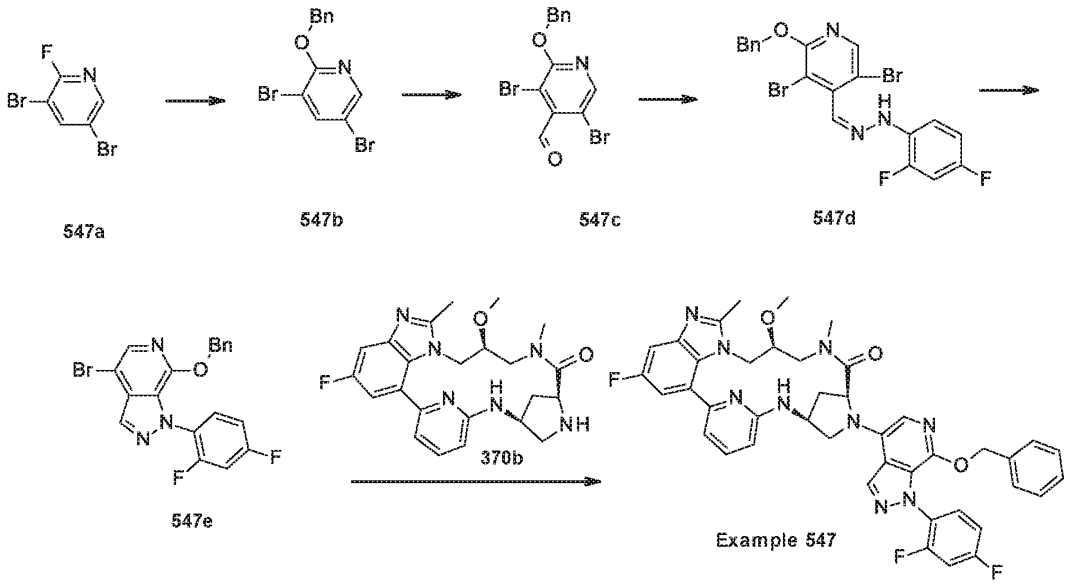
A mixture of compound **545a** (5.0 mg, 0.01 mmol), Cs_2CO_3 (7.2 mg, 0.02 mmol) and 2-bromoethyl methyl ether (2.0 mg, 0.015 mmol) in ACN (1 mL) was stirred at 90 °C for 2 hrs. The reaction was directly purified by prep-HPLC to give Example **546** (3.0 mg). LCMS ($M+H^+$): 742. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.00 (s, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.64 - 7.50 (m, 4H), 7.26 - 7.10 (m, 3H), 6.83 - 6.69 (m, 1H), 6.18 - 5.89 (m, 1H), 5.06 (br d, J = 8.4 Hz, 1H), 4.59 - 4.47 (m, 1H), 4.41 - 4.30 (m, 1H), 4.20 (t, J = 5.2 Hz, 1H), 4.16 - 3.94 (m, 2H), 3.90 - 3.75 (m, 1H), 3.71 (m, 1H), 3.65 - 3.57 (m, 1H), 3.38 - 3.34 (m, 3H), 3.14 - 3.09 (m, 2H), 3.07 - 3.01 (m, 1H), 3.00 - 2.94 (m, 4H), 2.93 - 2.87 (m, 2H), 2.87 - 2.81 (m, 3H), 2.58 (br dd, J = 4.0, 8.8 Hz, 2H).

Example 547

(8*S*,11*S*,15*R*)-10-[7-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 2-benzyloxy-3,5-dibromo-pyridine (compound 547b)

To a solution of compound **547b** (4.4 g, 17.3 mmol) in THF (44 mL) was added benzyl alcohol (1.68 g, 15.5 mmol) and *t*-BuOK (1.94 g, 17.3 mmol) at 0 °C, the mixture was stirred for 1 h at 0 °C. The reaction was quenched with ice water (300 mL), then the mixture was extracted with EA, the organic layer was dried and concentrated to give compound **547b** (5.0 g). LCMS ($M+H^+$): 344.

Step 2: preparation of 2-benzyloxy-3,5-dibromo-pyridine-4-carbaldehyde (compound 547c)

To a solution of compound **547b** (3.0 g, 8.7 mmol) in THF (24 mL) was added LDA (6.56 mL, 13.1 mmol) dropwise at -70 °C under N_2 and then the mixture was stirred at -70 °C for 1 h. DMF (3.4 mL, 44 mmol) was added slowly and the mixture was stirred at rt for 1 h. The reaction was quenched with ice water (100 mL), then the mixture was extracted with EtOAc, the organic layer was dried and concentrated to give compound **547c** (3.0 g) as a brown solid.

Step 3: preparation of *N*-[(2-benzyloxy-3,5-dibromo-4-pyridyl)methyleneamino]-2,4-difluoro-aniline (compound 547d)

A mixture of compound **547c** (3.0 g, 8.09 mmol) and 2,4-difluorophenylhydrazine hydrochloride (1.75 g, 9.7 mmol) in DMF (60 mL) was stirred at 20 °C for 16 hrs. The reaction was quenched with ice water, and then the mixture was extracted with EA. The organic layer was dried and concentrated to give compound **547d** (4.1 g). LCMS ($M+H^+$): 498.

Step 4: preparation of 7-benzyloxy-4-bromo-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridine (compound 547e)

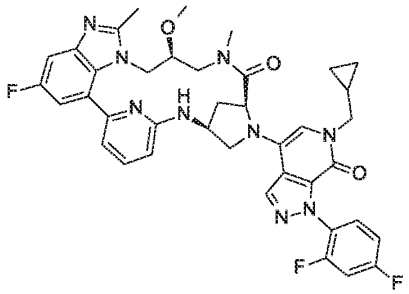
A mixture of compound **547d** (6.7 g, 13.5 mmol), K_2CO_3 (5.59 g, 40.4 mmol) and CuI (0.26 g, 1.35 mmol) in DMF (67 mL) was stirred at 100 °C for 1 h. The reaction mixture was diluted with water (300 mL), extracted with EA, the organic layer was dried and concentrated. The residue was purified by chromatography column and SFC [DAICEL CHIRALCEL OJ (250mm×30mm,10um), 0.1%NH_3H_2O ETOH, begin 60% B(ETOH) to 60% B, rate: 70mL/min)] to give compound **547e** (1200 mg). LCMS ($M+H^+$): 416.

Step 5: preparation of (8*S*,11*S*,15*R*)-10-[7-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 547)

To a solution of **compound 370b** (210.0 mg, 0.48 mmol) in THF (3 mL) was added **compound 547e** (200.0 mg, 0.48 mmol), BINAP (60.0 mg, 0.1 mmol), cesium carbonate (630.0 mg, 1.93 mmol) and bis(dibenzylideneacetone)palladium (30.0 mg, 0.05 mmol). The mixture was degassed with N_2 for 3 times and then stirred at 110 °C for 12 hrs under N_2. The mixture was diluted with H_2O (30 mL) and extracted with EA (20 mL). The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give Example **547** (100 mg). LCMS ($M+H^+$): 774. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.16 (s, 1H), 7.86 (br t, *J* = 8.0 Hz, 1H), 7.59 (br d, *J* = 4.4 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.27 - 7.24 (m, 3H), 7.13 (br d, *J* = 7.6 Hz, 1H), 7.08 - 6.92 (m, 5H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.12 (dd, *J* = 4.4, 15.6 Hz, 1H), 5.22 (s, 2H), 5.10 (br d, *J* = 8.8 Hz, 1H), 4.59 - 4.53 (m, 1H), 4.36 - 4.18 (m, 2H), 4.00 - 3.93 (m, 2H), 3.12 (s, 3H), 3.03 (br d, *J* = 13.6 Hz, 1H), 2.97 (s, 3H), 2.87 (br d, *J* = 13.2 Hz, 1H), 2.81 (s, 3H), 2.57 (dt, *J* = 4.4, 9.2 Hz, 2H).

Example 548

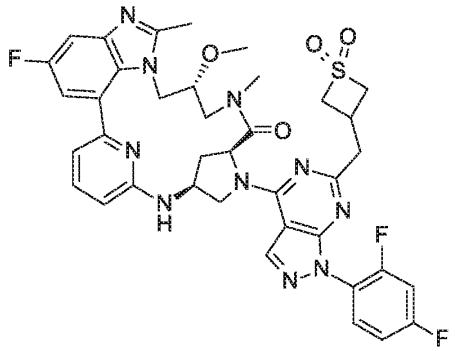
(8S,11S,15R)-10-[6-(cyclopropylmethyl)-1-(2,4-difluorophenyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



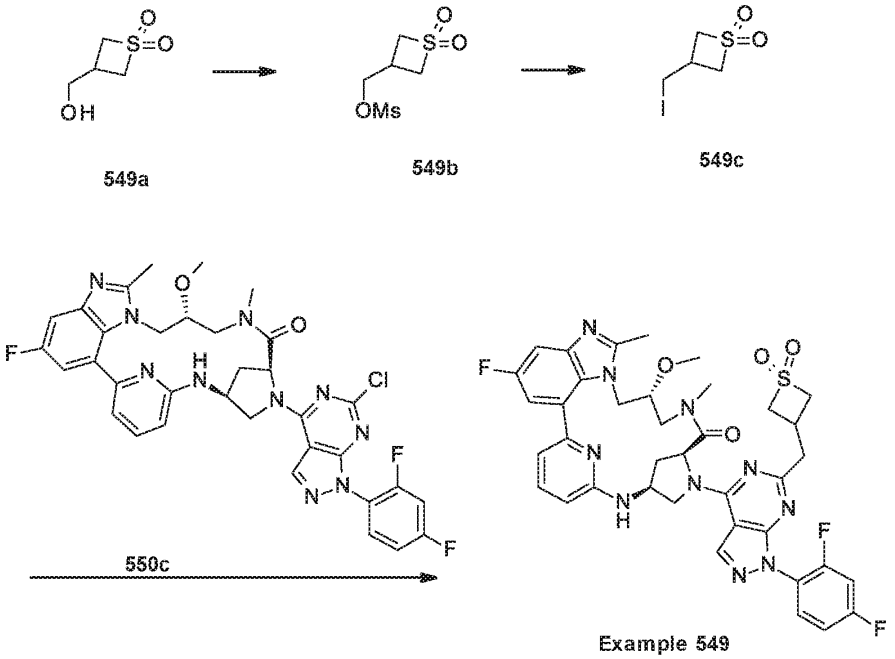
Example **548** was prepared in analogy to the preparation of Example **546** by using (bromomethyl)cyclopropane instead of 2-bromoethyl methyl ether. Example **548**. LCMS ($M+H^+$): 738. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.03 - 7.92 (m, 1H), 7.91 - 7.79 (m, 1H), 7.64 - 7.46 (m, 4H), 7.39 - 7.12 (m, 3H), 6.82 - 6.66 (m, 1H), 6.18 - 5.86 (m, 1H), 5.08 - 5.03 (m, 1H), 4.57 - 4.46 (m, 1H), 4.42 - 4.22 (m, 1H), 4.08 - 3.80 (m, 2H), 3.79 - 3.71 (m, 1H), 3.61 (q, J = 7.0 Hz, 2H), 3.10 (s, 1H), 3.07 - 2.91 (m, 5H), 2.91 - 2.82 (m, 4H), 2.71 - 2.64 (m, 1H), 2.63 - 2.43 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H), 0.58 - 0.53 (m, 1H), 0.47 - 0.42 (m, 1H).

Example 549

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (1,1-dioxothietan-3-yl)methyl methanesulfonate (compound 549b)

To a solution of compound **549a** (700 mg, 5.14 mmol) and TEA (2.14 mL, 15.42 mmol) in DCM (7 mL) was added methanesulfonic anhydride (1.07 g, 6.17 mmol,) at 0 °C, the mixture was stirred at 0 °C for 1 h. The mixture was dilluted with H_2O (30 mL), and then extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated to give compound **549b** (690 mg).

Step 2: preparation of 3-(iodomethyl)thietane 1,1-dioxide (compound 549c)

To a solution of compound **549b** (690 mg, 3.22 mmol) in acetone (45 mL) were added NaI (1.80 g, 12 mmol) in one portion under N_2. The reaction was stirred at 60 °C for 16 hours. The mixture was concentrated in *vacuo* to give a residue, which was added water (20 mL) and EA (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated to afford compound **549c** (690 mg) as a yellow solid.

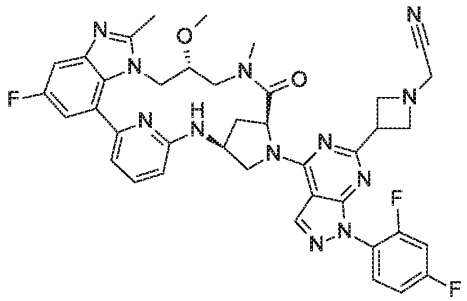
Step 3: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 549)

To a 15 mL vial equipped with a stir bar was added compound **550c** (50.0 mg, 0.06 mmol), compound **549c** (21.1 mg, 0.09 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbpy)(PF$_6$) (0.69 mg, 0.006 mmol),

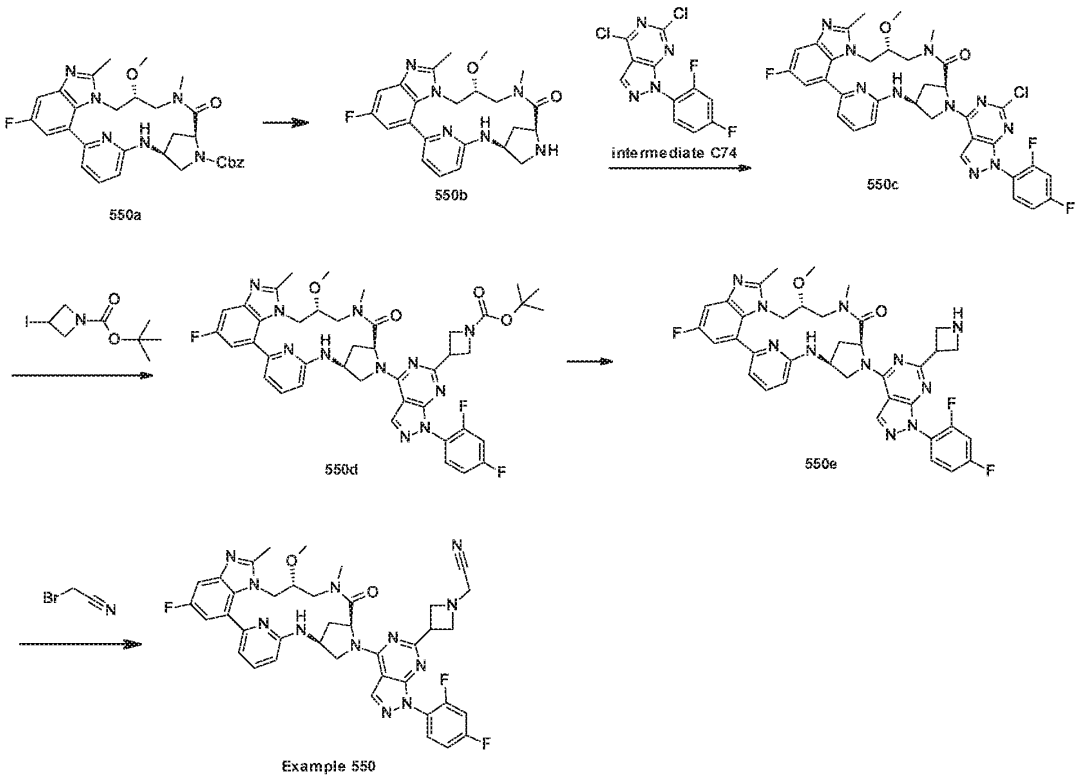
$NiCl_2$.dtbbpy (0.28 mg, 0.012 mmol), TTMSS (15.22 mg, 0.06 mmol), Na_2CO_3 (13.0 mg, 0.12 mmol) in DME (5 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25 °C for 14 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure and the residue was purified by flash-HPLC (TFA as additive) to give **Example 549**. LCMS ($M+H^+$):787. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.51 (s, 1H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.67 (dt, *J* = 6.4, 8.4 Hz, 1H), 7.57 (dd, *J* = 2.4, 7.2 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.36 - 7.27 (m, 1H), 7.27 - 7.18 (m, 1H), 7.10 - 6.98 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 9.2 Hz, 1H), 4.78 - 4.75 (m, 1H), 4.57 (br dd, *J* = 6.4, 11.2 Hz, 1H), 4.36 - 4.25 (m, 2H), 4.22 - 4.12 (m, 2H), 3.96 - 3.87 (m, 1H), 3.80 (br d, *J* = 12.4 Hz, 1H), 3.63 (q, *J* = 7.2 Hz, 2H), 3.25 - 3.19 (m, 2H), 3.16 (s, 3H), 3.09 - 3.02 (m, 2H), 2.98 (s, 4H), 2.87 (s, 3H), 2.79 - 2.71 (m, 1H), 2.66 - 2.56 (m, 1H).

Example 550

2-[3-[1-(2,4-difluorophenyl)-4-[(8S,11S,15S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*S*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 550b)

A reaction mixture of compound **550a** (500 mg, 0.87 mmol, synthesis refers to compound **12c** by using intermediate **A30** instead of intermediate **A11**) in TFA (5 mL) was stirred at 90 °C for 1 h. The reaction was concentrated to give compound **550b** (482 mg). LCMS (M+H$^+$): 439.

Step 2: preparation of (8*S*,11*S*,15*S*) (8S,11S,15S)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 550c)

A mixture of compound **550b** (450 mg, 0.81 mmol), intermediate **C74** (257.5 mg, 0.86 mmol) and DIPEA (0.57 mL, 3.26 mmol) in ACN (5 mL) was stirred at 85 °C for 1 h. Then the reaction mixture was directly purified by flash-HPLC to give compound **550c** (400 mg). LCMS (M+H$^+$): 703.

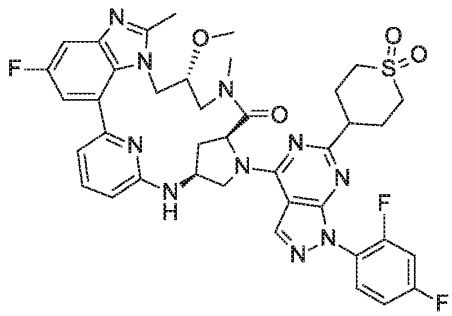
Step 3~5: preparation of 2-[3-[1-(2,4-difluorophenyl)-4-[(8S,11S,15S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile (Example 550)

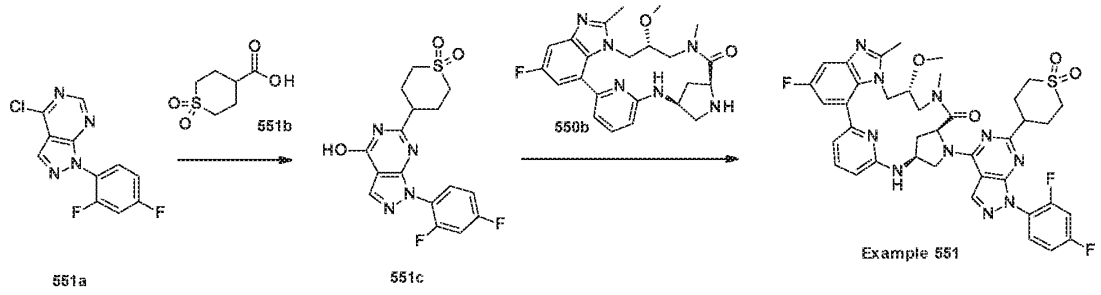
Examples **550** was prepared in analogy to the preparation of Example **443** by using bromoacetonitrile instead of methanesulfonic anhydride. LCMS (M+H$^+$): 763. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.47 (s, 1H), 7.79 - 7.72 (m, 1H), 7.68 - 7.62 (m, 1H), 7.29 - 7.23 (m, 2H), 7.21 - 7.15 (m, 1H), 7.05 - 7.02 (m, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 9.2 Hz, 1H), 4.82 (d, J = 4.4 Hz, 1H), 4.73 - 4.71 (m, 1H), 4.63 - 4.53 (m, 4H), 4.33 - 4.26 (m, 1H), 4.09 - 3.97 (m, 2H), 3.77 - 3.59 (m, 7H), 3.17 - 3.12 (m, 3H), 3.09 - 3.02 (m, 1H), 2.84 (s, 3H), 2.57 - 2.56 (m, 3H).

Example 551

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothian-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-(2, 4-difluorophenyl)-6-(1, 1-dioxothian-4-yl) pyrazolo[3,4-d]pyrimidin-4-ol (compound 551c)

To a solution of **compound 551a** (300 mg, 1.1 mmol) in ACN (4 mL) was added compound **551b** (402 mg, 2.3 mmol) and silver nitrate (1.53 g, 9.0 mmol). The reaction was heated at 60 °C and then a solution of ammonium persulfate (1284.0 mg, 5.6 mmol) in water (4

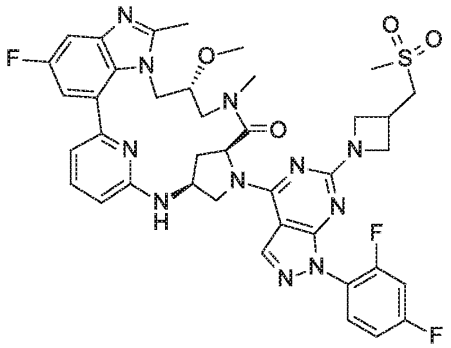
mL) was added slowly. After being stirred at 60 °C for 2 hours, the mixture was diluted with H_2O (30mL) and extracted with EA. The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give compound **551c** (60.0 mg) as a white solid. LCMS ($M+H^+$): 381.

Step 2: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothian-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 551)

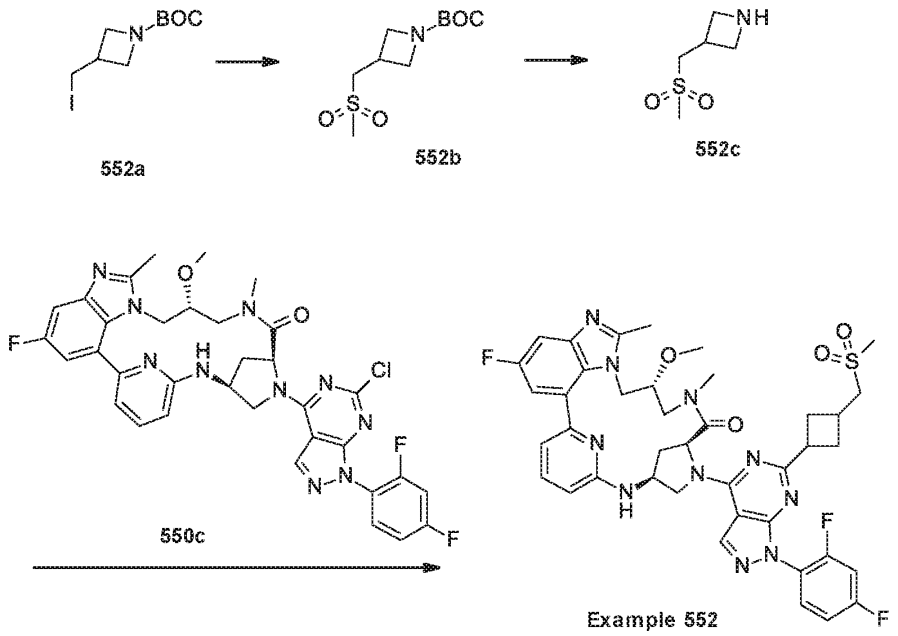
A mixture of compound **551c** (25 mg, 0.05 mmol), PyBOP (57.9 mg, 0.11 mmol) and *N,N*-diisopropylethylamine (0.02 mL, 0.13 mmol) in DMF (1 mL)was stirred at rt for 2 hours, then a solution of compound **550b** (27.9 mg, 0.05 mmol) and N,N-diisopropylethylamine (0.04 mL, 0.25 mmol) in DMF (1 mL) was added and stirred at 25 °C for 12 hrs. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **551** (5 mg). LCMS ($M+H^+$):801. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.51 (s, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.71 - 7.63 (m, 1H), 7.35 - 7.26 (m, 2H), 7.25 - 7.17 (m, 1H), 7.06 (br dd, J = 2.4, 10.8 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.52 (d, J = 9.2 Hz, 1H), 4.80 - 4.75 (m, 2H), 4.62 - 4.56 (m, 2H), 4.29 (d, J = 12.0 Hz, 1H), 4.09 - 3.97 (m, 2H), 3.82 - 3.71 (m, 1H), 3.30 (br s, 1H), 3.20 (s, 1H), 3.15 (s, 3H), 3.13 - 3.07 (m, 2H), 3.05 - 2.98 (m, 1H), 2.87 (s, 3H), 2.74 - 2.66 (m, 1H), 2.65 - 2.61 (m, 1H), 2.60 (s, 3H), 2.52 - 2.28 (m, 4H).

Example 552

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(methylsulfonylmethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-(methylsulfonylmethyl)azetidine-1-carboxylate (compound 552b)

To a solution of compound **552a** (200.0 mg, 0.67 mmol) in DMF (20 mL) was added methylsulfinyloxysodium (137.4 mg, 1.35 mmol), then the mixture was stirred at 60 °C for 12 hrs. The reaction was quenched with water (80 mL) and the mixture was extracted with EA, the organic layer was dried over Na_2SO_4, filtered and concentrated to give compound **552b** (150 mg) as a light yellow oil (crude). LCMS ($M-C_5H_9O_2+H^+$): 194.

Step 2: preparation of 3-(methylsulfonylmethyl)azetidine;hydrochloride (compound 552c)

To a solution of compound **552b** (150 mg, 0.6 mmol) in DCM (1.5 mL) was added HCl/dioxane (1.5 mL, 6.0 mmol) dropwise. After being stirred at 20 °C for 1 h, the mixture was concentrated to give compound **552c** (150 mg) as yellow oil that was used in next step directly.

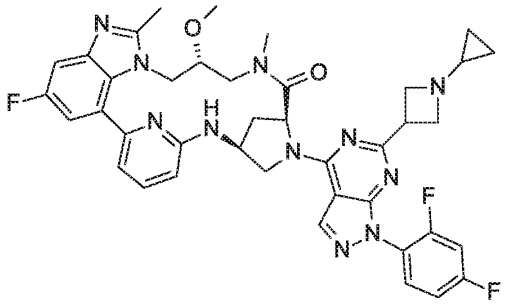
Step 3: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(methylsulfonylmethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 552)

A solution of compound **550c** (30.0 mg, 0.04 mmol), DIPEA (96 μL, 0.59 mmol) and compound **552b** (54.5 mg, 0.29 mmol) in MeCN (2 mL) was stirred at 80 °C for 2 hrs. The mixture was directly purified by prep-HPLC to give Example **552** (16.3 mg). LCMS ($M+H^+$): 816. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.65 - 7.55

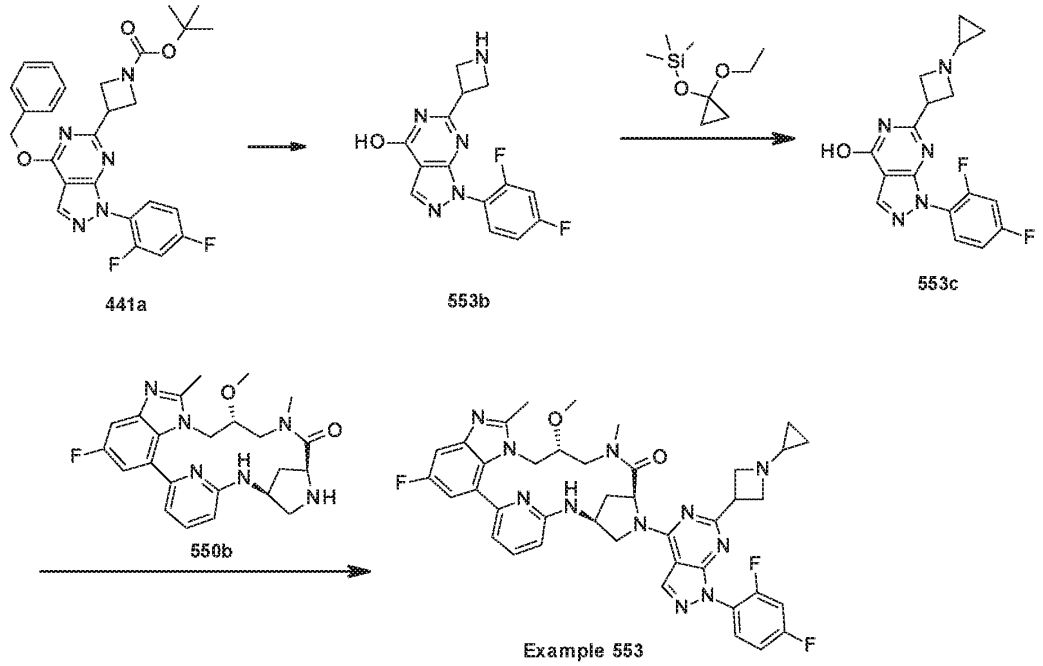
(m, 1H), 7.28 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.25 - 7.19 (m, 1H), 7.18 - 7.11 (m, 1H), 7.07 - 7.00 (m, 1H), 6.93 - 6.86 (m, 1H), 6.73 - 6.64 (m, 1H), 5.40 - 5.21 (m, 1H), 4.72 - 4.66 (m, 1H), 4.52 - 4.45 (m, 1H), 4.34 - 4.14 (m, 3H), 4.06 - 3.83 (m, 4H), 3.80 - 3.73 (m, 1H), 3.53 - 3.47 (m, 2H), 3.25 - 3.13 (m, 2H), 3.09 - 3.01 (m, 3H), 2.97 (s, 3H), 2.85 (s, 3H), 2.59 - 2.50 (m, 4H), 1.35 - 1.27 (m, 2H).

Example 553

(8S,11S,15S)-10-[6-(1-cyclopropylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 6-(azetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 553b)

To a stirred solution of **compound 441a** (120 mg, 0.24 mmol) in DCM (1 mL) was added TFA (0.33 mL) at 0 °C. After being stirred at 0 °C for 0.5 hrs, the reaction mixture was concentrated to give compound **553b** (100 mg). LCMS ($M+H^+$): 304.

Step 2: preparation of 6-(1-cyclopropylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 553c)

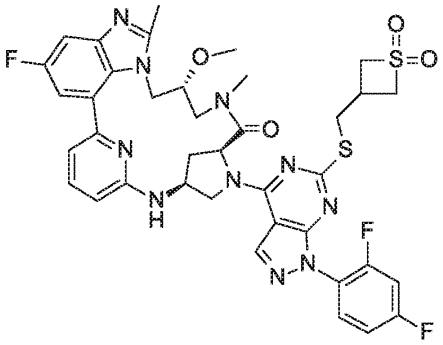
To a solution of compound **553b** (50 mg, 0.12 mmol) and (1-ethoxycyclopropoxy) trimethylsilane (208.9 mg, 1.2 mmol) in THF (1 mL) was added acetic acid (71.9 mg, 1.2 mmol) and sodium cyanoborohydride (11.3 mg, 0.18 mmol) at 25°C under N_2, and the reaction mixture was stirred at 60 °C for 1 h under N_2. The reaction mixture was poured into water (20 mL) and extracted with EA, the organic phase was concentrated and the residue was purified by prep-TLC to afford compound **553c** (15 mg). LCMS ($M+H^+$): 344.

Step 4: preparation of (8S,11S,15S)-10-[6-(1-cyclopropylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 553)

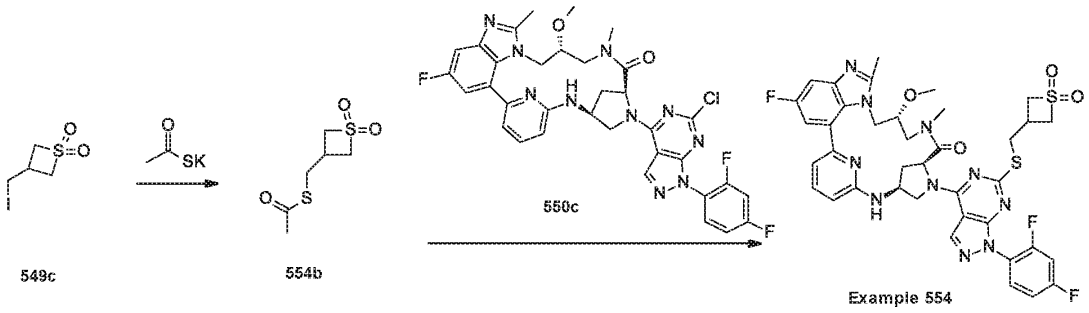
To the solution of compound **550b** (15 mg, 0.03 mmol) and compound **553c** (10.0 mg, 0.03 mmol) in DMF (0.5 mL) were added DIEA (13 μL, 0.08 mmol), PyBOP (21.4 mg, 0.04 mmol) at 25 °C. Then the mixture was stirred at 25 °C for 16 h. The reaction mixture was directly purified by prep-HPLC to give Example **553** (3.2 mg). LCMS ($M+H^+$): 764. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.48 (s, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.65 - 7.64 (m, 1H), 7.28 (dd, J = 2.0, 9.2 Hz, 2H), 7.21 - 7.17 (m, 1H), 7.04 (dd, J = 2.38, 10.0 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.74 - 6.72 (m, 1H), 5.63 (d, J = 8.8 Hz, 1H), 4.90 - 4.89 (m, 2H), 4.77 - 4.74 (m, 1H), 4.60 - 4.55 (m, 4H), 4.30 (d, J = 12.0 Hz, 1H), 4.08 - 3.98 (m, 2H), 3.75 - 3.67 (m, 4H), 3.55 - 3.47 (m, 1H), 3.12 (s, 3H), 2.84 (s, 3H), 2.58 (s, 3H), 2.00 - 1.97 (m, 1H), 0.47 - 0.36 (m, 4H).

Example 554

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methylsulfanyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of S-[(1,1-dioxothietan-3-yl)methyl] ethanethioate (compound 554b)

To a solution of compound **554b** (100 mg, 0.41 mmol) in DMF (5 mL) was added acetylsulfanylpotassium (100 mg, 0.88 mmol) and then the mixture was stirred at 25 °C for 12 hours. The reaction mixutre was diluted with ice-water (20 mL) and extracted with EA, the organic layer was concentrated and the residue was purified by prep-TLC to give compound **554b** (60 mg) as a white solid.

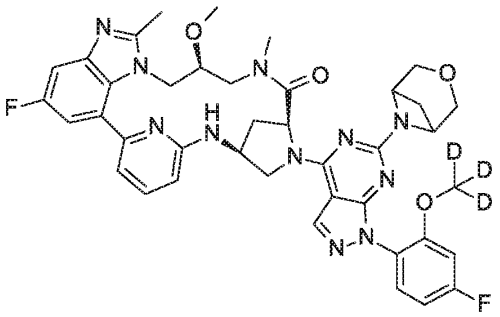
Step 2: preparation of (8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methylsulfanyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 554)

To a solution of compound **554b** (20 mg, 0.1 mmol) in THF (0.1 mL) was added KOH (32 mg, 0.57 mmol) at 0 °C and then after the reaction mixture was stirred at 25 °C for 1 h, compound **550c** (20 mg, 0.02 mmol) was added and such reaction mixture was stirred at 25 °C for another 11 hours. The reaction was quenched with water (20 mL), and then the mixture was extracted with ethyl acetate.The organic layer was washed with brine, dried and concentrated, the residue was purified by prep-TLC and prep-HPLC to give Example **554** (0.8 mg). LCMS

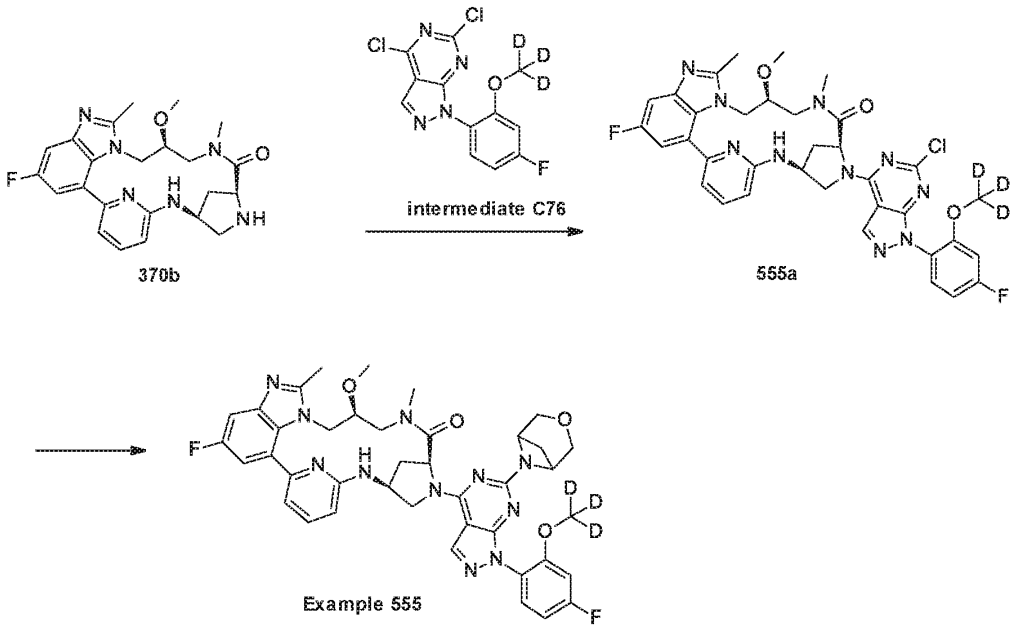
($M+H^+$): 819. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.43 (s, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.69 - 7.61 (m, 2H), 7.42 (br d, J = 5.3 Hz, 1H), 7.31 - 7.23 (m, 2H), 6.97 (br d, J = 7.1 Hz, 1H), 6.74 (br d, J = 7.9 Hz, 1H), 5.55 (br d, J = 9.0 Hz, 1H), 4.56 - 4.50 (m, 2H), 4.35 - 4.25 (m, 2H), 4.24 - 4.17 (m, 2H), 4.15 - 4.08 (m, 4H), 3.96 - 3.88 (m, 2H), 3.82 - 3.73 (m, 2H), 3.18 (s, 1H), 3.11 (s, 3H), 3.07 - 3.00 (m, 2H), 2.92 - 2.88 (m, 3H), 2.71 (d, J = 7.5 Hz, 3H).

Example 555

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



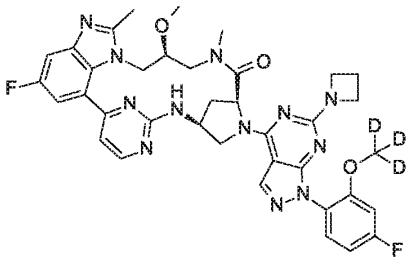
The title compound was prepared according to the following scheme:



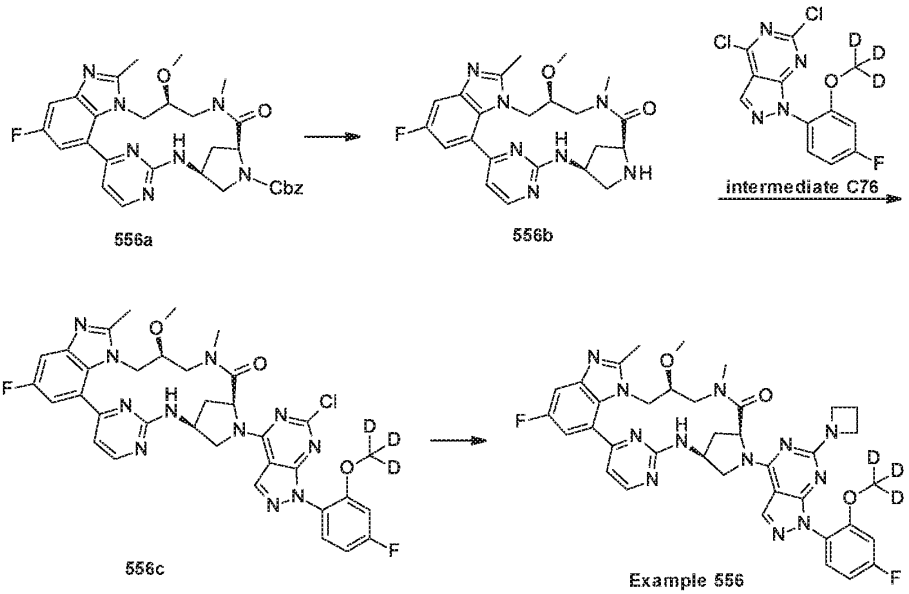
Example **555** was prepared in analogy to the preparation of Example **213** by using intermediate **C76** instead of intermediate **C74** and 3-oxa-6-azabicyclo[3.1.1]heptane instead of morpholine. LCMS ($M+H^+$):781. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.10 (s, 1H), 7.83 (dd, *J* = 2.4, 7.2 Hz, 2H), 7.39 - 7.31 (m, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.82 - 6.73 (m, 2H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.34 (d, *J* = 8.8 Hz, 1H), 5.18 (br d, *J* = 8.0 Hz, 1H), 4.60 - 4.48 (m, 2H), 4.47 - 4.31 (m, 4H), 4.30 - 4.16 (m, 4H), 3.93 (br dd, *J* = 8.8, 14.2 Hz, 2H), 3.80 (br d, *J* = 9.2 Hz, 1H), 3.74 (br d, *J* = 8.8 Hz, 1H), 3.00 (s, 3H), 2.98 - 2.93 (m, 3H), 2.91 - 2.80 (m, 4H), 2.62 - 2.44 (m, 2H).

Example 556

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 556b)

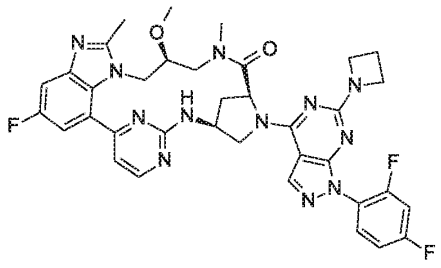
A solution of compound **556a** (200 mg, 0.29 mmol, synthesis refers to compound **12c** by using intermediate **A6** instead of intermediate **A11** and intermediate **B6** instead of intermediate **B10**) in TFA (3.0 mL) was stirred at 90 °C for 2 hs. The mixture was concentrated under vacuum to give compound **556** (180 mg). LCMS (M+H$^+$): 440.

Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 556)

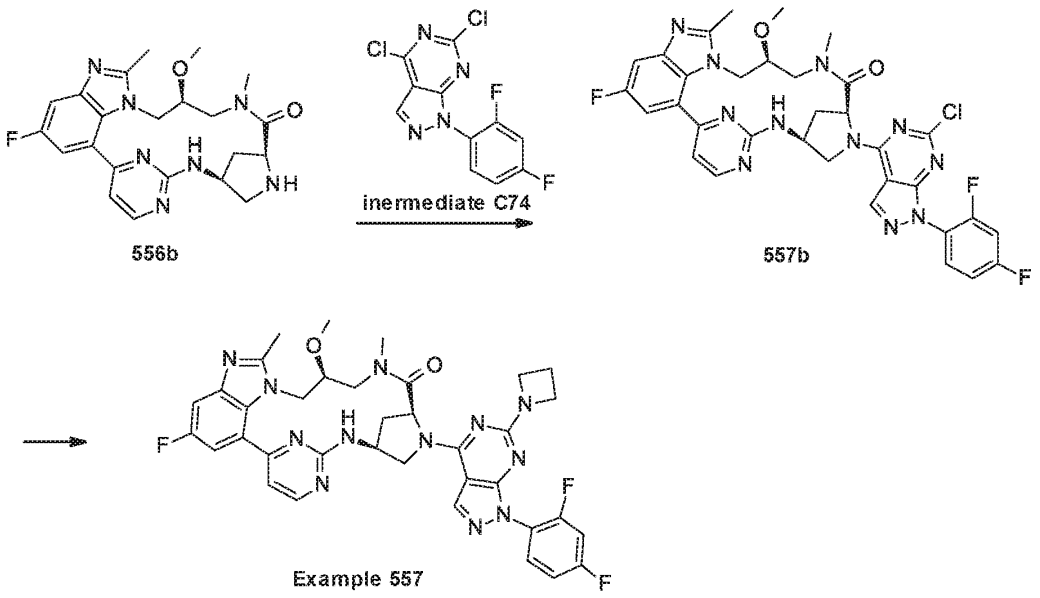
Example **556** was prepared in analogy to the preparation of Example **213** by using intermediate **C76** instead of intermediate **C74**, compound **556b** instead of compound **370b** and azetidine instead of morpholine. LCMS (M+H$^+$): 740. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.55 (d, *J* = 5.2 Hz, 1H), 8.03 (s, 1H), 7.51 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.18 (dd, *J* = 2.4, 10.4 Hz, 1H), 7.07 - 6.99 (m, 1H), 6.83 - 6.71 (m, 2H), 5.86 (dd, *J* = 4.0, 15.7 Hz, 1H), 5.68 (br d, *J* = 7.2 Hz, 1H), 5.32 (d, *J* = 8.6 Hz, 1H), 5.01 - 4.80 (m, 1H), 4.41 (dd, *J* = 6.1, 11.0 Hz, 1H), 4.32 - 4.02 (m, 4H), 3.98 (dt, *J* = 3.5, 7.4 Hz, 3H), 3.04 (s, 3H), 2.84 - 2.80 (m, 3H), 2.78 - 2.71 (m, 1H), 2.62 (s, 3H), 2.56 - 2.37 (m, 2H), 2.35 - 2.17 (m, 2H).

