

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 Adalimumab (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- κ B) to initiate the expression of type-I IFN and a myriad of pro-inflammatory cytokines (e.g., IL-6 and TNF α), respectively. Besides 2'3'-cGAMP,

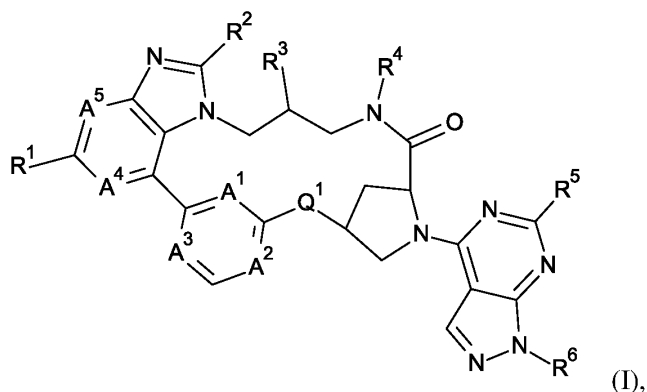
STING can be activated by other types of cyclic-di-nucleotides (CDNs), such as c-di-AMP, c-di-GMP, and 3',3'-cGAMP from bacteria. Following the signal transduction, STING is rapidly degraded to prevent it from constitutive signaling of the inflammatory responses.

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 known as familial chilblain lupus (FCL). 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. In addition, mutations in proteins, such as COP and WAS protein, that regulates STING intracellular trafficking and signaling also presented monogenic disorders known as COPA syndrome and Wiskott-Aldrich syndrome, respectively. Apart from genetic disorders, robust preclinical and clinical evidence supports a general pathogenic role of STING in a range of inflammation-associated disorders including but not limited to: SLE, IBD, RA, dermatomyositis, diabetic kidney disease (DKD), age-related macular degeneration (AMD), diabetic retinopathy (DR) and Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) associated vasculitis. For example: 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. In addition, cGAS- and cGAMP-independent mode of STING activation also affects neuropathology and provides a therapeutic target for the treatment of Niemann-Pick disease type C (NPC). 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 (I),



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wherein

A¹ is CH or N;

A² is CH or N;

A³ is CR⁷ or N; wherein R⁷ is H or halogen;

10 A⁴ is CH or N;

A⁵ is CH or N;

R¹ is H or halogen;

R² is C₁₋₆alkyl;

R³ is H or C₁₋₆alkoxy;

15 R⁴ is C₁₋₆alkyl;

R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,

1,1-dioxothietanyl,

1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or

20

oxetanylC₁₋₆alkyl,

3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3-oxo-3λ⁴-thia-6-azabicyclo[3.1.1]heptanyl,

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

6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,

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6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,

6-oxo-2-oxa-7-azaspiro[3.4]octanyl,

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7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,

9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,

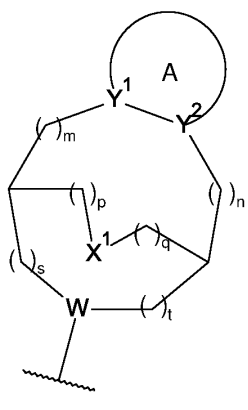
azetidiny which is once or twice substituted by substituents independently selected from

cyano, halogen, hydroxy, amino, C₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl,

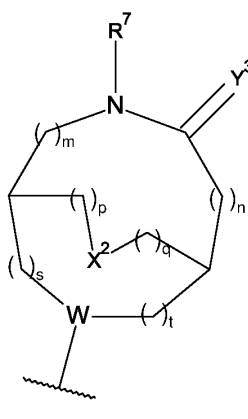
- 5 aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxy, heterocyclyl, heteroaryl, heteroarylcarbonyl and heterocyclcarbonyl,

cyanoC₁₋₆alkyl,

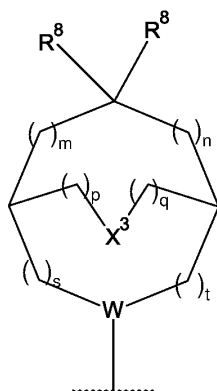
- 10 C₃₋₇cycloalkyl substituted by cyano,
morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
oxetanyl substituted by cyanoC₁₋₆alkyl,
oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl,
pyrrolidinyl substituted by hydroxyC₁₋₆alkyl,



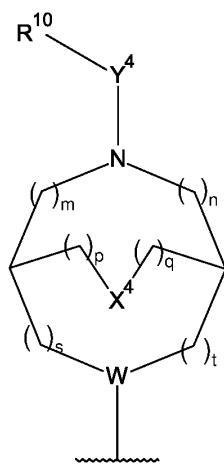
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, or



; wherein

Y¹ is CH, C or N;Y² is CH, C or N;5 Y³ is O or S;Y⁴ is a bond, C₁₋₆alkylene, -COO- or sulfonyl;

W is CH or N;

X¹, X², X³ and X⁴ are independently selected from C(R⁸)₂, O, S, SO₂, SO, NR⁹,N(CON(R⁹)₂) and N(COOR⁹);10 wherein each R⁸ is independently H, deuterio, halogen, hydroxy, cyano, C₁₋₆alkyl,C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₃₋7cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋7cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl,N(R⁹)₂, OR⁹, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl,15 heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋

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alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl or heterocyclisulfonyl;

each R⁹ is independently H, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋

5 alkyl, haloC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl, aryl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl or heterocyclisulfonyl;

R⁷ is C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heteroaryl or heteroarylC₁₋₆alkyl;

R¹⁰ is (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋₆alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, heterocyclylC₁₋₆alkyl, heteroarylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylcarbonyl, haloC₁₋₆alkoxycarbonyl, haloC₁₋₆alkylsulfonyl, heterocyclylC₁₋₆alkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, heteroarylC₁₋₆alkylcarbonyl, arylcarbonyl, aryl, heterocyclyl or heteroaryl;

30 Ring A is a aryl ring, heteroaryl ring or heterocyclyl ring, each of which is unsubstituted or substituted by C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, halogen, cyano or nitro;

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m, n, p, q, s, t are independently 0, 1 or 2, with the proviso that m, n, p, q, s, t are not 0 simultaneously;

R⁶ is phenyl twice or three times substituted by substituents independently selected from halogen, cyano, hydroxy and C₁₋₆alkoxy;

5 Q¹ is NH or O;

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, metabolic stability, hERG and SDPK profiles, as well as low CYP inhibition.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1. X-ray crystallographic analysis of compound 60d.

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 “C₁₋₆alkyl” 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 “C₁₋₆alkyl” groups are methyl, ethyl and *n*-propyl.

The term “C₁₋₆alkylene” denotes a divalent C₁₋₆alkyl. Examples of C₁₋₆alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

The term “C₁₋₆alkoxy” denotes C₁₋₆alkyl-O-.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term “haloC₁₋₆alkyl” denotes a C₁₋₆alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆alkyl 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 “haloC₁₋₆alkoxy” denotes haloC₁₋₆alkyl-O-.

- 5 The term “C₃₋₇cycloalkyl” 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
10 bicyclo[2.2.2]octanyl.

The term “haloC₃₋₇cycloalkoxy” denotes haloC₃₋₇cycloalkyl-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,
15 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,
20 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
25 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.
30 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, SO₂), and any nitrogen heteroatom may optionally be quaternized (e.g., [NR₄]⁺Cl⁻, [NR₄]⁺OH⁻). Examples of heterocycles include oxiranyl, aziridinyl, thiiranyl, azetidiny, 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,
- 5 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,
- 10 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-
- 15 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,
- 20 tetrahydroisoindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl, 2,3,4a,5,7,7a-hexahydro-[1,4]dioxino[2,3-c]pyrrolyl and oxopiperazinyl. Heterocyclyl can be further optionally substituted by halogen, hydroxy, cyano, amino, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, cyanoC₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, aminoC₁₋₆alkoxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkoxy, haloC₃₋₇cycloalkyl,
- 25 haloC₃₋₇cycloalkoxy, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkoxy, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkoxy, aminoC₃₋₇cycloalkyl, aminoC₃₋₇cycloalkoxy, C₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₁₋₆alkyl, aminoC₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, aminoC₁₋₆alkoxyC₃₋₇cycloalkyl, aryl or heteroaryl.
- 30 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.

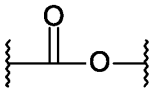
In certain embodiments, the heterocyclyl group or heteroaryl group is N-attached. By way of example, nitrogen bonded heterocyclyl or heteroaryl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 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 “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. Aryl can be further optionally substituted by halogen, hydroxy, cyano, amino, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, cyanoC₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, aminoC₁₋₆alkoxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkoxy, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkoxy, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkoxy, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkoxy, aminoC₃₋₇cycloalkyl, aminoC₃₋₇cycloalkoxy, C₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₁₋₆alkyl, aminoC₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, aminoC₁₋₆alkoxyC₃₋₇cycloalkyl, heterocyclyl or heteroaryl.

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. Heteroaryl can be further optionally substituted by halogen, hydroxy, cyano, amino, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, cyanoC₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, aminoC₁₋₆alkoxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkoxy, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkoxy, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkoxy, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkoxy, aminoC₃₋₇cycloalkyl, aminoC₃₋₇cycloalkoxy, C₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₁₋₆alkyl, aminoC₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, aminoC₁₋₆alkoxyC₃₋₇cycloalkyl, heterocyclyl or aryl.

The term “PG” denotes protecting groups.

The term “-COO-” 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, malonic 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 salicylic 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, 5 ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and polyamine resins.

The term “A pharmaceutically active metabolite” denotes a pharmacologically active 10 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 15 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 20 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.

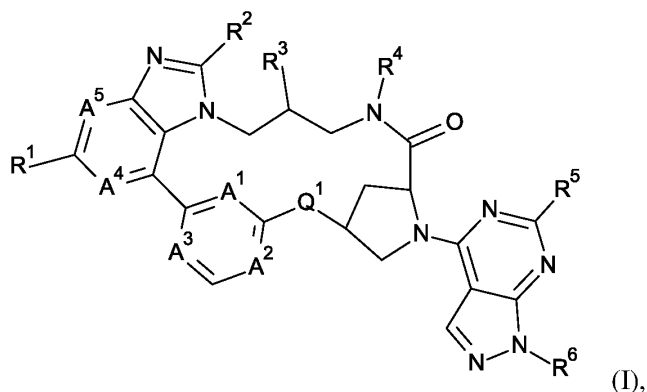
25 The term “pharmaceutical composition” denotes a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

The terms “pharmaceutically acceptable excipient”, “pharmaceutically acceptable carrier” 30 and “therapeutically inert excipient” can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers,

solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents or lubricants used in formulating pharmaceutical products.

ANTAGONIST OF STING

- 5 The present invention relates to (i) a compound of formula (I),

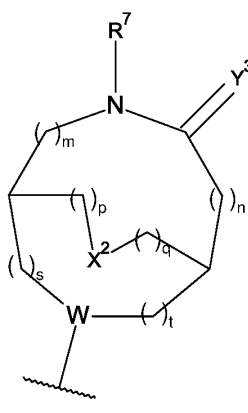
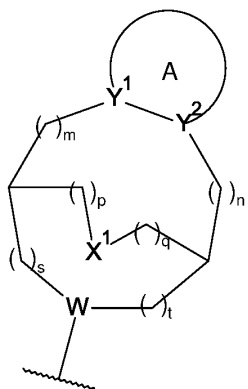


wherein

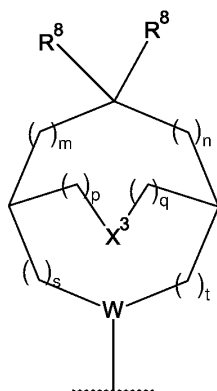
- A¹ is CH or N;
A² is CH or N;
10 A³ is CR⁷ or N; wherein R⁷ is H or halogen;
A⁴ is CH or N;
A⁵ is CH or N;
R¹ is H or halogen;
R² is C₁₋₆alkyl;
15 R³ is H or C₁₋₆alkoxy;
R⁴ is C₁₋₆alkyl;
R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,
1,1-dioxothietanyl,
1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,
20 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or
oxetanylC₁₋₆alkyl,
3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,
3-oxo-3λ⁴-thia-6-azabicyclo[3.1.1]heptanyl,
3-thia-6-azabicyclo[3.1.1]heptanyl,
25 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,
6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,

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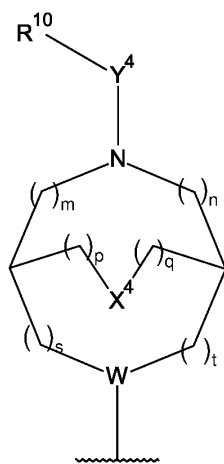
- 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,
 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,
 azetidiny which is once or twice substituted by substituents independently selected from
- 5 cyano, halogen, hydroxy, amino, C₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl,
 aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇
 cycloalkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl,
 cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxy, heterocyclyl, heteroaryl, heteroarylcarbonyl
 and heterocyclcarbonyl,
- 10 cyanoC₁₋₆alkyl,
 C₃₋₇cycloalkyl substituted by cyano,
 morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
 oxetanyl substituted by cyanoC₁₋₆alkyl,
 oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl,
- 15 pyrrolidinyl substituted by hydroxyC₁₋₆alkyl,



-15-



, or



; wherein

Y¹ is CH, C or N;Y² is CH, C or N;5 Y³ is O or S;Y⁴ is a bond, C₁₋₆alkylene, -COO- or sulfonyl;

W is CH or N;

X¹, X², X³ and X⁴ are independently selected from C(R⁸)₂, O, S, SO₂, SO, NR⁹,N(CON(R⁹)₂) and N(COOR⁹);10 wherein each R⁸ is independently H, deuterio, halogen, hydroxy, cyano, C₁₋₆alkyl,C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₃₋7cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋7cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl,N(R⁹)₂, OR⁹, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl,15 heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋

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alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl or heterocyclisulfonyl;

each R⁹ is independently H, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋

5 alkyl, haloC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl, aryl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl or heterocyclisulfonyl;

R⁷ is C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heteroaryl or heteroarylC₁₋₆alkyl;

R¹⁰ is (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋₆alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, heterocyclylC₁₋₆alkyl, heteroarylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylcarbonyl, haloC₁₋₆alkoxycarbonyl, haloC₁₋₆alkylsulfonyl, heterocyclylC₁₋₆alkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, heteroarylC₁₋₆alkylcarbonyl, arylcarbonyl, aryl, heterocyclyl or heteroaryl;

30 Ring A is a aryl ring, heteroaryl ring or heterocyclyl ring, each of which is unsubstituted or substituted by C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, halogen, cyano or nitro;

m, n, p, q, s, t are independently 0, 1 or 2, with the proviso that m, n, p, q, s, t are not 0 simultaneously;

R⁶ is phenyl twice or three times substituted by substituents independently selected from halogen, cyano, hydroxy and C₁₋₆alkoxy;

5 Q¹ is NH or O;

or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (ii) a compound of formula (I) according to (i), or a pharmaceutically acceptable salt thereof, wherein

R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,

10 1,1-dioxothietanyl,

1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dienyl substituted by C₁₋₆alkyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dienyl substituted by C₁₋₆alkyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or

15 oxetanylC₁₋₆alkyl,

2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C₁₋₆alkyl, C₁₋

alkoxyC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl,

cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, oxetanyl, oxetanylC₁₋₆alkyl or

tetrahydropyranyl,

20 2-oxo-3,8-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋

alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, (oxopyrrolidinyl)C₁₋

25 alkyl, 1,3,4-thiadiazolyl, 1H-pyrazolylC₁₋₆alkyl, 2-oxaspiro[3.3]heptanylcarbonyl,

C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋

alkyloxetanyl, C₁₋₆alkylpyrazolyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylC₁₋

alkylcarbonyl, cyanooxetanyl, haloC₁₋₆alkoxycarbonyl, oxazolyl, oxetanylC₁₋

alkylcarbonyl, oxetanylcarbonyl, pyrimidinyl, thiazolyl, thiazolylC₁₋₆alkyl or

30 thiazolylcarbonyl,

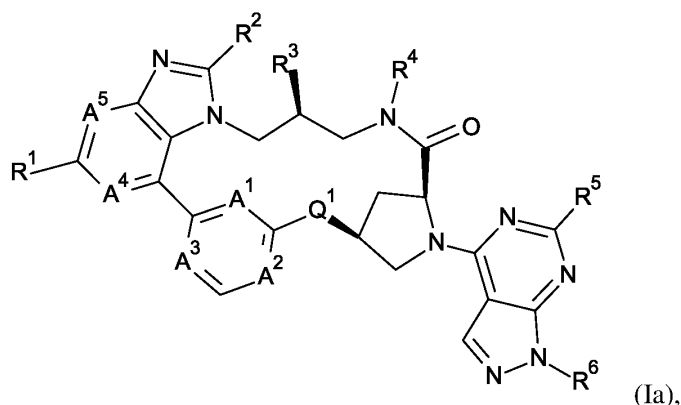
3-azabicyclo[3.1.1]heptanyl substituted by oxetanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by oxetanyl or oxetanylC₁₋₆alkyl,

3-oxo-2,6-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

- 3-oxo-3 λ^4 -thia-6-azabicyclo[3.1.1]heptanyl,
 3-thia-6-azabicyclo[3.1.1]heptanyl,
 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dienyl substituted by C₁₋₆alkyl,
 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dienyl substituted by C₁₋₆alkyl,
 5 4-oxo-3,7-diazabicyclo[4.1.1]octanyl substituted by C₁₋₆alkyl,
 4-oxo-8-oxa-3,10-diazabicyclo[4.3.1]decanyl substituted by C₁₋₆alkyl,
 5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decanyl,
 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,
 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently
 10 selected from hydroxy, cyano, C₁₋₆alkyl and cyanoC₃₋₇cycloalkyl,
 6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,
 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,
 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,
 15 azetidiny which is once substituted by pyrazolyl, 1,2,4-triazolyl or C₁₋₆alkyl-1,2,4-
 oxadiazolyl, or twice substituted by substituents independently selected from cyano,
 C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl and
 haloazetidiny carbonyl,
 cyanoC₁₋₆alkyl,
 20 C₃₋₇cycloalkyl substituted by cyano,
 morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
 oxetanyl substituted by cyanoC₁₋₆alkyl,
 oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl, or
 pyrrolidinyl substituted by hydroxyC₁₋₆alkyl.
 25 Another embodiment of present invention is (iii) a compound of formula (Ia) according to
 (i) or (ii),

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wherein

A¹ is CH or N;

A² is CH or N;

5 A³ is CR⁷ or N; wherein R⁷ is H or halogen;

A⁴ is CH or N;

A⁵ is CH or N;

R¹ is H or halogen;

R² is C₁₋₆alkyl;

10 R³ is H or C₁₋₆alkoxy;

R⁴ is C₁₋₆alkyl;

R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,

1,1-dioxothietanyl,

1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,

15 10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dienyl substituted by C₁₋₆alkyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dienyl substituted by C₁₋₆alkyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or
oxetanylC₁₋₆alkyl,

2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C₁₋₆alkyl, C₁₋

20 alkoxyC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl,
cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, oxetanyl, oxetanylC₁₋₆alkyl or
tetrahydropyranyl,

2-oxo-3,8-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

25 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

- 3,6-diazabicyclo[3.1.1]heptanyl substituted by (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋₆alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, (oxopyrrolidinyl)C₁₋₆alkyl, 1,3,4-thiadiazolyl, 1H-pyrazolylC₁₋₆alkyl, 2-oxaspiro[3.3]heptanylcarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkyloxetanyl, C₁₋₆alkylpyrazolyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylC₁₋₆alkylcarbonyl, cyanooxetanyl, haloC₁₋₆alkoxycarbonyl, oxazolyl, oxetanylC₁₋₆alkylcarbonyl, oxetanylcarbonyl, pyrimidinyl, thiazolyl, thiazolylC₁₋₆alkyl or thiazolylcarbonyl,
- 3-azabicyclo[3.1.1]heptanyl substituted by oxetanyl,
- 3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by oxetanyl or oxetanylC₁₋₆alkyl,
- 3-oxo-2,6-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,
- 3-oxo-3λ⁴-thia-6-azabicyclo[3.1.1]heptanyl,
- 3-thia-6-azabicyclo[3.1.1]heptanyl,
- 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dienyl substituted by C₁₋₆alkyl,
- 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dienyl substituted by C₁₋₆alkyl,
- 4-oxo-3,7-diazabicyclo[4.1.1]octanyl substituted by C₁₋₆alkyl,
- 4-oxo-8-oxa-3,10-diazabicyclo[4.3.1]decanyl substituted by C₁₋₆alkyl,
- 5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decanyl,
- 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,
- 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently selected from hydroxy, cyano, C₁₋₆alkyl and cyanoC₃₋₇cycloalkyl,
- 6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,
- 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
- 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,
- 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,
- azetidiny which is once substituted by pyrazolyl, 1,2,4-triazolyl or C₁₋₆alkyl-1,2,4-oxadiazolyl, or twice substituted by substituents independently selected from cyano, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl and haloazetidiny carbonyl,
- cyanoC₁₋₆alkyl,
- C₃₋₇cycloalkyl substituted by cyano,
- morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
- oxetanyl substituted by cyanoC₁₋₆alkyl,

oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl, or
pyrrolidinyl substituted by hydroxyC₁₋₆alkyl;

R⁶ is phenyl twice substituted by substituents independently selected from halogen, cyano,
hydroxy and C₁₋₆alkoxy;

5 Q¹ is NH or O;

or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (iv) a compound of formula (I) or (Ia), or a
pharmaceutically acceptable salt thereof, according to any one of (i) to (iii), wherein A³ is CH.

A further embodiment of present invention is (v) a compound of formula (I) or (Ia), or a
10 pharmaceutically acceptable salt thereof, according to any one of (i) to (iii), wherein R¹ is H or
fluoro.

A further embodiment of present invention is (vi) a compound of formula (I) or (Ia), or a
pharmaceutically acceptable salt thereof, according to any one of (i) to (v), wherein R² is methyl.

A further embodiment of present invention is (vii) a compound of formula (I) or (Ia), or a
15 pharmaceutically acceptable salt thereof, according to any one of (i) to (vi), wherein R³ is H,
methoxy or ethoxy.

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 R⁴ is
methyl.

20 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

R⁵ is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇
cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, oxetanyl or
tetrahydropyranyl,

25 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkylpyrazolyl, thiazolylcarbonyl, 1,3,4-
thiadiazolyl or thiazolyl,

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

30 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently
selected from hydroxy, cyano and C₁₋₆alkyl, or

azetidiny which is twice substituted by substituents independently selected from cyano,
C₁₋₆alkyl and C₁₋₆alkoxy.

- 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 R⁵ is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by 2,2-difluoroethyl, 2-cyanoethyl, 2-fluoroethyl, 3-cyanocyclobutyl, cyclobutyl, cyclopropyl, cyclopropylmethyl, ethyl, isopropyl, methyl, oxetan-3-yl or tetrahydropyran-4-yl,
- 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,
- 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,
- 3,6-diazabicyclo[3.1.1]heptanyl substituted by 1-methylpyrazol-3-yl, thiazole-2-carbonyl, 1,3,4-thiadiazol-2-yl or thiazol-2-yl,
- 3-thia-6-azabicyclo[3.1.1]heptanyl,
- 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently selected from hydroxy, cyano and methyl, or azetidiny which is twice substituted by substituents independently selected from cyano, methyl and methoxy.
- 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 R⁵ is 2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-cyanoethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(3-cyanocyclobutyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptan-6-yl, 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl, 3-cyano-3-methoxy-azetidin-1-yl, 3-cyano-3-methyl-azetidin-1-yl, 3-cyano-6-azabicyclo[3.1.1]heptan-6-yl, 3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl, 3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-thia-6-azabicyclo[3.1.1]heptan-6-yl or 3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl.

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 R⁶ is phenyl twice substituted by halogen.

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 R⁶ is phenyl twice substituted by fluoro.

A further embodiment of present invention is (xiv) a compound of formula (I) or (Ia),,
5 according to any one of (i) to (xiii), wherein R⁶ is 2,4-difluorophenyl.

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

A¹ is CH or N;

A² is CH or N;

10 A³ is CH;

A⁴ is CH or N;

A⁵ is CH or N;

R¹ is H or halogen;

R² is C₁₋₆alkyl;

15 R³ is H or C₁₋₆alkoxy;

R⁴ is C₁₋₆alkyl;

R⁵ is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋

₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, oxetanyl or tetrahydropyranyl,

20 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkylpyrazolyl, thiazolylcarbonyl, 1,3,4-thiadiazolyl or thiazolyl,

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

25 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently

selected from hydroxy, cyano and C₁₋₆alkyl, or

azetidiny which is twice substituted by substituents independently selected from cyano,

C₁₋₆alkyl and C₁₋₆alkoxy;

R⁶ is phenyl twice substituted by halogen;

30 Q¹ is NH or O;

or a pharmaceutically acceptable salt thereof.

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

- A^1 is CH or N;
 A^2 is CH or N;
 A^3 is CH;
 A^4 is CH or N;
5 A^5 is CH or N;
 R^1 is H or fluoro;
 R^2 is methyl;
 R^3 is H, methoxy or ethoxy;
 R^4 is methyl;
10 R^5 is 2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-cyanoethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(3-cyanocyclobutyl)-2-oxo-3,6-
15 diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3,3-dioxo-3 λ^6 -thia-6-azabicyclo[3.1.1]heptan-6-yl, 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl, 3-cyano-3-methoxy-azetidin-1-yl, 3-cyano-3-methyl-azetidin-1-yl, 3-cyano-6-
20 azabicyclo[3.1.1]heptan-6-yl, 3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl, 3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-thia-6-azabicyclo[3.1.1]heptan-6-yl or 3-thiazol-2-yl-
25 3,6-diazabicyclo[3.1.1]heptan-6-yl;
 R^6 is 2,4-difluorophenyl;
 Q^1 is NH or O;
or a pharmaceutically acceptable salt thereof.
Another embodiment of present invention (xvii) is a compound of formula (I) or (Ia),
30 selected from the following:
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(2-oxopyrrolidin-1-yl)ethyl]-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-[3-(trifluoromethyl)-6,8-dihydro-5*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 5 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-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-
- 10 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-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-
- 15 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-(thiazol-2-ylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 20 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-oxaspiro[3.3]heptane-6-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 25 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*H*-pyrazol-5-ylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 30 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,5*R*)-3-methyl-2-oxo-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-[(1*S*,5*R*)-3-methyl-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-
5 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;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-methyl-2-oxo-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-pentazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-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;
15 (8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-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-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-
20 6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-
6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
25 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*S*,5*R*)-3-methyl-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
30 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-methyl-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

- 7,10,13,17,19,23,26-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*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-
yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 5 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*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-
yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
10 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*,5*R*)-3-ethyl-2-oxo-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;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-ethyl-2-oxo-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;
3-[(1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-
20 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]-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;
3-[(1*S*,5*R*)-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-
25 1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-3-methyl-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-
30 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-[(3-fluorooxetan-3-yl)methyl]-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

- 7,10,13,17,19,23,26-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*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 5 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 10 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-hydroxyethyl)-5-oxo-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-[1-(2,4-difluorophenyl)-6-[1-(2-hydroxyethyl)-2-oxo-pyrrolidin-3-
- 15 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;
- 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]-*N,N*-dimethyl-3,6-diazabicyclo
- 20 [3.1.1]heptane-3-carboxamide;
- 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]-*N,N*-dimethyl-3,6-diazabicyclo
- [3.1.1]heptane-3-sulfonamide;
- 25 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyacetyl)-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-[3-(oxetane-2-carbonyl)-3,6-diazabicyclo[3.1.1]
- 30 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-(oxetane-3-carbonyl)-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;
- 5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methylsulfonylacetyl)-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;
- 6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-10 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]-*N*-methyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(oxetan-3-yl)acetyl]-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;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(difluoromethoxy)acetyl]-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methylsulfonyl-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;
- 25 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-methyl-9-oxo-1,8-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(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-methyl-6-oxo-1,7-diazaspiro[3.4]octan-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;
- 30 2-[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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]oxetan-3-yl]acetonitrile;

- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methyl-5-oxo-pyrrolidine-3-carbonyl)-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;
- 5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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;
- 3-fluoro-4-[4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-10 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]-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-1-yl]benzonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-15 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-(3-oxazol-2-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(hydroxymethyl)-5-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(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*S*)-2-(hydroxymethyl)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(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 25 methyl 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;
- 30 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-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-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-4-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;
- 5 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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]propanenitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothietan-3-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-
- 10 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-[(1*S*,5*R*)-3-methyl-2-oxo-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(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*S*,5*R*)-3-(oxetan-3-ylmethyl)-2-oxo-3,6-
- 20 diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-
- 25 diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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-(7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-
- 30 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-(1,3,4-thiadiazol-2-yl)-3,6-
- diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

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- 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*)-22-fluoro-10-[1-(2-fluoro-4-methoxy-phenyl)-6-(3-thiazol-2-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(24),2,4,6(26),18,20,22-heptaen-12-one;
- Trans*-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]cyclobutanecarbonitrile;
- Cis*-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]cyclobutanecarbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(3*R*)-3-(methoxymethyl)morpholin-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(24),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(hydroxymethyl)-2-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-[6-[7-(2,2-difluoroacetyl)-1,7-diazaspiro[3.4]octan-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-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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-[(1*R*,5*S*)-3-methyl-2-oxo-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-pyrimidin-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
- 5 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}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thia-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-
- 10 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-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-oxo-3 λ^4 -thia-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 1 1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-
- 15 7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-(methoxymethyl)azetidine-3-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3,3-dioxo-3 λ^6 -thia-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 20 2-[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}]hexacos-
- 1(23),2(26),3,5,18,20(24), 21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidin-3-yl]acetonitrile;
- 7-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-
- 25 5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-
- 1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxa-7-azaspiro[3.4]octan-6-one;
- (8*S*,11*S*,15*R*)-10-[6-[2-(2,2-difluoroethyl)-7-oxo-2,6-diazaspiro[3.4]octan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-
- 30 5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-
- 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-methyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 10 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(3-fluoroazetidine-1-carbonyl)-2-methylazetidin-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 15 (8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-methyl-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-(oxetan-3-ylmethyl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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-
- 20 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-(oxetan-3-yl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 25 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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methyl-azetidine-3-carbonitrile;
- 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}]hexacos-1(24),2,4,6(26),18,20,22-
- 30 heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidine-3-carbonitrile;

- 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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-5-oxo-pyrrolidine-3-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropylmethyl)-2-oxo-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}]hexacos-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*S*,5*R*)-3-(2-fluoroethyl)-2-oxo-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}]hexacos-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*,5*S*)-3-(2-fluoroethyl)-2-oxo-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}]hexacos-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-methyl-2-oxo-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}]hexacos-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-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-3,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 10-[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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methyl-8-oxa-3,10-diazabicyclo[4.3.1]decan-4-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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}]hexacos-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*,8*S*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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*S*,8*R*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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*R*,8*S*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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*S*,2*S*,8*R*)-5-oxo-6,9-diazatricyclo[6.1.1.0₂,6]decan-9-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*,2*R*,8*S*)-5-oxo-6,9-diazatricyclo[6.1.1.0₂,6]decan-9-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-[(3*R*)-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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]morpholin-3-yl]acetonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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-[7-(oxetan-3-ylmethyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-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*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-
- 5 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*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 10 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-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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;
- 15 (8*S*,11*S*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-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-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,23,26-
- 20 heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-(oxetan-3-yl)-3-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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(24),2,4,6(26),18,20,22-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-
- 25 6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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(24),2,4,6(26),18,20,22-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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(24),2(26),3,5,18,20,22-
- 30 heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(2-methoxyethyl)-2-oxo-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-[(1*S*,5*R*)-3-(2-methoxyethyl)-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
5 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,6*S*)-3-methyl-4-oxo-3,7-
diazabicyclo[4.1.1]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-
10 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*S*,6*R*)-3-methyl-4-oxo-3,7-
diazabicyclo[4.1.1]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),2,4,6(26),18,20,22-heptaen-12-one;
15 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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3,6-
diazabicyclo[3.1.1]heptan-3-yl]oxetane-3-carbonitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*S*)-2-methyl-3-oxo-2,6-
20 diazabicyclo[3.2.1]octan-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),2,4,6(26),18,20,22-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*R*)-2-methyl-3-oxo-2,6-
diazabicyclo[3.2.1]octan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
25 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*,8*S*)-4-methyl-4,5,11-
triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-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-
30 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*,8*R*)-4-methyl-4,5,11-
triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-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*R*,8*S*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-
- 5 methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,8*R*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-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-
- 10 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-pyrimidin-5-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 7,10,13,17,19,23,26-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;
- 15 (8*S*,11*S*,15*R*)-3-chloro-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 7,10,13,17,19,23,26-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-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-
- 20 (2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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-
- 25 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-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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-
- 30 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (1*S*,5*R*)-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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
(1*R*,5*S*)-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-
- 5 1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]]hexacosa-
- 10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]]hexacosa-
- 15 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-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-
- 20 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]]hexacosa-
- 25 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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-
- 30 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*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]]deca-2,4-dien-9-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-12-one;
(8*S*,11*S*,15*S*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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-[(1*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-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-[(1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-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*S*,5*R*)-3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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)-6-[(1*S*,5*R*)-3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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)-6-[(1*S*,5*R*)-3-(2-hydroxyethyl)-2-oxo-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-[(1*S*,5*R*)-2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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;
- Cis*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-

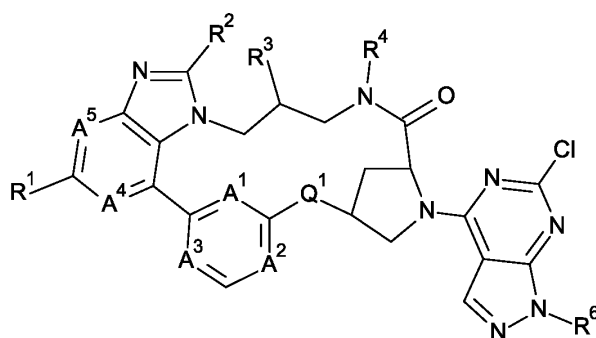
- 1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile;
- Trans*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
- 5 1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrazol-1-ylazetidin-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;
- 10 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-imidazol-1-ylazetidin-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;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1,2,4-triazol-1-yl)azetidin-1-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-
- 15 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-(3-methyl-1,2,4-oxadiazol-5-yl)azetidin-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;
- (1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-
- 20 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-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
- (1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-
- 25 1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-*exo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
- 30 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-*endo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

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- 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;
- (1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
- (1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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
- 1-[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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptan-3-yl]azetidine-3-carbonitrile;
- or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention (xviii) is a process for the preparation of a compound according to any one of (i) to (xvii) comprising any one of the following steps:

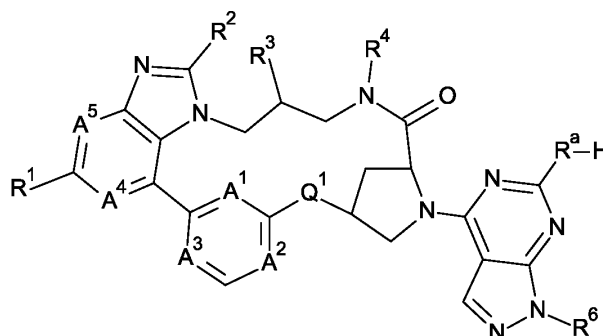
- a) the formation of compound of formula (I) via nucleophilic substitution or Buchwald cross coupling between compound of formula (VIII),



(VIII), and HR⁵;

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b) the formation of compound of formula (I) via nucleophilic substitution reaction

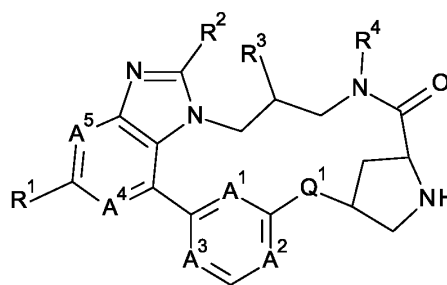


between compound of (IX),

(IX), and halide or acid anhydride; or condensation reaction between compound of formula (IX) and acid; or reductive amination between compound of formula (IX) and ketone or aldehyde;

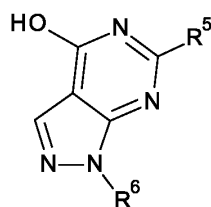
5

c) the formation of compound of formula (I) via condensation reaction between



compound of formula (VII),

(VII), and



compound of formula (VIIb),
reagent;

(VIIb), in the presence of coupling

10

wherein

the coupling reagent in step c) is PyBOP;

X is halogen; HR^a is heterocyclyl with reactive primary or secondary amino group;

R¹ to R⁶, Q¹ and A¹ to A⁶ are as defined as in any one of (i) to (xvi).

Another embodiment of present invention (xix) is related to a compound or

15

pharmaceutically acceptable salt according to any one of (i) to (xvii) for use as therapeutically active substance.

Another embodiment of present invention (xx) is related to a pharmaceutical composition comprising a compound in accordance with any one of (i) to (xvii) and a pharmaceutically acceptable excipient.

Another embodiment of present invention (xxi) is related to the use of a compound
5 according to any one of (i) to (xvii) 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 (xxii) is related to a compound or
10 pharmaceutically acceptable salt according to any one of (i) to (xvii) 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 (xxiii) is related to the use of a compound
15 according to any one of (i) to (xvii) 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 (xxiv) is related to the use of a compound according to any one of (i) to (xvii) for the treatment or prophylaxis of systemic lupus
20 erythematosus (SLE), dermatomyositis, diabetic kidney disease (DKD), diabetic retinopathy (DR), age-related macular degeneration (AMD), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) vasculitis, STING-associated vasculopathy with onset in infancy (SAVI), familial chilblain lupus (FCL), Niemann-Pick disease type C (NPC), Aicardi-Goutières Syndrome (AGS), COPA syndrome or Wiskott-Aldrich syndrome.

Another embodiment of present invention (xxv) is related to the use of a compound
25 according to any one of (i) to (xvii) for the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus (SLE), dermatomyositis, diabetic kidney disease (DKD), diabetic retinopathy (DR), age-related macular degeneration (AMD), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) vasculitis, STING-associated vasculopathy with onset in
30 infancy (SAVI), familial chilblain lupus (FCL), Niemann-Pick disease type C (NPC), Aicardi-Goutières Syndrome (AGS), COPA syndrome or Wiskott-Aldrich syndrome.

Another embodiment of present invention (xxvi) is related to the use of a compound according to any one of (i) to (xvii) for the inhibition of STING.

Another embodiment of present invention (xxvii) is related to the use of a compound according to any one of (i) to (xvii) for the preparation of a medicament for the inhibition of STING.

Another embodiment of present invention (xxvii) is related to a compound or
5 pharmaceutically acceptable salt according to any one of (i) to (xvii), when manufactured according to a process of (xviii).

Another embodiment of present invention (xxix) 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 (xvii).
10

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.
15 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
20 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
25 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
30 minimum amount necessary to inhibit STING interaction with IRF3, NF- κ B, NLRP3 etc., for blocking downstream type I IFN and pro-inflammatory cytokine (e.g. IL-6, TNF α , 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
5 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
10 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
15 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
20 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
25 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
30 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

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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.

20

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:

	<u>Per tablet</u>
25 Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
30	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:

	<u>Per capsule</u>
Active ingredient	100.0 mg
5 Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

10

INDICATIONS AND METHODS OF TREATMENT

The compound of the invention inhibit the binding of cGAMP to STING and its downstream signaling. Accordingly, the compound of the invention are useful for blocking STING activation, signaling, downstream cytokine, chemokine production and cellular processes such as apoptosis and autophagy. Compounds of the invention are useful for inhibition of STING. Alternatively, compounds of invention are useful for the treatment or prophylaxis of systemic lupus erythematosus (SLE), dermatomyositis, diabetic kidney disease (DKD), diabetic retinopathy (DR), age-related macular degeneration (AMD), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) vasculitis, STING-associated vasculopathy with onset in infancy (SAVI), familial chilblain lupus (FCL), Niemann-Pick disease type C (NPC), Aicardi-Goutières Syndrome (AGS), COPA syndrome or Wiskott-Aldrich syndrome. More broadly, the compound can be useful 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.

25

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.

30

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
5 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.

10 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.

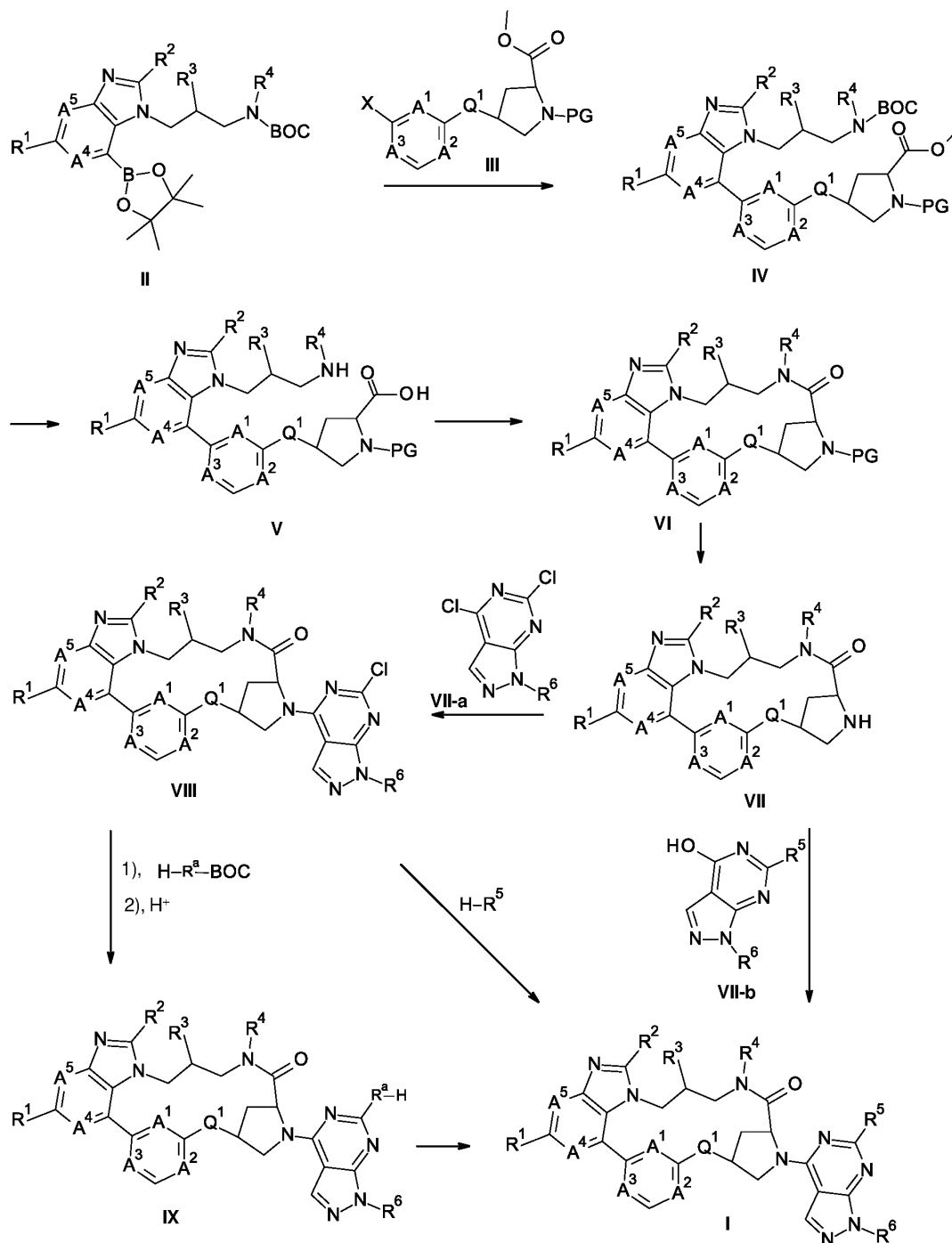
15 SYNTHESIS

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^6 , Q^1 , A^1 to A^5 are as defined above unless otherwise indicated. Furthermore, and unless explicitly
20 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

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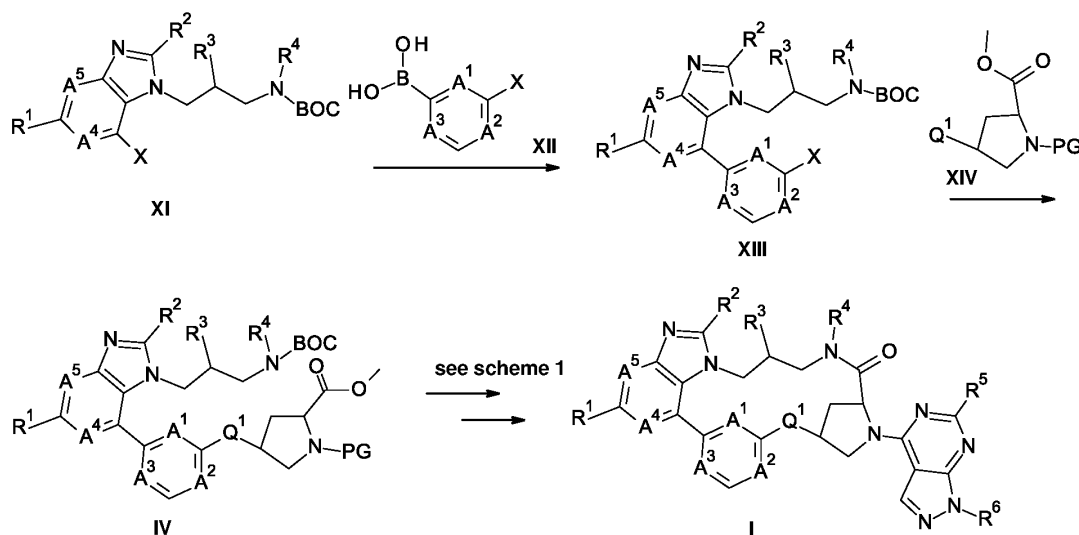
Wherein HR^a is heterocyclyl with reactive primary or secondary amino group; PG can be, for example, Boc or Cbz ; X is halogen.

As depicted in **Scheme 1**, the synthesis of compounds of the present invention started from
 5 boronic ester compound of formula (II). Suzuki coupling between compound of formula (II) and

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compound of formula (III) with a catalyst, such as Pd(dppf)Cl₂, and a base, such as K₂CO₃, provides compound of formula (IV). Compound of formula (IV) is hydrolyzed in the presence of LiOH directly and followed by Boc deprotection (HCl in dioxane or TFA in DCM) to give compound of formula (V). Compound of formula (V) can be cyclized to give compound of formula (VI) 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 H₂) or in acidic condition (TFA) to give compound of formula (VII). Compound of formula (VII) reacted with compound of formula (VIIa) via nucleophilic substitution in the presence of a base, such as DIEA to give compound of formula (VIII), which was directly reacted with H-R⁵ via nucleophilic substitution or Buchwald cross coupling to give the final compound of formula (I). On the other hand, compound of formula (VIII) reacted with H-R^a-Boc via nucleophilic substitution or Buchwald cross coupling, followed by Boc deprotection in acidic condition provide compound of formula (IX). The amino group of compound of formula (IX) reacts with halide or acid anhydride via nucleophilic substitution or with acid via condensation or with ketone or aldehyde via reductive amination to provide final compound of formula (I). Furthermore, compound of formula (I) can also be obtained via condensation reaction between compound of formula (VII) and compound of formula (VIIb) in the presence of coupling reagent, such as PyBOP.

Scheme 2



20

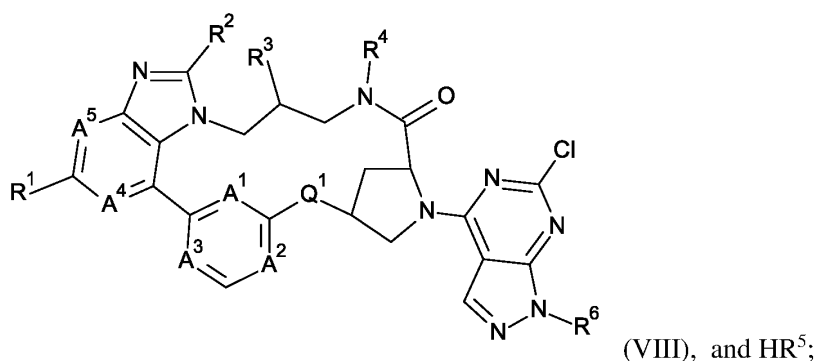
Wherein X is halogen.

As depicted in **Scheme 2**, the synthesis of compounds of the present invention started from halogen compound of formula (XI). Suzuki coupling between compound of formula (XI) and compound of formula (XII) with a catalyst, such as Pd(dppf)Cl₂, and a base, such as K₂CO₃, provides compound of formula (XIII). The following Buchwald coupling between compound of formula (XIII) and compound of formula (XIV) with a catalyst, such as RuPhos Pd G2, and a base, such as Cs₂CO₃, provides compound of formula (IV). The synthesis of final compound of formula (I) from compound of formula (IV) is the same as described in **Scheme 1**.

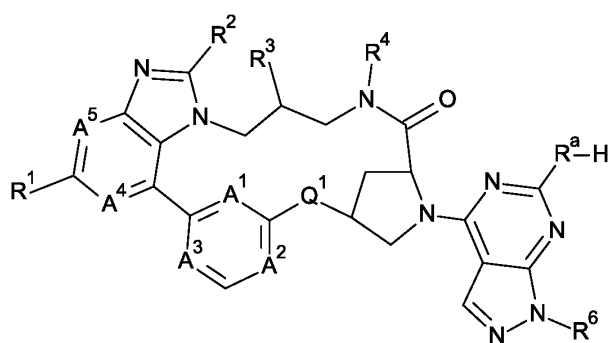
Compounds of this invention can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or SFC.

This invention also relates to a process for the preparation of a compound of formula (I) comprising any one of the following steps:

- a) the formation of compound of formula (I) via nucleophilic substitution or Buchwald cross coupling between compound of formula (VIII),



- b) the formation of compound of formula (I) via nucleophilic substitution reaction

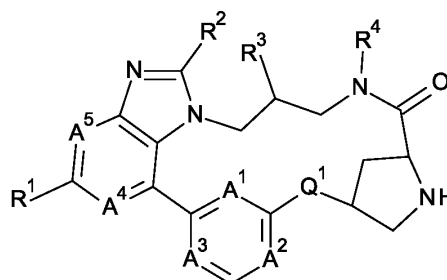


between compound of (IX),

(IX), and halide or acid anhydride; or condensation reaction between compound of formula (IX) and acid; or reductive amination between compound of formula (IX) and ketone or aldehyde;

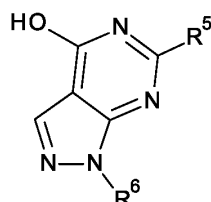
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c) the formation of compound of formula (I) via condensation reaction between



compound of formula (VII),

(VII), and



compound of formula (VIIb),

(VIIb), in the presence of coupling

reagent;

5 wherein

the coupling reagent in step c) can be, for example, PyBOP;

X is halogen; HR^a is heterocyclyl with reactive primary or secondary amino group.

A compound of formula (I) or (Ia) when manufactured according to the above process is also an object of the invention.