Example 557

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



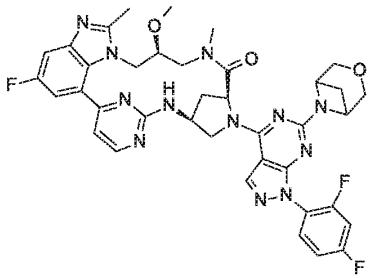
The title compound was prepared according to the following scheme:



Example **557** was prepared in analogy to the preparation of Example **213** by using compound **556b** instead of compound **370b** and azetidine instead of morpholine. LCMS ($M+H^+$): 725. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.54 (d, *J* = 5.2 Hz, 1H), 8.04 (s, 1H), 7.73 - 7.54 (m, 1H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.22 - 7.11 (m, 1H), 7.02 (br dd, *J* = 5.2, 12.0 Hz, 3H), 5.68 (br d, *J* = 7.2 Hz, 1H), 5.32 (br d, *J* = 8.4 Hz, 1H), 5.03 - 4.80 (m, 1H), 4.39 (br dd, *J* = 6.3, 10.8 Hz, 1H), 4.33 - 4.05 (m, 5H), 4.05 - 3.94 (m, 3H), 3.16 - 3.00 (m, 3H), 2.86 - 2.79 (m, 3H), 2.77 (br s, 1H), 2.61 (s, 3H), 2.55 - 2.39 (m, 2H), 2.37 - 2.19 (m, 2H).

Example 558

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

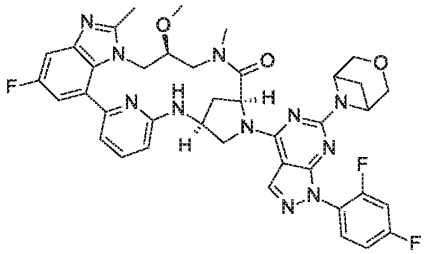


Example **558** was prepared in analogy to the preparation of Example **213** by using compound **557b** instead of compound **213a** and 3-oxa-6-azabicyclo[3.1.1]heptane instead of

morpholine. LCMS (M+H$^+$): 767. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.63 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H), 7.93 (br d, *J* = 6.9 Hz, 1H), 7.55 (br d, *J* = 6.1 Hz, 1H), 7.40 (br dd, *J* = 2.1, 9.4 Hz, 1H), 7.08 - 6.96 (m, 3H), 5.70 (br d, *J* = 6.9 Hz, 1H), 5.30 (br d, *J* = 8.8 Hz, 1H), 4.50 - 4.14 (m, 10H), 4.08 - 3.91 (m, 2H), 3.84 - 3.78 (m, 1H), 3.76 - 3.70 (m, 1H), 3.15 - 3.02 (m, 3H), 2.99 - 2.93 (m, 3H), 2.89 - 2.79 (m, 4H), 2.57 - 2.42 (m, 2H).

Example 559

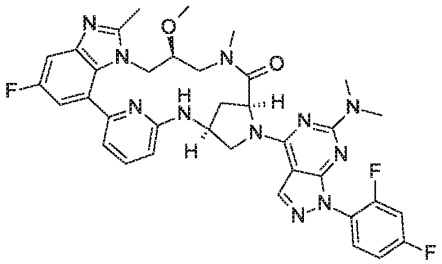
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **559** was prepared in analogy to the preparation of Example **483** by using 3-oxa-6-azabicyclo[3.1.1]heptane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **559**, LCMS (M+H$^+$): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.29 (s, 1H), 7.84 - 7.78 (m, 1H), 7.66 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.12 (m, 2H), 7.11 - 7.06 (m, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.67 (m, 1H), 5.39 - 5.29 (m, 1H), 4.65 (br t, *J* = 5.1 Hz, 1H), 4.50 - 4.41 (m, 1H), 4.39 - 4.33 (m, 1H), 4.31 - 4.11 (m, 5H), 3.87 (br dd, *J* = 9.0, 14.1 Hz, 1H), 3.77 - 3.63 (m, 2H), 3.11 (s, 1H), 3.00 (s, 3H), 2.92 - 2.86 (m, 1H), 2.85 - 2.81 (m, 3H), 2.79 - 2.74 (m, 1H), 2.68 - 2.61 (m, 1H), 2.60 - 2.54 (m, 3H), 2.53 - 2.43 (m, 2H).

Example 560

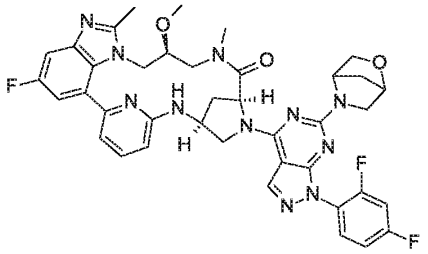
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(dimethylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **560** was prepared in analogy to the preparation of Example **483** by using N-methylmethanamine instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **560**, LCMS (M+H$^+$): 712. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.20 (s, 1H), 7.84 - 7.77 (m, 1H), 7.67 - 7.60 (m, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.21 (ddd, *J* = 2.8, 8.8, 10.3 Hz, 1H), 7.17 - 7.10 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.68 (m, 1H), 5.44 - 5.25 (m, 1H), 4.66 - 4.61 (m, 1H), 4.49 - 4.39 (m, 1H), 4.28 - 4.10 (m, 2H), 3.97 - 3.86 (m, 1H), 3.19 - 3.10 (m, 3H), 3.04 (s, 6H), 2.94 - 2.87 (m, 1H), 2.86 - 2.82 (m, 3H), 2.76 (d, *J* = 13.6 Hz, 1H), 2.59 - 2.55 (m, 3H), 2.53 - 2.42 (m, 2H).

Example 561

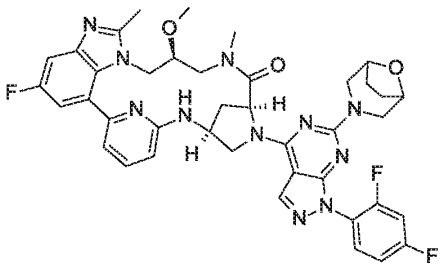
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **561** was prepared in analogy to the preparation of Example **483** by using 2-oxa-5-azabicyclo[2.2.1]heptane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **561**, LCMS (M+H$^+$): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.26 - 8.21 (m, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.11 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.88 - 5.67 (m, 1H), 5.44 - 5.26 (m, 1H), 4.67 - 4.62 (m, 1H), 4.62 - 4.51 (m, 2H), 4.44 (td, *J* = 5.5, 10.9 Hz, 1H), 4.25 - 4.11 (m, 2H), 3.93 (dd, *J* = 9.1, 14.2 Hz, 1H), 3.88 - 3.75 (m, 2H), 3.47 (br d, *J* = 11.1 Hz, 1H), 3.42 - 3.34 (m, 1H), 3.11 - 3.03 (m, 3H), 2.98 - 2.90 (m, 1H), 2.86 - 2.82 (m, 3H), 2.76 (br d, *J* = 13.4 Hz, 1H), 2.59 - 2.54 (m, 3H), 2.53 - 2.42 (m, 2H), 1.97 - 1.84 (m, 2H).

Example 562

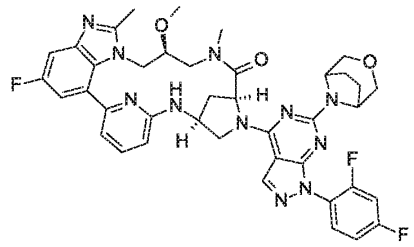
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **562** was prepared in analogy to the preparation of Example **483** by using 8-oxa-3-azabicyclo[3.2.1]octane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **562**, LCMS (M+H$^+$): 780. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.23 - 8.18 (m, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.30 (dd, J = 2.6, 8.5 Hz, 1H), 7.21 (ddd, J = 2.7, 8.8, 10.3 Hz, 1H), 7.17 - 7.10 (m, 2H), 7.08 (dd, J = 3.0, 7.5 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.89 - 5.66 (m, 1H), 5.41 - 5.25 (m, 1H), 4.66 - 4.61 (m, 1H), 4.48 - 4.41 (m, 1H), 4.40 - 4.32 (m, 2H), 4.26 - 4.08 (m, 4H), 3.97 - 3.82 (m, 1H), 3.12 - 3.04 (m, 4H), 3.04 - 2.98 (m, 1H), 2.97 - 2.89 (m, 1H), 2.87 - 2.81 (m, 3H), 2.77 (br d, J = 13.4 Hz, 1H), 2.59 - 2.54 (m, 3H), 2.54 - 2.41 (m, 2H), 1.92 - 1.83 (m, 2H), 1.83 - 1.71 (m, 2H).

Example 563

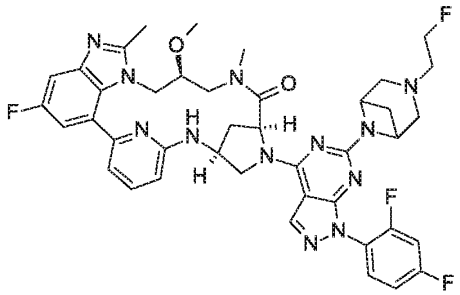
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



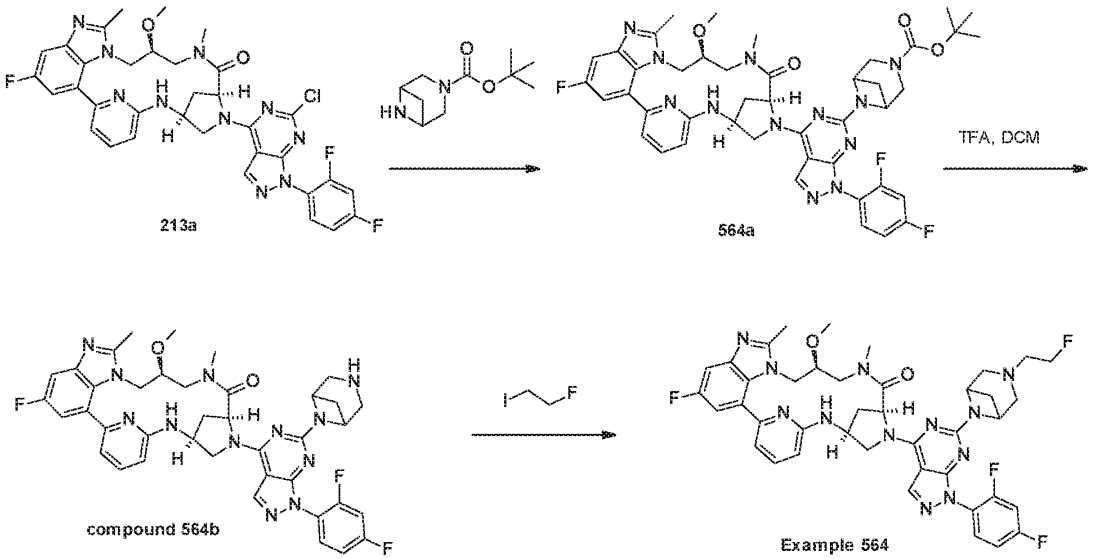
Example **563** was prepared in analogy to the preparation of Example **483** by using 3-oxa-8-azabicyclo[3.2.1]octane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. Example **563**, LCMS (M+H$^+$): 780. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.23 (s, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.31 (dd, J = 2.6, 8.4 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.18 - 7.11 (m, 2H), 7.10 - 7.06 (m, 1H), 6.67 (br d, J = 8.4 Hz, 1H), 5.88 - 5.67 (m, 1H), 5.41 - 5.26 (m, 1H), 4.69 - 4.61 (m, 1H), 4.60 - 4.39 (m, 3H), 4.25 - 4.10 (m, 2H), 3.88 - 3.69 (m, 3H), 3.64 - 3.47 (m, 2H), 3.12 - 2.99 (m, 3H), 2.98 - 2.88 (m, 1H), 2.87 - 2.81 (m, 3H), 2.75 (br d, J = 13.4 Hz, 1H), 2.61 - 2.54 (m, 3H), 2.54 - 2.42 (m, 2H), 2.06 - 1.88 (m, 4H).

Example 564

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **564** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (compound 564a)

To a tube was added compound **213a** (200 mg, 284.45 μmol), *tert*-butyl (3*R*,5*S*)-3,5-dimethylpiperazine-1-carboxylate (160.0 mg, 807 μmol), DIEA (110.3 mg, 149 μL, 853 μmol) and dimethyl sulfoxide (3 mL). The mixture was heated to 100 °C and stirred for 16 hrs. The mixture was concentrated to give a solid, then it was purified via flash column (EA/PE=0~

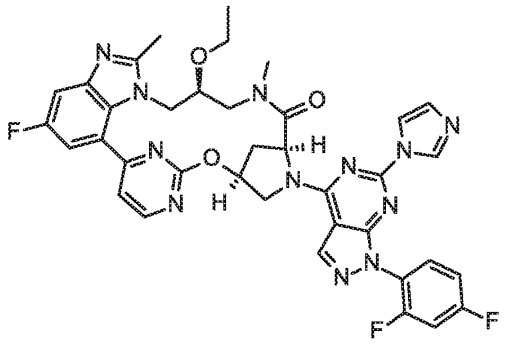
100%), the elution was concentrated to give compound **564a** (213 mg) as white solid. LCMS ($M+H^+$): 865.

Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 564)

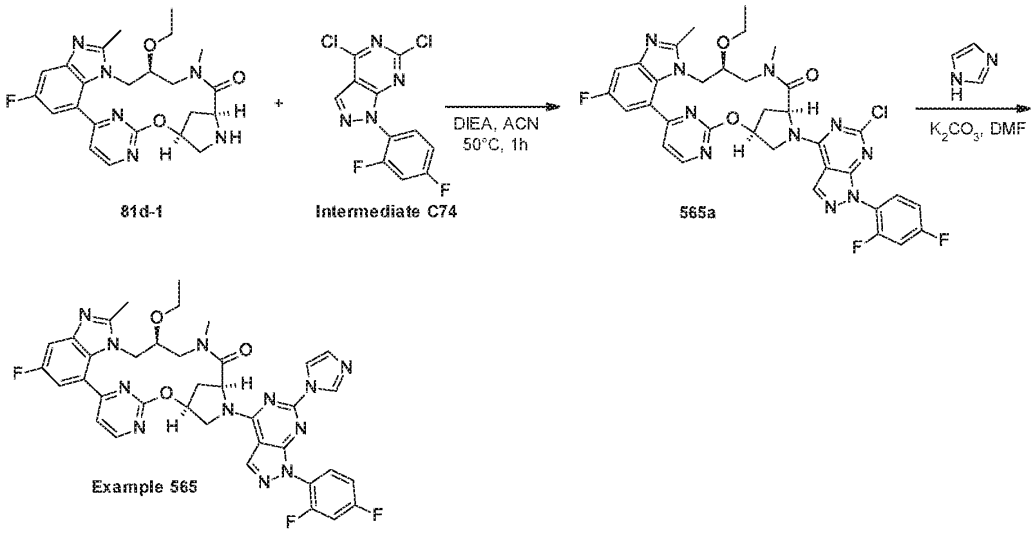
To the flask containing compound **564a** (213 mg, 246 μmol, 1.0 eq) was added dichloromethane (2 mL) and TFA (1.48 g, 12.98 mmol). The solution was stirred at r.t. for 1 hr. The mixture was concentrated to give an oil, which was obtained as a powder after freeze-drying. The powder (compound **564b**, 30 mg, 34.14 μmol) was added into a tube, then K_2CO_3 (18.9 mg, 136 μmol), 1-fluoro-2-iodo-ethane (35.6 mg, 205 μmol) and acetonitrile (500 μL) were added. The suspension was stirred at r.t. for 16 hrs. The mixture was filtered, the filtrate was purified via prep-HPLC, the elution was freezing dried to give Example **564** (6.7 mg), LCMS ($M+H^+$): 811. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.10 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.84 (dd, *J* = 4.4, 15.6 Hz, 1H), 5.32 (d, *J* = 8.9 Hz, 1H), 4.62 - 4.51 (m, 2H), 4.50 - 4.32 (m, 3H), 4.27 - 4.10 (m, 4H), 3.97 - 3.88 (m, 1H), 3.35 - 3.32 (m, 1H), 3.26 (br d, *J* = 10.4 Hz, 1H), 3.11 - 2.99 (m, 3H), 2.91 - 2.85 (m, 2H), 2.84 - 2.81 (m, 3H), 2.79 - 2.64 (m, 3H), 2.55 (s, 3H), 2.52 - 2.40 (m, 3H), 1.84 (d, *J* = 8.0 Hz, 1H).

Example 565

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-imidazol-1-yl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 565a)

A mixture of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **81d-1**, 110 mg, 0.19 mmol), 4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidine (Intermediate **C79**, 58.2 mg, 0.19 mmol) and DIEA (125.0 mg, 0.97 mmol) in anhydrous acetonitrile (2.6 mL) was stirred at 50 °C for 1 hr. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo* to give some residue. The residue was purified by flash chromatography to afford compound **565a** (108 mg) as a light yellow solid. LCMS (M+H)$^+$: 719.

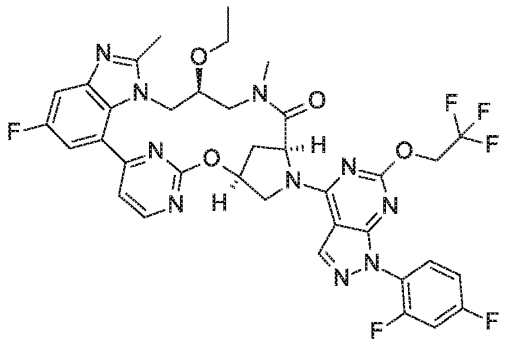
Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-imidazol-1-yl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-on (Example 565)

A mixture of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **565a**, 15.0 mg, 0.02 mmol), imidazole (1.4 mg, 0.02 mmol) and potassium carbonate (2.9 mg, 0.02 mmol) in DMF (0.5 mL) was stirred at 60 °C for 12 hrs. After being cooled to

room temperature, the reaction mixture was directly purified by prep-HPLC to give Example **565** (2.1 mg) as a white powder. LCMS $(M+H)^+$: 751. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.91 - 8.84 (m, 3H), 7.95 - 7.94 (m, 1H), 7.74 - 7.68 (m, 3H), 7.67 - 7.66 (m, 2H), 7.46 - 7.20 (m, 2H), 5.92 - 5.88 (m, 2H), 5.74 - 5.70 (m, 1H), 4.64 - 4.36 (m, 2H), 4.25 - 4.06 (m, 1H), 4.02 - 3.99 (m, 1H), 3.16 - 3.02 (m, 4H), 3.00 - 2.78 (m, 3H), 2.76 - 2.52 (m, 5H), 0.60 - 0.56 (m, 3H).

Example 566

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoroethoxy)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

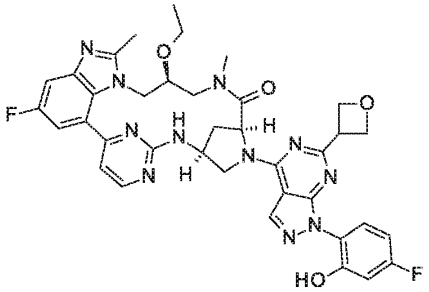


A mixture of 2,2,2-trifluoroethanol (0.01 mL, 0.1 mmol) and NaH (10.0 mg, 0.25 mmol) in anhydrous DMF (1 mL) was stirred at 0 °C for 1 hr, then (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound **565a**, 30.0 mg, 0.04 mmol) was added into the mixture. The resulting mixture was stirred at room temperature for 4 hrs. The reaction mixture was adjusted with 1 M aq. HCl to pH = 7, then directly purified by reversed flash chromatography to afford Example **566** (9.0 mg) as a white solid. LCMS $(M+H)^+$: 783. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.78 (d, *J* = 5.0 Hz, 1H), 8.48 - 7.74 (m, 1H), 7.70 - 7.59 (m, 2H), 7.50 - 7.38 (m, 2H), 7.32 - 7.14 (m, 2H), 5.88 - 5.65 (m, 2H), 5.57 - 5.39 (m, 1H), 4.97 - 4.68 (m, 1H), 4.62 - 4.24 (m, 3H), 4.24 - 4.11 (m, 1H), 4.08 - 3.95 (m, 1H), 3.16 - 2.86 (m, 5H), 2.85 - 2.48 (m, 7H), 0.62 - 0.49 (m, 3H).

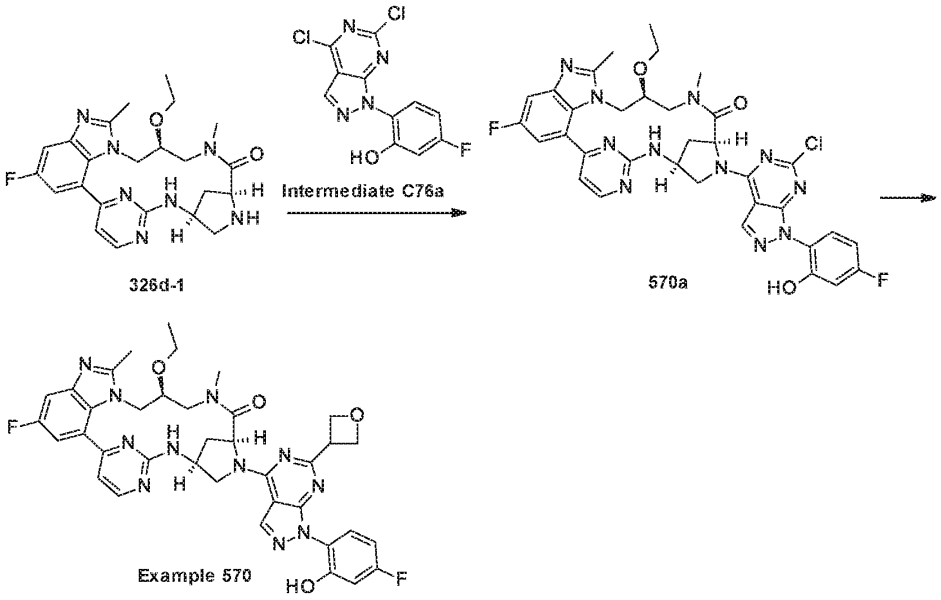
Example 570

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-

heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 570a)

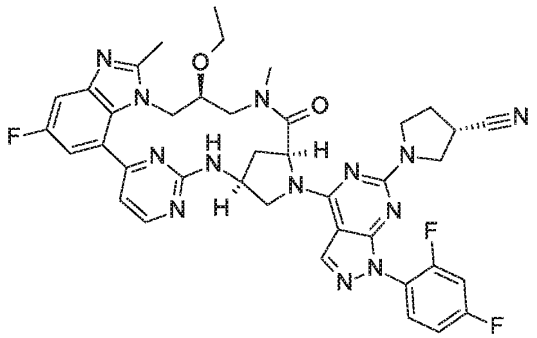
Compound **570a** was prepared in analogy to the preparation of compound **639a** by using compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 716.

Step 2: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 570)

Example **570** was prepared in analogy to the preparation of Example **432** by using 3-iodooxetane instead of 3-iodotetrahydrofuran and compound **570a** instead of compound **213a**. LCMS ($M+H^+$): 738. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.54 - 8.42 (m, 1H), 8.39 - 7.59 (m, 1H), 7.51 - 7.41 (m, 1H), 7.33 - 7.22 (m, 1H), 7.22 - 7.14 (m, 1H), 7.07 - 6.87 (m, 1H), 6.75 - 6.59 (m, 2H), 5.59 - 5.20 (m, 2H), 5.01 - 4.79 (m, 4H), 4.70 - 4.59 (m, 1H), 4.50 - 3.99 (m, 5H), 3.92 - 3.76 (m, 1H), 3.06 - 2.72 (m, 5H), 2.60 - 2.37 (m, 6H), 0.54 - 0.39 (m, 3H).

Example 571

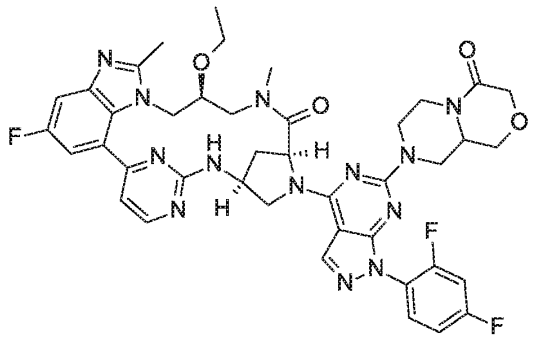
(3*S*)-1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidine-3-carbonitrile



Example **571** was prepared in analogy to the preparation of Example **213** by using compound **326d-1** instead of compound **213a** and (3*S*)-pyrrolidine-3-carbonitrile instead of morpholine. LCMS ($M+H^+$): 778. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.75 - 8.59 (m, 1H), 8.31 - 8.17 (m, 1H), 7.79 - 7.61 (m, 3H), 7.29 - 7.11 (m, 3H), 6.08 - 5.78 (m, 1H), 5.47 - 5.22 (m, 1H), 4.80 - 4.56 (m, 1H), 4.44 - 4.18 (m, 3H), 4.05 - 3.95 (m, 1H), 3.92 - 3.64 (m, 3H), 3.58 - 3.37 (m, 3H), 3.18 - 3.07 (m, 3H), 3.05 - 2.91 (m, 2H), 2.90 - 2.71 (m, 5H), 2.68 - 2.47 (m, 1H), 2.42 - 2.19 (m, 2H), 0.75 - 0.58 (m, 3H).

Example 572

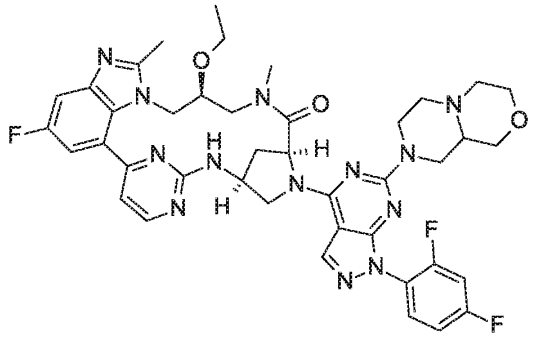
8-[1-(2,4-difluorophenyl)-4-[(8S,11S,15R)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6,7,9,9a-tetrahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-4-one



Example **572** was prepared in analogy to the preparation of Example **213** by using compound **326d-1** instead of compound **213a** and 1,6,7,8,9,9*a*-hexahydropyrazino[2,1-c][1,4]oxazin-4-one instead of morpholine. LCMS ($M+H^+$): 838. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.46 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.66 - 7.41 (m, 1H), 7.35 - 7.25 (m, 1H), 7.24 - 7.10 (m, 2H), 7.09 - 6.96 (m, 2H), 5.65 - 5.36 (m, 1H), 5.36 - 5.11 (m, 1H), 4.70 - 4.61 (m, 1H), 4.59 - 4.24 (m, 3H), 4.20 - 3.76 (m, 6H), 3.62 - 3.28 (m, 4H), 3.07 - 2.61 (m, 8H), 2.60 - 2.33 (m, 6H), 0.57 - 0.38 (m, 3H).

Example 573

(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

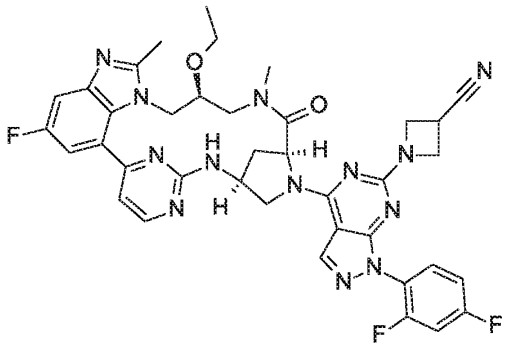


Example **573** was prepared in analogy to the preparation of Example **213** by using compound **326d-1** instead of compound **213a** and 1,3,4,6,7,8,9,9*a*-octahydropyrazino[2,1-c][1,4]oxazine instead of morpholine. LCMS ($M+H^+$): 824. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.53 - 8.42 (m, 1H), 8.18 - 8.08 (m, 1H), 7.56 - 7.47 (m, 1H), 7.36 - 7.27 (m, 1H), 7.21 - 6.96 (m, 4H), 5.65 - 5.36 (m, 1H), 5.32 - 5.14 (m, 1H), 4.69 - 4.62 (m, 1H), 4.54 - 4.41 (m, 2H), 4.35 - 4.02 (m, 4H), 3.93 - 3.77 (m, 1H), 3.76 - 3.50 (m, 3H), 3.04 - 2.75 (m, 6H), 2.72 - 2.34 (m,

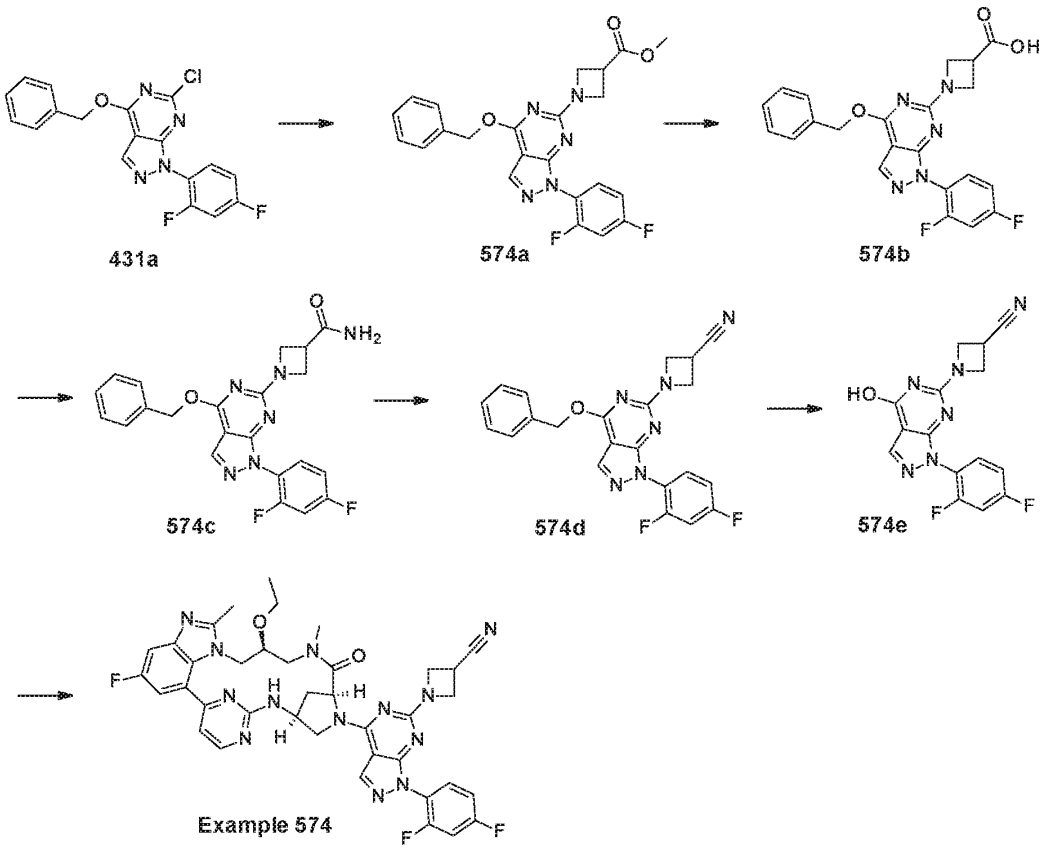
10H), 2.32 - 2.02 (m, 3H), 0.56 - 0.42 (m, 3H).

Example 574

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of methyl 1-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carboxylate (compound 574a)

A mixture of compound **431a** (400 mg, 1.1 mmol), azetidine-3-carboxylic acid methyl ester hydrochloride (488.0 mg, 3.2 mmol) and DIPEA (1.39 g, 10.7 mmol) in acetonitrile (50 mL) was stirred at 90 °C for 16 hours. Then the reaction solution was concentrated and the residue was dissolved in EA, washed with water and brine, the organic layer was dried and concentrated to give compound **574a** (500 mg), LCMS ($M+H^+$): 452.

Step 2: preparation of 1-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carboxylic acid (compound 574b)

A mixture of compound **574a** (400 mg, 0.88 mmol) and lithium hydroxide (2.22 mL, 2 M) in methanol (8 mL) was stirred at rt for 4 hours, then the pH was adjusted to 6, and the mixture was diluted with water. The resulting mixture was extracted with EA for 2 times, and then the organic layer was dried and concentrated to give compound **574b** (380 mg), LCMS ($M+H^+$): 438.

Step 3: preparation of 1-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carboxamide (compound 574c)

A mixture of compound **574b** (380 mg, 0.61 mmol), ammonium chloride (325 mg, 6.08 mmol), DIPEA (786 mg, 6.08 mmol) and HATU (462 mg, 1.22 mmol) in tetrahydrofuran (10 mL) was stirred at 40 °C for 2 hours, then the reaction mixture was concentrated and the residue was purified by silica gel chromatography to give compound **574c** (300 mg). LCMS ($M+H^+$): 437.

Step 4: preparation of 1-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile (compound 574d)

To a mixture of compound **574c** (280 mg, 0.65 mmol) and pyridine (253 mg, 3.21 mmol) in DCM (28 mL) was added TFAA (404 mg, 1.92 mmol) dropwise at rt. After being stirred at rt for 10 mins, the reaction mixture was diluted with DCM, washed with water and brine, the organic layer was dried and concentrated to give compound **574d** (260 mg). LCMS ($M+H^+$): 419.

Step 5: preparation of 1-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile (compound 574e)

A mixture of compound **574d** (240.0 mg, 0.49 mmol) in DCM (10 mL) and TFA (2 mL), was stirred at rt for 20 hours, then the reaction was concentrated to give compound **574e** (120 mg). LCMS ($M+H^+$): 329.

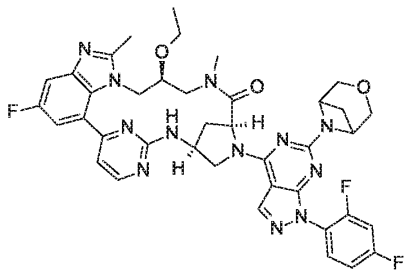
Step 6: preparation of 1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-

1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile (Example 574)

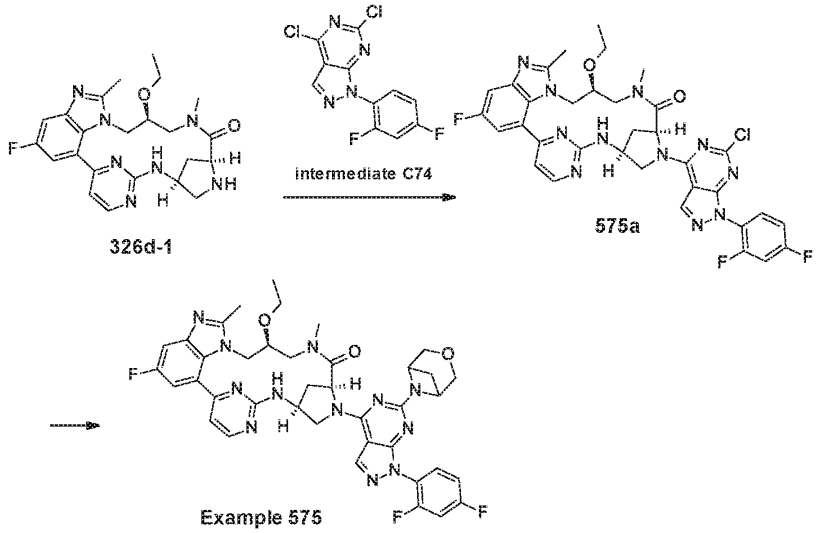
A mixture of compound **574e** (34.7 mg, 0.1 mmol), PyBOP (68.8 mg, 0.13 mmol) and DIPEA (57.0 mg, 0.44 mmol) in DMF (2 mL) was stirred at 50 °C for 3 hours. Then compound **326d-1** (40.0 mg, 0.09 mmol) was added and the reaction was stirred at 80 °C for 2 hours, the reaction mixture was directly purified by prep-HPLC to give Example **574** (20 mg). LCMS ($M+H^+$): 764. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.48 - 8.38 (m, 1H), 8.17 - 8.06 (m, 1H), 7.55 - 7.42 (m, 1H), 7.35 - 7.24 (m, 1H), 7.20 - 6.92 (m, 4H), 5.57 - 5.29 (m, 1H), 5.23 - 5.09 (m, 1H), 4.60 - 4.36 (m, 1H), 4.34 - 4.21 (m, 1H), 4.18 - 4.08 (m, 3H), 4.06 - 3.94 (m, 3H), 3.92 - 3.80 (m, 1H), 3.64 - 3.45 (m, 1H), 3.17 - 3.10 (m, 1H), 3.02 - 2.85 (m, 3H), 2.83 - 2.65 (m, 2H), 2.54 - 2.38 (m, 5H), 2.38 - 2.22 (m, 1H), 0.52 - 0.38 (m, 3H).

Example 575

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 575a)

Compound **575a** was prepared in analogy to the preparation of compound **213a** by using compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 718.

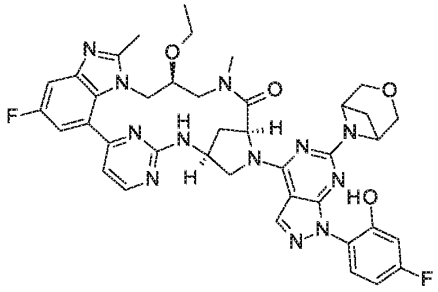
Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 575)

A mixture of compound **575a** (45 mg, 0.06 mmol), 3-oxa-6-azabicyclo[3.1.1]heptane; hydrochloride (34 mg, 0.25 mmol), CsF (29 mg, 0.19 mmol) and DIPEA (41 mg, 0.32 mmol) in dimethyl sulfoxide (2 mL) was stirred at 110 °C for 16 hours, then the reaction solution was directly purified by prep-HPLC to give Example **575** (25 mg). LCMS (M+H$^+$): 781. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.63 - 8.49 (m, 1H), 8.32 - 7.54 (m, 2H), 7.45 - 7.35 (m, 1H), 7.33 - 7.18 (m, 2H), 7.17 - 7.01 (m, 2H), 5.71 - 5.45 (m, 1H), 5.36 - 5.22 (m, 1H), 4.77 - 4.70 (m, 1H), 4.57 - 4.42 (m, 1H), 4.40 - 4.32 (m, 2H), 4.30 - 4.11 (m, 4H), 4.05 - 3.86 (m, 1H), 3.80 - 3.53 (m, 2H), 3.29 - 3.21 (m, 1H), 3.13 - 2.95 (m, 3H), 2.94 - 2.81 (m, 2H), 2.76 - 2.57 (m, 6H), 2.52 - 2.36 (m, 1H), 1.90 - 1.74 (m, 1H), 0.68 - 0.46 (m, 3H).

Example 576

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-

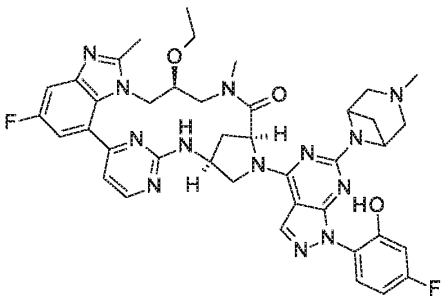
5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **576** was prepared in analogy to the preparation of Example **575** by using compound **570a** instead of compound **575a**. LCMS (M+H$^+$): 779. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.62 - 8.46 (m, 1H), 8.31 - 7.51 (m, 2H), 7.48 - 7.38 (m, 1H), 7.37 - 7.23 (m, 1H), 7.15 - 6.99 (m, 1H), 6.80 - 6.65 (m, 2H), 5.79 - 5.44 (m, 1H), 5.34 - 5.19 (m, 1H), 4.74 - 4.65 (m, 1H), 4.49 - 4.11 (m, 7H), 4.06 - 3.85 (m, 1H), 3.83 - 3.65 (m, 2H), 3.29 - 3.16 (m, 1H), 3.12 - 2.92 (m, 3H), 2.92 - 2.81 (m, 2H), 2.79 - 2.39 (m, 7H), 1.95 - 1.79 (m, 1H), 0.66 - 0.48 (m, 3H).

Example 577

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

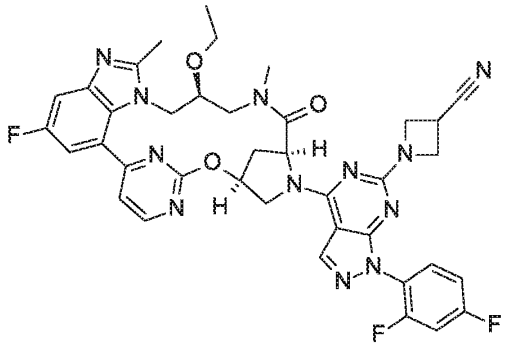


Example **577** was prepared in analogy to the preparation of Example **575** by using compound **570a** instead of compound **575a** and 3-methyl-3,6-diazabicyclo[3.1.1]heptane instead of 3-oxa-6-azabicyclo[3.1.1]heptane. LCMS (M+H$^+$): 792. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.62 - 8.53 (m, 1H), 8.29 - 7.55 (m, 2H), 7.45 - 7.35 (m, 1H), 7.32 - 7.22 (m, 1H), 7.16 - 7.03 (m, 1H), 6.83 - 6.63 (m, 2H), 5.72 - 5.46 (m, 1H), 5.38 - 5.24 (m, 1H), 4.79 - 4.69 (m, 1H),

4.48 - 4.09 (m, 5H), 4.04 - 3.88 (m, 1H), 3.26 - 3.17 (m, 2H), 3.13 - 2.84 (m, 7H), 2.70 - 2.43 (m, 8H), 2.42 - 2.31 (m, 3H), 2.01 - 1.89 (m, 1H), 0.67 - 0.50 (m, 3H).

Example 578

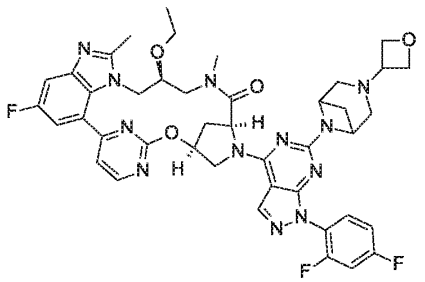
1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile



Example **578** was prepared in analogy to the preparation of Example **574** by using compound **81d-1** instead of compound **326d-1**. LCMS (M+H$^+$): 765. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.76 - 8.61 (m, 1H), 8.28 - 8.08 (m, 1H), 7.60 - 7.47 (m, 2H), 7.41 - 7.29 (m, 2H), 7.18 - 6.99 (m, 2H), 5.81 - 5.71 (m, 1H), 5.69 - 5.55 (m, 1H), 5.45 - 5.18 (m, 1H), 4.40 - 4.26 (m, 2H), 4.23 - 3.96 (m, 5H), 3.94 - 3.86 (m, 1H), 3.66 - 3.51 (m, 1H), 3.03 - 2.84 (m, 4H), 2.83 - 2.68 (m, 2H), 2.65 - 2.41 (m, 6H), 0.54 - 0.40 (m, 3H).