10 **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

15 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 ₂ O:	di- <i>tert</i> butyl dicarbonate
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-dinaphthalene
20 CataCXium A Pd G2:	Chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II)
DCM:	dichloromethane
DCE:	dichloroethane
DIPEA or DIEA:	<i>N,N</i> -diisopropylethylamine

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	DIBAL-H:	diisobutylaluminium hydride
	DIAD:	diisopropyl azodicarboxylate
	DMA:	<i>N,N</i> -Dimethylacetamine
	DMAP:	4-dimethylaminopyridine
5	DMF:	<i>N,N</i> -Dimethylformamide
	DMSO:	dimethyl sulfoxide
	DPPP:	1,3-Bis(diphenylphosphino)propane
	EA or EtOAc:	ethyl acetate
	FA:	formic acid
10	EDCI:	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	HATU:	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
	HOBt:	1-Hydroxybenzotriazole
	h(s) or hr(s):	hour (s)
15	HMPA:	Hexamethylphosphoric triamide
	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- <i>N</i> 1, <i>N</i> 1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- <i>N</i>]phenyl-C]Iridium(III)
20	hexafluorophosphate	
	IPA:	isopropanol
	LCMS:	liquid chromatography-mass spectrometry
	mCPBA:	meta-chloroperoxybenzoic acid
	min(s):	minute(s)
25	MS:	mass spectrometry
	MsCl:	methanesulfonyl chloride
	Ms ₂ O:	methanesulfonic anhydride
	NBS:	<i>N</i> -bromosuccinimide
	NIS:	<i>N</i> -iodosuccinimide
30	NMP:	<i>N</i> -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 <i>H</i> -benzotriazolato- <i>o</i>)tri-1-pyrrolidinylphosphorus
	hexafluorophosphate	
	PPh ₃ :	triphenylphosphine
5	Pd ₂ (dba) ₃ :	tris(dibenzylideneacetone)dipalladium(0)
	Pd(dppf)Cl ₂ :	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Pd-PEPPSI-IPentCl:	(SP-4-1)-[1,3-Bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-1,3-dihydro-2 <i>H</i> -imidazol-2-ylidene]dichloro(3-chloropyridine- κ N)-Palladium
	(<i>R</i>)-binap :	(<i>R</i>)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
10	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
15	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
20	<i>t</i> -BuXPhos:	2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl
	<i>t</i> BuXPhos Pd G3:	Methanesulfonato(2-di- <i>t</i> -butylphosphino-2',4',6'-tri- <i>i</i> -propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)
	<i>t</i> Bu ₃ P-Pd-G2	Chloro[(tri- <i>tert</i> -butylphosphine)(2-aminobiphenyl-2-yl)palladium(II)
25	TBD:	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
	T ₃ P:	Propylphosphonic anhydride
	TEA:	trimethylamine
	TFA:	trifluoroacetic acid
	TFAA:	trifluoroacetic anhydride
30	THF:	tetrahydrofuran
	TLC:	thin layer chromatography
	TEMPO:	2,2,6,6-tetramethylpiperidinyloxy
	TTMSS:	tris(trimethylsilyl)silane

	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)
5	v/v	volume ratio

GENERAL EXPERIMENTAL CONDITIONS

Intermediates and final compounds were purified by flash column chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) 10 ISCO combi-flash column 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, OBD™ 30 × 100 mm) column, SunFire™ Prep-C18 15 (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 20 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 25 Toledo Multigram III system SFC, Waters 80Q preparative SFC or Thar 80 preparative SFC, solvent system: CO₂ and IPA (0.5% TEA in IPA) or CO₂ and MeOH (0.1% NH₃·H₂O 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 30 ZQ), LC/MS conditions were as follows (running time 3 or 1.5 mins):

Acidic condition I: A: 0.1% TFA in H₂O; B: 0.1% TFA in acetonitrile;

Acidic condition II: A: 0.0375% TFA in H₂O; B: 0.01875% TFA in acetonitrile;

Basic condition I: A: 0.1% NH₃·H₂O in H₂O; B: acetonitrile;

Basic condition II: A: 0.025% $\text{NH}_3 \cdot \text{H}_2\text{O}$ 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^+).

5 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.

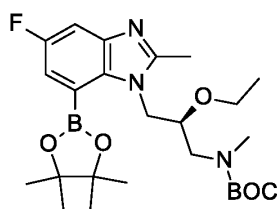
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PREPARATIVE EXAMPLES

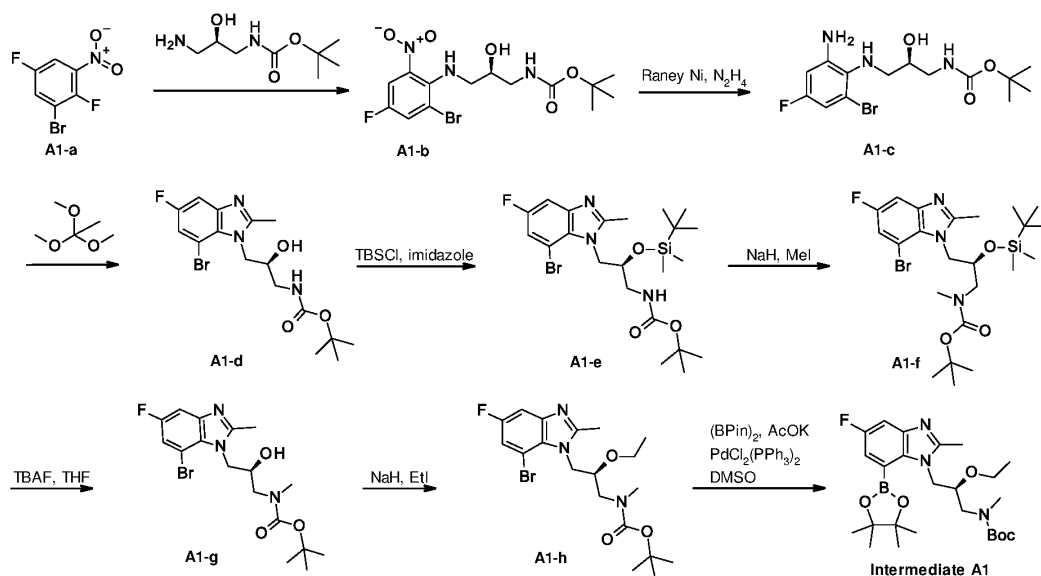
The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

Intermediate A1

15 *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 A1-b)

To a mixture of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate (59.6 g, 313.25 mmol) and 1-bromo-2,5-difluoro-3-nitro-benzene (compound A1-a, 71.0 g, 298.33 mmol) in ACN (710 mL) was added potassium carbonate (82.4 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 A1-b (131 g). LCMS (M+H)⁺: 408.

Step 2: preparation of *tert*-butyl *N*-[(2*R*)-3-(2-amino-6-bromo-4-fluoro-anilino)-2-hydroxy-propyl]carbamate (compound A1-c)

To a solution of compound A1-b (63.0 g, 154.33 mmol) in methanol (1000 mL) was added Raney Ni (36.2 g, 617.31 mmol) and hydrazine hydrate (29.2 g, 583.1 mmol). After being stirred at 25 °C for 1 hr, 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 A1-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 A1-d)

To a solution of compound A1-c (123.0 g, 325.19 mmol) in anhydrous THF (1500 mL) was added trimethyl orthoacetate (136.7 mL, 1104 mmol) and pyridinium *p*-toluenesulfonate (11.7 g, 46.62 mmol). The reaction was stirred for 1 hr at 20 °C. The mixture was concentrated under reduced pressure to give compound A1-d (160 g). LCMS (M+H)⁺: 402.

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 A1-e)

To a solution of compound **A1-d** (80.0 g, 198.88 mmol) and imidazole (40.6 g, 596.63 mmol) in DMF (765 mL) was added *tert*-butyldimethylchlorosilane (59.9 g, 397.75 mmol). The reaction was stirred for 18 hrs at 30 °C. The mixture was poured into cold NH₄Cl aq. (2000 mL), extracted with EtOAc (800 mL) twice. The organic layer was dried and concentrated to give compound **A1-e** (94 g). LCMS (M+H)⁺: 516.

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 A1-f)

To a solution of compound **A1-e** (82.0 g, 158.75 mmol) in DMF (800 mL) was added sodium hydride (60% in oil, 15.8 g, 396.89 mmol) at 0 °C and then stirred at 0 °C for 1 hr. Then iodomethane (90.1 g, 635.02 mmol) was added at 0 °C and The reaction was stirred at 0 °C for 1 hr. The reaction was quenched with water and extracted with EA. The organic layer was dried, concentrated and purified via column chromatography to give compound **A1-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 A1-g)

A mixture of compound **A1-f** (39.8 g, 75.02 mmol) and TBAF/THF (1M, 150.0 mL, 150 mmol) was stirred at 20 °C for 2 hrs. The mixture was concentrated and the residue was diluted with EtOAc (600mL), washed with water and brine. The organic layer was dried and concentrated to give compound **A1-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 A1-h)

To a solution of compound **A1-g** (17.4 g, 41.8 mmol) and iodoethane (5.0 mL, 62.7 mmol) in DMF (174 mL) was added sodium hydride (2.2 g, 55.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 3 hrs. The reaction was then quenched with water and extracted with EA. The organic layer was dried and concentrated to give compound **A1-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 A1)

To a mixture of compound **A1-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 (8.6 g, 87.3 mmol), bis(triphenylphosphine)palladium(II) chloride (4.6 g, 6.55 mmol) and butyldi-1-

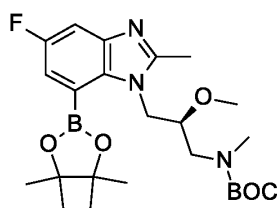
-61-

adamantylphosphine (4.7 g, 13.1 mmol). The mixture was degassed with N₂ for three times, and then stirred at 130 °C for 2 hrs. The reaction 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 via column chromatography to give intermediate **A1** (15 g). LCMS (M+H)⁺: 492.

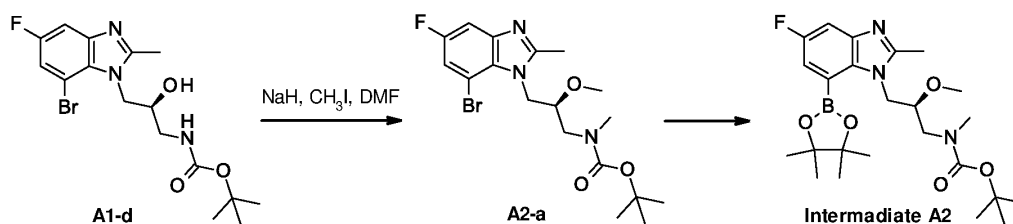
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Intermediate A2

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:



10

Step 1: preparation of *tert*-butyl *N*-[(2*R*)-3-(7-bromo-5-fluoro-2-methyl-benzimidazol-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (compound A2-a)

To a solution of compound **A1-d** (10.0 g, 26.02 mmol) in DMF (200 mL) was added CH₃I (11.08 g, 78.07 mmol) at -10 °C under N₂, then NaH (2.6 g, 65.06 mmol) was added slowly in portions. The reaction was stirred at -10 °C for 5 hrs. The reaction was stirred at 20 °C for another 12 hrs. The reaction was quenched with ice and cold NH₄Cl aq., and then it was extracted with EA twice. The organic layer was dried and concentrated to afford compound **A2-a** (11.7 g). LCMS (M+H)⁺: 430.

15

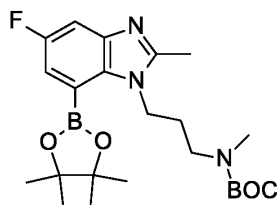
Step 2: preparation of *tert*-butyl *N*-[(2*R*)-3-[5-fluoro-2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (Intermediate A2)

20

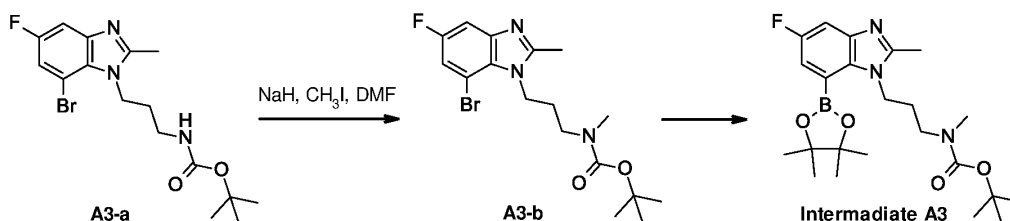
The title compound was prepared in analogy to the preparation of intermediate **A1** via using compound **A2-a** instead of compound **A1-h** in step 8. LCMS (M+H)⁺: 478.

Intermediate A3

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



The title compound was prepared according to the following scheme:



5

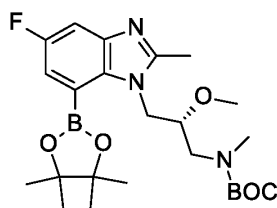
The title compound was prepared in analogy to the preparation of intermediate **A2** via using compound **A3-a** instead of compound **A1-d** in step 1. LCMS (M+H)⁺: 448.

The compound **A3-a** was prepared in analogy to the preparation of compound **A1-d** via using *tert*-butyl *N*-(3-aminopropyl)carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate in step 1. LCMS (M+H)⁺: 386.

10

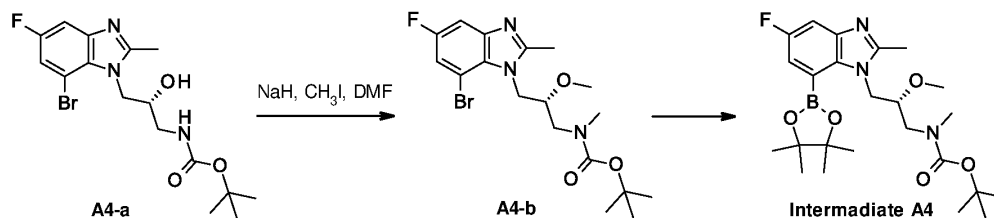
Intermediate A4

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



15

The title compound was prepared according to the following scheme:

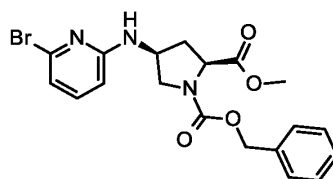


The title compound was prepared in analogy to the preparation of intermediate **A2** by using compound **A3-a** instead of compound **A1-d** in step 1. LCMS (M+H)⁺: 478.

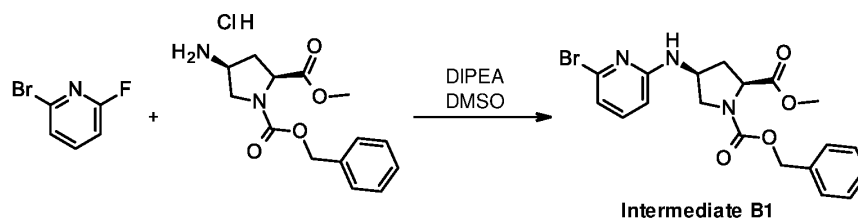
The compound **A4-a** was prepared in analogy to the preparation of compound **A1-d** by using *tert*-butyl *N*-[(2*S*)-3-amino-2-hydroxy-propyl]carbamate instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate in step 1. LCMS (M+H)⁺: 402.

Intermediate B1

***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:



10

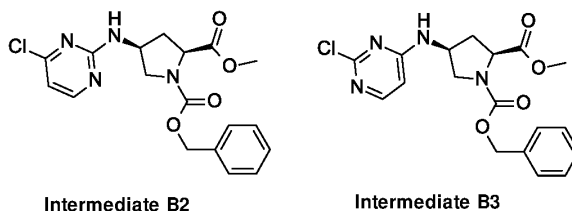
A mixture of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate;hydrochloride (4.7 g, 14.93 mmol), 2-bromo-6-fluoropyridine (3.15 g, 17.92 mmol) and DIPEA (13.0 mL, 74.66 mmol) in DMSO (20 mL) was stirred at 110 °C for 16 hrs. The mixture was cooled and poured into 150 mL water, then it was extracted with 25 mL EA for three times. The organic layer was concentrated to give an oil, then it was purified via prep-HPLC to give intermediate **B1** (5.1 g), LCMS (M+H)⁺: 434.

15

Intermediate B2 and B3

***O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(4-chloropyrimidin-2-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B2) and *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-[(2-chloropyrimidin-4-yl)amino]pyrrolidine-1,2-dicarboxylate (Intermediate B3)**

20

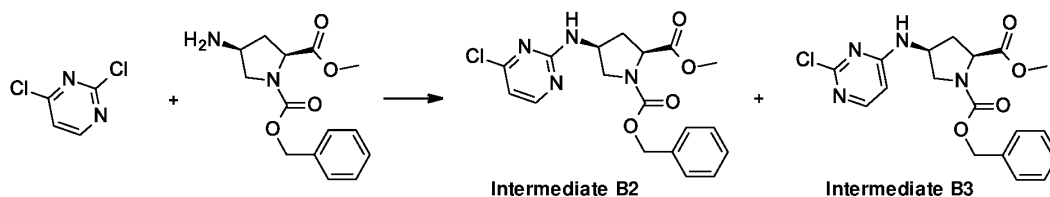


Intermediate B2

Intermediate B3

The title compound was prepared according to the following scheme:

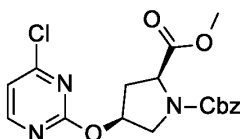
-64-



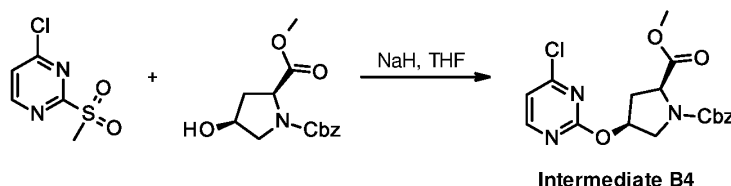
A mixture of 2,4-dichloropyrimidine (5.35 g, 35.9 mmol), 1-benzyl 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (5 g, 18 mmol), K₂CO₃ (4.97 g, 35.9 mmol) and DIPEA (4.64 g, 35.9 mmol) in MeCN was stirred at rt for 48 hrs. The reaction was filtered and concentrated, the residue was purified via silica gel column chromatography (eluting with 10%-30% PE in EtOAc) to give intermediate **B2** (faster eluted, 1 g) and intermediate **B3** (slower eluted, 6 g), LCMS (M+H)⁺: 391.

Intermediate B4

10 *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:

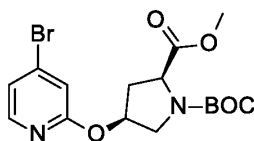


To a mixture of *O*1-benzyl *O*2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (30.0 g, 107.4 mmol) and 4-chloro-2-methylsulfonyl-pyrimidine (20.0 g, 103.8 mmol) in anhydrous THF (340 mL) was added sodium hydride (60% in oil, 4.4 g, 110 mmol) in portions at room temperature under nitrogen, the resulting mixture was stirred at r.t. for 16 hours. The mixture was poured into aq. NH₄Cl (200 mL) and extracted with EtOAc. The organic layer was dried and concentrated to give the crude product, then it was purified via silica gel column chromatography to give intermediate **B4** (27.0 g). LCMS (M+H)⁺: 392.

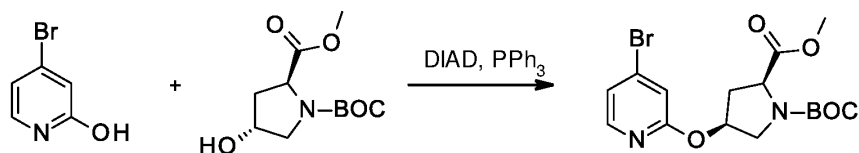
Intermediate B5

*O*1-*tert*-butyl *O*2-methyl (2*S*,4*S*)-4-[(4-bromo-2-pyridyl)oxy]pyrrolidine-1,2-dicarboxylate

-65-



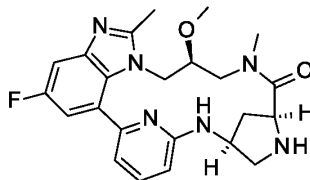
The title compound was prepared according to the following scheme:

**Intermediate B5**

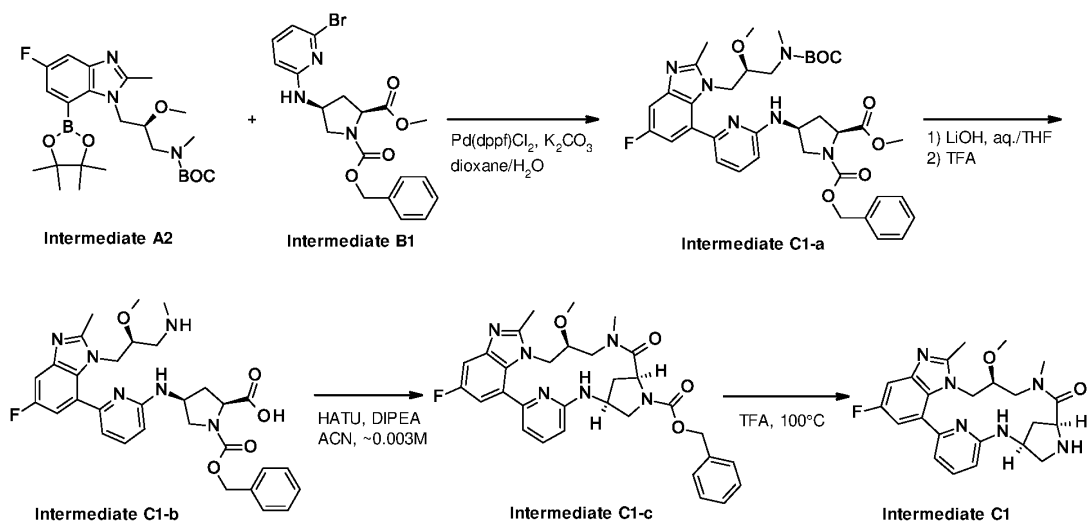
To a mixture of 4-bromo-2-hydroxypyridine (10.64 g, 61.16 mmol), *O*1-*tert*-butyl *O*2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (10.0 g, 40.77 mmol) and PPh₃ (16.04 g, 61.16 mmol) in Toluene (100 mL) was added DIAD (12.37 g, 61.16 mmol) at 0 °C under N₂. The reaction was stirred at 100 °C for 1 hr. The mixture was concentrated and the residue was purified via prep-HPLC to afford intermediate **B5** (12.5 g). LCMS (M-56+H)⁺: 345.

Intermediate C1

10 (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



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-[[6-[3-[(2*R*)-3-[*tert*-butoxycarbonyl(methyl)amino]-2-methoxy-propyl]-6-fluoro-2-methyl-benzimidazol-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound C1-a)

To a flask was added K₂CO₃ (3.36 g, 24.3 mmol), compound **B1** (5.28 g, 12.15 mmol),
5 compound **A2** (5.8 g, 12.15 mmol), 1,4-dioxane (60 mL) and water (1 mL). The suspension was
bubbled with N₂ for 5 mins and 1,1'-bis(diphenylphosphino)ferrocene-palladium(ii) dichloride
dichloromethane complex (992 mg, 1.21 mmol) was added. The mixture was heated to 90 °C and
stirred for 16 hrs. The mixture was poured into water and extracted with EA. The organic layer
was dried over Na₂SO₄ and concentrated, a brown oil was obtained. Then it was purified via
10 silica gel column chromatography to give compound **C1-a** (6.8 g) as yellow oil. LCMS (M+H)⁺:
705.

Step 2: 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]-2-pyridyl]amino]pyrrolidine-2-carboxylic acid (compound C1-b)

15 To the flask which contained compound **C1-a** (6.8 g, 9.65 mmol) was added
tetrahydrofuran (20 mL). The brown solution was stirred at r.t. and 2 M LiOH (aq.) (20 mL, 40
mmol) was added dropwise. The final mixture was stirred at r.t. for 2 hrs. The mixture was
diluted with water and pH was adjusted to 4 with 2 N aq. solution of HCl, and then it was
extracted with DCM. The organic layer was dried and concentrated to give a foamy solid, which
20 was dissolved in dichloromethane (5 mL) and TFA (5 mL). The brown solution was stirred at r.t.
for 1 hr. Then it was concentrated to give compound **C1-b** (4.9 g) as an oil. LCMS (M+H)⁺: 591.

Step 3: preparation of benzyl (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-heptaene-10-carboxylate (compound C1-c)

25 To a solution of HATU (4.57 g, 12.02 mmol) and DIEA (10.5 mL, 60.1 mmol) in
acetonitrile (1200 mL) was added another solution of compound **C1-b** (4.92 g, 6.01 mmol) in
acetonitrile (1200 mL) dropwise in 4 hrs. The reaction mixture was concentrated, and the residue
was purified via prep-HPLC to give compound **C1-c** (3.5 g) as yellow foam. LCMS (M+H)⁺:
573.

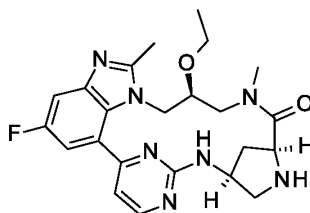
30 **Step 4: preparation of (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Intermediate C1)**

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To the flask containing compound **C1-c** (3.5 g, 6.11 mmol) was added TFA (30 mL). The brown solution was heated to reflux and stirred for 3 hrs. Then the reaction mixture was concentrated to give compound **C1** (7 g) as a crude oil. LCMS (M+H)⁺: 439.

Intermediate C2

- 5 (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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

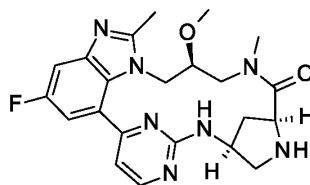


The title compound was prepared in analogy to the preparation of intermediate **C1** by using intermediate **A1** instead of intermediate **A2** and intermediate **B2** instead of intermediate **B1**.

- 10 LCMS (M+H)⁺: 440.

Intermediate C3

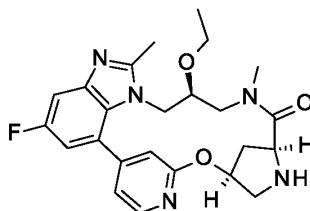
- (8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo
[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 15 The title compound was prepared in analogy to the preparation of intermediate **C1** by using intermediate **B2** instead of intermediate **B1**. LCMS (M+H)⁺: 440.

Intermediate C4

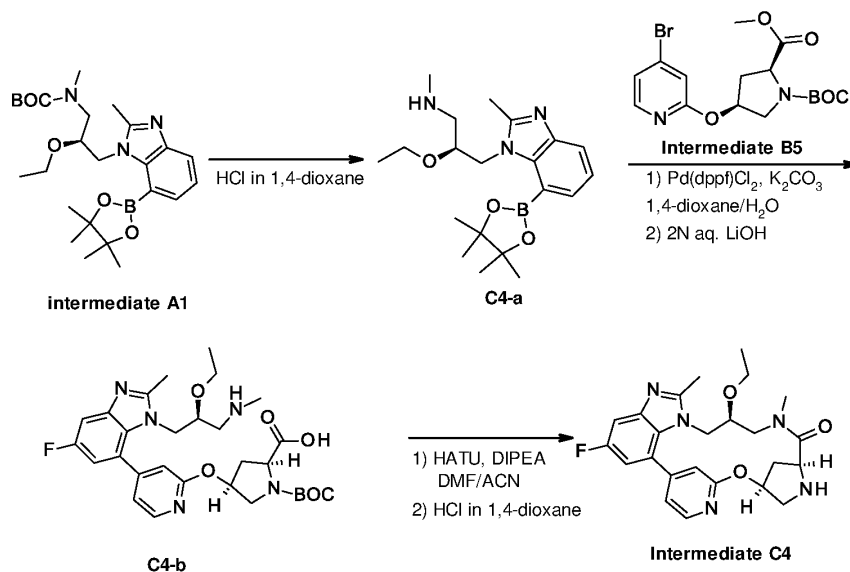
- (8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-7-oxa-5,10,13,17,19-pentazapentacyclo
[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 20

The title compound was prepared according to the following scheme:

-68-

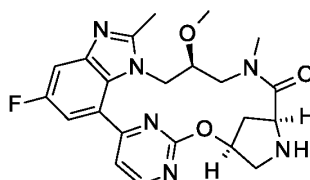


The title compound was prepared in analogy to the preparation of intermediate **C1** by using compound **C4-a** (obtained from deprotection of intermediate **A1** in acidic condition) instead of intermediate **A2** and intermediate **B5** instead of intermediate **B2**. LCMS (M+H)⁺: 454.

5

Intermediate C5

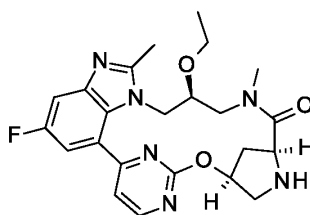
(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared in analogy to the preparation of intermediate **C1** by using intermediate **A3** instead of intermediate **A2** and using intermediate **B4** instead of intermediate **B1**. LCMS (M+H)⁺: 441.

Intermediate C6

(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

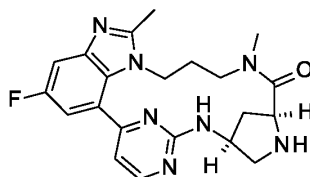


15

The title compound was prepared in analogy to the preparation of intermediate **C1** via using intermediate **A1** instead of intermediate **A2** and using intermediate **B4** instead of intermediate **B1** in step 1. LCMS (M+H)⁺: 455.

Intermediate C7

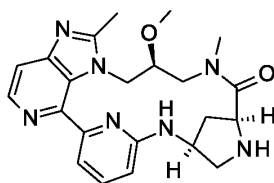
- 5 (8*S*,11*S*)-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo
[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- The title compound was prepared in analogy to the preparation of intermediate **C1** via using intermediate **A3** instead of intermediate **A2** and using intermediate **B2** instead of
10 intermediate **B1** in step 1. LCMS (M+H)⁺: 410.

Intermediate C8

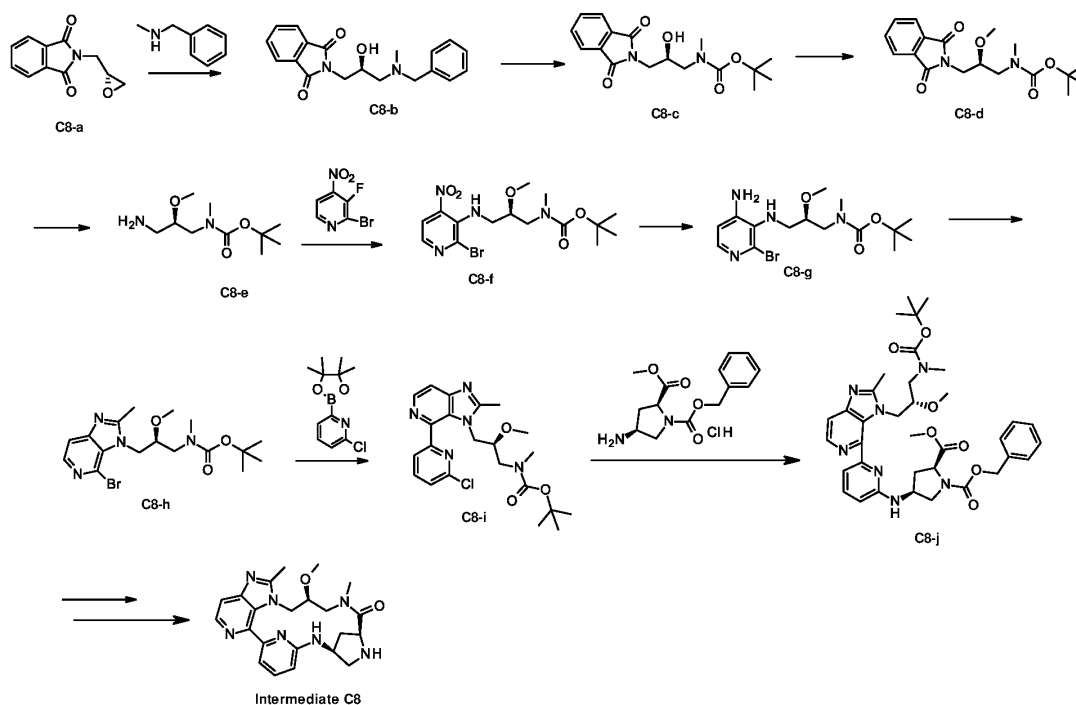
- (8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-
heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-
one



15

The title compound was prepared according to the following scheme:

-70-



Step 1: preparation of 2-[(2S)-3-[benzyl(methyl)amino]-2-hydroxy-propyl]isoindoline-1,3-dione (compound C8-b)

To a solution of compound **C8-a** (30.0 g, 147.65 mmol) in ethanol (300 mL) was added *N*-methylbenzylamine (23 mL, 177 mmol) at 20 °C in one portion. The reaction was stirred at 80 °C for 2 h and then concentrated. The residue was purified by silica gel column chromatography to give compound **C8-b** (40.0 g) as yellow oil. LCMS (M+H)⁺: 325.

Step 2: preparation of tert-butyl N-[(2R)-3-(1,3-dioxoisindolin-2-yl)-2-hydroxy-propyl]-N-methyl-carbamate (compound C8-c)

To a solution of compound **C8-b** (30.0 g, 92.49 mmol) and di-*t*-butyldicarbonate (30.28 g, 138.74 mmol) in methanol (667 mL) was added wet Pd(OH)₂/C (15.0 g, 10%) under N₂ at 20 °C. The reaction was stirred under 50 psi of H₂ at 40 °C for 12 h. Then the reaction mixture was filtered and the filtrate was concentrated, the residue was purified by flash chromatography to give compound **C8-c** (125 g, three batches workup together). LCMS (M-100+H)⁺: 235.

Step 3: preparation of tert-butyl N-[(2R)-3-(1,3-dioxoisindolin-2-yl)-2-methoxy-propyl]-N-methyl-carbamate (compound C8-d)

To a solution of NaH (5.8 g, 145 mmol) in dry DMF (220 mL) was added iodomethane (55 g, 387 mmol) at 0 °C under N₂. The reaction was stirred at 0 °C for 0.5 h. A solution of compound **C8-c** (32.25 g, 96.45 mmol, 1.0 eq) in dry DMF (130 mL) was added, and then the

reaction was stirred at 20 °C for 18 h. The reaction was quenched with ice aq. NH₄Cl (5 L) and extracted with EA(2 L×3). The organic layer was washed with brine (2 L×3), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography to give compound **C8-d** (110.0 g, , three batches workup together). LCMS (M-100+H)⁺: 249.

Step 4: preparation of *tert*-butyl *N*-[(2*R*)-3-amino-2-methoxy-propyl]-*N*-methyl-carbamate (compound C8-e)

To a solution of compound **C8-d** (100.0 g, 287.03 mmol) in ethanol (30 mL) was added methylamine/ethanol (557.97 g, 6.1 mol) dropwise at 20 °C. The reaction was stirred at 60°C for 2 h. Then the reaction mixture was filtered and the filtrate was concentrated to give compound **C8-e** (80.0 g).

Step 5: preparation of *tert*-butyl *N*-[(2*R*)-3-[(2-bromo-4-nitro-3-pyridyl)amino]-2-methoxy-propyl]-*N*-methyl-carbamate (compound C8-f)

The mixture of 2-bromo-3-fluoro-4-nitro-pyridine (20.0 g, 90.51 mmol), compound **C8-e** (29.2 g, 133.77 mmol) and K₂CO₃ (25.0 g, 180.9 mmol) in ACN (200 mL) was stirred at 50 °C for 2 h. The reaction mixture was filtered and the filtrate was concentrated to give compound **C8-f** (120.0 g, four batches workup together). LCMS (M-100+H)⁺: 321.

Step 6: preparation of *tert*-butyl *N*-[(2*R*)-3-(4-bromo-2-methyl-imidazo[4,5-*c*]pyridin-3-yl)-2-ethoxy-propyl]-*N*-methyl-carbamate (compound C8-g)

To a solution of compound **C8-f** (30.0 g, 71.55 mmol) in methanol (300 mL) was added Raney Ni (42.0 g, 715.62 mmol) under N₂. Then hydrazine hydrate (35.82 g, 715.54 mmol) was added dropwise at 20 °C. The reaction was stirred at 20 °C for 4 h and then the mixture was filtered, the filtrate was concentrated to give a residue, which was extracted with DCM to give compound **C8-g** (28.2 g). LCMS (M+H)⁺: 391.

Step 7: preparation of *tert*-butyl *N*-[(2*R*)-3-(4-bromo-2-methyl-imidazo[4,5-*c*]pyridin-3-yl)-2-ethoxy-propyl]-*N*-methyl-carbamate (compound C8-h)

To a solution of compound **C8-g** (50.0 g, 123.97 mmol) in anhydrous THF (500 mL) was added trimethyl orthoacetate (56 mL, 417 mmol) and pyridinium *p*-toluenesulfonate (5.0 g, 19.9 mmol). The reaction was stirred for 12 h at 80 °C and then concentrated. The residue was diluted with H₂O and extracted with EA, the organic layer was dried and concentrated to give compound **C8-h** (47.0 g). LCMS (M+H)⁺: 415.

Step 8: preparation of *tert*-butyl *N*-[(2*R*)-3-[4-(6-chloro-2-pyridyl)-2-methyl-imidazo[4,5-*c*]pyridin-3-yl]-2-methoxy-propyl]-*N*-methyl-carbamate (compound C8-i)

To a solution of compound **C8-h** (40.0 g, 96.78 mmol), 6-chloropyridine-2-boronic acid pinacol ester (20.69 g, 86.38 mmol) and K_3PO_4 (41.38 g, 194.94 mmol) in 1,4-dioxane (400 mL) and water (40 mL) was added CataCXium A Pd G2 (12.94 g, 19.35 mmol) in one portion under N_2 at 25°C. The reaction was stirred at 60 °C for 5 h under N_2 . The mixture was concentrated and the residue was purified by silica gel column chromatography to give compound **C8-i** (26.0 g). LCMS (M+H)⁺: 446.

Step 9: 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]-2-methyl-imidazo[4,5-*c*]pyridin-4-yl]-2-pyridyl]amino]pyrrolidine-1,2-dicarboxylate (compound **C8-j)**

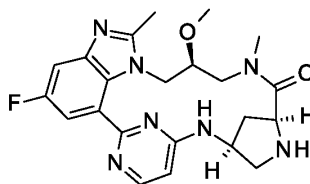
To a solution of compound **C8-i** (26.0 g, 58.3 mmol), 1-benzyl 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (19.47 g, 69.96 mmol) and cesium carbonate (47.5 g, 145.79 mmol) in 1,4-Dioxane (520 mL) was added Ruphos Pd G2 (6.8 g, 8.75 mmol) in one portion under N_2 . The reaction was stirred at 90 °C for 16 h under N_2 . The mixture was concentrated and the residue was purified by silica gel column chromatography to give compound **C8-j** (12.0 g). LCMS (M+H)⁺: 688.

Step 10~13: preparation of (8*S*,11*S*,15*R*)-15-methoxy-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 (Intermediate **C8)**

The title compound was prepared in analogy to the preparation of intermediate **C1** via using compound **C8-j** instead of compound **C1-a**. LCMS (M+H)⁺: 422.

Intermediate **C9**

(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-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(26),3,5,18,20(24),21-heptaen-12-one



25

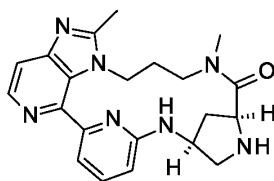
The title compound was prepared in analogy to the preparation of intermediate **C1** by using intermediate **B3** instead of intermediate **B1**. LCMS (M+H)⁺: 440.

Intermediate **C10**

(8*S*,11*S*)-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),2,4,6(26),18,20(24),21-heptaen-12-one

30

-73-



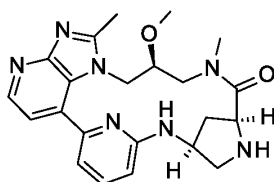
Intermediate **C10** was prepared in analogy to the preparation of intermediate **C8** by using *N*-(3-aminopropyl)-*N*-methylcarbamic acid *tert*-butylester instead of *tert*-butyl *N*-[(2*R*)-3-amino-2-hydroxy-propyl]carbamate. LCMS (M+H)⁺: 392.

5

Intermediate C11

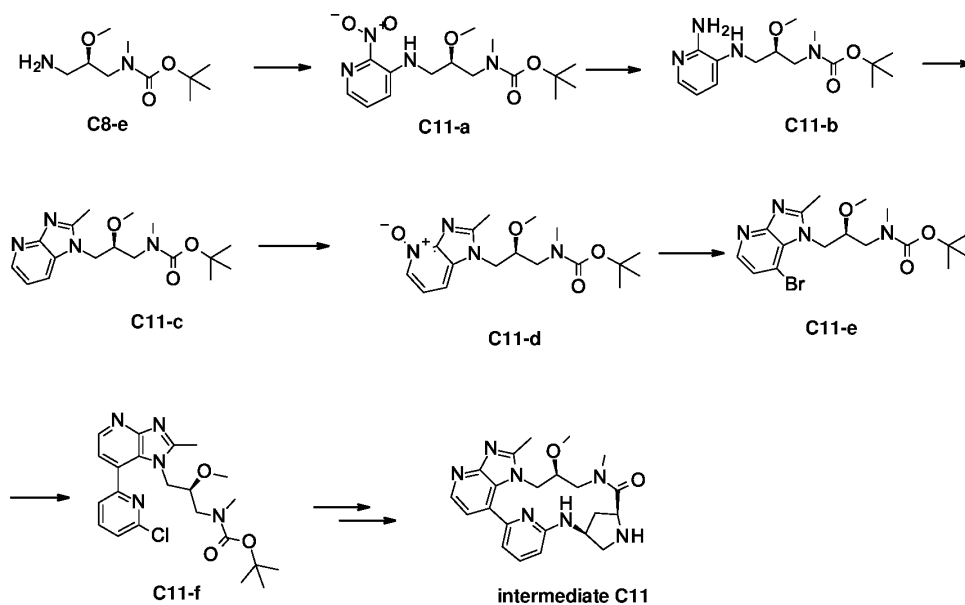
(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-

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



10

The title compound was prepared according to the following scheme:



Step 1~3: preparation of *tert*-butyl *N*-[(2*R*)-2-methoxy-3-(2-methylimidazo[4,5-*b*]pyridin-1-yl)propyl]-*N*-methyl-carbamate (compound **C11-c)**

Compound **C11-c** was prepared in analogy to the preparation of compound **C8-h** by using 3-fluoro-2-nitropyridine instead of 2-bromo-3-fluoro-4-nitro-pyridine. LCMS (M+H⁺): 335.

Step 4: preparation of *tert*-butyl *N*-[(2*R*)-2-methoxy-3-(2-methyl-4-oxido-imidazo[4,5-*b*]pyridin-4-ium-1-yl)propyl]-*N*-methyl-carbamate (compound **C11-d)**

To a solution of compound **C11-c** (10.0 g, 29.9 mmol) in DCM (100 mL) was added 3-chlorobenzenecarboperoxoic acid (9.1 g, 44.82 mmol). The reaction mixture was stirred at 40 °C for 5 h, and then washed with saturated NaHCO₃ (100 mL) and Na₂SO₃ (100 mL). The organic layer was dried and concentrated to give compound **C11-d** (10.0 g) as yellow oil. LCMS (M+H⁺): 351.

Step 5: preparation of *tert*-butyl *N*-[(2*R*)-3-(7-bromo-2-methyl-imidazo[4,5-*b*]pyridin-1-yl)-2-methoxy-propyl]-*N*-methyl-carbamate (compound **121f)**

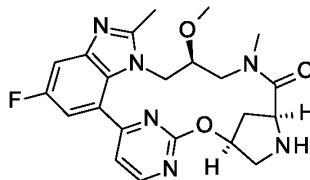
To a solution of compound **C11-d** (9.0 g, 0.23 mmol) in DMF (90 mL) and THF (90 mL) was added POBr₃ (18 g, 1.57 mmol) in one portion at 0 °C. The reaction mixture was stirred at 20 °C for 3 h, and then the mixture was quenched with ice saturated NaHCO₃ (500 mL). The resulted mixture was extracted with DCM, the organic layer was dried and concentrated to give a crude product, which was purified by prep-HPLC to give compound **C11-e** (2.7 g) as yellow oil. LCMS (M+H⁺): 413.

Step 6~11: preparation of (8*S*,11*S*,15*R*)-15-methoxy-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 (Intermediate **C11)**

Intermediate **C11** was prepared in analogy to the preparation of intermediate **C8** by using compound **C11-e** instead of compound **C8-h**. LCMS (M+H⁺): 422.

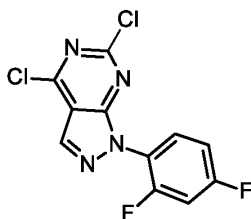
Intermediate C12

(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

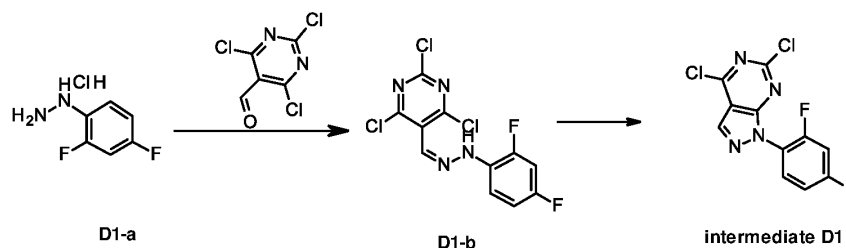


The title compound was prepared in analogy to the preparation of intermediate **C1** by using intermediate **A4** instead of intermediate **A2** and using intermediate **B4** instead of intermediate **B1**. LCMS (M+H⁺): 441.

-75-

4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine

The title compound was prepared according to the following scheme:

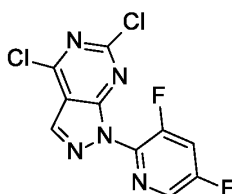


Step 1: preparation of 2,4-difluoro-N-[(Z)-(2,4,6-trichloropyrimidin-5-yl)methyleneamino]aniline (compound D1-b)

A mixture of compound **D1-a** (22.9 g, 126.9 mmol) and 2,4,6-trichloropyrimidine-5-carbaldehyde (22.4 g, 105.8 mmol) in DMF (400 mL) was stirred at 20 °C for 2 h. The reaction mixture was poured into water, a yellow solid formed, which was collected by filtration to give compound **D1-b** (41 g) as a yellow solid. LCMS (M+H⁺): 337

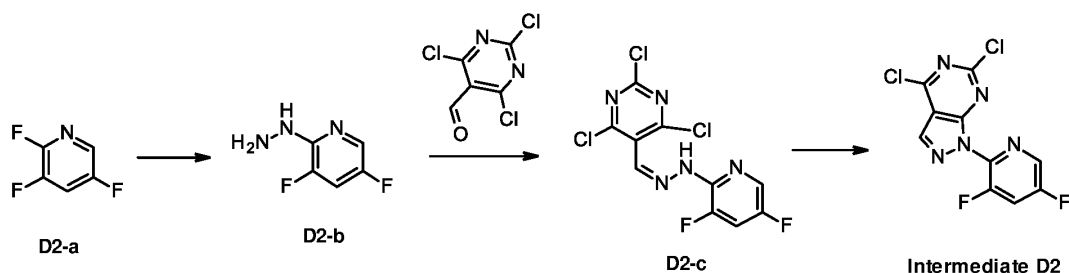
Step 2: preparation of 4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (intermediate D1)

To a mixture of compound **D1-b** (42.0 g, 124.4 mmol) and 4 Å MS (40.0 g) in NMP (400 mL) was stirred at 110 °C for 12 h. Then the reaction mixture was filtered and the filtrate was poured into water, and then extracted with EA. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give intermediate **D1** (15.5 g) as a yellow solid. LCMS (M+H⁺): 301.

Intermediate D2**4,6-dichloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine**

The title compound was prepared according to the following scheme:

-76-



Step 1: preparation of (3,5-difluoro-2-pyridyl)hydrazine (compound D2-b)

A mixture of compound **D2-a** (5.0 g, 37.57 mmol) and hydrazine hydrate (18.63 mL, 375.72 mmol) in ethanol (50 mL) was stirred at 65 °C for 16 h. After cooling to rt, white solid
 5 formed, which was collected by filtration to give compound **D2-b** (3.7 g). LCMS (M+H)⁺: 146.

Step 2: preparation of 3,5-difluoro-N-[(Z)-(2,4,6-trichloropyrimidin-5-yl)methyleneamino]pyridin-2-amine (compound D2-c)

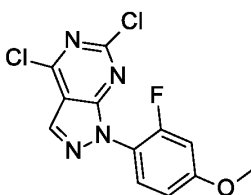
To a solution of 2,4,6-trichloropyrimidine-5-carbaldehyde (3.0 g, 14.19 mmol) in DMF (30 mL) was added compound **D2-b** (2.0 g, 13.78 mmol) and then it was stirred at 25 °C for 2 h. The
 10 reaction mixture was poured into water and a solid formed, which was collected by filtration to give compound **D2-c** (4.0 g). LCMS (M+H)⁺: 338.

Step 3: preparation of 4,6-dichloro-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-d]pyrimidine (Intermediate D2)

A solution of compound **D2-c** (3.5 g, 10.34 mmol) in 1,4-dioxane (35 mL) was stirred at
 15 120 °C for 4 h. The reaction mixture poured into ice water and EA. The organic layer was separated, dried and concentrated, the residue was purified by silica gel column chromatography to give Intermediate **D2** (1.2 g) as a yellow solid. LCMS (M+H)⁺: 302.

Intermediate D3

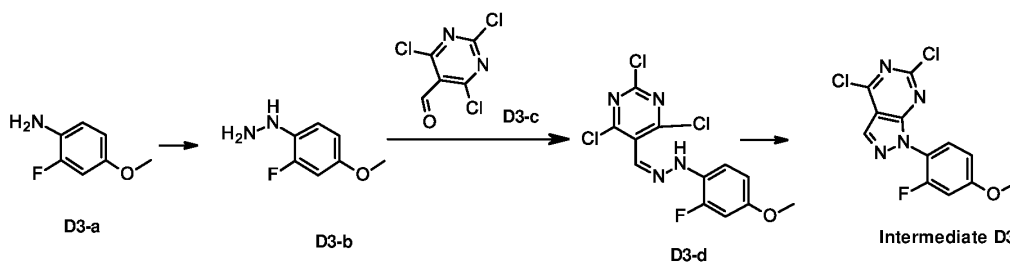
4,6-dichloro-1-(2-fluoro-4-methoxy-phenyl)pyrazolo[3,4-d]pyrimidine



20

The title compound was prepared according to the following scheme:

-77-



Step 1: preparation of (2-fluoro-4-methoxy-phenyl) hydrazine (compound D3-b)

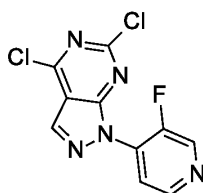
To a solution of 2-fluoro-4-methoxyaniline (5.0 g, 35.43 mmol) in HCl/water (59 mL, 354 mmol) was added a solution of NaNO₂ (3.67 g, 53.14 mmol) in water (17.5 mL) dropwise at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, a solution of tin(II) chloride dihydrate (19.98 g, 88.56 mmol) in conc. HCl (29.5 mL, 354.3 mmol) was added dropwise at 0 °C. The reaction was stirred at 25 °C for 16 h and then the reaction mixture was poured into ice water. The pH of aqueous layer was adjusted to around 10-12 with 20% aqueous sodium hydroxide and then it was extracted with EA. The organic layer was dried and concentrated to give the crude product compound **D3-b** (4.8 g) as a dark brown solid, which was used directly without further purification.

Step 2~3: preparation of 4, 6-dichloro-1-(2-fluoro-4-methoxy-phenyl)pyrazolo[3, 4-d]pyrimidine(Intermediate D3)

The title compound was prepared in analogy to the preparation of intermediate **D2** by using compound **D3-b** instead of compound **D2-b**. LCMS (M+H)⁺: 313.

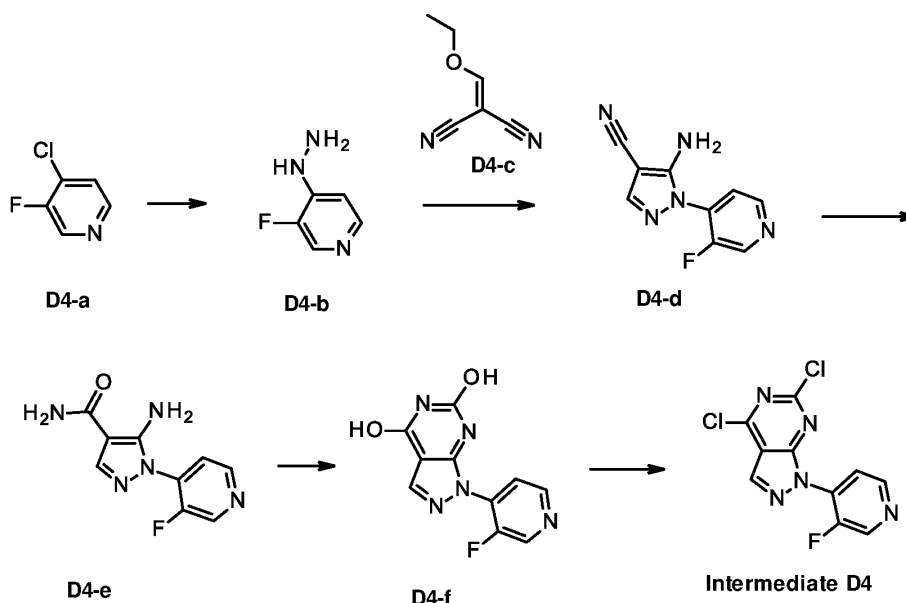
Intermediate D4

4,6-dichloro-1-(3-fluoro-4-pyridyl)pyrazolo[3,4-d]pyrimidine



The title compound was prepared according to the following scheme:

-78-



Step 1: preparation of (3-fluoro-4-pyridyl)hydrazine (compound **D4-b**)

To a solution of compound **D4-a** (1.0 g, 7.6 mmol) in 1,4-dioxane (10 mL) was added hydrazine hydrate (9.71 mL, 195.77 mmol) at 0 °C. The reaction was stirred at 100 °C for 16 h. Then the reaction was diluted with water and extracted with EtOAc. The organic layer was dried and concentrated to give compound **D4-b** (700.0 mg) as a light yellow solid. LCMS ($M+H^+$): 128.

Step 2: preparation of 5-amino-1-(3-fluoro-4-pyridyl)pyrazole-4-carbonitrile (compound **D4-d**)

A mixture of compound **D4-b** (700.0 mg, 5.51 mmol), compound **D4-c** (672 mg, 5.51 mmol) and DIEA (2.9 mL, 16.52 mmol) in ethanol (12 mL) was heated to 80 °C for 2 h. Then the reaction mixture was concentrated, the residue was purified by silica gel column chromatography to give compound **D4-d** (1 g) as a light brown solid. LCMS ($M+H^+$): 204.