Example 579

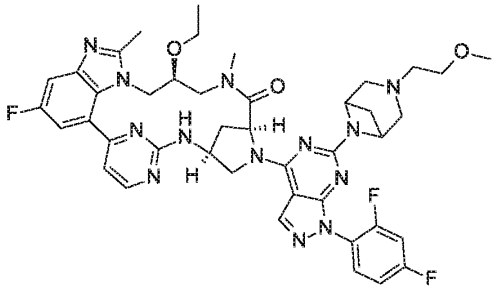
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



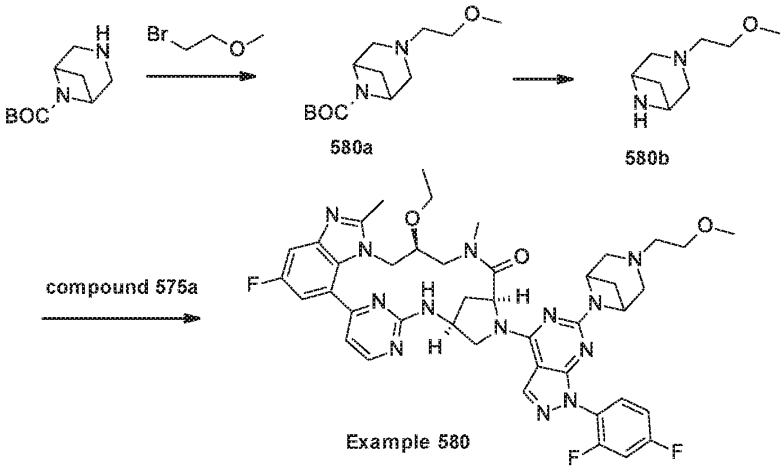
Example **579** was prepared in analogy to the preparation of Example **431** by using **Intermediate C89** instead of compound **431c** and compound **81d-1** instead of compound **370b**. LCMS ($M+H^+$): 837. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.71 - 8.59 (m, 1H), 8.20 - 8.10 (m, 1H), 7.59 - 7.46 (m, 2H), 7.38 - 7.26 (m, 2H), 7.19 - 6.98 (m, 2H), 5.84 - 5.63 (m, 2H), 5.40 - 5.16 (m, 1H), 4.61 - 4.45 (m, 4H), 4.37 - 4.26 (m, 2H), 4.22 - 4.03 (m, 3H), 3.95 - 3.80 (m, 1H), 3.80 - 3.62 (m, 1H), 3.32 - 3.25 (m, 1H), 3.18 - 3.09 (m, 2H), 2.97 - 2.82 (m, 3H), 2.78 - 2.66 (m, 4H), 2.63 - 2.37 (m, 7H), 1.79 - 1.68 (m, 1H), 0.53 - 0.40 (m, 3H).

Example 580

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 580a)

A mixture of 1-bromo-2-methoxy-ethane (701.0 mg, 5.0 mmol), *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (500 mg, 2.5 mmol) and K_2CO_3 (697 mg, 5.0 mmol) in acetonitrile (10 mL) was stirred at 60 °C for 6 hours, then the solid was filtered off, the filtrate was concentrated to give compound **580a** (600.0 mg), LCMS ($M+H^+$): 257.

Step 2: preparation of 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptane (compound 580b)

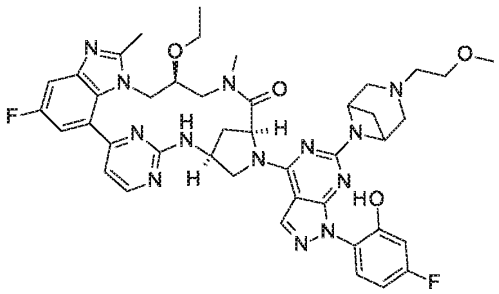
A mixture of compound **580a** (500 mg, 1.76 mmol) in TFA (2 mL) and DCM (2 mL) was stirred at rt for 30 mins, then the reaction was concentrated to give compound **580b** (300 mg), LCMS ($M+H^+$): 157.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 580)

A mixture of compound **575a** (30 mg, 0.04 mmol), compound **580b** (26 mg, 0.16 mmol), CsF (19 mg, 0.12 mmol) and DIPEA (27 mg, 0.2 mmol) in DMSO (2 mL) was stirred at 110 °C for 16 hours, then the reaction solution was directly purified by prep-HPLC to give Example **580** (8 mg). LCMS ($M+H^+$): 838. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.64 - 8.52 (m, 1H), 8.36 - 8.26 (m, 1H), 7.70 - 7.56 (m, 1H), 7.47 - 7.39 (m, 1H), 7.35 - 7.06 (m, 4H), 5.73 - 5.65 (m, 1H), 5.41 - 5.32 (m, 1H), 4.62 - 4.55 (m, 4H), 4.46 - 4.41 (m, 1H), 4.33 - 4.27 (m, 2H), 4.21 - 4.15 (m, 1H), 4.02 - 3.96 (m, 1H), 3.64 - 3.52 (m, 4H), 3.30 - 3.28 (m, 2H), 3.17 - 2.85 (m, 8H), 2.74 - 2.43 (m, 8H), 2.03 - 1.89 (m, 1H), 0.70 - 0.52 (m, 3H).

Example 581

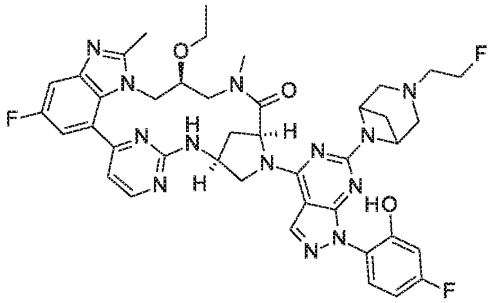
(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **581** was prepared in analogy to the preparation of Example **580** by using compound **570a** instead of compound **575a**. LCMS ($M+H^+$): 836. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.56 - 8.46 (m, 1H), 8.30 - 8.19 (m, 1H), 7.58 - 7.44 (m, 1H), 7.42 - 7.22 (m, 2H), 7.09 - 7.00 (m, 1H), 6.75 - 6.57 (m, 2H), 5.70 - 5.50 (m, 1H), 5.33 - 5.22 (m, 1H), 4.71 - 4.64 (m, 2H), 4.50 - 4.40 (m, 1H), 4.38 - 4.25 (m, 2H), 4.22 - 4.03 (m, 2H), 3.92 - 3.70 (m, 2H), 3.65 - 3.49 (m, 4H), 3.26 - 3.25 (m, 3H), 3.18 - 3.10 (m, 3H), 3.07 - 2.90 (m, 4H), 2.87 - 2.71 (m, 2H), 2.66 - 2.36 (m, 6H), 1.96 - 1.81 (m, 1H), 0.57 - 0.45 (m, 3H)

Example 582

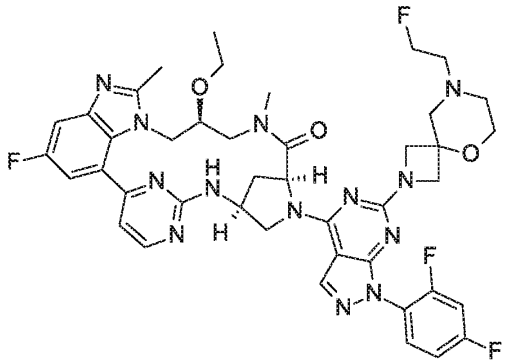
(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **581** was prepared in analogy to the preparation of Example **580** by using 1-fluoro-2-iodo-ethane instead of 1-bromo-2-methoxy-ethane and compound **570a** instead of compound **575a**. LCMS ($M+H^+$): 824. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.58 - 8.48 (m, 1H), 8.26 - 8.19 (m, 1H), 7.59 - 7.36 (m, 3H), 7.10 - 7.00 (m, 1H), 6.74 - 6.60 (m, 2H), 5.79 - 5.56 (m, 1H), 5.28 - 5.17 (m, 1H), 4.70 - 4.59 (m, 2H), 4.50 - 4.23 (m, 3H), 4.23 - 4.08 (m, 2H), 3.96 - 3.80 (m, 2H), 3.79 - 3.60 (m, 3H), 3.43 - 3.26 (m, 3H), 3.08 - 2.72 (m, 6H), 2.67 - 2.52 (m, 6H), 2.47 - 2.35 (m, 1H), 1.98 - 1.89 (m, 1H), 0.55 - 0.47 (m, 3H).

Example 583

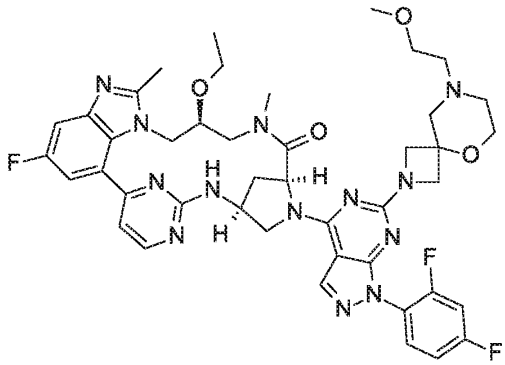
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-fluoroethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **583** was prepared in analogy to the preparation of Example **564** by using *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate instead of *tert*-butyl (3*R*,5*S*)-3,5-dimethylpiperazine-1-carboxylate and compound **575a** instead of compound **213a**. LCMS (M+H$^+$): 856. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 - 8.54 (m, 1H), 8.33 - 8.21 (m, 1H), 7.68 - 7.47 (m, 3H), 7.28 - 7.12 (m, 3H), 5.88 - 5.67 (m, 1H), 5.43 - 5.31 (m, 1H), 4.74 - 4.60 (m, 2H), 4.44 - 4.12 (m, 5H), 4.10 - 3.82 (m, 7H), 3.44 - 3.36 (m, 2H), 3.26 - 3.20 (m, 2H), 3.18 - 3.02 (m, 5H), 3.00 - 2.89 (m, 2H), 2.79 - 2.41 (m, 6H), 0.73 - 0.56 (m, 3H).

Example 584

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-methoxyethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

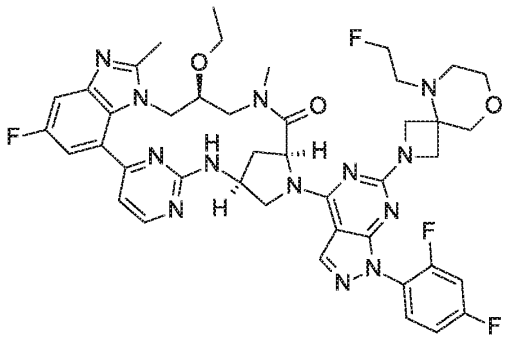


Example **584** was prepared in analogy to the preparation of Example **564** by using 8-oxa-2,5-diazaspiro[3.5]nonane-2-carboxylic acid tert-butyl ester instead of *tert*-butyl (3*R*,5*S*)-3,5-dimethylpiperazine-1-carboxylate, 1-bromo-2-methoxy-ethane instead of 1-fluoro-2-iodo-ethane and compound **575a** instead of compound **213a**. LCMS (M+H$^+$): 868. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.44 (m, 1H), 8.21 - 8.12 (m, 1H), 7.58 - 7.47 (m, 1H), 7.44 - 7.34

(m, 1H), 7.32 - 7.24 (m, 1H), 7.19 - 6.98 (m, 3H), 5.68 - 5.51 (m, 1H), 5.30 - 5.21 (m, 1H), 4.36 - 4.03 (m, 6H), 4.02 - 3.78 (m, 8H), 3.70 - 3.59 (m, 3H), 3.33 - 3.30 (m, 3H), 3.06 - 2.91 (m, 4H), 2.90 - 2.72 (m, 3H), 2.63 - 2.31 (m, 7H), 0.57 - 0.38 (m, 3H).

Example 585

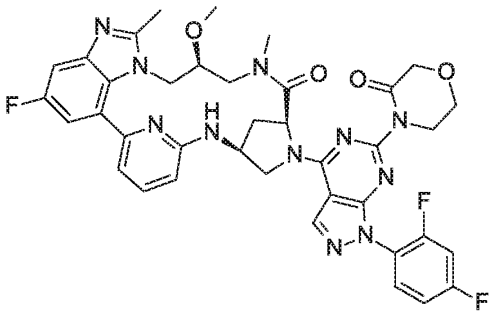
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[5-(2-fluoroethyl)-8-oxa-2,5-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



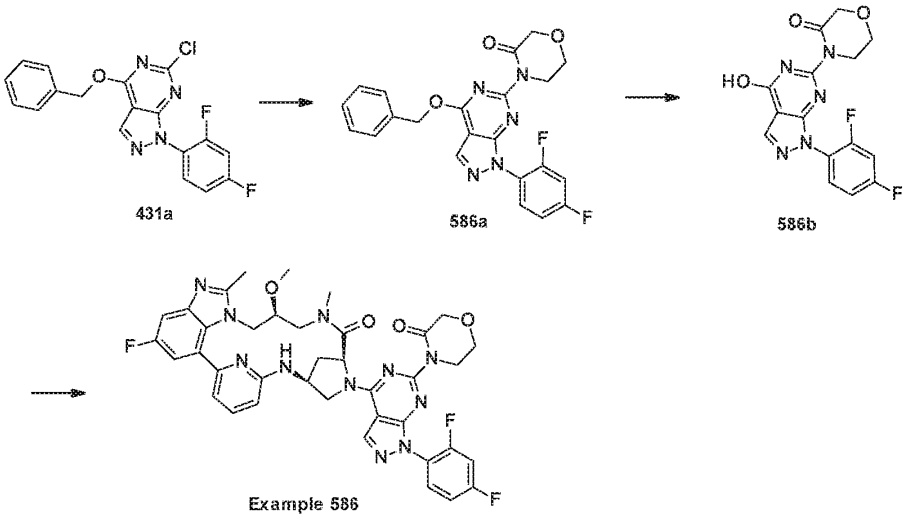
Example **585** was prepared in analogy to the preparation of Example **580** by using 1-fluoro-2-iodo-ethane instead of 1-bromo-2-methoxy-ethane and *tert*-butyl 8-oxa-2,5-diazaspiro[3.5]nonane-2-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate. LCMS (M+H$^+$): 856. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.65 (d, J = 5.1 Hz, 1H), 8.35 - 8.23 (m, 1H), 7.71 - 7.54 (m, 3H), 7.34 - 7.08 (m, 3H), 5.97 - 5.69 (m, 1H), 5.46 - 5.27 (m, 1H), 4.82 - 4.76 (m, 1H), 4.68 - 4.62 (m, 1H), 4.61 - 4.49 (m, 1H), 4.46 - 4.35 (m, 1H), 4.35 - 4.13 (m, 3H), 4.11 - 3.84 (m, 3H), 3.83 - 3.73 (m, 5H), 3.49 - 3.39 (m, 1H), 3.20 - 3.04 (m, 5H), 3.02 - 2.93 (m, 2H), 2.91 - 2.71 (m, 7H), 2.68 - 2.49 (m, 1H), 0.70 - 0.57 (m, 3H).

Example 586

4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one (compound 586a)

A mixture of compound **431a** (680 mg, 1.82 mmol), morpholin-3-one (368.0 mg, 3.64 mmol), K_3PO_4 (968 mg, 4.56 mmol,), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (211 mg, 0.36 mmol) and tris(dibenzylideneacetone) dipalladium (167.0 mg, 0.18 mmol) in 1,4-dioxane (8.00 mL) was stirred for 1 h at 110 °C under nitrogen atmosphere. The reaction mixture was poured into 100 mL of water/ice and extracted with ethyl acetate (100 mL×2). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography to afford compound **586a** (350 mg) as an off-white solid. LCMS ($M+H^+$): 438.

Step 2: preparation of 4-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one (compound 586b)

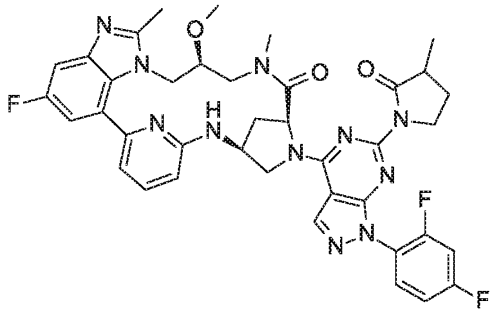
A mixture of compound **586a** (330 mg, 0.75 mmol) in dichloromethane (3.00 mL) and trifluoroacetic acid (3.00 mL) was stirred for 3 h at 25 °C. Then the reaction mixture was concentrated to give compound **586b** (250 mg). LCMS ($M+H^+$): 348.

Step 3: preparation of 4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one (Example 586)

A mixture of compound **586b** (35.0 mg, 0.100 mmol), *N,N*-diisopropylethylamine (47.0 μL, 0.27 mmol) and PyBOP (53.0 mg, 0.100 mmol, 1.49 eq) in DMF (2 mL) was stirred for 1 h at 25 °C. Then compound **370b** was added and the reaction mixture was stirred for 2 h at 50 °C. The reaction mixture was directly purified by prep-HPLC to give Example 586 (21 mg). LCMS ($M+H^+$): 768. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.55 - 7.84 (m, 1H), 7.78 - 7.72 (m, 2H), 7.64 - 7.60 (m, 1H), 7.38 - 7.33 (m, 2H), 7.14 - 7.07 (m, 2H), 6.67 - 6.61 (m, 1H), 5.84 - 5.61 (m, 2H), 5.55 - 5.35 (m, 1H), 4.65 - 4.30 (m, 2H), 4.28 - 3.60 (m, 9H), 3.05 - 2.80 (m, 4H), 2.77 - 2.61 (m, 4H), 2.47 - 2.30 (m, 5H).

Example 587

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

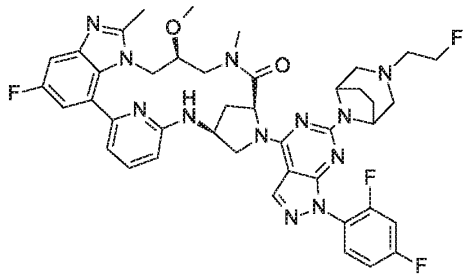


A mixture of compound **213a** (40.0 mg, 0.06 mmol), 3-methyl-2-pyrrolidinone (28.0 mg, 0.28 mmol), K_3PO_4 (36.0 mg, 0.17 mmol), tris(dibenzylideneacetone)dipalladium (0) (15.0 mg, 0.02 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (20.0 mg, 0.03 mmol) in 1,4-dioxane (2 mL) was stirred for 1 h at 110 °C under nitrogen atmosphere. Then the reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **587** (19.2 mg). LCMS ($M+H^+$): 766. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.47 (s, 1H), 7.80 - 7.75 (m, 2H), 7.62 - 7.55 (m, 1H), 7.38 - 7.31 (m, 2H), 7.14 - 7.07 (m, 2H), 6.67 - 6.61 (m, 1H), 5.80 - 5.61 (m,

2H), 5.45-5.37 (m, 1H), 4.66 - 3.58 (m, 7H), 3.05 - 2.56 (m, 9H), 2.47 - 2.43 (m, 4H), 2.41 - 2.13 (m, 2H), 1.68 - 1.52 (m, 1H), 1.14 - 1.09 (m, 3H).

Example 588

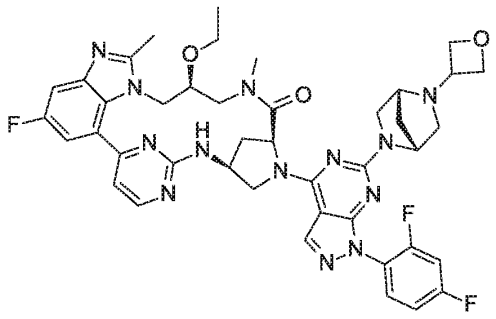
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **588** was prepared in analogy to the preparation of Example **564** by using *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS (M+H$^+$): 825. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.68 - 7.58 (m, 1H), 7.30 (dd, J = 2.6, 8.5 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.15 (br dd, J = 2.8, 10.8 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 6.73 - 6.66 (m, 1H), 5.89 - 5.69 (m, 1H), 5.41 - 5.28 (m, 1H), 4.67 - 4.45 (m, 6H), 4.25 - 4.19 (m, 1H), 4.19 - 4.10 (m, 1H), 3.97 - 3.82 (m, 1H), 3.14 - 3.11 (m, 1H), 3.05 (s, 3H), 2.99 - 2.93 (m, 1H), 2.91 (br d, J = 14.3 Hz, 1H), 2.86 - 2.84 (m, 3H), 2.77 (br d, J = 13.0 Hz, 2H), 2.71 - 2.60 (m, 2H), 2.56 (s, 3H), 2.53 - 2.45 (m, 2H), 2.05 - 1.88 (m, 4H), 1.36 - 1.25 (m, 1H).

Example 589

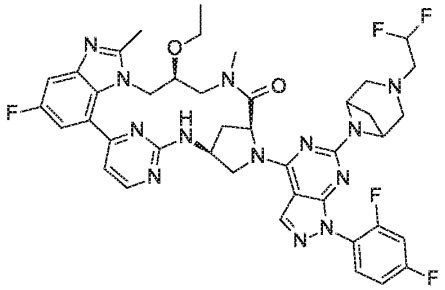
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **589** was prepared in analogy to the preparation of Example **431** by using **Intermediate C88** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 836. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (d, J = 5.1 Hz, 1H), 8.17 (s, 1H), 7.62 (br d, J = 6.1 Hz, 1H), 7.40 (d, J = 2.2, 8.3 Hz, 1H), 7.27 (dd, J = 2.0, 10.1 Hz, 1H), 7.24 - 7.17 (m, 1H), 7.13 (br d, J = 4.6 Hz, 1H), 7.08 (br d, J = 5.1 Hz, 1H), 5.71 - 5.43 (m, 1H), 5.38 - 5.17 (m, 1H), 4.75 - 4.61 (m, 4H), 4.53 - 4.48 (m, 1H), 4.47 - 4.41 (m, 1H), 4.27 (br dd, J = 5.8, 10.9 Hz, 1H), 4.21 - 4.08 (m, 2H), 4.04 - 3.95 (m, 1H), 3.93 - 3.83 (m, 1H), 3.65 - 3.54 (m, 1H), 3.52 - 3.40 (m, 2H), 3.29 - 3.23 (m, 1H), 3.11 - 2.98 (m, 3H), 2.93 - 2.80 (m, 3H), 2.80 - 2.74 (m, 1H), 2.64 - 2.54 (m, 5H), 2.45 (ddd, J = 4.3, 8.9, 13.3 Hz, 1H), 1.97 - 1.79 (m, 2H), 0.63 - 0.51 (m, 3H).

Example 590

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

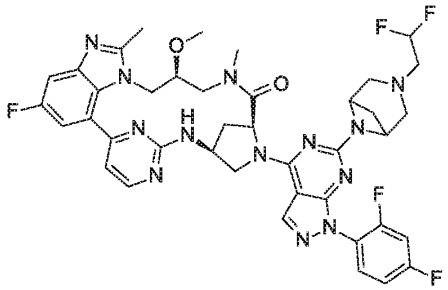


Example **590** was prepared in analogy to the preparation of Example **431** by using **Intermediate C81** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 844. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.56 (d, J = 5.1 Hz, 1H), 8.24 (s, 1H), 7.70 - 7.56 (m, 1H), 7.41 (dd, J = 2.3, 8.4 Hz, 1H), 7.32 - 7.20 (m, 2H), 7.18 - 7.06 (m, 2H), 5.66 (br dd, J = 3.8, 15.5 Hz, 1H), 5.31 (br d, J = 8.8 Hz, 1H), 4.99 (br d, J = 12.0 Hz, 2H), 4.69 (br s, 1H), 4.61 (s, 1H), 4.46 - 3.73 (m, 6H), 3.66 - 3.35 (m, 2H), 3.32 - 3.20 (m, 1H), 3.00 (s, 3H), 2.97 - 2.74 (m, 5H), 2.62 (br s, 1H), 2.59 (s, 3H), 2.57 - 2.38 (m, 2H), 1.71 (br d, J = 8.0 Hz, 1H), 0.59 (t, J = 6.9 Hz, 3H).

Example 591

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

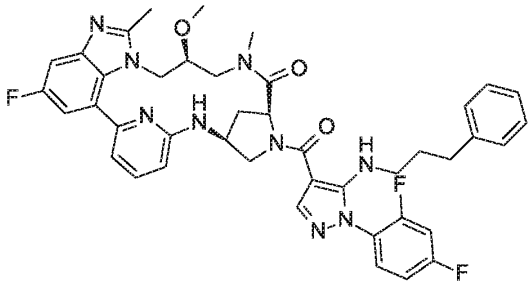
5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



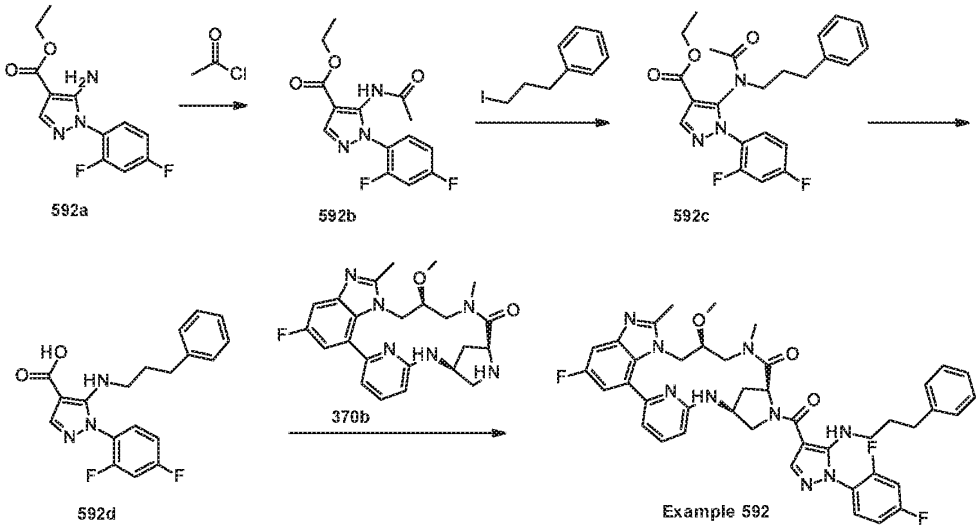
Example **591** was prepared in analogy to the preparation of Example **431** by using **Intermediate C81** instead of compound **431c** and compound **556b** instead of compound **370b**.. LCMS (M+H$^+$): 830. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, J = 5.3 Hz, 1H), 8.24 (s, 1H), 7.71 - 7.53 (m, 1H), 7.39 (dd, J = 2.5, 8.5 Hz, 1H), 7.31 - 7.18 (m, 2H), 7.17 - 7.04 (m, 2H), 5.66 (br dd, J = 4.1, 15.6 Hz, 1H), 5.31 (d, J = 8.9 Hz, 1H), 5.05 - 4.88 (m, 2H), 4.69 (br s, 1H), 4.59 (br s, 1H), 4.32 (br dd, J = 5.7, 11.2 Hz, 1H), 4.27 - 4.04 (m, 3H), 3.91 (br dd, J = 9.2, 14.1 Hz, 1H), 3.69 - 3.31 (m, 3H), 3.01 (s, 3H), 2.89 (br dd, J = 7.8, 12.9 Hz, 4H), 2.82 (s, 3H), 2.80 (br d, J = 3.9 Hz, 1H), 2.55 (s, 3H), 2.53 - 2.40 (m, 2H), 1.70 (d, J = 8.1 Hz, 1H).

Example 592

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(3-phenylpropylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 5-acetamido-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 592b)

To a mixture of compound **592a** (1.8 g, 6.7 mmol) in Chloroform (10 mL) were added acetyl chloride (0.62 mL, 8.8 mmol) under N_2. After being heated to 65 °C for 16 hrs, the reaction mixture was poured into water, extracted with DCM. The organic layer was dried and concentrated, the residue was purified by flash chromatography to give compound **592b** (1 g) as a yellow solid. LCMS ($M+H^+$): 310.

Step 2: preparation of ethyl 5-[acetyl(3-phenylpropyl)amino]-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (compound 592c)

To a solution of compound **592b** (200 mg, 0.65 mmol) in DMF (2 mL) was added sodium hydride (38.8 mg, 0.97 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 0.5 hrs and then 1-iodo-3-phenylpropane (239 mg, 0.97 mmol) was added dropwise. After being stirred at 25 °C for 2 hrs, the reaction mixture was poured into sat. NH_4Cl (10 mL), and then extracted with ethyl acetate. The organic phase was dried and concentrated, the residue was purified by flash chromatography to afford compound **592c** (90 mg) as a colorless oil. LCMS ($M+H^+$): 428.

Step 3: preparation of 1-(2,4-difluorophenyl)-5-(3-phenylpropylamino)pyrazole-4-carboxylic acid (compound 592d)

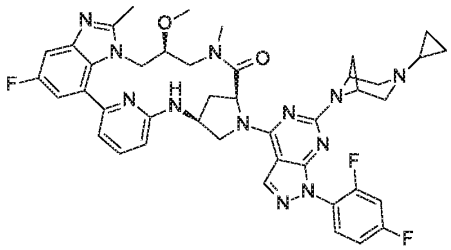
To a solution of compound **592c** (90 mg, 0.21 mmol) in ethanol (1 mL) was added KOH (120 mg, 1.07 mmol) at 25 °C and then stirred at 60 °C for 3 hrs. The pH was adjusted to about 6, then the reaction mixture was concentrated, the residue was purified by prep-TLC to give compound **592d** (35.0 mg) as colorless oil. LCMS ($M+H^+$): 358.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(3-phenylpropylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 592)

To a solution of compound **592d** (35.0 mg, 0.1 mmol) in DMF (1 mL) were added HATU (81.9 mg, 0.22 mmol), compound **370b** (43.0 mg, 0.1 mmol) and *N*,*N*-diisopropylethylamine (0.05 mL, 0.29 mmol) at rt, and then the mixture was stirred at rt for 1 h. The reaction mixture was directly purified by prep-HPLC to give **Example 592**(22.2 mg). LCMS (M+H$^+$): 778. ^{1}H NMR (400 MHz, METHANOL-d_4) δ= 8.05 (br s, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.59 - 7.44 (m, 1H), 7.36 - 7.26 (m, 1H), 7.25 - 7.12 (m, 5H), 7.10 - 7.02 (m, 4H), 6.62 (d, J = 8.3 Hz, 1H), 5.89 - 5.71 (m, 1H), 5.25 - 5.10 (m, 1H), 4.63 - 4.56 (m, 1H), 4.55 - 4.31 (m, 2H), 4.22 - 4.09 (m, 2H), 3.99 - 3.88 (m, 1H), 2.98 (s, 3H), 2.83 (s, 3H), 2.74 (br t, J = 6.8 Hz, 3H), 2.62 - 2.56 (m, 2H), 2.54 (s, 3H), 2.50 - 2.33 (m, 2H), 1.71 (br t, J = 7.0 Hz, 2H).

Example 593

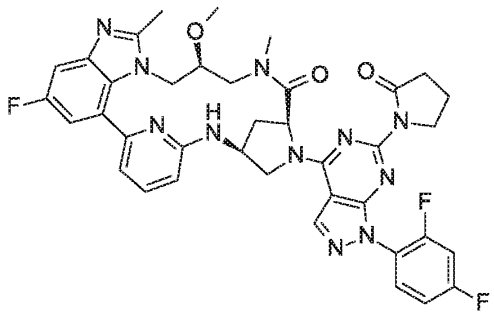
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*S*)-3-cyclopropyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **593** was prepared in analogy to the preparation of Example **431** by using **Intermediate C91** instead of compound **431c**. LCMS (M+H$^+$): 805. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.66 - 7.52 (m, 1H), 7.30 (dd, J = 2.3, 8.4 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.16 (br dd, J = 2.4, 10.4 Hz, 2H), 7.09 (d, J = 7.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.89 (br dd, J = 4.0, 15.1 Hz, 1H), 5.36 (d, J = 8.9 Hz, 1H), 4.59 (br d, J = 5.3 Hz, 1H), 4.41 (br dd, J = 6.1, 11.1 Hz, 1H), 4.25 - 4.06 (m, 4H), 3.94 (br dd, J = 9.2, 14.1 Hz, 1H), 3.49 - 3.33 (m, 2H), 3.01 (s, 3H), 2.91 (br d, J = 13.8 Hz, 1H), 2.85 (s, 4H), 2.78 - 2.70 (m, 2H), 2.68 - 2.58 (m, 1H), 2.55 (s, 3H), 2.53 - 2.39 (m, 3H), 1.66 (br d, J = 8.1 Hz, 1H), 0.52 - 0.04 (m, 4H).

Example 594

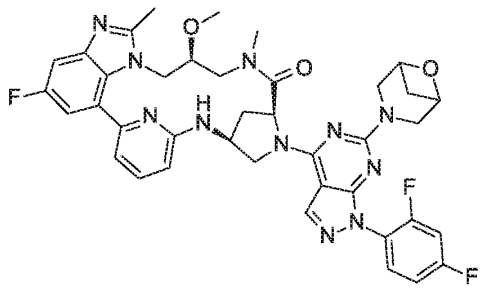
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **594** was prepared in analogy to the preparation of Example **586** by using 2-pyrrolidone instead of morpholin-3-one. LCMS (M+H$^+$): 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.48 - 7.80 (m, 3H), 7.62 - 7.55 (m, 1H), 7.40 - 7.28 (m, 2H), 7.16 - 7.07 (m, 2H), 6.71 - 6.60 (m, 1H), 5.79 - 5.68 (m, 1H), 5.63 - 5.51 (m, 1H), 5.45 - 5.36 (m, 1H), 4.67 - 3.90 (m, 5H), 3.89 - 3.65 (m, 2H), 3.04 - 2.68 (m, 7H), 2.60 - 2.52 (m, 1H), 2.49 - 2.39 (m, 6H), 2.38 - 2.28 (m, 1H), 2.07 - 1.86 (m, 2H).

Example 595

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

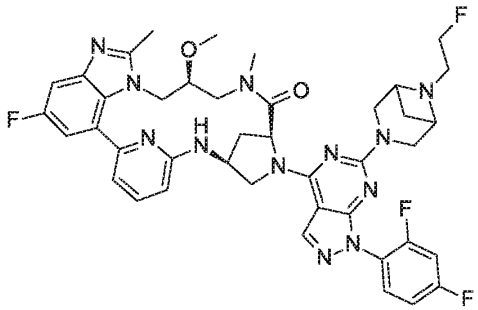


Example **595** was prepared in analogy to the preparation of Example **483** by using 6-oxa-3-azabicyclo[3.1.1]heptane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. LCMS (M+H$^+$): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.83 - 7.78 (m, 1H), 7.69 - 7.63 (m, 1H), 7.29 (dd, J = 2.5, 8.5 Hz, 1H), 7.24 - 7.19 (m, 1H), 7.14 (dd, J = 2.5, 10.5 Hz, 2H), 7.08 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.89 - 5.66 (m, 1H), 5.43 (d, J = 9.0 Hz, 1H), 4.66 (br

d, J = 6.4 Hz, 2H), 4.59 (s, 2H), 4.46 - 4.42 (m, 1H), 4.32 - 4.09 (m, 4H), 3.89 (br dd, J = 8.8, 13.6 Hz, 2H), 3.22 - 3.17 (m, 1H), 3.11 (s, 1H), 3.04 (s, 3H), 2.98 - 2.86 (m, 2H), 2.84 (s, 3H), 2.56 - 2.55 (m, 3H), 2.52 - 2.45 (m, 2H).

Example 596

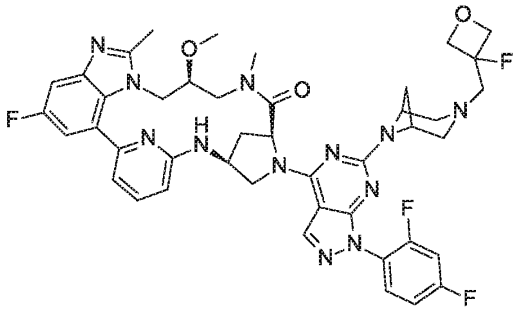
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **596** was prepared in analogy to the preparation of Example **431** by using **Intermediate C85** instead of compound **431c**. LCMS (M+H$^+$): 811. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.22 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.32 (dd, J = 2.4, 8.4 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.19 - 7.11 (m, 2H), 7.11 - 7.06 (m, 1H), 6.71 - 6.64 (m, 1H), 5.92 - 5.65 (m, 1H), 5.45 - 5.22 (m, 1H), 4.50 - 4.37 (m, 2H), 4.23 - 4.11 (m, 2H), 3.99 - 3.82 (m, 2H), 3.77 - 3.69 (m, 2H), 3.65 - 3.60 (m, 2H), 3.12 - 3.03 (m, 3H), 2.99 - 2.90 (m, 1H), 2.87 - 2.83 (m, 3H), 2.75 (br d, J = 13.5 Hz, 1H), 2.68 - 2.59 (m, 2H), 2.59 - 2.55 (m, 3H), 2.48 (dt, J = 4.5, 8.7 Hz, 2H), 2.05 (s, 1H), 1.65 - 1.54 (m, 1H), 1.18 - 1.18 (m, 1H), 1.20 (t, J = 7.1 Hz, 2H).

Example 597

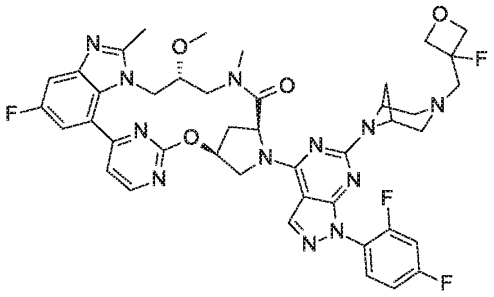
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **597** was prepared in analogy to the preparation of Example **431** by using **Intermediate C90** instead of compound **431c**. LCMS (M+H$^+$): 853. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 8.06 (s, 1H), 7.77 - 7.71 (m, 1H), 7.60 - 7.53 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 - 6.98 (m, 3H), 6.47 (d, *J* = 8.1 Hz, 1H), 6.16 - 5.98 (m, 1H), 5.29 (d, *J* = 9.0 Hz, 1H), 5.23 - 5.13 (m, 1H), 4.65 - 4.58 (m, 2H), 4.51 - 4.41 (m, 2H), 4.26 - 4.15 (m, 4H), 4.02 - 3.93 (m, 1H), 3.57 - 3.47 (m, 1H), 3.07 (s, 1H), 3.03 - 2.93 (m, 6H), 2.85 - 2.83 (m, 3H), 2.76 - 2.62 (m, 7H), 2.54 - 2.47 (m, 2H), 2.39 (br s, 2H).

Example 598

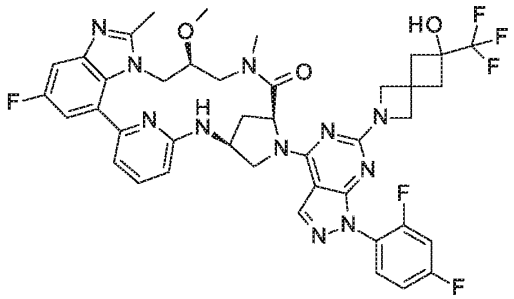
(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **598** was prepared in analogy to the preparation of Example **431** by using **Intermediate C90** instead of compound **431c** and compound **78d-2** instead of compound **370b**.. LCMS (M+H$^+$): 855. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.60 - 8.52 (m, 1H), 7.56 - 7.47 (m, 1H), 7.46 - 7.39 (m, 1H), 7.34 - 7.23 (m, 2H), 7.17 - 7.09 (m, 1H), 7.01 - 6.92 (m, 2H), 5.84 - 5.77 (m, 1H), 5.39 - 5.22 (m, 1H), 4.75 - 4.43 (m, 4H), 4.38 - 4.27 (m, 2H), 4.24 - 4.16 (m, 2H), 4.15 - 3.99 (m, 2H), 3.44 (s, 3H), 3.34 - 3.18 (m, 2H), 3.02 (s, 2H), 2.97 - 2.82 (m, 5H), 2.79 - 2.65 (m, 5H), 2.63 - 2.45 (m, 5H).

Example 599

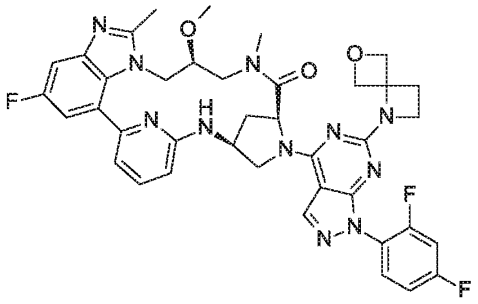
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-hydroxy-6-(trifluoromethyl)-2-azaspiro[3.3]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **599** was prepared in analogy to the preparation of Example **483** by using 6-(trifluoromethyl)-2-azaspiro[3.3]heptan-6-ol instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. LCMS (M+H$^+$): 848. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.24 (s, 1H), 7.86 - 7.76 (m, 1H), 7.65 - 7.56 (m, 1H), 7.31 (dd, J = 2.4, 8.6 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.18 - 7.05 (m, 3H), 6.67 (d, J = 8.4 Hz, 1H), 5.88 - 5.65 (m, 1H), 5.42 - 5.25 (m, 1H), 4.62 - 4.57 (m, 2H), 4.49 - 4.36 (m, 1H), 4.24 - 4.10 (m, 3H), 4.04 - 3.92 (m, 3H), 3.14 - 3.02 (m, 3H), 2.98 - 2.88 (m, 1H), 2.88 - 2.81 (m, 3H), 2.80 - 2.70 (m, 1H), 2.70 - 2.61 (m, 2H), 2.60 - 2.54 (m, 3H), 2.53 - 2.42 (m, 2H), 2.41 - 2.31 (m, 2H).

Example 600

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

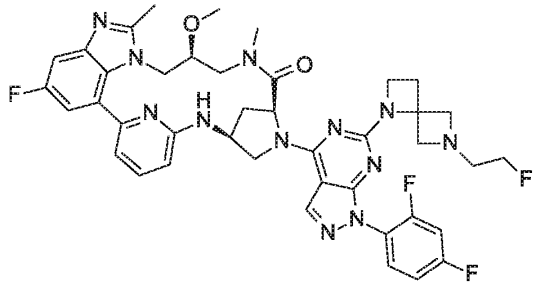


Example **600** was prepared in analogy to the preparation of Example **483** by using 6-oxa-1-azaspiro[3.3]heptane instead of 2λ^6-thia-6-azaspiro[3.3]heptane 2,2-dioxide. LCMS (M+H$^+$): 766. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.27 (s, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.61

(dt, J = 6.1, 8.7 Hz, 1H), 7.31 (dd, J = 2.6, 8.4 Hz, 1H), 7.25 - 7.15 (m, 2H), 7.09 (d, J = 7.6 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 5.80 (dd, J = 4.2, 15.5 Hz, 1H), 5.59 - 5.47 (m, 2H), 5.33 (d, J = 6.2 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 4.63 - 4.53 (m, 3H), 4.48 - 4.37 (m, 1H), 4.27 (d, J = 11.0 Hz, 1H), 4.15 (dd, J = 10.9, 15.4 Hz, 1H), 3.94 - 3.83 (m, 1H), 3.83 - 3.76 (m, 2H), 3.02 - 2.93 (m, 3H), 2.88 - 2.83 (m, 3H), 2.80 - 2.74 (m, 1H), 2.62 - 2.56 (m, 3H), 2.56 - 2.43 (m, 4H).

Example 601

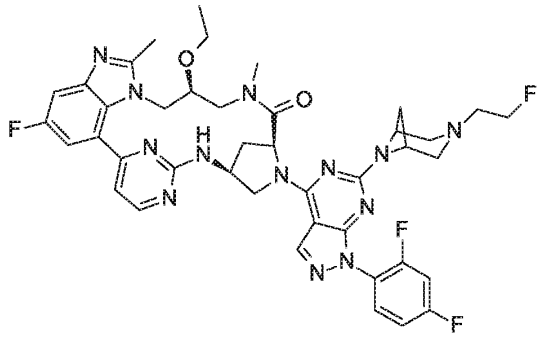
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-1,6-diazaspiro[3.3]heptan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **601** was prepared in analogy to the preparation of Example **564** by using *tert*-butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS (M+H$^+$): 811. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.27 (s, 1H), 7.88 - 7.79 (m, 1H), 7.71 - 7.61 (m, 1H), 7.33 (dd, J = 2.5, 8.5 Hz, 1H), 7.30 - 7.23 (m, 1H), 7.22 - 7.14 (m, 2H), 7.11 (d, J = 7.4 Hz, 1H), 6.69 (br d, J = 8.3 Hz, 1H), 5.87 - 5.70 (m, 1H), 5.47 - 5.28 (m, 1H), 4.66 - 4.57 (m, 2H), 4.51 - 4.40 (m, 2H), 4.33 - 4.24 (m, 2H), 4.23 - 4.15 (m, 2H), 4.15 - 4.06 (m, 1H), 4.05 - 3.91 (m, 2H), 3.90 - 3.72 (m, 2H), 3.59 - 3.47 (m, 2H), 3.10 - 2.94 (m, 3H), 2.92 - 2.82 (m, 4H), 2.70 - 2.61 (m, 2H), 2.61 - 2.56 (m, 4H), 2.56 - 2.49 (m, 2H).