Step 3: preparation of 5-amino-1-(3-fluoro-4-pyridyl)pyrazole-4-carboxamide (compound **D4-e**)

A solution of compound **D4-d** (1 g, 4.92 mmol) in sulfuric acid (6.0 mL) was stirred at 25 °C for 2 h. Then the mixture was poured into 50 mL ice-cold water and adjusted pH to 8, the aqueous phase was freeze-dried to give the crude product, which was dissolved in 50 mL of DCM/CH₃OH (10:1). The solid was filtered off and the filtrate was concentrated to give compound **D4-e** (1 g) as a light yellow solid, which was used directly without further purification. LCMS ($M+H^+$): 222.

Step 4: preparation of 1-(3-fluoro-4-pyridyl)pyrazolo[3,4-d]pyrimidine-4,6-diol (compound D4-f)

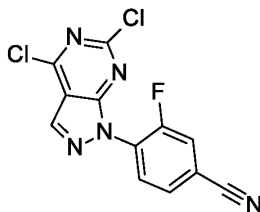
A mixture of compound **D4-e** (1 g, 4.52 mmol) and urea (13.6 g, 226.05 mmol) was stirred at 200 °C for 16 h. The reaction mixture was cooled to 25 °C and then water (100 mL) was added. The mixture was filtered and the filtrate was freeze-dried to give the crude product, which was purified by prep-HPLC to give compound **D4-f** (240.0 mg) as a light yellow solid. LCMS (M+H⁺): 248.

Step 5: preparation of 4,6-dichloro-1-(3-fluoro-4-pyridyl)pyrazolo[3,4-d]pyrimidine (Intermediate D4)

To a solution of compound **D4-f** (140.0 mg, 0.57 mmol) in phosphorus oxychloride (3.0 mL) was added phosphorus pentachloride (590 mg, 2.83 mmol). The reaction was stirred at 80 °C for 16 h. Then the mixture was concentrated and the residue was quenched with ice-cold sat.aq NaHCO₃ and DCM. The organic layer was separated, dried and concentrated, the residue was purified by prep-TLC to give Intermediate **D4** (30.0 mg) as a white solid. LCMS (M+H⁺): 284.

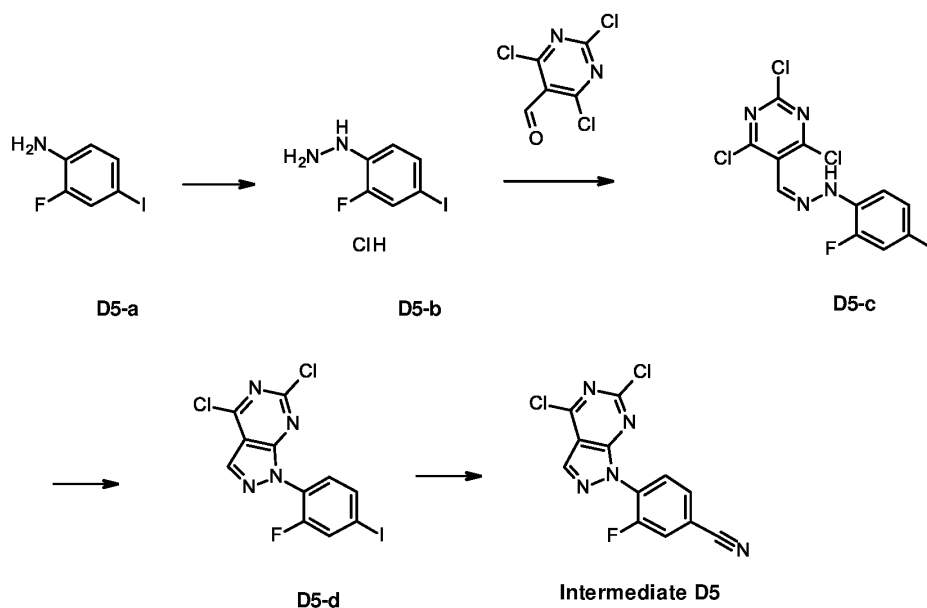
Intermediate D5

4-(4,6-dichloropyrazolo[3,4-d]pyrimidin-1-yl)-3-fluoro-benzonitrile



The title compound was prepared according to the following scheme:

-80-



Step 1~3: preparation of 4, 6-dichloro-1-(2-fluoro-4-iodo-phenyl)pyrazolo [3,4-d]pyrimidine (compound D5-d)

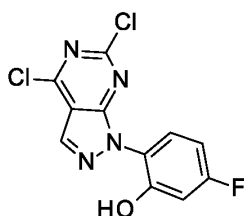
Compound **D5-d** was prepared in analogy to the preparation of intermediate **D3** by using compound **D5-a** instead of compound **D3-a**.

Step 4: preparation of 4-(4,6-dichloropyrazolo[3,4-d]pyrimidin-1-yl)-3-fluorobenzonitrile (Intermediate D5)

To a solution of compound **D5-d** (400.0 mg, 0.98 mmol) in DMF (3 mL) was added cuprous cyanide (438 mg, 4.89 mmol) at 25 °C. The reaction was stirred at 100 °C for 3 h. Then the reaction mixture was diluted with water and extracted with EA. The organic layer was dried and concentrated, the residue was purified by prep-HPLC to give Intermediate **D5** (60.0 mg) as a light yellow solid. LCMS ($M+H^+$): 308.

Intermediate D6

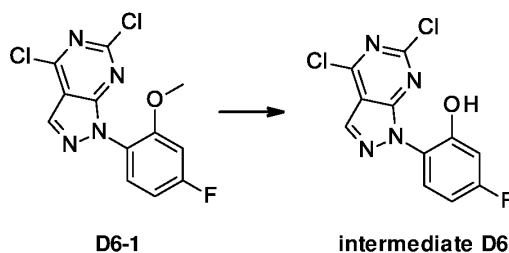
2-(4,6-dichloropyrazolo[3,4-d]pyrimidin-1-yl)-5-fluoro-phenol



15

The title compound was prepared according to the following scheme:

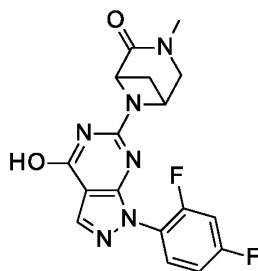
-81-



To a solution of compound **D6-1** (2.0 g, 6.39 mmol, the synthesis refer to the preparation of Intermediate **D3** by using (4-fluoro-2-methoxy-phenyl)hydrazine instead of compound **D3-a**) in DCM (40 mL) was added BCl₃/THF (32 mL, 32 mmol) at -78 °C and then stirred at 25 °C for 12 hours. The reaction was poured into ice-water (100 mL) and then extracted with DCM. The organic layer was dried and concentrated to give intermediate **D6** (1.51 g), LCMS (M+H⁺): 299.

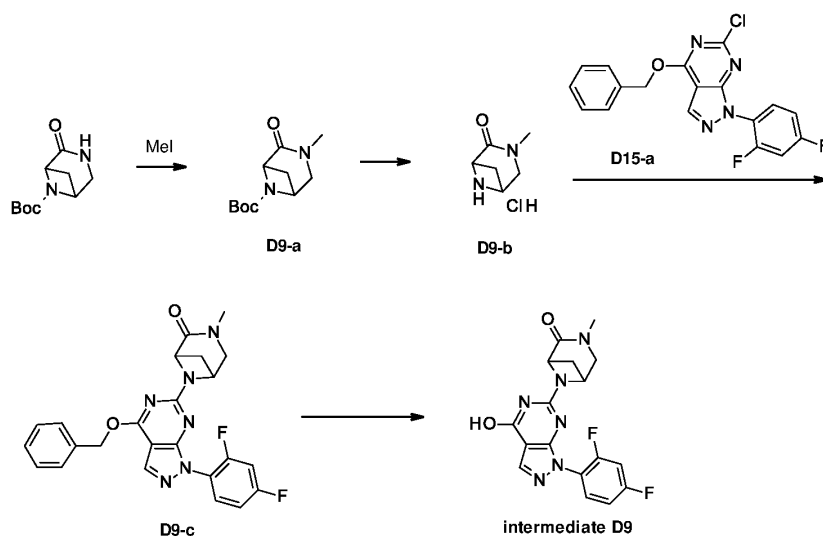
Intermediate D9

6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3-methyl-3,6-diazabicyclo[3.1.1]heptan-2-one



10

The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound D9-a)

To a stirred mixture of *tert*-butyl 2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (1.3 g, 6.1 mmol) in THF (20 mL) was added sodium hydride (441 mg, 18.3 mmol) in portions at 0 °C under nitrogen atmosphere. After 0.5 hours, iodomethane (1.82 g, 12.8 mmol) in THF (5 mL) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 25 °C for 1 h. The reaction solution was purified by reversed phase flash column to afford compound **D9-a** (1.3 g) as a white solid. LCMS (M+H⁺): 227.

Step 2: preparation of 3-methyl-3,6-diazabicyclo[3.1.1]heptan-2-one (compound D9-b)

A mixture of compound **D9-a** (1.30 g, 5.75 mmol) in 4 M HCl in dioxane (15.0 mL) was stirred at 25 °C for 2 h. The reaction was concentrated. The residue was lyophilized to give compound **D9-b** (800 mg) as a yellow oil. LCMS (M+H⁺): 127.

Step 3: preparation of 6-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]-3-methyl-3,6-diazabicyclo[3.1.1]heptan-2-one (compound D9-c)

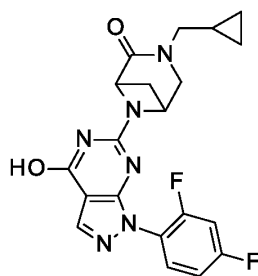
A stirred mixture of compound **D9-b** (800 mg, 6.34 mmol), compound **D15-a** (1.18 g, 3.17 mmol) and DIPEA (2.50 g, 19.3 mmol) in ACN (10.0 mL) was stirred at 80 °C for 48 h. The reaction was concentrated and the residue was purified by silica gel column chromatography to give compound **D9-c** (1.20 g) as a yellow oil. LCMS (M+H⁺): 463.

Step 4: preparation of 6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3-methyl-3,6-diazabicyclo[3.1.1]heptan-2-one (intermediate D9)

A mixture of compound **D9-c** (1.20 g, 2.59 mmol) in DCM (12.0 mL) and trifluoroacetic acid (12.0 mL) was stirred at 25 °C for 2 h. The reaction was concentrated and the residue was lyophilized to give intermediate **D9** (860 mg) as an off-white solid. LCMS (M+H⁺): 373.

Intermediate D10

3-(cyclopropylmethyl)-6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-2-one



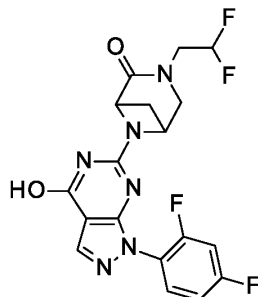
25

Intermediate D10 was prepared in analogy to the preparation of **Intermediate D9** by using bromomethylcyclopropane instead of iodomethane. LCMS (M+H⁺): 413.

Intermediate D11

-83-

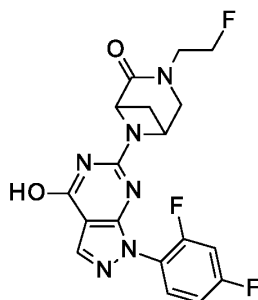
3-(2,2-difluoroethyl)-6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-2-one



Intermediate D11 was prepared in analogy to the preparation of **Intermediate D9** by using 2,2-difluoroethyl trifluoromethanesulfonate instead of iodomethane. LCMS ($M+H^+$): 423.

Intermediate D12

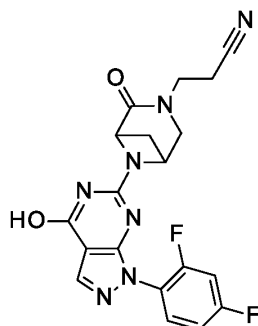
6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3-(2-fluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-2-one



Intermediate D12 was prepared in analogy to the preparation of **Intermediate D9** by using 1-fluoro-2-iodo-ethane instead of iodomethane. LCMS ($M+H^+$): 405.

Intermediate D13

3-[6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile

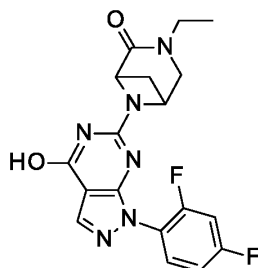


15

Intermediate D13 was prepared in analogy to the preparation of **Intermediate D9** by using 3-iodopropanenitrile instead of iodomethane. LCMS ($M+H^+$): 412.

Intermediate D14

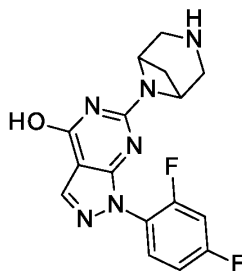
- 6-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]-3-ethyl-3,6-diazabicyclo[3.1.1]heptan-2-one



Intermediate D14 was prepared in analogy to the preparation of **Intermediate D9** by using iodoethane instead of iodomethane. LCMS ($M+H^+$): 387.

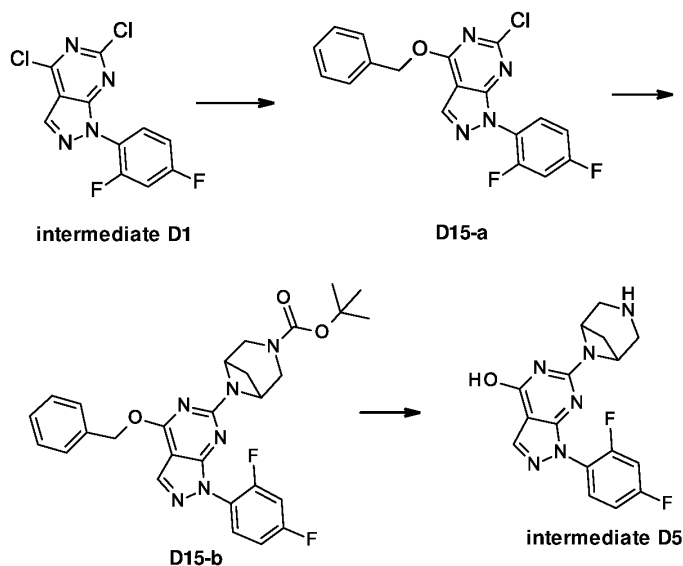
Intermediate D15

- 6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:

-85-



Step 1: preparation of 4-benzyloxy-6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (compound D15-a)

A mixture of 4,6-dichloro-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidine (**intermediate D1**, 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. 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 column chromatography to give compound **D15-a** (400 mg). LCMS ($M+H^+$): 373. Multiple batches were repeated and combined.

Step 2: 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 D15-b)

To a solution of compound **D15-a** (1.25 g, 3.35 mmol), *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (731 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 was poured into water (300 mL) and extracted with ethyl acetate (300 mL). The organic layer was dried and concentrated to give compound **D15-b** (2.0 g) as a brow oil. LCMS ($M+H^+$): 535. Multiple batches were repeated and combined.

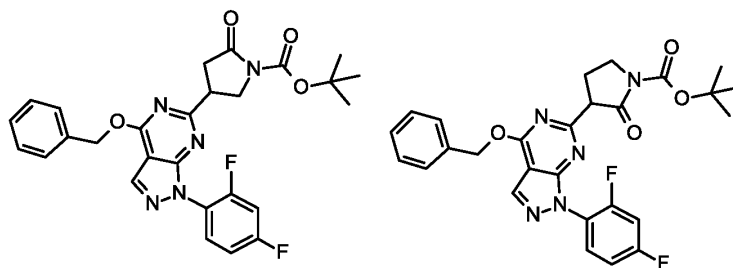
Step 3: preparation of 6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (Intermediate D15)

To a solution of compound **D15-b** (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 was concentrated and the residue was

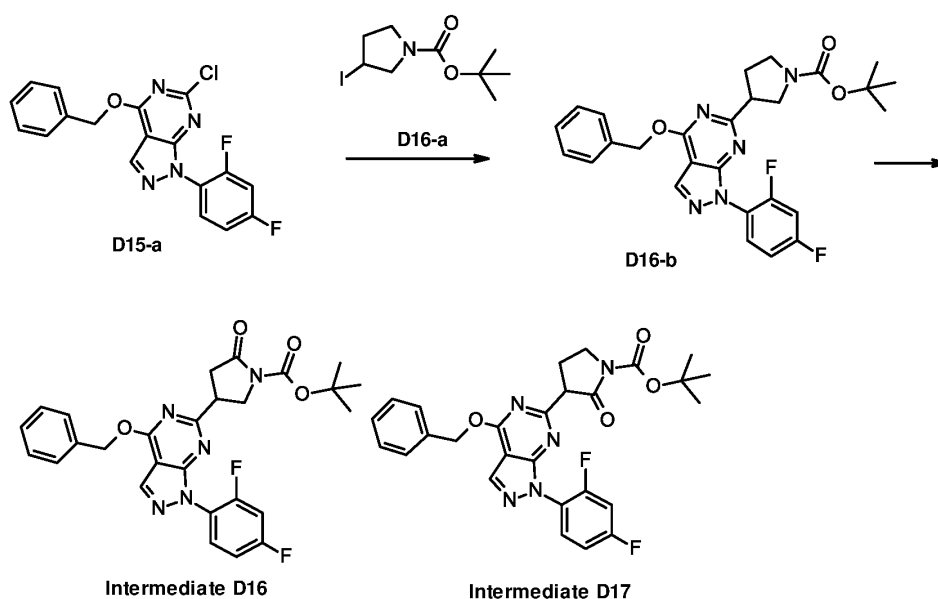
diluted with water (50 mL), which was lyophilized to give Intermediate **D15** (2.5 g) as a yellow solid. LCMS ($M+H^+$): 345.

Intermediate D16 and Intermediate D17

tert-butyl 4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-
 5 pyrrolidine-1-carboxylate and *tert*-butyl 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-pyrrolidine-1-carboxylate



The title compound was prepared according to the following scheme:



10 **Step 1: preparation of *tert*-butyl 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-6-yl]pyrrolidine-1-carboxylate (Intermediate D16-b)**

To a 40 mL vial equipped with a stir bar was added compound **D15-a** (1 g, 2.68 mmol), compound **D16-a** (1.3 g, 4.29 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)(PF₆) (30. mg, 0.03 mmol), NiCl₂.dtbbpy (5 mg, 0.01 mmol), tris(trimethylsilyl)silane (0.83 mL, 2.68 mmol), sodium carbonate (568 mg, 5.37 mmol) in DMA (10 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 a cooling fan to keep the reaction temperature at 25 °C for 14 hr. The reaction

-87-

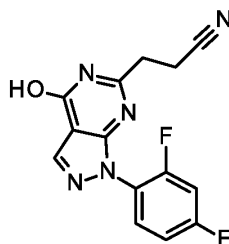
was poured into water and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give compound **D16-b** (1 g) as a yellow oil. LCMS ($M+H^+$): 508.

Step 2: preparation of *tert*-butyl 4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]-2-oxo-pyrrolidine-1-carboxylate (Intermediate D16) and *tert*-butyl 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]-2-oxo-pyrrolidine-1-carboxylate (Intermediate D17)

To a solution of compound **D16-b** (800.0 mg, 1.58 mmol) in DCM (15 mL) was added ruthenium(IV) oxide (209 mg, 1.58 mmol) and a solution of sodium periodate (1.35 g, 6.31 mmol) in water (15 mL). The reaction was stirred at 30 °C for 16 h and then the reaction mixture was filtered. The filtrate was extracted with DCM, dried and concentrated, the residue was purified by prep-TLC to give Intermediate **D16** (170.0 mg, faster eluted, EtOAc:PE=1:2) and Intermediate **D17** (130.0 mg, slower eluted, EtOAc:PE=1:2). LCMS ($M+H^+$): 522.

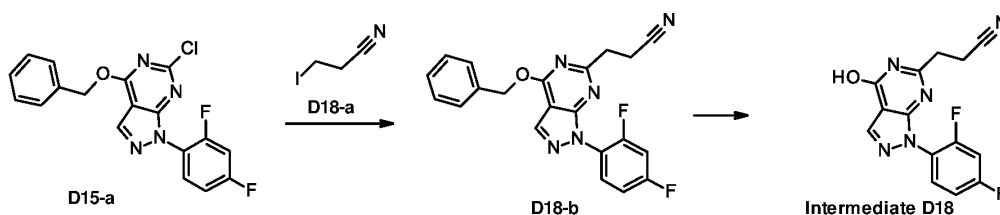
Intermediate D18

3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]propanenitrile



Intermediate D18

The title compound was prepared according to the following scheme:



Step 1: preparation of 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]propanenitrile (compound D18-a)

To a 40 mL vial equipped with a stir bar was added compound **D15-a** (100.0 mg, 0.27 mmol), compound **D18-a** (78 mg, 0.43 mmol), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbpy})(\text{PF}_6)$ (3.0 mg), $\text{NiCl}_2 \cdot \text{dtbbpy}$ (1 mg), tris(trimethylsilyl)silane (0.08 mL, 0.27 mmol), sodium carbonate (57 mg, 0.54 mmol) in DMA (10 mL). The vial was sealed and placed under nitrogen. The reaction was

-88-

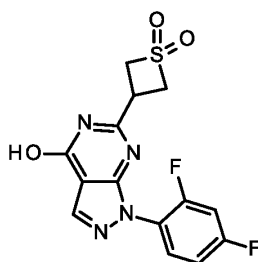
stirred and irradiated with a 34 W blue LED lamp (7 cm away), with a cooling fan to keep the reaction temperature at 25 °C for 14 hr. The reaction was poured into water (20 ml) and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by prep-TLC to give compound **D18-b** (35.0 mg) as colorless oil. LCMS (M+H⁺): 392.

Step 2: preparation of 3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]propanenitrile (Intermediate D18)

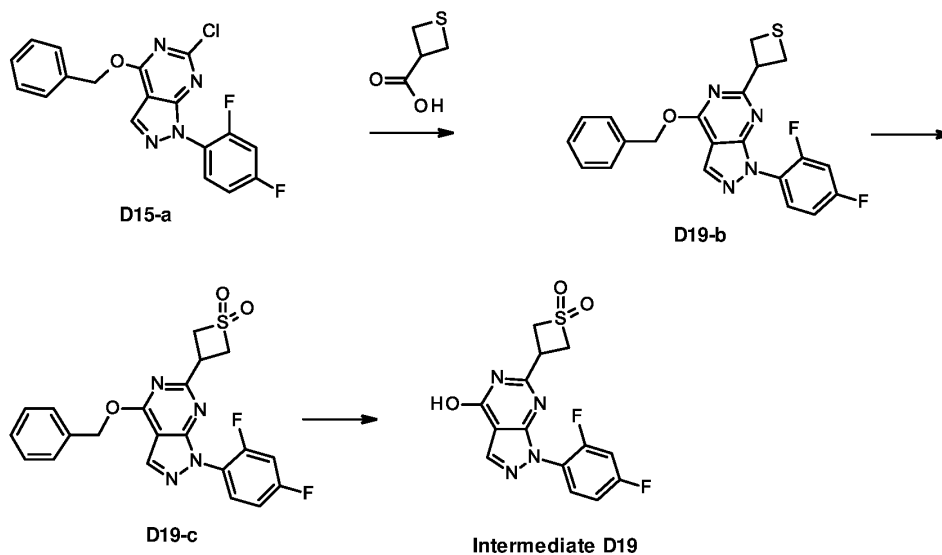
To a solution of compound **D18-b** (35.0 mg, 0.09 mmol) in DCM (0.500 mL) was added TFA (0.5 mL) at 0 °C. The reaction was stirred at 40 °C for 1 hr under nitrogen, and then the mixture was concentrated, the residue was purified by prep-HPLC to afford **Intermediate D18** (18.0 mg) as a white solid. LCMS (M+H⁺): 302.

Intermediated D19

1-(2,4-difluorophenyl)-6-(1,1-dioxothietan-3-yl)pyrazolo[3,4-d]pyrimidin-4-ol



The title compound was prepared according to the following scheme:



15

Step 1: preparation of 4-benzyloxy-1-(2,4-difluorophenyl)-6-(thietan-3-yl)pyrazolo[3,4-d]pyrimidine (compound D19-b)

To an 20 mL vial equipped with a stir bar was added compound **D15-a** (500.0 mg, 1.34 mmol), thietane-3-carboxylic acid (317 mg, 2.68 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)(PF₆) (15.0 mg, 0.01 mmol), NiCl₂.dtbbpy (53.4 mg, 0.13 mmol), cesium carbonate (1311 mg, 4.02 mmol) in DMF (6 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 a cooling fan to keep the reaction temperature at 25 °C for 14 hr. The reaction mixture was filtered, and the filtrate was concentrated, the residue was purified by silica gel column chromatography to give compound **D19-b** (0.4 g) as a yellow solid. LCMS (M+H⁺): 411

Step 2: preparation of 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]thietane 1,1-dioxide (compound D19-c)

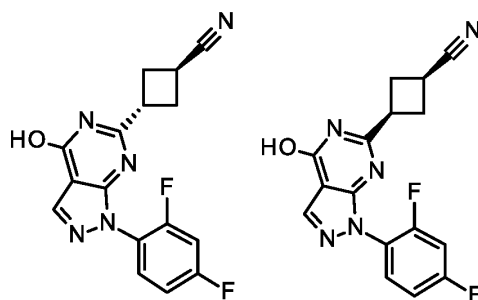
To a solution of compound **D19-b** (200.0 mg, 0.49 mmol) in DCM (3 mL) was added m-CPBA (210.2 mg, 0.97 mmol) at 0 °C and stirred at 20 °C for 1 h. The reaction was filtered, and the filtrate was washed with saturated Na₂SO₃, dried over Na₂SO₄ and then concentrated. The residue was purified by prep-TLC to give **compound D19-c** (50.0 mg) as colorless oil. LCMS (M+H⁺): 443

Step 3: preparation of 1-(2,4-difluorophenyl)-6-(1,1-dioxothietan-3-yl)pyrazolo[3,4-d]pyrimidin-4-ol (intermediate D19)

To a solution of compound **D19-c** (50.0 mg, 0.11 mmol) in DCM (0.5 mL) was added TFA (0.5 mL) at 0 °C and then stirred at 40 °C for 2 h. The reaction mixture was concentrated to give intermediate **D19** (50.0 mg) as a brown oil. LCMS (M+H⁺): 353.

Intermediated D20 and Intermediated D21

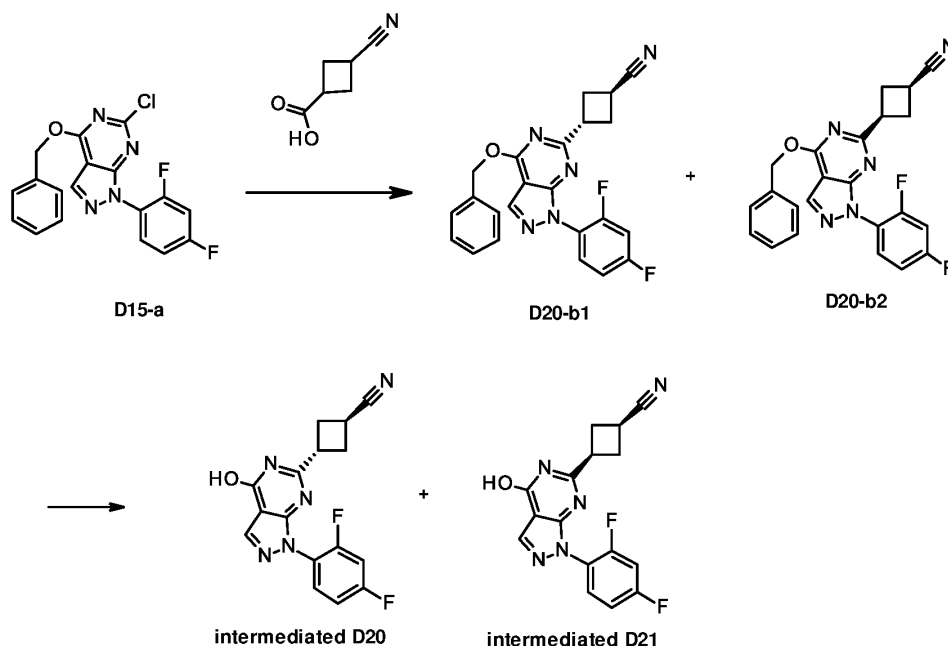
Trans-3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile and cis-3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile



25

The title compound was prepared according to the following scheme:

-90-



Step 1: preparation of 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile and 3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile (compound D20-b1 & compound D20-b2)

To a 40 mL vial equipped with a stir bar was added compound **D15-a** (1 g, 2.7 mmol), 3-cyanocyclobutanecarboxylic acid (503 mg, 4.0 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)(PF₆) (300 mg, 0.03 mmol), NiCl₂.dtbbpy (107 mg, 0.27 mmol), cesium carbonate (2.6 g, 8.05 mmol) in DMA (20 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling a fan to keep the reaction temperature at 25 °C for 14 hr. The reaction was poured into water, extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give compound **D20-b1** (300.0 mg, faster eluted) and compound **D20-b2** (170.0 mg, slower eluted). LCMS (M+H⁺): 418. The configuration of compound **D20-b1** and compound **D20-b2** were confirmed by 2D NMR.

Step 2: preparation of *trans*-3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile (intermediated D20) and *cis*-3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile (intermediated D21)

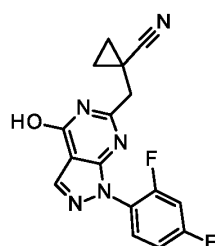
-91-

To a solution of compound **D20-b1** (100.0 mg, 0.24 mmol) in DCM (1 mL) was added TFA(1 mL) at 0°C and then stirred at 20 °C for 1 h. The reaction was concentrated to give intermediated **D20** (100.0 mg) as brown oil. LCMS (M+H): 328

To a solution of compound **D21-b2** (100.0 mg, 0.24 mmol) in DCM (1 mL) was added TFA(1 mL) at 0°C and then stirred at 20 °C for 1 h. The reaction was concentrated to give intermediated **D21** (100.0 mg) as brown oil. LCMS (M+H⁺): 328

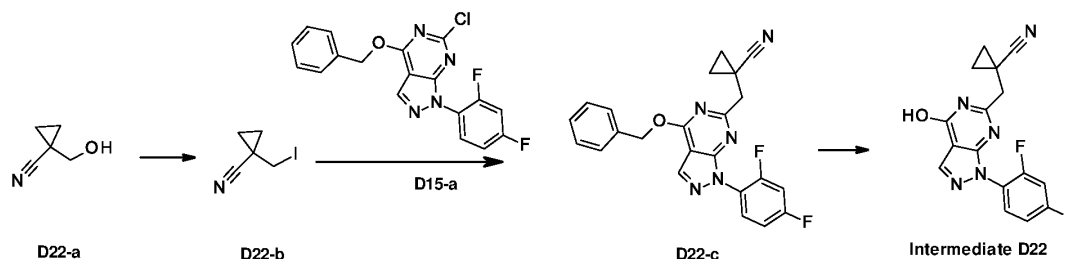
Intermediate D22

1-[[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile



10

The title compound was prepared according to the following scheme:



Step 1: preparation of 1-(iodomethyl)cyclopropanecarbonitrile (compound D22-b)

To a solution of PPh₃ (3.5 g, 13.39 mmol) and 1*H*-imidazole (0.91 g, 13.39 mmol) in DCM (15 mL) was added iodine (3.4 g, 13.39 mmol) slowly at 0 °C under N₂. The reaction was stirred at 0° C for 0.5 h under N₂ and then compound **D22-a** (1.0 g, 10.3 mmol) in DCM (5 mL) was added slowly. The reaction mixture was stirred at 25 °C for 15 hrs and then concentrated, the residue was purified by silica gel column chromatography to give compound **D22-b** (1.2 g) as a colorless oil.

Step 2: preparation of 1-[[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile (compound D22-c)

To a 40 mL vial equipped with a stir bar was added compound **D15-a** (300.0 mg, 0.8 mmol), compound **D22-b** (267 mg, 1.29 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)(PF₆) (9 mg, 0.01 mmol), NiCl₂.dtbbpy (1.6 mg), tris(trimethylsilyl)silane (0.25 mL, 0.8 mmol), sodium carbonate

20

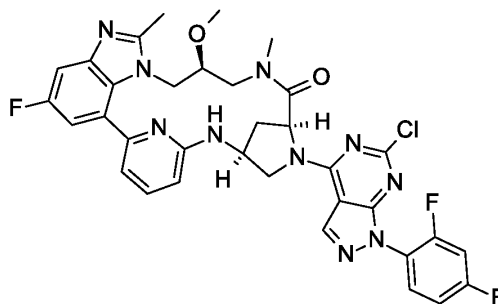
(170 mg, 1.61 mmol) in DMA (6 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with a cooling fan to keep the reaction temperature at 25 °C for 14 hr. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was
 5 purified by prep-TLC to give compound **D22-c** (110.0 mg) as yellow oil. LCMS (M+H⁺): 418.

Step 3: preparation of 1-[[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile (Intermediate D22)

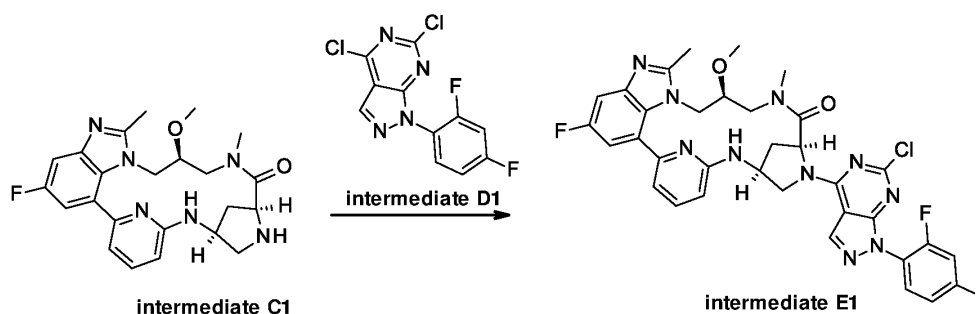
To a solution of compound **D22-c** (60.0 mg, 0.14 mmol) in DCM (0.5 mL) was added TFA (1.0 mL) at 0 °C. The reaction was stirred at 40 °C for 1 hr and then concentrated, the residue
 10 was purified by prep-HPLC to afford Intermediate **D22** (55.0 mg) as a yellow oil. LCMS (M+H⁺): 328.

Intermediate E1

(8S,11S,15R)-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-
 15 **hexazapentacyclo[15.6.1.1^{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:

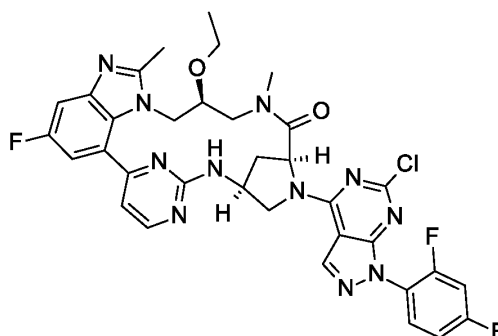


A mixture of intermediate **C1** (0.90 g, 2.05 mmol), intermediate **D1** (618 mg, 2.05 mmol)
 20 and DIPEA (1.33 g, 10.26 mmol) in acetonitrile (60 mL) was stirred at 45 °C for 3 hours, The

reaction was concentrated and the residue was purified by silica gel column chromatography to give intermediate **E1** (1 g), LCMS (M+H⁺): 703.

Intermediate E2

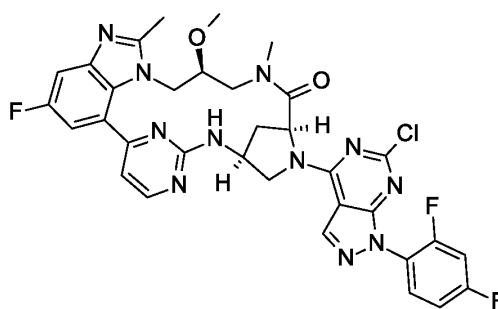
(8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-
 22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-
 heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-
 one



Intermediate E2 was prepared in analogy to the preparation of **Intermediate E1** by using
 intermediate **C2** instead of intermediate **C1**. LCMS (M+H⁺): 718.

Intermediate E3

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



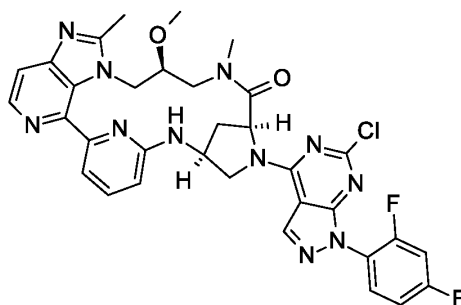
Intermediate E3 was prepared in analogy to the preparation of **Intermediate E1** by using
 intermediate **C3** instead of intermediate **C1**. LCMS (M+H⁺): 704.

Intermediate E4

(8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-

methoxy-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



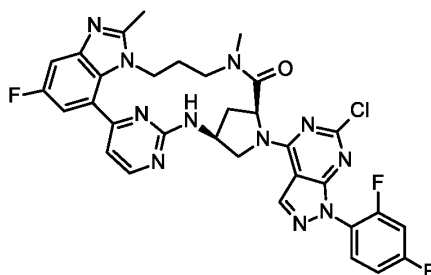
- 5 **Intermediate E4** was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C8** instead of intermediate **C1**. LCMS (M+H⁺): 686.

Intermediated E5

(8*S*,11*S*)-10-[6-chloro-1-(2,4-difluorophenyl)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-

- 10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one

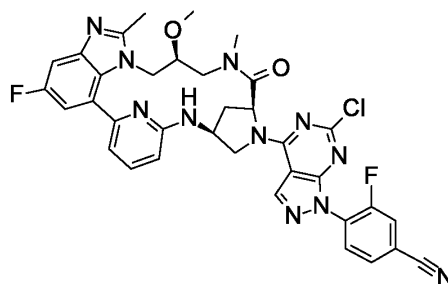


Intermediate E5 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C7** instead of intermediate **C1**. LCMS (M+H⁺): 674.

Intermediate E6

- 15 4-[6-chloro-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-1-yl]-3-fluoro-benzonitrile

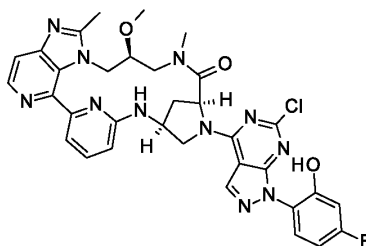
-95-



Intermediate E6 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **D5** instead of intermediate **D1**. LCMS ($M+H^+$): 710.

Intermediate E7

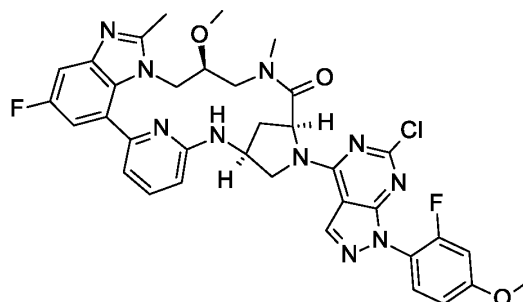
- 5 (8*S*,11*S*,15*R*)-10-[6-chloro-1-(4-fluoro-2-hydroxy-phenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 10 **Intermediate E7** was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C8** instead of intermediate **C1** and intermediate **D6** instead of intermediate **D1**. LCMS ($M+H^+$): 684.

Intermediate E8

- 15 (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2-fluoro-4-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

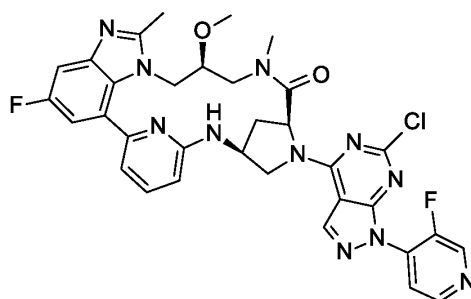


-96-

Intermediate E8 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **D3** instead of intermediate **D1**. LCMS (M+H⁺): 715.

Intermediate E9

(8*S*,11*S*,15*R*)-10-[6-chloro-1-(3-fluoro-4-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(24),2(26),3,5,18,20,22-heptaen-12-one

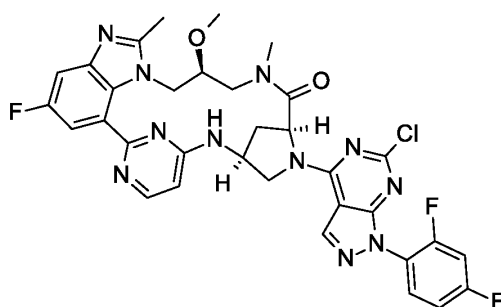


Intermediate E9 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **D4** instead of intermediate **D1**. LCMS (M+H⁺): 715.

10

Intermediate E10

(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-3,7,10,13,17,19,26-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



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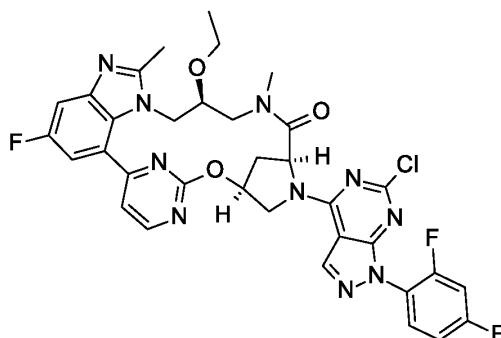
Intermediate E10 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C9** instead of intermediate **C1**. LCMS (M+H⁺): 704.

Intermediate E11

(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

20

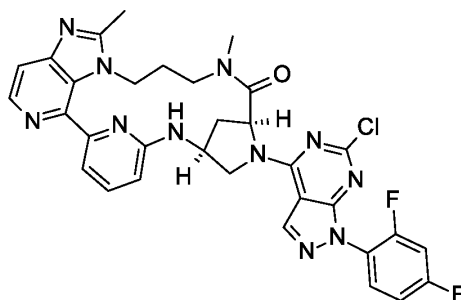
-97-



Intermediate E11 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C6** instead of intermediate **C1**. LCMS ($M+H^+$): 719.

Intermediate E12

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

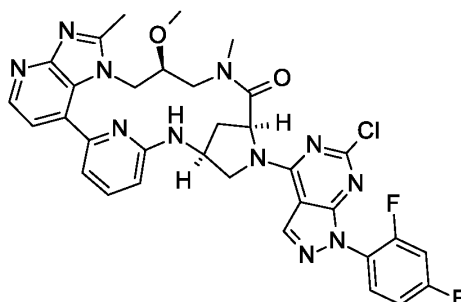


- 10 **Intermediate E12** was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C10** instead of intermediate **C1**. LCMS ($M+H^+$): 656.

Intermediate E13

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

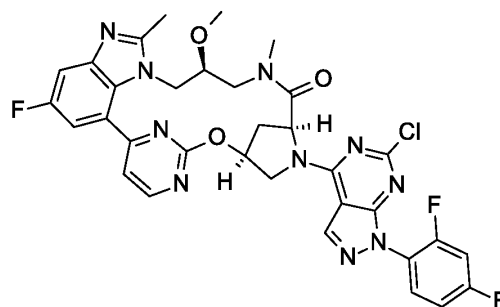
-98-



Intermediate E13 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C11** instead of intermediate **C1**. LCMS ($M+H^+$): 686.

Intermediate E14

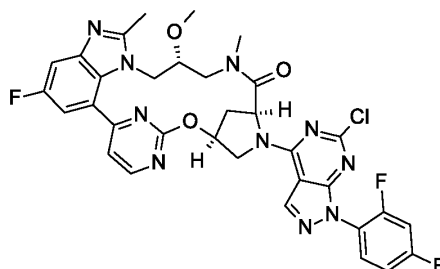
- 5 (8*S*,11*S*,15*R*)-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7-oxa-5,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 10 **Intermediate E14** was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C5** instead of intermediate **C1**. LCMS ($M+H^+$): 705.

Intermediate E15

- (8*S*,11*S*,15*S*)-10-[6-chloro-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

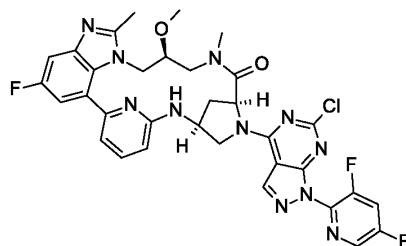


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Intermediate E15 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **C12** instead of intermediate **C1**. LCMS (M+H⁺): 705.

Intermediate E16

(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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

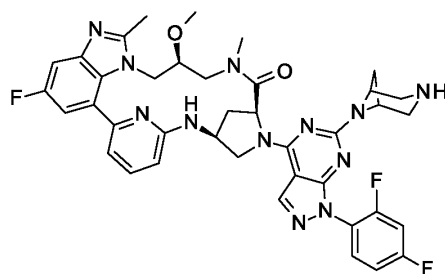


Intermediate E16 was prepared in analogy to the preparation of **Intermediate E1** by using intermediate **D2** instead of intermediate **D1**. LCMS (M+H⁺): 705.

10

Intermediate F1

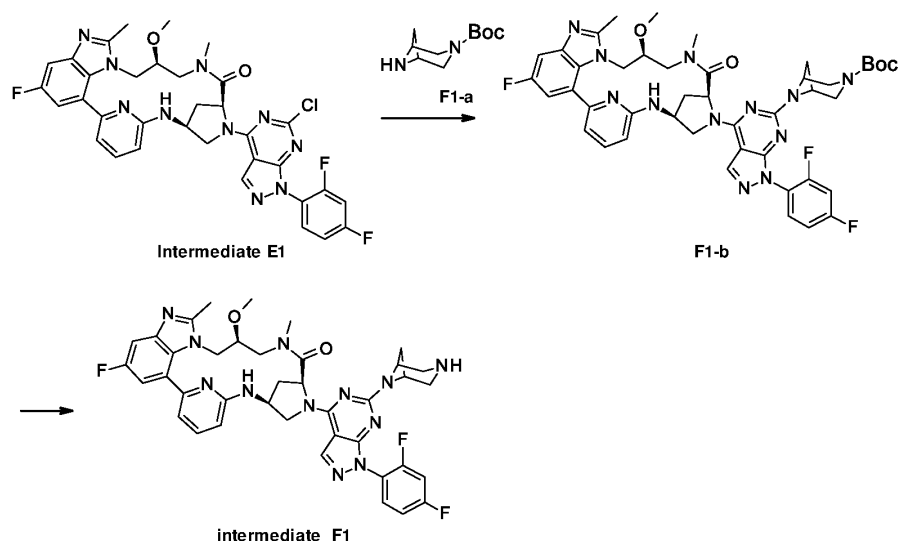
(8*S*, 11*S*, 15*R*)-10-[6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



15

The title compound was prepared according to the following scheme:

-100-



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}]hexacos-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]heptane-3-carboxylate (compound F1-b)

A solution of Intermediate **E1** (1 g, 1.42 mmol), compound **F1-a** (1.4 g, 7.11 mmol), CsF (1.08 g, 7.11 mmol) and *N,N*-diisopropylethylamine (1.2 mL, 7.11 mmol) in DMA (10 mL) was stirred at 120 °C for 15 hrs. The reaction solution was diluted with water and extracted with EA. The organic layer was dried and concentrated to give compound **F1-b** (1 g) as an off-white solid.

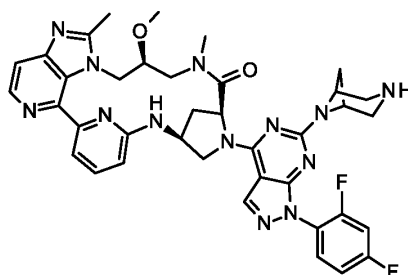
LCMS (M+H)⁺: 865.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[6-(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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Intermediate F1)

To a solution of compound **F1-b** (1 g, 1.16 mmol) in DCM (10 mL) was added TFA (5.0 mL) at 0° C. The reaction mixture was stirred at 20 °C for 1 h and then concentrated to give Intermediate **F1** (1 g) as yellow oil. LCMS (M+H)⁺: 765.

Intermediate F2
(8*S*,11*S*,15*R*)-10-[6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

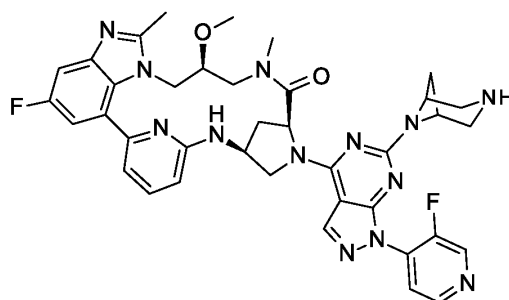
-101-



Intermediate F2 was prepared in analogy to the preparation of **Intermediate F1** by using intermediate **E4** instead of intermediate **E1**. LCMS ($M+H^+$): 748.

Intermediate F3

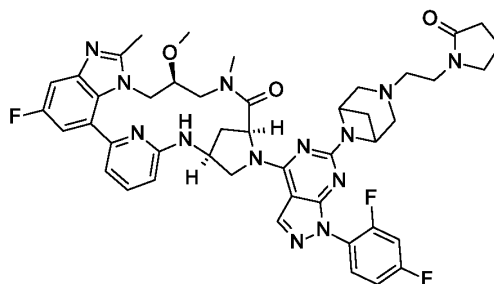
- 5 (8*S*,11*S*,15*R*)-10-[6-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-1-(3-fluoro-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-12-one



- 10 **Intermediate F3** was prepared in analogy to the preparation of **Intermediate F1** by using intermediate **E9** instead of intermediate **E1**. LCMS ($M+H^+$): 748.

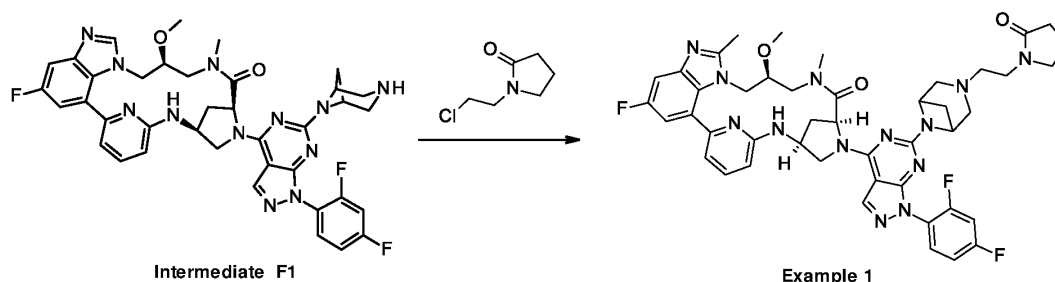
Example 1

- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(2-oxopyrrolidin-1-yl)ethyl]-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
- 15



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The title compound was prepared according to the following scheme:

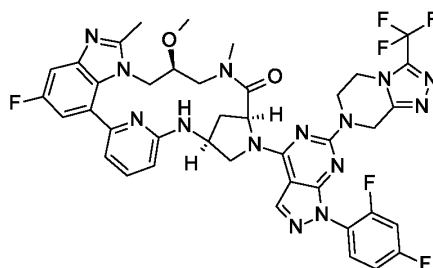


To a tube was added intermediate **F1** (20 mg, 22.76 μmol), 1-(2-chloroethyl)-2-pyrrolidone (17 mg, 113.79 μmol), potassium carbonate (15.7 mg, 113.79 μmol), sodium iodide (13.6 mg, 91.03 μmol) and DMF (1 mL). The suspension was heated to 100 $^{\circ}\text{C}$ and stirred for 16 hrs. The mixture was filtered and purified via prep-HPLC to give Example **1** (3 mg) as a white powder. LCMS ($\text{M}+\text{H}^{+}$): 876, ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ = 8.37 (s, 1H), 7.86 (t, J = 7.9 Hz, 1H), 7.69 - 7.61 (m, 1H), 7.52 - 7.46 (m, 1H), 7.39 (dd, J = 2.0, 10.0 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.22 - 7.16 (m, 1H), 7.15 - 7.11 (m, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.03 (br dd, J = 4.1, 15.1 Hz, 1H), 5.42 - 5.36 (m, 1H), 4.71 - 4.66 (m, 1H), 4.55 - 4.48 (m, 1H), 4.40 - 4.30 (m, 2H), 4.29 - 4.20 (m, 2H), 4.13 - 4.02 (m, 1H), 3.96 - 3.78 (m, 3H), 3.64 - 3.50 (m, 2H), 3.47 - 3.33 (m, 3H), 3.16 - 3.14 (m, 1H), 3.06 (s, 3H), 3.05 - 2.94 (m, 2H), 2.94 - 2.92 (m, 3H), 2.86 - 2.77 (m, 2H), 2.74 - 2.67 (m, 3H), 2.59 - 2.48 (m, 2H), 2.46 - 2.31 (m, 2H), 2.12 - 2.00 (m, 2H), 1.98 - 1.84 (m, 1H).