Example 602

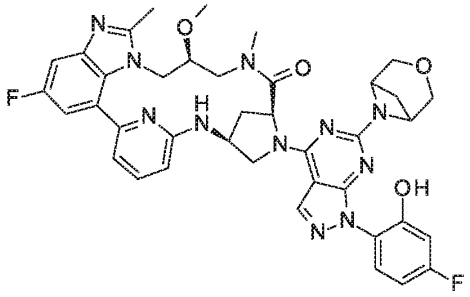
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



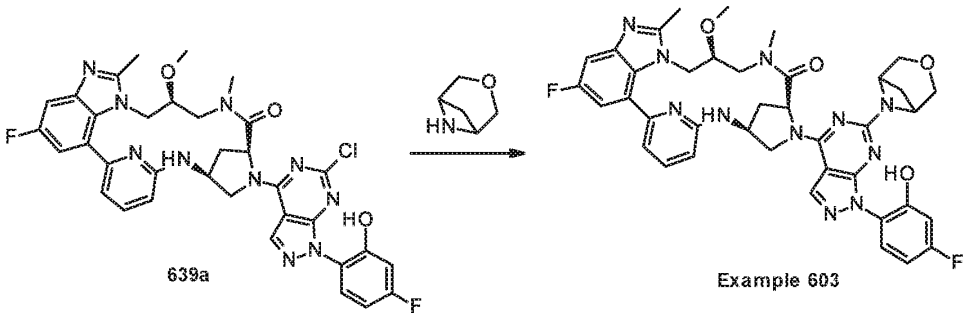
Example **602** was prepared in analogy to the preparation of Example **431** by using **Intermediate C80** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS ($M+H^+$): 826. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 (d, J = 5.3 Hz, 1H), 8.28 (s, 1H), 7.71 - 7.55 (m, 1H), 7.41 (dd, J = 2.5, 8.5 Hz, 1H), 7.30 (dd, J = 2.5, 10.3 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.20 - 7.14 (m, 1H), 7.12 (d, J = 5.1 Hz, 1H), 5.69 (dd, J = 4.1, 15.4 Hz, 1H), 5.34 (d, J = 8.8 Hz, 1H), 4.86 - 4.82 (m, 1H), 4.80 - 4.71 (m, 1H), 4.65 - 4.36 (m, 4H), 4.31 - 4.13 (m, 4H), 4.06 - 3.94 (m, 1H), 3.36 (br s, 1H), 3.30 - 3.23 (m, 1H), 3.12 (s, 1H), 3.09 - 2.96 (m, 3H), 2.94 - 2.84 (m, 3H), 2.83 - 2.70 (m, 2H), 2.68 - 2.64 (m, 1H), 2.61 (s, 4H), 2.56 - 2.45 (m, 2H), 0.61 (t, J = 6.9 Hz, 3H).

Example 603

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



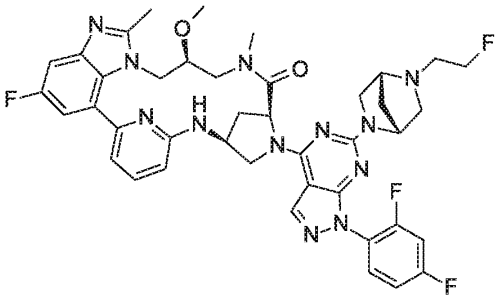
The title compound was prepared according to the following scheme:



To a solution of compound **639a** (40.0 mg, 0.06 mmol), 3-oxa-6-azabicyclo[3.1.1] heptane; hydrochloride (38.7 mg, 0.29 mmol) in ACN (1 mL) was added potassium carbonate (78.8 mg, 0.57 mmol) and then stirred at 95 °C for 16 hrs. The reaction mixture was poured into water (20 mL) and then extracted with EA (20 mL), the organic layer was dried and concentrated, the residue was purified by prep-HPLC to give Example **603** (25 mg). LCMS ($M+H^+$): 764. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.34 (s, 1H), 7.87 (t, J = 7.9 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.62 - 7.58 (m, 2H), 7.16 (d, J = 7.4 Hz, 1H), 6.80 - 6.73 (m, 3H), 6.21 (dd, J = 4.6, 15.4 Hz, 1H), 5.41 (d, J = 9.0 Hz, 1H), 4.72 - 4.64 (m, 1H), 4.56 - 4.18 (m, 8H), 4.01 - 3.52 (m, 4H), 3.17 - 2.99 (m, 4H), 2.98 (s, 3H), 2.85 (s, 3H), 2.75 (s, 1H), 2.69 - 2.46 (m, 2H).

Example 604

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

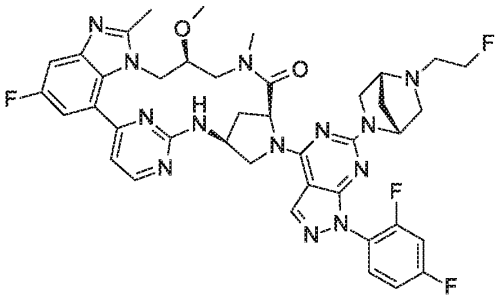


Example **604** was prepared in analogy to the preparation of Example **431** by using **Intermediate C83** instead of compound **431c**. LCMS ($M+H^+$): 811. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.14 (s, 1H), 7.77 (t, J = 7.9 Hz, 1H), 7.62 (dt, J = 5.9, 8.6 Hz, 1H), 7.29 (dd, J = 2.5, 8.5 Hz, 1H), 7.25 - 7.17 (m, 1H), 7.13 (br dd, J = 2.6, 10.6 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 5.81 (dd, J = 4.5, 15.5 Hz, 1H), 5.29 (br d, J = 7.8 Hz, 1H),

4.69 - 4.48 (m, 3H), 4.44 (br t, *J* = 4.8 Hz, 1H), 4.30 (br dd, *J* = 5.9, 11.1 Hz, 1H), 4.19 - 4.04 (m, 2H), 3.83 (br dd, *J* = 9.1, 14.1 Hz, 1H), 3.74 - 3.65 (m, 1H), 3.59 (br s, 1H), 3.00 (s, 4H), 2.96 - 2.85 (m, 3H), 2.82 (s, 4H), 2.71 - 2.59 (m, 2H), 2.53 (s, 3H), 2.48 - 2.35 (m, 2H), 1.96 - 1.76 (m, 2H).

Example 605

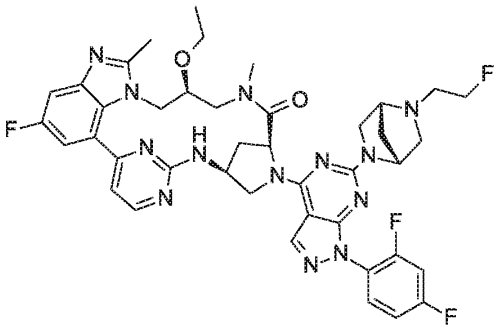
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **605** was prepared in analogy to the preparation of Example **431** by using **Intermediate C83** instead of compound **431c** and compound **556b** instead of compound **370b**. LCMS (M+H$^+$): 812. 1H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.62 (dt, *J* = 6.1, 8.6 Hz, 1H), 7.39 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.29 - 7.18 (m, 2H), 7.16 - 7.06 (m, 2H), 5.66 (dd, *J* = 4.1, 15.6 Hz, 1H), 5.34 (br d, *J* = 8.8 Hz, 1H), 4.70 (br t, *J* = 4.8 Hz, 1H), 4.58 (br dd, *J* = 5.3, 10.4 Hz, 2H), 4.44 (br d, *J* = 4.9 Hz, 1H), 4.35 - 4.26 (m, 1H), 4.23 - 4.08 (m, 2H), 3.88 (br dd, *J* = 9.1, 14.1 Hz, 1H), 3.74 - 3.67 (m, 1H), 3.65 - 3.62 (m, 1H), 3.28 (br s, 1H), 3.12 - 3.02 (m, 3H), 2.98 - 2.87 (m, 3H), 2.86 - 2.79 (m, 5H), 2.66 (br d, *J* = 9.8 Hz, 1H), 2.61 - 2.53 (m, 3H), 2.52 - 2.41 (m, 2H), 1.88 (br d, *J* = 14.1 Hz, 2H).

Example 606

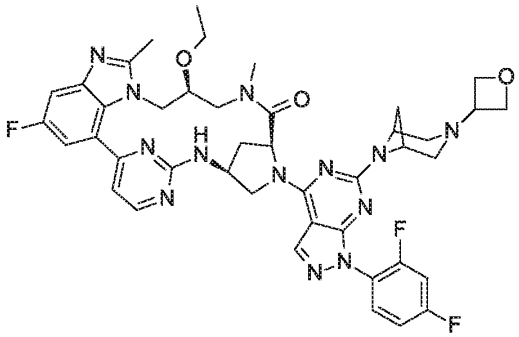
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **606** was prepared in analogy to the preparation of Example **431** by using **Intermediate C83** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 826. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.53 (d, J = 5.3 Hz, 1H), 8.14 (s, 1H), 7.62 (dt, J = 5.9, 8.6 Hz, 1H), 7.39 (dd, J = 2.4, 8.4 Hz, 1H), 7.26 (dd, J = 2.5, 10.3 Hz, 1H), 7.23 - 7.17 (m, 1H), 7.15 - 7.03 (m, 2H), 5.63 (dd, J = 4.1, 15.6 Hz, 1H), 5.35 - 5.13 (m, 1H), 4.66 (br s, 1H), 4.57 (br d, J = 4.9 Hz, 2H), 4.44 (s, 1H), 4.28 - 4.19 (m, 1H), 4.17 - 4.06 (m, 2H), 3.89 (br dd, J = 9.3, 14.0 Hz, 1H), 3.71 (br d, J = 11.0 Hz, 1H), 3.61 (d, J = 7.1 Hz, 1H), 3.30 - 3.16 (m, 2H), 3.09 - 2.98 (m, 3H), 2.96 - 2.77 (m, 5H), 2.60 (br s, 2H), 2.60 - 2.51 (m, 4H), 2.43 (ddd, J = 4.3, 8.9, 13.5 Hz, 1H), 1.98 - 1.81 (m, 2H), 0.64 - 0.47 (m, 3H).

Example 607

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

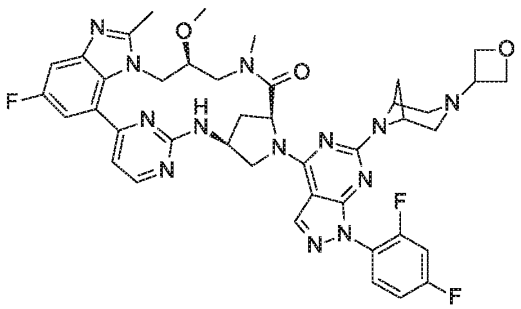


Example **607** was prepared in analogy to the preparation of Example **431** by using **Intermediate C89** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 836. ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ = 8.55 (d, J = 5.1 Hz, 1H), 8.15 (s, 1H), 7.66 (dt, J = 6.1, 8.6 Hz, 1H), 7.44 (dd, J = 2.4, 8.9 Hz, 1H), 7.29 - 7.12 (m, 3H), 7.09 (d, J = 5.3 Hz, 1H), 5.85 - 5.62 (m, 2H), 5.26 (d, J = 8.8 Hz, 1H), 4.73 (br d, J = 4.6 Hz,

1H), 4.62 - 4.44 (m, 4H), 4.35 (br dd, *J* = 5.9, 11.2 Hz, 1H), 4.25 - 4.05 (m, 4H), 3.91 (br dd, *J* = 9.0, 13.8 Hz, 1H), 3.74 (br d, *J* = 10.4 Hz, 1H), 3.30 (s, 1H), 3.22 (br d, *J* = 9.5 Hz, 2H), 2.95 (s, 3H), 2.85 - 2.69 (m, 4H), 2.61 (dt, *J* = 3.1, 6.8 Hz, 2H), 2.55 (s, 3H), 2.51 - 2.40 (m, 2H), 0.64 - 0.51 (m, 3H).

Example 608

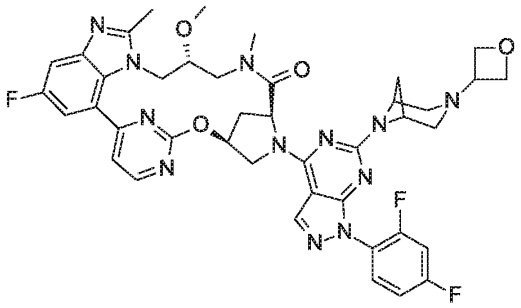
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **608** was prepared in analogy to the preparation of Example **431** by using **Intermediate C89** instead of compound **431c** and compound **556b** instead of compound **370b**. LCMS (M+H$^+$): 822. ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ = 8.55 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 7.73 - 7.58 (m, 1H), 7.44 (dd, *J* = 2.5, 8.9 Hz, 1H), 7.26 - 7.12 (m, 3H), 7.09 (d, *J* = 5.1 Hz, 1H), 5.85 - 5.62 (m, 2H), 5.26 (d, *J* = 8.6 Hz, 1H), 4.73 (br d, *J* = 4.6 Hz, 1H), 4.63 - 4.43 (m, 4H), 4.35 (br dd, *J* = 6.0, 11.1 Hz, 1H), 4.27 - 4.05 (m, 4H), 3.91 (br dd, *J* = 8.8, 14.2 Hz, 1H), 3.81 - 3.68 (m, 1H), 3.30 (s, 1H), 3.27 - 3.13 (m, 2H), 2.97 (s, 3H), 2.80 (s, 6H), 2.53 (s, 3H), 2.51 - 2.40 (m, 3H).

Example 609

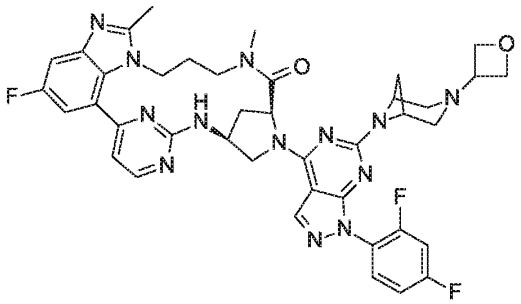
(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



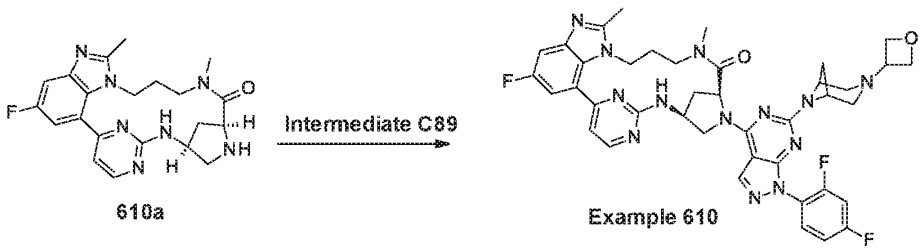
Example **609** was prepared in analogy to the preparation of Example **431** by using **Intermediate C89** instead of compound **431c** and compound **78d-2** instead of compound **370b**. LCMS ($M+H^+$): 823. ^1H NMR (400 MHz, ACETONITRILE-d_3) δ = 8.67 (d, J = 5.3 Hz, 1H), 8.17 (s, 1H), 7.71 - 7.60 (m, 1H), 7.51 - 7.37 (m, 2H), 7.29 - 7.10 (m, 3H), 5.85 - 5.58 (m, 2H), 5.38 (br d, J = 8.1 Hz, 1H), 4.65 - 4.31 (m, 6H), 4.30 - 3.92 (m, 5H), 3.85 - 3.60 (m, 1H), 3.49 - 3.36 (m, 1H), 3.35 - 3.18 (m, 2H), 2.94 (s, 4H), 2.80 (br s, 1H), 2.79 - 2.73 (m, 3H), 2.73 - 2.65 (m, 2H), 2.55 (br d, J = 8.8 Hz, 5H).

Example 610

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title was prepared according to the following scheme:

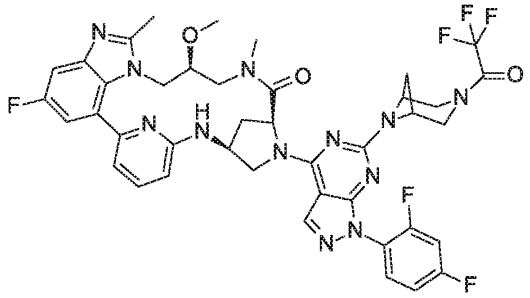


Example **610** was prepared in analogy to the preparation of Example **431** by using **Intermediate C89** instead of compound **431c** and compound **610a** (the synthesis refer to

compound **289d** by using intermediate **A14** instead of intermediate **A12**) instead of compound **370b**. LCMS (M+H$^+$): 792. ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ = 8.53 (d, J = 5.1 Hz, 1H), 8.14 (s, 1H), 7.64 (dd, J = 6.1, 8.6 Hz, 1H), 7.40 (dd, J = 2.5, 9.0 Hz, 1H), 7.24 - 7.05 (m, 3H), 6.94 (d, J = 5.0 Hz, 1H), 5.91 (br d, J = 8.1 Hz, 1H), 5.26 (br d, J = 5.5 Hz, 2H), 4.83 (br s, 1H), 4.50 (br d, J = 6.5 Hz, 5H), 4.24 - 4.11 (m, 3H), 4.06 - 3.88 (m, 2H), 3.70 (br t, J = 6.5 Hz, 1H), 3.30 (s, 1H), 3.17 (br d, J = 9.5 Hz, 2H), 2.94 (s, 3H), 2.86 - 2.68 (m, 3H), 2.54 (s, 3H), 2.50 - 2.44 (m, 2H), 1.78 (d, J = 7.9 Hz, 1H), 1.36 - 1.18 (m, 1H).

Example 611

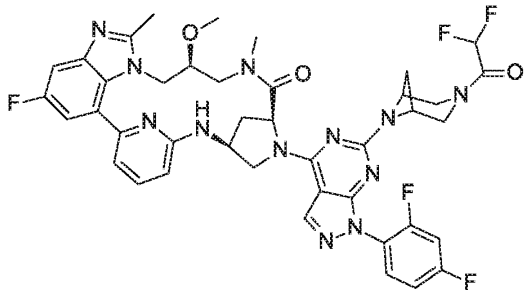
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **611** was prepared in analogy to the preparation of Example **431** by using **Intermediate C92** instead of compound **431c**. LCMS (M+H$^+$): 861. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.19 (d, J = 8.9 Hz, 1H), 7.77 (dt, J = 3.7, 7.9 Hz, 1H), 7.61 - 7.52 (m, 1H), 7.32 - 7.25 (m, 1H), 7.25 - 7.20 (m, 1H), 7.17 - 7.10 (m, 2H), 7.09 - 7.01 (m, 1H), 6.64 - 6.57 (m, 1H), 5.80 - 5.60 (m, 1H), 5.28 - 5.18 (m, 1H), 4.59 (br s, 1H), 4.54 - 4.39 (m, 2H), 4.35 - 4.25 (m, 3H), 4.24 - 4.04 (m, 3H), 3.92 - 3.64 (m, 2H), 3.60 - 3.43 (m, 1H), 3.09 - 2.96 (m, 3H), 2.94 - 2.85 (m, 1H), 2.84 - 2.79 (m, 3H), 2.78 - 2.64 (m, 2H), 2.64 - 2.51 (m, 3H), 2.50 - 2.32 (m, 2H).

Example 612

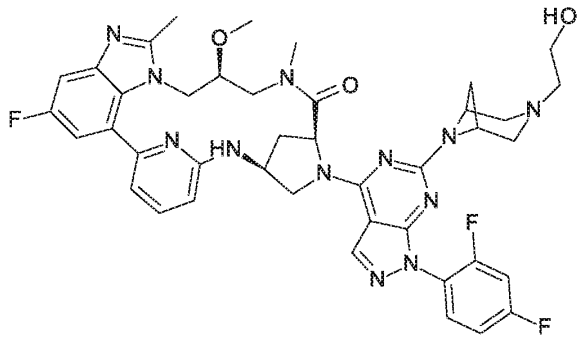
(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **612** was prepared in analogy to the preparation of Example **431** by using **Intermediate C93** instead of compound **431c**. LCMS ($M+H^+$): 843. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 - 8.20 (m, 1H), 7.80 - 7.73 (m, 1H), 7.61 - 7.53 (m, 1H), 7.29 - 7.16 (m, 2H), 7.15 - 7.00 (m, 3H), 6.65 - 6.58 (m, 1H), 5.80 - 5.61 (m, 1H), 5.32 - 5.22 (m, 1H), 4.54 (br s, 4H), 4.40 - 4.33 (m, 1H), 4.30 - 4.18 (m, 3H), 4.16 - 4.09 (m, 1H), 3.91 - 3.79 (m, 1H), 3.70 - 3.57 (m, 1H), 3.49 - 3.36 (m, 2H), 2.99 (s, 3H), 2.94 - 2.85 (m, 1H), 2.83 - 2.77 (m, 3H), 2.77 - 2.61 (m, 2H), 2.60 - 2.50 (m, 3H), 2.48 - 2.34 (m, 2H).

Example 613

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

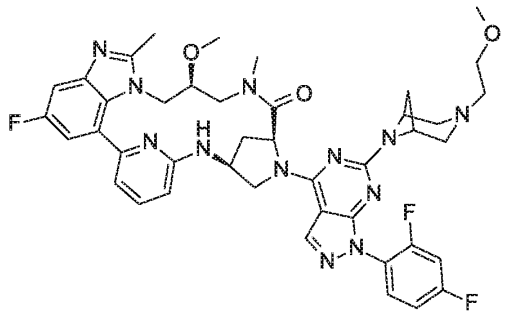


Example **613** was prepared in analogy to the preparation of Example **431** by using **Intermediate C86** instead of compound **431c**. LCMS ($M+H^+$): 809. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.80 (br t, J = 7.3 Hz, 1H), 7.67 - 7.59 (m, 1H), 7.30 (br d, J = 7.8 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.15 (br d, J = 9.4 Hz, 2H), 7.08 (br d, J = 7.1 Hz, 1H), 6.65 (br d, J = 8.3 Hz, 1H), 5.91 - 5.70 (m, 1H), 5.34 (br d, J = 8.6 Hz, 1H), 4.69 - 4.51 (m, 2H), 4.42 (br s, 2H), 4.30 - 4.07 (m, 4H), 3.95 - 3.83 (m, 1H), 3.68 - 3.43 (m, 3H), 3.23 (br d, J = 10.5 Hz,

1H), 3.11 - 3.00 (m, 3H), 2.90 (br d, *J* = 15.8 Hz, 2H), 2.84 (br s, 3H), 2.74 (br d, *J* = 13.9 Hz, 1H), 2.58 (br s, 4H), 2.47 (br d, *J* = 6.6 Hz, 2H), 2.21 - 1.72 (m, 2H).

Example 614

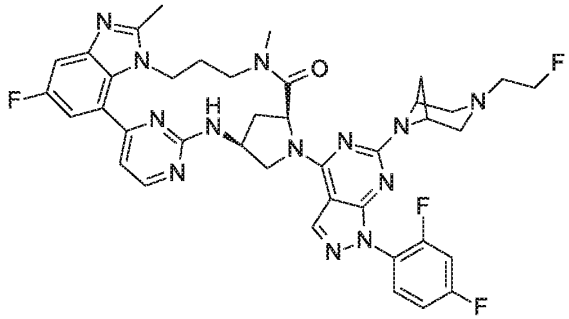
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **614** was prepared in analogy to the preparation of Example **431** by using **Intermediate C87** instead of compound **431c**. LCMS (M+H$^+$): 823. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.26 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.30 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.12 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.87 (dd, *J* = 4.1, 15.4 Hz, 1H), 5.37 (br d, *J* = 8.9 Hz, 1H), 4.64 (br d, *J* = 4.6 Hz, 1H), 4.46 (br dd, *J* = 6.4, 11.5 Hz, 2H), 4.24 - 4.09 (m, 4H), 3.91 (br dd, *J* = 8.9, 14.1 Hz, 1H), 3.47 - 3.37 (m, 3H), 3.26 - 3.21 (m, 4H), 3.01 (s, 3H), 2.94 - 2.88 (m, 2H), 2.85 (s, 4H), 2.75 (br d, *J* = 14.1 Hz, 1H), 2.65 - 2.60 (m, 2H), 2.58 (s, 3H), 2.53 - 2.41 (m, 3H).

Example 615

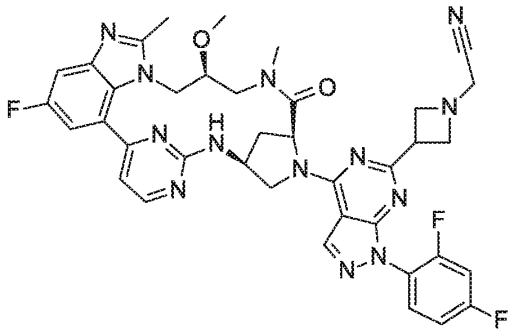
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **615** was prepared in analogy to the preparation of Example **431** by using **Intermediate C80** instead of compound **431c** and compound **610a** instead of compound **370b**. LCMS ($M+H^+$): 782. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.54 (d, J = 5.1 Hz, 1H), 8.24 (s, 1H), 7.66 - 7.53 (m, 1H), 7.39 - 7.33 (m, 1H), 7.25 - 7.10 (m, 3H), 6.97 (d, J = 5.1 Hz, 1H), 5.36 - 5.22 (m, 2H), 4.82 (d, J = 4.1 Hz, 1H), 4.65 - 4.31 (m, 4H), 4.26 - 4.11 (m, 3H), 4.08 - 3.97 (m, 2H), 3.24 (d, J = 10.5 Hz, 1H), 3.10 - 2.98 (m, 3H), 2.96 - 2.81 (m, 3H), 2.79 - 2.62 (m, 3H), 2.59 (s, 3H), 2.55 - 2.42 (m, 2H), 1.96 - 1.75 (m, 2H), 1.35 - 1.21 (m, 1H).

Example 616

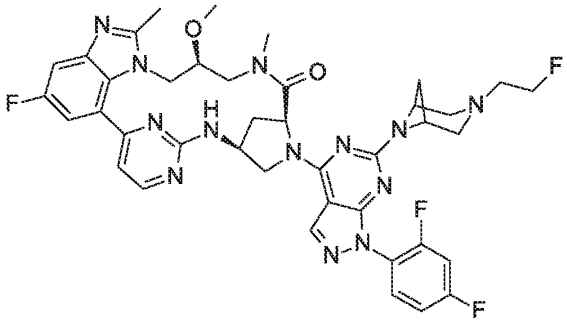
2-[3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile



Examples **616** was prepared in analogy to the preparation of Example **443** by using compound **557b** instead of compound **213a**, compound *tert*-butyl 3-iodoazetidine-1-carboxylate instead of *tert*-butyl 3-iodopyrrolidine-1-carboxylate and bromoacetonitrile instead of methanesulfonic anhydride. LCMS ($M+H^+$): 764. ^1H NMR (400 MHz, ACETONITRILE-d_3) δ = 8.64 (d, J = 5.1 Hz, 1H), 8.40 (s, 1H), 7.82 (br dd, J = 1.8, 7.3 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.51 (dd, J = 2.1, 10.3 Hz, 1H), 7.30 - 7.17 (m, 2H), 7.15 - 7.08 (m, 1H), 5.95 - 5.84 (m, 1H), 5.81 - 5.71 (m, 1H), 5.60 - 5.20 (m, 1H), 4.82 - 4.56 (m, 1H), 4.46 - 4.29 (m, 3H), 4.27 - 4.10 (m, 4H), 4.08 - 3.85 (m, 4H), 3.17 - 3.11 (m, 1H), 3.11 - 3.04 (m, 3H), 2.95 - 2.91 (m, 3H), 2.80 - 2.79 (m, 3H), 2.58 - 2.47 (m, 2H).

Example 617

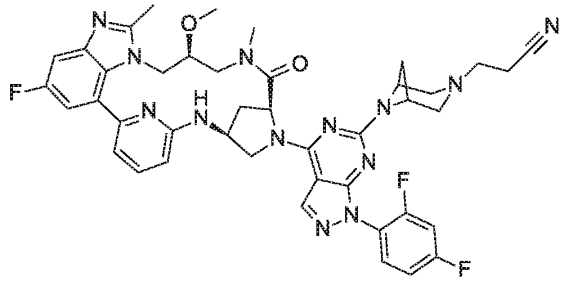
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **617** was prepared in analogy to the preparation of Example **431** by using **Intermediate C80** instead of compound **431c** and compound **556b** instead of compound **370b**. LCMS (M+H$^+$): 812. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, J = 5.3 Hz, 1H), 8.21 (s, 1H), 7.68 - 7.59 (m, 1H), 7.41 (dd, J = 2.4, 8.4 Hz, 1H), 7.31 - 7.20 (m, 2H), 7.16 - 7.05 (m, 2H), 5.76 - 5.41 (m, 1H), 5.27 (br d, J = 8.8 Hz, 1H), 4.74 - 4.35 (m, 4H), 4.33 - 4.11 (m, 5H), 3.95 (br dd, J = 9.2, 14.2 Hz, 1H), 3.44 - 3.35 (m, 1H), 3.27 (br d, J = 10.3 Hz, 1H), 3.11 (s, 1H), 3.01 (s, 3H), 2.88 (br d, J = 4.5 Hz, 2H), 2.84 (s, 4H), 2.79 - 2.66 (m, 2H), 2.57 (s, 3H), 2.53 - 2.36 (m, 3H).

Example 618

3-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile

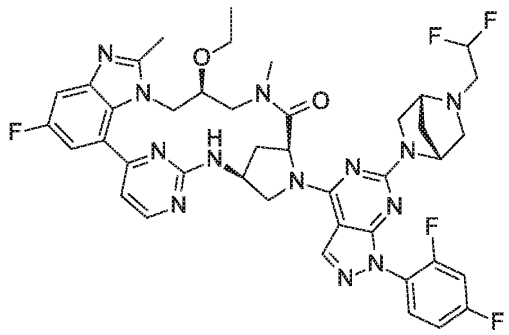


Example **618** was prepared in analogy to the preparation of Example **564** by using 3-bromopropanenitrile instead of 1-fluoro-2-iodo-ethane. LCMS (M+H$^+$): 818. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.27 (s, 1H), 7.82 (t, J = 7.9 Hz, 1H), 7.66 (dt, J = 6.1, 8.5 Hz, 1H), 7.32 (dd, J = 2.4, 8.5 Hz, 1H), 7.24 (br s, 1H), 7.17 (dd, J = 2.4, 10.4 Hz, 2H), 7.10 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.86 (dd, J = 4.4, 15.6 Hz, 1H), 5.40 (d, J = 8.9 Hz, 1H), 4.67 - 4.55 (m, 1H), 4.42 (br dd, J = 6.1, 11.1 Hz, 2H), 4.30 - 4.08 (m, 4H), 3.90 (br dd, J = 8.9, 14.1

Hz, 1H), 3.47 - 3.35 (m, 2H), 3.14 - 3.02 (m, 3H), 2.99 - 2.89 (m, 2H), 2.88 - 2.82 (m, 5H), 2.81 - 2.72 (m, 3H), 2.61 (s, 3H), 2.52 - 2.43 (m, 3H), 2.41 - 2.32 (m, 1H).

Example 619

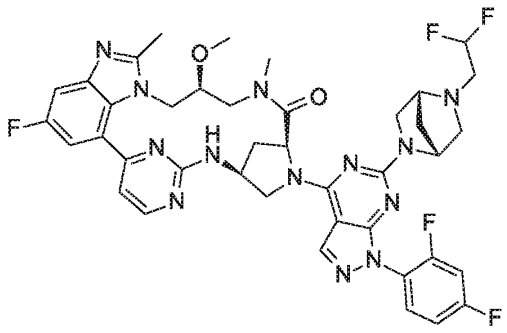
(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **619** was prepared in analogy to the preparation of Example **431** by using **Intermediate C84** instead of compound **431c** and compound **326d-1** instead of compound **370b**. LCMS (M+H$^+$): 844. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, *J* = 5.1 Hz, 1H), 8.19 (s, 1H), 7.53 (s, 1H), 7.40 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.31 - 7.18 (m, 2H), 7.17 - 7.05 (m, 2H), 6.04 - 5.70 (m, 1H), 5.69 - 5.44 (m, 1H), 5.39 - 5.20 (m, 1H), 4.78 - 4.67 (m, 2H), 4.59 (s, 3H), 4.32 (br dd, *J* = 5.9, 11.1 Hz, 1H), 4.22 - 4.10 (m, 2H), 3.90 (br dd, *J* = 9.4, 13.9 Hz, 1H), 3.69 - 3.53 (m, 2H), 3.35 (s, 3H), 3.09 (s, 1H), 3.02 (s, 3H), 2.92 - 2.80 (m, 3H), 2.60 - 2.57 (m, 3H), 2.47 (ddd, *J* = 4.6, 8.9, 13.6 Hz, 1H), 1.98 - 1.77 (m, 2H), 0.59 (t, *J* = 6.9 Hz, 3H).

Example 620

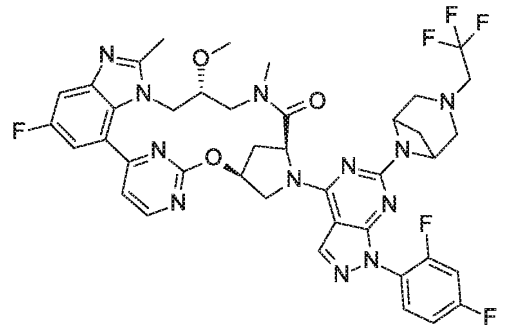
(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **619** was prepared in analogy to the preparation of Example **431** by using **Intermediate C84** instead of compound **431c** and compound **556b** instead of compound **370b**. LCMS (M+H$^+$): 830. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, J = 5.1 Hz, 1H), 8.18 (s, 1H), 7.63 (dt, J = 6.0, 8.6 Hz, 1H), 7.39 (dd, J = 2.4, 8.4 Hz, 1H), 7.26 (dd, J = 2.5, 10.3 Hz, 1H), 7.23 - 7.16 (m, 1H), 7.15 - 7.04 (m, 2H), 6.04 - 5.81 (m, 1H), 5.74 - 5.60 (m, 1H), 5.33 (br d, J = 8.6 Hz, 1H), 4.75 - 4.50 (m, 3H), 4.29 (br dd, J = 5.8, 11.2 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.00 - 3.84 (m, 1H), 3.70 - 3.52 (m, 2H), 3.35 (s, 3H), 3.10 (s, 1H), 3.03 (s, 3H), 2.98 - 2.87 (m, 3H), 2.83 (s, 3H), 2.67 (br d, J = 9.4 Hz, 1H), 2.58 - 2.53 (m, 3H), 1.95 - 1.75 (m, 2H).

Example 621

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

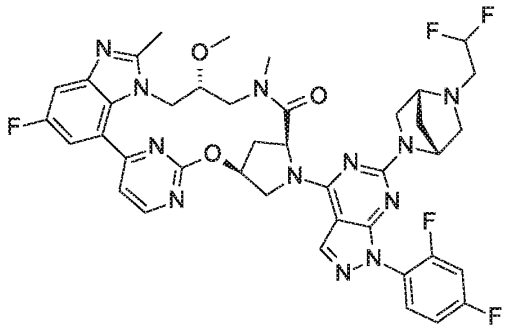


Example **621** was prepared in analogy to the preparation of Example **431** by using **Intermediate C82** instead of compound **431c** and compound **78d-2** instead of compound **370b**. LCMS (M+H$^+$): 849. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 (d, J = 5.3 Hz, 1H), 8.28 (s, 1H), 7.68 - 7.56 (m, 1H), 7.48 - 7.38 (m, 2H), 7.32 - 7.13 (m, 3H), 5.90 - 5.63 (m, 2H), 5.51 - 5.41 (m, 1H), 4.59 (s, 2H), 4.54 - 4.39 (m, 2H), 4.36 - 4.08 (m, 4H), 4.07 - 3.93 (m, 1H), 3.68 -

3.52 (m, 1H), 3.52 - 3.33 (m, 3H), 3.13 - 3.04 (m, 3H), 3.02 (s, 3H), 2.81 (s, 3H), 2.76 - 2.70 (m, 1H), 2.62 - 2.57 (m, 3H), 2.56 (br s, 1H).

Example 622

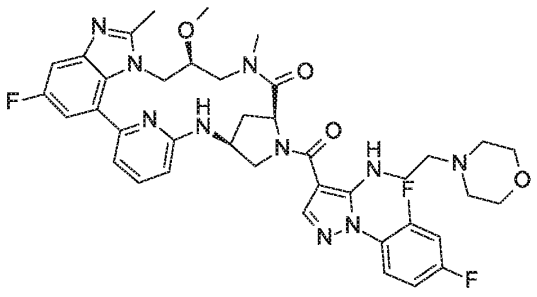
(8*S*,11*S*,15*S*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **622** was prepared in analogy to the preparation of Example **431** by using **Intermediate C84** instead of compound **431c** and compound **78d-2** instead of compound **370b**. LCMS (M+H$^+$): 831. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 7.70 - 7.55 (m, 1H), 7.47 - 7.43 (m, 1H), 7.42 - 7.38 (m, 1H), 7.31 (br s, 1H), 7.26 - 7.11 (m, 2H), 5.85 (br d, J = 3.9 Hz, 1H), 5.58 (s, 1H), 5.54 - 5.31 (m, 1H), 4.59 (br s, 4H), 4.51 - 4.36 (m, 2H), 4.28 - 4.04 (m, 2H), 3.99 (br d, J = 14.4 Hz, 1H), 3.72 - 3.58 (m, 2H), 3.12 (s, 2H), 3.04 (s, 3H), 2.98 (br d, J = 11.0 Hz, 1H), 2.81 (s, 3H), 2.78 - 2.65 (m, 3H), 2.62 - 2.58 (m, 3H), 1.98 - 1.81 (m, 2H).

Example 623

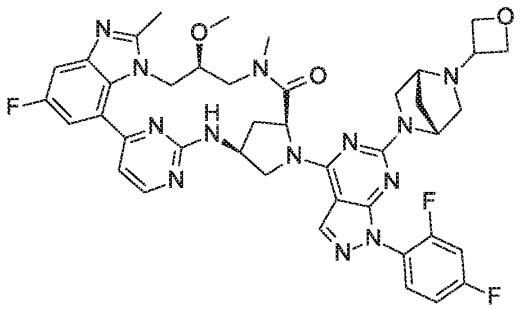
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(2-morpholinoethylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **623** was prepared in analogy to the preparation of Example **592** by using 4-(2-chloroethyl)morpholine instead of 1-iodo-3-phenylpropane. LCMS (M+H$^+$): 773. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.13 - 7.99 (m, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.71 - 7.57 (m, 1H), 7.35 - 7.24 (m, 2H), 7.23 - 7.13 (m, 2H), 7.08 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.87 - 5.74 (m, 1H), 5.18 - 5.09 (m, 1H), 4.83 (s, 2H), 4.64 - 4.51 (m, 4H), 4.43 - 4.33 (m, 1H), 4.25 - 4.10 (m, 2H), 4.02 - 3.89 (m, 1H), 3.64 - 3.57 (m, 2H), 3.35 (s, 3H), 3.01 - 2.97 (m, 2H), 2.94 - 2.89 (m, 2H), 2.84 (s, 3H), 2.62 - 2.58 (m, 2H), 2.43 - 2.32 (m, 6H).

Example 624

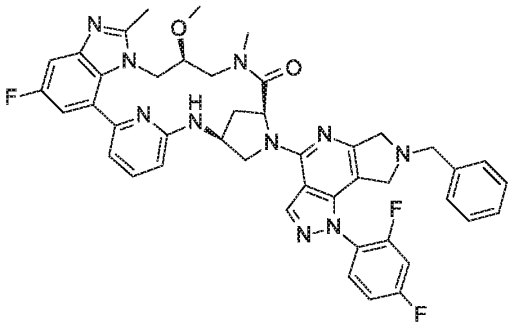
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **624** was prepared in analogy to the preparation of Example **431** by using **Intermediate C88** instead of compound **431c** and compound **556b** instead of compound **370b**. LCMS (M+H$^+$): 822. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 (d, J = 5.1 Hz, 1H), 8.19 (s, 1H), 7.62 (dt, J = 6.1, 8.4 Hz, 1H), 7.39 (dd, J = 2.4, 8.4 Hz, 1H), 7.26 (dd, J = 2.4, 10.2 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.06 (m, 2H), 5.69 - 5.44 (m, 1H), 5.40 - 5.22 (m, 1H), 4.75 - 4.67 (m, 3H), 4.66 - 4.58 (m, 2H), 4.54 - 4.49 (m, 1H), 4.48 - 4.41 (m, 1H), 4.31 (br dd, J = 5.8, 11 Hz, 1H), 4.23 - 4.09 (m, 2H), 4.04 - 3.96 (m, 1H), 3.87 (br dd, J = 8.9, 14 Hz, 1H), 3.59 - 3.49 (m, 1H), 3.46 (br d, J = 10.4 Hz, 1H), 3.35 (s, 1H), 3.28 - 3.17 (m, 1H), 3.12 - 3.02 (m, 3H), 2.88 (br d, J = 14.0 Hz, 2H), 2.84 - 2.80 (m, 3H), 2.56 (s, 3H), 2.54 - 2.42 (m, 2H), 1.96 - 1.78 (m, 2H).

Example 625

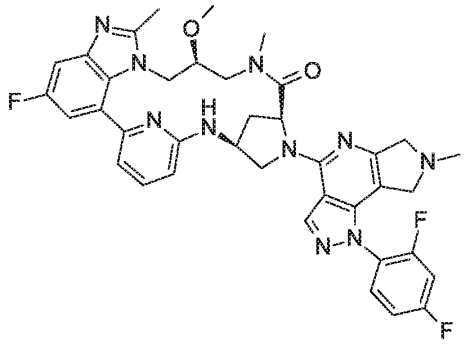
(8*S*,11*S*,15*R*)-10-[11-benzyl-3-(2,4-difluorophenyl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **625** was prepared in analogy to the preparation of Example **646** by using compound **646j** instead of compound **646l**. LCMS (M+H$^+$): 799. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.87 (t, J = 7.9 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.56 (dd, J = 2.6, 7.4 Hz, 1H), 7.53 - 7.47 (m, 7H), 7.40 - 7.34 (m, 1H), 7.29 - 7.22 (m, 1H), 7.16 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.17 - 6.04 (m, 1H), 5.44 (d, J = 9.1 Hz, 1H), 4.57 (s, 3H), 4.53 - 4.44 (m, 2H), 4.40 - 4.32 (m, 3H), 4.30 - 4.19 (m, 2H), 3.96 - 3.86 (m, 1H), 3.22 - 3.15 (m, 1H), 3.15 - 3.12 (m, 1H), 3.12 - 3.04 (m, 3H), 2.96 (s, 3H), 2.78 (s, 3H), 2.62 - 2.49 (m, 2H).

Example 626

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-methyl-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

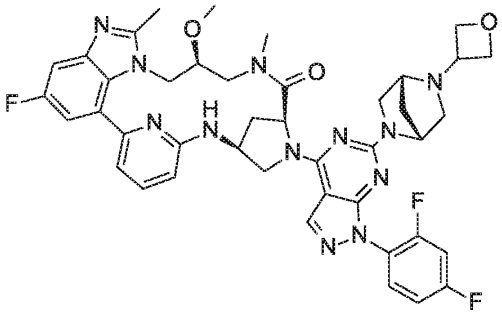


Example **626** was prepared in analogy to the preparation of Example **646** by using formaldehyde instead of 3-oxetanone. LCMS (M+H$^+$): 723. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.62 (s, 1H), 7.91 - 7.85 (m, 1H), 7.74 - 7.65 (m, 1H), 7.59 (dd, J = 2.5, 7.3 Hz, 1H), 7.54 (dd, J = 2.5, 10.1 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.32 - 7.24 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.19 - 6.09 (m, 1H), 5.46 (d, J = 8.8 Hz, 1H), 4.69 - 4.59 (m, 2H), 4.58 - 4.46 (m, 2H), 4.46 - 4.33 (m, 2H), 4.27 (br dd, J = 10.8, 15.2 Hz, 2H), 3.93 (br dd, J = 9.4, 13.9

Hz, 1H), 3.15 (s, 1H), 3.10 (s, 5H), 3.05 - 3.00 (m, 1H), 2.97 (s, 3H), 2.94 - 2.85 (m, 1H), 2.81 (s, 3H), 2.65 - 2.51 (m, 2H).