15

Example 2

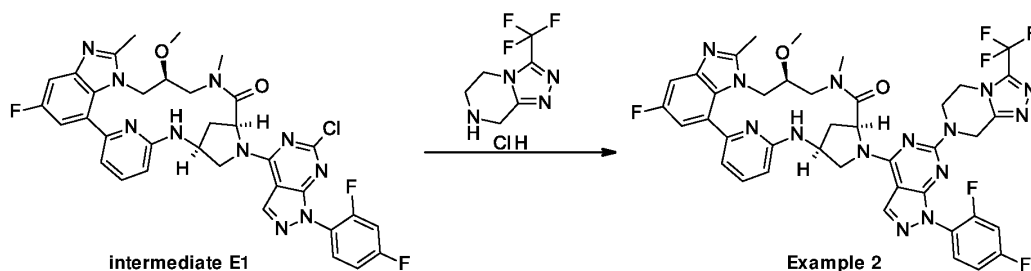
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(trifluoromethyl)-6,8-dihydro-5*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



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The title compound was prepared according to the following scheme:

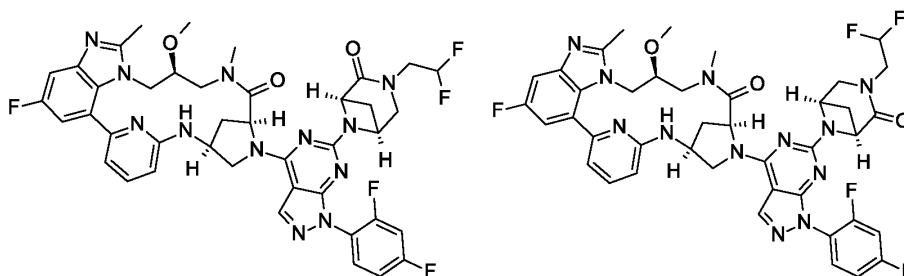
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To a tube was added intermediate **E1** (30 mg, 42.67 μmol), DIEA (27 mg, 37 μL , 213.3 μmol), 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine;hydrochloride (19 mg, 85.33 μmol), cesium fluoride (13 mg, 85.33 μmol) and dimethyl sulfoxide (1 mL). The solution was stirred at 100 °C for 16 hrs. The mixture was purified via prep-HPLC to give Example **2** (8 mg) as a white powder. LCMS (M+H)⁺: 859, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.91 - 7.84 (m, 1H), 7.65 (dt, *J* = 5.9, 8.7 Hz, 1H), 7.61 - 7.57 (m, 1H), 7.57 - 7.52 (m, 1H), 7.26 (ddd, *J* = 2.7, 8.8, 10.3 Hz, 1H), 7.21 - 7.14 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.21 (dd, *J* = 4.6, 15.5 Hz, 1H), 5.47 (d, *J* = 8.9 Hz, 1H), 5.30 - 5.03 (m, 2H), 4.68 (t, *J* = 4.8 Hz, 1H), 4.49 (dd, *J* = 5.9, 11.3 Hz, 1H), 4.39 - 4.32 (m, 1H), 4.31 - 4.20 (m, 4H), 4.18 - 4.08 (m, 1H), 3.86 (dd, *J* = 9.1, 14.4 Hz, 1H), 3.17 - 3.13 (m, 3H), 3.13 - 3.07 (m, 1H), 3.02 - 2.95 (m, 3H), 2.81 (s, 3H), 2.80 - 2.76 (m, 1H), 2.65 - 2.50 (m, 2H).

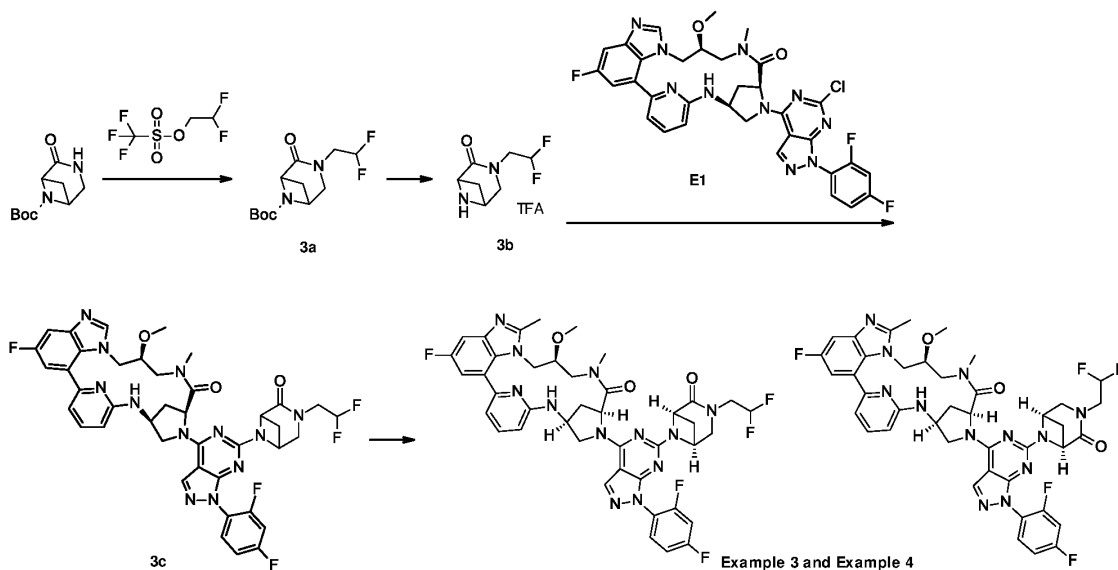
Example 3 and Example 4

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-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}]hexacosan-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-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}]hexacosan-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 3a)

To a tube was added *tert*-butyl 2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (80 mg, 376.91 μ mol) and DMF (1 mL). The solution was stirred at r.t. and NaH (40 mg, 1.51 mmol) was added. A few minutes later, 2,2-difluoroethyl trifluoromethanesulfonate (161 mg, 99.94 μ L, 753.83 μ mol) was added. The final mixture was heated to 60 °C and stirred for 16 hrs. The reaction was quenched with water, and diluted with DCM. The organic layer was separated, dried and concentrated. The crude oil was purified via silica gel chromatography to give compound **3a** (20 mg) as an oil. LCMS (M+H)⁺: 277.

Step 2: preparation of 3-(2,2-difluoroethyl)-3,6-diazabicyclo[3.1.1]heptan-2-one (compound 3b)

To the flask containing compound **3a** (20 mg, 72.39 μ mol) was added TFA (1.48 g, 1 mL, 12.98 mmol, 179.308 eq) and dichloromethane (1 mL). The solution was stirred at r.t. for 1 hr and concentrated to give compound **3b** (37 mg) as a crude oil, which was used directly in the next step. LCMS (M+H)⁺: 177.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-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 3 & Example 4)

To a tube was added intermediate **E1** (30 mg, 42.67 μ mol), DIEA (44.1 mg, 60 μ L, 341.34 μ mol), compound **3b** (37 mg, 128. μ mol), cesium fluoride (13 mg, 85 μ mol) and dimethyl sulfoxide (1 mL). The reaction mixture was stirred at 100 °C for 16 hrs and then purified via prep-HPLC to give Example **3** (2 mg, faster eluted) and Example **4** (2 mg, slower eluted) as white powders.

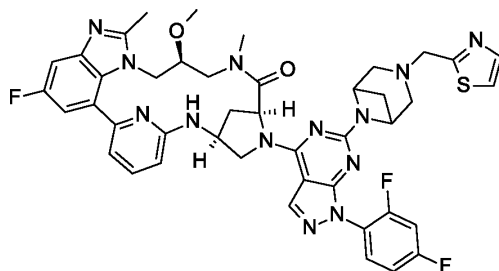
Example **3**, LCMS (M+H)⁺: 843, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.33 (s, 1H), 7.89 - 7.82 (m, 1H), 7.68 - 7.58 (m, 1H), 7.51 (dd, *J* = 2.3, 7.8 Hz, 1H), 7.44 (dd, *J* = 2.5, 10.3 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.20 - 7.12 (m, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.18 - 6.07 (m, 1H), 5.41 - 5.37 (m, 1H), 5.37 - 5.34 (m, 1H), 4.69 - 4.64 (m, 1H), 4.59 - 4.54 (m, 1H), 4.51 - 4.39 (m, 1H), 4.32 - 4.21 (m, 2H), 4.20 - 4.08 (m, 1H), 4.05 - 3.99 (m, 1H), 3.96 - 3.86 (m, 1H), 3.84 - 3.73 (m, 1H), 3.46 - 3.37 (m, 2H), 3.13 - 3.09 (m, 3H), 3.01 (br d, *J* = 13.5 Hz, 1H), 2.95 (s, 3H), 2.89 - 2.81 (m, 1H), 2.76 (s, 4H), 2.60 - 2.53 (m, 1H), 2.52 - 2.43 (m, 1H), 1.79 (d, *J* = 9.0 Hz, 1H).

Example **4**, LCMS (M+H)⁺: 843, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.34 (s, 1H), 7.90 - 7.81 (m, 1H), 7.63 - 7.57 (m, 1H), 7.56 - 7.46 (m, 2H), 7.28 - 7.21 (m, 1H), 7.20 - 7.11 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.11 (br dd, *J* = 4.5, 15.3 Hz, 1H), 6.04 - 5.80 (m, 1H), 5.46 (d, *J* = 8.6 Hz, 1H), 4.67 - 4.63 (m, 1H), 4.61 - 4.56 (m, 1H), 4.54 - 4.48 (m, 1H), 4.43 (dd, *J* = 6.2, 11.4 Hz, 1H), 4.34 - 4.27 (m, 1H), 4.25 - 4.16 (m, 2H), 4.15 - 4.01 (m, 2H), 3.40 (br d, *J* = 11.4 Hz, 1H), 3.15 - 3.10 (m, 1H), 3.07 (s, 3H), 2.98 - 2.95 (m, 1H), 2.95 - 2.92 (m, 3H), 2.87 - 2.80 (m, 1H), 2.78 (s, 1H), 2.75 (s, 3H), 2.61 - 2.43 (m, 2H), 2.09 - 1.98 (m, 1H).

Example 5

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(thiazol-2-ylmethyl)-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

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Example **5** was prepared in analogy to the preparation of Example **1** by using 2-(chloromethyl)thiazole instead of 1-(2-chloroethyl)-2-pyrrolidone in step 1. Example **5** (5 mg) was obtained as a white solid. LCMS (M+H)⁺: 862., ¹H NMR (400 MHz, METHANOL-d₄) δ =

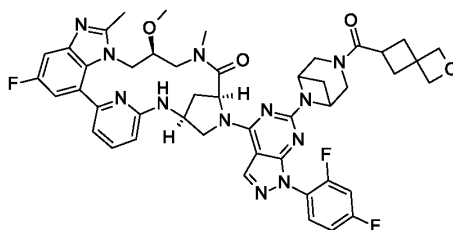
5 8.31 (s, 1H), 7.86 - 7.79 (m, 1H), 7.66 - 7.56 (m, 2H), 7.48 - 7.41 (m, 1H), 7.38 (dd, *J* = 2.4, 8.1 Hz, 1H), 7.29 - 7.19 (m, 2H), 7.18 - 7.13 (m, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.94 (br dd, *J* = 4.4, 15.6 Hz, 1H), 5.38 - 5.30 (m, 1H), 4.67 (t, *J* = 4.8 Hz, 1H), 4.52 - 4.44 (m, 1H), 4.43 - 4.33 (m, 1H), 4.30 - 4.23 (m, 2H), 4.23 - 4.18 (m, 1H), 4.17 - 3.93 (m, 3H), 3.92 - 3.83 (m, 1H), 3.67 - 3.43 (m, 2H), 3.16 - 3.05 (m, 2H), 3.04 - 2.96 (m, 3H), 2.91 - 2.86 (m, 3H),

10 2.83 - 2.72 (m, 1H), 2.70 - 2.59 (m, 4H), 2.59 - 2.44 (m, 2H), 1.89 - 1.79 (m, 1H).

Example 6

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-oxaspiro[3.3]heptane-6-carbonyl)-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-

15 1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **6** was prepared in analogy to the preparation of Example **34** by using 2-oxaspiro[3.3]heptane-6-carboxylic acid instead of oxetane-2-carboxylic acid. Example **6** (12 mg) was obtained as a white solid. LCMS (M+H)⁺: 889, ¹H NMR (400 MHz, METHANOL-d₄) δ =

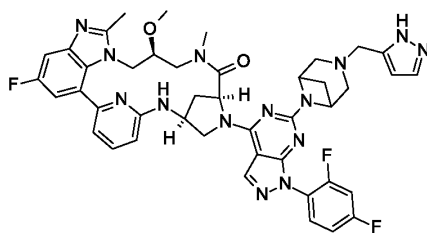
20 8.28 (d, *J* = 4.5 Hz, 1H), 7.87 - 7.79 (m, 1H), 7.67 - 7.55 (m, 1H), 7.42 - 7.32 (m, 1H), 7.31 - 7.21 (m, 2H), 7.17 (br t, *J* = 8.5 Hz, 1H), 7.14 - 7.08 (m, 1H), 6.75 - 6.67 (m, 1H), 5.95 (br dd, *J* = 4.3, 15.7 Hz, 1H), 5.42 - 5.28 (m, 1H), 4.72 - 4.57 (m, 3H), 4.54 - 4.39 (m, 3H), 4.38 - 4.33 (m, 1H), 4.32 - 4.26 (m, 2H), 4.26 - 4.10 (m, 3H), 4.00 - 3.86 (m, 1H), 3.44 - 3.34 (m, 2H), 3.15 -

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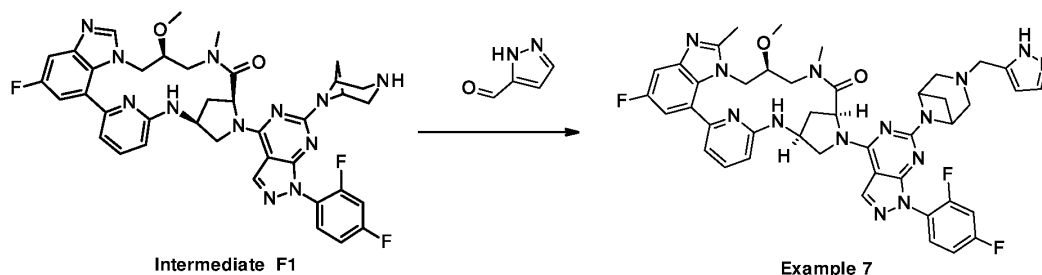
3.02 (m, 4H), 3.02 - 2.93 (m, 1H), 2.92 - 2.86 (m, 3H), 2.86 - 2.79 (m, 1H), 2.79 - 2.57 (m, 5H), 2.55 - 2.26 (m, 5H), 2.22 - 1.91 (m, 1H).

Example 7

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1*H*-pyrazol-5-ylmethyl)-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



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To a tube was added intermediate **F1** (30 mg, 34.1 μ mol), 1*H*-pyrazole-5-carbaldehyde (10 mg, 102.41 μ mol), DIEA (13 mg, 18 μ L, 102.4 μ mol) and ethanol (2 mL). The suspension was heated to 60 °C and stirred for 2 hrs, then sodium triacetoxyborohydride (25 mg, 119.4 μ mol) was added. The mixture was kept stirring at the temperature for another 2 hrs. The mixture was concentrated and purified via prep-HPLC to give **Example 7** (11 mg) as a white powder.

LCMS (M+H)⁺: 845, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.26 (s, 1H), 7.84 - 7.77 (m, 1H), 7.57 - 7.49 (m, 1H), 7.29 (dd, *J* = 2.6, 8.4 Hz, 1H), 7.25 - 7.17 (m, 2H), 7.17 - 7.11 (m, 2H), 7.10 - 7.05 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.19 - 5.94 (m, 1H), 5.88 (br d, *J* = 13.0 Hz, 1H), 5.40 - 5.25 (m, 1H), 4.69 - 4.63 (m, 1H), 4.50 - 4.41 (m, 1H), 4.39 - 4.10 (m, 5H), 3.90 (br dd, *J* = 9.2, 13.9 Hz, 1H), 3.71 - 3.61 (m, 2H), 3.39 (br d, *J* = 9.9 Hz, 1H), 3.15 - 2.96 (m, 4H), 2.91 - 2.85 (m, 1H), 2.84 (s, 3H), 2.82 - 2.73 (m, 2H), 2.55 (s, 3H), 2.51 - 2.41 (m, 3H), 1.90 - 1.81 (m, 1H).

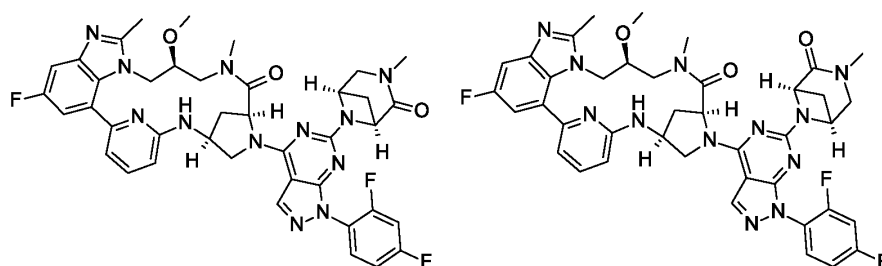
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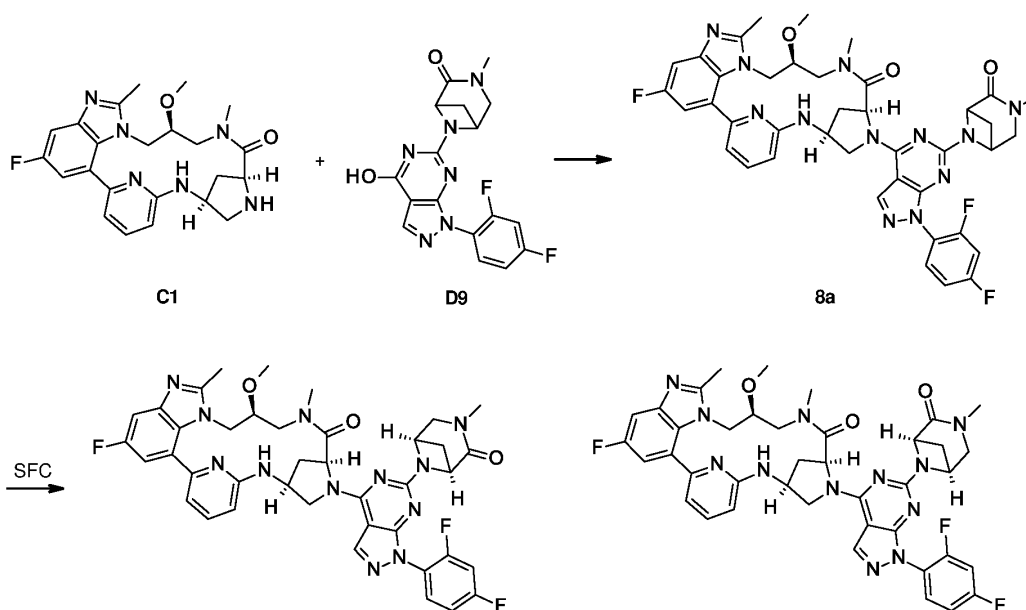
Example 8 and Example 9

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(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-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 and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-methyl-2-oxo-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



The title compound was prepared according to the following scheme:



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Example 8 and Example 9

To a tube was added (1-hydroxy-1*H*-benzotriazolato-*o*)tri-1-pyrrolidinylphosphorus hexafluorophosphate (209 mg, 402.87 μ mol), compound **D9** (100 mg, 268.5 μ mol), DIPEA (139 mg, 187 μ L, 1.07 mmol) and DMF (6 mL). The solution was stirred at 50 °C for 2 hrs and compound **C1** (179 mg, 322.3 μ mol) was added. The mixture was stirred at 80 °C for another 2 hrs and purified via prep-HPLC to give compound **8a** (110 mg) as a white powder. The

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compound **8a** was separated via SFC to give Example **8** (42 mg, faster eluted) and Example **9** (50 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 µm.; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 45%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column

5 temperature: 35 °C)

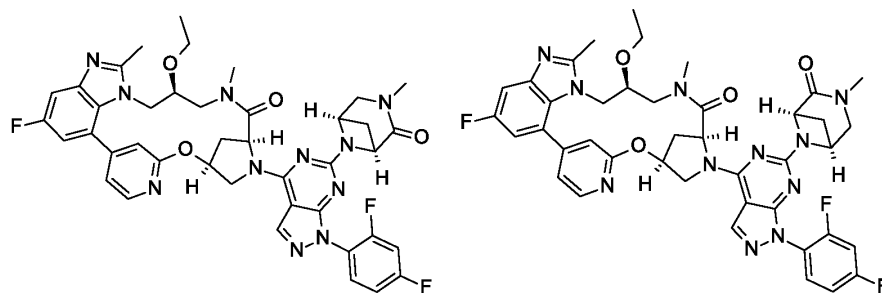
Example **8**, LCMS (M+H)⁺: 793, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 (s, 1H), 7.84 - 7.76 (m, 1H), 7.68 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.16 (dt, *J* = 2.4, 9.8 Hz, 2H), 7.12 - 7.06 (m, 1H), 6.70 - 6.61 (m, 1H), 5.81 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.45 (d, *J* = 8.8 Hz, 1H), 4.67 - 4.60 (m, 1H), 4.59 - 4.54 (m, 1H), 4.49 - 4.40 (m, 1H), 4.35 -
10 3.99 (m, 5H), 3.98 - 3.88 (m, 1H), 3.12 - 3.03 (m, 3H), 2.95 (br d, *J* = 13.3 Hz, 1H), 2.91 - 2.86 (m, 1H), 2.85 - 2.81 (m, 3H), 2.81 - 2.73 (m, 4H), 2.59 - 2.54 (m, 3H), 2.53 - 2.39 (m, 2H), 1.73 (d, *J* = 8.8 Hz, 1H).

Example **9**, LCMS (M+H)⁺: 793, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.57 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.26 - 7.20 (m, 1H),
15 7.15 (br dd, *J* = 2.6, 10.4 Hz, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.82 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.38 (d, *J* = 9.0 Hz, 1H), 4.67 - 4.59 (m, 1H), 4.58 - 4.49 (m, 1H), 4.47 - 4.37 (m, 1H), 4.32 - 4.10 (m, 3H), 4.10 - 3.98 (m, 1H), 3.97 - 3.82 (m, 2H), 3.12 - 3.04 (m, 3H), 2.96 - 2.88 (m, 1H), 2.87 - 2.81 (m, 3H), 2.80 - 2.72 (m, 4H), 2.71 - 2.59 (m, 1H), 2.59 - 2.53 (m, 3H), 2.52 - 2.38 (m, 2H), 1.75 (d, *J* = 8.8 Hz, 1H).

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Example 10 and Example 11

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-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-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*R*)-10-[1-(2,4-difluorophenyl)-6-
25 [(1*R*,5*S*)-3-methyl-2-oxo-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-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 **10** and Example **11** were prepared in analogy to the preparation of Example **8** and Example **9** by using Intermediate **C4** instead of Intermediate **C1**. The mixture was separated via

5 white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 μm.; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 30%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column temperature: 35 °C).

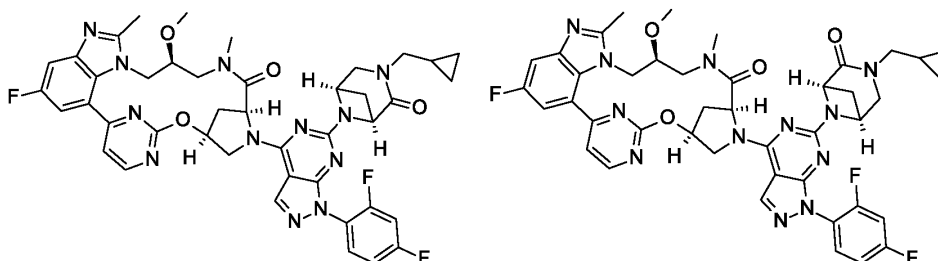
Example **10**, LCMS (M+H)⁺: 808, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.36 - 8.30 (m, 2H), 7.69 - 7.57 (m, 1H), 7.36 - 7.31 (m, 1H), 7.27 - 7.20 (m, 1H), 7.19 - 7.08 (m, 2H), 7.07 - 7.02 (m, 1H), 6.99 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.77 (t, *J* = 3.9 Hz, 1H), 5.43 (d, *J* = 9.3 Hz, 1H), 4.69 - 4.59 (m, 1H), 4.58 - 4.52 (m, 1H), 4.50 - 4.28 (m, 3H), 4.20 - 4.02 (m, 3H), 3.52 - 3.42 (m, 1H), 3.41 - 3.33 (m, 1H), 3.30 - 3.26 (m, 1H), 3.08 - 2.98 (m, 3H), 2.91 - 2.78 (m, 2H), 2.78 - 2.73 (m, 4H), 2.73 - 2.63 (m, 2H), 2.63 - 2.58 (m, 3H), 1.73 (d, *J* = 8.8 Hz, 1H), 0.69 - 0.59 (m, 3H).

15 Example **11**, LCMS (M+H)⁺: 808, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 - 8.30 (m, 2H), 7.65 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.33 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.20 - 7.13 (m, 1H), 7.12 - 7.03 (m, 2H), 6.99 (dd, *J* = 2.5, 10.0 Hz, 1H), 5.76 (t, *J* = 3.6 Hz, 1H), 5.34 (d, *J* = 9.6 Hz, 1H), 4.74 - 4.62 (m, 1H), 4.59 - 4.51 (m, 1H), 4.50 - 4.43 (m, 1H), 4.36 (br dd, *J* = 4.0, 11.4 Hz, 1H), 4.15 - 4.01 (m, 3H), 3.94 - 3.84 (m, 1H), 3.50 - 3.39 (m, 1H), 3.38 - 3.33 (m, 20 1H), 3.29 - 3.25 (m, 1H), 3.10 (br d, *J* = 14.9 Hz, 1H), 3.07 - 3.00 (m, 3H), 2.90 - 2.79 (m, 2H), 2.79 - 2.72 (m, 3H), 2.72 - 2.63 (m, 2H), 2.62 - 2.58 (m, 3H), 1.75 (d, *J* = 8.8 Hz, 1H), 0.65 (t, *J* = 7.0 Hz, 3H).

Example 12 and Example 13

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-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



5 Example 12 and Example 13 were prepared in analogy to the preparation of Example 8 and Example 9 by using Intermediate C5 instead of Intermediate C1 and using Intermediate D10 instead of Intermediate D9. The mixture was separated via SFC to give Example 12 (41 mg, faster eluted) and Example 13 (37 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 µm.; Mobile phase: A for CO₂ and B for
10 Ethanol «Mobile_phasePrep»; Gradient: B 40%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column temperature: 35 °C)

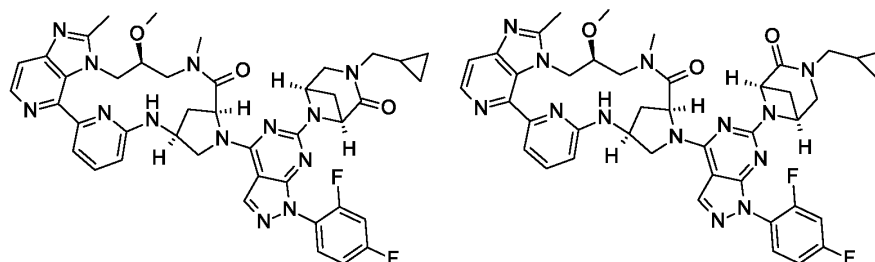
Example 12, LCMS (M+H)⁺: 835, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.79 - 8.74 (m, 1H), 8.31 (s, 1H), 7.68 - 7.58 (m, 2H), 7.47 - 7.39 (m, 2H), 7.28 - 7.20 (m, 1H), 7.20 - 7.13 (m, 1H), 5.88 - 5.64 (m, 2H), 5.53 (d, *J* = 8.8 Hz, 1H), 4.68 - 4.56 (m, 1H), 4.46 - 4.40 (m, 1H),
15 4.35 - 4.26 (m, 1H), 4.23 - 3.91 (m, 4H), 3.44 - 3.33 (m, 2H), 3.07 - 2.97 (m, 3H), 2.94 - 2.84 (m, 2H), 2.83 - 2.76 (m, 5H), 2.71 - 2.63 (m, 1H), 2.63 - 2.57 (m, 3H), 2.56 - 2.47 (m, 1H), 1.73 (d, *J* = 8.6 Hz, 1H), 0.96 - 0.82 (m, 1H), 0.39 - 0.13 (m, 4H).

Example 13, LCMS (M+H)⁺: 835, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.77 (d, *J* = 5.3 Hz, 1H), 8.31 (s, 1H), 7.68 - 7.58 (m, 2H), 7.48 - 7.38 (m, 2H), 7.29 - 7.20 (m, 1H), 7.20 -
20 7.11 (m, 1H), 5.90 - 5.61 (m, 2H), 5.52 (br d, *J* = 8.5 Hz, 1H), 4.70 - 4.50 (m, 1H), 4.49 - 4.42 (m, 1H), 4.41 - 4.35 (m, 1H), 4.19 (br dd, *J* = 11.4, 15.3 Hz, 1H), 4.14 - 4.04 (m, 2H), 3.98 (br dd, *J* = 9.7, 13.8 Hz, 1H), 3.43 - 3.31 (m, 2H), 3.11 - 2.98 (m, 3H), 2.93 - 2.72 (m, 7H), 2.70 - 2.63 (m, 1H), 2.62 - 2.57 (m, 3H), 2.53 (br t, *J* = 8.5 Hz, 1H), 1.75 (d, *J* = 8.8 Hz, 1H), 0.82 - 0.49 (m, 1H), 0.40 - -0.19 (m, 4H).

25 **Example 14 and Example 15**

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-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-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-
- 5 1(23),2(26),3,5,18,20(24),21-heptaen-12-one



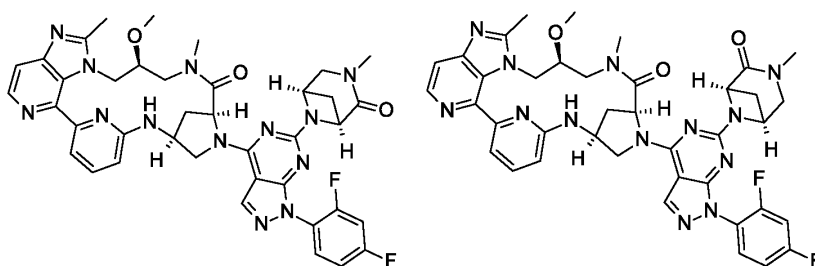
- Example **14** and Example **15** were prepared in analogy to the preparation of Example **8** and Example **9** by using Intermediate **C8** instead of Intermediate **C1** and using Intermediate **D10** instead of Intermediate **D9**. The mixture was separated via SFC to give Example **14** (17 mg, faster eluted) and Example **15** (20 mg, slower eluted) as a white solid. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 μm.; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 50%; Flow rate: «Flow_Rate» mL/min; Back pressure: 100 bar; Column temperature: 35 °C).

- Example **14**, LCMS (M+H)⁺: 816, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, *J* = 5.5 Hz, 1H), 8.31 (s, 1H), 7.89 - 7.82 (m, 1H), 7.67 - 7.57 (m, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.20 - 7.12 (m, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.02 (dd, *J* = 4.2, 15.3 Hz, 1H), 5.47 (d, *J* = 8.6 Hz, 1H), 4.69 - 4.54 (m, 2H), 4.51 - 4.38 (m, 1H), 4.37 - 4.04 (m, 5H), 3.58 - 3.45 (m, 1H), 3.44 - 3.34 (m, 1H), 3.12 - 3.02 (m, 3H), 3.02 - 2.94 (m, 1H), 2.92 - 2.85 (m, 1H), 2.85 - 2.82 (m, 3H), 2.81 - 2.69 (m, 2H), 2.68 - 2.62 (m, 3H), 2.59 - 2.51 (m, 1H), 2.51 - 2.40 (m, 1H), 1.73 (d, *J* = 8.8 Hz, 1H), 0.97 - 0.56 (m, 1H), 0.34 - -0.13 (m, 4H).

- Example **15**, LCMS (M+H)⁺: 816, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, *J* = 5.4 Hz, 1H), 8.31 (s, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.56 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.11 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.03 (br dd, *J* = 3.1, 14.9 Hz, 1H), 5.44 (br d, *J* = 8.9 Hz, 1H), 4.65 (br t, *J* = 4.9 Hz, 1H), 4.60 - 4.51 (m, 1H), 4.50 - 4.35 (m, 1H), 4.32 - 4.10 (m, 3H), 4.09 - 3.92 (m, 2H), 3.45 - 3.32 (m, 2H), 3.19 - 3.02 (m, 3H), 3.01 - 2.85 (m, 2H), 2.85 - 2.75 (m, 4H), 2.75 - 2.68 (m, 1H), 2.65 (s, 3H), 2.60 - 2.50 (m, 1H), 2.49 - 2.38 (m, 1H), 1.74 (br d, *J* = 8.9 Hz, 1H), 0.92 - 0.49 (m, 1H), 0.40 - -0.18 (m, 4H).

Example 16 and Example 17

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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)-6-[(1*R*,5*S*)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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 **16** and Example **17** were prepared in analogy to the preparation of Example **8** and Example **9** by using Intermediate **C8** instead of Intermediate **C1**. The mixture was separated via SFC to give Example **16** (22 mg, faster eluted) and Example **17** (24 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 μm.; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 50%; Flow rate: «Flow_Rate» mL/min; Back pressure: 100 bar; Column temperature: 35 °C)

Example **16**, LCMS (M+H)⁺: 776, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, *J* = 5.5 Hz, 1H), 8.32 (s, 1H), 7.91 - 7.82 (m, 1H), 7.68 - 7.57 (m, 2H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.12 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.02 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.48 (d, *J* = 8.8 Hz, 1H), 4.69 - 4.61 (m, 1H), 4.60 - 4.53 (m, 1H), 4.47 (br dd, *J* = 6.6, 11.4 Hz, 1H), 4.33 - 4.03 (m, 4H), 3.98 - 3.88 (m, 1H), 3.30 - 3.27 (m, 1H), 3.14 - 3.03 (m, 3H), 3.02 - 2.90 (m, 1H), 2.87 - 2.80 (m, 4H), 2.80 - 2.75 (m, 3H), 2.74 - 2.68 (m, 1H), 2.67 - 2.62 (m, 3H), 2.62 - 2.51 (m, 1H), 2.46 (ddd, *J* = 4.4, 8.7, 13.4 Hz, 1H), 1.74 (d, *J* = 8.6 Hz, 1H).

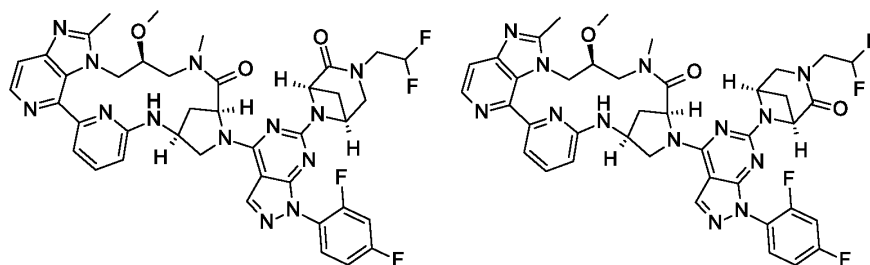
Example **17**, LCMS (M+H)⁺: 776, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, *J* = 5.4 Hz, 1H), 8.31 (s, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.57 (m, 2H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.18 - 7.11 (m, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.03 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.40 (d, *J* = 8.9 Hz, 1H), 4.68 - 4.62 (m, 1H), 4.57 - 4.51 (m, 1H), 4.50 - 4.39 (m, 1H), 4.31 - 4.16 (m, 2H), 4.13 - 4.03 (m, 1H), 3.95 (br dd, *J* = 9.1, 14.1 Hz, 1H), 3.87 (dd, *J* = 1.9, 11.8 Hz, 1H), 3.30 - 3.26 (m, 1H), 3.14 - 3.07 (m, 3H), 2.95 (br d, *J* = 13.9 Hz, 1H), 2.84 (s, 3H), 2.80 (br

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d, $J = 12.4$ Hz, 2H), 2.76 - 2.68 (m, 3H), 2.65 (s, 3H), 2.60 - 2.52 (m, 1H), 2.48 (ddd, $J = 4.3, 9.1, 13.5$ Hz, 1H), 1.75 (d, $J = 8.8$ Hz, 1H).

Example 18 and Example 19

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example 18 and Example 19 were prepared in analogy to the preparation of Example 3 and Example 4 by using Intermediate E4 instead of Intermediate E1. The mixture was separated via prep-HPLC to give Example 18 (17 mg, faster eluted) and Example 19 (18 mg, slower eluted) as a white powder.

Example 18, LCMS (M+H)⁺: 826, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, $J = 5.5$ Hz, 1H), 8.33 (s, 1H), 7.87 (t, $J = 7.9$ Hz, 1H), 7.66 - 7.54 (m, 2H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.12 (m, 1H), 6.76 (d, $J = 8.4$ Hz, 1H), 6.34 - 6.14 (m, 1H), 6.03 (dd, $J = 4.4, 15.4$ Hz, 1H), 5.40 (d, $J = 8.9$ Hz, 1H), 4.70 - 4.64 (m, 1H), 4.60 - 4.52 (m, 1H), 4.51 - 4.41 (m, 1H), 4.36 (dt, $J = 4.3, 14.0$ Hz, 1H), 4.30 - 4.20 (m, 2H), 4.18 - 4.06 (m, 1H), 4.02 (br d, $J = 11.3$ Hz, 1H), 3.98 - 3.87 (m, 1H), 3.86 - 3.69 (m, 1H), 3.47 - 3.39 (m, 1H), 3.17 - 3.05 (m, 3H), 2.96 (br d, $J = 13.6$ Hz, 1H), 2.84 (s, 3H), 2.81 - 2.79 (m, 1H), 2.73 (br d, $J = 12.5$ Hz, 1H), 2.68 - 2.60 (m, 3H), 2.60 - 2.52 (m, 1H), 2.51 - 2.41 (m, 1H), 1.79 (br d, $J = 9.0$ Hz, 1H).

Example 19, LCMS (M+H)⁺: 826, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 (d, $J = 5.5$ Hz, 1H), 8.34 (s, 1H), 7.86 (t, $J = 7.9$ Hz, 1H), 7.64 (d, $J = 5.4$ Hz, 1H), 7.62 - 7.56 (m, 1H), 7.45 (d, $J = 7.4$ Hz, 1H), 7.24 (ddd, $J = 2.8, 8.9, 10.1$ Hz, 1H), 7.20 - 7.13 (m, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 5.97 (dd, $J = 4.1, 15.4$ Hz, 1H), 5.93 - 5.79 (m, 1H), 5.45 (d, $J = 8.6$ Hz, 1H), 4.68 -

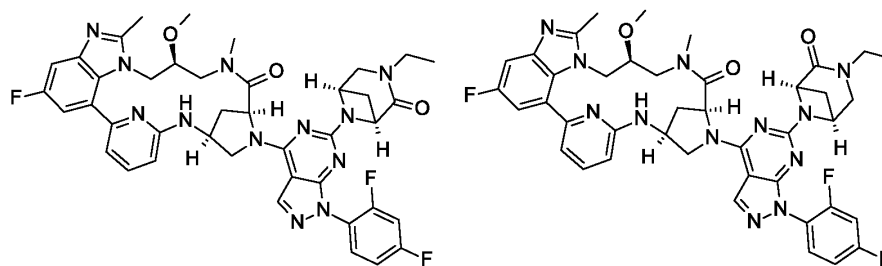
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4.62 (m, 1H), 4.62 - 4.55 (m, 1H), 4.43 (dd, $J = 6.4, 11.4$ Hz, 1H), 4.28 (d, $J = 11.4$ Hz, 1H), 4.24 - 4.14 (m, 2H), 4.14 - 4.06 (m, 2H), 4.05 - 3.98 (m, 1H), 3.40 (d, $J = 11.5$ Hz, 1H), 3.15 - 3.01 (m, 4H), 2.93 - 2.83 (m, 2H), 2.82 (s, 3H), 2.75 (d, $J = 13.5$ Hz, 1H), 2.62 (s, 3H), 2.54 (dt, $J = 4.1, 9.6$ Hz, 1H), 2.50 - 2.41 (m, 1H), 1.77 (d, $J = 8.9$ Hz, 1H).

5

Example 20 and Example 21

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-ethyl-2-oxo-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 and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-ethyl-2-oxo-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 **20** and Example **21** were prepared in analogy to the preparation of Example **3** and Example **4** by using compound iodoethane instead of compound 2,2-difluoroethyl trifluoromethanesulfonate in step 1. The mixture was separated via SFC to give Example **20** (26 mg, faster eluted) and Example **21** (19 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 μm.; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 50%; Flow rate: «Flow_Rate» mL/min; Back pressure: 100 bar; Column temperature: 35 °C)

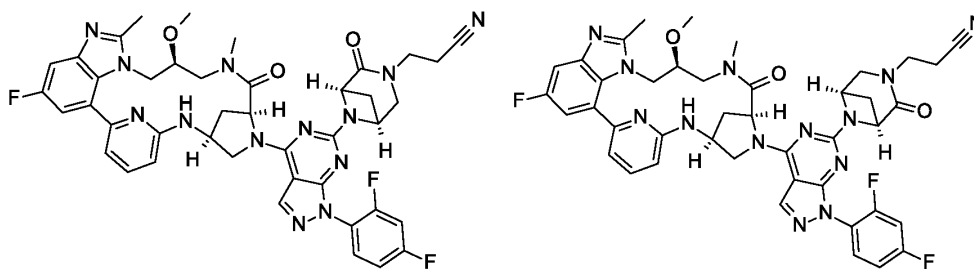
Example **20**, LCMS (M+H)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.29 (s, 1H), 7.83 - 7.77 (m, 1H), 7.65 - 7.59 (m, 1H), 7.32 - 7.27 (m, 1H), 7.27 - 7.20 (m, 1H), 7.16 (dt, $J = 2.5, 9.8$ Hz, 2H), 7.10 (d, $J = 7.6$ Hz, 1H), 6.64 (dd, $J = 8.4, 14.4$ Hz, 1H), 5.81 (dd, $J = 4.3, 15.5$ Hz, 1H), 5.43 (d, $J = 8.6$ Hz, 1H), 4.68 - 4.51 (m, 2H), 4.46 - 4.35 (m, 1H), 4.20 (br d, $J = 11.5$ Hz, 1H), 4.17 - 4.02 (m, 3H), 4.02 - 3.89 (m, 1H), 3.46 - 3.35 (m, 1H), 3.30 - 3.23 (m, 1H), 3.14 - 3.00 (m, 4H), 2.96 - 2.87 (m, 1H), 2.87 - 2.80 (m, 4H), 2.79 - 2.72 (m, 1H), 2.59 - 2.53 (m, 3H), 2.52 - 2.37 (m, 2H), 1.79 - 1.66 (m, 1H), 0.99 - 0.72 (m, 3H).

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Example **21**, LCMS (M+H)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.63 (dt, *J* = 3.4, 8.9 Hz, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.19 - 7.11 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.69 - 6.63 (m, 1H), 5.81 (br dd, *J* = 4.2, 15.6 Hz, 1H), 5.40 (d, *J* = 9.0 Hz, 1H), 4.68 - 4.58 (m, 1H), 4.58 - 4.48 (m, 1H), 4.47 - 4.34 (m, 1H), 4.30 - 4.21 (m, 1H), 4.20 - 4.00 (m, 2H), 3.98 - 3.82 (m, 2H), 3.50 - 3.35 (m, 1H), 3.27 (br d, *J* = 11.9 Hz, 1H), 3.08 (br s, 3H), 2.99 - 2.87 (m, 2H), 2.84 (s, 3H), 2.81 - 2.74 (m, 2H), 2.57 (s, 3H), 2.52 - 2.38 (m, 2H), 1.73 (d, *J* = 8.8 Hz, 1H), 0.88 - 0.63 (m, 3H).

Example 22 and Example 23

3-[(1*R*,5*S*)-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]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile and 3-[(1*S*,5*R*)-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]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile



Example **22** and Example **23** were prepared in analogy to the preparation of Example **3** and Example **4** by using compound 3-bromopropionitrile instead of compound 2,2-difluoroethyl trifluoromethanesulfonate in step 1. The mixture was purified and separated via prep-HPLC to give Example **22** (19 mg, faster eluted) and Example **23** (19 mg, slower eluted) as a white powder.

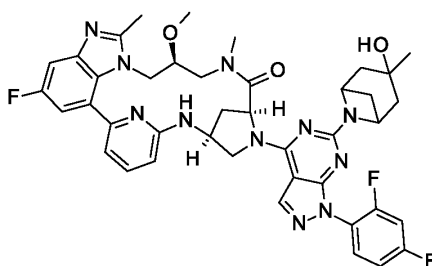
Example **22**, LCMS (M+H)⁺: 832, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.71 - 7.60 (m, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.12 (m, 2H), 7.11 - 7.05 (m, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.82 (dd, *J* = 4.4, 15.5 Hz, 1H), 5.40 (br d, *J* = 8.8 Hz, 1H), 4.68 - 4.43 (m, 3H), 4.39 - 4.06 (m, 4H), 4.05 - 3.99 (m, 1H), 3.98 - 3.85 (m, 2H), 3.13 - 2.99 (m, 4H), 2.93 (br d, *J* = 13.9 Hz, 1H), 2.89 - 2.82 (m, 4H), 2.81 - 2.65 (m, 1H), 2.62 - 2.54 (m, 3H), 2.53 - 2.28 (m, 4H), 1.78 (br d, *J* = 8.9 Hz, 1H).

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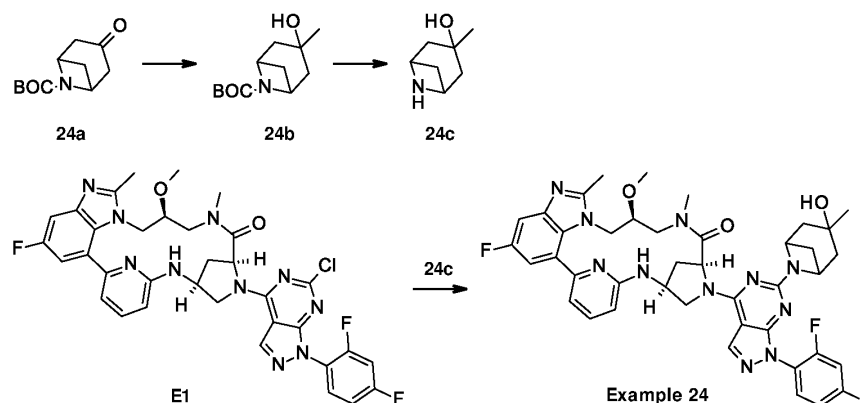
Example 23, LCMS (M+H)⁺: 832, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.32 (s, 1H), 7.85 - 7.77 (m, 1H), 7.71 - 7.63 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.24 (ddd, *J* = 2.7, 8.8, 10.3 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.82 (dd, *J* = 4.3, 15.5 Hz, 1H), 5.48 (br d, *J* = 8.6 Hz, 1H), 4.67 - 4.61 (m, 1H), 4.61 - 4.54 (m, 1H), 4.41 (dd, *J* = 6.3, 11.4 Hz, 1H), 4.31 - 4.24 (m, 1H), 4.23 - 4.05 (m, 4H), 4.02 - 3.89 (m, 1H), 3.43 - 3.33 (m, 1H), 3.10 - 3.04 (m, 3H), 3.03 - 2.95 (m, 1H), 2.94 - 2.87 (m, 1H), 2.87 - 2.83 (m, 3H), 2.83 - 2.77 (m, 2H), 2.60 (s, 3H), 2.57 - 2.47 (m, 2H), 2.46 - 2.33 (m, 2H), 1.77 (d, *J* = 8.9 Hz, 1H).

Example 24

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-3-methyl-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



The title compound was prepared according to the following scheme:



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Step 1: preparation of *tert*-butyl 3-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound 24b)

The flask contained compound **24a** (20 mg, 94.67 μmol) was cooled with dry ice/ethanol bath and methylmagnesium bromide (1 M in THF) (600 μL, 600 μmol) was added portion-wise. The final mixture was warmed to r.t. slowly and stirred for 1 hr. The reaction was quenched with

20

ice and then diluted with EA and water. The two-phase mixture was separated and the organic layer was dried and concentrated. The compound **24b** (32 mg) was obtained as a crude oil and used in the next step directly. LCMS (M+H)⁺: 228.

Step 2: preparation of 3-methyl-6-azabicyclo[3.1.1]heptan-3-ol (compound 24c)

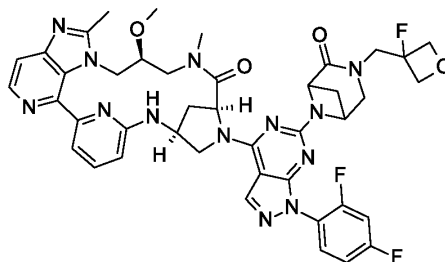
To the flask contained compound **24b** (32 mg, 140.78 μmol) was added dichloromethane (1 mL) and TFA (1.48 g, 1 mL, 12.98 mmol). The solution was stirred at r.t. for 1 hr and concentrated to give compound **24c** (45 mg) as a yellow oil, which was used in the next step directly. LCMS (M+H)⁺: 128.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-3-methyl-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 24)

To a tube was added intermediate **E1** (40 mg, 56.89 μmol), DIEA (44 mg, 60 μL, 343.55 μmol), compound **24c** (45 mg, 139.92 μmol) and DMSO (1.5 mL). The solution was stirred at 110 °C for 16 hrs. The mixture was purified via prep-HPLC to give Example **24** (25 mg) as a white powder. LCMS (M+H)⁺: 794, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.26 (s, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.65 - 7.57 (m, 1H), 7.48 (dd, *J* = 2.6, 7.7 Hz, 1H), 7.40 (dd, *J* = 2.6, 10.4 Hz, 1H), 7.23 (ddd, *J* = 2.8, 8.8, 10.3 Hz, 1H), 7.19 - 7.11 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.13 (dd, *J* = 4.6, 15.6 Hz, 1H), 5.38 (d, *J* = 8.9 Hz, 1H), 4.66 (t, *J* = 4.9 Hz, 1H), 4.46 (dd, *J* = 6.1, 11.2 Hz, 1H), 4.39 - 4.11 (m, 4H), 4.01 - 3.85 (m, 1H), 3.14 - 3.03 (m, 3H), 2.99 (br d, *J* = 12.9 Hz, 1H), 2.95 - 2.91 (m, 3H), 2.77 - 2.69 (m, 4H), 2.68 - 2.61 (m, 1H), 2.61 - 2.46 (m, 3H), 2.44 - 2.33 (m, 1H), 2.21 (d, *J* = 8.1 Hz, 1H), 1.88 - 1.68 (m, 2H), 1.06 (s, 3H).

Example 26

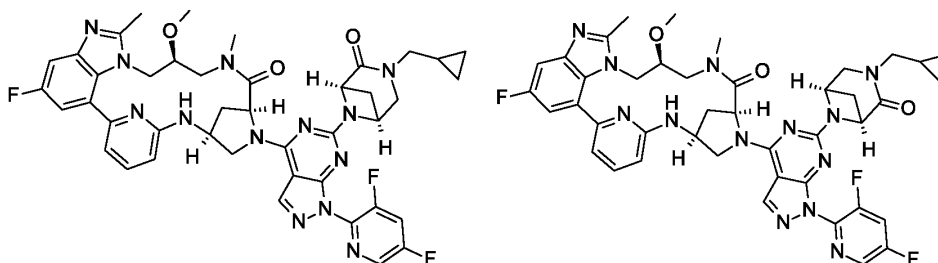
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[(3-fluorooxetan-3-yl)methyl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **26** was prepared in analogy to the preparation of Example **3** by using compound 3-fluoro-3-(iodomethyl)oxetane instead of 2,2-difluoroethyl trifluoromethanesulfonate. LCMS (M+H)⁺: 850, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.39 - 8.18 (m, 2H), 7.90 - 7.82 (m, 1H), 7.66 - 7.53 (m, 2H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.20 - 7.12 (m, 1H), 6.74 (dd, *J* = 8.3, 19.3 Hz, 1H), 6.09 - 5.94 (m, 1H), 5.48 - 5.34 (m, 1H), 4.71 - 4.40 (m, 6H), 4.39 - 4.01 (m, 6H), 4.00 - 3.75 (m, 2H), 3.42 - 3.32 (m, 2H), 3.19 - 3.04 (m, 3H), 3.00 - 2.91 (m, 1H), 2.90 - 2.81 (m, 3H), 2.81 - 2.72 (m, 1H), 2.72 - 2.59 (m, 3H), 2.59 - 2.39 (m, 2H), 1.86 - 1.73 (m, 1H).

Example 27 and Example 28

(8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-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 and (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-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 **27** and Example **28** were prepared in analogy to the preparation of Example **3** and Example **4** by using intermediate **E16** instead of intermediate **E1** and iodomethylcyclopropane instead of 2,2-difluoroethyl trifluoromethanesulfonate. The mixture was separated via SFC to give Example **27** (14 mg, faster eluted) and Example **28** (11 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: Ethyl pyridine II 250 × 30 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for IPA «Mobile_phasePrep»; Gradient: B 25%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column temperature: 35 °C).

Example **27**, LCMS (M+H)⁺: 834, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.46 (br s, 1H), 8.37 (s, 1H), 7.93 (br t, *J* = 6.9 Hz, 1H), 7.86 - 7.78 (m, 1H), 7.39 (dd, *J* = 2.1, 8.0 Hz, 1H), 7.28 (br dd, *J* = 2.3, 10.4 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.96 (dd, *J*

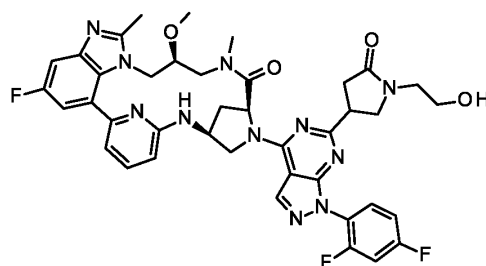
-120-

= 4.6, 15.4 Hz, 1H), 5.42 (d, $J = 8.9$ Hz, 1H), 4.68 - 4.64 (m, 1H), 4.60 - 4.53 (m, 1H), 4.48 - 4.38 (m, 1H), 4.34 - 4.32 (m, 1H), 4.30 (dd, $J = 1.9, 4.0$ Hz, 1H), 4.28 - 4.22 (m, 1H), 4.20 - 4.13 (m, 3H), 4.12 - 4.02 (m, 2H), 3.98 - 3.85 (m, 1H), 3.14 - 3.05 (m, 3H), 3.00 - 2.93 (m, 1H), 2.91 - 2.85 (m, 3H), 2.81 - 2.77 (m, 1H), 2.69 - 2.62 (m, 3H), 2.57 - 2.40 (m, 2H), 1.75 (d, $J = 8.8$ Hz, 1H), 0.68 - 0.50 (m, 1H), 0.24 - -0.18 (m, 4H).

Example 28, LCMS (M+H)⁺: 834, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.46 (br s, 1H), 8.37 (s, 1H), 7.98 - 7.89 (m, 1H), 7.87 - 7.77 (m, 1H), 7.39 (dd, $J = 2.4, 8.1$ Hz, 1H), 7.30 (br dd, $J = 2.4, 10.4$ Hz, 1H), 7.16 - 7.08 (m, 1H), 6.74 - 6.65 (m, 1H), 5.93 (dd, $J = 4.3, 15.4$ Hz, 1H), 5.47 (d, $J = 8.8$ Hz, 1H), 4.68 - 4.55 (m, 2H), 4.50 - 4.40 (m, 1H), 4.30 - 4.23 (m, 1H), 4.23 - 3.89 (m, 4H), 3.59 - 3.34 (m, 2H), 3.12 - 3.01 (m, 3H), 3.00 - 2.91 (m, 1H), 2.90 - 2.82 (m, 4H), 2.82 - 2.70 (m, 2H), 2.68 - 2.61 (m, 3H), 2.60 - 2.39 (m, 2H), 1.74 (d, $J = 8.8$ Hz, 1H), 0.90 - 0.54 (m, 1H), 0.34 - -0.12 (m, 4H).

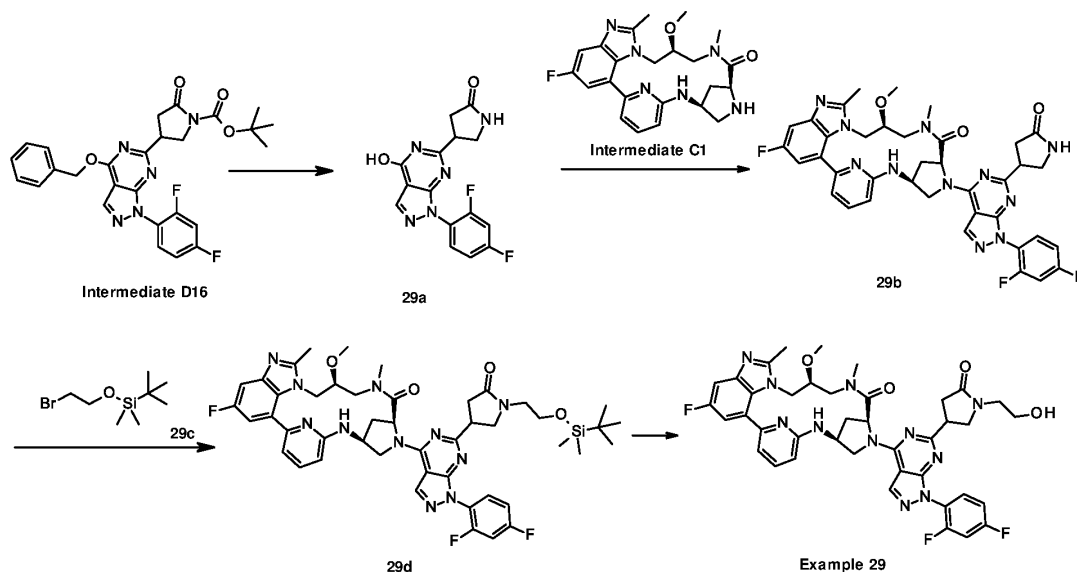
Example 29

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-hydroxyethyl)-5-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

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Step 1: preparation of 4-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-2-one (compound 29a)

To a solution of compound Intermediate **D16** (100.0 mg, 0.19 mmol) in DCM (2 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h and then concentrated to give compound **29a** (100.0 mg) as light yellow oil, which was used directly without further purification. LCMS ($M+H^+$): 332.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(5-oxopyrrolidin-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 29b)

To a solution of compound **29a** (100.0 mg, 0.3 mmol), PyBOP (48 mg, 0.09 mmol) in DMF (0.5 mL) was added DIEA (0.03 mL, 0.15 mmol) at 25 °C. The reaction was stirred at 25 °C for 0.5 h and then a mixture of compound Intermediate **C1** (150 mg, 0.27 mmol), DIEA (0.03 mL, 0.15 mmol) in DMF (0.5 mL) was added and stirred at 25 °C for 2 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by prep-TLC to give compound **29b** (70.0 mg) as a light yellow solid. LCMS ($M+H^+$): 752.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[6-[1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-oxo-pyrrolidin-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 29d)

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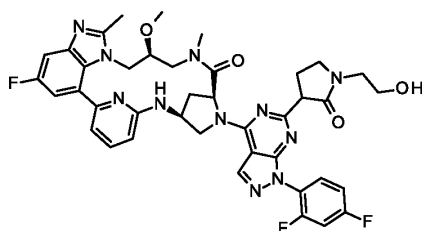
To a solution of compound **29b** (50.0 mg, 0.07 mmol) in DMF (1 mL) was added NaH (5 mg, 0.2 mmol) at 0 °C under N₂. After being stirred at 0 °C for 2 h, a solution of compound **29c** (24 mg, 0.1 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 25 °C for 6 h, then quenched with ice-cold NH₄Cl solution and extracted with EtOAc. The organic layer was
 5 dried and concentrated, the residue was purified by prep-TLC to give compound **29d** (25.0 mg) as a light yellow solid. LCMS (M+H⁺): 910.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-hydroxyethyl)-5-oxo-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-
 10 **1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 29)**

To a solution of compound **29d** (25.0 mg, 0.03 mmol) in THF (1 mL) was added TBAF in THF (0.05 mL, 0.07 mmol) at 0 °C. The reaction was stirred at 25 °C for 2 h and then diluted with water. The aqueous layer was extracted with EtOAc, the organic layer was washed with brine, dried and concentrated. The crude product was purified by prep-HPLC to give Example **29**
 15 (8.0 mg) as a light yellow solid. LCMS (M+H⁺): 796. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 (d, *J* = 1.9 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.51 - 7.42 (m, 2H), 7.25 - 7.16 (m, 1H), 7.15 - 7.03 (m, 2H), 6.69 (br d, *J* = 8.3 Hz, 1H), 6.10 - 6.01 (m, 1H), 5.42 - 5.29 (m, 1H), 4.64 - 4.58 (m, 1H), 4.44 - 4.38 (m, 1H), 4.25 - 4.17 (m, 2H), 3.87 - 3.78 (m, 2H), 3.58 - 3.48 (m, 4H), 3.08 - 3.04 (m, 1H), 3.00 - 2.94 (m, 3H), 2.90 - 2.83 (m, 4H), 2.77 - 2.67 (m, 5H),
 20 2.50 - 2.42 (m, 2H), 1.64 - 1.53 (m, 1H), 1.34 - 1.30 (m, 1H).

Example 30

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[1-(2-hydroxyethyl)-2-oxo-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



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Example **30** was prepared in analogy to the preparation of Example **29** by using Intermediate **D17** instead of Intermediate **D16**. Example **30** (2.8 mg) as a white solid. LCMS (M+H⁺): 796. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.55 - 8.45 (m, 1H), 7.95 - 7.86 (m, 1H), 7.72 - 7.64 (m, 1H), 7.62 - 7.58 (m, 1H), 7.57 - 7.52 (m, 1H), 7.34 - 7.27 (m, 1H), 7.26 -

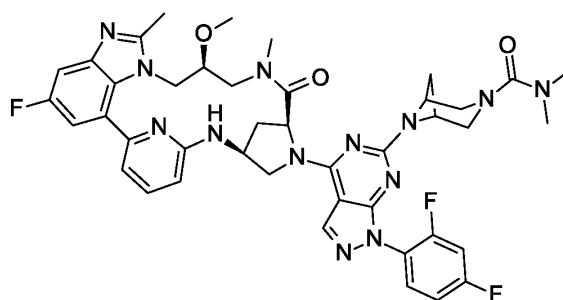
-123-

7.16 (m, 2H), 6.80 (d, $J = 8.5$ Hz, 1H), 6.22 - 6.13 (m, 1H), 5.45 (d, $J = 9.1$ Hz, 1H), 4.74 - 4.69 (m, 1H), 4.56 - 4.51 (m, 1H), 4.36 - 4.29 (m, 2H), 3.99 - 3.91 (m, 2H), 3.71 - 3.60 (m, 4H), 3.51 - 3.41 (m, 1H), 3.19 - 3.14 (m, 1H), 3.11 - 3.06 (m, 3H), 3.03 - 2.97 (m, 4H), 2.87 - 2.79 (m, 5H), 2.72 - 2.64 (m, 1H), 2.61 - 2.52 (m, 2H).

5

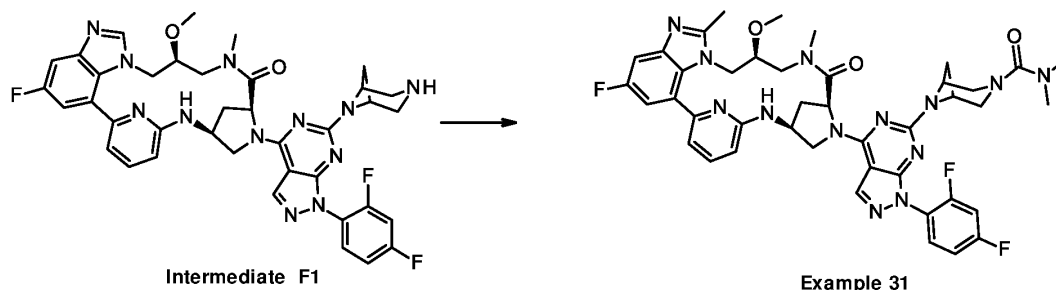
Example 31

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]-*N,N*-dimethyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide



10

The title compound was prepared according to the following scheme:

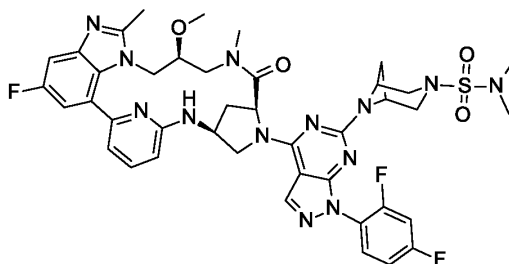


To a solution of Intermediate **F1** (40.0 mg, 0.05 mmol), TEA (60.0 mg, 0.59 mmol) in DCM (1 mL) was added dimethylcarbamyl chloride (0.01 mL, 0.05 mmol) at 0 °C. The reaction was stirred at 25 °C for 1 h and then concentrated. The residue was purified by prep-HPLC to give Example **31** (24 mg) as a white solid. LCMS ($M+H$)⁺: 836. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.91 - 7.83 (m, 1H), 7.65 - 7.53 (m, 3H), 7.30 - 7.12 (m, 3H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.27 - 6.04 (m, 1H), 5.42 - 5.31 (m, 1H), 4.67 (t, $J = 4.7$ Hz, 1H), 4.46 (d, $J = 5.9, 11.4$ Hz, 1H), 4.41 - 4.33 (m, 1H), 4.28 (d, $J = 7.1$ Hz, 2H), 4.26 - 4.15 (m, 2H), 4.07 - 3.87 (m, 2H), 3.55 - 3.41 (m, 2H), 3.17 - 3.10 (m, 1H), 3.09 - 3.02 (m, 3H), 3.00 - 2.97 (m, 3H), 2.88 - 2.81 (m, 3H), 2.76 (s, 1H), 2.74 - 2.68 (m, 6H), 2.67 - 2.61 (m, 1H), 2.61 - 2.47 (m, 2H), 1.61 - 1.50 (m, 1H).

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Example 32

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]-*N,N*-dimethyl-3,6-diazabicyclo[3.1.1]heptane-3-sulfonamide

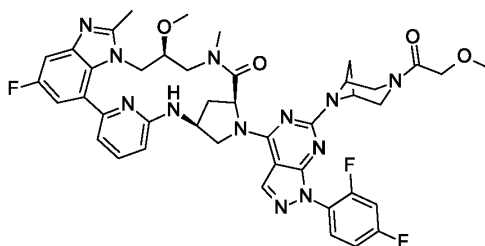


Example **32** was prepared in analogy to the preparation of Example **31** by using dimethylsulfamoylchloride instead of dimethylcarbamyl chloride. Example **32** (25 mg) was obtained as a white solid. LCMS (M+H)⁺: 872. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.28 (s, 1H), 7.87 - 7.81 (m, 1H), 7.62 - 7.55 (m, 2H), 7.54 - 7.48 (m, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.10 (m, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.23 (dd, *J* = 4.8, 15.4 Hz, 1H), 5.31 (d, *J* = 9.0 Hz, 1H), 4.62 (t, *J* = 4.6 Hz, 1H), 4.47 - 4.36 (m, 2H), 4.30 (br s, 2H), 4.22 (br d, *J* = 11.3 Hz, 1H), 4.10 - 3.91 (m, 3H), 3.26 - 3.09 (m, 2H), 3.02 (s, 3H), 2.97 - 2.92 (m, 4H), 2.81 - 2.78 (m, 3H), 2.73 - 2.62 (m, 2H), 2.51 (s, 7H), 2.50 - 2.44 (m, 1H), 1.61 - 1.52 (m, 1H).

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Example 33

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyacetyl)-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



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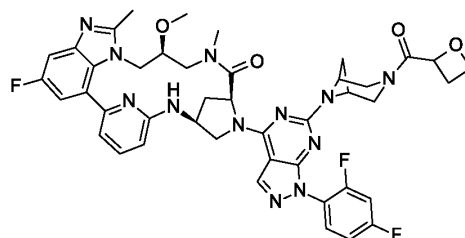
Example **33** was prepared in analogy to the preparation of Example **31** by using methoxyacetyl chloride instead of dimethylcarbamyl chloride. Example **33** (25 mg) was obtained as a white solid. LCMS (M+H)⁺:837. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.29 (d, *J* = 1.4

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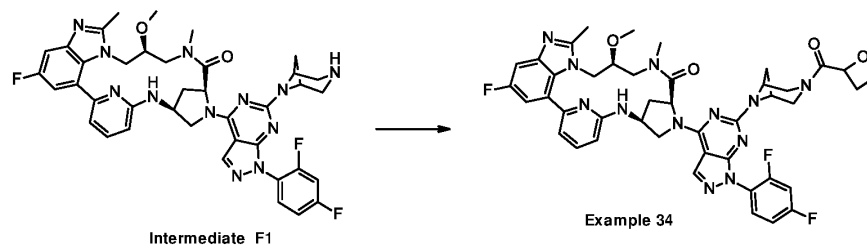
Hz, 1H), 7.87 (dt, $J = 4.2, 8.0$ Hz, 1H), 7.67 - 7.52 (m, 3H), 7.30 - 7.22 (m, 1H), 7.21 - 7.12 (m, 2H), 6.78 (d, $J = 5.6, 8.4$ Hz, 1H), 6.28 - 6.04 (m, 1H), 5.41 - 5.31 (m, 1H), 4.65 (m, 1H), 4.46 (d, $J = 5.7, 11.3$ Hz, 2H), 4.33 (d, $J = 5.1$ Hz, 2H), 4.31 - 4.17 (m, 4H), 4.17 - 4.11 (m, 1H), 4.00 - 3.91 (m, 1H), 3.57 - 3.43 (m, 2H), 3.38 - 3.34 (m, 3H), 3.14 (s, 1H), 3.07 (s, 3H), 3.02 - 2.97 (m, 3H), 2.92 (s, 1H), 2.88 - 2.81 (m, 2H), 2.80 - 2.67 (m, 2H), 2.63 - 2.48 (m, 2H), 1.64 - 1.51 (m, 1H).

Example 34

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetane-2-carbonyl)-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:

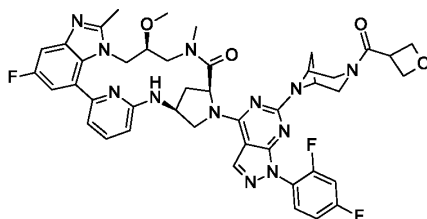


To a solution of Intermediate **F1** (40.0 mg, 0.05 mmol), HATU (21 mg, 0.05 mmol), DIEA (0.03 mL, 0.18 mmol) in MeCN (0.5 mL) was added a mixture of oxetane-2-carboxylic acid (6 mg, 0.05 mmol) in MeCN (0.5 mL). The reaction was stirred at 0° C for 0.2 h, then stirred at 20 °C for 5h. The reaction solution was purified by prep-HPLC to give Example **34** (13 mg) as a white solid. LCMS ($M+H$)⁺: 849. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.33 - 8.22 (m, 1H), 7.87 - 7.78 (m, 1H), 7.65 - 7.58 (m, 1H), 7.34 - 7.23 (m, 2H), 7.21 - 7.08 (m, 3H), 6.69 (t, $J = 8.0$ Hz, 1H), 5.96 - 5.62 (m, 1H), 5.40 - 5.35 (m, 1H), 4.73 - 4.61 (m, 2H), 4.60 - 4.39 (m, 3H), 4.36 - 4.18 (m, 5H), 4.12 - 3.91 (m, 2H), 3.65 - 3.52 (m, 1H), 3.51 - 3.37 (m, 2H), 3.09 - 3.00 (m, 3H), 2.98 - 2.93 (m, 1H), 2.90 - 2.82 (m, 4H), 2.81 - 2.74 (m, 1H), 2.71 - 2.64 (m, 3H), 2.59 - 2.56 (m, 1H), 2.55 - 2.42 (m, 2H), 1.63 - 1.53 (m, 1H).

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Example 35

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetane-3-carbonyl)-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

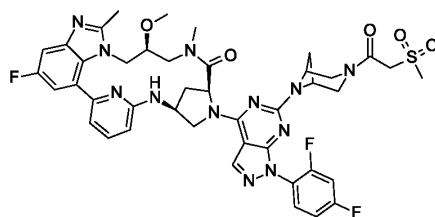


Example **35** was prepared in analogy to the preparation of Example **34** by using oxetane-3-carboxylic acid instead of oxetane-2-carboxylic acid. Example **35** (18 mg) was obtained as a white solid. LCMS (M+H)⁺: 849. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.34 - 8.27 (m, 1H), 7.87 - 7.79 (m, 1H), 7.66 - 7.59 (m, 1H), 7.35 - 7.24 (m, 2H), 7.22 - 7.08 (m, 3H), 6.75 - 6.65 (m, 1H), 5.95 - 5.65 (m, 1H), 5.44 - 5.30 (m, 1H), 4.71 - 4.57 (m, 2H), 4.54 - 4.39 (m, 2H), 4.34 - 4.19 (m, 5H), 4.16 - 4.07 (m, 1H), 4.02 (s, 1H), 3.52 - 3.36 (m, 2H), 3.22 - 3.10 (m, 2H), 3.09 - 3.03 (m, 3H), 3.00 (s, 1H), 2.91 - 2.81 (m, 4H), 2.81 - 2.71 (m, 1H), 2.71 - 2.65 (m, 3H), 2.61 - 2.43 (m, 3H), 1.60 - 1.50 (m, 1H).

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Example 36

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methylsulfonylacetyl)-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



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Example **36** was prepared in analogy to the preparation of Example **34** by using methanesulfonylacetic acid instead of oxetane-2-carboxylic acid. Example **36** (15 mg) was obtained as a white solid. LCMS (M+H)⁺: 885. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.35 - 8.25 (m, 1H), 7.87 - 7.77 (m, 1H), 7.72 - 7.59 (m, 1H), 7.34 - 7.23 (m, 2H), 7.21 - 7.12 (m, 2H), 7.11 - 7.04 (m, 1H), 6.75 - 6.64 (m, 1H), 5.90 - 5.67 (m, 1H), 5.47 - 5.26 (m, 1H), 4.71 - 4.60 (m,

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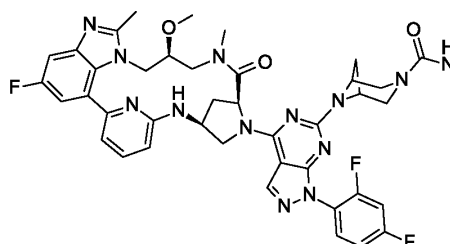
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1H), 4.45 (d, $J = 6.2, 11.4$ Hz, 1H), 4.42 - 4.21 (m, 5H), 4.21 - 4.10 (m, 1H), 4.10 - 3.98 (m, 1H), 3.77 - 3.61 (m, 1H), 3.57 - 3.44 (m, 1H), 3.17 - 3.10 (m, 1H), 3.10 - 3.03 (m, 5H), 3.02 - 2.90 (m, 2H), 2.90 - 2.81 (m, 4H), 2.78 (d, $J = 14.8$ Hz, 1H), 2.74 - 2.67 (m, 1H), 2.66 - 2.57 (m, 3H), 2.55 - 2.43 (m, 2H), 1.63 - 1.52 (m, 1H).

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Example 37

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]-*N*-methyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide



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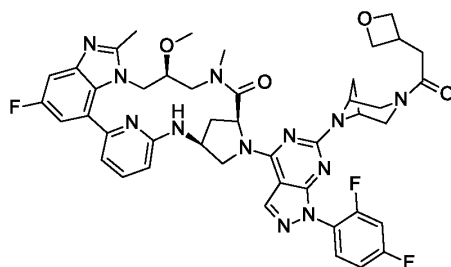
Example **37** was prepared in analogy to the preparation of Example **31** by using methylaminoformyl chloride instead of dimethylcarbonyl chloride. Example **37** (28 mg) was obtained as a white solid. LCMS ($M+H$)⁺: 822. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.33 - 8.24 (m, 1H), 7.90 - 7.83 (m, 1H), 7.67 - 7.57 (m, 2H), 7.56 - 7.52 (m, 1H), 7.27 - 7.19 (m, 1H), 7.18 - 7.11 (m, 2H), 6.81 - 6.73 (m, 1H), 6.28 - 6.01 (m, 1H), 5.42 - 5.29 (m, 1H), 4.65 (t, $J = 4.5$ Hz, 1H), 4.46 (d, $J = 6.1, 11.2$ Hz, 2H), 4.38 - 4.28 (m, 2H), 4.27 - 4.15 (m, 2H), 3.97 - 3.90 (m, 1H), 3.51 - 3.34 (m, 1H), 3.28 - 3.18 (m, 1H), 3.14 (s, 1H), 3.10 - 3.01 (m, 3H), 3.01 - 2.94 (m, 4H), 2.91 - 2.81 (m, 3H), 2.78 - 2.71 (m, 1H), 2.70 - 2.60 (m, 4H), 2.60 - 2.46 (m, 2H), 1.61 - 1.47 (m, 1H).

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Example 38

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(oxetan-3-yl)acetyl]-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

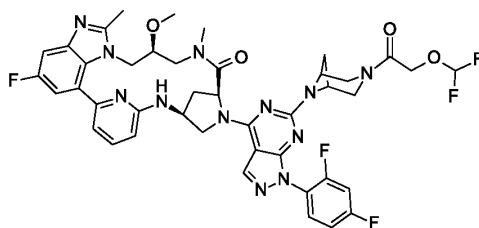
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Example **38** was prepared in analogy to the preparation of Example **34** by using 2-(oxetan-3-yl)acetic acid instead of oxetane-2-carboxylic acid. Example **38** (13 mg) was obtained as a white solid. LCMS (M+H)⁺: 863. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 - 8.23 (m, 1H), 7.87 - 7.76 (m, 1H), 7.66 - 7.58 (m, 1H), 7.35 - 7.22 (m, 2H), 7.21 - 7.07 (m, 3H), 6.74 - 6.62 (m, 1H), 5.93 - 5.65 (m, 1H), 5.47 - 5.25 (m, 1H), 4.81 - 4.71 (m, 2H), 4.69 - 4.59 (m, 1H), 4.49 - 4.43 (m, 1H), 4.43 - 4.28 (m, 3H), 4.28 - 4.12 (m, 4H), 4.00 - 3.88 (m, 1H), 3.46 - 3.36 (m, 1H), 3.14 - 3.10 (m, 1H), 3.04 (d, *J* = 5.3 Hz, 3H), 3.00 - 2.91 (m, 2H), 2.88 - 2.82 (m, 4H), 2.80 - 2.73 (m, 2H), 2.72 - 2.67 (m, 1H), 2.63 (s, 1H), 2.62 - 2.54 (m, 3H), 2.54 - 2.40 (m, 2H), 1.61 - 1.49 (m, 1H).

Example 39

(8*S*,11*S*,15*R*)-10-[6-[3-[2-(difluoromethoxy)acetyl]-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



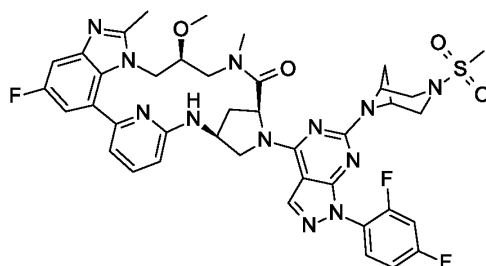
Example **39** was prepared in analogy to the preparation of Example **34** by using 2-(difluoromethoxy)acetic acid instead of oxetane-2-carboxylic acid. Example **39** (14 mg) was obtained as a white solid. LCMS (M+H)⁺: 873. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.36 (d, *J* = 3.3 Hz, 1H), 7.93 - 7.83 (m, 1H), 7.74 - 7.62 (m, 1H), 7.62 - 7.51 (m, 2H), 7.33 - 7.24 (m, 1H), 7.24 - 7.12 (m, 2H), 6.92 - 6.62 (m, 1H), 6.38 - 6.04 (m, 1H), 5.49 - 5.33 (m, 1H), 4.71 - 4.58 (m, 2H), 4.53 - 4.48 (m, 1H), 4.48 - 4.36 (m, 3H), 4.34 - 4.25 (m, 2H), 4.24 - 4.14 (m, 1H), 4.11 - 3.99 (m, 1H), 3.95 - 3.83 (m, 1H), 3.62 - 3.54 (m, 1H), 3.53 - 3.43 (m, 1H), 3.17 - 3.10 (m,

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1H), 3.10 - 3.04 (m, 3H), 3.04 - 2.95 (m, 4H), 2.94 - 2.85 (m, 2H), 2.85 - 2.79 (m, 2H), 2.79 - 2.72 (m, 1H), 2.66 - 2.47 (m, 2H), 1.68 - 1.57 (m, 1H).

Example 40

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methylsulfonyl-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}]hexacos-1(23),2(26),3,5,18,20(24), 21-heptaen-12-one

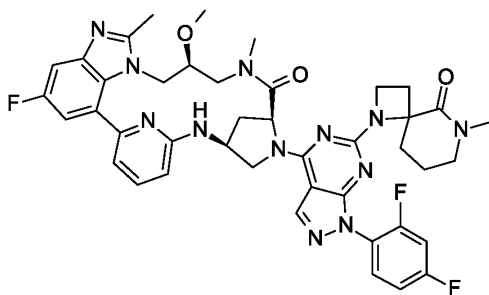


Example **40** was prepared in analogy to the preparation of Example **31** by using methanesulfonic anhydride instead of dimethylcarbamyl chloride. Example **40** (24 mg) was obtained as a white solid. LCMS (M+H)⁺: 843. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 (s, 1H), 7.91 - 7.83 (m, 1H), 7.65 (t, *J* = 5.9, 8.6 Hz, 1H), 7.60 (dd, *J* = 2.5, 7.3 Hz, 1H), 7.53 (dd, *J* = 2.5, 10.3 Hz, 1H), 7.29 (ddd, *J* = 2.7, 8.5, 10.7 Hz, 1H), 7.23 - 7.17 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.25 (dd, *J* = 4.8, 15.6 Hz, 1H), 5.35 (d, *J* = 9.0 Hz, 1H), 4.66 (t, *J* = 4.9 Hz, 1H), 4.53 - 4.43 (m, 2H), 4.37 - 4.28 (m, 2H), 4.25 (d, *J* = 11.0 Hz, 1H), 4.09 (dd, *J* = 8.9, 14.2 Hz, 1H), 4.04 - 3.94 (m, 2H), 3.38 (d, *J* = 11.3 Hz, 1H), 3.19 - 3.10 (m, 1H), 3.07 (s, 3H), 3.01 - 2.94 (m, 4H), 2.84 (s, 3H), 2.76 (d, *J* = 13.9 Hz, 1H), 2.70 - 2.63 (m, 1H), 2.60 - 2.49 (m, 2H), 2.47 (s, 3H), 1.61 (d, *J* = 8.9 Hz, 1H).

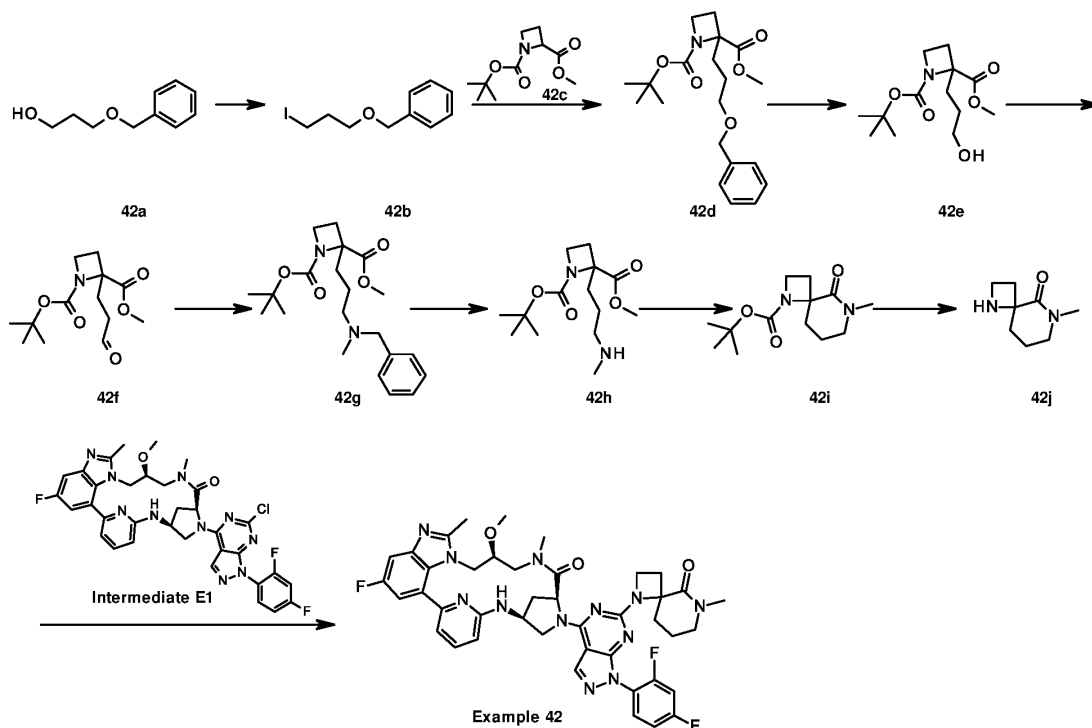
Example 42

(8*S*, 11*S*, 15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-methyl-9-oxo-1,8-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

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The title compound was prepared according to the following scheme:



5 Step 1: preparation of *tert*-butyl (2*S*)-2-(iodomethyl) morpholine-4-carboxylate (compound 42b)

To a solution of triphenylphosphine (16.42 g, 62.61 mmol) and 1*H*-imidazole (4.26 g, 62.61 mmol) in DCM (120 mL) was added iodine (15.89 g, 62.61 mmol) slowly at 0 °C under N₂. The reaction was stirred at 0° C for 0.5 h, then a solution of compound **42a** (8.0 g, 48.16 mmol) in DCM (40 mL) was added. After being stirred at 25 °C for 15 h under N₂, the reaction mixture was washed with water, the organic layer was concentrated and the residue was purified by silica gel column chromatography to give compound **42b** (10.2 g) as colorless oil.

Step 2: preparation of *O*1-*tert*-butyl *O*2-methyl 2-(3-benzyloxypropyl) azetidine-1, 2-dicarboxylate (compound 42d)

To a solution of LDA (14 mL, 28 mmol) in THF (50 mL) was added a solution of compound **42c** (5.0 g, 23 mmol) in THF (50 mL) slowly at -78 °C, then *N*-[bis(dimethylamino)phosphoryl]-*N*-methylmethanamine (8.33 g, 46.46 mmol) was added. After being stirred at -78 °C for 0.3 h, compound **42b** (16.03 g, 58.07 mmol) was added slowly, then the reaction mixture was stirred at 20 °C for 1 h. The reaction was quenched with NH₄Cl, extracted with EA, the organic layer was dried and concentrated. The residue was purified by silica gel column chromatography to give compound **42d** (2.67 g) as colorless oil.

Step 3: preparation of *O*1-*tert*-butyl *O*2-methyl 2-(3-hydroxypropyl) azetidine-1, 2-dicarboxylate (compound 42e)

A mixture of compound **42d** (1.0 g, 2.75 mmol) and Pd(OH)₂/C(300 mg) in methanol (15 mL) was stirred at 40 °C for 16 h under the H₂ (45 psi). Then the mixture was filtered and the filtrate was concentrated to give compound **42e** (700.0 mg) as light brown oil. LCMS (M-100+H)⁺: 174.

Step 4: preparation of *O*1-*tert*-butyl *O*2-methyl 2-(3-oxopropyl) azetidine-1, 2-dicarboxylate (compound 42f)

To a solution of compound **42e** (700.0 mg, 2.56 mmol) in DCM (40 mL) was added Dess-Martin periodinane (1303 mg, 3.07 mmol) at 0 °C. The reaction was stirred at 20 °C for 2 h, then the reaction was quenched with saturated sodium bicarbonate solution, and extracted with DCM. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography to give compound **42f** (500.0 mg) as colorless oil.

Step 5: preparation of *O*1-*tert*-butyl *O*2-methyl 2-[3-[benzyl (methyl) amino] propyl] azetidine-1, 2-dicarboxylate (compound 42g)

To a solution of compound **42f** (500.0 mg, 1.84 mmol) and *N*-methylbenzylamine (670 mg, 5.53 mmol) in methanol (7.5 mL) was added sodium cyanoborohydride (231 mg, 3.69 mmol) at 0 °C. The reaction was stirred at 20 °C for 2 h, then the reaction was quenched with water, and extracted with EtOAc. The organic layer was dried and concentrated, The residue was purified by silica gel column chromatography to give compound **42g** (240.0 mg) as colorless oil. LCMS (M+H)⁺: 377.

Step 6: preparation of *O*1-*tert*-butyl *O*2-methyl 2-[3-(methylamino) propyl] azetidine-1, 2-dicarboxylate (compound 42h)

A mixture of compound **42g** (100.0 mg, 0.27 mmol) and Pd(OH)₂/C (40 mg) in IPA (2.5 mL) and THF (10 mL) was stirred at 40 °C for 3 h under the H₂ (45 psi). Then the mixture was filtered and the filtrate was concentrated to give compound **42h** (75.0 mg) as colorless oil. LCMS (M+H)⁺: 287.

5 **Step 7: preparation of *tert*-butyl 8-methyl-9-oxo-1, 8-diazaspiro [3.5] nonane-1-carboxylate (compound 42i)**

To a solution of compound **42h** (75.0 mg, 0.26 mmol) in THF (10 mL) was added TBD (18 mg, 0.13 mmol) at 0 °C. The reaction was stirred at 20 °C for 1 h. The reaction solvent was concentrated and the residue was purified by silica gel column chromatography to give
10 compound **42i** (30.0 mg) as colorless oil. LCMS (M-56+H)⁺: 199.

Step 8: preparation of 8-methyl-1, 8-diazaspiro [3.5] nonan-9-one (compound 42j)

To a solution of compound **42i** (15.0 mg, 0.06 mmol) in DCM (0.5 mL) was added TFA (0.2 mL) at 0 °C. The reaction was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give compound **42j** (15 mg) as light brown oil, which was used in next step
15 directly.

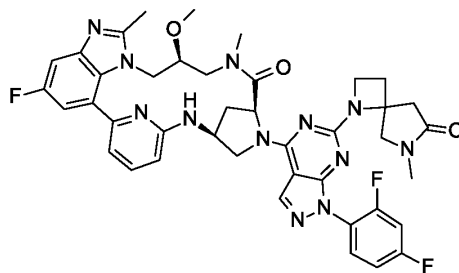
Step 9: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(8-methyl-9-oxo-1,8-diazaspiro[3.5]nonan -1-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26 -hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 42)

20 A solution of Intermediate **E1** (20.0 mg, 0.03 mmol), compound **42g** (15 mg, 0.06 mmol), CsF (21 mg, 0.14 mmol) and DIEA (0.05 mL, 0.28 mmol) in DMA (0.3 mL) was stirred at 120 °C for 12 h. The reaction was quenched with water, extracted with EA, the organic layer was dried and concentrated. The residue was purified by prep-HPLC to give Example **42** (10 mg) as a white solid. LCMS (M+H)⁺: 821. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.21 (d, *J* = 9.2
25 Hz, 1H), 7.83 - 7.75 (m, 1H), 7.60 - 7.51 (m, 1H), 7.32 - 7.19 (m, 2H), 7.18 - 7.11 (m, 2H), 7.07 (s, 1H), 6.65 (br d, *J* = 8.1 Hz, 1H), 5.87 - 5.64 (m, 1H), 5.46 - 5.20 (m, 1H), 4.61 - 4.52 (m, 1H), 4.46 - 4.34 (m, 1H), 4.26 - 4.02 (m, 4H), 3.98 - 3.87 (m, 2H), 3.66 - 3.50 (m, 1H), 3.20 (s, 1H), 3.08 (s, 2H), 3.01 (d, *J* = 11.1 Hz, 3H), 2.97 (s, 1H), 2.83 (d, *J* = 7.5 Hz, 3H), 2.79 - 2.68 (m, 2H), 2.61 - 2.53 (m, 4H), 2.50 - 2.41 (m, 2H), 2.29 - 2.07 (m, 2H), 2.06 - 1.67 (m, 2H).

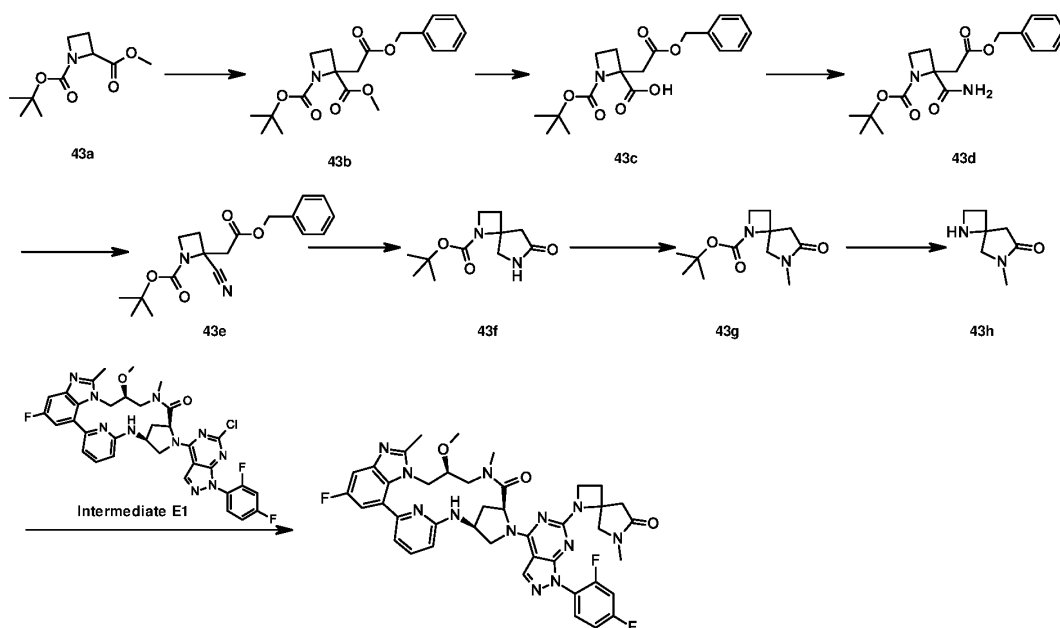
30 **Example 43**

(8*S*, 11*S*, 15*R*)-10-[1-(2,4-difluorophenyl)-6-(7-methyl-6-oxo-1,7-diazaspiro[3.4]octan-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

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The title compound was prepared according to the following scheme:



Example 43

Step 1: preparation of *tert*-butyl 2-(2-benzyloxy-2-oxo-ethyl)-2-(2-methoxyacetyl)

5 azetidine-1-carboxylate (compound 43b)

To a solution of LDA (13 mL, 26 mmol) in THF (50 mL) was added a solution of compound **43a** (5.0 g, 22 mmol) in THF (50 mL) slowly at -78 °C. The reaction was stirred at -78 °C for 1 h, and then a solution of HMPA (7.82 g, 43.62 mmol) in THF (5 mL) was added. After being stirred at -78 °C for 0.3 h, a solution of benzyl 2-bromoacetate (12.49 g, 54.52 mmol) in THF (25 mL) was added at -78 °C, then the reaction mixture was stirred at 20 °C for 1 h. The reaction was quenched with NH₄Cl, extracted with EA, the organic layer was dried and concentrated. The residue was purified by prep-HPLC to give compound **43b** (2 g) as light yellow oil. LCMS ([M-100+H⁺]: 264.

15 Step 2: preparation of 2-(2-benzyloxy-2-oxo-ethyl)-1-*tert*-butoxycarbonyl-azetidine-2-carboxylic acid (compound 43c)

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A mixture of compound **43b** (2 g, 5.5 mmol), lithium bromide (4.78 g, 55.04 mmol), TEA (2.78 g, 27.52 mmol) and water (0.5 mL, 27.52 mmol) in ACN (50 mL) was stirred at 20 °C for 3 h. The reaction mixture was concentrated and extracted with EA, the combined organic layer was dried and concentrated. The residue was purified by prep-HPLC to give compound **43c** (1.2 g) as yellow oil. LCMS ($[M-100+H]^+$): 250.

Step 3: preparation of *tert*-butyl 2-(2-benzyloxy-2-oxo-ethyl)-2-carbamoyl-azetidine-1-carboxylate (compound 43d)

A mixture of compound **43c** (1.2 g, 3.43 mmol), DIPEA (1.8 g, 13.8 mmol), ammonium chloride (5.5 g, 10.3 mmol) and HATU (1.5 g, 3.8 mmol) in DMF (17.5 mL) was stirred at 0 °C for 1 h. The reaction mixture was purified by prep-HPLC to afford compound **43d** (1 g) as yellow oil. LCMS ($[M-100+H]^+$): 249.

Step 4: preparation of *tert*-butyl 2-(2-benzyloxy-2-oxo-ethyl)-2-cyano-azetidine-1-carboxylate (compound 43e)

To a solution of compound **43d** (750.0 mg, 2.15 mmol) in DCM (15 mL) was added pyridine (0.7 mL, 8.61 mmol) and TFAA (904 mg, 4.31 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated. The residue was purified by silica gel column chromatography to give compound **43e** (750.0 mg) as yellow oil. LCMS ($[M-56+H]^+$): 275.

Step 5: preparation of *tert*-butyl 6-oxo-1, 7-diazaspiro [3.4] octane-1-carboxylate (compound 43f)

To a solution of compound **43e** (400.0 mg, 1.21 mmol) in methanol (17 mL) was added $CoCl_2 \cdot 6H_2O$ (216 mg, 0.91 mmol) and $NaBH_4$ (460 mg, 12.11 mmol) at -40 °C. After being stirred at -30 °C for 2 hrs, the reaction mixture was quenched with water and then filtered. The filtrate was concentrated and the residue was purified by prep-HPLC to give compound **43f** (450.0 mg) as light red oil. LCMS ($[M-56+H]^+$): 171.

Step 6: preparation of *tert*-butyl 7-methyl-6-oxo-1, 7-diazaspiro [3.4] octane-1-carboxylate (compound 43g)

To a mixture of compound **43f** (50.0 mg, 0.22 mmol) and sodium hydroxide (22 mg, 0.33 mmol) in DMF (1 mL) was added iodomethane (38 mg, 0.27 mmol) at -10 °C and then stirred for 0.5 h. The reaction mixture was purified by prep-HPLC to give compound **43g** (13.0 mg) as colorless oil. LCMS ($[M-56+H]^+$): 185.

Step 7: preparation of 7-methyl-1, 7-diazaspiro [3.4] octan-6-one (compound 43h)

To a solution of compound **43g** (13.0 mg, 0.05 mmol) in DCM (0.6 mL) was added TFA (0.5 mL, 0.02 mmol) at 0 °C. The reaction was stirred at 20 °C for 0.5 h. The reaction mixture

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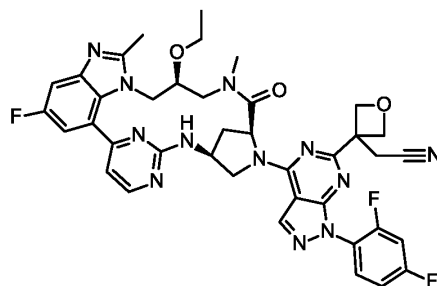
was concentrated to give compound **43h** (13.0 mg) as light brown oil, which was used for next step directly.

Step 8: preparation of (8*S*, 11*S*, 15*R*)-10-[1-(2,4-difluorophenyl)-6-(7-methyl-6-oxo-1,7-diazaspiro[3.4] octan-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 43)

A mixture of Intermediate **E1** (10 mg, 0.01 mmol), compound **43h** (11 mg, 0.04 mmol), DIEA (18 mg, 0.14 mmol) and CsF (11 mg, 0.07 mmol) in DMA (0.2 mL) was stirred at 120 °C for 16 h. Then the reaction mixture was purified by prep-HPLC to give Example **43** (2 mg) as a white solid. LCMS ($M+H^+$): 807. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.25 (s, 1H), 7.81 (s, 1H), 7.62 - 7.52 (m, 1H), 7.32 - 7.28 (m, 1H), 7.26 - 7.18 (m, 1H), 7.18 - 7.12 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.69 - 6.64 (m, 1H), 5.85 - 5.64 (m, 1H), 5.40 - 5.21 (m, 1H), 4.64 - 4.58 (m, 2H), 4.45 - 4.39 (m, 1H), 4.27 - 4.13 (m, 2H), 3.95 - 3.86 (m, 3H), 3.58 - 3.45 (m, 1H), 3.10 (s, 1H), 3.05 - 2.97 (m, 2H), 2.96 - 2.88 (m, 3H), 2.84 (d, *J* = 3.4 Hz, 4H), 2.59 - 2.55 (m, 4H), 2.54 - 2.37 (m, 6H).

Example 44

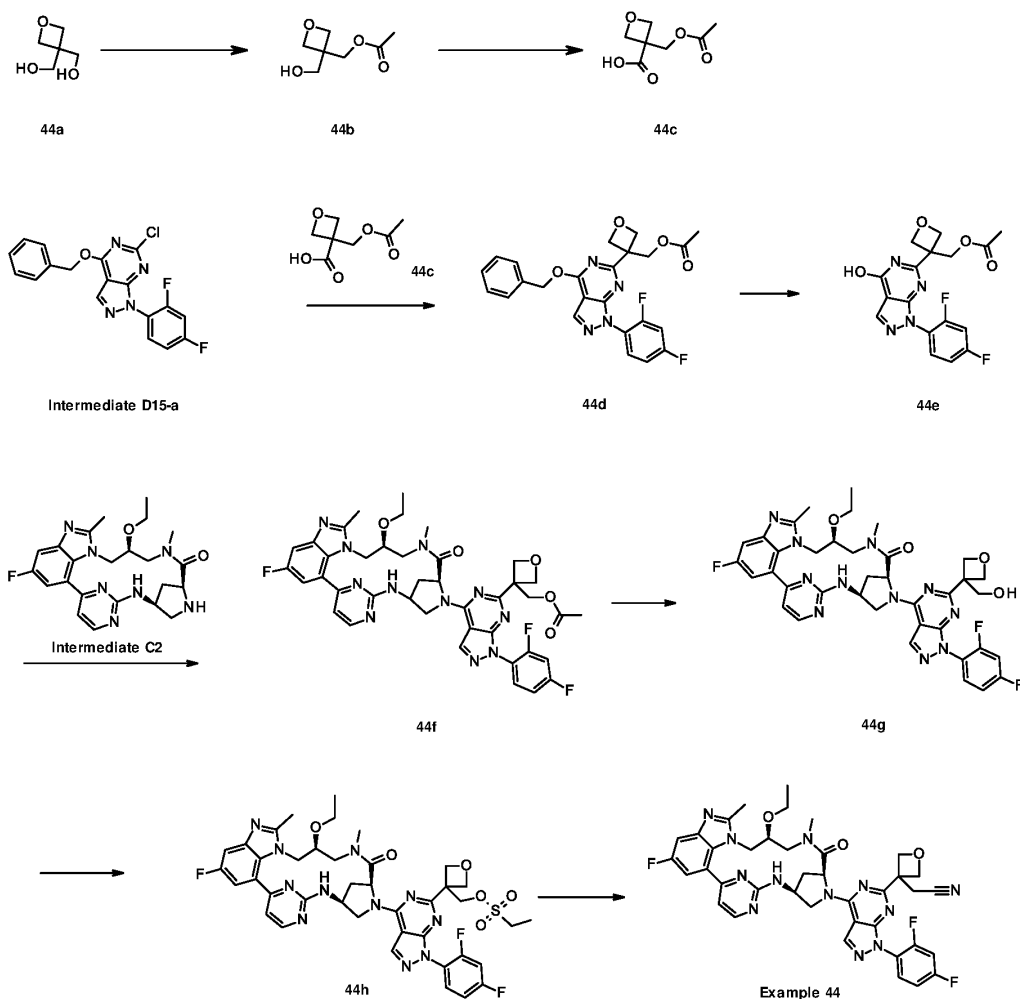
2-[3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]oxetan-3-yl]acetonitrile



20

The title compound was prepared according to the following scheme:

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Step 1: preparation of [3-(hydroxymethyl)oxetan-3-yl]methyl acetate (compound **44b**)

To a solution of compound **44a** (3 g, 25.4 mmol), TEA (11 mL, 76.3 mmol) and DMAP (310 mg, 2.54 mmol) in THF (50 mL) was added acetyl chloride (1.5 mL, 20.4 mmol) slowly at 0 °C. The reaction mixture was stirred at 25 °C for 16 h, and then it was poured into ice water and extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give compound **44b** (1 g) as light yellow oil.

Step 2: preparation of 3-(acetoxymethyl)oxetane-3-carboxylic acid (compound **44c**)

To a solution of compound **44b** (1 g, 6.24 mmol) in DCM (12 mL) and water (4 mL) was added (diacetoxyiodo)benzene (4 g, 12.5 mmol) and TEMPO (147 mg, 0.94 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 16 h, and then it was extracted with DCM. The organic layer was dried and concentrated, the residue was purified by prep-TLC to give compound **44c** (450.0 mg) as a light yellow solid.