Example 627

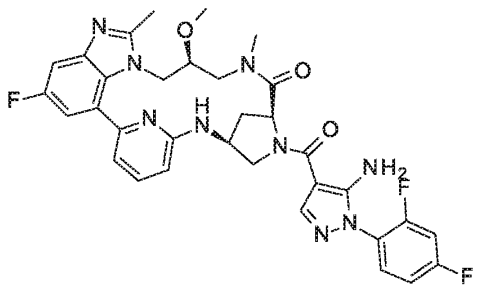
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **627** was prepared in analogy to the preparation of Example **431** by using **Intermediate C88** instead of compound **431c**. LCMS (M+H$^+$): 821. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.17 (br s, 1H), 7.78 (br t, *J* = 7.6 Hz, 1H), 7.67 - 7.56 (m, 1H), 7.30 (br d, *J* = 8.3 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.17 - 7.03 (m, 3H), 6.63 (br d, *J* = 8.4 Hz, 1H), 5.90 - 5.61 (m, 1H), 5.41 - 5.19 (m, 1H), 4.76 - 4.60 (m, 3H), 4.59 - 4.41 (m, 3H), 4.40 - 4.31 (m, 1H), 4.20 - 4.07 (m, 2H), 4.04 - 3.94 (m, 1H), 3.92 - 3.77 (m, 1H), 3.61 - 3.43 (m, 2H), 3.35 (br s, 1H), 3.10 - 2.99 (m, 3H), 2.98 - 2.87 (m, 2H), 2.87 - 2.78 (m, 4H), 2.71 (br d, *J* = 13.6 Hz, 1H), 2.53 (br s, 3H), 2.46 (br s, 2H), 1.98 - 1.79 (m, 2H).

Example 628

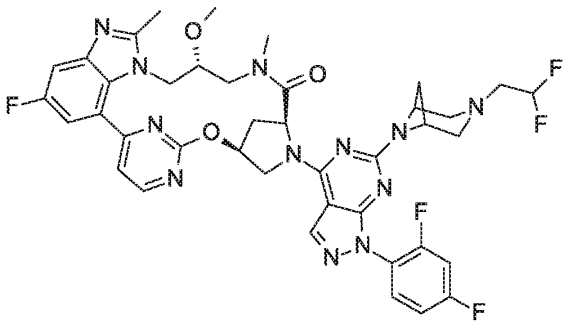
(8*S*,11*S*,15*R*)-10-[5-amino-1-(2,4-difluorophenyl)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **628** was prepared in analogy to the preparation of Example **592** by using compound **592a** instead of compound **592c**. LCMS (M+H$^+$): 660. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.03 (br s, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.61 - 7.52 (m, 1H), 7.35 - 7.24 (m, 2H), 7.30 - 7.15 (m, 2H), 7.09 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.81 (br d, J = 14.6 Hz, 1H), 5.18 - 5.10 (m, 1H), 4.81 - 4.72 (m, 1H), 4.64 - 4.51 (m, 2H), 4.36 (br s, 1H), 4.27 - 4.13 (m, 2H), 4.02 - 3.90 (m, 1H), 3.33 (s, 3H), 2.98 (br s, 2H), 2.84 (s, 3H), 2.61 (s, 3H), 2.54 - 2.43 (m, 1H), 2.37 (br s, 1H).

Example 629

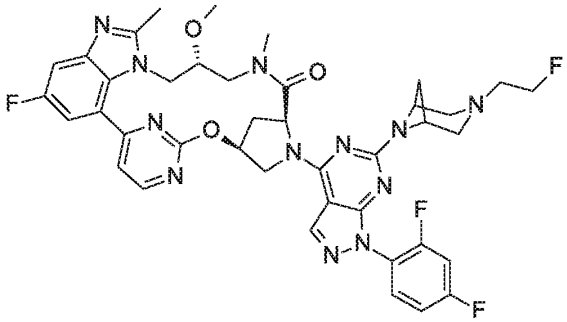
(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **629** was prepared in analogy to the preparation of Example **431** by using **Intermediate C81** instead of compound **431c** and compound **78d-2** instead of compound **370b**. LCMS (M+H$^+$): 831. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 (br d, J = 5.0 Hz, 1H), 8.27 (s, 1H), 7.73 - 7.53 (m, 1H), 7.51 - 7.37 (m, 2H), 7.35 - 7.03 (m, 3H), 5.84 (br s, 1H), 5.46 (br d, J = 7.8 Hz, 1H), 5.13 - 4.90 (m, 2H), 4.59 (s, 2H), 4.53 - 4.30 (m, 2H), 4.27 - 3.95 (m, 4H), 3.66 - 3.33 (m, 3H), 3.01 (s, 4H), 2.86 (br s, 2H), 2.81 (s, 3H), 2.75 (br s, 2H), 2.59 (s, 3H), 2.54 - 2.42 (m, 1H), 1.75 (br d, J = 8.0 Hz, 1H).

Example 630

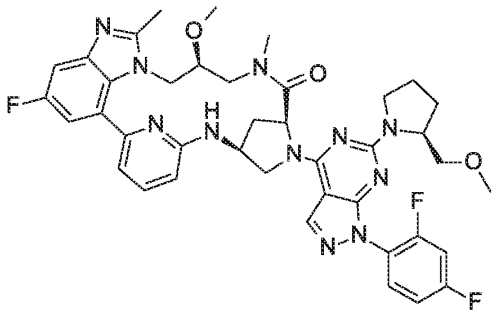
(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **630** was prepared in analogy to the preparation of Example **431** by using **Intermediate C80** instead of compound **431c** and compound **78d-2** instead of compound **370b**. LCMS (M+H$^+$): 813. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.70 (d, J = 5.2 Hz, 1H), 8.28 (s, 1H), 7.65 - 7.56 (m, 1H), 7.47 - 7.39 (m, 2H), 7.33 - 7.28 (m, 1H), 7.25 - 7.19 (m, 1H), 7.18 - 7.12 (m, 1H), 5.93 - 5.67 (m, 2H), 5.49 - 5.34 (m, 1H), 4.58 (s, 3H), 4.50 - 4.43 (m, 2H), 4.39 - 4.31 (m, 1H), 4.26 - 4.14 (m, 3H), 4.10 - 4.04 (m, 1H), 3.50 - 3.43 (m, 1H), 3.16 - 2.96 (m, 5H), 2.91 - 2.80 (m, 5H), 2.77 - 2.69 (m, 3H), 2.60 (s, 3H), 2.52 - 2.43 (m, 1H), 1.86 (d, J = 8.0 Hz, 1H).

Example 631

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one

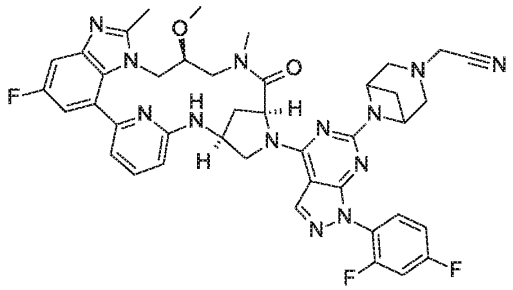


Example **631** was prepared in analogy to the preparation of Example **213** by using (2*S*)-2-(methoxymethyl)pyrrolidine of morpholine. LCMS (M+H$^+$): 782. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.23 (s, 1H), 7.86 (t, J = 7.9 Hz, 1H), 7.65 (dt, J = 6.0, 8.5 Hz, 1H), 7.57 - 7.53 (m, 1H), 7.48 (dd, J = 2.3, 10.3 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.18 - 7.11 (m, 2H), 6.77 (d, J = 8.6 Hz, 1H), 6.25 - 6.00 (m, 1H), 5.39 - 5.28 (m, 1H), 4.73 - 4.61 (m, 1H), 4.47 (dd, J = 5.8, 10.8 Hz, 1H), 4.36 - 4.20 (m, 2H), 4.07 (br d, J = 4.4 Hz, 1H), 3.90 (dd, J = 9.3, 14.5 Hz, 1H), 3.81 - 3.65 (m, 1H), 3.44 (br s, 2H), 3.36 - 3.32 (m, 3H), 3.28 - 3.22 (m, 1H), 3.15 - 3.06 (m, 3H),

3.01 (br s, 1H), 2.98 - 2.95 (m, 3H), 2.82 - 2.77 (m, 3H), 2.73 (br d, *J* = 13.8 Hz, 1H), 2.62 - 2.48 (m, 2H), 2.04 - 1.86 (m, 4H).

Example 632

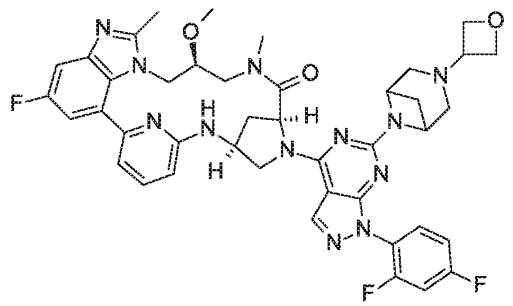
2-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]acetonitrile



Example **632** was prepared in analogy to the preparation of Example **564** by using bromoacetonitrile instead of 1-fluoro-2-iodo-ethane in step 2. Example **632**, LCMS (M+H$^+$): 804. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ = 8.26 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.57 (m, 1H), 7.36 - 7.30 (m, 1H), 7.26 - 7.12 (m, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.89 (dd, *J* = 4.5, 15.6 Hz, 1H), 5.38 (d, *J* = 8.9 Hz, 1H), 4.69 - 4.62 (m, 1H), 4.50 - 4.42 (m, 1H), 4.40 - 4.07 (m, 4H), 4.00 - 3.91 (m, 1H), 3.65 - 3.51 (m, 2H), 3.47 - 3.32 (m, 3H), 3.12 - 2.99 (m, 3H), 2.92 (br d, *J* = 14.4 Hz, 1H), 2.88 - 2.85 (m, 3H), 2.85 - 2.73 (m, 2H), 2.66 - 2.59 (m, 3H), 2.58 - 2.54 (m, 1H), 2.54 - 2.44 (m, 2H), 1.84 - 1.72 (m, 1H).

Example 633

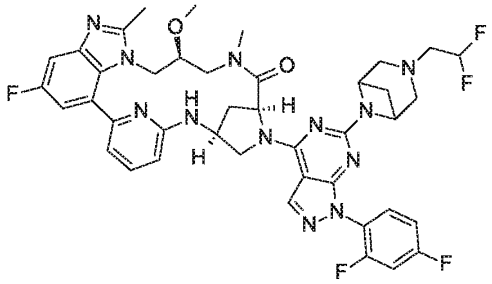
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **633** was prepared in analogy to the preparation of Example **564** by using oxetan-3-one instead of 1-fluoro-2-iodo-ethane in step 2 (reaction condition: reductive amination via $NaBH(OAc)_3$ in hot EtOH instead of alkylation via K_2CO_3 in ACN). Example **633**, LCMS ($M+H^+$): 821. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.30 (s, 1H), 7.86 - 7.79 (m, 1H), 7.67 - 7.59 (m, 1H), 7.34 - 7.28 (m, 1H), 7.27 - 7.21 (m, 1H), 7.21 - 7.13 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.74 - 6.65 (m, 1H), 5.84 (dd, *J* = 4.4, 15.6 Hz, 1H), 5.39 (d, *J* = 9.0 Hz, 1H), 4.73 - 4.65 (m, 3H), 4.64 - 4.55 (m, 4H), 4.49 (br dd, *J* = 5.8, 11.2 Hz, 1H), 4.33 - 4.20 (m, 3H), 4.01 - 3.88 (m, 1H), 3.68 - 3.63 (m, 1H), 3.32 - 3.26 (m, 2H), 3.14 - 3.02 (m, 3H), 2.96 - 2.87 (m, 2H), 2.86 (s, 3H), 2.85 - 2.77 (m, 2H), 2.68 - 2.60 (m, 1H), 2.60 - 2.55 (m, 3H), 2.55 - 2.46 (m, 2H).

Example 634

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

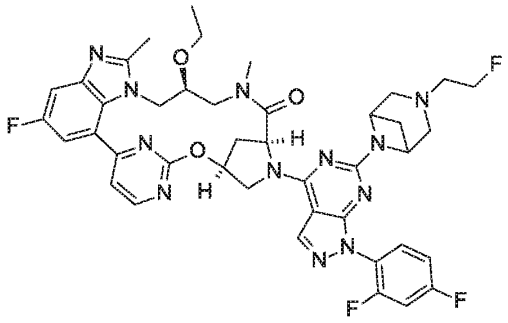


Example **634** was prepared in analogy to the preparation of Example **564** by using trifluoromethanesulfonic acid 2,2-difluoroethyl ester instead of 1-fluoro-2-iodo-ethane in step 2 (reaction condition: DIPEA in THF instead of K_2CO_3 in ACN). Example **634**, LCMS ($M+H^+$): 829. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.25 (s, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.15 (br dd, *J* = 2.6, 10.4 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.64 (br d, *J* = 8.4 Hz, 1H), 6.00 - 5.65 (m, 2H), 5.34 (d, *J* = 8.9 Hz, 1H), 4.62 - 4.53 (m, 1H), 4.40 (br dd, *J* = 5.9, 10.9 Hz, 1H), 4.27 - 4.19 (m, 2H), 4.19 - 4.08 (m, 2H), 3.89 (dd, *J* = 9.1, 14.0 Hz, 1H), 3.42 (dd, *J* = 2.0, 10.3 Hz, 1H), 3.36 - 3.32 (m, 1H), 3.11 - 2.98 (m, 3H), 2.98 - 2.85 (m, 3H), 2.83 (s, 3H), 2.82 - 2.69 (m, 3H), 2.54 (s, 3H), 2.53 - 2.39 (m, 3H), 1.71 (d, *J* = 8.0 Hz, 1H).

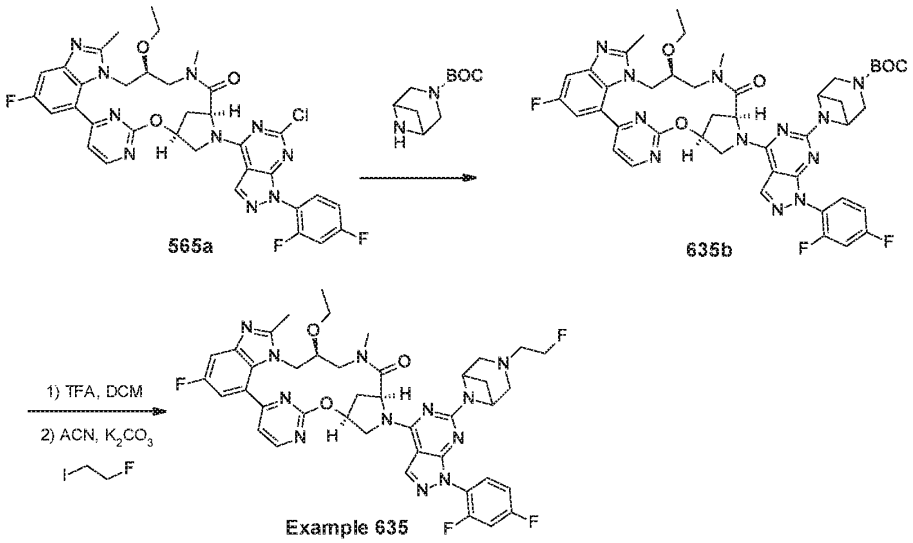
Example 635

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-

5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **635** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (compound 635b)

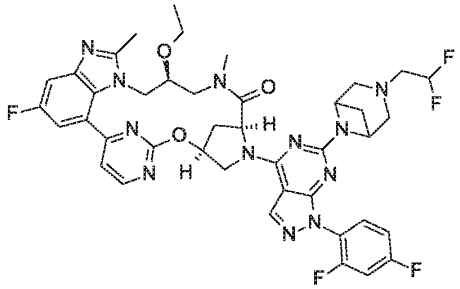
To a tube was added **565a** (109.0 mg, 151 μmol), DIEA (25.5 mg, 34 μL, 197 μmol), *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (45.0 mg, 227 μmol), cesium fluoride (40.0 mg, 263 μmol) and dimethyl sulfoxide (1 mL). The mixture was heated to 100 °C and stirred for 4 hrs. Then it was poured into water and extracted with EA, the organic layer was concentrated and purified to give **635b** (82 mg) as solid. LCMS (M+H$^+$): 881.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

To the flask containing **635b** (41 mg, 46 μmol) was added dichloromethane (2 mL) and TFA (1.48 g, 1 mL, 12.98 mmol). The solution was stirred at r.t. for 1 hr and then concentrated to give an oil. The oil was dissolved in acetonitrile (2 mL) and then 1-fluoro-2-iodo-ethane (40.0 mg, 230 μmol), potassium carbonate (31.8 mg, 230 μmol) were added. After being heated to 80 °C and stirred for 2 hrs, the mixture was filtered and the filtrate was purified by prep-HPLC give Example **635** (27.7 mg). LCMS (M+H$^+$): 827. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.79 (d, *J* = 5.3 Hz, 1H), 8.37 (s, 1H), 7.68 - 7.58 (m, 2H), 7.49 - 7.41 (m, 2H), 7.28 - 7.21 (m, 1H), 7.20 - 7.13 (m, 1H), 5.89 - 5.84 (m, 1H), 5.83 - 5.68 (m, 1H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.78 - 4.58 (m, 3H), 4.55 - 4.43 (m, 2H), 4.39 - 4.30 (m, 2H), 4.26 - 4.12 (m, 1H), 4.05 - 3.96 (m, 1H), 3.95 - 3.74 (m, 2H), 3.73 - 3.53 (m, 2H), 3.46 - 3.37 (m, 1H), 3.29 - 3.23 (m, 1H), 3.09 - 2.96 (m, 3H), 2.95 - 2.69 (m, 4H), 2.68 - 2.63 (m, 1H), 2.63 (s, 3H), 2.60 - 2.54 (m, 1H), 2.06 - 1.91 (m, 1H), 0.58 (t, *J* = 6.9 Hz, 3H).

Example 636

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

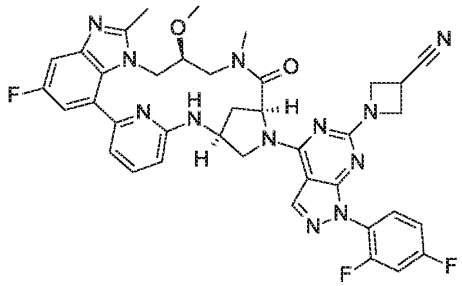


Example **636** was prepared in analogy to the preparation of Example **635** by using trifluoromethanesulfonic acid 2,2-difluoroethyl ester instead of 1-fluoro-2-iodo-ethane in step 3 (reaction condition: DIPEA in THF instead of K_2CO_3 in ACN). LCMS (M+H$^+$): 845. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.79 - 8.75 (m, 1H), 8.28 (s, 1H), 7.65 - 7.59 (m, 2H), 7.47 - 7.40 (m, 2H), 7.26 - 7.19 (m, 1H), 7.19 - 7.11 (m, 1H), 5.86 (dd, *J* = 3.9, 15.6 Hz, 1H), 5.81 (t, *J*

= 3.8 Hz, 1H), 5.45 (d, *J* = 8.9 Hz, 1H), 4.51 - 4.40 (m, 2H), 4.37 - 4.27 (m, 1H), 4.25 - 4.14 (m, 3H), 3.98 (dd, *J* = 9.6, 14.0 Hz, 1H), 3.38 (ddd, *J* = 1.7, 10.2, 18.5 Hz, 2H), 3.29 - 3.23 (m, 1H), 3.06 - 2.95 (m, 3H), 2.95 - 2.86 (m, 2H), 2.81 (br d, *J* = 14.5 Hz, 3H), 2.77 - 2.63 (m, 2H), 2.63 - 2.60 (m, 3H), 2.60 - 2.53 (m, 2H), 2.53 - 2.46 (m, 1H), 1.73 (d, *J* = 8.1 Hz, 1H), 0.61 - 0.54 (m, 3H)

Example 637

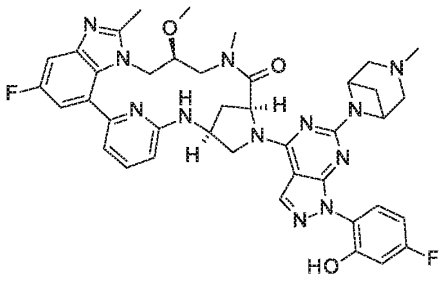
1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile



Example **637** was prepared in analogy to the preparation of Example **574** by using compound **370b** instead of compound **326d-1**. Example **637**, LCMS (M+H$^+$): 749. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.26 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.56 (m, 1H), 7.31 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.25 - 7.19 (m, 1H), 7.19 - 7.11 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.87 - 5.66 (m, 1H), 5.39 - 5.27 (m, 1H), 4.60 (br s, 1H), 4.43 - 4.34 (m, 1H), 4.31 - 4.20 (m, 3H), 4.19 - 4.12 (m, 2H), 4.12 - 4.04 (m, 1H), 3.93 (dd, *J* = 9.1, 14.3 Hz, 1H), 3.68 - 3.59 (m, 1H), 3.10 - 3.01 (m, 3H), 2.90 (br d, *J* = 14.3 Hz, 1H), 2.86 - 2.81 (m, 3H), 2.76 (br d, *J* = 13.5 Hz, 1H), 2.60 - 2.54 (m, 3H), 2.53 - 2.40 (m, 2H).

Example 638

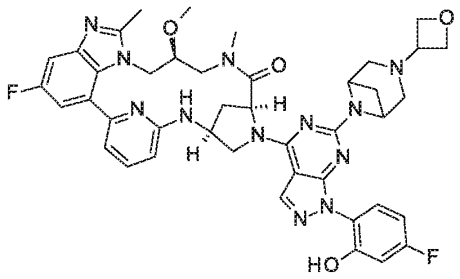
(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



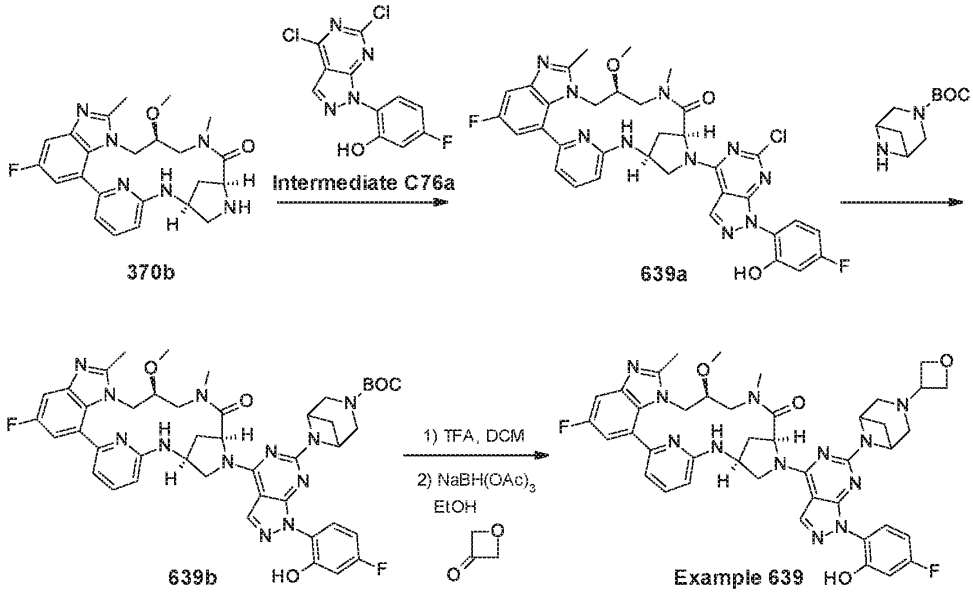
Example **638** was prepared in analogy to the preparation of Example **639b** by using 3-methyl-3,6-diazabicyclo[3.1.1]heptane instead of *tert*-butyl 3,6-diazabicyclo[3.1.1] heptane-3-carboxylate in step 2. LCMS ($M+H^+$): 777. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.34 (s, 1H), 7.85 (t, J = 7.9 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.44 (dd, J = 2.5, 7.9 Hz, 1H), 7.34 (dd, J = 2.1, 10.4 Hz, 1H), 7.14 (dd, J = 2.4, 7.4 Hz, 1H), 6.79 - 6.71 (m, 3H), 6.02 - 5.86 (m, 1H), 5.44 - 5.36 (m, 1H), 4.56 - 4.47 (m, 2H), 4.44 - 4.37 (m, 1H), 4.30 - 4.15 (m, 3H), 3.98 - 3.83 (m, 2H), 3.74 - 3.62 (m, 2H), 3.15 - 3.03 (m, 4H), 3.02 - 2.95 (m, 1H), 2.93 - 2.90 (m, 3H), 2.87 - 2.83 (m, 1H), 2.80 (br s, 3H), 2.71 - 2.66 (m, 3H), 2.66 - 2.61 (m, 1H), 2.59 - 2.48 (m, 2H), 1.96 - 1.86 (m, 1H).

Example 639

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **639** was prepared according to the following scheme:



Step 1: preparation of (8*S*,11*S*,15*R*)-10-[6-chloro-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (compound 639a)

To a tube was added **370b** (370.8 mg, 669 μmol), intermediate **C76a** (200 mg, 669 μmol), DIPEA (345.7 mg, 467 μL, 2.67 mmol) and acetonitrile (5 mL). The solution was stirred at 60 °C for 1 hr. Then it was concentrated and purified by silica gel to give compound **639a** (402 mg) as a pale yellow solid. LCMS (M+H$^+$): 701.

Step 2: preparation of *tert*-butyl 6-[1-(4-fluoro-2-hydroxy-phenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (compound 639b)

To a tube was added *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (106.04 mg, 534.86 μmol), compound **639a** (150 mg, 214 μmol), DIEA (55 mg, 75 μL, 428 μmol) and dimethyl sulfoxide (3 mL). After being stirred at 100 °C for 16 hrs, the reaction mixture was poured into water and extracted with EA. The organic layer was concentrated and purified by silica gel to give compound **639b** (120 mg) as a pale brown solid. LCMS (M+H$^+$): 863.

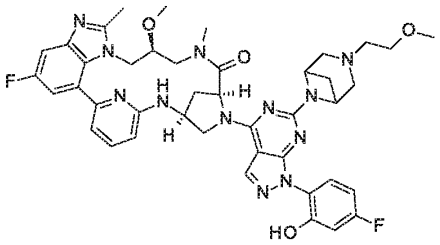
Step 3: preparation of (8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-

methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 639)

To a flask was added compound **639b** (120 mg, 139 μmol), dichloromethane (2 mL) and TFA (1.48 g, 1 mL). The solution was stirred at r.t. for 1 hr. Then it was concentrated and purified via prep-HPLC to give a white powder (120 mg). To a tube was added the white powder (40 mg, 46 μmol), oxetan-3-one (30 mg, 416 μmol), DIEA (17.7 mg, 24 μL, 137 μmol) and ethanol (2 mL). The solution was heated to reflux for 1 hr, and then sodium triacetoxyborohydride (24.17 mg, 114.05 μmol) was added. After being refluxed for 2 hrs, the reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **639** (3 mg). LCMS (M+H$^+$): 819. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.27 (s, 1H), 7.84 - 7.77 (m, 1H), 7.74 - 7.68 (m, 1H), 7.32 - 7.26 (m, 1H), 7.16 - 7.10 (m, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.78 - 6.71 (m, 2H), 6.67 (d, J = 8.4 Hz, 1H), 5.81 (dd, J = 4.4, 15.6 Hz, 1H), 5.37 (d, J = 9.0 Hz, 1H), 4.68 - 4.59 (m, 3H), 4.59 - 4.53 (m, 6H), 4.49 - 4.41 (m, 1H), 4.37 - 4.29 (m, 2H), 4.28 - 4.18 (m, 2H), 4.04 - 3.95 (m, 1H), 3.94 - 3.86 (m, 1H), 3.27 - 3.21 (m, 1H), 3.12 - 3.00 (m, 3H), 2.94 - 2.86 (m, 2H), 2.84 (s, 3H), 2.65 - 2.57 (m, 1H), 2.57 - 2.53 (m, 3H), 2.48 (dt, J = 4.4, 8.7 Hz, 2H).

Example 640

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

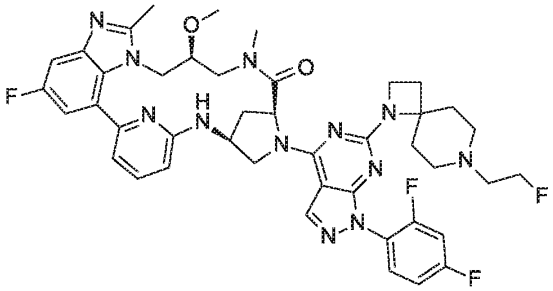


Example **640** was prepared in analogy to the preparation of Example **580** by using compound **213a** instead of compound **575a**. LCMS (M+H$^+$): 819. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.34 (s, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.62 - 7.53 (m, 2H), 7.49 (br dd, J = 1.5, 10.3 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 6.81 - 6.71 (m, 3H), 6.14 (br dd, J = 4.1, 15.4 Hz, 1H), 5.42 (d, J = 9.0 Hz, 1H), 4.72 - 4.67 (m, 1H), 4.57 - 4.46 (m, 2H), 4.43 - 4.36 (m, 1H), 4.31 - 4.20 (m, 2H), 4.10 - 3.79 (m, 3H), 3.74 - 3.59 (m, 4H), 3.30 - 3.20 (m, 6H), 3.16 - 3.05 (m, 3H),

3.04 - 2.98 (m, 1H), 2.96 (s, 3H), 2.88 - 2.82 (m, 1H), 2.81 - 2.76 (m, 3H), 2.65 - 2.47 (m, 2H), 2.10 - 1.97 (m, 1H).

Example 641

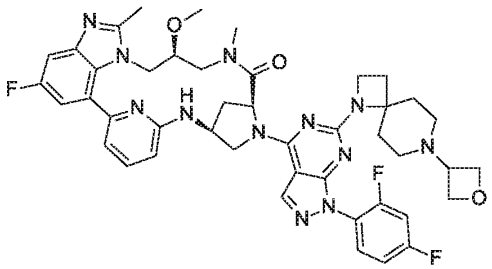
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(2-fluoroethyl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



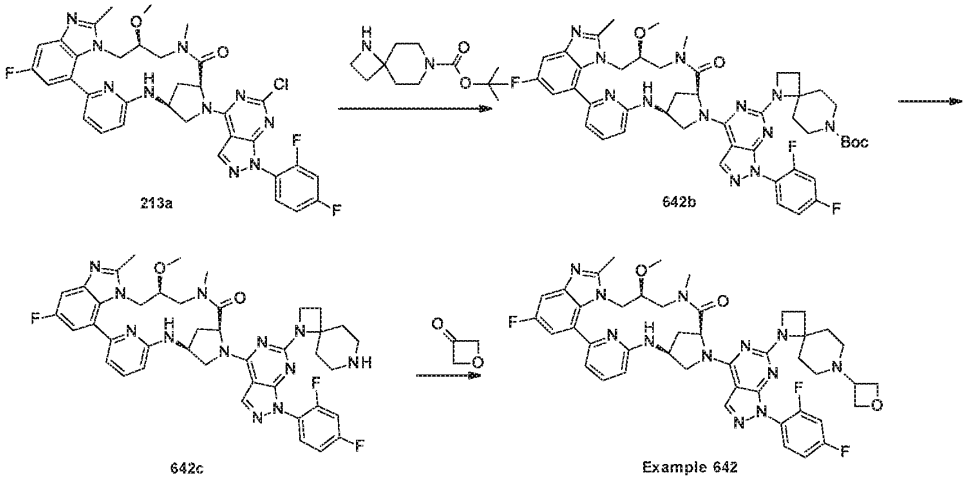
Example **641** was prepared in analogy to the preparation of Example **564** by using *tert*-butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS (M+H$^+$): 839. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.30 - 8.23 (m, 1H), 7.92 - 7.86 (m, 1H), 7.62 - 7.58 (m, 2H), 7.57 - 7.51 (m, 2H), 7.18 (d, J = 7.4 Hz, 2H), 6.84 - 6.77 (m, 1H), 6.12 - 6.05 (m, 1H), 5.35 (br d, J = 8.9 Hz, 1H), 4.70 (br d, J = 3.8 Hz, 1H), 4.57 - 4.45 (m, 2H), 4.36 - 4.22 (m, 3H), 4.01 - 3.89 (m, 3H), 3.73 - 3.61 (m, 2H), 3.55 - 3.45 (m, 1H), 3.21 - 3.14 (m, 3H), 3.09 - 3.03 (m, 2H), 3.02 - 2.99 (d, J = 3.5 Hz, 1H), 2.83 (d, J = 7.0 Hz, 4H), 2.81 - 2.74 (m, 5H), 2.68 - 2.55 (m, 3H), 2.37 - 2.25 (m, 2H), 2.19 - 2.11 (m, 1H), 2.07 - 1.98 (m, 1H).

Example 642

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-1,7-diazaspiro[3.5]nonane-7-carboxylate (compound 642b)

To a mixture of compound **213a** (60.0 mg, 0.09 mmol), *tert*-butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate (96.5 mg, 0.43 mmol) and CsF (12.9 mg, 0.09 mmol) in DMA (2 mL) was added *N,N*-diisopropylethylamine (0.04 mL, 0.26 mmol). After being heated to 120 °C for 18 hrs, the reaction mixture was cooled to 25 °C and diluted with water (15 mL), extracted with EtOAc. The organic layer was dried and concentrated, the crude product was purified by TLC to give compound **642b** (70 mg) as a light yellow solid. LCMS (M+H$^+$): 893.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-(1,7-diazaspiro[3.5]nonan-1-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (compound 642c)

To a solution of compound **642b** (70 mg, 0.08 mmol) in DCM (2 mL) was added TFA (2 mL) at 0 °C. Then the mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched with sat. $NaHCO_3$ solution (50 mL), and then extracted with DCM (3×30 mL). The organic layer was dried and concentrated to give the compound **642c** (60 mg) as a light yellow solid. LCMS (M+H$^+$): 793.

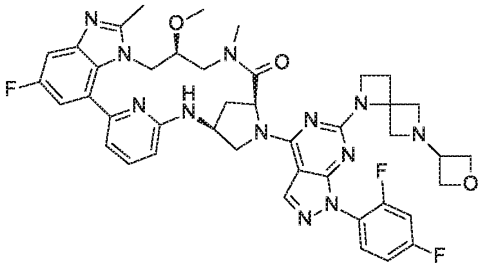
Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 642)

To a solution of compound **642c** (50.0 mg, 0.06 mmol) in DCE (2 mL) were added 3-oxetanone (45.44 mg, 0.63 mmol) and sodium triacetoxyborohydride (66.83 mg, 0.32 mmol) at 0 °C under N_2. Then the mixture was stirred at 25 °C for 6 hrs. The reaction solution was concentrated and the residue was purified by prep-HPLC to give Example **642** (27.5 mg). LCMS ($M+H^+$): 849. ^{1}H NMR (400 MHz, METHANOL-*d*4) δ = 8.22 (m, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.20 (m, 1H), 7.18 - 7.08 (m, 3H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.98 - 5.84 (m, 1H), 5.40 (d, *J* = 9.0 Hz, 1H), 4.75 - 4.69 (m, 2H), 4.66 - 4.60 (m, 2H), 4.55 - 4.49 (m, 2H), 4.48 - 4.40 (m, 1H), 4.27 - 4.16 (m, 2H), 4.01 - 3.79 (m, 3H), 3.24 (s, 2H), 3.16 - 3.04 (m, 1H), 2.92 - 2.85 (m, 3H), 2.80 - 2.67 (m, 4H), 2.64 - 2.49 (m, 6H), 2.44 - 2.30 (m, 1H), 2.16 - 2.06 (m, 2H), 1.85 - 1.69 (m, 4H).

Example 643

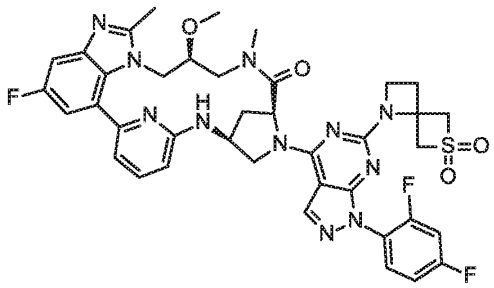
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(oxetan-3-yl)-1,6-diazaspiro[3.3]heptan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **643** was prepared in analogy to the preparation of Example **642** by using *tert*-butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate;oxalic acid instead of *tert*-butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate. LCMS ($M+H^+$): 821. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.26 (s, 1H), 7.87 - 7.77 (m, 1H), 7.68 - 7.56 (m, 1H), 7.38 - 7.27 (m, 2H), 7.26 - 7.13 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.74 - 6.62 (m, 1H), 5.86 - 5.65 (m, 1H), 5.44 - 5.25 (m, 1H), 4.61 (br d, *J* = 3.9 Hz, 2H), 4.55 - 4.42 (m, 2H), 4.41 - 4.34 (m, 1H), 4.33 - 4.24 (m, 2H), 4.21 - 4.09 (m, 2H), 4.06 - 3.91 (m, 2H), 3.90 - 3.72 (m, 2H), 3.62 - 3.51 (m, 1H), 3.48 - 3.38 (m, 2H), 3.16 - 3.01 (m, 3H), 2.98 - 2.74 (m, 5H), 2.65 - 2.43 (m, 7H).

Example 644

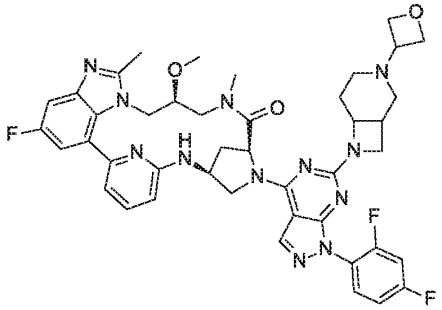
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6,6-dioxo-6λ⁶-thia-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **644** was prepared in analogy to the preparation of Example **483** by using 6λ⁶-thia-1-azaspiro[3.3]heptane 6,6-dioxide instead of 2λ⁶-thia-6-azaspiro[3.3]heptane 2,2-dioxide. LCMS (M+H⁺): 814. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.29 (s, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.30 (dd, J = 2.5, 8.5 Hz, 1H), 7.26 - 7.15 (m, 2H), 7.14 - 7.06 (m, 2H), 6.67 (d, J = 8.4 Hz, 1H), 5.76 - 5.60 (m, 1H), 5.21 - 5.01 (m, 1H), 4.51 - 4.33 (m, 2H), 4.27 (br d, J = 11.1 Hz, 1H), 4.21 - 4.00 (m, 4H), 3.97 - 3.89 (m, 2H), 3.15 - 3.01 (m, 2H), 2.97 (s, 3H), 2.90 - 2.75 (m, 5H), 2.75 - 2.63 (m, 2H), 2.60 - 2.54 (m, 3H), 2.53 - 2.42 (m, 2H).

Example 645

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,7-diazabicyclo[4.2.0]octan-7-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

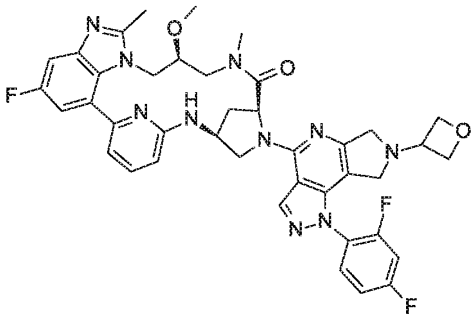


Example **645** was prepared in analogy to the preparation of Example **642** by using *tert*-butyl 3,7-diazabicyclo[4.2.0]octane-3-carboxylate;hydrochloride instead of *tert*-butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate. LCMS (M+H⁺): 835. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.29 - 8.20 (m, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.29 (br d, J = 8.4 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.14 (br d, J = 10.1 Hz, 2H), 7.08 (br d, J = 7.5 Hz, 1H), 6.65 (br d, J = 8.4 Hz, 1H), 5.82 (dt, J = 4.4, 15.8 Hz, 1H), 5.42 - 5.19 (m, 2H), 4.73 - 4.67 (m, 2H), 4.58 (br s,

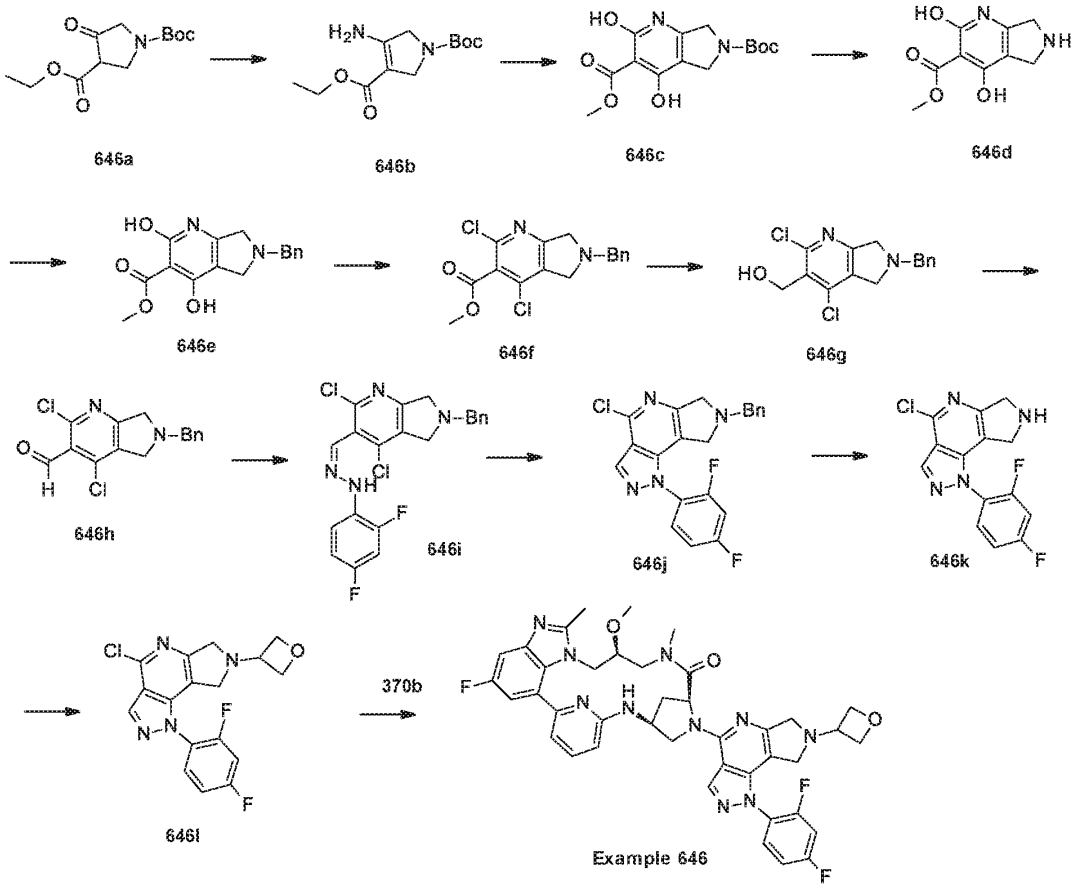
2H), 4.44 - 4.30 (m, 2H), 4.21 - 4.12 (m, 2H), 3.94 - 3.76 (m, 2H), 3.60 - 3.39 (m, 3H), 3.13 - 2.96 (m, 5H), 2.95 - 2.88 (m, 1H), 2.87 - 2.81 (m, 3H), 2.74 (br t, J = 13.2 Hz, 1H), 2.63 - 2.45 (m, 7H), 2.27 - 2.15 (m, 2H).

Example 646

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-(oxetan-3-yl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of 1-*tert*-butyl O3-ethyl 4-amino-2,5-dihydropyrrole-1,3-dicarboxylate (compound 646b)

To a solution of compound **646a** (50.0 g, 194.3 mmol) in ethanol (500 mL) was added ammonium acetate (150.0 g, 1946.0 mmol). The mixture was stirred at 80 °C for 12 hrs, then the mixture was diluted with H_2O (2 L) and extracted with EA (1 L×2). The combined organic layer was dried and concentrated, the residue was purified by column chromatography to give compound **646b** (42.0 g) as a yellow solid. LCMS ($M-C_4H_9+H^+$): 201.

Step 2: preparation of 6-*tert*-butyl O3-methyl 2,4-dihydroxy-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (compound 646c)

To a solution of compound **646b** (10.0 g, 39.0 mmol) in ethanol (60 mL) was added diethyl malonate (24.0 mL, 158.1 mmol) and sodium methoxide in MeOH (29.0 mL, 156.6 mmol). After being stirred at 120 °C for 12 hrs, the mixture was adjust pH = 7, and then poured into ice-water (1000 mL), while solid precipitated. The solid was collected by filtration and then dried to give compound **646c** (38.0 g) as a brown solid. LCMS ($M+H^+$): 311.

Step 3: preparation of methyl 2,4-dihydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridine-3-carboxylate (compound 646d)

To a solution of compound **646c** (38.0 g, 122.5 mmol) in DCM (300 mL) was added TFA (300.0 mL) at 0 °C, the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give compound **646d** (38.0 g) as a brown oil. LCMS ($M+H^+$):211.

Step 4: preparation of methyl 6-benzyl-2,4-dihydroxy-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxylate (compound 646e)

To a solution of compound **646d** (20.0 g, 95.15 mmol) and benzaldehyde (5.8 mL, 57.06 mmol) in methanol (160 mL) was added $NaBH(OAc)_3$ (36.0 g, 169.81 mmol) at 0 °C. After being stirred at 25 °C for 1 h, the reaction was quenched with water (1 L), and then extracted with EA (500 mL×3). The combined organic layer was dried and concentrated to give compound **646e** (16.0 g) as a brown oil. LCMS ($M+H^+$): 301.

Step 5: preparation of methyl 6-benzyl-2,4-dichloro-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxylate(compound 646f)

A mixture of compound **646e** (3.0 g, 10.0 mmol) in $POCl_3$ (30.0 mL, 10.0 mmol) was stirred at 120 °C for 36 hrs. Then the mixture was concentrated and then adjust pH = 8 by adding aq.sat.$NAHCO_3$, the resulted mixture was extracted with EtOAc. The organic layer was concentrated and the residue was purified by column chromatography to give compound **646f** (1.5 g) as a yellow oil. LCMS ($M+H^+$):337.

Step 6: preparation of (6-benzyl-2,4-dichloro-5,7-dihydropyrrolo[3,4-b]pyridin-3-yl)methanol(compound 646g)

To a solution of compound **646f** (1.3 g, 3.9 mmol) in DCM (25 mL) was added DIBAL-H (20.0 mL, 20.0 mmol) dropwise at 0 °C, then the mixture was stirred at 25 °C for 2 hrs. The reaction was quenched by adding water (1 mL), 15% NaOH (1 mL) and water (3 mL) slowly at 0 °C sequentially. Then 40 g of Na_2SO_4 was added, and the mixture was stirred at 25 °C for 0.5 hrs. The mixture was filtered and the filtrate was concentrated to give compound **646g** (1.1 g) as a yellow oil. LCMS ($M+H^+$): 309.

Step 7: preparation of 6-benzyl-2,4-dichloro-5,7-dihydropyrrolo[3,4-b]pyridine-3-carbaldehyde(compound 646h)

To a solution of oxalyl chloride (0.33 mL, 3.88 mmol) in DCM (50 mL) was added DMSO (0.46 mL, 6.47 mmol) in DCM (10 mL) dropwise at -70 °C. Then a solution of compound **646g** (1.0 g, 3.23 mmol) in DCM (10 mL) was added dropwise to the reaction mixture at -70°C, which was stirred at -70 °C for 2 hrs, then TEA (2.25 mL, 16.17 mmol, 5.0 eq) in DCM (20 mL) was

then added at -70 °C. The reaction mixture was stirred at rt for 12 hours and then diluted with DCM (100 mL), the mixture was washed with brine (50 mL), dried and concentrated. The residue was purified by prep-TLC to give compound **646h** (350.0 mg) as a yellow oil. LCMS ($M+H^+$): 307.

Step 8: preparation of *N*-[(*Z*)-(6-benzyl-2,4-dichloro-5,7-dihydropyrrolo[3,4-b]pyridin-3-yl)methyleneamino]-2,4-difluoro-aniline (compound 646i)

To a solution of **compound 646h** (350.0 mg, 1.14 mmol) in DMF (3 mL) was added 2,4-difluorophenylhydrazine hydrochloride (247.0 mg, 1.37 mmol), and then the mixture stirred at 25 °C for 2 hrs. The reaction was poured into water (20 mL) and extracted with ethyl acetate. The organic layer was dried and concentrated to give compound **646i** (550.0 mg) as a yellow oil. LCMS ($M+H^+$): 433.

Step 9: preparation of 11-benzyl-7-chloro-3-(2,4-difluorophenyl)-3,4,8,11-tetrazatricyclo[7.3.0.02,6]dodeca-1(9),2(6),4,7-tetraene (compound 646j)

To a suspension of compound **646i** (350.0 mg, 0.81 mmol) in DMF (3.5 mL) was added K_2CO_3 (350.0 mg, 2.53 mmol), CuI (17.5 mg, 0.09 mmol) and (1*R*,2*R*)-cyclohexane-1,2-diamine (21.0 mg, 0.18 mmol). The mixture was stirred at 80 °C for 12 hrs and then concentrated, the residue was purified by flash chromatography to give compound **646j** (120.0 mg) as a red solid. LCMS ($M+H^+$): 397.

Step 10: preparation of 7-chloro-3-(2,4-difluorophenyl)-3,4,8,11-tetrazatricyclo[7.3.0.02,6]dodeca-1(9),2(6),4,7-tetraene(compound 646k)

To a solution of compound **646j** (210.0 mg, 0.53 mmol) in DCE (2 mL) was added DIEA (0.13 mL, 0.81 mmol) and ACE-Cl (115.0 mg, 0.81 mmol) at 0 °C. The reaction mixture was stirred 25 °C for 2 hrs and then concentrated, the residue was dissolved in methanol (2 mL) and then heated at 60 °C for 2 hrs. The reaction mixture was directly purified by prep-HPLC to give compound **646k** (110.0 mg) as a red solid. LCMS ($M+H^+$): 307.

Step 11: preparation of 7-chloro-3-(2,4-difluorophenyl)-11-(oxetan-3-yl)-3,4,8,11-tetrazatricyclo[7.3.0.02,6]dodeca-1(9),2(6),4,7-tetraene(compound 646l)

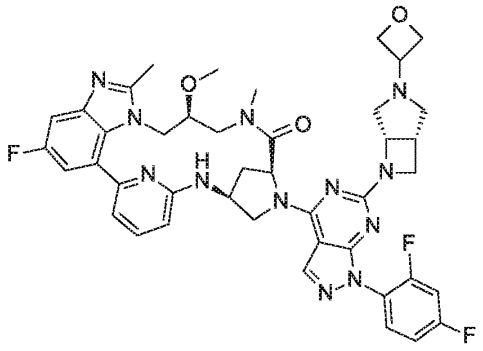
A mixture of compound **646k** (50.0 mg, 0.16 mmol) and 3-oxetanone (120.0 mg, 1.67 mmol) in methanol (1 mL) was stirred at 0 °C for 0.5 hrs, and then $NaBH_3CN$ (51.0 mg, 0.81 mmol) and AcOH (20.0 mg, 0.33 mmol) was added at 0 °C. After being stirred at 25 °C for 7 hrs, the mixture was diluted with water, and then extracted with EA. The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give compound **646l** (50.0 mg) as a brown solid. LCMS ($M+H^+$): 363.

Step 12: preparation of (8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-(oxetan-3-yl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 646)

A mixture of compound **370b** (190.0 mg, 0.34 mmol), compound **646l** (65.0 mg, 0.18 mmol), CsF (52.0 mg, 0.34 mmol) and *N,N*-diisopropylethylamine (0.18 mL, 1.03 mmol) in DMA (2 mL) was stirred at 130 °C for 12 hrs. The reaction mixture was purified by prep-HPLC to give Example **646** (22.0 mg). LCMS (M+H$^+$): 765. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.57 - 8.20 (m, 1H), 7.84 - 7.75 (m, 1H), 7.67 - 7.58 (m, 1H), 7.35 - 7.25 (m, 2H), 7.23 - 7.13 (m, 2H), 7.07 (d, J = 7.4 Hz, 1H), 6.61 (br d, J = 7.9 Hz, 1H), 5.70 (br dd, J = 4.1, 15.4 Hz, 1H), 5.39 (br d, J = 8.8 Hz, 1H), 4.77 - 4.66 (m, 2H), 4.64 - 4.50 (m, 3H), 4.49 - 4.07 (m, 4H), 4.03 - 3.84 (m, 3H), 3.84 - 3.72 (m, 1H), 3.64 - 3.41 (m, 2H), 3.09 - 2.95 (m, 2H), 2.93 - 2.83 (m, 2H), 2.81 (s, 3H), 2.64 - 2.58 (m, 1H), 2.53 (s, 2H), 2.50 - 2.39 (m, 2H).

Example 647

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(oxetan-3-yl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one

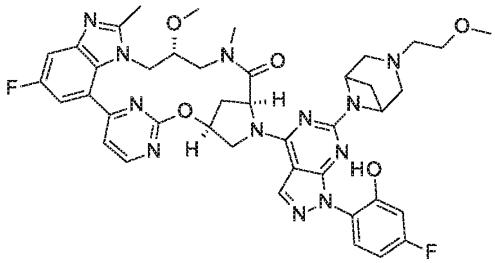


Example **647** was prepared in analogy to the preparation of Example **642** by using *tert*-butyl (1*R*,5*R*)-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate;hydrochloride instead of *tert*-butyl 1,7-diazaspiro[3.5]nonane-7-carboxylate. LCMS (M+H$^+$): 821. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.24 (s, 1H), 7.86 - 7.79 (m, 1H), 7.64 (dt, J = 5.9, 8.6 Hz, 1H), 7.37 - 7.28 (m, 1H), 7.23 (ddd, J = 2.6, 8.8, 10.1 Hz, 1H), 7.18 - 7.06 (m, 3H), 6.70 (d, J = 8.5 Hz, 1H), 5.90 - 5.78 (m, 1H), 5.45 - 5.32 (m, 1H), 4.78 - 4.74 (m, 2H), 4.67 - 4.63 (m, 1H), 4.59 (br s, 2H), 4.51 - 4.40 (m, 1H), 4.28 - 4.10 (m, 3H), 4.09 - 3.99 (m, 1H), 3.96 - 3.74 (m, 3H), 3.53 - 3.45 (m,

1H), 3.13 (s, 1H), 3.09 - 3.04 (m, 3H), 3.03 - 2.96 (m, 1H), 2.93 - 2.84 (m, 4H), 2.78 (br d, *J* = 13.5 Hz, 1H), 2.59 (s, 3H), 2.55 - 2.44 (m, 2H), 2.21 - 2.12 (m, 1H), 2.04 - 1.97 (m, 1H).

Example 648

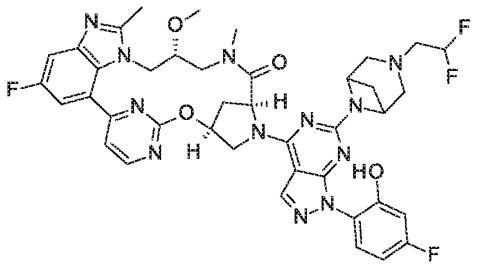
(8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **648** was prepared in analogy to the preparation of Example **639b** by using compound **78d-2** and **580b** instead of compound **370b** and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS (M+H$^+$): 823. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.77 (d, *J* = 5.1 Hz, 1H), 8.36 (s, 1H), 7.63 (br s, 2H), 7.54 - 7.49 (m, 2H), 6.80 - 6.72 (m, 2H), 5.92 (br s, 1H), 5.87 - 5.70 (m, 1H), 5.52 - 5.43 (m, 1H), 4.57 - 4.46 (m, 2H), 4.44 - 4.34 (m, 2H), 4.26 - 4.17 (m, 1H), 4.15 - 3.95 (m, 3H), 3.87 (br d, *J* = 12.0 Hz, 1H), 3.76 - 3.53 (m, 6H), 3.27 - 3.17 (m, 3H), 3.16 - 3.01 (m, 4H), 2.97 - 2.89 (m, 1H), 2.89 - 2.86 (m, 3H), 2.86 - 2.77 (m, 2H), 2.76 - 2.71 (m, 3H), 2.09 - 1.98 (m, 1H).

Example 649

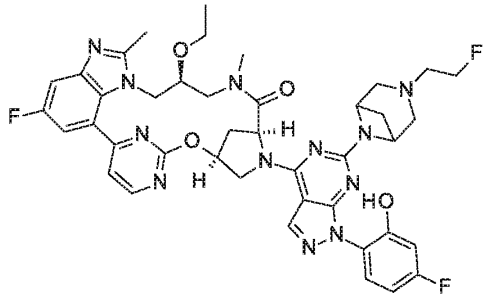
(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



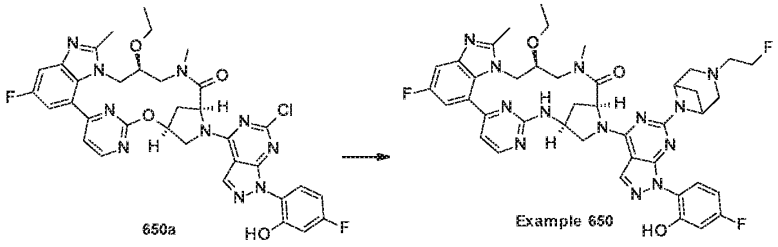
Example **649** was prepared in analogy to the preparation of Example **639b** by using compound **78d-2** and **651b** instead of compound **370b** and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS ($M+H^+$): 829. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.71 (d, J = 5.1 Hz, 1H), 8.28 (s, 1H), 7.71 (dd, J = 6.2, 8.7 Hz, 1H), 7.46 (d, J = 5.1 Hz, 1H), 7.42 (dd, J = 2.6, 8.4 Hz, 1H), 7.33 (dd, J = 2.3, 10.1 Hz, 1H), 6.79 - 6.70 (m, 2H), 5.89 - 5.84 (m, 1H), 5.82 - 5.66 (m, 1H), 5.46 (d, J = 8.3 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.47 - 4.42 (m, 1H), 4.42 - 4.33 (m, 1H), 4.32 - 4.27 (m, 1H), 4.26 - 4.21 (m, 1H), 4.18 (br d, J = 16.6 Hz, 1H), 4.04 (d, J = 14.5 Hz, 1H), 3.51 - 3.43 (m, 1H), 3.42 - 3.34 (m, 2H), 3.19 - 3.13 (m, 1H), 3.13 - 3.01 (m, 4H), 3.01 - 2.97 (m, 1H), 2.95 - 2.88 (m, 1H), 2.88 - 2.83 (m, 1H), 2.82 (s, 3H), 2.79 - 2.71 (m, 2H), 2.64 - 2.59 (m, 3H), 2.58 - 2.52 (m, 1H), 1.79 (d, J = 8.1 Hz, 1H).

Example 650

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

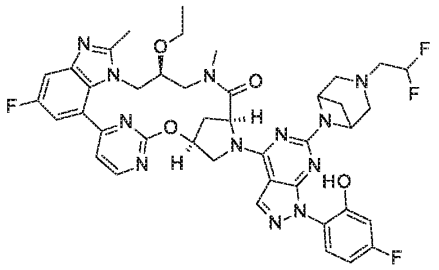


Example **650** was prepared in analogy to the preparation of Example **580** by using compound **582b** instead of compound **580b** and compound **650a** (the synthesis refer to compound **213a** by using compound **81d-1** instead of compound **370b**) instead of compound **575a**. LCMS ($M+H^+$): 825. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.74 - 8.61 (m, 1H), 8.21 - 8.10 (m, 1H), 7.72 - 7.58 (m, 1H), 7.56 - 7.43 (m, 1H), 7.40 - 7.22 (m, 2H), 6.70 - 6.54 (m, 2H),

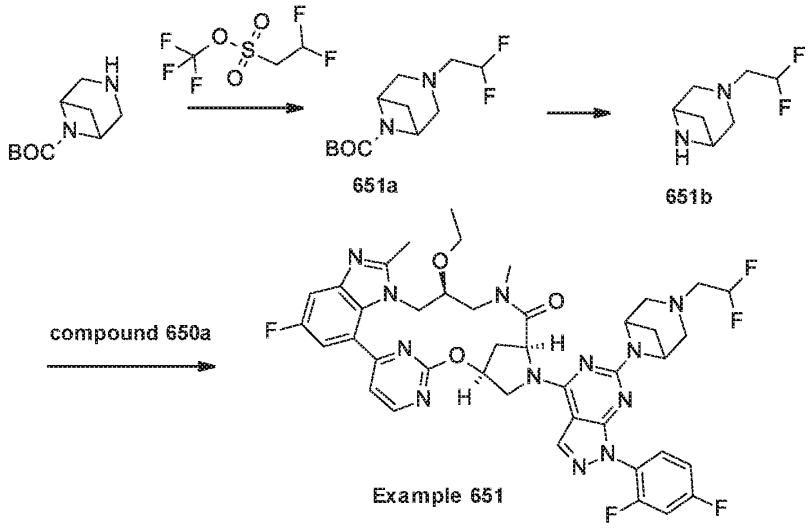
5.82 - 5.62 (m, 2H), 5.36 - 5.21 (m, 1H), 4.58 - 4.00 (m, 7H), 3.95 - 3.80 (m, 1H), 3.19 - 3.11 (m, 2H), 3.05 - 2.82 (m, 5H), 2.81 - 2.57 (m, 6H), 2.56 - 2.39 (m, 6H), 1.85 - 1.71 (m, 1H), 0.56 - 0.36 (m, 3H).

Example 651

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



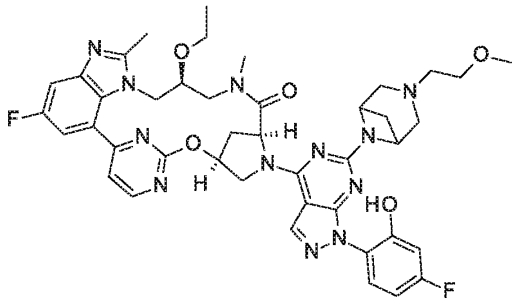
The title compound was prepared according to the following scheme:



Example **651** was prepared in analogy to the preparation of Example **580** by using trifluoromethyl 2,2-difluoroethanesulfonate instead of 1-bromo-2-methoxy-ethane and compound **650a** instead of compound **575a**. LCMS (M+H$^+$): 843. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.76 - 8.60 (m, 1H), 8.28 - 8.06 (m, 1H), 7.73 - 7.44 (m, 2H), 7.41 - 7.27 (m, 2H), 6.73 - 6.54 (m, 2H), 5.95 - 5.50 (m, 3H), 5.38 - 5.15 (m, 1H), 4.43 - 4.26 (m, 2H), 4.26 - 4.02 (m, 3H), 4.00 - 3.74 (m, 1H), 3.45 - 3.25 (m, 2H), 3.02 - 2.66 (m, 10H), 2.61 - 2.38 (m, 7H), 1.86 - 1.60 (m, 1H), 0.54 - 0.40 (m, 3H).

Example 652

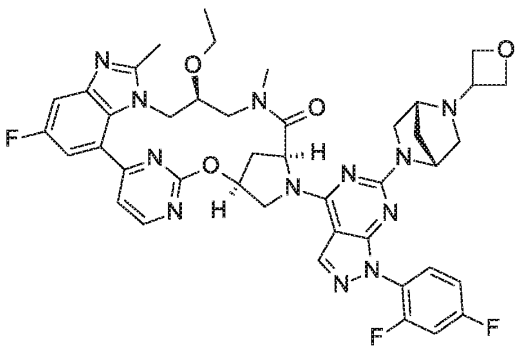
(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **652** was prepared in analogy to the preparation of Example **580** by using compound **650a** instead of compound **575a**. LCMS (M+H$^+$): 837. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.69 (d, J = 5.3 Hz, 1H), 8.29 - 8.17 (m, 1H), 7.65 - 7.46 (m, 2H), 7.44 - 7.26 (m, 2H), 6.75 - 6.58 (m, 2H), 5.83 - 5.58 (m, 2H), 5.41 - 5.26 (m, 1H), 4.57 - 4.20 (m, 5H), 4.17 - 3.72 (m, 4H), 3.71 - 3.36 (m, 6H), 3.13 - 2.85 (m, 6H), 2.82 - 2.40 (m, 9H), 2.00 - 1.78 (m, 1H), 0.59 - 0.40 (m, 3H).

Example 653

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

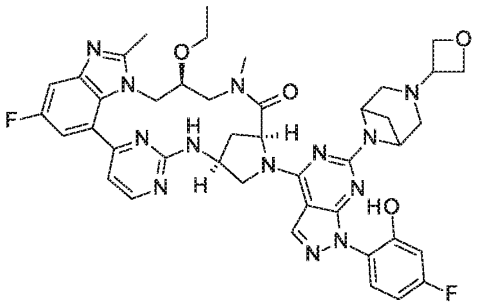


Example **653** was prepared in analogy to the preparation of Example **574** by using compound **81d-1** instead of compound **326d-1** and intermediate **C88** instead of compound **574e**.

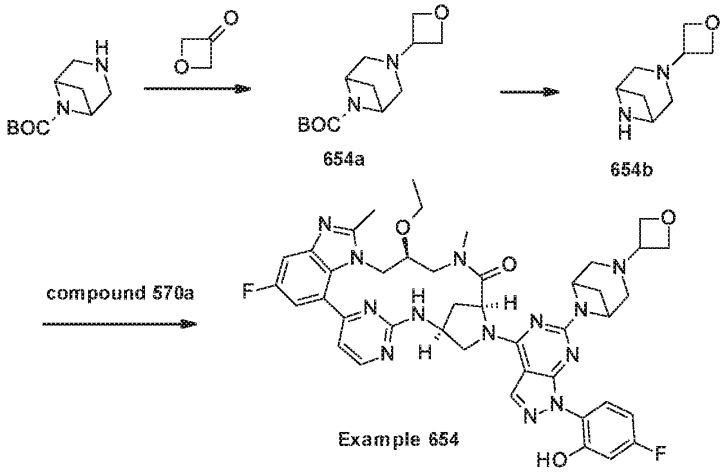
LCMS (M+H$^+$): 837. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.77 - 8.58 (m, 1H), 8.24 - 8.08 (m, 1H), 7.63 - 7.41 (m, 2H), 7.41 - 7.26 (m, 2H), 7.21 - 6.93 (m, 2H), 5.83 - 5.52 (m, 2H), 5.44 - 5.21 (m, 1H), 4.69 - 4.60 (m, 3H), 4.52 - 4.22 (m, 4H), 4.19 - 3.71 (m, 4H), 3.69 - 3.39 (m, 2H), 3.11 - 2.84 (m, 5H), 2.81 - 2.66 (m, 2H), 2.67 - 2.38 (m, 6H), 1.99 - 1.81 (m, 2H), 1.33 - 1.17 (m, 1H), 0.55 - 0.41 (m, 3H).

Example 654

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 654a)

A mixture of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (200 mg, 1 mmol) and oxetan-3-one (218 mg, 3 mmol) in ethanol (4 mL) was stirred at 60 °C for 2 hours, then $NaBH_3CN$ (317 mg, 5 mmol) was added and stirred at 60 °C for 6 hours. The reaction mixture

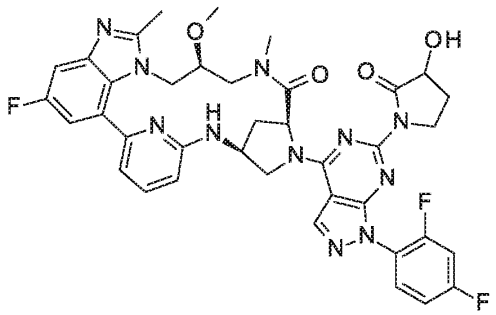
was filtered and the filtrate was purified by prep-HPLC to give compound **654a** (50 mg). LCMS ($M+H^+$): 255.

Step 2-3: preparation of (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 654)

Example **654** was prepared in analogy to the preparation of Example **580** by using compound **570a** instead of compound **575a** and compound **654a** instead of compound **580a**. LCMS ($M+H^+$): 834. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.45 (d, J = 5.1 Hz, 1H), 8.24 - 8.09 (m, 1H), 7.66 - 7.57 (m, 1H), 7.38 - 7.26 (m, 1H), 7.24 - 7.05 (m, 1H), 7.03 - 6.91 (m, 1H), 6.74 - 6.56 (m, 2H), 5.57 - 5.40 (m, 1H), 5.28 - 5.16 (m, 1H), 4.64 - 4.41 (m, 6H), 4.39 - 4.03 (m, 5H), 4.00 - 3.75 (m, 2H), 3.18 - 3.09 (m, 2H), 3.06 - 2.69 (m, 7H), 2.61 - 2.33 (m, 7H), 1.79 (d, J = 8.1 Hz, 1H), 0.58 - 0.40 (m, 3H).

Example 655

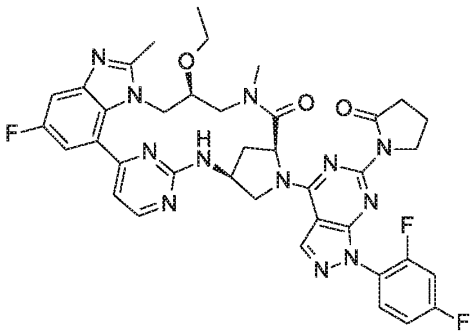
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **655** was prepared in analogy to the preparation of Example **587** by using 3-hydroxypyrrolidin-2-one instead of 3-methyl-2-pyrrolidinone. LCMS ($M+H^+$): 766. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.48 (s, 1H), 7.80 - 7.73 (m, 2H), 7.65 - 7.56 (m, 1H), 7.40 - 7.28 (m, 2H), 7.18 - 7.07 (m, 2H), 6.67 - 6.63 (m, 1H), 5.80 - 5.50 (m, 3H), 5.45 - 5.38 (m, 1H), 4.64 - 3.45 (m, 8H), 3.04 - 2.78 (m, 4H), 2.76 - 2.70 (m, 3H), 2.62 - 2.55 (m, 2H), 2.47 - 2.40 (m, 3H), 2.39 - 2.25 (m, 2H), 1.82 - 1.67 (m, 1H).

Example 656

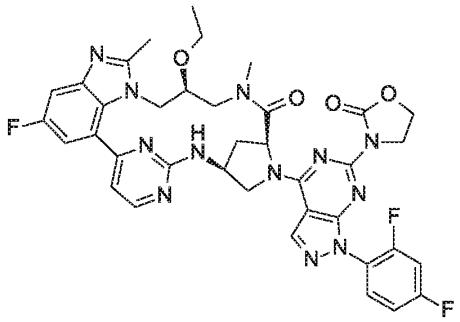
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **656** was prepared in analogy to the preparation of Example **587** by using 2-pyrrolidinone instead of 3-methyl-2-pyrrolidinone and compound **575a** instead of compound **370b**. LCMS (M+H$^+$): 767. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.50 - 8.37 (m, 1H), 8.35 - 8.26 (m, 1H), 7.70 - 7.52 (m, 1H), 7.36 - 7.11 (m, 3H), 7.09 - 6.92 (m, 2H), 5.49 - 5.41 (m, 1H), 5.39 - 5.33 (m, 1H), 4.52 - 4.35 (m, 2H), 4.16 - 4.00 (m, 2H), 3.97 - 3.82 (m, 2H), 3.82 - 3.65 (m, 2H), 3.17 - 3.06 (m, 1H), 3.01 - 2.88 (m, 3H), 2.88 - 2.80 (m, 1H), 2.74 - 2.67 (m, 1H), 2.53 - 2.47 (m, 4H), 2.43 - 2.28 (m, 3H), 1.94 - 1.72 (m, 2H), 0.54 - 0.37 (m, 3H).

Example 657

3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one

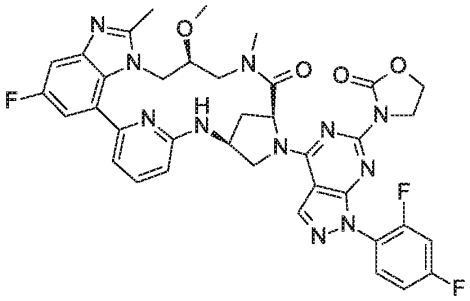


Example **657** was prepared in analogy to the preparation of Example **587** by using oxazolidin-2-one instead of 3-methyl-2-pyrrolidinone and compound **575a** instead of compound **370b**. LCMS (M+H$^+$): 769. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.55 - 8.41 (m, 1H), 8.36 - 7.52 (m, 2H), 7.39 - 7.24 (m, 1H), 7.24 - 7.10 (m, 2H), 7.09 - 6.93 (m, 2H), 5.57 - 5.14 (m, 2H),

4.68 - 4.64 (m, 1H), 4.34 - 4.17 (m, 3H), 4.16 - 4.04 (m, 2H), 4.02 - 3.75 (m, 3H), 3.18 - 3.12 (m, 1H), 3.00 - 2.87 (m, 3H), 2.87 - 2.64 (m, 2H), 2.59 - 2.29 (m, 6H), 0.55 - 0.40 (m, 3H).

Example 658

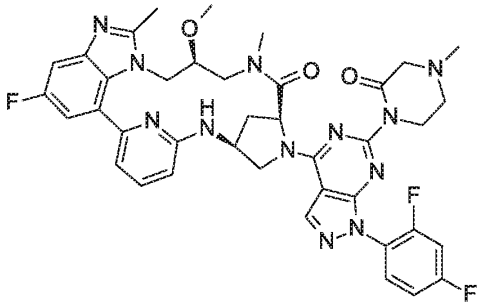
3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one



Example **658** was prepared in analogy to the preparation of Example **587** by using oxazolidin-2-one instead of 3-methyl-2-pyrrolidinone. LCMS (M+H$^+$): 754. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.37 (s, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.30 - 7.24 (m, 1H), 7.24 - 7.19 (m, 1H), 7.19 - 7.08 (m, 2H), 7.07 - 7.01 (m, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.70 (br dd, *J* = 3.4, 15.6 Hz, 1H), 5.43 (d, *J* = 8.9 Hz, 1H), 4.61 - 4.52 (m, 1H), 4.42 - 4.24 (m, 3H), 4.24 - 4.11 (m, 2H), 4.10 - 3.97 (m, 2H), 3.91 (br dd, *J* = 9.1, 14.2 Hz, 1H), 3.08 - 2.95 (m, 3H), 2.93 - 2.81 (m, 1H), 2.81 - 2.78 (m, 3H), 2.77 - 2.70 (m, 1H), 2.55 - 2.50 (m, 3H), 2.49 - 2.37 (m, 2H).

Example 659

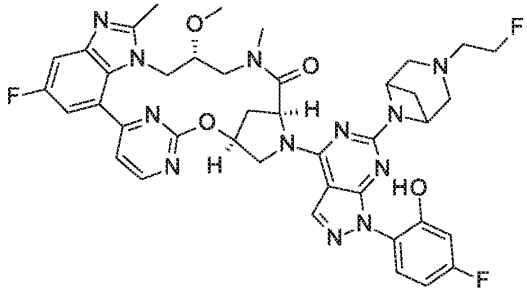
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-2-oxo-piperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **659** was prepared in analogy to the preparation of Example **587** by using 4-methylpiperazin-2-one instead of 3-methyl-2-pyrrolidinone. LCMS ($M+H^+$): 771. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (s, 1H), 7.84 - 7.78 (m, 1H), 7.71 - 7.60 (m, 1H), 7.30 (dd, J = 2.6, 8.6 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.20 - 7.12 (m, 2H), 7.12 - 7.06 (m, 1H), 6.70 - 6.63 (m, 1H), 5.82 - 5.64 (m, 1H), 5.49 - 5.37 (m, 1H), 4.69 - 4.64 (m, 1H), 4.61 - 4.55 (m, 1H), 4.51 (dd, J = 6.0, 11.5 Hz, 1H), 4.35 - 4.23 (m, 1H), 4.18 - 4.10 (m, 1H), 3.95 - 3.87 (m, 2H), 3.80 (t, J = 5.8 Hz, 1H), 3.27 - 3.18 (m, 2H), 3.12 - 2.99 (m, 3H), 2.91 - 2.84 (m, 2H), 2.84 - 2.81 (m, 3H), 2.81 - 2.72 (m, 1H), 2.58 - 2.54 (m, 3H), 2.53 - 2.44 (m, 2H), 2.41 - 2.34 (m, 3H).

Example 660

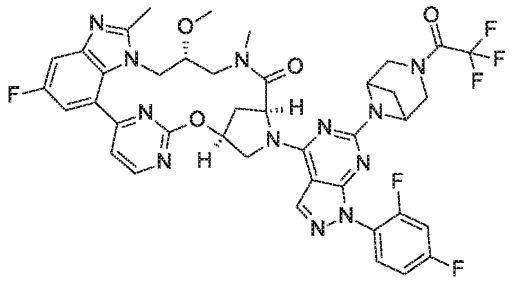
(8*S*,11*S*,15*S*)-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **660** was prepared in analogy to the preparation of Example **639b** by using compound **78d-2** and **582b** instead of compound **370b** and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS ($M+H^+$): 811.

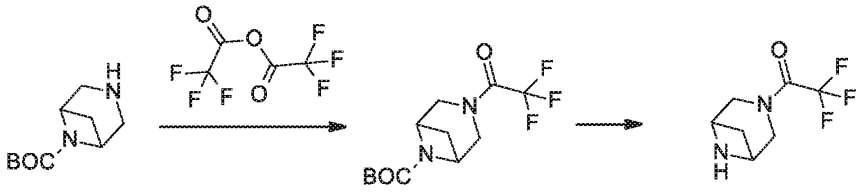
Example 661

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **661** was prepared in analogy to the preparation of Example **575** by using compound **78d-2** instead of compound **326d-1** and compound **661b** instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. Example **661**, LCMS ($M+H^+$): 863. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.81 - 8.75 (m, 1H), 8.33 - 8.28 (m, 1H), 7.70 - 7.50 (m, 4H), 7.28 - 7.21 (m, 1H), 7.20 - 7.12 (m, 1H), 6.19 - 5.92 (m, 1H), 5.89 - 5.78 (m, 1H), 5.45 (br d, J = 8.9 Hz, 1H), 4.54 - 4.39 (m, 3H), 4.36 (br d, J = 6.1 Hz, 2H), 4.32 - 4.22 (m, 1H), 4.21 - 4.10 (m, 1H), 3.84 - 3.72 (m, 1H), 3.68 - 3.53 (m, 2H), 3.52 - 3.45 (m, 1H), 3.28 - 3.19 (m, 2H), 3.15 - 3.02 (m, 3H), 2.94 - 2.81 (m, 6H), 2.81 - 2.69 (m, 2H), 1.68 - 1.57 (m, 1H).

The compound **661b** was prepared according to the following scheme:



661a **661b**

Step 1: preparation *tert*-butyl 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1] heptane-6-carboxylate (compound 661a)

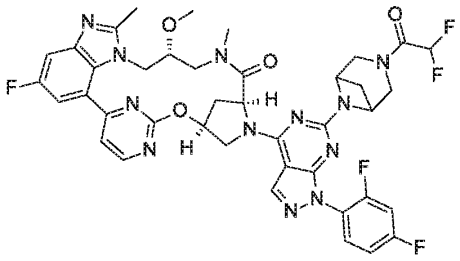
To a tube was added *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (500 mg, 2.5 mmol), DIEA (587 mg, 4.54 mmol), dichloromethane (5 mL) and TFAA (900 mg, 4.29 mmol). After being stirred at r.t. for 40 hrs, the reaction mixture was concentrated to give an oil, which was purified by silica gel to give compound **661a** as an oil. LCMS ($M+H^+$): 295.

Step 2: preparation 1-[3,6-diazabicyclo[3.1.1]heptan-3-yl]-2,2,2-trifluoro-ethanone (compound 661b)

A mixture of compound **661b** (656 mg, 2.23 mmol) in dichloromethane (2 mL) and TFA (2 mL) was stirred at r.t. for 4 hrs. Then the mixture was concentrated to give compound **661b** as an oil. LCMS ($M+H^+$): 195.

Example 662

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

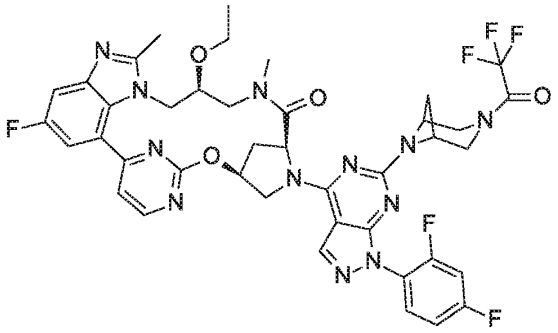


Example **662** was prepared in analogy to the preparation of Example **575** by using compound **78d-2** instead of compound **326d-1** and compound **662b** instead of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate. LCMS (M+H$^+$): 845. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.79 (t, *J* = 5.3 Hz, 1H), 8.31 (d, *J* = 2.8 Hz, 1H), 7.71 - 7.65 (m, 2H), 7.65 - 7.58 (m, 1H), 7.55 (dd, *J* = 5.3, 6.6 Hz, 1H), 7.24 (tt, *J* = 1.8, 9.1 Hz, 1H), 7.20 - 7.12 (m, 1H), 6.32 (t, *J* = 53.0 Hz, 1H), 6.15 - 5.91 (m, 1H), 5.89 - 5.81 (m, 1H), 5.46 (d, *J* = 9.0 Hz, 1H), 4.53 - 4.45 (m, 2H), 4.44 - 4.29 (m, 4H), 4.29 - 4.18 (m, 1H), 4.14 - 3.97 (m, 1H), 3.76 - 3.65 (m, 1H), 3.64 - 3.55 (m, 1H), 3.54 - 3.43 (m, 1H), 3.30 - 3.18 (m, 2H), 3.15 - 3.05 (m, 3H), 2.95 - 2.90 (m, 3H), 2.90 - 2.82 (m, 3H), 2.81 - 2.69 (m, 2H), 1.60 (dd, *J* = 4.1, 9.0 Hz, 1H).

The compound **662b** was prepared in analogy to the preparation of compound **661b** by using (2,2-difluoroacetyl) 2,2-difluoroacetate instead of (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (TFAA).

Example 663

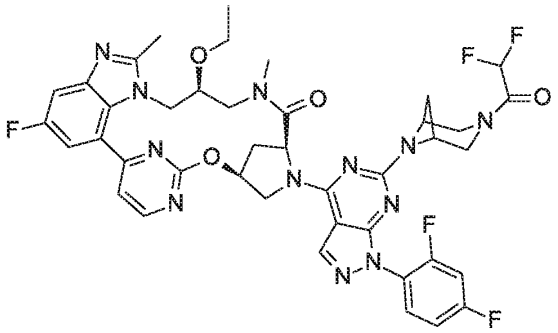
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **663** was prepared in analogy to the preparation of Example **575** by using compound **565a** instead of compound **575a** and compound **661b** instead of 3-oxa-6-azabicyclo[3.1.1]heptane. LCMS ($M+H^+$): 877. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.97 - 8.81 (m, 1H), 8.36 - 8.27 (m, 1H), 7.80 - 7.54 (m, 4H), 7.35 - 7.10 (m, 2H), 6.13 - 5.96 (m, 1H), 5.90 - 5.79 (m, 1H), 5.50 - 5.35 (m, 1H), 4.62 - 3.94 (m, 8H), 3.90 - 3.73 (m, 1H), 3.68 - 3.39 (m, 2H), 3.15 - 2.99 (m, 3H), 2.99 - 2.61 (m, 9H), 1.67 - 1.56 (m, 1H), 0.70 - 0.54 (m, 3H).

Example 664

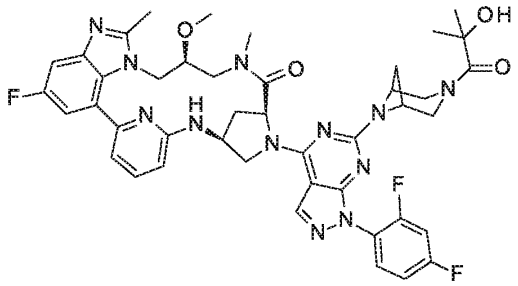
(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



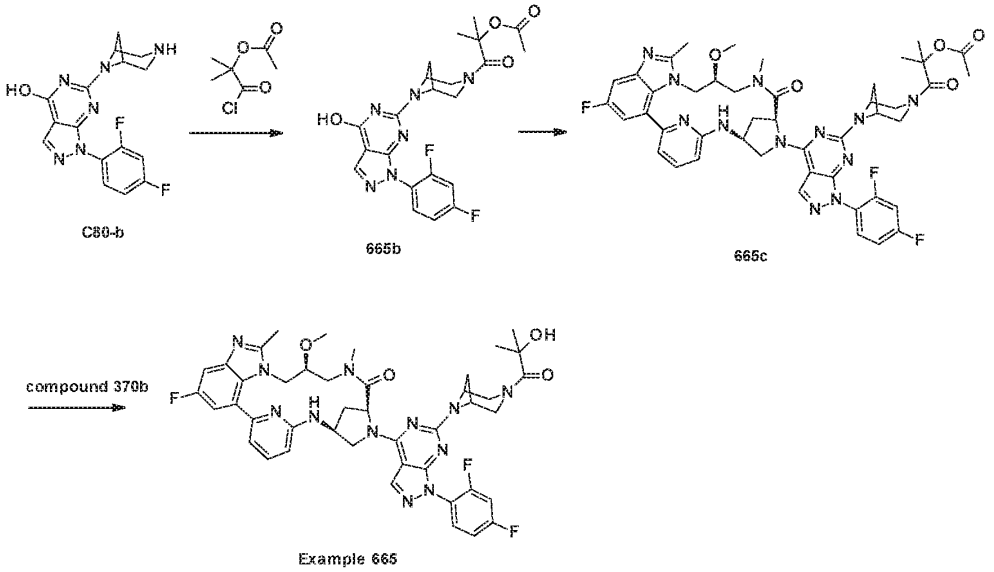
Example **664** was prepared in analogy to the preparation of Example **575** by using compound **565a** instead of compound **575a** and compound **662b** instead of 3-oxa-6-azabicyclo[3.1.1]heptane. LCMS ($M+H^+$): 859. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.94 - 8.82 (m, 1H), 8.40 - 8.23 (m, 1H), 7.80 - 7.57 (m, 4H), 7.34 - 7.12 (m, 2H), 6.14 - 5.96 (m, 1H), 5.91 - 5.71 (m, 1H), 5.50 - 5.38 (m, 1H), 4.56 - 4.21 (m, 7H), 4.15 - 3.92 (m, 1H), 3.85 - 3.61 (m, 1H), 3.57 - 3.39 (m, 2H), 3.12 - 2.65 (m, 13H), 1.67 - 1.58 (m, 1H), 0.71 - 0.55 (m, 3H).

Example 665

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



Step 1: preparation of [2-[6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]-1,1-dimethyl-2-oxo-ethyl] acetate (compound 665b)

To a solution of compound **C80-b** (100 mg, 0.22 mmol), *N,N*-diisopropylethylamine (0.15 mL, 0.87 mmol) was added 2-acetoxyisobutyryl chloride (43 mg, 0.26 mmol). After being stirred at 20°C for 1.5 hrs, the reaction was diluted with water and extracted with EA. The organic layer was dried and concentrated *in vacuo* to give compound **665b** (52 mg) as yellow gum. LCMS ($M+H^+$): 473.