Step 3: preparation of [3-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]oxetan-3-yl]methyl acetate (compound 44d)

To a 40 mL vial equipped with a stir bar was added Intermediate **D15-a** (100.0 mg, 0.27 mmol), compound **44c** (117 mg, 0.67 mmol), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (3 mg), NiCl₂(dtbbpy) (11 mg, 0.03 mmol), Cs₂CO₃ (262 mg, 0.8 mmol) in DMA (2 mL). The vial was sealed and placed under nitrogen, then the reaction mixture was stirred and irradiated with a 34 W blue LED lamp (7 cm away) with a cooling fan to keep the reaction temperature at 30 °C for 48 h. The reaction mixture was poured into water (10 ml), extracted with EA. The combined organic layer was dried and concentrated, the residue was purified by prep-HPLC to give compound **44d** (25.0 mg) as light yellow oil. LCMS (M+H⁺): 467.

Step 4: preparation of [3-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]oxetan-3-yl]methyl acetate (compound 44e)

To a solution of compound **44d** (25.0 mg, 0.05 mmol) in THF (3 mL) was added Pd/C (30 mg) at 25 °C under N₂. The reaction mixture was stirred at 25 °C for 2 h under the H₂ (balloon), then it was filtered and the filtrate was concentrated to give compound **44e** (20.0 mg) as colorless oil. LCMS (M+H⁺): 377.

Step 5: preparation of [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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]oxetan-3-yl]methyl acetate (compound 44f)

To a solution of compound **44e** (20.0 mg, 0.05 mmol), PyBOP (41 mg, 0.08 mmol) in DMF (0.2 mL) was added DIEA (0.02 mL, 0.13 mmol) at 25 °C. The reaction was stirred at 25 °C for 0.5 h, and then a mixture of Intermediate **C2** (28 mg, 0.06 mmol), DIEA (0.02 mL, 0.13 mmol) in DMF (0.2 mL) was added. After being stirred at 25 °C for 2 h, the reaction mixture was purified by prep-HPLC to give compound **44f** (10.0 mg) as a white solid. LCMS (M+H⁺): 812.

Step 6: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(hydroxymethyl)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(24),2(26),3,5,18,20,22-heptaen-12-one (compound 44g)

To a solution of compound **44f** (10.0 mg, 0.01 mmol) in methanol (0.5 mL) was added NaOH (0.5 mL, 0.05 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 2 h and then concentrated. The residue was diluted with water and extracted with EtOAc, the organic layer

was dried and was concentrated to give compound **44g** (5.0 mg) as a light yellow solid. LCMS ($M+2+H^+$): 770. Multiple batches were repeated and combined.

Step 7: preparation of [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-

5 **heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]oxetan-3-yl]methyl ethanesulfonate (compound **44h**)**

To a solution of TEA (16 mg, 0.16 mmol) and compound **44g** (40.0 mg, 0.05 mmol) in DCM (0.5 mL) was added ethanesulfonyl chloride (13.36 mg, 0.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated; the residue was purified by
10 prep-TLC to give compound **44h** (35.0 mg) as a light brown solid. LCMS ($M+H^+$): 862.

Step 8: preparation of 2-[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-

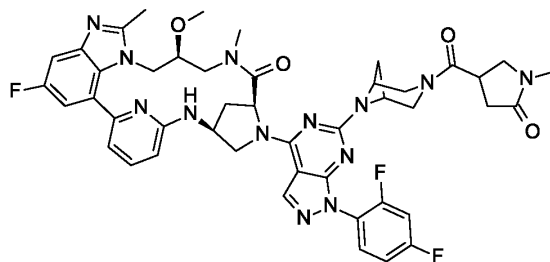
heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]oxetan-3-yl]acetonitrile (Example **44)**

15 To a solution of compound **44h** (35.0 mg, 0.04 mmol) in DMF (0.8 mL) was added 18-crown-6 (1 mg, 0.0 mmol) and sodium cyanide (50.0 mg, 1.02 mmol). The reaction was stirred at 50 °C for 2 h, and then it was purified by prep-HPLC to afford Example **44** (22 mg) as a white solid. LCMS ($M+H^+$): 779. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.57 (d, *J* = 5.3 Hz, 1H), 8.51 (s, 1H), 7.75 - 7.65 (m, 1H), 7.40 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.32 - 7.24 (m, 2H), 7.23 - 7.15
20 (m, 1H), 7.14 - 7.09 (m, 1H), 5.66 - 5.37 (m, 2H), 5.23 - 5.04 (d, *J* = 6.0 Hz, 2H), 4.79 - 4.69 (d, *J* = 5.9 Hz, 1H), 4.62 - 4.60 (m, 3H), 4.36 (m, 1H), 4.33 (m, 1H), 4.20 - 4.10 (m, 1H), 3.96 (dd, *J* = 9.6, 14.1 Hz, 1H), 3.27 (d, *J* = 4.8 Hz, 2H), 3.16 - 3.02 (m, 4H), 2.95 - 2.86 (m, 1H), 2.65 - 2.61 (m, 2H), 2.61 - 2.59 (m, 3H), 2.58 (dt, *J* = 4.6, 9.1 Hz, 1H), 0.62 - 0.55 (m, 3H).

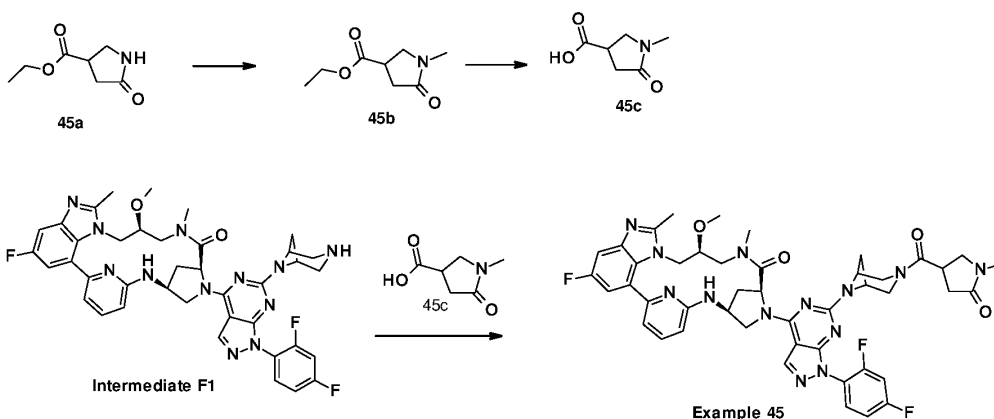
Example 45

25 **(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methyl-5-oxo-pyrrolidine-3-carbonyl)-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}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one**

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The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 1-methyl-5-oxo-pyrrolidine-3-carboxylate (compound 45b)

To a solution of compound **45a** (200.0 mg, 1.27 mmol) in DMF (2 mL) was added NaH (102 mg, 2.55 mmol) at 0 °C and then stirred at 10 °C for 1 h. Iodomethane (361 mg, 2.55 mmol) was added at 0 °C and then stirred at 10 °C for 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried and concentrated to give compound **45b** (150.0 mg) as brown oil.

Step 2: preparation of 1-methyl-5-oxo-pyrrolidine-3-carboxylic acid (compound 45c)

To a solution of compound **45b** (150.0 mg, 0.88 mmol) in THF (0.5 mL) and ethanol (0.5 mL) was added a solution of LiOH·H₂O (184 mg, 4.38 mmol) in water (0.5 mL) at 0 °C and then stirred at 10 °C for 1 h. The reaction mixture was acidified with HCl (12 M) to pH 2~3, extracted with EA, the organic layer was dried and concentrated to give compound **45c** (20.0 mg) as yellow oil.

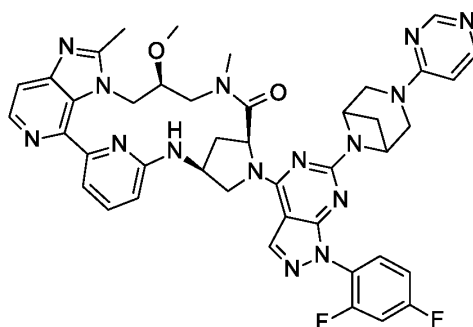
Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methyl-5-oxo-pyrrolidine-3-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-

hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one
(Example 45)

To a solution of Intermediate **F1** (50.0 mg, 0.06 mmol), compound **45c** (8 mg, 0.06 mmol), HATU (43 mg, 0.11 mmol) and DIPEA (0.1 mL, 0.57 mmol) in DMF (1 mL) was stirred at 10 °C for 1 h. The reaction mixture was purified by prep-HPLC to give Example **45** (16 mg) as a white solid. LCMS (M+H⁺): 890. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.32 (d, *J* = 3.8 Hz, 1H), 7.94 - 7.81 (m, 1H), 7.66 - 7.51 (m, 3H), 7.37 - 7.14 (m, 3H), 6.85 - 6.73 (m, 1H), 5.41 - 5.32 (m, 1H), 4.71 - 4.64 (m, 2H), 4.49 (br dd, *J* = 4.6, 10.4 Hz, 2H), 4.41 - 4.31 (m, 3H), 4.29 - 4.20 (m, 3H), 3.55 - 3.47 (m, 2H), 3.45 - 3.37 (m, 2H), 3.13 - 3.04 (m, 4H), 3.01 - 2.95 (m, 4H), 2.90 (br d, *J* = 9.4 Hz, 2H), 2.84 - 2.79 (m, 3H), 2.75 - 2.68 (m, 3H), 2.62 - 2.48 (m, 3H), 1.61 - 1.52 (m, 1H), 1.32 - 1.28 (m, 1H).

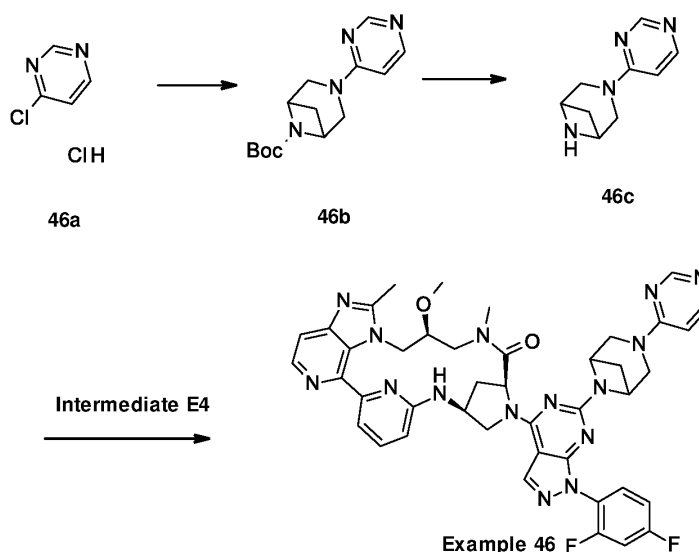
Example 46

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 3-pyrimidin-4-yl-3, 6-diazabicyclo [3.1.1]heptane-6-carboxylate (compound 46b)

A solution of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (300.0 mg, 1.51 mmol), compound **46a** (457 mg, 3.03 mmol), CsF (1914.0 mg, 7.56 mmol), DIEA (1170.0 mg, 9.05 mmol) in DMA (3 mL) was stirred at 120°C for 12 h. The reaction mixture was poured into H₂O, extracted with ethyl acetate. The organic layer was dried and concentrated to give compound **46b** (400.0 mg) as yellow oil. LCMS (M+H⁺): 277.

Step 2: preparation of 3-pyrimidin-4-yl-3, 6-diazabicyclo [3.1.1] heptane (compound 46c)

To a solution of compound **46b** (200.0 mg, 0.72 mmol) in DCM (1 mL) was added TFA (1.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h and then concentrated to give compound **46c** (200.0 mg) as yellow oil. LCMS (M+H⁺): 177.

Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosan-1(24),2(26),3,5,18,20,22-heptaen-12-one (Example 46)

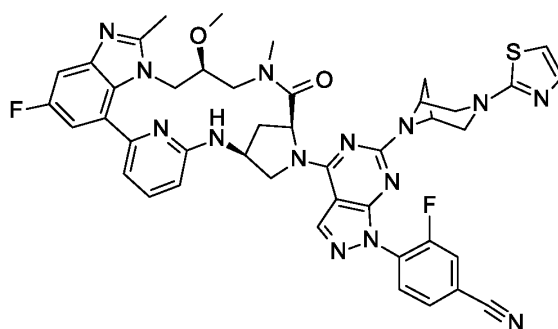
To a solution of Intermediate **E4** (40.0 mg, 0.06 mmol), compound **46c** (85 mg, 0.29 mmol), CsF (44.0 mg, 0.29 mmol) in DMA (0.5 mL) was added DIEA (0.06 mL, 0.34 mmol). The reaction was stirred at 120 °C for 15 hrs. Then the reaction mixture was purified by prep-HPLC to give Example **46** (9 mg) as a white solid. LCMS (M+H⁺): 826. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.52 - 8.40 (m, 1H), 8.39 - 8.34 (m, 1H), 8.24 (s, 1H), 8.11 (br d, *J* = 6.3

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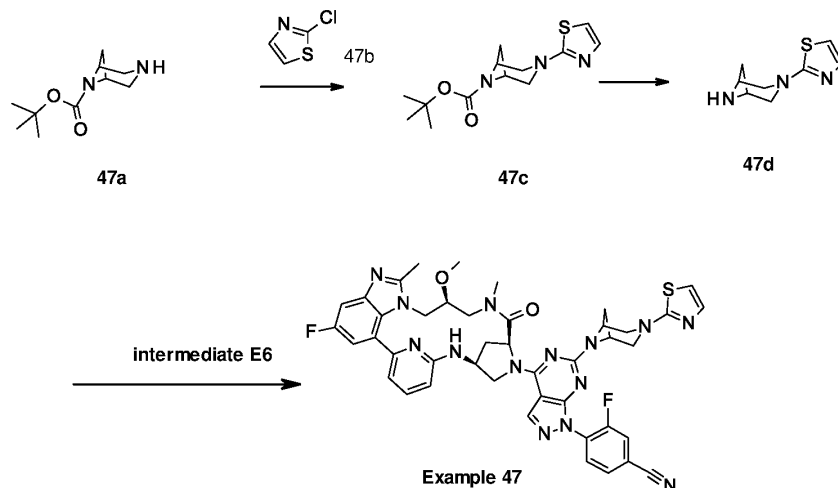
Hz, 1H), 7.86 (t, $J = 7.9$ Hz, 1H), 7.66 - 7.56 (m, 2H), 7.55 - 7.38 (m, 1H), 7.29 - 7.21 (m, 1H), 7.20 - 7.12 (m, 1H), 6.78 - 6.71 (m, 1H), 6.64 - 6.57 (m, 1H), 6.07 - 5.81 (m, 1H), 5.49 - 5.26 (m, 1H), 4.80 - 4.77 (m, 1H), 4.69 - 4.64 (m, 1H), 4.57 (br s, 6H), 4.45 (br d, $J = 5.9$ Hz, 2H), 4.22 - 4.14 (m, 2H), 3.12 - 3.06 (m, 3H), 2.89 (s, 2H), 2.81 (s, 1H), 2.78 - 2.67 (m, 4H), 2.65 - 2.60 (m, 2H), 2.56 - 2.46 (m, 1H), 1.68 - 1.57 (m, 1H).

Example 47

3-fluoro-4-[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]-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-1-yl]benzonitrile



The title compound was prepared according to the following scheme:



Example **47** was prepared in analogy to the preparation of Example **46** by using compound **47b** instead of compound **46a** and intermediate **E6** instead of intermediate **E4**. LCMS ($M+H^+$): 855. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.22 (s, 1H), 7.86 - 7.76 (m, 3H), 7.75 - 7.67 (m, 1H), 7.34 - 7.27 (m, 1H), 7.17 - 7.11 (m, 2H), 7.08 (d, $J = 7.4$ Hz, 1H), 6.64 - 6.60 (m, 2H), 5.79

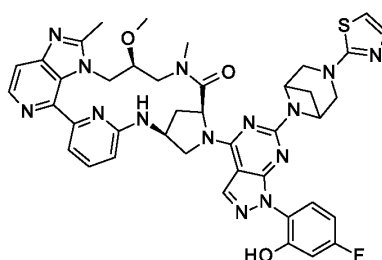
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(dd, $J = 4.4, 15.5$ Hz, 1H), 5.33 - 5.19 (m, 1H), 4.58 - 4.54 (m, 4H), 4.42 (br s, 1H), 4.37 - 4.31 (m, 2H), 4.27 - 4.08 (m, 4H), 4.00 (br d, $J = 9.5$ Hz, 1H), 3.51 - 3.42 (m, 1H), 3.08 - 3.01 (m, 3H), 3.00 - 2.93 (m, 1H), 2.85 (s, 2H), 2.81 - 2.67 (m, 2H), 2.61 (s, 2H), 2.52 - 2.43 (m, 2H), 1.71 - 1.58 (m, 1H).

5

Example 48

(8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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



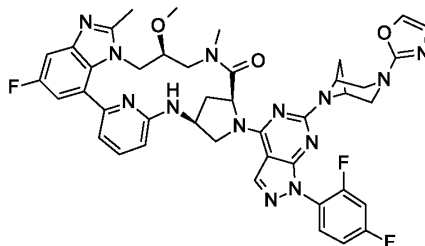
10

Example **48** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c** and intermediate **E7** instead of intermediate **E4**. LCMS ($M+H^+$): 829. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.39 - 8.34 (m, 1H), 8.16 (s, 1H), 7.87 - 7.80 (m, 1H), 7.66 - 7.60 (m, 2H), 7.45 - 7.35 (m, 1H), 7.12 (d, $J = 3.6$ Hz, 1H), 6.79 - 6.73 (m, 1H), 6.72 - 6.66 (m, 2H), 6.63 (br d, $J = 3.4$ Hz, 1H), 5.99 (dd, $J = 4.3, 15.3$ Hz, 1H), 5.34 - 5.15 (m, 1H), 4.57 (br s, 5H), 4.49 - 4.36 (m, 2H), 4.28 - 4.19 (m, 2H), 4.11 (br d, $J = 11.6$ Hz, 1H), 4.02 - 3.91 (m, 1H), 3.51 - 3.45 (m, 1H), 3.08 - 2.94 (m, 4H), 2.85 (s, 3H), 2.78 (s, 1H), 2.69 - 2.65 (m, 3H), 2.58 - 2.45 (m, 2H), 1.71 - 1.60 (m, 1H).

15

Example 49

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxazol-2-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

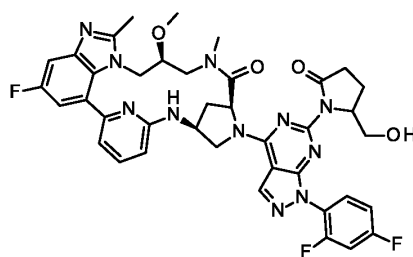


20

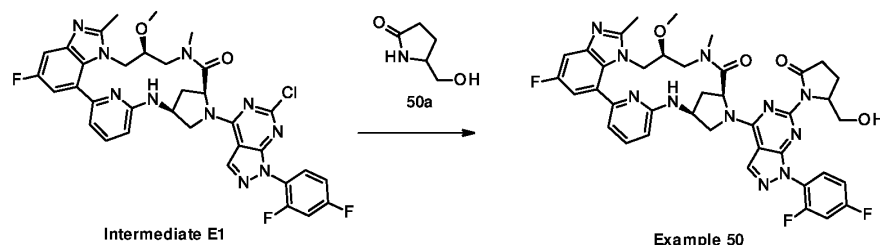
Example **49** was prepared in analogy to the preparation of Example **46** by using 2-iodooxazole instead of compound **46a** and intermediate **E1** instead of intermediate **E4**. LCMS (M+H⁺): 832. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.23 (s, 1H), 7.84 - 7.75 (m, 1H), 7.65 - 7.57 (m, 1H), 7.33 (s, 1H), 7.31 - 7.27 (m, 1H), 7.23 (br s, 1H), 7.15 (br dd, *J* = 2.6, 10.4 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.79 (s, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.82 (dd, *J* = 4.4, 15.6 Hz, 1H), 5.38 (d, *J* = 8.9 Hz, 1H), 4.65 - 4.56 (m, 1H), 4.38 (br d, *J* = 6.1 Hz, 2H), 4.24 - 4.00 (m, 5H), 3.48 (br d, *J* = 11.5 Hz, 1H), 3.16 - 2.99 (m, 4H), 2.98 - 2.89 (m, 1H), 2.86 (s, 3H), 2.80 - 2.68 (m, 2H), 2.61 (s, 3H), 2.51 - 2.41 (m, 2H), 1.63 (d, *J* = 8.8 Hz, 1H), 1.31 (br d, *J* = 18.5 Hz, 1H).

Example 50

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(hydroxymethyl)-5-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(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



15

A mixture of Intermediate **E1** (50.0 mg, 0.07 mmol), compound **50a** (33 mg, 0.28 mmol), K₃PO₄ (38 mg, 0.18 mmol), tris(dibenzylideneacetone)dipalladium (0) (19 mg, 0.02 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (16 mg, 0.03 mmol) in 1,4-dioxane (2 mL) was stirred at 110 °C for 1 h under nitrogen atmosphere. The reaction mixture was concentrated, the residue was purified by prep-HPLC to afford Example **50** (15 mg) as a white solid. LCMS (M+H⁺): 782. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.41 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.74 - 7.63 (m, 1H), 7.28 (s, 1H), 7.26 - 7.21 (m, 1H), 7.14 (br s, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.69 - 6.60 (m, 1H), 5.85 - 5.64 (m, 1H), 5.49 - 5.31 (m, 1H), 4.66 - 4.52 (m, 2H), 4.44 (br s, 1H), 4.28 (br d, *J* = 5.8 Hz, 1H), 4.15 - 4.09 (m, 1H), 3.98 - 3.92 (m, 1H), 3.88 (s, 1H), 3.68 - 3.59 (m,

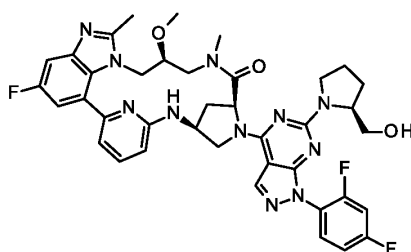
20

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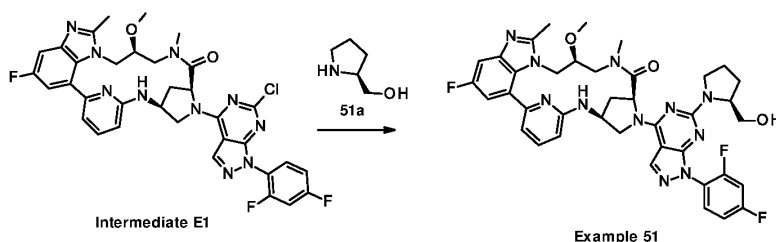
1H), 3.03 (br d, $J = 1.3$ Hz, 3H), 2.84 (s, 5H), 2.79 - 2.69 (m, 1H), 2.55 (s, 3H), 2.51 - 2.38 (m, 3H), 2.35 - 2.18 (m, 1H), 2.17 - 2.05 (m, 1H).

Example 51

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(2*S*)-2-(hydroxymethyl)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(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

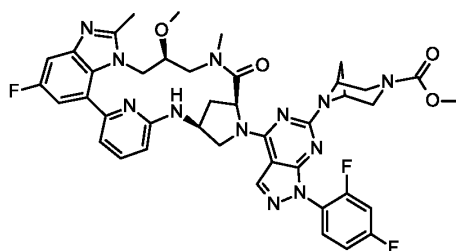


A solution of Intermediate **E1** (30.0 mg, 0.04 mmol), compound **51a** (22 mg, 0.21 mmol), CsF (32 mg, 0.21 mmol) and DIEA (0.07 mL, 0.43 mmol) in DMA (1 mL) was stirred at 120 °C for 12 h. The reaction mixture was purified by prep-HPLC to give Example **51** (10 mg) as a white solid. LCMS ($M+H^+$): 768. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.26 (s, 1H), 7.88 - 7.77 (m, 1H), 7.72 - 7.61 (m, 2H), 7.57 - 7.49 (m, 1H), 7.47 - 7.40 (m, 1H), 7.33 - 7.22 (m, 1H), 7.20 - 7.06 (m, 1H), 6.83 - 6.67 (m, 1H), 5.85 - 5.63 (m, 1H), 5.40 - 5.27 (m, 1H), 5.27 - 5.19 (m, 1H), 4.69 - 4.55 (m, 1H), 4.49 - 4.36 (m, 1H), 4.34 - 4.26 (m, 1H), 4.23 - 4.07 (m, 2H), 3.93 - 3.78 (m, 4H), 3.03 (s, 2H), 2.97 (s, 2H), 2.85 (s, 3H), 2.80 (s, 1H), 2.70 - 2.66 (m, 3H), 2.35 - 2.28 (m, 1H), 2.02 - 1.72 (m, 5H).

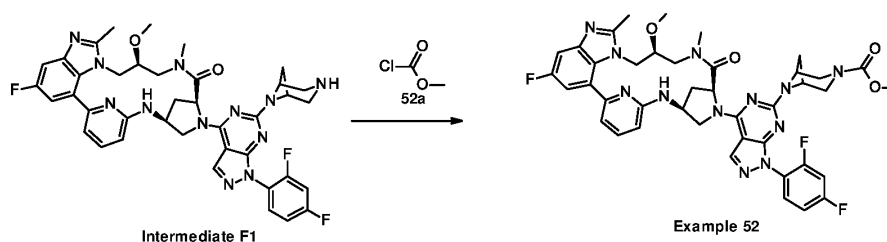
Example 52

methyl 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

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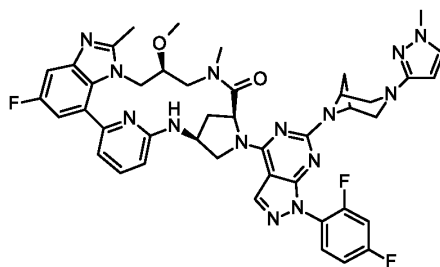
The title compound was prepared according to the following scheme:



To a solution of Intermediate **F1** (50.0 mg, 0.07 mmol), DIEA (0.06 mL, 0.33 mmol) in DCM (0.5 mL) was added compound **52a** (90.0 mg, 0.95 mmol) in DCM (0.5 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h and then concentrated. The residue was purified by prep-HPLC to afford Example **52** (12 mg) as a white solid. LCMS ($M+H^+$): 823. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.36 - 8.26 (m, 1H), 7.93 - 7.82 (m, 1H), 7.64 - 7.50 (m, 3H), 7.32 - 7.09 (m, 3H), 6.84 - 6.72 (m, 1H), 6.39 - 6.11 (m, 1H), 5.36 (d, J = 8.9 Hz, 1H), 4.74 - 4.61 (m, 1H), 4.57 - 4.42 (m, 2H), 4.31 (br d, J = 6.0 Hz, 2H), 4.28 - 4.21 (m, 1H), 4.02 (br t, J = 11.2 Hz, 2H), 3.71 (s, 1H), 3.67 (s, 2H), 3.64 - 3.60 (m, 1H), 3.10 - 3.05 (m, 3H), 3.02 - 2.97 (m, 3H), 2.92 - 2.81 (m, 3H), 2.79 - 2.73 (m, 1H), 2.72 - 2.61 (m, 2H), 2.60 - 2.45 (m, 2H), 2.04 (s, 1H), 1.65 - 1.44 (m, 1H), 1.19 (t, J = 7.1 Hz, 1H).

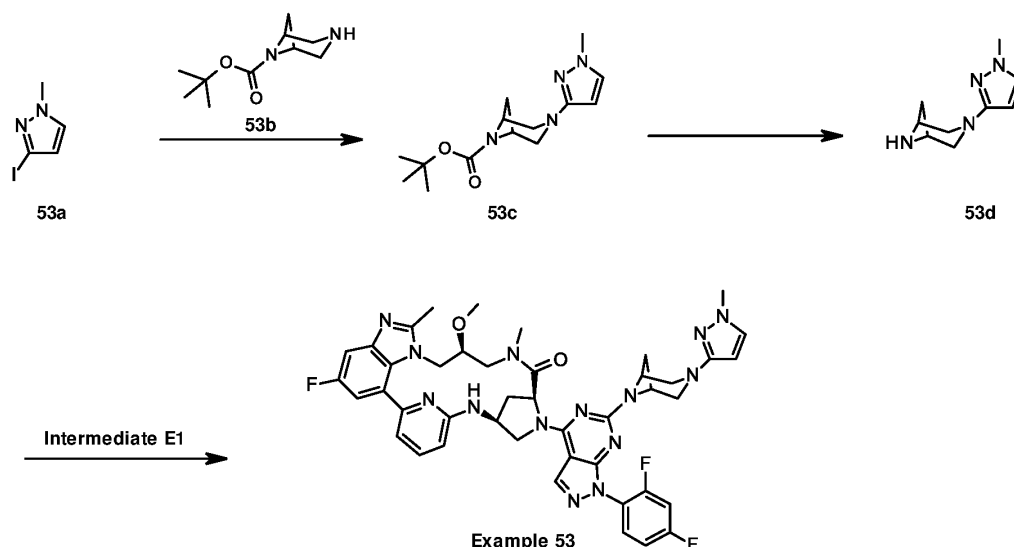
Example 53

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



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The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 53c)

5 A mixture of compound **53a** (100.0 mg, 0.48 mmol), compound **53b** (143 mg, 0.72 mmol), *t*BuXPhos Pd G3 (38 mg, 0.05 mmol) and *t*-BuONa (138 mg, 1.44 mmol) in 1,4-dioxane (1 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated, the residue was purified by prep-TLC to give compound **53c** (45.0 mg) as a colorless oil. LCMS (M-56+H⁺): 223.

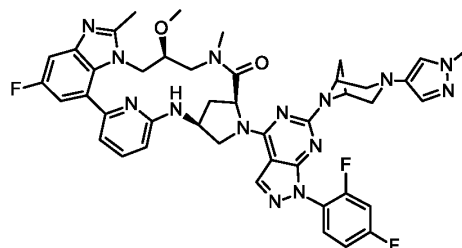
10 **Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 53)**

15 Example **53** was prepared in analogy to the preparation of Example **46** by using compound **53c** instead of compound **46b** and intermediate **E1** instead of intermediate **E4**. LCMS (M+H⁺): 845. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.28 (s, 1H), 7.92 - 7.83 (m, 1H), 7.68 - 7.52 (m, 5H), 7.32 - 7.22 (m, 1H), 7.21 - 7.14 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.32 - 6.02 (m, 1H), 5.46 - 5.27 (m, 1H), 4.72 - 4.63 (m, 1H), 4.61 - 4.53 (m, 1H), 4.52 - 4.40 (m, 2H), 4.36 - 4.27 (m, 1H),
 20 4.24 (br d, *J* = 10.8 Hz, 1H), 4.19 - 4.06 (m, 2H), 4.04 - 3.97 (m, 1H), 3.97 - 3.88 (m, 1H), 3.79 - 3.74 (m, 3H), 3.14 (s, 1H), 3.11 - 3.06 (m, 3H), 3.03 - 2.96 (m, 3H), 2.88 (s, 2H), 2.81 (s, 2H), 2.66 - 2.47 (m, 2H), 2.12 - 1.98 (m, 1H), 1.80 - 1.61 (m, 1H), 1.44 - 1.26 (m, 1H).

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Example 54

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-4-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

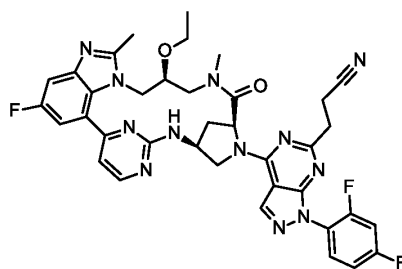


Example **54** was prepared in analogy to the preparation of Example **53** by using 4-iodo-1-methyl-pyrazole instead of 3-iodo-1-methyl-pyrazole (**53a**). LCMS ($M+H^+$): 845. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.27 - 8.18 (m, 1H), 7.84 - 7.78 (m, 1H), 7.67 - 7.56 (m, 1H), 7.35 - 7.27 (m, 1H), 7.27 - 7.18 (m, 2H), 7.18 - 7.13 (m, 2H), 7.11 - 7.05 (m, 2H), 6.77 - 6.63 (m, 1H), 5.92 - 5.64 (m, 1H), 5.47 - 5.23 (m, 1H), 4.67 - 4.61 (m, 2H), 4.50 - 4.37 (m, 1H), 4.26 - 4.08 (m, 5H), 3.95 - 3.85 (m, 2H), 3.81 - 3.68 (m, 5H), 3.25 - 3.20 (m, 1H), 3.11 - 3.05 (m, 3H), 2.91 - 2.82 (m, 3H), 2.62 - 2.54 (m, 3H), 2.13 - 1.99 (m, 1H), 1.75 - 1.64 (m, 1H), 1.32 - 1.27 (m, 1H), 1.18 (t, *J* = 7.0 Hz, 1H).

15

Example 55

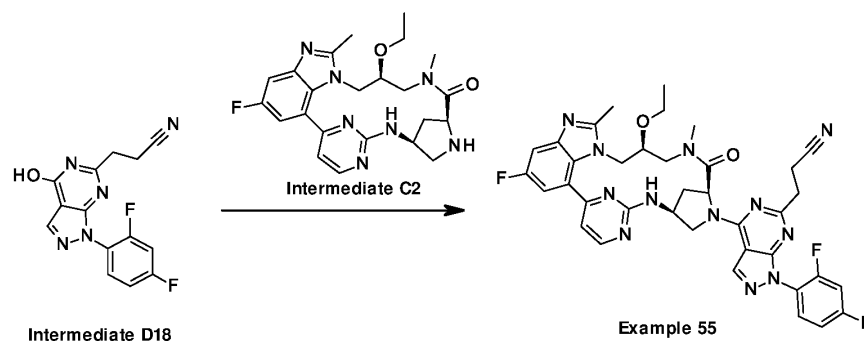
3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]propanenitrile



20

The title compound was prepared according to the following scheme:

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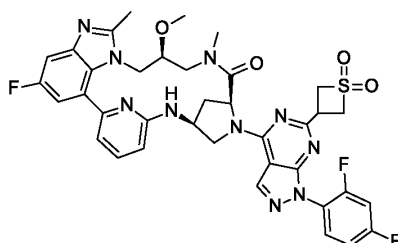


To a solution of Intermediate **D18** (40.0 mg, 0.13 mmol), PyBOP (48 mg, 0.09 mmol) in DMF (0.5 mL) was added DIEA (0.03 mL, 0.15 mmol) at 25 °C. The reaction was stirred at 25 °C for 0.5 h and then a mixture of Intermediate **C2** (68 mg, 0.12 mmol) and DIEA (0.03 mL, 0.15 mmol) in DMF (0.5 mL) was added. The reaction mixture was stirred at 25 °C for 2 h and then the mixture was purified by prep-HPLC to give Example **55** (17 mg) as a white solid.

LCMS (M+H⁺): 737. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.61 - 8.51 (m, 1H), 8.43 (s, 1H), 7.69 - 7.55 (m, 1H), 7.44 - 7.35 (m, 1H), 7.31 - 7.21 (m, 2H), 7.19 - 7.11 (m, 1H), 7.11 - 7.04 (m, 1H), 5.61 - 5.51 (m, 1H), 5.47 - 5.22 (m, 1H), 4.70 (br d, *J* = 4.0 Hz, 1H), 4.43 - 4.25 (m, 2H), 4.23 - 4.07 (m, 1H), 4.04 - 3.93 (m, 1H), 3.30 - 3.20 (m, 2H), 3.10 - 3.05 (m, 1H), 3.03 - 2.97 (m, 3H), 2.97 - 2.92 (m, 1H), 2.91 - 2.85 (m, 1H), 2.77 (br d, *J* = 13.0 Hz, 1H), 2.73 - 2.67 (m, 2H), 2.60 - 2.54 (m, 4H), 2.52 - 2.35 (m, 1H), 0.63 - 0.47 (m, 3H).

Example 56

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothietan-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}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **56** was prepared in analogy to the preparation of Example **55** by using intermediate **D19** instead of intermediate **D18** and intermediate **C1** instead of intermediate **C2**.

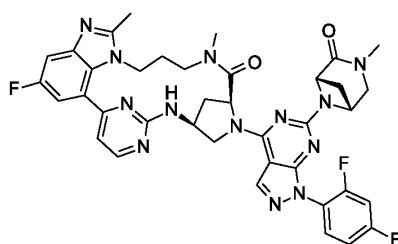
LCMS (M+H⁺): 773. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.62 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.74 - 7.65 (m, 1H), 7.32 - 7.27 (m, 2H), 7.24 - 7.06 (m, 3H), 6.75 - 6.61 (m, 1H), 5.86 - 5.73 (m, 1H), 5.62 - 5.54 (m, 1H), 5.40 - 5.34 (m, 1H), 4.71 - 4.64 (m, 1H), 4.57 - 4.51 (m, 1H),

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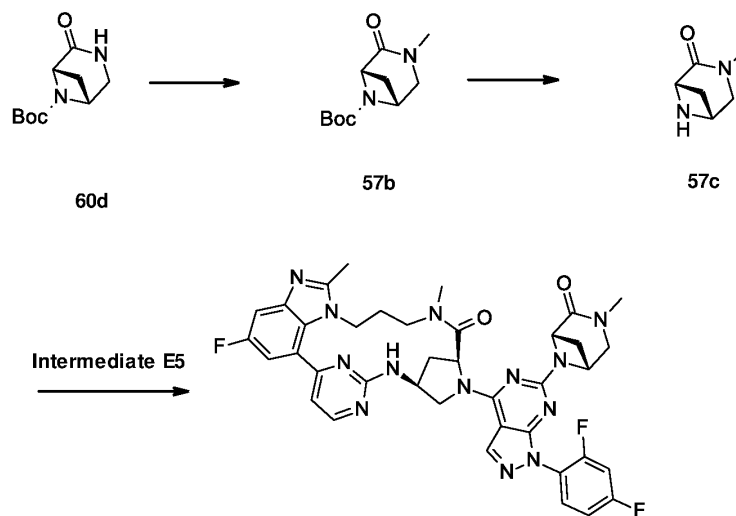
4.43 - 4.30 (m, 2H), 4.29 - 4.20 (m, 1H), 4.18 - 4.01 (m, 2H), 3.92 (br d, $J = 14.0$ Hz, 1H), 3.18 - 3.13 (m, 1H), 3.12 - 3.01 (m, 3H), 2.98 - 2.86 (m, 2H), 2.83 (s, 3H), 2.67 - 2.60 (m, 1H), 2.56 (s, 3H), 2.52 - 2.45 (m, 1H).

Example 57

- 5 **(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**



- 10 The title compound was prepared according to the following scheme:

**Example 57**

Step 1: preparation of *tert*-butyl (1*S*,5*R*)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 57b)

- To a solution of compound **60d** (200.0 mg, 0.94 mmol) in DMF (5 mL) was added NaH (45 mg, 1.13 mmol) at 0°C and then stirred at 15 °C for 1 h. Iodomethane (160 mg, 1.13 mmol) was added at 0°C. The reaction was stirred at 15 °C for 2 h. The reaction was poured into saturated ammonium chloride solution (20 mL), extracted with Ethyl acetate (20 mL × 2). The

combined organic layers were washed with brine (10 mL× 2), dried over Na₂SO₄, filtered and concentrated to give compound **57b** (230 mg) as light yellow oil.

Step 2: preparation of (1*S*,5*R*)-3-methyl-3,6-diazabicyclo[3.1.1]heptan-2-one (compound **57c)**

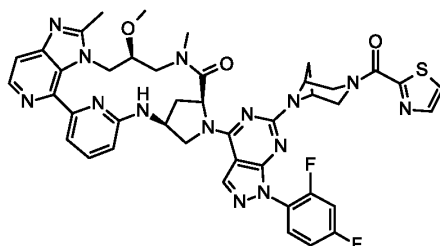
To a solution of compound **57b** (220.0 mg, 0.97 mmol) in DCM (2 mL) was added TFA (2.0 mL) at 0 °C and then stirred at 15 °C for 1 h. The reaction was concentrated to give compound **57c** (200.0 mg) as light yellow oil.

Step 3: preparation of (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-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(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example **57)**

To a solution of intermediated **E5** (50.0 mg, 0.07 mmol), compound **57c** (19 mg, 0.15 mmol), cesium fluoride (56 mg, 0.37 mmol) in DMA (1 mL) was added DIEA (0.1 mL, 0.74 mmol) and then stirred at 120 °C for 12 h. The mixture was concentrated and the residue was purified by prep- HPLC to give Example **57** (13 mg) as a white solid. LCMS (M+H⁺): 764. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.55 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 7.68 - 7.56 (m, 1H), 7.42 - 7.31 (m, 1H), 7.22 (br s, 1H), 7.18 - 7.10 (m, 2H), 6.97 (d, *J* = 5.1 Hz, 1H), 5.37 (br d, *J* = 8.6 Hz, 1H), 5.31 - 5.15 (m, 1H), 4.70 - 4.49 (m, 2H), 4.46 - 4.34 (m, 1H), 4.32 - 4.12 (m, 2H), 4.12 - 3.95 (m, 3H), 3.86 (br d, *J* = 11.5 Hz, 1H), 3.09 (br s, 3H), 2.97 - 2.87 (m, 1H), 2.85 - 2.78 (m, 1H), 2.73 (s, 3H), 2.67 (br d, *J* = 13.6 Hz, 1H), 2.61 (s, 3H), 2.55 - 2.45 (m, 1H), 2.06 - 1.90 (m, 1H), 1.75 (br d, *J* = 8.8 Hz, 1H), 1.40 - 1.23 (m, 1H).

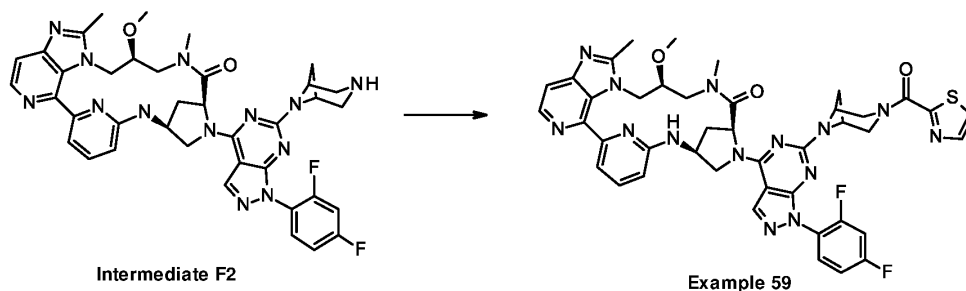
Example 59

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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:

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To a solution of Intermediate **F2** (50.0 mg, 0.06 mmol), TBD (24 mg, 0.17 mmol) in THF (0.500 mL) was added methyl thiazole-2-carboxylate (12 mg, 0.09 mmol) at 0° C. The reaction was stirred at 20 °C for 16 h. Then the reaction mixture was concentrated, the residue was

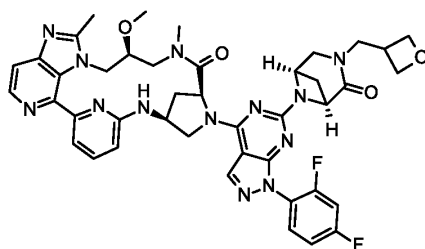
5 purified by prep-HPLC to afford Example **59** (23 mg) as a white solid. LCMS ($M+H^+$): 859. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.40 - 8.32 (m, 1H), 8.23 - 8.10 (m, 1H), 8.02 - 7.90 (m, 1H), 7.87 - 7.73 (m, 2H), 7.68 - 7.61 (m, 1H), 7.59 - 7.50 (m, 1H), 7.49 - 7.35 (m, 1H), 7.29 - 7.16 (m, 1H), 7.15 - 7.05 (m, 1H), 6.77 - 6.58 (m, 1H), 5.97 - 5.80 (m, 1H), 5.42 - 5.19 (m, 1H), 4.61 (s, 2H), 4.44 - 4.29 (m, 4H), 4.24 - 4.03 (m, 3H), 4.01 - 3.85 (m, 1H), 3.78 - 3.57 (m, 1H),

10 3.09 - 3.00 (m, 3H), 2.98 - 2.90 (m, 1H), 2.88 (s, 1H), 2.83 (s, 1H), 2.79 (br d, J = 5.0 Hz, 1H), 2.74 (br s, 1H), 2.70 - 2.62 (m, 2H), 2.59 (br d, J = 7.5 Hz, 1H), 2.55 - 2.40 (m, 3H), 1.57 (br d, J = 9.0 Hz, 1H).

Example 60

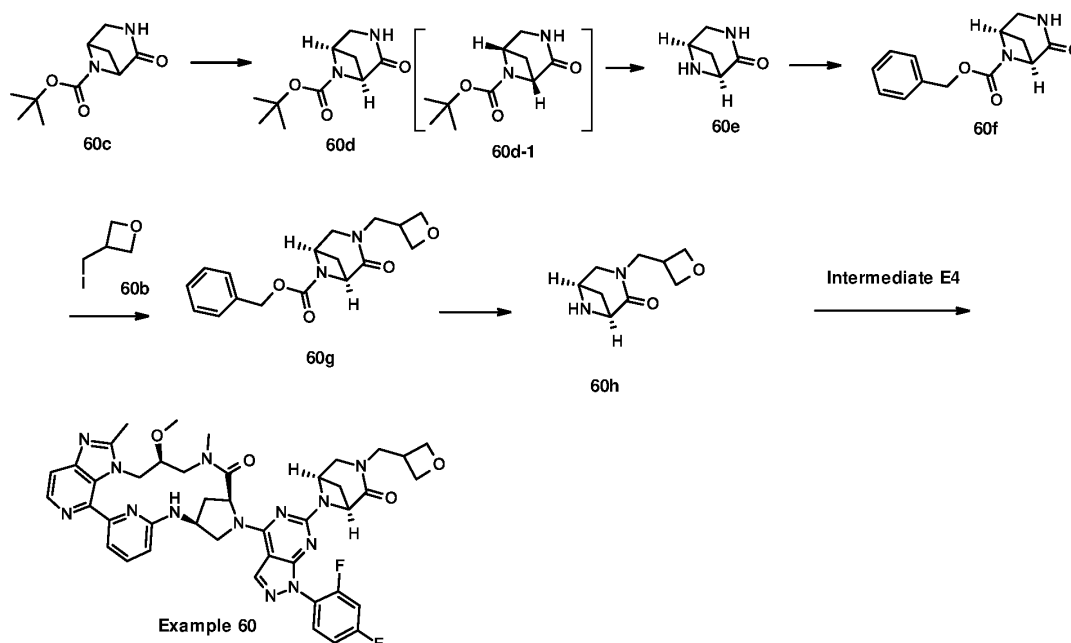
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-ylmethyl)-2-oxo-3,6-

15 diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl (1*R*,5*S*)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 60d)

The compound **60c** (2.5 g, 11.80 mmol) was purified by SFC, concentrated to give
 5 compound **60d-1** (1.25 g) (peak 1, R_t =1.299 min, ee%=100%) as a white solid, and compound **60d** (1.25 g) (peak 2, R_t =2.261 min, ee%= 99.13%) as a white solid.

Condition of SFC: Instrument CASWH-Prep-SFC-H, Method Column DAICEL
 CHIRALPAK AD (250mm×30mm,10um), Condition CO₂-EtOH (0.1%NH₃H₂O) Begin B 40,
 End B 40 Gradient Time (min) 3.9, 100% B Hold Time (min): 0, Flowrate (mL/min): 150.

10 The structure of compound **60d** was confirmed by X-Ray Single Crystal Diffraction in Figure 1.

Step 2: preparation of (1*R*,5*S*)-3,6-diazabicyclo[3.1.1]heptan-2-one (compound 60e)

To a solution of compound **60d** (400.0 mg, 1.88 mmol) in DCM (4 mL) was added TFA (4.0 mL) at 0 °C. The reaction was stirred at 25 °C for 1 hr under N₂ atmosphere. The mixture
 15 was concentrated to give compound **60e** (560.0 mg) as colorless oil, which was used directly without further purification.

Step 3: preparation of benzyl (1*R*,5*S*)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 60f)

To a solution of compound **60e** (560.0 mg, 2.48 mmol) and sodium carbonate (315 mg,
 20 2.97 mmol) in THF (5 mL) and water (5 mL) was added *N*-(benzyloxycarbonyloxy)succinimide

(740 mg, 2.97 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 16 h, and then the mixture was purified by prep-HPLC to give compound **60f** (410.0 mg) as colorless oil. LCMS (M+H⁺): 247.

Step 4: preparation of benzyl (1*R*,5*S*)-3-(oxetan-3-ylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 60g)

To a solution of compound **60f** (100.0 mg, 0.41 mmol) in DMF (2 mL) was added sodium hydride (32 mg, 0.81 mmol). The reaction was stirred for 0.5 h at 0 °C, and then compound **60b** (120 mg, 0.61 mmol) was added. After being stirred for 2 h at 25 °C, the reaction mixture was poured into ice water and extracted with EA. The organic layer was dried and concentrated to give compound **60g** (150.0 mg) as colorless oil, which was used directly without further purification. LCMS (M+H⁺): 317.

Step 5: preparation of (1*S*,5*R*)-3-(oxetan-3-ylmethyl)-3,6-diazabicyclo[3.1.1]heptan-2-one (compound 60h)

To a solution of compound **60g** (150.0 mg, 0.47 mmol) in methanol (3 mL) was added wet Pd/C (30.0 mg) under N₂ at 25 °C. The reaction was stirred under H₂ at 25 °C for 2 h, and then the mixture was filtered, the filtrate was concentrated to give compound **60h** (60.0 mg) as a white solid, which was used directly without further purification.

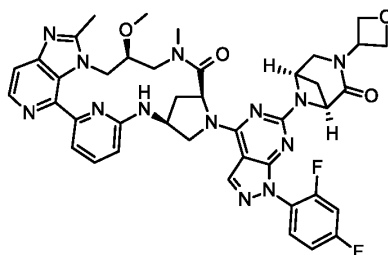
Step 6: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-ylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 60)

A mixture of intermediate **E4** (40.0 mg, 0.06 mmol), compound **60h** (32 mg, 0.17 mmol), CsF (22 mg, 0.15 mmol) and DIEA (0.02 mL, 0.15 mmol) in DMA (0.5 mL) was stirred at 120 °C for 16 h. Then the reaction mixture was purified by prep-HPLC to give Example **60** (13 mg) as a white solid. LCMS (M+H⁺): 832. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.43 - 8.28 (m, 2H), 7.91 - 7.77 (m, 1H), 7.68 - 7.58 (m, 2H), 7.50 - 7.37 (m, 1H), 7.33 - 7.11 (m, 2H), 6.81 - 6.63 (m, 1H), 6.09 - 5.85 (m, 1H), 5.53 - 5.30 (m, 1H), 4.69 - 4.61 (m, 2H), 4.56 (br s, 4H), 4.52 - 4.42 (m, 2H), 4.32 - 4.23 (m, 4H), 4.19 - 4.13 (m, 2H), 4.11 - 4.02 (m, 2H), 4.01 - 3.91 (m, 1H), 3.18 - 3.14 (m, 1H), 3.12 (br s, 2H), 3.05 (br s, 3H), 2.86 - 2.81 (m, 3H), 2.68 - 2.61 (m, 3H), 2.57 - 2.46 (m, 1H), 1.82 - 1.68 (m, 1H).

Example 61

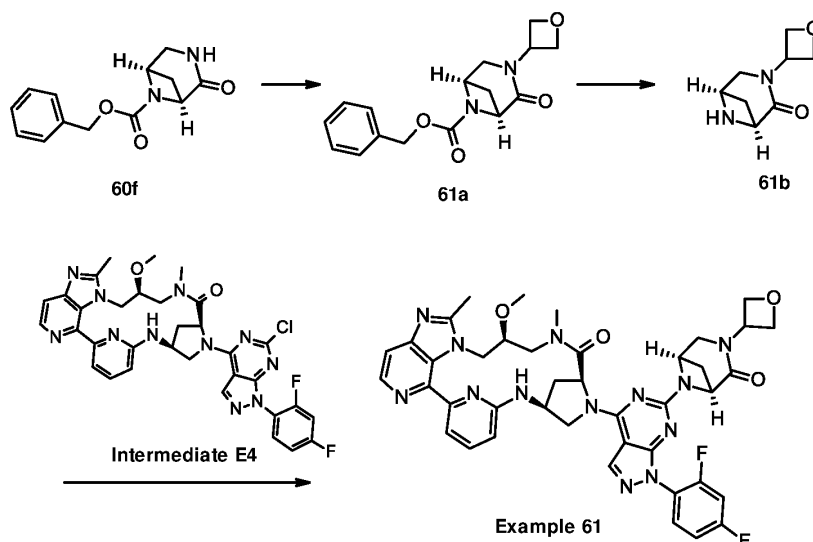
-155-

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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



5

The title compound was prepared according to the following scheme:



Example **61** was prepared in analogy to the preparation of Example **60** by using 3-bromooxetane instead of compound **60b**. LCMS ($M+H^+$): 818. 1H NMR (400 MHz,

10 METHANOL- d_4) δ = 8.42 - 8.28 (m, 2H), 7.92 - 7.80 (m, 1H), 7.66 - 7.62 (m, 2H), 7.50 - 7.40 (m, 1H), 7.31 - 7.23 (m, 1H), 7.13 (d, J = 3.4 Hz, 1H), 6.78 - 6.71 (m, 1H), 6.07 - 5.92 (m, 1H), 5.48 - 5.33 (m, 1H), 4.75 - 4.72 (m, 2H), 4.65 (br s, 1H), 4.58 (s, 4H), 4.49 - 4.44 (m, 1H), 4.26 - 4.16 (m, 5H), 3.11 (s, 1H), 3.05 (s, 3H), 2.93 - 2.86 (m, 2H), 2.85 (s, 3H), 2.83 - 2.81 (m, 1H), 2.72 (br d, J = 12.6 Hz, 1H), 2.68 (s, 3H), 2.63 (s, 1H), 1.75 (d, J = 9.1 Hz, 1H).