Step 2: preparation of [2-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]-1,1-dimethyl-2-oxo-ethyl] acetate (compound 665c)

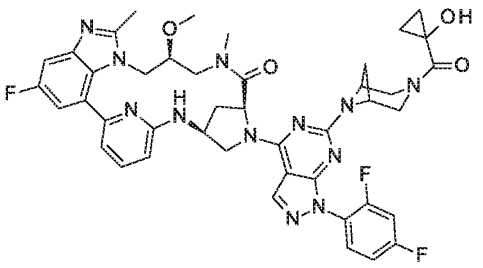
To a solution of compound **665b** (52 mg, 0.11 mmol) was added DIEA (116 mg, 0.9 mmol) and PyBOP (70 mg, 0.14 mmol). After being stirred at rt for 10 mins, the reaction mixture was added with compound **370b** (50.0 mg, 0.09 mmol) and stirred at 25 °C for 1 h, then diluted with water and extracted with EA, the organic layer was dried and concentrated to give compound **665c** (35.0 mg) as yellow solid. LCMS (M+H$^+$): 893.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 665)

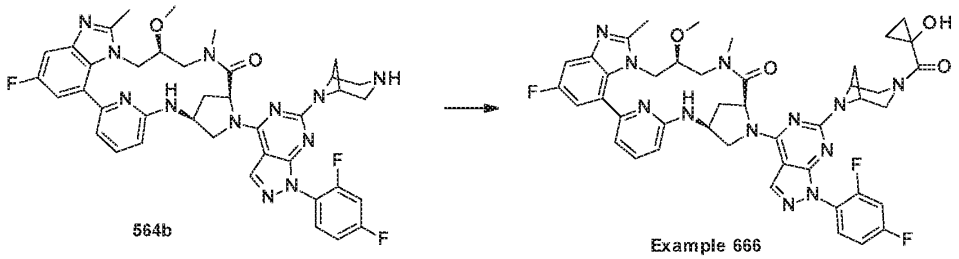
A mixture of compound **665c** (35.0 mg, 0.04 mmol) and K_2CO_3 (27 mg, 0.2 mmol) in methanol (2 mL) was at 60 °C for 5 hrs. The reaction was filtered and the filtrate was purified by prep-HPLC to give Example **665** (8 mg). LCMS (M+H$^+$): 851. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37 - 8.26 (m, 1H), 7.88 - 7.78 (m, 1H), 7.68 - 7.55 (m, 3H), 7.46 - 7.40 (m, 1H), 7.32 - 7.25 (m, 1H), 7.18 - 7.11 (m, 1H), 6.82 - 6.65 (m, 1H), 5.99 - 5.67 (m, 1H), 5.57 - 5.31 (m, 1H), 5.28 - 5.15 (m, 1H), 4.68 - 4.49 (m, 1H), 4.48 - 4.29 (m, 2H), 4.28 - 4.03 (m, 6H), 2.95 (s, 3H), 2.91 - 2.83 (m, 2H), 2.83 - 2.79 (m, 3H), 2.71 - 2.63 (m, 4H), 2.40 - 2.30 (m, 2H), 1.57 - 1.35 (m, 2H), 1.35 - 1.17 (m, 6H).

Example 666

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



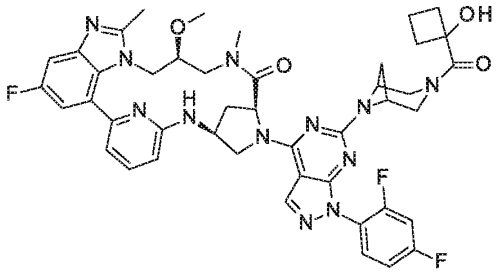
The title compound was prepared according to the following scheme:



A mixture of compound **564b** (30 mg, 0.04 mmol), 1-hydroxycyclopropane-1-carboxylic acid (26 mg, 0.2 mmol), DIEA (53 mg, 0.41 mmol) and T_3P (52.0 mg, 0.08 mmol) in DMF (1 mL) was stirred at 25 °C for 16 hrs. Then reaction mixture was purified by prep-HPLC to give Example **666** (12.5 mg). LCMS ($M+H^+$): 849. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.18 - 7.99 (m, 1H), 7.89 - 7.65 (m, 2H), 7.61 - 7.49 (m, 1H), 7.23 - 6.91 (m, 4H), 6.64 - 6.39 (m, 1H), 5.31 - 5.20 (m, 1H), 4.64 - 4.57 (m, 1H), 4.51 - 4.34 (m, 3H), 4.32 - 4.21 (m, 2H), 4.19 - 4.06 (m, 2H), 3.99 - 3.86 (m, 1H), 3.13 - 3.06 (m, 1H), 3.04 - 2.96 (m, 3H), 2.95 - 2.88 (m, 4H), 2.87 - 2.81 (m, 3H), 2.79 - 2.74 (m, 1H), 2.67 (br s, 2H), 2.58 (br s, 2H), 2.08 - 1.98 (m, 2H), 1.65 - 1.41 (m, 2H), 0.96 - 0.79 (m, 2H).

Example 667

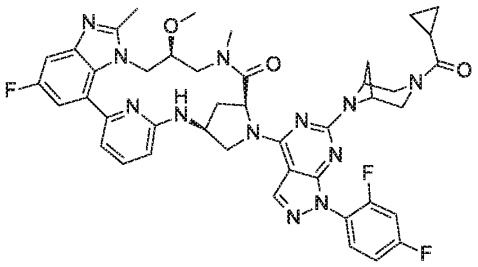
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **667** was prepared in analogy to the preparation of Example **666** by using 1-hydroxycyclobutanecarboxylic acid instead of 1-hydroxycyclopropane-1-carboxylic acid. LCMS ($M+H^+$): 863. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.07 (d, *J* = 7.8 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.57 - 7.49 (m, 1H), 7.07 - 6.99 (m, 4H), 6.50 (br d, *J* = 8.0 Hz, 1H), 5.30 - 5.22 (m, 1H), 4.56 (s, 1H), 4.45 - 4.36 (m, 4H), 4.32 - 4.27 (m, 1H), 4.22 - 4.14 (m, 2H), 3.08 (s, 1H), 3.04 (s, 1H), 2.99 (s, 2H), 2.97 - 2.92 (m, 5H), 2.91 (s, 1H), 2.85 - 2.78 (m, 3H), 2.68 - 2.60 (m, 2H), 2.52 - 2.43 (m, 4H), 1.56 - 1.43 (m, 4H), 1.30 - 1.22 (m, 2H).

Example 668

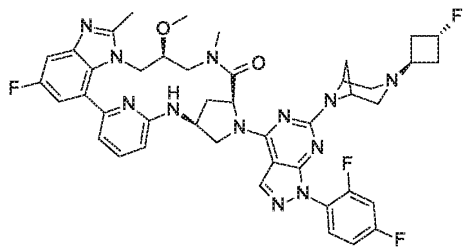
(8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **668** was prepared in analogy to the preparation of compound **665c** by using cyclopropanecarbonyl chloride instead of 2-acetoxyisobutyryl chloride. LCMS (M+H$^+$): 833. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.06 (d, *J* = 2.9 Hz, 1H), 7.78 - 7.69 (m, 1H), 7.60 - 7.39 (m, 2H), 7.20 - 7.06 (m, 2H), 7.05 - 6.92 (m, 2H), 6.46 (br t, *J* = 7.8 Hz, 1H), 6.07 - 5.70 (m, 1H), 5.34 - 5.15 (m, 1H), 4.65 - 4.38 (m, 4H), 4.36 - 4.26 (m, 2H), 4.21 - 4.05 (m, 3H), 3.76 - 3.45 (m, 2H), 3.09 - 2.96 (m, 3H), 2.84 - 2.75 (m, 5H), 2.74 - 2.59 (m, 4H), 2.53 - 2.31 (m, 2H), 1.38 - 1.28 (m, 2H), 0.98 - 0.85 (m, 2H), 0.80 - 0.66 (m, 2H).

Example 669

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-fluorocyclobutyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **669** was prepared in analogy to the preparation of Example **431** by using Intermediate **C95** instead of compound **431c**. LCMS (M+H$^+$): 837. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.10 - 7.98 (m, 1H), 7.75 - 7.66 (m, 1H), 7.60 - 7.49 (m, 1H), 7.40 (dd, *J*

= 2.3, 8.6 Hz, 1H), 7.14 - 7.04 (m, 2H), 6.99 (br t, *J* = 9.0 Hz, 2H), 6.48 - 6.37 (m, 1H), 5.99 - 5.73 (m, 1H), 5.36 - 5.23 (m, 1H), 5.19 - 5.07 (m, 1H), 5.06 - 4.73 (m, 1H), 4.68 - 4.52 (m, 1H), 4.46 - 4.36 (m, 1H), 4.28 (br s, 1H), 4.22 - 4.12 (m, 2H), 4.12 - 3.70 (m, 2H), 3.12 (br s, 1H), 3.11 - 2.99 (m, 2H), 2.95 (s, 3H), 2.82 (br d, *J* = 10.0 Hz, 1H), 2.77 (s, 3H), 2.74 - 2.62 (m, 2H), 2.57 (s, 3H), 2.55 - 2.40 (m, 4H), 2.38 - 2.15 (m, 2H), 2.12 - 1.90 (m, 2H).

Example 670

Microliter plate-based TR-FRET assay for binders of STING

This is the competition-binding assay to test the compounds' potency to the C-terminal Domain (CTD) and ligand-binding domain of human stimulator of interferon genes (STING). STING (139-379, Q86WV6, http://www.uniprot.org/uniprot) recombinant protein (in 20mM Tris, 150mM NaCl, pH 8.0, and expression in Escherichia coli (E. coil) BL21 (DE3)) with a C-terminal flag-tag was employed for the assay. When Alexa-488 labeled active site probe (refer to patent WO2017/175156 A1) bounds to STING (139-379), it accepts the 485 nm emission from Tb-M2-Flag-STING and results in an increase in fluorescence at 520 nm. Compounds that compete for the probe-binding site will reduce 520 nm signal. The assay was run in proxiplate-384 plus (PerkinElmer, cat: 60150300) containing of 2.5 nM STING, 2.5 nM M2-Tb (Cisbio, 61FG2TLA, Lot: 17A) and 250 nM Alexa488 probe. Plates were centrifuged for 1 min at 1000 rpm, incubated for 30 min at room temperature, and then measured the dual fluorescence emission at 520 nM / 485 nM following 320 nm laser excitation on an Envision plate reader (Perkin-Elmer). The compounds' effect on the STING binding is detected by measuring ratiometric fluorescence from time-resolved FRET. The percentage of inhibition of at each compound concentration is calculated on the basis of their changes of TR-FRET efficiency relative to the change of TR-FRET caused by positive control 2'3'cGAMP (Sigma, cat: SML1229).

Example NO.	FRET_IC50 (nM)	Example NO.	FRET_IC50 (nM)	Example NO.	FRET_IC50 (nM)
1	9.3	**239**	2.7	**483**	1.7
2	174.7	**241**	4.9	**484**	1.6
4	0.2	**243**	1.5	**485**	1.7
5	9.5	**244**	2.3	**486**	2.3
7	1.4	**245**	2.3	**487**	2.8
9	12	**246**	4.6	**488**	1.3
11	6.1	**247**	4.8	**489**	1.3

12	2.2	**248**	1.6	**490**	1
13A	8.3	**250**	1.9	**491**	1.1
13B	1.7	**251**	6.2	**492**	1
14A	4.2	**252**	1.5	**493**	1
14B	1.7	**253**	2	**494**	1.6
15	2.7	**254**	2.2	**495**	1.1
16	2	**255**	3.6	**496**	1
17	2.4	**256**	2.7	**497**	1.2
18	2.3	**257**	1.7	**498**	1.1
21	6.1	**258**	1.6	**499**	1.1
22	12.2	**265**	1.4	**500**	1
23	5.3	**266**	1.2	**501**	0.9
24	2	**267**	1.4	**502**	1
25	5	**268**	1.5	**503**	0.7
26	2.6	**269**	0.9	**504**	1.1
27	2.8	**270**	1.7	**505**	1.3
28	3.5	**279**	4	**506**	1.7
29	2.2	**283**	17.4	**507**	2.6
30	4.2	**284**	37.6	**508**	0.9
31	5.3	**285**	143.1	**509**	1
32	4.5	**286**	61.2	**510**	1
34	5	**287**	15.5	**511**	1
35	2.5	**289**	2.1	**512**	0.9
36	4.2	**292**	32.2	**513**	0.9
37	5.1	**294**	33.8	**514**	1.1
38	3	**295**	39.5	**515**	1.3
40	2.8	**296**	60.5	**516**	1
41	4.9	**298**	85	**517**	1.7
42	2.9	**299**	8.8	**518**	1.3
43	3.3	**301A**	7.6	**519**	0.8
44	4.3	**301B**	10.6	**520**	1.1
45	3.7	**303**	4	**521**	1
46	9.8	**304**	7.5	**522**	0.5
47	22.7	**305**	4.2	**523**	4.6
48	21.1	**306**	7.5	**524**	1.3
53	7.1	**307**	2.4	**525**	1
54	6.6	**308**	11.4	**526**	1.2
55	10	**309A**	2	**527**	0.8
56	3.2	**309B**	4.8	**528**	2.3
57	12.7	**311A**	1.7	**529**	1
58	3.6	**311B**	6.1	**530**	3.7
59	9.4	**313A**	4.2	**531**	50.1
60	5.2	**313B**	4.8	**532**	5.9

61	8.7	**315A**	3.5	**533**	2.5
62	6.3	**315B**	4.6	**534**	59.4
63	3.8	**317A**	12.3	**535**	78.3
64	11.4	**317B**	13.5	**536**	19.8
66	11.9	**318**	16.7	**537**	12.2
67	3.9	**319A**	2.2	**538**	11.6
69	7.5	**319B**	2.1	**539**	18.6
70	8.8	**322A**	1.8	**540**	2.4
72	4.8	**322B**	1.5	**542**	1.2
73	8.2	**324A**	1.8	**543**	0.8
75	5.2	**324B**	3	**545**	95.1
76	6.3	**326**	18.5	**547**	49.8
77	7.3	**327**	37.1	**548**	118
78	6	**328A**	2	**549**	1.5
79	9.9	**328B**	3.9	**550**	1.4
80	5.4	**330**	2.5	**551**	1.8
81	8.6	**331**	5.5	**552**	1
82	3.6	**332**	2	**553**	1.9
83	5.5	**333**	2.6	**554**	3.4
84	2.5	**336**	1.8	**555**	0.7
85	10.5	**337**	67.3	**556**	1.6
86	7.4	**338**	0.2	**557**	2.6
89	6.5	**340**	0.6	**558**	1.7
90	7.1	**344**	5.7	**559**	1.1
91	39.3	**345**	12.4	**560**	2.5
92	31.9	**349**	22.6	**561**	1.3
93	39.5	**360**	1.6	**562**	2.5
94	29.4	**361**	1.3	**563**	2.6
95	167.7	**362**	5.1	**564**	1.2
96	106.5	**363**	1.2	**565**	8.4
98	14.3	**364**	1.5	**566**	16.8
100	46.3	**365**	131.2	**570**	2.8
101	4.1	**366**	9.6	**571**	3.9
102	3.3	**367**	6.7	**572**	2.2
103	1.8	**368**	162.3	**573**	3.3
104	2.4	**369**	112.7	**574**	2.1
106	1.7	**370**	1.1	**575**	1.1
107	1.1	**371**	3.6	**576**	2.4
109	2	**372**	2.3	**577**	1.4
111	5.3	**373A**	3.2	**578**	2
112	18.8	**373B**	3.3	**579**	1.3
113	7.3	**375**	2.9	**580**	1.6
114	7.7	**376**	3.6	**581**	2.9

115	24.2	**377**	26	**582**	2.1
116	41.7	**378**	2.3	**583**	2.8
118	5.9	**379**	31.6	**584**	2.4
121	17.8	**380**	2.7	**585**	1.4
122	3.1	**381**	51.9	**586**	1
123	53.4	**382A**	10.9	**587**	1.8
124	20	**382B**	20.5	**588**	7.8
126	2.3	**384A**	2.1	**589**	1.8
127	0.9	**384B**	11.2	**590**	3.5
129	1.8	**386A**	4.2	**591**	5
130	1.6	**386B**	23.9	**592**	61.4
131	2.2	**388**	100.6	**593**	1.5
132	4.2	**390**	44.3	**594**	1.3
133	4.1	**392**	1.9	**595**	2.5
134	11.8	**394**	130.2	**596**	1.5
135	5.4	**395**	4.5	**597**	1.6
136	3.9	**396**	6.9	**598**	1.7
137	0.2	**397**	6.3	**599**	3.2
138	17.2	**400**	5.6	**600**	2.2
140	3.2	**401**	8	**601**	3.2
143	3.9	**402**	4.9	**602**	1.1
144	3.3	**403**	7.7	**603**	3.6
146	78.7	**404**	1.6	**604**	1.4
147	14.5	**405**	3.6	**605**	2.1
149	6	**406**	136.5	**606**	2.5
150	2.8	**407**	40.8	**607**	1.1
151	2.1	**409**	1.1	**608**	1.5
153	1.4	**410**	0.9	**609**	2.1
155	0.2	**411**	1.8	**610**	1.6
156	0.7	**412**	1.4	**611**	2.6
157	0.7	**413**	131.6	**612**	3.3
158	0.8	**414**	12.3	**613**	1.4
159	0.7	**415**	12.4	**614**	1.7
161	1.4	**417**	12.7	**615**	1.8
162	1.8	**419**	5	**616**	2.6
163	1.8	**420**	30.2	**617**	0.9
164	1.2	**421**	5.1	**618**	1.3
166A	0.6	**422**	9.2	**619**	1.5
166B	0.2	**425**	3.1	**620**	1.7
168	1.3	**427**	20.2	**621**	4.9
169	2.9	**428**	6.4	**622**	2.7
170	3.3	**430**	6.6	**623**	3.7
172	4.6	**431**	2.4	**624**	1.4

173A	4.5	**432**	1.4	**625**	6.8
173B	4.7	**433**	1.7	**626**	2.1
179	2.7	**434**	0.8	**627**	1.4
180	4.2	**435**	1.7	**628**	1.6
183	3.7	**436**	3	**629**	3
184	4.2	**437**	1.9	**630**	1.5
187	1.8	**438**	2	**631**	5.6
188	1.8	**439**	1.6	**632**	0.7
189	1.4	**440**	3.2	**633**	1
190	1.6	**441**	2.6	**634**	1.1
192	1.7	**442**	2	**635**	1.4
193	4	**443**	1.7	**636**	2.3
194	1.6	**444**	4	**637**	1.7
195	3.1	**445**	1.3	**638**	1.3
196	8	**446**	1.7	**639**	1.5
197	1.7	**447**	4	**640**	1.9
198	1	**448**	1.4	**641**	7.5
199	0.4	**449**	1	**642**	4
200	2.4	**452**	1.7	**643**	1.4
201	3.5	**453**	2	**644**	1.8
202	1.8	**454**	2.3	**645**	1.3
203	5.7	**455**	1.8	**646**	1.3
204	1.2	**456**	1.4	**647**	1.5
205	5.3	**457**	1.5	**648**	5.9
206	22.6	**458**	1.7	**649**	2.9
207	3.3	**459**	1.8	**650**	1.5
208	2.7	**460**	1.1	**651**	2.9
209	5.7	**461**	1.6	**652**	2.4
210	1.8	**463**	5.6	**653**	1
211	2.4	**465**	37.1	**654**	1.2
212	22.5	**466**	2.2	**655**	0.9
213	1.9	**467**	2.3	**656**	1.7
214	5.2	**468**	2.5	**657**	1.3
215	3	**469**	2.5	**658**	1.1
216	1.9	**470**	6.4	**659**	1.2
217	4.8	**471**	4.2	**660**	2.8
218	173.5	**472**	1.8	**661**	3.1
219	2.8	**473**	1.2	**662**	1.4
220	35.7	**474**	3.1	**663**	1.7
223	4.1	**475**	81.3	**664**	1.4
224	7.9	**476**	32.9	**665**	1.6
225	19.1	**477**	8.3	**666**	1.6
226	7.7	**478**	1.8	**667**	1.8

227	7.9	**479**	2.6	**668**	1.1
230	5.9	**480**	2.7	**669**	2.3
231	2.2	**481**	0.8		
232	1.6	**482**	1		

Example 671

THP1-Dual Lucia Reporter Gene Assay

This is the cellular reporter assay to evaluate compounds' antagonism to interferon regulatory factor (IRF) pathway in THP1-Dual™ cells (InvivoGen, cat number thpd-nfis) . THP1-Dual™ cells were derived from the human THP-1 monocyte cell line by stable integration lucia luciferase gene, a new secreted luciferase reporter gene, under the control of an ISG54 (interferon-stimulated gene) minimal promoter in conjunction with five interferon (IFN)-stimulated response elements. As a result, THP1-Dual™ cells allow the study of the IRF pathway, by assessing the activity of Lucia luciferase. Lucia luciferase protein is readily measurable in the cell culture supernatant when using QUANTI-Luc™ (InvivoGen, cat: rep-qlcg-500). 2'3'cGAMP or baculovirus (a double stranded DNA virus, purchased from Genescript, pCMV-Dest Vector virus generation P2 BV stock virus, Sf-900 II medium with 5% FBS, Lot C9835DK230-2/P4DL001) were used as stimulator to induce the activation of IRF pathway. After co-incubation with compound for 20-24 h, the compounds' antagonism to IRF pathway and cell toxicity were tested by measuring luminescence and OD 450 on an Envision plate reader. On the day of experiment, 25 µL of test medium (RPMI 1640, 2 mM L-glutamine, 25 mM HEPES, 10% heat-inactivated fetal bovine serum) was dispensed in a white, 384-well plate (Grenier, cat: 781098). 24 µL of stimulator (final concentration is 20 µM of 2'3'cGAMP, or final concentration is 10 MOI baculovirus virus,) was added before 6 µL of compound solution per well (final 1% DMSO) was transferred by Agilent Bravo. Then 30 µL of cell suspension (~33,000 cells, 1.1 x10^6 cells/ml) per well was added immediately by thermo multidrop combi dispenser for incubation 20-24 h at 37 °C, 5% CO_2. At the end of the incubation, 10 µL of cellular supernatant was transferred to proxiplate 384-plus plate for IRF detection, and then 10 µL of QUANTI-Luc™ Gold solution was added to the plate that proceeded with the measurement immediately. To detect cell viability, 30 µL of the CCK-8 working solution (Dojindo Molecular Technologies, cat: CK04-20) was added to the cell plate, which was Incubated for 2 h in the incubator to measure the absorbance at 450 nm using Envision.

Example NO.	THP1_ IC50 (nM)	Example NO.	THP1_ IC50 (nM)	Example NO.	THP1_ IC50 (nM)
1	337	**252**	19	**501**	17
4	975	**253**	40	**502**	5
5	106	**254**	77	**503**	9
7	220	**255**	195	**504**	8
9	198	**256**	60	**505**	10
12	125	**257**	23	**506**	15
13A	266	**258**	10	**507**	16
13B	15	**265**	10	**508**	35
14A	388	**266**	59	**509**	22
14B	36	**267**	27	**510**	138
15	32	**268**	91	**511**	4
16	95	**269**	24	**512**	14
17	41	**270**	170	**513**	163
18	72	**279**	441	**514**	10
21	76	**283**	672	**515**	6
22	464	**284**	553	**516**	965
23	505	**287**	776	**517**	18
24	115	**289**	284	**518**	71
25	415	**292**	521	**519**	3
26	224	**299**	477	**520**	32
27	182	**301A**	277	**521**	18
28	289	**301B**	367	**522**	3
29	188	**303**	309	**523**	38
30	360	**304**	549	**524**	104
31	271	**305**	230	**525**	2
32	630	**306**	514	**526**	393
38	89	**307**	89	**527**	12
40	157	**308**	322	**528**	6
42	131	**309A**	47	**529**	11
43	662	**309B**	138	**530**	940
44	260	**311A**	43	**532**	72
45	652	**311B**	158	**533**	744
46	212	**313A**	197	**540**	490
47	674	**313B**	242	**542**	9
48	511	**315A**	269	**543**	21
53	447	**315B**	180	**548**	837
54	972	**317A**	559	**549**	24
55	820	**317B**	609	**550**	37
56	241	**319A**	59	**551**	101
57	604	**319B**	125	**552**	165
58	60	**322A**	96	**553**	92
59	373	**322B**	123	**554**	158
60	149	**324A**	93	**555**	20
61	592	**324B**	144	**556**	52
62	768	**328A**	77	**557**	109

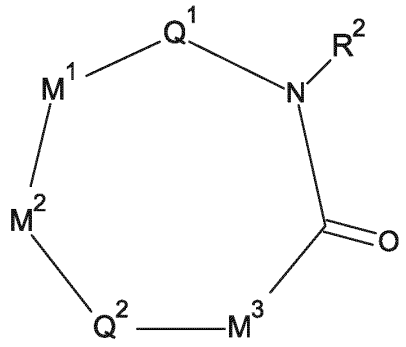
63	102	**328B**	128	**558**	60
64	287	**326**	599	**559**	6
66	623	**330**	67	**560**	25
67	353	**331**	150	**561**	17
69	251	**332**	55	**562**	28
70	208	**333**	93	**563**	16
72	102	**338**	29	**564**	2
73	398	**340**	197	**565**	196
75	167	**344**	488	**566**	251
76	88	**360**	28	**570**	48
77	656	**361**	24	**571**	15
78	235	**362**	252	**572**	16
79	751	**363**	28	**573**	17
80	536	**364**	26	**574**	13
81	851	**366**	296	**575**	18
82	307	**367**	233	**576**	79
83	757	**370**	301	**577**	21
84	273	**371**	435	**578**	100
85	432	**372**	91	**579**	20
89	283	**373A**	125	**580**	12
90	869	**373B**	180	**581**	27
101	8	**375**	63	**582**	26
103	57	**376**	59	**583**	41
104	21	**378**	143	**584**	25
106	59	**380**	167	**585**	10
107	268	**384A**	62	**586**	52
109	71	**384B**	281	**587**	9
113	849	**386A**	329	**588**	7
118	806	**392**	79	**589**	7
122	880	**395**	314	**590**	<2
126	84	**396**	266	**591**	2
127	374	**397**	153	**592**	446
129	375	**400**	362	**593**	<2
130	184	**401**	926	**594**	12
131	309	**402**	185	**595**	14
132	440	**403**	829	**596**	9
133	136	**404**	223	**597**	2
134	466	**409**	17	**598**	47
135	245	**410**	16	**599**	17
136	252	**411**	35	**600**	9
137	33	**412**	32	**601**	11
140	221	**419**	248	**602**	9
143	126	**421**	98	**603**	19
144	49	**422**	701	**604**	<2
149	429	**425**	67	**605**	9
150	134	**428**	448	**606**	3
151	84	**430**	578	**607**	5
153	53	**431**	15	**608**	7

155	41	**432**	14	**609**	29
156	292	**433**	9	**610**	18
157	174	**434**	17	**611**	<2
161	251	**435**	30	**612**	<2
162	424	**436**	7	**613**	10
163	576	**437**	80	**614**	5
166A	147	**438**	33	**615**	11
166B	166	**439**	125	**616**	160
168	78	**440**	80	**617**	11
169	219	**441**	12	**618**	5
170	294	**442**	50	**619**	<2
172	223	**443**	20	**620**	3
173A	104	**444**	14	**621**	28
173B	371	**445**	116	**622**	42
179	26	**446**	18	**623**	143
180	84	**447**	7	**624**	24
183	53	**448**	105	**625**	117
184	90	**449**	62	**626**	24
187	47	**452**	150	**627**	3
188	371	**453**	470	**628**	53
189	28	**454**	428	**629**	12
190	446	**455**	144	**630**	92
192	32	**456**	30	**631**	12
193	155	**457**	50	**632**	44
194	42	**458**	38	**633**	3
195	311	**459**	256	**634**	<2
196	456	**461**	721	**635**	13
199	2	**463**	71	**636**	3
200	96	**466**	189	**637**	40
201	578	**467**	83	**638**	17
202	20	**468**	662	**639**	3
203	111	**469**	841	**640**	17
204	113	**470**	36	**641**	33
205	808	**471**	39	**642**	22
206	455	**472**	14	**643**	24
207	145	**473**	13	**644**	22
208	140	**474**	79	**645**	22
209	494	**476**	420	**646**	16
210	293	**477**	558	**647**	29
211	22	**478**	31	**648**	244
212	65	**479**	53	**649**	43
213	33	**480**	33	**650**	43
214	21	**481**	14	**651**	18
215	130	**482**	9	**652**	38
216	62	**483**	33	**653**	28
217	48	**484**	46	**654**	10
219	12	**485**	11	**655**	18
223	217	**486**	9	**656**	44

224	110	**487**	56	**657**	12
225	442	**488**	48	**658**	15
231	73	**489**	120	**659**	128
232	44	**490**	13	**660**	200
239	275	**491**	23	**661**	16
241	97	**492**	111	**662**	24
243	20	**493**	47	**663**	5
244	81	**494**	33	**664**	6
245	95	**495**	999	**665**	7
246	215	**496**	286	**666**	22
247	42	**497**	45	**667**	5
248	18	**498**	23	**668**	<2
250	25	**499**	48	**669**	2
251	283	**500**	16		

CLAIMS

1. A compound of formula (Ia),



(Ia),

wherein

M^1 is heteroarylene optionally substituted by R^1; wherein

R^1 is deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, $(R)_2N$, RCO, RSO_2, $RNHSO_2$, R_2NSO_2, RSO(NR), R_3Si, $ROC_{1-6}alkyl$, $RSC_{1-6}alkyl$, $RNHC_{1-6}alkyl$, $(R)_2NC_{1-6}alkyl$, $RSO_2C_{1-6}alkyl$, $RNHSO_2C_{1-6}alkyl$, $R_2NSO_2C_{1-6}alkyl$, $RSO(NR)C_{1-6}alkyl$ or $R_3SiC_{1-6}alkyl$; wherein R is H, R^a, R^b or R^c;

R^a is $C_{1-6}alkyl$ optionally substituted by R^b or R^c;

R^b is $C_{3-7}cycloalkyl$, heterocyclyl, heteroaryl or aryl, said $C_{3-7}cycloalkyl$, heterocyclyl, heteroaryl and aryl being unsubstituted or optionally substituted by deuterio, halogen or R^c;

R^c is selected from deuterio, $C_{1-6}alkyl$, $(C_{1-6}alkyl)_3Si$, $haloC_{1-6}alkyl$, $deuterioC_{1-6}alkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, $deuterioC_{1-6}alkoxy$, $C_{2-6}alkenyl$, $haloC_{2-6}alkenyl$, $deuterioC_{2-6}alkenyl$, $C_{2-6}alkynyl$, $haloC_{2-6}alkynyl$, $deuterioC_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $haloC_{3-7}cycloalkyl$, $deuterioC_{3-7}cycloalkyl$, amino, $C_{1-6}alkylamino$, $(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylcarbonylamino$, $haloC_{1-6}alkylamino$, $haloC_{1-6}alkylcarbonylamino$, $(haloC_{1-6}alkyl)_2amino$, $C_{3-7}cycloalkylamino$, $C_{3-7}cycloalkylcarbonylamino$, $(C_{3-7}cycloalkyl)_2amino$, $haloC_{3-7}cycloalkylamino$, $(haloC_{3-7}cycloalkyl)_2amino$, $C_{3-7}cycloalkyl(C_{1-6}alkyl)amino$, $haloC_{3-7}cycloalkyl(C_{1-6}alkyl)amino$, $C_{1-6}alkylsulfonylamino$, $haloC_{1-6}alkylsulfonylamino$, $C_{1-6}alkoxyC_{1-6}alkyl$, $(haloC_{1-6}alkoxy)C_{1-6}alkyl$, $C_{1-6}alkoxy(halo)C_{1-6}alkyl$, $C_{3-7}cycloalkylC_{1-6}alkyl$, $C_{3-7}cycloalkylhaloC_{1-6}alkyl$, $C_{1-6}alkylcarbonyl$, $haloC_{1-6}alkylcarbonyl$, $C_{3-7}cycloalkylcarbonyl$, $haloC_{3-7}cycloalkylcarbonyl$, $C_{1-6}alkoxycarbonyl$, $haloC_{1-6}alkoxycarbonyl$, C_{3-}

$_{7}$cycloalkoxycarbonyl, haloC_{3-7}cycloalkoxycarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, C_{3-7}cycloalkylaminocarbonyl, (C_{3-7}cycloalkyl)$_2$aminocarbonyl, C_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, haloC_{1-6}alkylaminocarbonyl, halo(C_{1-6}alkyl)$_2$aminocarbonyl, haloC_{3-7}cycloalkylaminocarbonyl, halo(C_{3-7}cycloalkyl)$_2$aminocarbonyl, haloC_{1-6}alkylC_{3-7}cycloalkylaminocarbonyl, C_{1-6}alkylhaloC_{3-7}cycloalkylaminocarbonyl, (C_{1-6}alkyl)$_3$ammonio, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfanyl, C_{3-7}cycloalkylsulfinyl, C_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkylsulfanyl, haloC_{1-6}alkylsulfinyl, haloC_{1-6}alkylsulfonyl, haloC_{3-7}cycloalkylsulfanyl, haloC_{3-7}cycloalkylsulfinyl, haloC_{3-7}cycloalkylsulfonyl, haloC_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, (haloC_{1-6}alkylamino)sulfonyl, (C_{1-6}alkyl)$_2$aminosulfonyl, (haloC_{1-6}alkyl)$_2$aminosulfonyl, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkoxy)$_2$phosphoryl, hydroxy(C_{1-6}alkoxy)phosphoryl, C_{1-6}alkoxyphosphoryl, hydroxy, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, hydroxylhaloC_{1-6}alkoxy, hydroxyC_{3-7}cycloalkyl, hydroxyhaloC_{3-7}cycloalkyl and sulfonimidoyl optionally substituted by H, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, heteroaryl and heterocyclyl;

M^2 is arylene, heterocyclylene or heteroarylene, said arylene, heterocyclylene or heteroarylene being optionally substituted by R^1;

M^3 is heterocyclylene which is unsubstituted or optionally substituted by R^3;

R^2 is deuterio, R, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RSO_2C_{1-6}alkyl, RNHC_{1-6}alkyl or (R)$_2$NC_{1-6}alkyl;

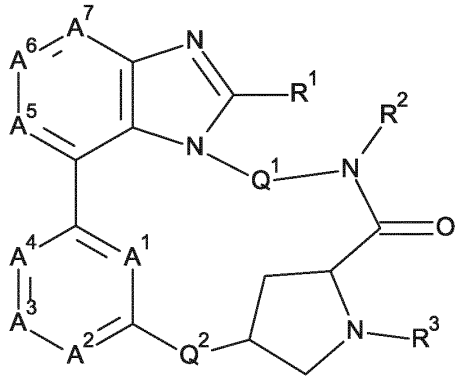
R^3 is heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl or arylcarbonyl, said heterocyclyl, heteroaryl, aryl, heterocyclylcarbonyl, heteroarylcarbonyl and arylcarbonyl being unsubstituted or optionally substituted by R^1;

Q^1 is -M-, -M-O-M-, -M-S-M-, -M-SO_2-M-, -M-SO(NH)-M-, -M-SO(NR)-M-, -M-SiR_2-M- or -M-N(R)-M-; wherein M is C_{1-6}alkylene unsubstituted or optionally substituted by the substituents independently selected from deuterio, halogen, cyano, carboxy, R, RO, RS, RNH, R_2N, RSO_2, ROC_{1-6}alkyl, RSC_{1-6}alkyl, RNHC_{1-6}alkyl, (R)$_2$NC_{1-6}alkyl and RSO_2C_{1-6}alkyl;

Q^2 is NH, O, S, SO, SO_2, P(O)R, PO(NR), Se, N(R), SiR_2, heterocyclyl, heteroaryl or aryl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1,

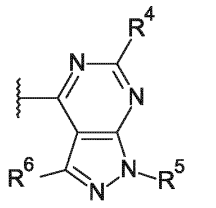
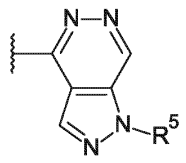
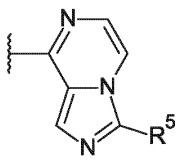
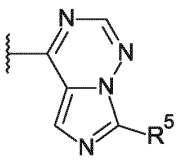
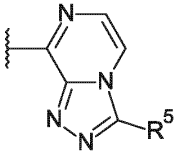
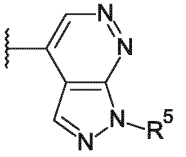
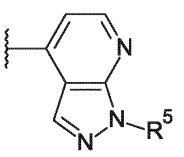
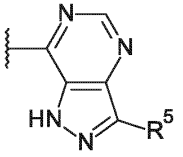


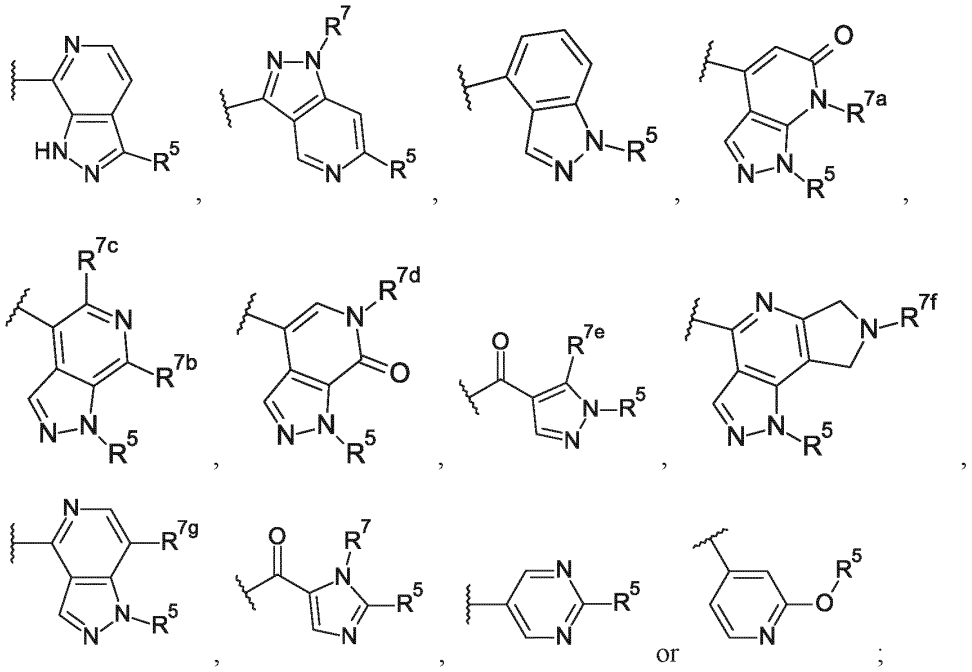
(I),

wherein

R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

R^2 is H, (2-oxa-5-azabicyclo[2.2.1]heptanyl)C_{1-6}alkyl, (2-oxa-6-azaspiro[3.3]heptanyl)C_{1-6}alkyl, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, ((C_{1-6}alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  ,



wherein

R^4 is H,

$(C_{1-6}alkyl)_2amino$,

$(C_{1-6}alkyl)_2aminocarbonyl$,

$(C_{1-6}alkyl)_2phosphoryl$,

1,1-dioxothianyl,

1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by $C_{1-6}alkyl$,

1,6-diazaspiro[3.3]heptanyl substituted by $haloC_{1-6}alkyl$ or oxetanyl,

1,7-diazaspiro[3.5]nonanyl substituted by $haloC_{1-6}alkyl$ or oxetanyl,

2,2-dioxo-2λ⁶-thia-6-azaspiro[3.3]heptanyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by $C_{1-6}alkyl$,

2,5-diazabicyclo[2.2.1]heptanyl substituted by $C_{1-6}alkyl$, $haloC_{1-6}alkyl$ or oxetanyl,

2-azaspiro[3.3]heptanyl once or twice substituted by substituents independently selected from $haloC_{1-6}alkyl$ and hydroxy,

2-oxa-5-azabicyclo[2.2.1]heptanyl,

2-oxa-6-azaspiro[3.3]heptanyl,

3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl,

3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylcarbonyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, haloC_{3-7}cycloalkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3,6-diazabicyclo[3.2.0]heptanyl substituted by oxetanyl,

3,7-diazabicyclo[4.2.0]octanyl substituted by oxetanyl,

3,8-diazabicyclo[3.2.1]octanyl substituted by haloC_{1-6}alkyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

3-oxa-8-azabicyclo[3.2.1]octanyl,

4,7-diazaspiro[2.5]octanyl unsubstituted or substituted by C_{1-6}alkyl,

4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,

5-oxa-2,8-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl,

6,6-dioxo-6λ^6-thia-1-azaspiro[3.3]heptanyl,

6-oxa-1-azaspiro[3.3]heptanyl,

6-oxa-3-azabicyclo[3.1.1]heptanyl,

8-oxa-2,5-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl,

8-oxa-3-azabicyclo[3.2.1]octanyl,

amino,

aminocarbonyl,

azetidinyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkyl)$_2$amino, (C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, amino, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylC_{1-6}alkyl, C_{3-7}cycloalkyl, cyano, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinyl and morpholinylC_{1-6}alkyl,

azetidinyloxy substituted by haloC_{1-6}alkyl or C_{3-7}cycloalkyl,

C_{1-6}alkoxy unsubstituted or substituted by (haloC_{1-6}alkylcarbonyl)azetidinyl, C_{1-6}alkylazetidinyl, C_{1-6}alkylpiperazinyl, C_{1-6}alkylpyrrolidinyl, halo-1,2,3,5,6,7-hexahydropyrrolizinyl, haloC_{1-6}alkylazetidinyl, morpholinyl, oxetanyl or tetrahydrofuranyl,

C_{1-6}alkoxyC_{1-6}alkylamino,

C_{1-6}alkoxycarbonyl,

C_{1-6}alkyl unsubstituted or once or twice substituted by substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkylcarbonyl)azetidinyl, (haloC_{1-6}alkylcarbonyl)pyrrolidinyl, 1,1-dioxothietanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 4,7-diazaspiro[2.5]octanyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkylcarbonylpyrrolidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{1-6}alkylsulfonylpyrrolidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, cyano, haloC_{1-6}alkylazetidinyl, hydroxy, hydroxyC_{1-6}alkyl, morpholinyl and oxetanyl,

C_{1-6}alkylamino,

C_{1-6}alkylsulfanyl unsubstituted or substituted by 1,1-dioxothietanyl,

C_{1-6}alkylsulfonyl,

C_{3-7}cycloalkyl unsubstituted or substituted by C_{1-6}alkoxy or hydroxy,

carboxy,

cyano,

haloC_{1-6}alkoxy,

haloC_{1-6}alkyl substituted by hydroxy,

hydroxy,

hydroxyC_{1-6}alkylcarbamoyl,

imidazolyl,

morpholinyl,

morpholinylcarbonyl,

oxetanyl,

oxomorpholinyl,

oxooxazolidinyl,

oxopiperazinyl substituted by C_{1-6}alkyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy,

piperazinyl once or twice substituted by substituents independently selected from C_{1-6}alkyl, carboxy, oxetanyl and phenylC_{1-6}alkyl,

piperidinyl substituted by C_{1-6}alkyl, 2H-tetrazolyl or oxazolyl,

pyrrolidinyl once or twice substituted by substituents independently selected from amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, cyano, haloC_{1-6}alkylcarbonyl and halogen,

pyrrolidinylcarbonyl,

tetrahydrofuranyl, or

tetrahydropyranyl;

R^5 is 1,3-dihydroisobenzofuranyl,

1H-indazolyl substituted by halogen,

C_{2-6}alkynyl,

thienyl,

bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,

phenyl substituted once, twice or three times by the substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkyl)C_{3-7}cycloalkyloxy, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkylmorpholinyl)C_{1-6}alkoxy, (C_{1-6}alkylsulfonylazetidinyl)C_{1-6}alkoxy, 2-oxa-6-azaspiro[3.3]heptanyl, azetidinyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{2-6}alkynyl, C_{1-6}alkoxyC_{3-7}cycloalkyloxy, C_{1-6}alkoxypyrrolidinyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, carboxy, cyano, cyanoC_{1-6}alkoxy, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, halogen, hydroxy, morpholinyl, morpholinylC_{1-6}alkoxy, oxetanylC_{1-6}alkoxy, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl, tetrahydrofuranyloxy and trideuterioC_{1-6}alkoxy,

pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy, C_{1-6}alkylsulfanyl and C_{1-6}alkoxy, or

pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or C_{1-6}alkyl;

R^7 is C_{1-6}alkyl;

R^{7a} is C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7b} is H, C_{1-6}alkoxy or phenylC_{1-6}alkoxy;

R^{7c} is H or C_{1-6}alkoxy;

R^{7d} is C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7e} is H, amino, phenylC_{1-6}alkylamino or morpholinylC_{1-6}alkylamino;

R^{7f} is C_{1-6}alkyl, phenylC_{1-6}alkyl or oxetanyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene unsubstituted or substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkyl, C_{1-}

$_{6}$alkylcarbonyloxy, carboxy, hydroxy, hydroxyC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkoxy and trideuterioC_{1-6}alkoxy, or

-M-O-M-, wherein M is C_{1-6}alkylene;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8 or N, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkoxyamino, cyano, haloazetidinylC_{1-6}alkyl, haloC_{1-6}alkoxy, halogen, morpholinylC_{1-6}alkyl or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

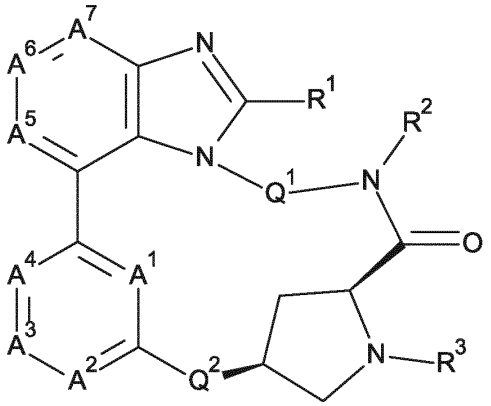
A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (Ib) according to claim 1,



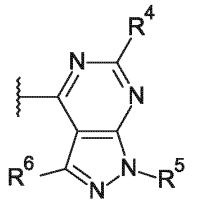
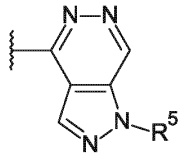
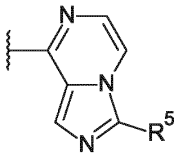
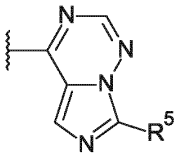
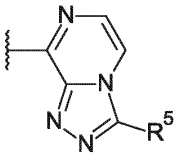
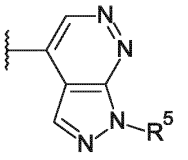
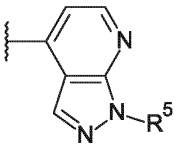
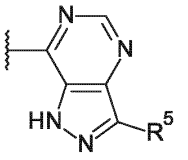
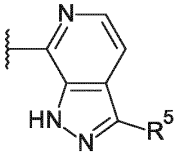
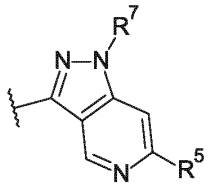
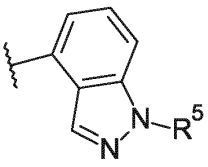
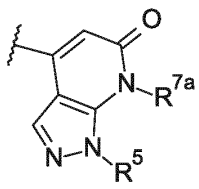
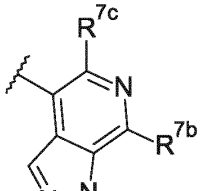
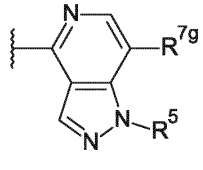
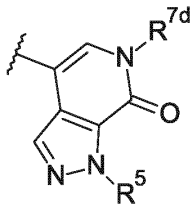
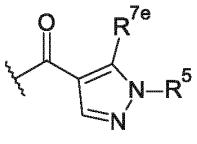
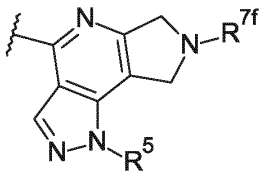
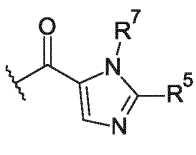
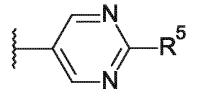
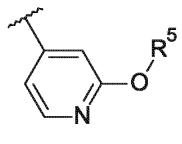
(Ib)

wherein

R^1 is deuterio, H, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylcarbonylamino, C_{3-}

$_{7}$cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxy, pyrazolylC_{1-6}alkyl or triazolylC_{1-6}alkyl;

R^2 is H, (2-oxa-5-azabicyclo[2.2.1]heptanyl)C_{1-6}alkyl, (2-oxa-6-azaspiro[3.3]heptanyl)C_{1-6}alkyl, (2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl)C_{1-6}alkyl, ((C$_{1-6}$alkyl)$_3$ammonio)C_{1-6}alkyl, (C_{1-6}alkylsulfonylpiperazinyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkyl, phenylC_{1-6}alkyl, pyrimidinyloxyC_{1-6}alkyl, tetrazolylC_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , ,  ,  ,  ,  , ,  ,  , or  ;

wherein

R^4 is H,

(C_{1-6}alkyl)$_2$amino,
(C_{1-6}alkyl)$_2$aminocarbonyl,
(C_{1-6}alkyl)$_2$phosphoryl,
1,1-dioxothianyl,
1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by C_{1-6}alkyl,
1,6-diazaspiro[3.3]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,
1,7-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or oxetanyl,
2,2-dioxo-2λ^6-thia-6-azaspiro[3.3]heptanyl,
2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C_{1-6}alkyl,
2,5-diazabicyclo[2.2.1]heptanyl substituted by C_{1-6}alkyl, haloC_{1-6}alkyl or oxetanyl,
2-azaspiro[3.3]heptanyl once or twice substituted by substituents independently selected from haloC_{1-6}alkyl and hydroxy,
2-oxa-5-azabicyclo[2.2.1]heptanyl,
2-oxa-6-azaspiro[3.3]heptanyl,
3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl,
3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,
3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylcarbonyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, haloC_{3-7}cycloalkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,
3,6-diazabicyclo[3.2.0]heptanyl substituted by oxetanyl,
3,7-diazabicyclo[4.2.0]octanyl substituted by oxetanyl,
3,8-diazabicyclo[3.2.1]octanyl substituted by haloC_{1-6}alkyl,
3-oxa-6-azabicyclo[3.1.1]heptanyl,
3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,
3-oxa-8-azabicyclo[3.2.1]octanyl,
4,7-diazaspiro[2.5]octanyl unsubstituted or substituted by C_{1-6}alkyl,
4-oxo-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazinyl,
5-oxa-2,8-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl,
6,6-dioxo-6λ^6-thia-1-azaspiro[3.3]heptanyl,
6-oxa-1-azaspiro[3.3]heptanyl,
6-oxa-3-azabicyclo[3.1.1]heptanyl,
8-oxa-2,5-diazaspiro[3.5]nonanyl substituted by haloC_{1-6}alkyl,

8-oxa-3-azabicyclo[3.2.1]octanyl,
amino,
aminocarbonyl,
azetidinyl unsubstituted or once or twice substituted by substituents independently selected from $(C_{1-6}alkyl)_2amino$, $(C_{1-6}alkyl)_2aminoC_{1-6}alkyl$, amino, $C_{1-6}alkyl$, $C_{1-6}alkylcarbonyl$, $C_{1-6}alkylsulfonyl$, $C_{1-6}alkylsulfonylC_{1-6}alkyl$, $C_{3-7}cycloalkyl$, cyano, $cyanoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $hydroxyC_{1-6}alkyl$, morpholinyl and $morpholinylC_{1-6}alkyl$,
azetidinyloxy substituted by $haloC_{1-6}alkyl$ or $C_{3-7}cycloalkyl$,
$C_{1-6}alkoxy$ unsubstituted or substituted by $(haloC_{1-6}alkylcarbonyl)$azetidinyl, $C_{1-6}alkylazetidinyl$, $C_{1-6}alkylpiperazinyl$, $C_{1-6}alkylpyrrolidinyl$, halo-1,2,3,5,6,7-hexahydropyrrolizinyl, $haloC_{1-6}alkylazetidinyl$, morpholinyl, oxetanyl or tetrahydrofuranyl,
$C_{1-6}alkoxyC_{1-6}alkylamino$,
$C_{1-6}alkoxycarbonyl$,
$C_{1-6}alkyl$ unsubstituted or once or twice substituted by substituents independently selected from $(C_{1-6}alkoxyC_{1-6}alkylcarbonyl)$azetidinyl, $(haloC_{1-6}alkylcarbonyl)$pyrrolidinyl, 1,1-dioxothietanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 3-oxa-6-azabicyclo[3.1.1]heptanyl, 4,7-diazaspiro[2.5]octanyl, $C_{1-6}alkoxy$, $C_{1-6}alkylcarbonylazetidinyl$, $C_{1-6}alkylcarbonyloxy$, $C_{1-6}alkylcarbonylpyrrolidinyl$, $C_{1-6}alkylsulfonylazetidinyl$, $C_{1-6}alkylsulfonylpyrrolidinyl$, $C_{3-7}cycloalkylsulfonylazetidinyl$, cyano, $haloC_{1-6}alkylazetidinyl$, hydroxy, $hydroxyC_{1-6}alkyl$, morpholinyl and oxetanyl,
$C_{1-6}alkylamino$,
$C_{1-6}alkylsulfanyl$ unsubstituted or substituted by 1,1-dioxothietanyl,
$C_{1-6}alkylsulfonyl$,
$C_{3-7}cycloalkyl$ unsubstituted or substituted by $C_{1-6}alkoxy$ or hydroxy,
carboxy,
cyano,
$haloC_{1-6}alkoxy$,
$haloC_{1-6}alkyl$ substituted by hydroxy,
hydroxy,
$hydroxyC_{1-6}alkylcarbamoyl$,

imidazolyl,
morpholinyl,
morpholinylcarbonyl,
oxetanyl,
oxomorpholinyl,
oxooxazolidinyl,
oxopiperazinyl substituted by C_{1-6}alkyl,
oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy,
piperazinyl once or twice substituted by substituents independently selected from C_{1-6}alkyl, carboxy, oxetanyl and phenylC_{1-6}alkyl,
piperidinyl substituted by C_{1-6}alkyl, 2H-tetrazolyl or oxazolyl,
pyrrolidinyl once or twice substituted by substituents independently selected from amino, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, cyano, haloC_{1-6}alkylcarbonyl and halogen,
pyrrolidinylcarbonyl,
tetrahydrofuranyl, or
tetrahydropyranyl;

R^5 is 1,3-dihydroisobenzofuranyl,
1H-indazolyl substituted by halogen,
C_{2-6}alkynyl,
thienyl,
bicyclo[1.1.1]pentanyl unsubstituted or substituted by halogen or C_{1-6}alkyl,
phenyl substituted once, twice or three times by the substituents independently selected from (C_{1-6}alkoxyC_{1-6}alkyl)C_{3-7}cycloalkyloxy, (C_{1-6}alkyl)$_2$phosphoryl, (C_{1-6}alkylmorpholinyl)C_{1-6}alkoxy, (C_{1-6}alkylsulfonylazetidinyl)C_{1-6}alkoxy, 2-oxa-6-azaspiro[3.3]heptanyl, azetidinyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{2-6}alkynyl, C_{1-6}alkoxyC_{3-7}cycloalkyloxy, C_{1-6}alkoxypyrrolidinyl, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, carboxy, cyano, cyanoC_{1-6}alkoxy, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, halogen, hydroxy, morpholinyl, morpholinylC_{1-6}alkoxy, oxetanylC_{1-6}alkoxy, oxetanyloxy, oxopyrrolidinyl, phenyl, tetrahydrofuranyl, tetrahydrofuranyloxy and trideuterioC_{1-6}alkoxy,

pyridinyl unsubstituted or substituted once or twice by the substituents independently selected from halogen, hydroxy, C_{1-6}alkylsulfanyl and C_{1-6}alkoxy, or

pyrimidinyl unsubstituted or substituted by halogen;

R^6 is H or C_{1-6}alkyl;

R^7 is C_{1-6}alkyl;

R^{7a} is C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7b} is H, C_{1-6}alkoxy or phenylC_{1-6}alkoxy;

R^{7c} is H or C_{1-6}alkoxy;

R^{7d} is C_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^{7e} is H, amino, phenylC_{1-6}alkylamino or morpholinylC_{1-6}alkylamino;

R^{7f} is C_{1-6}alkyl, phenylC_{1-6}alkyl or oxetanyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene unsubstituted or substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylcarbonyloxy, carboxy, hydroxy, hydroxyC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, morpholinylC_{1-6}alkoxy and trideuterioC_{1-6}alkoxy, or

-M-O-M-, wherein M is C_{1-6}alkylene;

Q^2 is NH, O or S;

A^1 is CH or N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8 or N, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkoxy, C_{3-7}cycloalkoxyamino, cyano, haloazetidinylC_{1-6}alkyl, haloC_{1-6}alkoxy, halogen, morpholinylC_{1-6}alkyl or oxetanyl;

A^4 is CR^9 or N, wherein R^9 is H; or R^8 and R^9 together with the atoms that they are attached to form a heterocyclyl;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11} or N, wherein R^{11} is H, deuterio, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

A^7 is CR^{12} or N, wherein R^{12} is H or halogen;

provided that no more than two of A^1, A^2, A^3 and A^4 are N simultaneously; and no more than one of A^5, A^6 and A^7 is N;

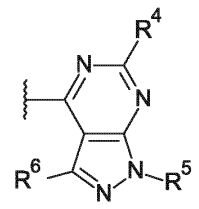
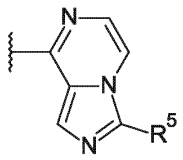
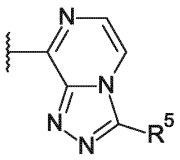
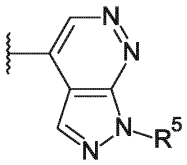
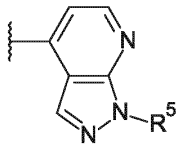
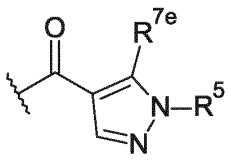
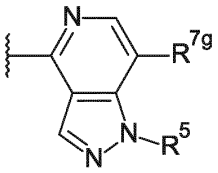
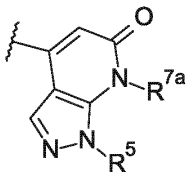
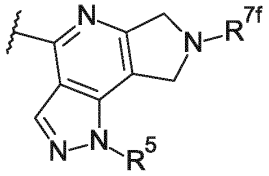
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 2 or 3, wherein R^1 is H or C_{1-6}alkyl.

5. A compound according to any one of claims 1-4, wherein R^1 is H or methyl.

6. A compound according to any one of claims 1-5, wherein R^2 is C_{1-6}alkyl or trideuterioC_{1-6}alkyl.

7. A compound according to any one of claims 1-6, wherein R^2 is methyl, ethyl or trideuteriomethyl.

8. A compound according to any one of claims 1-7, wherein R^3 is  ,  ,  ,  ,  ,  ,  ,  or  ;

wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl, or

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

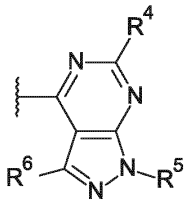
R^6 is H;

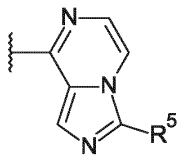
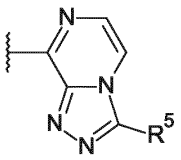
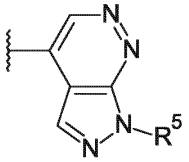
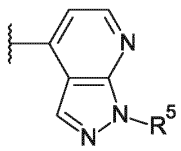
R^{7a} is C_{1-6}alkyl;

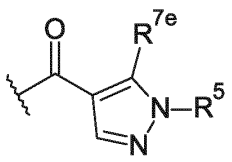
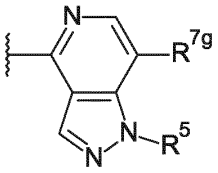
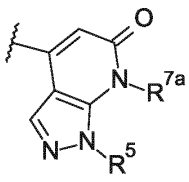
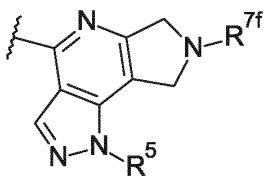
R^{7e} is amino;

R^{7f} is C_{1-6}alkyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl.

9. A compound according to any one of claims 1-8, wherein R^3 is  ,

 ,  ,  ,  ,

 ,  ,  or  ;

wherein

R^4 is H,

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

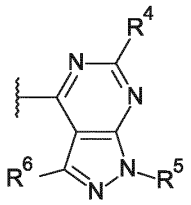
R^6 is H;

R^{7a} is methyl;

R^{7e} is amino;

R^{7f} is methyl;

R^{7g} is H or methoxymethyl.

10. A compound according to any one of claims 1-8, wherein R^3 is  ; wherein R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl, or

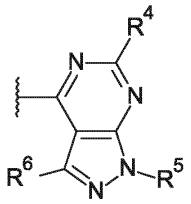
oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H.

11. A compound according to any one of claims 1-10, wherein R^3 is  ; wherein

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H.

12. A compound according to any one of claims 1-11, wherein Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy, C_{1-6}alkyl and trideuterioC_{1-6}alkoxy.

13. A compound according to any one of claims 1-12, wherein Q^1 is propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl, acetoxy and trideuteriomethoxy.

14. A compound according to any one of claims 1-13, wherein Q^1 is C_{1-6}alkylene substituted by C_{1-6}alkoxy.

15. A compound according to any one of claim 1-14, wherein Q^1 is propylene substituted by methoxy or ethoxy.

16. A compound according to any one of claims 1-15, wherein Q^2 is NH or O.

17. A compound according to any one of claims 1-16, wherein A^1 is N.

18. A compound according to any one of claims 1-17, wherein A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy or halogen.

19. A compound according to any one of claims 18, wherein A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy, difluoromethoxy or fluoro.

20. A compound according to any one of claims 1-19, wherein A^3 is CR^8, wherein R^8 is H.

21. A compound according to any one of claims 1-20, wherein A^4 is CR^9, wherein R^9 is H.

22. A compound according to any one of claims 1-21, wherein A^5 is CR^{10} or N, wherein R^{10} is H or fluoro.

23. A compound according to any one of claims 1-22, wherein A^5 is CR^{10}, wherein R^{10} is H.

24. A compound according to any one of claims 1-22, wherein A^6 is CR^{11}, wherein R^{11} is H or halogen.

25. A compound according to any one of claims 1-24, wherein A^6 is CR^{11}, wherein R^{11} is H or fluoro.

26. A compound according to any one of claims 1-25, wherein A^6 is CR^{11}, wherein R^{11} is halogen.

27. A compound according to any one of claims 1-26, wherein A^6 is CR^{11}, wherein R^{11} is fluoro.

28. A compound according to any one of claims 1-27, wherein A^7 is CR^{12}, wherein R^{12} is H or halogen.

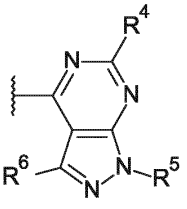
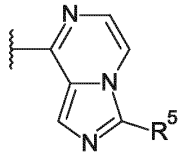
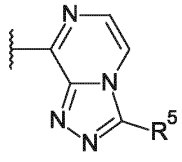
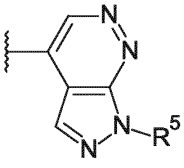
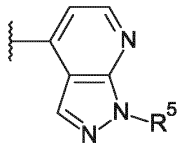
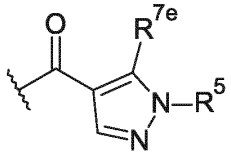
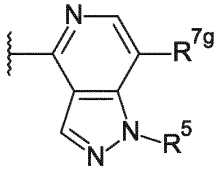
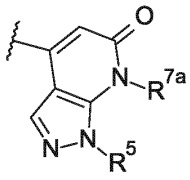
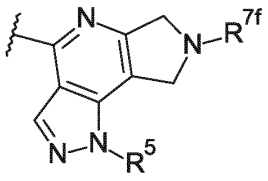
29. A compound according to any one of claims 1-28, wherein A^7 is CR^{12}, wherein R^{12} is H or fluoro.

30. A compound according to any one of claims 1-29, wherein A^7 is CR^{12}, wherein R^{12} is H.

31. A compound according to claim 2 or 3, wherein

R^1 is H or C_{1-6}alkyl;

R^2 is C_{1-6}alkyl or trideuterioC_{1-6}alkyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H;

R^{7a} is C_{1-6}alkyl;

R^{7e} is amino;

R^{7f} is C_{1-6}alkyl;

R^{7g} is H or C_{1-6}alkoxyC_{1-6}alkyl;

Q^1 is C_{1-6}alkylene substituted once or twice by the substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, hydroxy, C_{1-6}alkyl and trideuterioC_{1-6}alkoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is C_{1-6}alkyl;

A^3 is CR^8, wherein R^8 is H, C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-7}cycloalkoxy, haloC_{1-6}alkoxy or halogen;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or halogen;

A^6 is CR^{11}, wherein R^{11} is H or halogen;

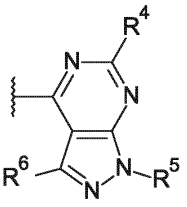
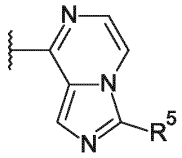
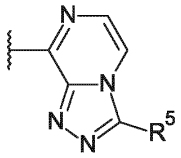
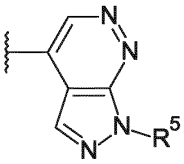
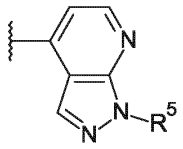
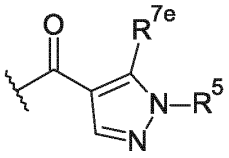
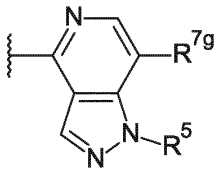
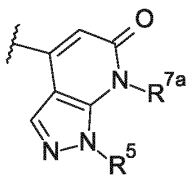
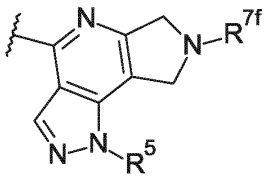
A^7 is CR^{12}, wherein R^{12} is H or halogen;

or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 31, wherein

R^1 is H or methyl;

R^2 is methyl, ethyl or trideuteriomethyl;

R^3 is  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein

R^4 is H,

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-

diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H;

R^{7a} is methyl;

R^{7e} is amino;

R^{7f} is methyl;

R^{7g} is H or methoxymethyl;

Q^1 is propylene substituted once or twice by the substituents independently selected from ethoxy, methoxy, hydroxy, methyl, acetoxy and trideuteriomethoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH, CR^{7h} or N; wherein R^{7h} is methyl;

A^3 is CR^8, wherein R^8 is H, methoxy, methyl, cyclopropoxy, difluoromethoxy or fluoro;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H or fluoro;

A^6 is CR^{11}, wherein R^{11} is H or fluoro;

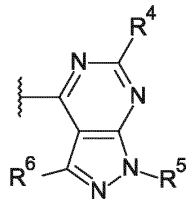
A^7 is CR^{12}, wherein R^{12} is H or fluoro;

or a pharmaceutically acceptable salt thereof.

33. A compound according to claim 31, wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl;

R^3 is  ; wherein

R^4 is H,

2,5-diazabicyclo[2.2.1]heptanyl substituted by haloC_{1-6}alkyl or oxetanyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkylcarbonyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{3-7}cycloalkylcarbonyl or oxetanyl,

3-oxa-6-azabicyclo[3.1.1]heptanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkyl,

amino,

azetidinyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or cyano,

C_{1-6}alkoxy,

C_{1-6}alkyl unsubstituted or substituted by C_{1-6}alkoxy, C_{1-6}alkylcarbonylazetidinyl, C_{1-6}alkylsulfonylazetidinyl, C_{3-7}cycloalkylsulfonylazetidinyl, haloC_{1-6}alkylazetidinyl, hydroxy, morpholinyl or oxetanyl,

oxetanyl,

oxooxazolidinyl,

oxopyrrolidinyl unsubstituted or substituted by C_{1-6}alkyl or hydroxy;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from C_{1-6}alkoxy, C_{3-7}cycloalkyloxy, cyano, haloC_{1-6}alkoxy, halogen, hydroxy and trideuterioC_{1-6}alkoxy,

pyridinyl twice substituted by halogen, or

pyrimidinyl substituted by halogen;

R^6 is H;

Q^1 is C_{1-6}alkylene substituted by C_{1-6}alkoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is halogen;

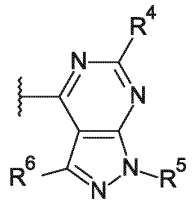
A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

34. A compound according to claim 33, wherein

R^1 is methyl;

R^2 is methyl;

R^3 is  ; wherein

R^4 is H, (1-acetylazetidin-3-yl)methyl, (1-cyclopropylsulfonylazetidin-3-yl)methyl, (1-ethylsulfonylazetidin-3-yl)methyl, (1-methylsulfonylazetidin-3-yl)methyl, [1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl, 1-acetylazetidin-3-yl, 1-methylsulfonylazetidin-3-yl, 2-oxooxazolidin-3-yl, 2-oxopyrrolidin-1-yl, 3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyanoazetidin-1-yl, 3-hydroxy-2-oxo-pyrrolidin-1-yl, 3-methyl-2-oxo-pyrrolidin-1-yl, 3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-oxa-6-azabicyclo[3.1.1]heptan-6-yl, 5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl, amino, azetidin-1-yl, ethoxy, hydroxymethyl, methoxy, methoxymethyl, methyl, morpholinylmethyl, oxetan-2-ylmethyl or oxetan-3-yl;

R^5 is phenyl substituted once, twice or three times by the substituents independently selected from ethoxy, methoxy, cyclopropoxy, cyano, difluoromethoxy, fluoro, hydroxy and trideuteriomethoxy,

pyridinyl twice substituted by fluoro, or

pyrimidinyl substituted by fluoro;

R^6 is H;

Q^1 is propylene substituted by methoxy or ethoxy;

Q^2 is NH or O;

A^1 is N;

A^2 is CH or N;

A^3 is CR^8, wherein R^8 is H;

A^4 is CR^9, wherein R^9 is H;

A^5 is CR^{10} or N, wherein R^{10} is H;

A^6 is CR^{11}, wherein R^{11} is fluoro;

A^7 is CR^{12}, wherein R^{12} is H;

or a pharmaceutically acceptable salt thereof.

35. A compound selected from:

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2,4-difluorophenyl)-3-methyl-imidazole-4-carbonyl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,16,18-tetrazapentacyclo[14.6.1.$1^{2,6}$.$1^{8,11}$.$0^{19,23}$]pentacosa-1(22),2,4,6(25),17,19(23),20-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-hydroxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-benzyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-morpholinopropyl)-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

3-[(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24), 21-heptaen-13-yl]propyl-trimethyl-ammonium;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyridazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-methyl-10-[3-(3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[7-(2,4-difluorophenyl)imidazo[5,1-f][1,2,4]triazin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl] -15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl] -15-(2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15- (2-methoxyethoxy)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(oxetan-3-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(2-fluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,6-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[3-(2,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(3,4-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-(3-methyl-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

5-fluoro-2-[4-[(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile;

[(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl) pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy) -4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18, 20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-4,5,10,13,17,19-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-(4-fluoro-2-methoxy-phenyl)-4-[(8S,11S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide;

1-(4-fluoro-2-methoxy-phenyl)-N,N-dimethyl-4-[(8S,11S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxamide;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-hydroxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

8S,11S)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(2-morpholinoethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-10,13,17,19,26-pentazapentacyclo-[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(6-fluoro-2-hydroxy-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,6-difluoro-3-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-methyl-10-[3-(2-thienyl)imidazo[1,5-a]pyrazin-8-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(5-fluoro-3-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(3-fluoro-5-methoxy-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(3,5-difluoro-2-pyridyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2-chloro-4-fluoro-phenyl)pyrimidin-5-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(methylamino)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,22,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-morpholinoethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(2-methoxyethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(oxetan-3-ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(oxetan-3-ylmethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(oxetan-3-yloxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-[(4-methylmorpholin-2-yl)methoxy]phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-methoxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-18-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-(2-hydroxyethyl)-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-[2-[(4aR,7aS)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]ethyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(4-methylsulfonylpiperazin-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-[2-(1,2,4-triazol-1-yl)ethyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(2-pyrazol-1-ylethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-23-fluoro-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-3-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[4-fluoro-2-(trifluoromethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

5-fluoro-2-[4-[(8S,11S)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzonitrile;

5-fluoro-2-[4-[(8S,11S)-13-methyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-1-yl]benzoic acid;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-ethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(2-methoxyethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-(2-morpholinoethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-hydroxypropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-2-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(tetrazol-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-[3-(4-methylsulfonylpiperazin-1-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(2-hydroxyethoxy)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-15-(2-morpholinoethoxy)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18,22-dideuterio-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-hydroxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-hydroxy-13,15,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

[(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

[(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-15-yl] acetate;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-dimethylphosphoryl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylic acid;

1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carbonitrile;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridazin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-b]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-23-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-morpholino-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

Ethyl 1-(2,4-difluorophenyl)-4-[(8S,11S)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidine-6-carboxylate;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfanyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methylsulfonyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-dimethylphosphoryl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-[(3,3-difluoroazetidin-1-yl)methyl]-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-4-(morpholinomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,15-dimethoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-4,13-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[6-amino-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-13-(cyclopropylmethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-hydroxy-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-vinyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2-cyclopropyl-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2-bromo-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,22-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-(difluoromethoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-4-(cyclopropoxy)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-13-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-[2-(difluoromethyl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-ethyl-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-18-ethyl-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-(hydroxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[6-cyclobutyl-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4,5-difluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-(difluoromethoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-15-methoxy-10-[1-(2-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(5-chloro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-4-(methoxymethyl)-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-4-carbonitrile;

(8S,11S)-10-[1-[4-fluoro-2-(trifluoromethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-18-(trifluoromethyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13-ethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)-6-methyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2-ethoxy-4-fluoro-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-4,13-dimethyl-3,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-3,5,7,10,13,17,19-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-thia-10,13,17,19,26-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)triazolo[4,5-c]pyridin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(methoxymethyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[4,3-c]pyridin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-3,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

8S,11S,15S)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-4,10,13,17,19-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(1-bicyclo[1.1.1]pentanyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-10-[1-(5-fluoropyrimidin-2-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-fluoro-4-phenyl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(4,4,4-trifluorobutyl)-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-chloro-4-fluoro-phenyl)pyrazole-4-carbonyl]-22-fluoro-13-(3-pyrimidin-2-yloxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]-hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-22-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-21-chloro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-15-methoxy-13-methyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S,15R)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-(3-methoxypropyl)-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13-methyl-4,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-16-oxa-7,10,13,19,21,28-hexazapentacyclo[17.6.1.1^{2,6}.1^{8,11}.0^{22,26}]octacosa-1(25),2(28),3,5,20,22(26),23-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-(1-pyrimidin-5-ylpyrazolo[3,4-d]pyrimidin-4-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(11S,14S,18R)-13-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-25-fluoro-18-methoxy-16,21-dimethyl-5-oxa-10,13,16,20,22,29-hexazahexacyclo[18.6.1.1^{2,9}.1^{11,14}.0^{3,7}.0^{23,27}]nonacosa-1(26),2(29),3(7),8,21,23(27),24-heptaen-15-one;

(8S,11S,15R)-22-fluoro-15-methoxy-13,18-dimethyl-10-[1-methyl-6-(3-thienyl)pyrazolo[4,3-c]pyridin-3-yl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-(2,4-difluorophenyl)-1-methyl-pyrazolo[4,3-c]pyridin-3-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-21,23-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[3-(2,4-difluorophenyl)imidazo[1,5-a]pyrazin-8-yl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-10-[2-(2,4-difluorophenoxy)-4-pyridyl]-15-ethoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S)-15-ethoxy-10-[1-[4-fluoro-2-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,15,18-trimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-21-fluoro-18-hydroxy-13-methyl-7-oxa-10,13,17,19-tetrazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaene-14-carboxylic acid;

(8S,11S,15R)-10-[6-ethoxy-1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-methoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-ethoxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(morpholinomethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-isopropyl-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

methyl (8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxylate;

(8S,11S)-18-(chloromethyl)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-18-hydroxy-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-amino-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-N,13-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaene-18-carboxamide;

(8S,11S,15R)-10-[1-[2-(cyclopropoxy)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

N-[(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-18-yl]acetamide;

(8S,11S,15R)-10-[1-(2,4-difluoro-6-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-18-cyclopropyl-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13-methyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S)-10-[1-(2-fluoro-4-tetrahydrofuran-3-yl-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22,23-difluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8S,11S)-10-[1-[2-fluoro-4-(2-oxopyrrolidin-1-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2,4,6(26),18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-15-(trideuteriomethoxy)-13-(trideuteriomethyl)-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydrofuran-3-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-tetrahydropyran-4-yl-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-2-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-acetylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-hydroxy-1-(hydroxymethyl)ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(hydroxymethyl)-2-methoxy-ethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylazetidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-acetylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methylsulfonylpyrrolidin-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-acetylpyrrolidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylsulfonylpyrrolidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-acetylpyrrolidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methyl-4-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-(3-morpholinopropyl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-13-[3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propyl]-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-13-[3-[(4a*R*,7a*S*)-2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrol-6-yl]propyl]-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-18-methyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-ethylsulfonylazetidin-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1-cyclopropylsulfonylazetidin-3-yl)methyl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[1-(2,2,2-trifluoroethyl)azetidin-3-yl]methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(pyrrolidine-1-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-(2,4-difluorophenyl)-4-[(8S,11S)-22-fluoro-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]-N-(2-hydroxyethyl)pyrazolo[3,4-d]pyrimidine-6-carboxamide;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(morpholine-4-carbonyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(methoxymethyl)pyrazolo[4,3-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-5,13,18-trimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(1,3-dihydroisobenzofuran-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methyl-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoro-1-hydroxy-ethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[7-cyclopropyl-1-(2,4-difluorophenyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-(2-methoxyethyl)-6-oxo-pyrazolo[3,4-b]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26- hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-7-methoxy-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-methoxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1-hydroxycyclopropyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-[2-(azetidin-1-yl)-4-fluoro-phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(2-fluoro-4-morpholino-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluor-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-(methoxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(3-methoxycyclobutoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-[1-(methoxymethyl)cyclopropoxy]phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(hydroxymethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-4,22-difluoro-10-[1-(4-fluoro-2-methoxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2-dioxo-2λ^{6}-thia-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(hydroxymethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxy-1-methyl-ethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3*R*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(dimethylamino)methyl]azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methylsulfonylazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(tetrahydrofuran-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(1-cyclopropylazetidin-3-yl)oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(4-methylpiperazin-1-yl)ethoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroacetyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methylpiperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylazetidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1-methylpyrrolidin-3-yl)methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-fluoroethyl)azetidin-3-yl]oxy-pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(oxetan-3-ylmethoxy)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(dimethylamino)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(3-amino-3-methyl-azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo [3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]oxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[[1-(2,2-difluoroethyl)azetidin-3-yl]methoxy]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[1-(2,2-difluoroethyl)azetidin-3-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]ethyl acetate;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(5-fluoro-3-methylsulfanyl-2-pyridyl)-6-methylsulfanyl-pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*)-1-hydroxyethyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(morpholinomethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-ylmethyl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(oxetan-3-yl)piperazin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(4,7-diazaspiro[2.5]octan-7-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[4-(2H-tetrazol-5-yl)-1-piperidyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(3,5-difluoro-2-pyridyl)-6-(3-morpholinoazetidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(3a*R*,6a*S*)-2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-cyclopentyl-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-ylmethyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(4a*R*,7a*R*)-4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}] hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-benzyl-4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]piperazine-2-carboxylic acid;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-oxazol-5-yl-1-piperidyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-methylsulfonyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-10-(3-prop-1-ynylimidazo[1,5-*a*]pyrazin-8-yl)-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methylsulfanyl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-methoxy-phenyl)-6-[[1-(2-methoxyacetyl)azetidin-3-yl]methyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxy-3-methyl-but-1-ynyl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(3-methoxypyrrolidin-1-yl)phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluoro-6-tetrahydrofuran-3-yloxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[2-[4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-1-yl]-3,5-difluoro-phenoxy]acetonitrile;

(8*S*,11*S*,15*S*)-10-[1-[2,4-difluoro-6-[(1-methylsulfonylazetidin-3-yl)methoxy]phenyl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-4-(cyclopropylamino)-10-[1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(6-fluoro-1H-indazol-5-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)indazol-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-methyl-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-methoxyethyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[7-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-10-[6-(cyclopropylmethyl)-1-(2,4-difluorophenyl)-7-oxo-pyrazolo[3,4-c]pyridin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

2-[3-[1-(2,4-difluorophenyl)-4-[(8S,11S,15S)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothian-4-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(methylsulfonylmethyl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15S)-10-[6-(1-cyclopropylazetidin-3-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[(1,1-dioxothietan-3-yl)methylsulfanyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-[4-fluoro-2-(trideuteriomethoxy)phenyl]-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-[4-fluoro-2-(trideuteriomethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-(azetidin-1-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(dimethylamino)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-imidazol-1-yl-pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2,2,2-trifluoroethoxy)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(oxetan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(3*S*)-1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidine-3-carbonitrile;

8-[1-(2,4-difluorophenyl)-4-[(8S,11S,15R)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6,7,9,9a-tetrahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-4-one;

(8*S*,11*S*,15*R*)-10-[6-(3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8S,11S,15R)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-oxa-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-fluoroethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[8-(2-methoxyethyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[5-(2-fluoroethyl)-8-oxa-2,5-diazaspiro[3.5]nonan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

4-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(3-phenylpropylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*S*)-3-cyclopropyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-hydroxy-6-(trifluoromethyl)-2-azaspiro[3.3]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6-oxa-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(2-fluoroethyl)-1,6-diazaspiro[3.3]heptan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(2-fluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

2-[3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidin-1-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

3-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[(1*R*,4*R*)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-5-(2-morpholinoethylamino)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[11-benzyl-3-(2,4-difluorophenyl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-

dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-methyl-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[5-amino-1-(2,4-difluorophenyl)pyrazole-4-carbonyl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

2-[6-[1-(2,4-difluorophenyl)-4-[(8*S*,11S,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]acetonitrile;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-

7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]azetidine-3-carbonitrile;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(2-fluoroethyl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-1,7-diazaspiro[3.5]nonan-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[6-(oxetan-3-yl)-1,6-diazaspiro[3.3]heptan-1-

yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(6,6-dioxo-6λ^{6}-thia-1-azaspiro[3.3]heptan-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3,7-diazabicyclo[4.2.0]octan-7-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[3-(2,4-difluorophenyl)-11-(oxetan-3-yl)-3,4,8,11-tetrazatricyclo[7.3.0.0^{2,6}]dodeca-1(9),2(6),4,7-tetraen-7-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(oxetan-3-yl)-3,6-diazabicyclo[3.2.0]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(2-methoxyethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,4*R*)-5-(oxetan-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-[3-(oxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-2-oxo-pyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(2-oxopyrrolidin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one;

3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxazolidin-2-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(4-methyl-2-oxo-piperazin-1-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;

(8*S*,11*S*,15*S*)-22-fluoro-10-[6-[3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-

diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*S*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[6-[3-(2,2-difluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-hydroxy-2-methyl-propanoyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-hydroxycyclobutanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

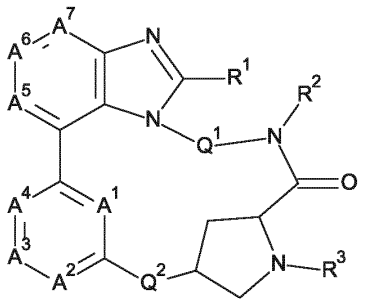
(8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropanecarbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one; and

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-fluorocyclobutyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.$1^{2,6}$.$1^{8,11}$.$0^{20,24}$]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one;

or a pharmaceutically acceptable salt thereof.

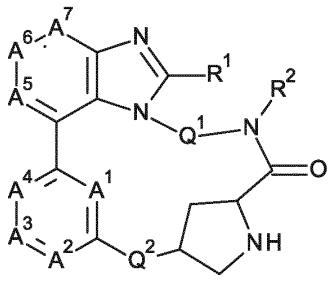
36. A process for the preparation of a compound according to any one of claims 1 to 35 comprising any of the following steps:

a) the formation of compound of formula (I),



(I),

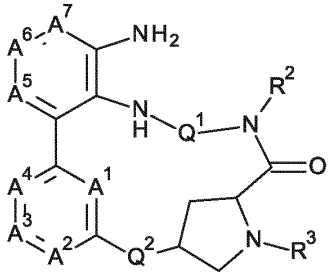
via nucleophilic substitution between compound of formula (VIII),

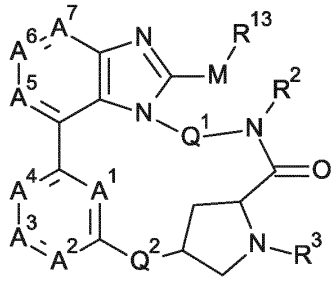
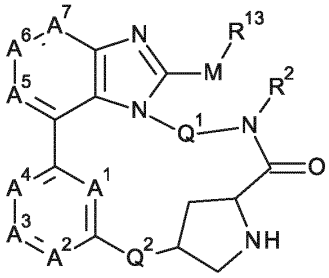


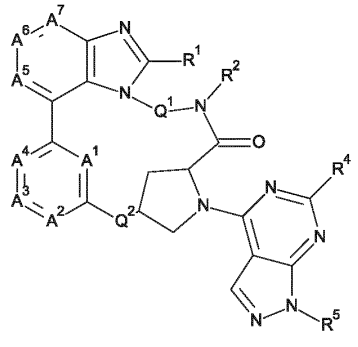
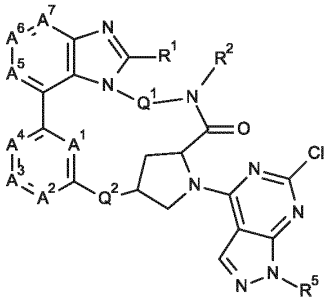
(VIII), and R^3X, in the presence of a base;

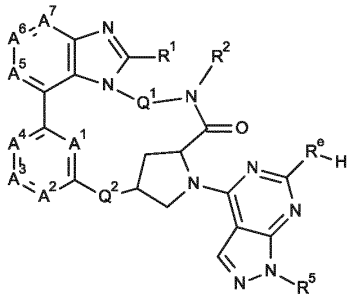
b) the formation of compound of formula (I) via Buchwald-Hartwig reaction between compound of formula (VIII) and R^3X, in the presence of a catalyst;

c) the formation of compound of formula (I) via condensation reaction between compound of formula (VIII) and R^3OH, in the presence of coupling reagent;

d) the formation of compound of formula (I) via cyclization reaction between compound of formula (XVIII) ,  (XVIII), and regents;

e) the formation of compound of formula (XXI),  (XXI), via nucleophilic substitution between compound of formula (XX),  (XX), and R^3X in the presence of a base;

f) the formation of compound of formula (XXII),  (XXII), via reaction between compound of formula (Ic),  (Ic), and alcohols or amines (R^4-X) in the presence of a base;

g) the amino group of compound of formula (XXIV),  (XXIV), reacts with halide via nucleophilic substitution or with ketone via reductive amination to provide final compound of formula (XXII);

wherein

in step a) and e) , the base is DIEA;

in step b), the catalyst is $Pd_2(dba)_3$;

in step c), the coupling reagent is HATU;

in step d), the regents is CDI, BrCN or $R^1(OCH_3)_3$;

in step e), the base is DIEA;

in step f), the base is DIPEA, K_2CO_3 or NaH;

X is halogen; R^{13} is R^a, R^b or R^c; M is $C_{1\text{-}6}$alkylene; R^e is a substituent bearing primary or secondary amino groups; R^1 to R^7, Q^1, Q^2, A^1 to A^7 are as defined as in any one of claims 1 to 34.

37. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 35 for use as therapeutically active substance.

38. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 35 and a therapeutically inert carrier.

39. The use of a compound according to any one of claims 1 to 35 for the treatment or prophylaxis of autoimmune diseases, inflammatory diseases, neurological disorders diseases, metabolic diseases, cardiovascular diseases, ocular diseases, or selective types of cancers where overexpression or activation of STING is implicated.

40. The use of a compound according to any one of claims 1 to 35 for the treatment to subjects suffered from an inteferonopathy or auto-inflammatory diseases in which the STING activation are the root-cause of disease pathologies.

41. The use of a compound according to any one of claims 1 to 35 for the inhibition of STING.

42. The use of a compound according to any one of claims 1 to 35 for the preparation of a medicament for the inhibition of STING.

43. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 35, when manufactured according to a process of claim 36.

44. A method for the treatment or prophylaxis of autoimmune diseases, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 35.