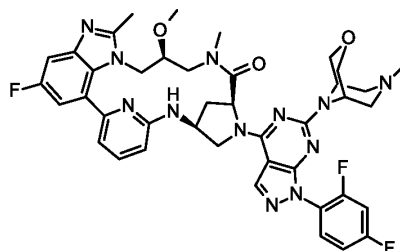
15

Example 62

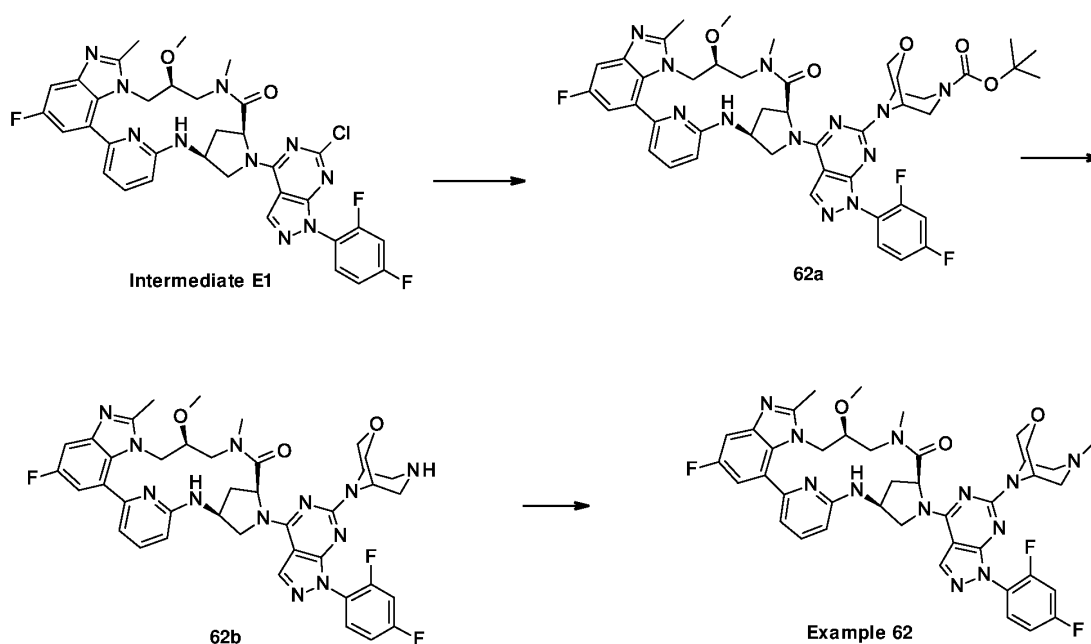
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-

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hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



The title compound was prepared according to the following scheme:



5

Step 1: preparation of *tert*-butyl 9-[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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylate

10 (compound 62a)

A mixture of Intermediate E1 (150.0 mg, 0.21 mmol), 7-BOC-3-oxa-7,9-diazabicyclo[3.3.1]nonane (146 mg, 0.64 mmol), CsF (162 mg, 1.07 mmol) and DIEA (0.18 mL, 1.07 mmol) in DMA (2 mL) was stirred at 120 °C for 24 h. Then the reaction mixture was purified by prep-HPLC to give compound 62a (100 mg) as a brown solid. LCMS (*M*+*H*⁺): 895.

15

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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 (compound 62b)

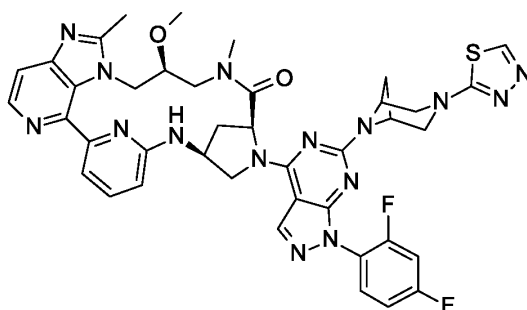
To a solution of compound 62a (100 mg, 0.11 mmol) in DCM (1 mL) was added TFA (0.5 mL) at 0 °C. The reaction was stirred at 25 °C for 1 h and then concentrated to give compound
5 62b (130 mg) as yellow oil, which was used directly without further purification. LCMS (M+H⁺): 795.

**Step 3: preparation of (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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-
10 1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 62)**

To a solution of compound 62b (40.0 mg, 0.04 mmol) in DCM (0.5 mL) and methanol (0.5 mL) was added formaldehyde (20.0 mg, 0.25 mmol) and sodium cyanoborohydride (6 mg, 0.09 mmol). The reaction mixture was stirred at 25 °C for 12 h, then it was purified by prep-HPLC to give Example 62 (5 mg) as a white solid. LCMS (M+H⁺): 809. ¹H NMR (400 MHz,
15 METHANOL-*d*₄) δ = 8.24 (s, 1H), 7.86 - 7.77 (m, 1H), 7.66 - 7.53 (m, 1H), 7.32 - 7.27 (m, 1H), 7.24 - 7.18 (m, 1H), 7.17 - 7.11 (m, 2H), 7.10 - 7.05 (m, 1H), 6.73 - 6.62 (m, 1H), 5.89 - 5.60 (m, 1H), 5.41 - 5.23 (m, 1H), 4.67 - 4.62 (m, 2H), 4.59 - 4.55 (m, 2H), 4.49 - 4.44 (m, 2H), 4.27 - 4.09 (m, 3H), 4.00 - 3.90 (m, 2H), 3.86 - 3.71 (m, 3H), 3.13 - 3.09 (m, 1H), 3.01 (s, 3H), 2.97 - 2.89 (m, 1H), 2.86 - 2.81 (m, 3H), 2.59 - 2.54 (m, 3H), 2.51 - 2.45 (m, 1H), 2.40 - 2.34 (m, 1H),
20 2.20 - 2.14 (m, 3H), 2.03 (s, 1H).

Example 63

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[3-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
25 1(23),2(26),3,5,18,20(24),21-heptaen-12-one



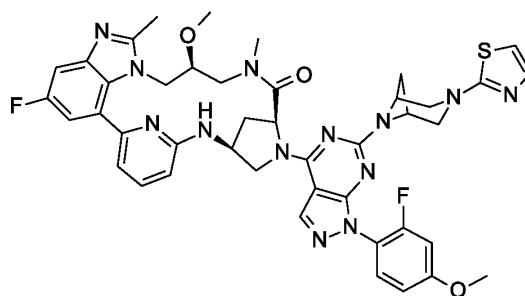
-158-

Example **63** was prepared in analogy to the preparation of Example **53** by using 2-bromo-1,3,4-thiadiazole instead of 3-iodo-1-methyl-pyrazole (**53a**). LCMS (M+H⁺): 832. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.61 (s, 1H), 8.49 (d, *J* = 6.3 Hz, 1H), 8.21 (s, 1H), 8.09 (d, *J* = 6.4 Hz, 1H), 7.99 (br t, *J* = 8.0 Hz, 1H), 7.57 (br dd, *J* = 5.1, 7.3 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.29 - 7.21 (m, 1H), 7.19 - 7.10 (m, 1H), 6.96 (br d, *J* = 8.6 Hz, 1H), 5.98 (br dd, *J* = 4.4, 15.7 Hz, 1H), 5.37 (br d, *J* = 8.6 Hz, 1H), 4.69 - 4.61 (m, 1H), 4.56 - 4.48 (m, 1H), 4.41 (br dd, *J* = 5.4, 11.6 Hz, 3H), 4.26 - 4.11 (m, 3H), 3.68 - 3.41 (m, 3H), 3.10 (s, 4H), 2.97 (s, 3H), 2.93 (br s, 3H), 2.77 (s, 1H), 2.70 - 2.62 (m, 1H), 2.58 (br dd, *J* = 4.1, 8.6 Hz, 1H), 2.51 (br dd, *J* = 4.9, 6.6 Hz, 1H), 1.67 (br d, *J* = 9.0 Hz, 1H).

10

Example 64

(8*S*,11*S*,15*R*)-22-fluoro-10-[1-(2-fluoro-4-methoxy-phenyl)-6-(3-thiazol-2-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



15

Example **64** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c** and intermediate **E8** instead of intermediate **E4**. LCMS (M+H⁺): 860. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.25 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.58 (br d, *J* = 7.1 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.48 - 7.38 (m, 1H), 7.29 (d, *J* = 3.9 Hz, 1H), 7.20 - 7.13 (m, 1H), 6.97 - 6.85 (m, 3H), 6.78 (br d, *J* = 8.0 Hz, 1H), 6.19 (br dd, *J* = 4.8, 15.0 Hz, 1H), 5.41 (br d, *J* = 8.9 Hz, 1H), 4.69 - 4.56 (m, 2H), 4.46 (br d, *J* = 6.4 Hz, 2H), 4.39 - 4.27 (m, 2H), 4.26 - 4.16 (m, 2H), 4.15 - 3.97 (m, 2H), 3.65 - 3.48 (m, 2H), 3.15 - 3.05 (m, 4H), 3.03 - 2.94 (m, 4H), 2.86 (s, 3H), 2.83 - 2.74 (m, 2H), 2.67 - 2.36 (m, 2H), 1.81 - 1.67 (m, 1H), 1.43 (s, 1H).

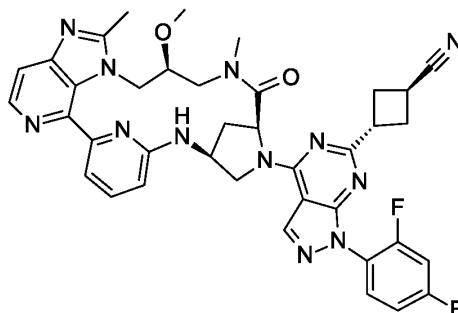
20

Example 65

Trans-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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}]hexacos-

25

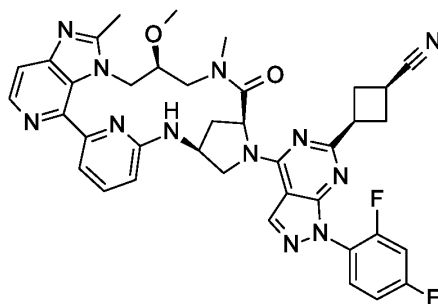
1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile



Example **65** was prepared in analogy to the preparation of Example **55** by using
 5 intermediate **D20** instead of intermediate **D18** and intermediate **C8** instead of intermediate **C2**.
 LCMS (M+H⁺): 731. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.47 (s, 1H), 8.37 (d, *J* = 5.5 Hz, 1H), 7.88 (t, *J* = 7.9 Hz, 1H), 7.66 (br d, *J* = 5.4 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.32 - 7.23 (m, 1H), 7.22 - 7.11 (m, 1H), 6.86 - 6.67 (m, 1H), 6.02 (dd, *J* = 4.4, 15.4 Hz, 1H), 5.58 (d, *J* = 8.8 Hz, 1H), 4.75 - 4.67 (m, 1H), 4.54 (br dd, *J* = 6.2, 11.4 Hz, 1H), 4.37 - 4.18 (m, 2H), 3.98 - 3.85 (m,
 10 1H), 3.79 - 3.69 (m, 1H), 3.68 - 3.59 (m, 1H), 3.48 - 3.39 (m, 1H), 3.18 - 3.15 (m, 1H), 3.10 (s, 3H), 2.99 (s, 1H), 2.88 - 2.82 (m, 4H), 2.73 - 2.68 (m, 2H), 2.66 - 2.63 (m, 3H), 2.60 - 2.51 (m, 2H).

Example 66

Cis-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-
 15 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-10-yl]pyrazolo[3,4-d]pyrimidin-6-
 yl]cyclobutanecarbonitrile



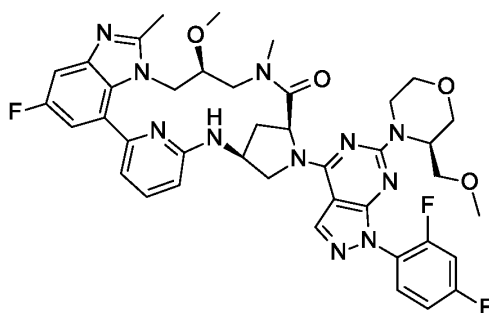
Example **66** was prepared in analogy to the preparation of Example **55** by using
 20 intermediate **D21** instead of intermediate **D18** and intermediate **C8** instead of intermediate **C2**.
 LCMS (M+H⁺): 731. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.47 (s, 1H), 8.37 (d, *J* = 5.5 Hz,

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1H), 7.88 (t, $J = 7.9$ Hz, 1H), 7.63 (d, $J = 5.4$ Hz, 2H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.32 - 7.23 (m, 1H), 7.22 - 7.15 (m, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.05 (dd, $J = 4.4, 15.4$ Hz, 1H), 5.65 (d, $J = 8.9$ Hz, 1H), 4.77 - 4.68 (m, 1H), 4.62 - 4.50 (m, 2H), 4.35 - 4.17 (m, 2H), 3.96 (dd, $J = 9.2, 14.3$ Hz, 1H), 3.56 (t, $J = 8.7$ Hz, 1H), 3.26 (d, $J = 9.1$ Hz, 1H), 3.15 (s, 3H), 3.00 (br d, $J = 13.3$ Hz, 1H), 2.91 - 2.79 (m, 5H), 2.74 - 2.66 (m, 2H), 2.65 (s, 3H), 2.61 - 2.55 (m, 2H).

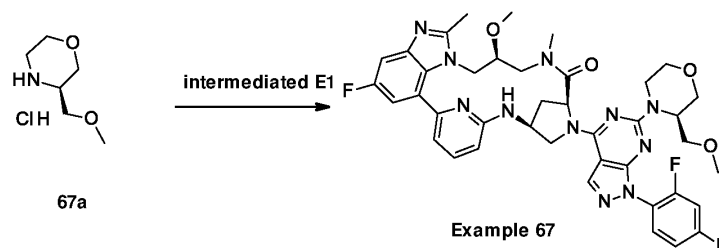
Example 67

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(3*R*)-3-(methoxymethyl)morpholin-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



10

The title compound was prepared according to the following scheme:

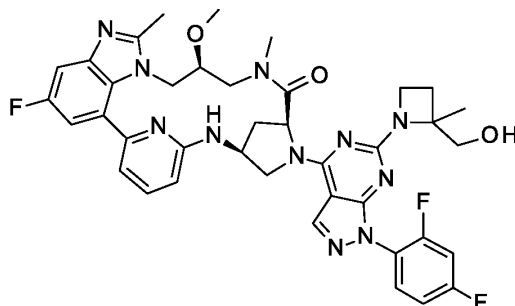


To a solution of intermediated **E1** (50.0 mg, 0.07 mmol), compound **67a** (60 mg, 0.36 mmol), cesium fluoride (54 mg, 0.36 mmol) in DMA (1 mL) was added *N,N*-diisopropylethylamine (0.1 mL, 0.43 mmol) and then stirred at 120 °C for 12 h. The reaction solution was purified by prep-HPLC to give Example **67** (7. mg) as a light yellow solid. LCMS ($M+H^+$): 798. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.25 (s, 1H), 7.87 (t, $J = 8.0$ Hz, 1H), 7.66 - 7.51 (m, 3H), 7.27 - 7.10 (m, 3H), 6.79 (br d, $J = 8.3$ Hz, 1H), 6.25 (dd, $J = 4.3, 15.2$ Hz, 1H), 5.39 - 5.26 (m, 1H), 4.71 - 4.63 (m, 1H), 4.52 - 4.41 (m, 2H), 4.37 - 4.18 (m, 3H), 4.00 (br d, $J = 11.8$ Hz, 1H), 3.89 - 3.83 (m, 1H), 3.74 (br t, $J = 9.4$ Hz, 1H), 3.54 - 3.45 (m, 2H), 3.43 - 3.40 (m, 1H), 3.34 (s, 3H), 3.18 - 3.05 (m, 4H), 2.99 (s, 4H), 2.88 - 2.79 (m, 3H), 2.64 - 2.49 (m, 2H), 2.45 - 2.26 (m, 1H), 2.13 - 1.96 (m, 1H).

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Example 68

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(hydroxymethyl)-2-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

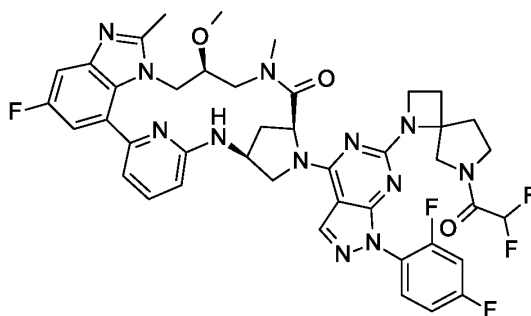


5

Example **68** was prepared in analogy to the preparation of Example **67** by using (2-methylazetidin-2-yl)methanol;hydrochloride instead of compound **67a**. LCMS ($M+H^+$): 768. 1H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (d, J = 3.8 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.68 - 7.58 (m, 2H), 7.54 (dd, J = 2.6, 10.3 Hz, 1H), 7.30 - 7.22 (m, 1H), 7.21 - 7.14 (m, 2H), 6.78 (d, J = 8.4 Hz, 1H), 6.28 - 6.02 (m, 1H), 5.43 - 5.28 (m, 1H), 4.68 (br s, 1H), 4.54 - 4.44 (m, 1H), 4.40 - 4.16 (m, 3H), 4.04 - 3.70 (m, 4H), 3.61 (q, J = 7.0 Hz, 1H), 3.15 - 3.04 (m, 4H), 3.00 - 2.96 (m, 3H), 2.87 - 2.80 (m, 3H), 2.66 - 2.48 (m, 2H), 2.45 - 2.17 (m, 1H), 2.02 - 1.91 (m, 1H), 1.61 - 1.27 (m, 3H).

Example **69**

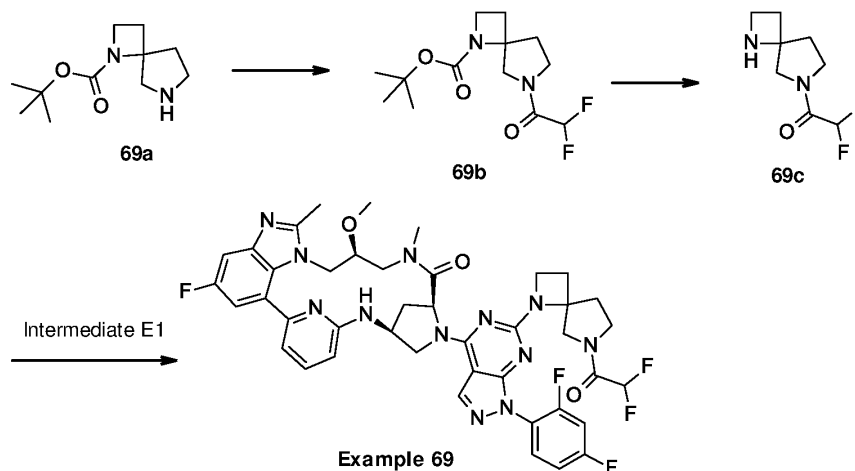
15 (8*S*,11*S*,15*R*)-10-[6-[7-(2,2-difluoroacetyl)-1,7-diazaspiro[3.4]octan-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



20

The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 7-(2,2-difluoroacetyl)-1,7-diazaspiro[3.4]octane-1-carboxylate (compound 69b)

To a solution of compound **69a** (200.0 mg, 0.94 mmol), triethylamine (0.41 mL, 2.96 mmol) in DCM (2 mL) was added 2,2-difluoroacetate (240.0 mg, 1.38 mmol) at 0 °C and then stirred at 25 °C for 1 h. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give compound **69b** (140.0 mg) as brown oil. LCMS (M-100+H⁺): 291.

Step 2: preparation of 1-(1,7-diazaspiro[3.4]octan-7-yl)-2,2-difluoro-ethanone (compound 69c)

To a solution of compound **69b** (140.0 mg, 0.48 mmol) in DCM (2 mL) was added TFA (2.0 mL) at 0 °C and then stirred at 20 °C for 1 h. The reaction mixture was concentrated to give compound **69c** (140.0 mg) as brown oil. LCMS (M+H⁺): 191.

Step 3: (8*S*,11*S*,15*R*)-10-[6-[7-(2,2-difluoroacetyl)-1,7-diazaspiro[3.4]octan-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}]hexacosane-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 69)

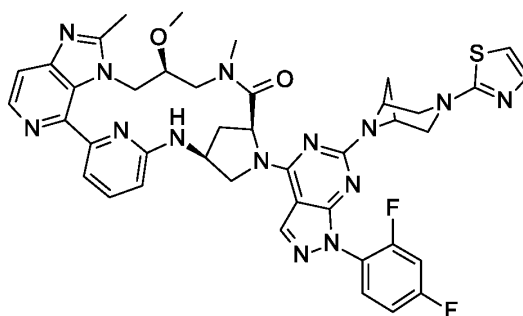
A solution of Intermediate **E1** (50.0 mg, 0.07 mmol), compound **69c** (68 mg, 0.36 mmol), CsF (54 mg, 0.36 mmol) and DIEA (0.1 mL, 0.71 mmol) in DMA (2 mL) was stirred at 120 °C for 15 h. The reaction solution was purified by prep-HPLC to give Example **69** (10 mg) as a red solid. LCMS (M+H⁺): 857. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.21 (d, *J* = 3.5 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.65 - 7.50 (m, 1H), 7.29 (br d, *J* = 8.5 Hz, 1H), 7.22 - 7.12 (m, 2H), 7.11 - 7.03 (m, 2H), 6.62 (br d, *J* = 8.4 Hz, 1H), 5.83 - 5.61 (m, 1H), 5.32 - 5.15 (m, 1H), 4.55 (br d, *J* = 1.9 Hz, 1H), 4.40 - 4.30 (m, 1H), 4.27 - 4.03 (m, 3H), 4.03 - 3.71 (m, 5H), 3.71 - 3.43

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(m, 2H), 3.11 - 3.06 (m, 1H), 3.03 - 2.95 (m, 1H), 2.91 (br s, 2H), 2.85 - 2.78 (m, 4H), 2.78 - 2.71 (m, 1H), 2.59 - 2.51 (m, 3H), 2.50 - 2.22 (m, 4H), 2.12 - 1.94 (m, 1H).

Example 70

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

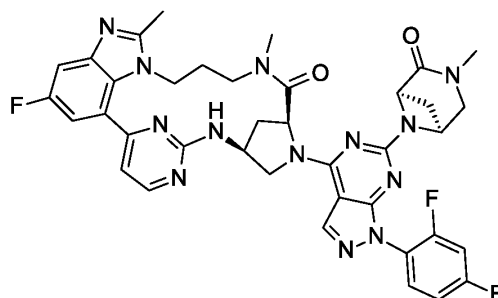


Example **70** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c**. LCMS ($M+H^+$): 831. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.50 (d, J = 6.3 Hz, 1H), 8.28 (s, 1H), 8.11 - 8.06 (m, 1H), 8.01 (dd, J = 7.7, 8.3 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.41 - 7.33 (m, 2H), 7.29 - 7.22 (m, 1H), 7.21 - 7.14 (m, 1H), 7.01 - 6.92 (m, 2H), 6.08 - 5.85 (m, 1H), 5.44 - 5.32 (m, 1H), 4.73 - 4.66 (m, 1H), 4.65 - 4.51 (m, 1H), 4.50 - 4.43 (m, 2H), 4.42 - 4.31 (m, 2H), 4.25 (br d, J = 11.4 Hz, 1H), 4.13 - 4.01 (m, 1H), 3.70 - 3.53 (m, 2H), 3.15 - 3.08 (m, 3H), 3.07 - 3.01 (m, 1H), 3.00 - 2.89 (m, 4H), 2.84 (s, 3H), 2.76 (s, 1H), 2.73 - 2.64 (m, 1H), 2.57 (tdd, J = 4.4, 8.8, 13.2 Hz, 1H), 1.85 - 1.68 (m, 1H), 1.44 - 1.28 (m, 1H).

Example 71

(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-methyl-2-oxo-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one

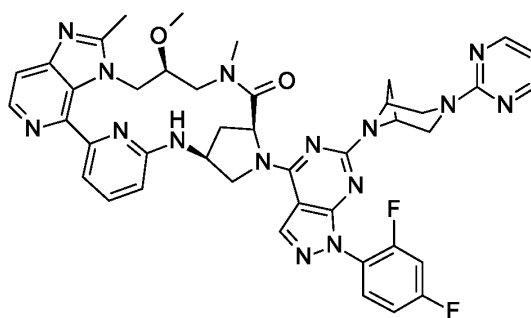
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Example **71** was prepared in analogy to the preparation of compound **D9-c** by using compound **60d-1** instead of *tert*-butyl 2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate and intermediate **E5** instead of intermediate **D15-a**. LCMS ($M+H^+$): 764. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.56 (d, J = 5.1 Hz, 1H), 8.31 (s, 1H), 7.70 - 7.58 (m, 1H), 7.37 (dd, J = 2.3, 8.5 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.21 - 7.11 (m, 2H), 7.01 - 6.94 (m, 1H), 5.46 (d, J = 8.4 Hz, 1H), 5.29 (br d, J = 8.6 Hz, 1H), 4.74 - 4.53 (m, 2H), 4.42 (br dd, J = 6.7, 11.4 Hz, 1H), 4.35 - 4.12 (m, 3H), 4.11 - 3.86 (m, 2H), 3.07 (s, 4H), 2.98 - 2.80 (m, 2H), 2.77 (s, 3H), 2.67 (br s, 1H), 2.63 (s, 3H), 2.56 - 2.44 (m, 1H), 2.23 - 2.00 (m, 1H), 1.74 (br d, J = 8.8 Hz, 1H), 1.44 - 1.21 (m, 1H).

Example 72

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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



15

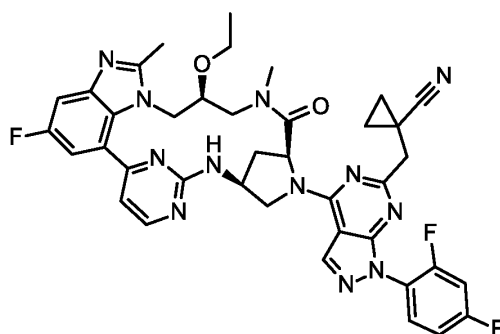
Example **72** was prepared in analogy to the preparation of Example **46** by using 2-chloropyrimidine instead of compound **46c**. LCMS ($M+H^+$): 826. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.55 - 8.31 (m, 3H), 8.24 (s, 1H), 8.10 (d, J = 6.4 Hz, 1H), 8.00 (t, J = 7.9 Hz, 1H), 7.60 (dt, J = 6.1, 8.5 Hz, 1H), 7.42 - 7.34 (m, 1H), 7.28 - 7.20 (m, 1H), 7.19 - 7.09 (m, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.84 - 6.73 (m, 1H), 6.06 - 5.75 (m, 1H), 5.48 - 5.28 (m, 1H), 4.69 - 4.58 (m, 1H), 4.54 - 4.36 (m, 3H), 4.33 - 4.15 (m, 4H), 4.10 (br d, J = 11.1 Hz, 1H), 3.72 (br dd, J = 7.1, 12.0

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Hz, 1H), 3.62 (br d, $J = 11.9$ Hz, 1H), 3.13 - 3.07 (m, 3H), 3.07 - 2.95 (m, 3H), 2.93 - 2.80 (m, 4H), 2.78 - 2.74 (m, 1H), 2.71 - 2.62 (m, 1H), 2.61 - 2.43 (m, 2H), 1.75 - 1.60 (m, 1H).

Example 73

1-[[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-
5 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-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile

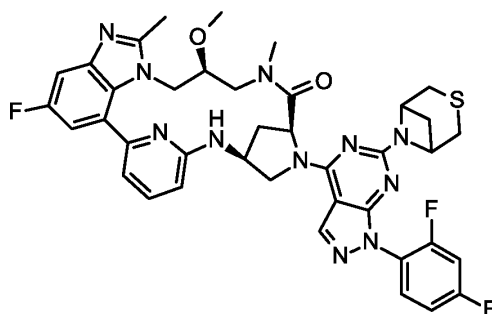


Example 73 was prepared in analogy to the preparation of Example 55 by using intermediate **D22** instead of intermediate **D18**. LCMS ($M+H^+$): 763. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.55 (d, $J = 5.3$ Hz, 1H), 8.43 (s, 1H), 7.82 - 7.53 (m, 1H), 7.45 - 7.36 (m, 1H), 7.33 - 7.21 (m, 2H), 7.20 - 7.14 (m, 1H), 7.10 (br d, $J = 5.3$ Hz, 1H), 5.88 - 5.72 (m, 1H), 5.65 - 5.43 (m, 2H), 4.73 (br t, $J = 4.6$ Hz, 1H), 4.41 - 4.32 (m, 1H), 4.32 - 4.27 (m, 1H), 4.24 - 4.08 (m, 1H), 4.06 - 3.92 (m, 1H), 3.71 - 3.53 (m, 1H), 3.29 - 3.22 (m, 1H), 3.13 - 3.02 (m, 3H), 3.02 - 2.98 (m, 1H), 2.95 - 2.88 (m, 1H), 2.88 - 2.77 (m, 2H), 2.68 (br t, $J = 7.4$ Hz, 1H), 2.62 (br
15 d, $J = 2.4$ Hz, 1H), 2.60 - 2.56 (m, 3H), 2.53 - 2.42 (m, 1H), 2.03 - 1.76 (m, 1H), 1.39 - 1.23 (m, 1H), 0.66 - 0.49 (m, 3H).

Example 76

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thia-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-
20 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one

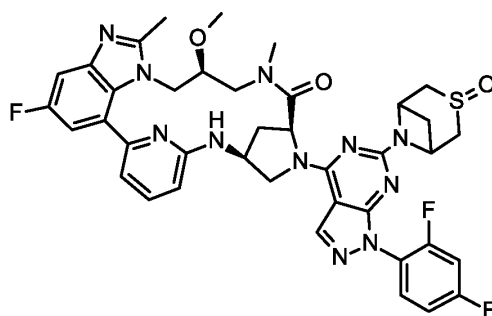
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A mixture of Intermediate **E1** (100.0 mg, 0.14 mmol), 3-thia-6-azabicyclo[3.1.1]heptane (123 mg, 0.43 mmol), CsF (108 mg, 0.71 mmol) and DIEA (0.14 mL, 0.85 mmol) in DMA (1 mL) was stirred at 120 °C for 15 h. The mixture was purified by prep-HPLC to give Example **76** (30 mg) as a white solid. LCMS (M+H⁺): 782. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.28 (s, 1H), 7.87 - 7.74 (m, 1H), 7.68 - 7.53 (m, 1H), 7.34 - 7.26 (m, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.11 (m, 2H), 7.10 - 7.05 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.92 - 5.63 (m, 1H), 5.46 - 5.25 (m, 1H), 4.66 - 4.55 (m, 2H), 4.50 - 4.38 (m, 3H), 4.29 - 4.08 (m, 3H), 3.91 - 3.79 (m, 1H), 3.78 - 3.69 (m, 1H), 3.66 - 3.55 (m, 1H), 3.10 (s, 1H), 3.06 - 2.92 (m, 3H), 2.87 - 2.81 (m, 3H), 2.74 - 2.68 (m, 2H), 2.59 - 2.54 (m, 3H), 2.52 - 2.43 (m, 2H), 1.96 - 1.86 (m, 1H).

Example 77

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxo-3 λ^4 -thia-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



15

To a solution of Example **76** (26.0 mg, 0.03 mmol) in DCM (0.5 mL) was added mCPBA (7 mg, 0.03 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h and then filtered. The filtrate was concentrated, the residue was purified by prep-HPLC to afford Example **77** (13 mg) as a white solid. LCMS (M+H⁺): 798. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 - 8.23 (m, 1H), 7.85 - 7.76 (m, 1H), 7.68 - 7.56 (m, 1H), 7.33 - 7.28 (m, 1H), 7.27 - 7.21 (m, 1H), 7.18 - 7.12 (m, 2H), 7.10 - 7.05 (m, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.84 - 5.64 (m, 1H), 5.41 - 5.26 (m,

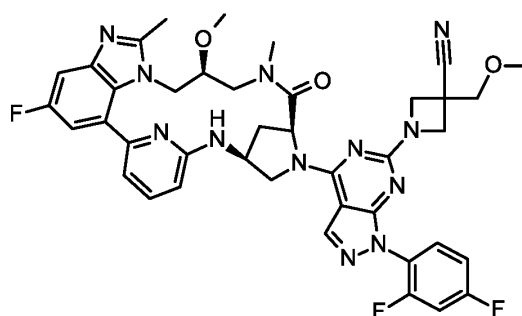
20

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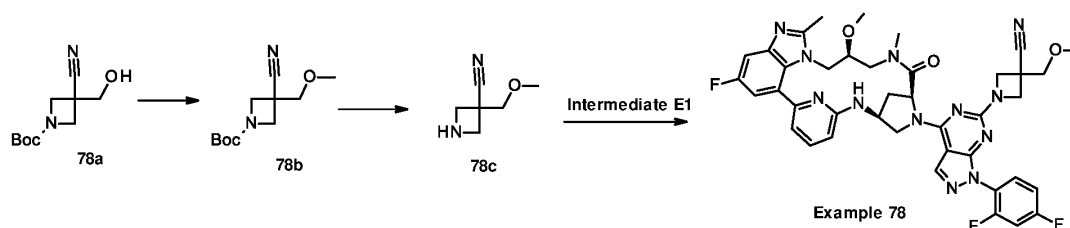
1H), 4.58 (br s, 4H), 4.46 - 4.35 (m, 2H), 4.26 - 4.12 (m, 3H), 4.06 - 3.86 (m, 2H), 3.09 (s, 1H), 3.01 (s, 2H), 2.96 - 2.89 (m, 1H), 2.88 - 2.83 (m, 3H), 2.80 - 2.71 (m, 3H), 2.60 - 2.53 (m, 3H), 2.51 - 2.40 (m, 2H).

Example 78

- 5 **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]-3-(methoxymethyl)azetidine-3-carbonitrile**



- 10 The title compound was prepared according to the following scheme:

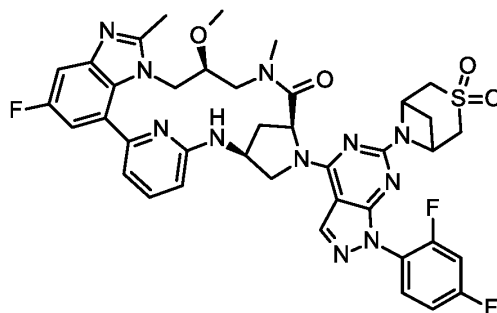


- Example **71** was prepared in analogy to the preparation of compound **D9-c** by using compound **78a** instead of *tert*-butyl 2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate and intermediate **E1** instead of intermediate **D15-a**. LCMS ($M+H^+$): 793. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.26 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.68 - 7.52 (m, 1H), 7.36 - 7.27 (m, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.11 (m, 2H), 7.10 - 7.05 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.90 - 5.59 (m, 1H), 5.40 - 5.25 (m, 1H), 4.64 - 4.55 (m, 2H), 4.46 - 4.37 (m, 1H), 4.35 - 4.27 (m, 1H), 4.24 - 4.18 (m, 2H), 4.17 - 4.11 (m, 2H), 4.07 - 3.98 (m, 1H), 3.95 - 3.87 (m, 1H), 3.77 - 3.71 (m, 2H), 3.44 (s, 3H), 3.12 - 3.01 (m, 3H), 2.97 - 2.88 (m, 1H), 2.87 - 2.81 (m, 3H), 2.59 - 2.54 (m, 3H), 2.52 - 2.42 (m, 2H).

Example 79

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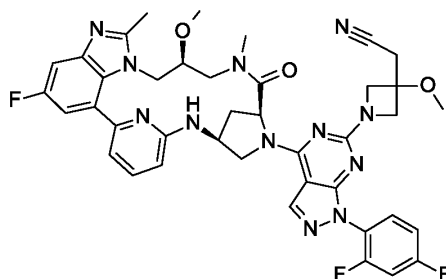
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 5 To a solution of Example **76** (30.0 mg, 0.04 mmol) in DCM (0.5 mL) was added M-CPBA (18 mg, 0.08 mmol) at 0 °C. The reaction was stirred at 20 °C for 1 h. Then the reaction mixture was purified by prep-HPLC to afford **Example 79** (9 mg) as a white solid. LCMS (M+H⁺): 814. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 (s, 1H), 7.88 - 7.75 (m, 1H), 7.61 (s, 1H), 7.36 - 7.19 (m, 2H), 7.15 (br d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.1 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.79 (br d, *J* = 15.4 Hz, 1H), 5.37 (d, *J* = 9.2 Hz, 1H), 4.61 (br d, *J* = 11.7 Hz, 2H), 4.56 - 4.41 (m, 3H), 4.28 - 4.06 (m, 4H), 3.92 (br d, *J* = 14.1 Hz, 1H), 3.46 (br s, 2H), 3.11 (s, 1H), 3.00 (s, 2H), 2.90 (br d, *J* = 14.9 Hz, 1H), 2.86 - 2.82 (m, 3H), 2.78 (s, 1H), 2.60 - 2.54 (m, 3H), 2.48 (br s, 2H), 2.30 (br d, *J* = 9.8 Hz, 1H).

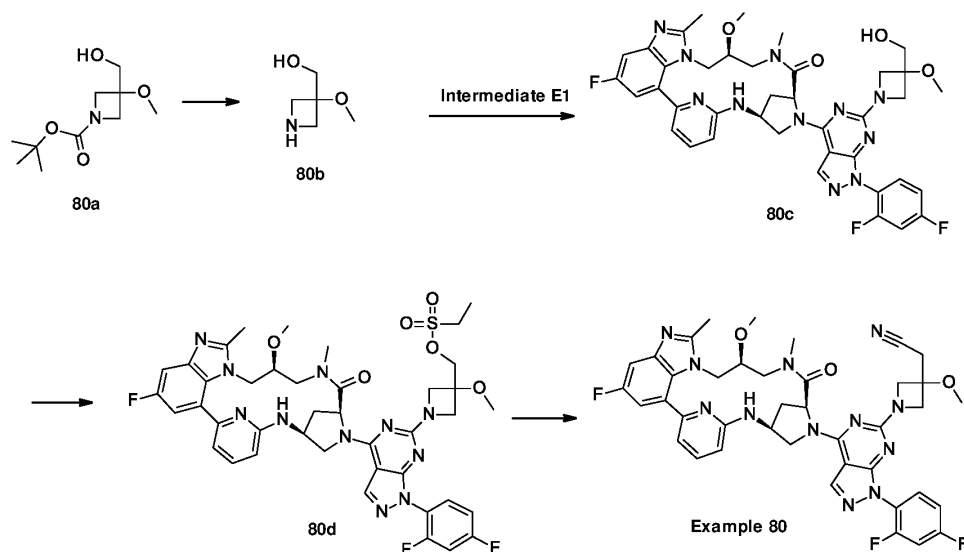
Example 80

- 15 2-[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]-3-methoxy-azetidin-3-yl]acetonitrile



The title compound was prepared according to the following scheme:

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Step 1: preparation of (3-methoxyazetidin-3-yl) methanol (compound 80b)

To a solution of compound **80a** (300.0 mg, 1.38 mmol) in DCM (7 mL) was added TFA (1.0 mL, 1.38 mmol) at 0 °C. The reaction was stirred at 20 °C for 1 h and then concentrated to give compound **80b** (300.0 mg) as light brown oil, which was used for next step directly.

Step 2: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(hydroxymethyl)-3-methoxy-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 (compound 80c)

A solution of Intermediate **E1** (100.0 mg, 0.14 mmol), compound **80b** (100.0 mg, 0.43 mmol), CsF (108 mg, 0.71 mmol) and DIEA (0.25 mL, 1.42 mmol) in DMA (1.5 mL) was stirred at 80 °C for 2 h. The reaction mixture was purified by prep-HPLC to give compound **80c** (80.0 mg) as a light brown solid. LCMS ($M+H^+$): 784.

Step 3: 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]-3-methoxy-azetidin-3-yl]methyl ethanesulfonate (compound 80d)

To a solution of compound **80c** (80.0 mg, 0.1 mmol) and TEA (13 mg, 0.13 mmol) in DCM (2 mL) was added ethanesulfonyl chloride (20 mg, 0.15 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h. Then the reaction mixture was filtered, the filtrate was concentrated, the

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residue was purified by prep-TLC to give compound **80d** (50.0 mg) as a light brown solid. LCMS (M+H⁺): 876.

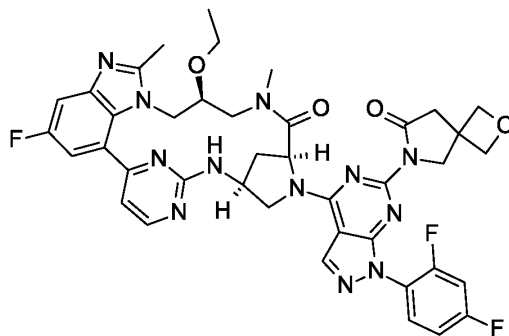
Step 4: preparation of 2-[1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-

5 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18, 20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidin-3-yl] acetonitrile(Example 80)

To a solution of compound **80d** (50.0 mg, 0.06 mmol) in DMF (1 mL) was added 18-crown-6 (2 mg, 0.01 mmol) and sodium cyanide (40.0 mg, 0.82 mmol). The reaction mixture was stirred at 50 °C for 2 h, and then the reaction mixture was purified by prep-HPLC to afford
 10 Example **80** (29 mg) as a white solid. LCMS (M+H⁺): 793. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.26 (s, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.23 (t, *J* = 9.5 Hz, 1H), 7.18 - 7.12 (m, 2H), 7.08 (d, *J* = 7.1 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 1H), 5.86 - 5.66 (m, 1H), 5.40 - 5.28 (m, 1H), 4.66 - 4.54 (m, 1H), 4.46 - 4.41 (m, 1H), 4.24 - 4.13 (m, 3H), 4.08 - 4.00 (m, 2H), 3.94 - 3.87 (m, 2H), 3.37 - 3.34 (m, 3H), 3.10 (d, *J* = 7.9 Hz, 3H), 3.05
 15 (s, 2H), 2.97 - 2.90 (m, 1H), 2.87 - 2.83 (m, 3H), 2.83 - 2.73 (m, 1H), 2.58 - 2.55 (m, 3H), 2.53 - 2.43 (m, 2H).

Example 81

7-[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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxa-7-azaspiro[3.4]octan-6-one



A mixture of intermediate **E2** (30 mg, 0.04 mmol), 2-oxa-7-azaspiro[3.4]octan-6-one (26 mg, 0.2 mmol), potassium phosphate (18 mg, 0.08 mmol), tris(dibenzylideneacetone)dipalladium
 25 (8mg, 0.008 mmol), dimethylbis(diphenylphosphino)xanthene (10 mg, 0.016 mol) in 1,4-dioxane (2 mL) was heated to 110 °C for 16 h. Then the reaction was concentrated and the residue was purified by prep-HPLC to give Example **81** (8 mg) as white powder. LCMS (M+H⁺): 809. ¹H

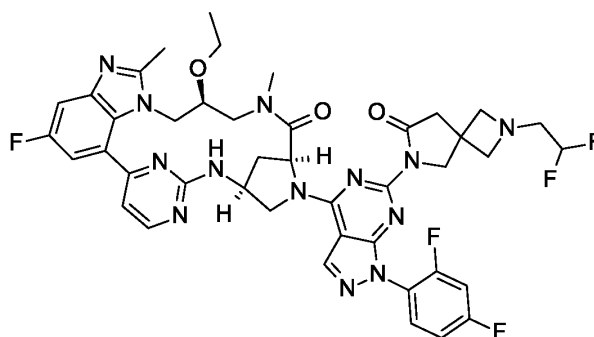
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NMR (400 MHz, METHANOL-*d*₄) δ = 8.46 (d, *J* = 5.3 Hz, 1H), 8.32 (s, 1H), 7.71 - 7.41 (m, 1H), 7.35 - 7.24 (m, 1H), 7.22 - 6.96 (m, 4H), 5.56 - 5.18 (m, 2H), 4.61 - 4.51 (m, 4H), 4.49 - 4.44 (m, 1H), 4.36 - 3.99 (m, 6H), 3.92 - 3.78 (m, 1H), 3.04 - 2.70 (m, 7H), 2.62 - 2.35 (m, 6H), 0.55 - 0.37 (m, 3H).

5

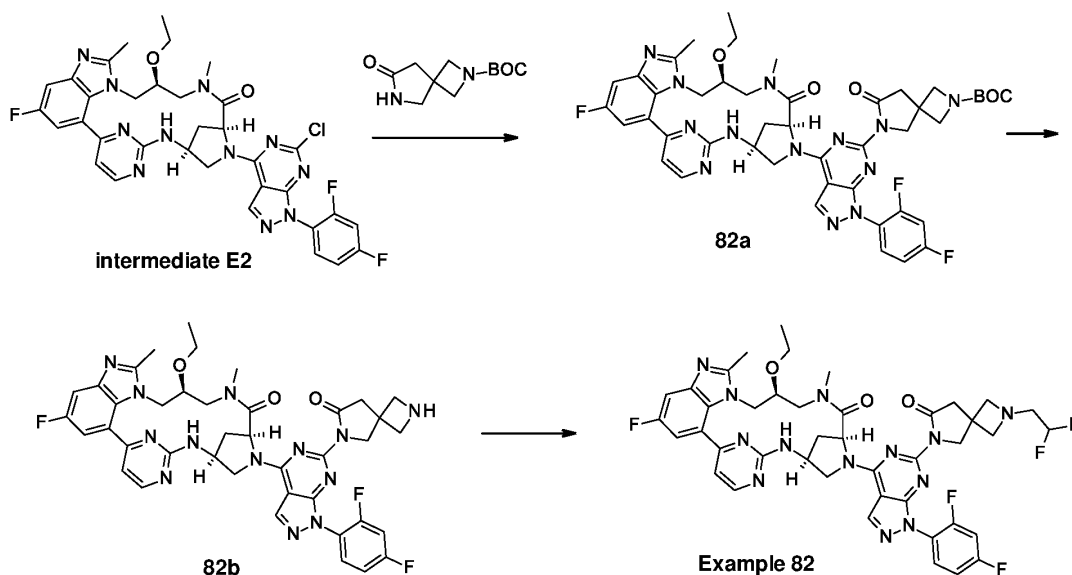
Example 82

(8*S*,11*S*,15*R*)-10-[6-[2-(2,2-difluoroethyl)-7-oxo-2,6-diazaspiro[3.4]octan-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



10

The title compound 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-5,7,10,13,17,19,26-

heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-

15

**yl]pyrazolo[3,4-d]pyrimidin-6-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate
(compound 82a)**

Compound **82a** was prepared in analogy to the preparation of Example **81** by using *tert*-butyl 6-oxo-2,7-diazaspiro[3.4]octane-2-carboxylate instead of 2-oxa-7-azaspiro[3.4]octan-6-one.

5 LCMS (M+H⁺): 908.

Step 2: preparation of (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(7-oxo-2,6-diazaspiro[3.4]octan-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 (compound 82b)

10 Compound **82b** was prepared in analogy to the preparation of compound **62b** by using compound **82a** instead of compound **62a**. LCMS (M+H⁺): 808.

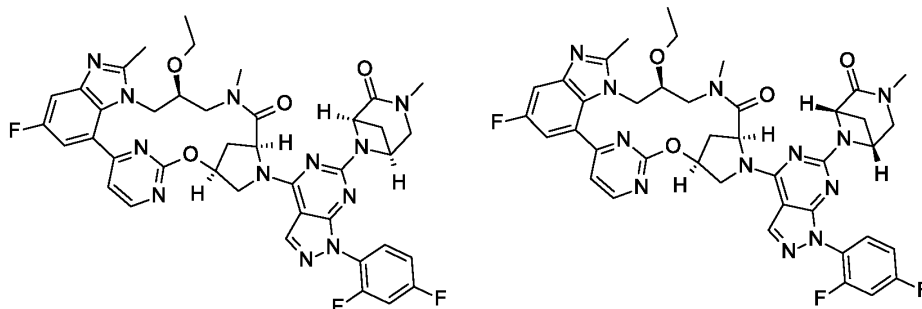
Step 3: preparation of (8S,11S,15R)-10-[6-[2-(2,2-difluoroethyl)-7-oxo-2,6-diazaspiro[3.4]octan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-

15 **heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 82)**

Example **82** was prepared in analogy to the preparation of Example **52** by using 2,2-difluoroethyl trifluoromethanesulfonate instead of compound **52a** and compound **82b** instead of intermediate **F1**. LCMS (M+H⁺): 872. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.54 - 8.40 (m, 20 1H), 8.36 - 8.25 (m, 1H), 7.67 - 7.55 (m, 1H), 7.33 - 7.24 (m, 1H), 7.22 - 6.93 (m, 4H), 5.89 - 5.47 (m, 2H), 5.44 - 5.17 (m, 1H), 4.70 - 4.65 (m, 1H), 4.39 - 4.27 (m, 1H), 4.26 - 3.97 (m, 4H), 3.95 - 3.76 (m, 1H), 3.42 - 3.26 (m, 4H), 3.17 - 3.11 (m, 1H), 3.06 - 2.93 (m, 3H), 2.89 - 2.63 (m, 6H), 2.61 - 2.35 (m, 6H), 0.56 - 0.39 (m, 3H).

Example 83 and 84

25 **(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[(1R,5S)-3-methyl-2-oxo-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 and (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[(1S,5R)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-**
30 **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**



Examples **83** and **84** were prepared in analogy to the preparation of Example **55** by using intermediate **D9** instead of intermediate **D18** and intermediate **C6** instead of intermediate **C2**.

SFC condition: Instrument: SFC 150 Mgm; Column: OD, 200×30 mm I.D., 5 μm; Mobile
 5 phase: A for CO₂ and B for Methanol (0.1% NH₃H₂O); Gradient: B 30%; Flow rate: 80 mL /min; Back pressure: 100bar; Column temperature: 35 °C.

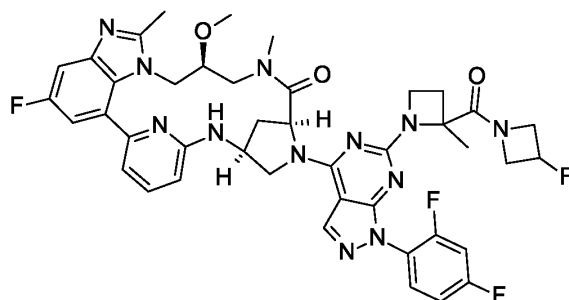
Example **83**, faster eluted. LCMS (M+H⁺): 809. ¹H NMR (400 MHz, METHANOL-*d*₄) δ =
 8.83 - 8.73 (m, 1H), 8.37 - 8.18 (m, 1H), 7.74 - 7.60 (m, 2H), 7.50 - 7.40 (m, 2H), 7.32 - 7.11(m,
 2H), 5.89 - 5.63 (m, 2H), 5.55 - 5.29 (m, 1H), 4.68 - 4.55 (m, 1H), 4.46 - 4.24 (m, 2H), 4.22 -
 10 4.08 (m, 3H), 4.07 - 3.84 (m, 1H), 3.31 - 3.25 (m, 1H), 3.17 - 2.93 (m, 4H), 2.91 - 2.74 (m, 6H),
 2.71 - 2.50 (m, 6H), 1.85 - 1.68 (m, 1H), 0.65 - 0.52 (m, 3H).

Example **84**, slower eluted. LCMS (M+H⁺): 809. ¹H NMR (400 MHz, METHANOL-*d*₄) δ =
 = 8.90 - 8.73 (m, 1H), 8.40 - 8.23 (m, 1H), 7.73 - 7.56 (m, 2H), 7.51 - 7.35 (m, 2H), 7.31 - 7.10
 (m, 2H), 5.92 - 5.60 (m, 2H), 5.54 - 5.22 (m, 1H), 4.69 - 4.50 (m, 1H), 4.47 - 4.26 (m, 2H), 4.24
 15 - 4.08 (m, 2H), 4.04 - 3.78 (m, 2H), 3.32 - 3.17 (m, 2H), 3.11 - 2.97 (m, 3H), 2.92 - 2.72 (m, 6H),
 2.71 - 2.50 (m, 6H), 1.88 - 1.71 (m, 1H), 0.69 - 0.52 (m, 3H).

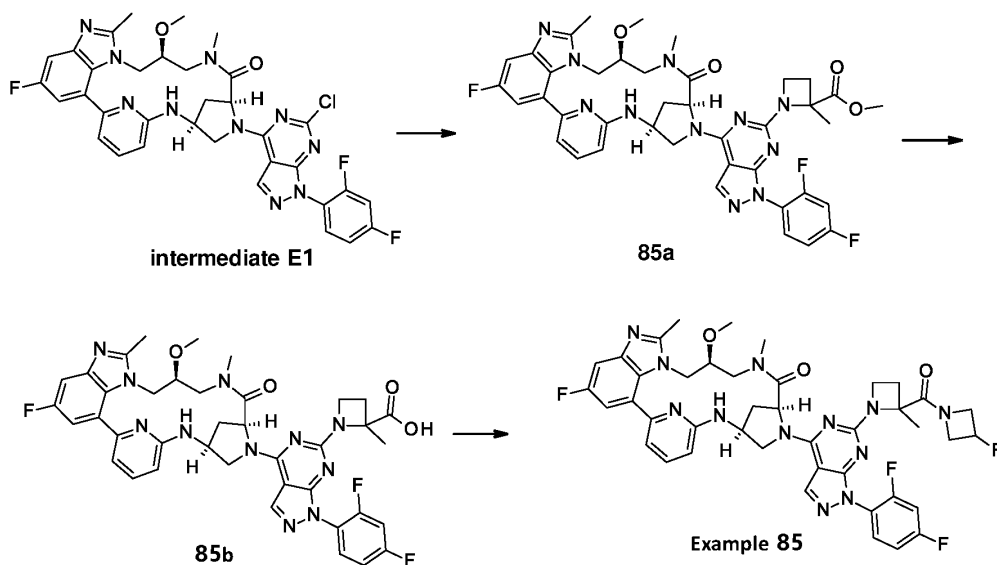
Example 85

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

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The title compound was prepared according to the following scheme:



Step 1: preparation of methyl 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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-methyl-azetidine-2-carboxylate (compound 85a)

Compound 85a was prepared in analogy to the preparation of compound 62a by using methyl 2-methylazetidine-2-carboxylate instead of 7-BOC-3-oxa-7,9-diazabicyclo[3.3.1]nonane.
LCMS ($M+H^+$): 796.

Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(3-fluoroazetidine-1-carbonyl)-2-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 85)

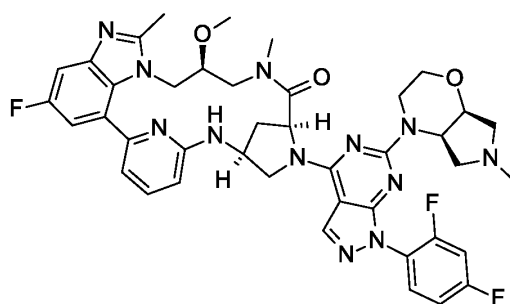
Example 85 was prepared in analogy to the preparation of compound 109d by using

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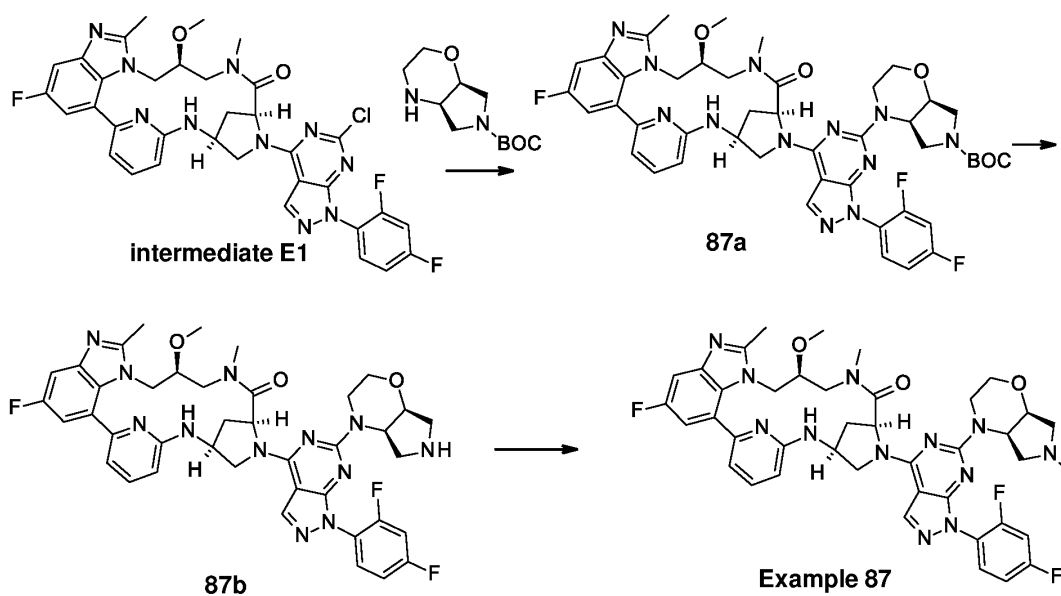
compound **85a** instead of compound **109b** and 3-fluoroazetidine instead of NH_4Cl . LCMS ($\text{M}+\text{H}^+$): 839. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ = 8.27 (br d, J = 3.8 Hz, 1H), 7.90 - 7.75 (m, 1H), 7.72 - 7.54 (m, 1H), 7.39 - 7.03 (m, 5H), 6.76 - 6.58 (m, 1H), 5.94 - 5.66 (m, 1H), 5.46 - 5.07 (m, 2H), 4.67 - 4.29 (m, 4H), 4.29 - 3.76 (m, 8H), 3.17 - 2.70 (m, 9H), 2.68 - 2.40 (m, 6H),
 5 2.25 - 2.04 (m, 1H), 1.82 - 1.68 (m, 1H).

Example 87

(8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-methyl-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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-
 10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one



The title compound was prepared according to the following scheme:



Example **87** was prepared in analogy to the preparation of Example **62** by using *tert*-butyl
 15 (4*aR*,7*aS*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazine-6-carboxylate instead of 7-
 BOC-3-oxa-7,9-diazabicyclo[3.3.1]nonane. LCMS ($\text{M}+\text{H}^+$): 809. ^1H NMR (400 MHz,

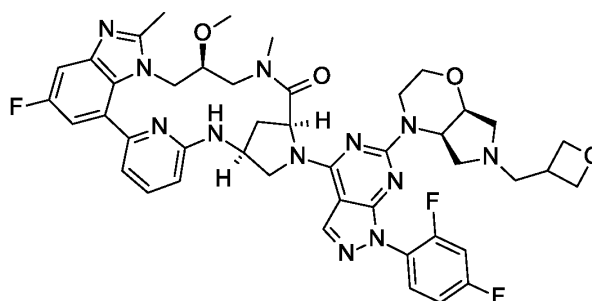
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METHANOL- d_4) δ = 8.36 - 8.26 (m, 1H), 7.92 - 7.79 (m, 1H), 7.71 - 7.59 (m, 1H), 7.39 - 7.23 (m, 2H), 7.21 - 7.04 (m, 3H), 6.77 - 6.66 (m, 1H), 5.91 - 5.67 (m, 1H), 5.48 - 5.29 (m, 1H), 4.71 - 4.63 (m, 1H), 4.54 - 4.40 (m, 2H), 4.31 - 4.12 (m, 5H), 4.09 - 3.84 (m, 4H), 3.68 - 3.60 (m, 2H), 3.21 - 3.03 (m, 5H), 3.00 - 2.79 (m, 7H), 2.70 - 2.47 (m, 5H).

5

Example 88

(8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-(oxetan-3-ylmethyl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-
b][1,4]oxazin-4-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



10

Example **88** was prepared in analogy to the preparation of Example **113** by using compound **87b** instead of compound **62b**. LCMS ($M+H^+$): 865. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.35 - 8.21 (m, 1H), 7.88 - 7.76 (m, 1H), 7.69 - 7.54 (m, 1H), 7.35 - 7.05 (m, 5H), 6.76 - 6.65 (m, 1H), 5.87 (br dd, J = 4.4, 15.6 Hz, 1H), 5.45 - 5.26 (m, 1H), 4.81 - 4.74 (m, 3H), 4.71 - 4.56 (m, 2H), 4.51 - 4.41 (m, 3H), 4.32 - 4.10 (m, 3H), 4.07 - 3.85 (m, 3H), 3.58 - 3.48 (m, 1H), 3.27 - 3.03 (m, 7H), 3.00 - 2.83 (m, 6H), 2.74 - 2.46 (m, 7H).

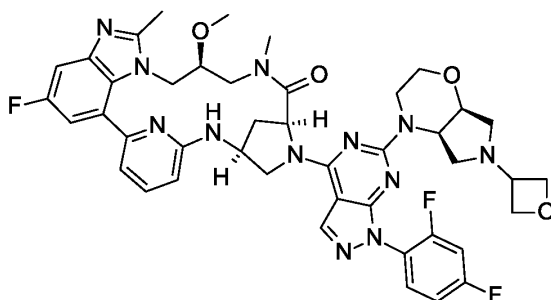
15

Example 89

(8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-(oxetan-3-yl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-
b][1,4]oxazin-4-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

20

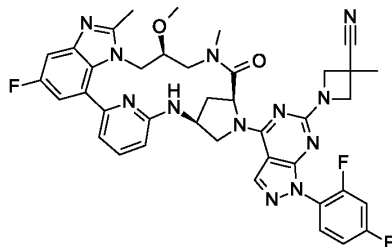
-177-



Example **89** was prepared in analogy to the preparation of Example **112** by using compound **87b** instead of compound **62b**. LCMS ($M+H^+$): 851. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.34 - 8.23 (m, 1H), 7.87 - 7.79 (m, 1H), 7.73 - 7.61 (m, 1H), 7.37 - 7.08 (m, 5H), 6.78 - 6.65 (m, 1H), 5.85 - 5.75 (m, 1H), 5.39 - 5.32 (m, 1H), 4.67 - 4.61 (m, 2H), 4.53 - 4.47 (m, 1H), 4.32 - 4.12 (m, 4H), 4.03 - 3.88 (m, 4H), 3.59 - 3.47 (m, 2H), 3.19 - 3.04 (m, 7H), 2.99 - 2.84 (m, 5H), 2.81 - 2.66 (m, 3H), 2.63 - 2.49 (m, 5H).

Example 90

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(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methyl-azetidine-3-carbonitrile

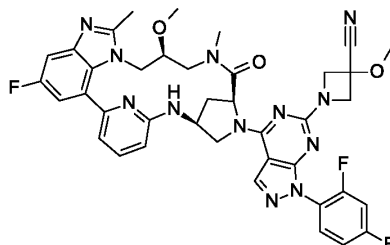


A mixture of intermediate **C1** (30.0 mg, 0.04 mmol), 3-methylazetidine-3-carbonitrile (17 mg, 0.130 mmol) and DIPEA (0.04 mL, 0.21 mmol) in IPA (0.5 mL) was stirred for 4 h at 120 °C. Then the reaction mixture was purified by prep-HPLC to give Example **90** (15 mg) as a white solid. LCMS ($M+H^+$): 763. 1H NMR (400 MHz, DMSO- d_6) δ 8.33 (s, 1H), 7.81 - 7.76 (m, 1H), 7.73 - 7.65 (m, 1H), 7.59 - 7.53 (m, 1H), 7.39 - 7.36 (m, 1H), 7.32 - 7.27 (m, 1H), 7.15 - 7.07 (m, 2H), 6.68 - 6.61 (m, 1H), 5.76 - 5.70 (m, 1H), 5.57 - 5.53 (m, 1H), 5.37 - 5.30 (m, 1H), 4.62 - 4.58 (m, 1H), 4.41 - 4.36 (m, 1H), 4.30 - 4.28 (m, 1H), 4.22 - 4.18 (m, 1H), 4.13 - 4.03 (m, 2H), 3.99 - 3.96 (m, 1H), 3.90 - 3.78 (m, 2H), 3.01 - 2.94 (m, 3H), 2.86 - 2.83 (m, 1H), 2.75 - 2.71 (m, 3H), 2.56 - 2.53 (m, 1H), 2.51 - 2.47 (m, 3H), 2.39 - 2.35 (m, 2H), 1.62 - 1.55 (m, 3H).

Example 91

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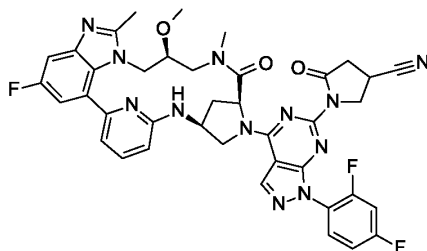
1-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidine-3-carbonitrile



- 5 A mixture of intermediate **C1** (30.0 mg, 0.04 mmol), 3-methoxyazetidine-3-carbonitrile (25 mg, 0.170 mmol) and DIPEA (0.04 mL, 0.21 mmol) in IPA (0.5 mL) was stirred for 4 h at 120 °C. Then the reaction mixture was purified by prep-HPLC to give Example **91** (15 mg) as a white solid. LCMS (*M*+*H*⁺): 779. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 (s, 1H), 7.80 - 7.55 (m, 3H), 7.38 - 7.29 (m, 2H), 7.14 - 7.07 (m, 2H), 6.67 - 6.63 (m, 1H), 5.73 - 5.70 (m, 1H), 5.57 - 5.53 (m, 1H), 5.38 - 5.30 (m, 1H), 4.62 - 4.58 (m, 1H), 4.44 - 4.34 (m, 3H), 4.26 - 4.16 (m, 2H), 4.12 - 4.07 (m, 2H), 3.97 - 3.95 (m, 1H), 3.82 - 3.79 (m, 1H), 3.42 - 3.33 (m, 3H), 3.01 - 2.95 (m, 3H), 2.88 - 2.85 (m, 1H), 2.75 - 2.71 (m, 3H), 2.49 - 2.45 (m, 3H), 2.42 - 2.33 (m, 2H).

Example 92

- 15 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(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-5-oxo-pyrrolidine-3-carbonitrile



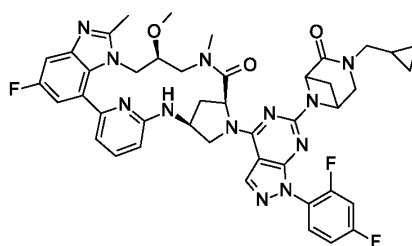
- To a stirred mixture of intermediate **C1** (70 mg, 0.1 mmol) and 5-oxopyrrolidine-3-carbonitrile (55 mg, 0.5 mmol) in 1,4-dioxane (3 mL) were added K₃PO₄ (63 mg, 0.3 mmol), tris(dibenzylideneacetone)dipalladium (36 mg, 0.04 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (46 mg, 0.08 mmol). The mixture was stirred for 6 h at 110 °C under nitrogen atmosphere. The reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **92** (17.0 mg) as a white solid. LCMS (*M*+*H*⁺): 777. ¹H NMR

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(400 MHz, DMSO-*d*₆) δ 8.51 (s, 1H), 7.80 - 7.44 (m, 4H), 7.38 - 7.30 (m, 3H), 7.15 - 7.10 (m, 2H), 6.68 - 6.62 (m, 1H), 5.80 - 5.38 (m, 3H), 4.62 - 4.42 (m, 1H), 4.30 - 4.05 (m, 4H), 3.94 - 3.59 (m, 3H), 3.02 - 2.75 (m, 6H), 2.72 - 2.53 (m, 3H), 2.49 - 2.44 (m, 3H), 2.37 - 2.34 (m, 1H).

Example 93

- 5 **(8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropylmethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one**

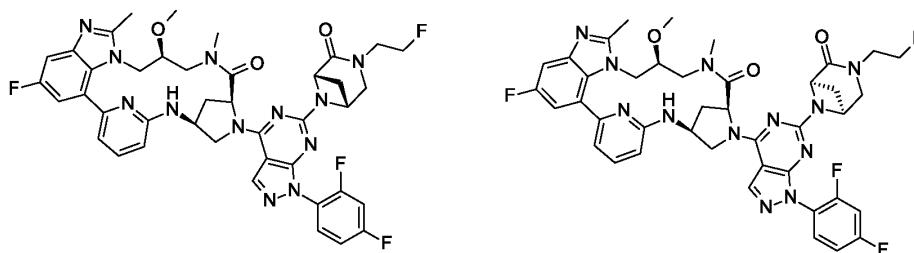


- 10 Example **93** was prepared in analogy to the preparation of Example **55** by using intermediate **D10** instead of intermediate **D18** and intermediate **C1** instead of intermediate **C2**.
 LCMS (M+H⁺): 833. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.35 - 8.33 (m, 1H), 7.84 - 7.81 (m, 1H), 7.67 - 7.56 (m, 3H), 7.41 - 7.39 (m, 1H), 7.30 - 7.28 (m, 1H), 7.16 - 7.12 (m, 1H), 6.74 - 6.68 (m, 1H), 6.00 - 5.90 (m, 1H), 5.74 - 5.52 (m, 2H), 5.37 - 5.24 (m, 1H), 4.63 - 4.60 (m, 1H),
 15 4.44 - 4.35 (m, 2H), 4.22 - 4.01 (m, 4H), 3.85 - 3.75 (m, 2H), 3.05 - 2.89 (m, 4H), 2.83 - 2.78 (m, 4H), 2.71 - 2.60 (m, 5H), 2.42 - 2.37 (m, 2H), 1.72 - 1.65 (m, 1H), 0.85 - 0.45 (m, 1H), 0.15 - 0.00 (m, 1H), -0.05 - -0.20 (m, 2H).

Example 94 and 95

- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(2-fluoroethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one** and **(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(2-fluoroethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one**
 20
 25

-180-



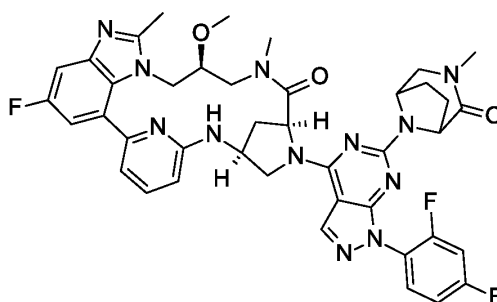
Examples **94** and **95** were prepared in analogy to the preparation of Example **55** by using intermediate **D12** instead of intermediate **D18** and intermediate **C1** instead of intermediate **C2**.

Example **94**: faster eluted, LCMS ($M+H^+$): 825. 1H NMR (400 MHz, $DMSO-d_6$) δ = 8.90 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.89 - 7.75 (m, 2H), 7.74 - 7.61 (m, 2H), 7.60 - 7.48 (m, 1H), 7.36 - 7.20 (m, 1H), 5.81 - 5.55 (m, 2H), 5.48 - 5.24 (m, 1H), 4.67 - 3.71 (m, 9H), 3.70 - 3.11 (m, 4H), 3.01 - 2.89 (m, 3H), 2.88 - 2.52 (m, 9H), 1.73 - 1.69 (m, 1H), 0.51 - 0.39 (m, 3H).

Example **95**: slower eluted, LCMS ($M+H^+$): 825. 1H NMR (400 MHz, $DMSO-d_6$) δ = 8.89 (s, 1H), 8.41 (s, 1H), 7.90 - 7.74 (m, 2H), 7.73 - 7.61 (m, 2H), 7.60 - 7.51 (m, 1H), 7.37 - 7.21 (m, 1H), 5.79 - 5.52 (m, 2H), 5.48 - 5.32 (m, 1H), 4.60 - 3.80 (m, 9H), 3.63 - 3.13 (m, 4H), 3.01 - 2.75 (m, 5H), 2.74 - 2.40 (m, 7H), 1.79 - 1.59 (m, 1H), 0.52 - 0.39 (m, 3H).

Example 100

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



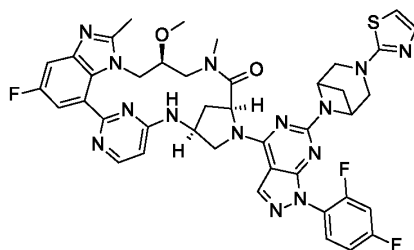
Example **100** was prepared in analogy to the preparation of Example **51** by using 3-methyl-3,8-diazabicyclo[3.2.1]octan-2-one instead of compound **51a**. LCMS ($M+H^+$): 807. 1H NMR (400 MHz, $METHANOL-d_4$) δ = 8.34 - 8.22 (m, 1H), 7.90 - 7.72 (m, 1H), 7.67 - 7.56 (m, 1H), 7.38 - 7.28 (m, 1H), 7.25 - 7.07 (m, 4H), 6.74 - 6.61 (m, 1H), 5.91 - 5.69 (m, 1H), 5.47 - 5.23 (m, 1H), 4.74 - 4.69 (m, 1H), 4.66 - 4.60 (m, 1H), 4.49 - 4.38 (m, 1H), 4.26 - 4.12 (m, 2H), 3.97 - 3.86 (m, 1H), 3.81 - 3.67 (m, 1H), 3.12 - 3.05 (m, 3H), 3.04 - 2.93 (m, 2H), 2.89 - 2.83 (m, 3H),

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2.82 - 2.73 (m, 4H), 2.66 - 2.54 (m, 4H), 2.53 - 2.42 (m, 2H), 2.35 - 2.10 (m, 2H), 2.09 - 1.98 (m, 1H), 1.96 - 1.79 (m, 1H).

Example 101

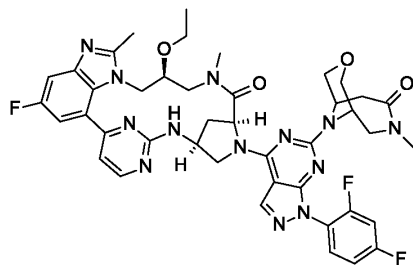
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-3,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **101** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c** and intermediate **E10** instead of intermediate **E4**. LCMS (M+H⁺): 849. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.60 - 8.48 (m, 1H), 8.32 - 8.21 (m, 1H), 7.84 - 7.69 (m, 1H), 7.67 - 7.52 (m, 2H), 7.34 - 7.14 (m, 3H), 6.91 - 6.69 (m, 2H), 6.04 - 5.74 (m, 1H), 5.52 - 5.30 (m, 1H), 4.78 - 4.57 (m, 2H), 4.54 - 4.40 (m, 2H), 4.37 - 4.23 (m, 3H), 4.21 - 3.93 (m, 2H), 3.68 - 3.42 (m, 3H), 3.23 - 3.04 (m, 4H), 3.01 - 2.89 (m, 3H), 2.86 - 2.54 (m, 7H).

Example 102

10-[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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methyl-8-oxa-3,10-diazabicyclo[4.3.1]decan-4-one



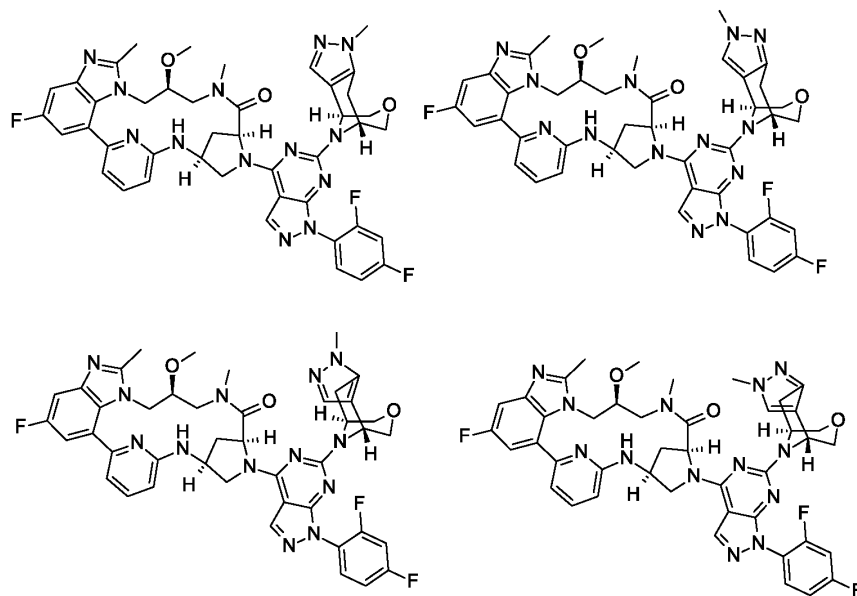
Example **102** was prepared in analogy to the preparation of Example **57** by using *tert*-butyl 4-oxo-8-oxa-3,10-diazabicyclo[4.3.1]decan-10-carboxylate instead of compound **60d** and

intermediate **E2** instead of intermediate **E5**. LCMS (M+H⁺): 852. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.57 - 8.40 (m, 1H), 8.26 - 8.07 (m, 1H), 7.63 - 7.42 (m, 1H), 7.35 - 7.25 (m, 1H), 7.22 - 6.93 (m, 4H), 5.60 - 5.40 (m, 1H), 5.36 - 5.26 (m, 1H), 4.58 - 4.38 (m, 6H), 4.35 - 4.24 (m, 1H), 4.19 - 4.04 (m, 2H), 3.93 - 3.56 (m, 6H), 3.04 - 2.89 (m, 4H), 2.89 - 2.77 (m, 3H),
 5 2.71 - 2.30 (m, 8H), 0.57 - 0.41 (m, 3H).

Example 103, 104, 105 and 106

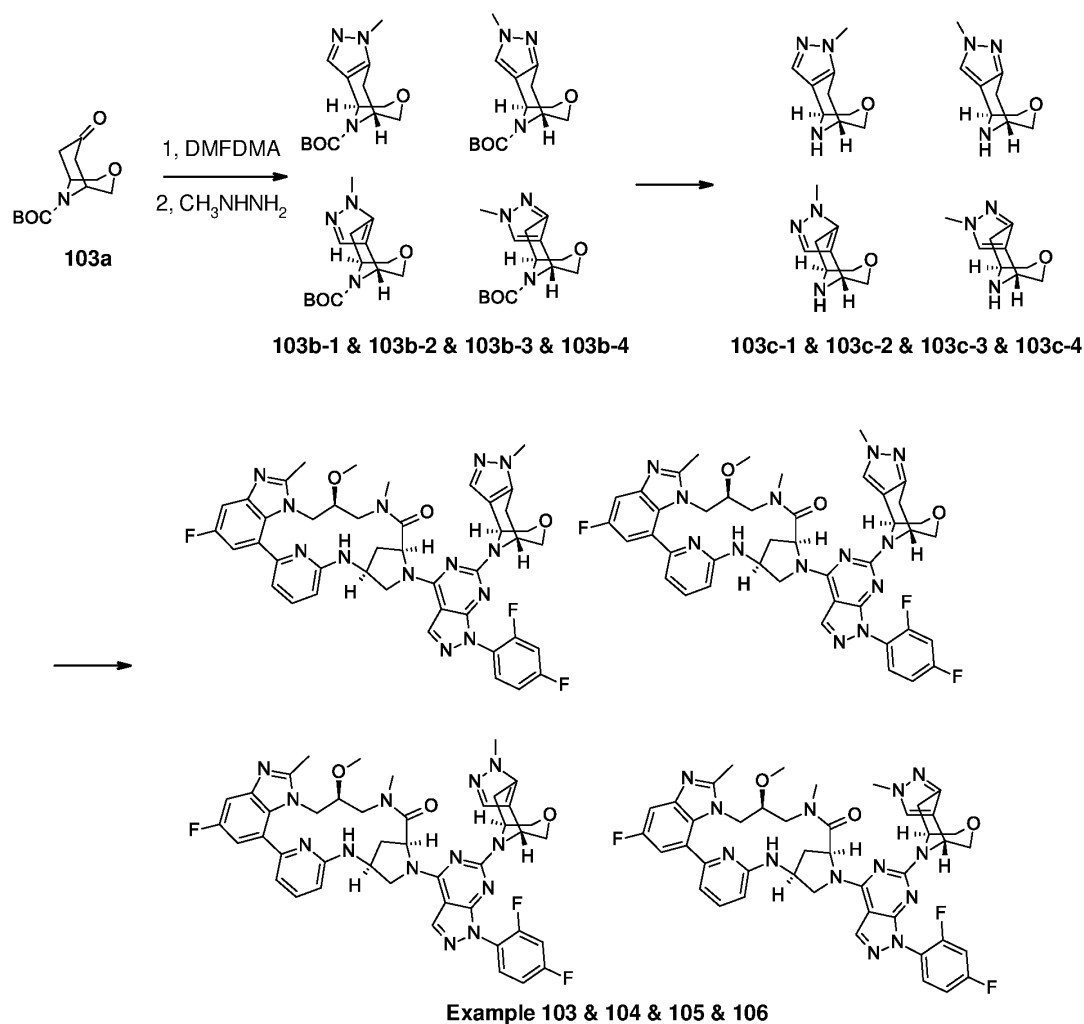
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
 10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one; (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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;
 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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;
 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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

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The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl (1*S*,8*R*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-diene-12-carboxylate; *tert*-butyl (1*R*,8*S*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-diene-12-carboxylate; *tert*-butyl (1*S*,8*R*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-diene-12-carboxylate; *tert*-butyl (1*R*,8*S*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-diene-12-carboxylate (compound 103b-1, 103b-2, 103b-3 and 103b-4)

A mixture of compound **103a** (2 g, 8.29 mmol) and DMF-DMA (9.88 g, 82.9 mmol) in 1,4-dioxane (10 mL) was stirred at 110 °C for 16 hours, then the reaction mixture was concentrated to give a residue, to which was added DIPEA (4.8 g, 37 mmol), methylhydrazine;sulfuric acid (2.68 g, 18.57 mmol) and ethanol (88 mL). The resulted mixture was stirred at 80 °C for 4 hours and then concentrated. The residue was purified by reversed

flash column chromatography and SFC to give compound **103b-1** (100 mg, the second eluted), **103b-2** (60 mg, the forth eluted), **103b-3** (the first eluted) and **103b-4** (the third eluted). LCMS (M+H⁺): 280.

SFC condition: Instrument: SFC 150 Mgm; Column: AD-H, 250×30 mm I.D., 5 μm;

- 5 Mobile phase: A for CO₂ and B for ethanol (0.1 % NH₃H₂O); Gradient: B 10%; Flow rate: 80 mL/min; Back pressure: 100 bar; Column temperature: 35 °C.

Step 2-3: preparation of (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[(1S,8R)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-

- 10 **hexazapentacyclo[15.6.1.1^{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-[(1R,8S)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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,15R)-10-[1-(2,4-difluorophenyl)-6-**
- 15 **[(1S,8R)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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,15R)-10-[1-(2,4-difluorophenyl)-6-[(1R,8S)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-**
- 20 **15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 103 & 104 & 105 & 106)**

Examples **103**, **104**, **105** and **106** were prepared in analogy to the preparation of Example **57** by using compound **103b-1**, **103b-2**, **103b-3** and **103b-4** instead of compound **57b** and

- 25 intermediate **E1** instead of intermediate **E5**.

Example **103**, LCMS (M+H⁺): 846. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 - 8.20 (m, 1H), 7.96 - 7.82 (m, 1H), 7.64 - 7.50 (m, 3H), 7.46 - 7.34 (m, 1H), 7.32 - 7.10 (m, 3H), 6.85 - 6.74 (m, 1H), 6.32 - 5.98 (m, 1H), 5.66 - 5.24 (m, 2H), 4.68 - 4.49 (m, 1H), 4.45 - 4.15 (m, 3H), 4.08 - 3.51 (m, 9H), 3.25 - 2.92 (m, 9H), 2.89 - 2.74 (m, 4H), 2.70 - 2.47 (m, 2H).

- 30 Example **104**, LCMS (M+H⁺): 846. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 - 8.19 (m, 1H), 7.92 - 7.78 (m, 1H), 7.69 - 7.56 (m, 1H), 7.35 - 7.22 (m, 3H), 7.21 - 7.06 (m, 3H), 6.77 - 6.62 (m, 1H), 5.93 - 5.80 (m, 1H), 5.60 - 5.51 (m, 1H), 4.52 - 4.44 (m, 2H), 4.24 - 4.15 (m, 3H),

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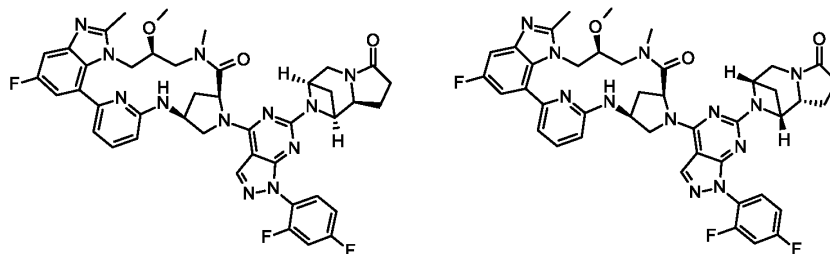
4.04 - 3.93 (m, 3H), 3.85 - 3.70 (m, 5H), 3.15 - 3.03 (m, 5H), 2.94 - 2.79 (m, 5H), 2.68 - 2.48 (m, 6H).

Example **105**, LCMS (M+H⁺): 846. ¹H NMR (400 MHz, DMSO-*d*₆ & METHANOL-*d*₄) δ = 8.31 - 8.17 (m, 1H), 7.82 - 7.73 (m, 1H), 7.69 - 7.57 (m, 1H), 7.45 - 6.98 (m, 6H), 6.71 - 6.54 (m, 1H), 5.85 - 5.56 (m, 1H), 5.51 - 5.41 (m, 1H), 5.34 - 5.04 (m, 1H), 4.79 - 4.54 (m, 1H), 4.46 - 4.32 (m, 1H), 3.95 - 3.47 (m, 10H), 3.20 - 2.92 (m, 7H), 2.89 - 2.65 (m, 5H), 2.47 - 2.30 (m, 4H).

Example **106**, LCMS (M+H⁺): 846. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.37 - 8.16 (m, 1H), 7.93 - 7.76 (m, 1H), 7.71 - 7.57 (m, 1H), 7.39 - 7.04 (m, 6H), 6.78 - 6.61 (m, 1H), 5.91 - 5.65 (m, 1H), 5.52 - 5.23 (m, 1H), 4.71 - 4.51 (m, 2H), 4.48 - 4.32 (m, 1H), 4.30 - 3.56 (m, 11H), 3.23 - 2.95 (m, 5H), 2.93 - 2.69 (m, 5H), 2.63 - 2.42 (m, 5H).

Example 107 and 108

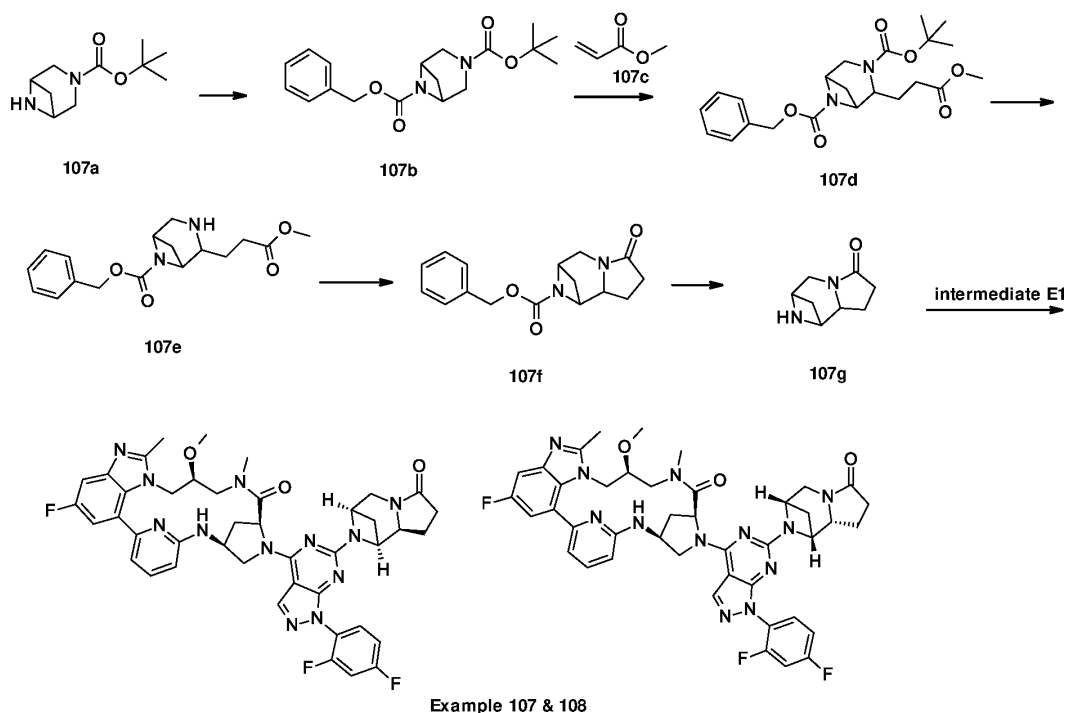
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,2*S*,8*R*)-5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,2*R*,8*S*)-5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-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



20

The title compound was prepared according to the following scheme:

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Step 1: preparation of 6-benzyl 3-*tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate (compound 107b)

To a solution of compound **107a** (5 g, 25.22 mmol) and sodium carbonate (8 g, 75.66 mmol) in THF (50 mL) and water (50 mL) was added *N*-(benzyloxycarbonyloxy) succinimide (7.5 g, 30.26 mmol). The reaction was stirred at 25 °C for 16 h and then quenched with water, and extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by flash chromatography to give compound **107b** (8 g) as colorless oil. LCMS ($M+Na^+$): 355.

Step 2: preparation of 6-benzyl 3-*tert*-butyl 2-(3-methoxy-3-oxo-propyl)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate (compound 107d)

To a solution of compound **107b** (1.5 g, 4.51 mmol) in CD_3CN (3.0 mL, 4.51 mmol) was added diphenylmethanone (411 mg, 2.26 mmol), $Cu(OAc)_2$ (16 mg, 0.09 mmol) and compound **107c** (600 mg, 6.97 mmol) under N_2 . The mixture was stirred at 30 °C for 4 h under 365 nm LED irradiation. The reaction mixture was filtered and concentrated to give a crude product, which was purified by flash chromatography to give compound **107d** (250 mg) as light yellow oil. LCMS ($M+Na^+$): 441.

Step 3: preparation of benzyl 2-(3-methoxy-3-oxo-propyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 107e)

To a solution of compound **107d** (300 mg, 0.72 mmol) in DCM (5 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was stirred for 2 h at 25 °C and then concentrated, the residue was purified by prep-HPLC to give compound **107e** (110.0 mg) as light yellow oil. LCMS (M+H⁺): 319.

5 **Step 4: preparation of benzyl 5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-carboxylate (compound 107f)**

To a solution of compound **107e** (110.0 mg, 0.35 mmol) in THF (70 mL) was added TBD (24 mg, 0.17 mmol) at 25 °C. The mixture was stirred at 60 °C for 16 h and then concentrated, the residue was purified by prep-HPLC to give compound **107f** (55.0 mg) as light yellow
10 semisolid. LCMS (M+H⁺): 287.

Step 5: preparation of 6,9-diazatricyclo[6.1.1.0^{2,6}]decan-5-one (compound 107g)

To a solution of compound **107f** (55.0 mg, 0.19 mmol) in methanol (3 mL) was added wet Pd/C (55 mg) under N₂ at 25 °C. The mixture was stirred under H₂ (balloon) at 25 °C for 2 h. Then the mixture was filtered, the filtrate was concentrated to give compound **107g** (40.0 mg) as
15 light yellow semisolid.

**Step 6: preparation of (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[(1S,2S,8R)-5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-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 and (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-
20 [(1R,2R,8S)-5-oxo-6,9-diazatricyclo [6.1.1.0^{2,6}]decan-9-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 107 and 108)**

A solution of Intermediate **E1** (40.0 mg, 0.06 mmol), compound **107g** (17 mg, 0.11 mmol),
25 CsF (21 mg, 0.14 mmol) and DIPEA (0.02 mL, 0.14 mmol) in DMA (0.5 mL) was stirred at 120 °C for 16 h. Then the reaction mixture was purified by prep-HPLC and SFC to give Example **107** and Example **108**. SFC Method: Column DAICEL CHIRALPAK AD (250 mm×30 mm, 10 μm); Condition CO₂-EtOH (0.1% NH₃·H₂O); Begin B 60%; End B 60%; Gradient Time (min) 4.5; 100% B Hold Time (min) 0; Flow Rate (ml/min) 120.

30 Example **107** (6 mg), faster eluted. LCMS (M+H⁺): 819. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.18 (s, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.58 - 7.49 (m, 1H), 7.23 - 7.17 (m, 1H), 7.17 - 7.11 (m, 1H), 7.08 - 7.02 (m, 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 5.76 - 5.55 (m, 1H), 5.30 - 5.19 (m, 1H), 4.57 - 4.52 (m, 1H), 4.47 (s, 3H), 4.38 - 4.33 (m, 1H),

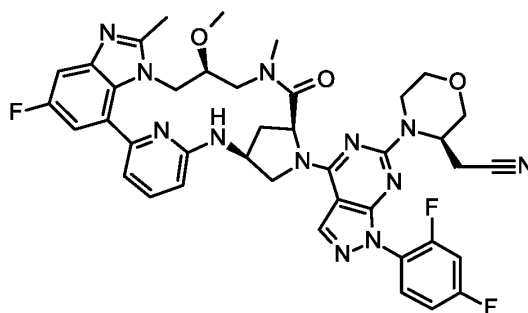
-189-

4.26 - 4.21 (m, 1H), 4.16 - 4.01 (m, 3H), 3.90 - 3.73 (m, 1H), 3.60 - 3.49 (m, 1H), 3.04 - 2.93 (m, 3H), 2.84 (br d, $J = 14.1$ Hz, 1H), 2.77 - 2.71 (m, 3H), 2.67 (br d, $J = 13.9$ Hz, 1H), 2.55 - 2.44 (m, 4H), 2.44 - 2.34 (m, 2H), 2.24 - 2.15 (m, 1H), 2.06 - 1.97 (m, 1H), 1.65 - 1.46 (m, 2H).

Example **108** (5 mg), slower eluted. LCMS ($M+H^+$): 819. 1H NMR (400 MHz, METHANOL- d_4) $\delta = 8.18$ (s, 1H), 7.75 - 7.68 (m, 1H), 7.57 - 7.48 (m, 1H), 7.23 - 7.18 (m, 1H), 7.17 - 7.11 (m, 1H), 7.09 - 7.03 (m, 2H), 7.01 - 6.97 (m, 1H), 6.57 (d, $J = 8.3$ Hz, 1H), 5.73 - 5.55 (m, 1H), 5.32 (br d, $J = 8.5$ Hz, 1H), 4.55 (br t, $J = 5.3$ Hz, 1H), 4.41 - 4.33 (m, 2H), 4.25 (br s, 1H), 4.16 - 4.10 (m, 3H), 4.00 - 3.49 (m, 3H), 3.01 (s, 1H), 2.94 (s, 3H), 2.91 - 2.88 (m, 1H), 2.78 - 2.69 (m, 4H), 2.52 - 2.44 (m, 4H), 2.43 - 2.35 (m, 2H), 2.26 - 2.18 (m, 1H), 1.96 - 1.85 (m, 1H), 1.70 - 1.58 (m, 1H), 1.54 - 1.50 (m, 1H), 1.49 - 1.47 (m, 1H).

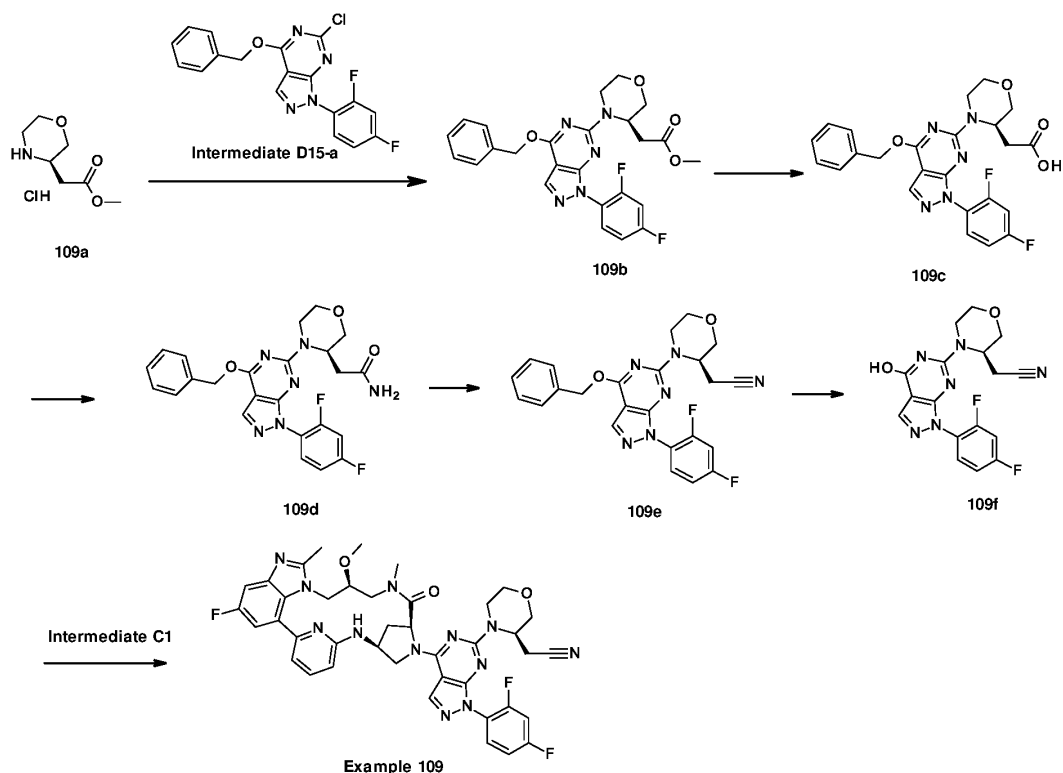
Example 109

2-[(3*R*)-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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]morpholin-3-yl]acetonitrile



The title compound was prepared according to the following scheme:

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Step 1: preparation of methyl 2-[(3R)-4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetate (compound 109b)

To a solution of Intermediate **D15-a** (500.0 mg, 1.34 mmol), compound **109a** (262 mg, 1.34 mmol) in 1,4-dioxane (5 mL) was added Pd-PEPPSI-IPentCl o-picoline (231 mg, 0.27 mmol) and Cs₂CO₃ (2.2 g, 6.71 mmol) at 25 °C. The reaction was stirred at 100 °C for 3 h under N₂ and then poured into water, extracted with EtOAc. The organic layer was dried and concentrated, the residue was purified by flash chromatography to give compound **109b** (330.0 mg) as a light yellow solid. LCMS (M+H⁺): 496.

Step 2: preparation of 2-[(3R)-4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetic acid (compound 109c)

To a solution of compound **109b** (400.0 mg, 0.81 mmol) in THF (4 mL) and methanol (4 mL) was added a solution of LiOH·H₂O (169 mg, 4.04 mmol) in water (4 mL) at 0 °C. The reaction was stirred at 25 °C for 3 h and then concentrated. The residue was dissolved in EtOAc, washed with brine (10 mL), dried and concentrated to give compound **109c** (300.0 mg) as a light yellow solid. LCMS (M+H⁺): 482.

Step 3: preparation of 2-[(3R)-4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetamide (compound 109d)

A mixture of compound **109c** (300.0 mg, 0.62 mmol), NH₄Cl (66 mg, 1.25 mmol), HATU (249 mg, 1.06 mmol) and DIEA (0.18 mL, 1.06 mmol) in DMF (5 mL) was stirred at 25 °C for 16 h. The reaction mixture was poured into water and then extracted with EtOAc, the organic layer was concentrated to give a crude product, which was purified by prep-TLC to give

5 compound **109d** (280.0 mg) as a light yellow solid. LCMS (M+H⁺): 481.

Step 4: preparation of 2-[(3R)-4-[4-benzyloxy-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetonitrile (compound 109e)

To a solution of compound **109d** (50.0 mg, 0.1 mmol) and pyridine (0.03 mL, 0.31 mmol) in THF (5 mL) was added TFAA (0.02 mL, 0.12 mmol) slowly at 0 °C and then stirred at 0 °C
10 for 1 h. The reaction mixture was poured into ice water, extracted with EtOAc, the organic layer was dried and concentrated to give compound **109e** (50.0 mg) as light yellow oil. LCMS (M+H⁺): 463.

Step 5: preparation of 2-[(3R)-4-[1-(2,4-difluorophenyl)-4-hydroxy-pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetonitrile (compound 109f)

15 To a solution of compound **109e** (50.0 mg, 0.11 mmol) in DCM (2 mL) was added TFA (2 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h and then concentrated to give compound **109f** (50.0 mg) as light yellow oil. LCMS (M+H⁺): 373.

Step 6: preparation of 2-[(3R)-4-[1-(2,4-difluorophenyl)-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}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]morpholin-3-yl]acetonitrile (Example 109)

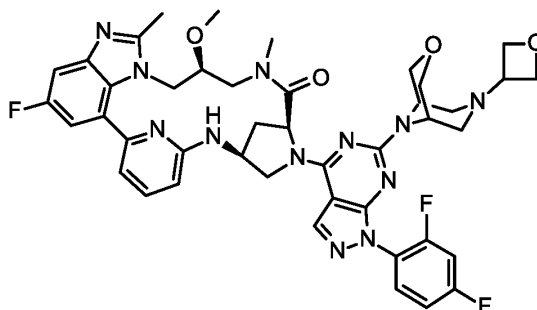
To a solution of compound **109f** (50.0 mg, 0.1 mmol), PyBOP (80 mg, 0.15 mmol), DIEA (0.04 mL, 0.26 mmol) in DMF (1 mL) was added a solution of Intermediate **C1** (51 mg, 0.09 mmol), DIEA (0.04 mL, 0.26 mmol) in DMF (1 mL) at 25 °C. The mixture was stirred at 25 °C
25 for 2 h and then purified by prep-HPLC to give Example **109** (16 mg) as a white solid. LCMS (M+H⁺): 793. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.30 (s, 1H), 7.95 - 7.85 (m, 1H), 7.70 - 7.51 (m, 3H), 7.31 - 7.21 (m, 1H), 7.20 - 7.12 (m, 2H), 6.88 - 6.74 (m, 1H), 6.28 - 6.06 (m, 1H), 5.47 - 5.33 (m, 1H), 4.72 - 4.62 (m, 2H), 4.55 - 4.45 (m, 1H), 4.38 - 4.21 (m, 3H), 4.03 - 3.88 (m, 3H), 3.74 - 3.63 (m, 1H), 3.58 - 3.48 (m, 1H), 3.28 - 3.19 (m, 4H), 3.09 - 3.08 (m, 1H), 3.10 -
30 2.96 (m, 5H), 2.88 - 2.82 (m, 3H), 2.80 - 2.77 (m, 1H), 2.67 - 2.52 (m, 2H).

Example 112

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

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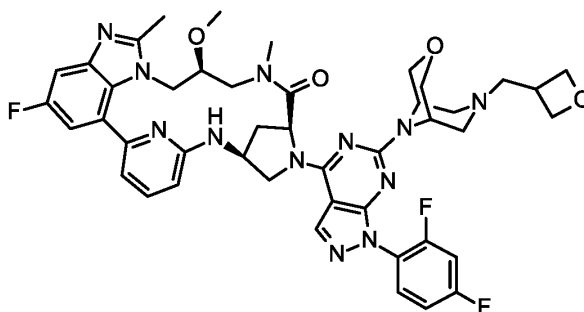
dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
1(24),2,4,6(26),18,20,22-heptaen-12-one



To a solution of compound **62b** (30.0 mg, 0.03 mmol) in methanol (0.5 mL) was added 3-oxetanone (7 mg, 0.1 mmol) and sodium cyanoborohydride (4 mg, 0.07 mmol). The reaction mixture was stirred at 25 °C for 12 hr under N₂, then the mixture was purified by prep-HPLC to give Example **112** (8 mg) as a white solid. LCMS (M+H⁺): 851. ¹H NMR (400 MHz, METHANOL-*d*₄) δ (ppm) = 8.25 (s, 1H), 7.86 - 7.76 (m, 1H), 7.68 - 7.58 (m, 1H), 7.34 - 7.29 (m, 1H), 7.26 - 7.18 (m, 1H), 7.17 - 7.11 (m, 2H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.71 - 6.65 (m, 1H), 5.89 - 5.63 (m, 1H), 5.41 - 5.27 (m, 1H), 4.73 (br t, *J* = 6.3 Hz, 2H), 4.66 - 4.57 (m, 6H), 4.51 - 4.42 (m, 2H), 4.28 - 4.09 (m, 3H), 3.98 - 3.77 (m, 5H), 3.12 - 3.01 (m, 3H), 2.95 - 2.88 (m, 2H), 2.87 - 2.82 (m, 3H), 2.76 (br d, *J* = 13.4 Hz, 1H), 2.59 - 2.55 (m, 3H), 2.52 - 2.43 (m, 2H), 2.35 - 2.24 (m, 1H).

Example 113

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-ylmethyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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



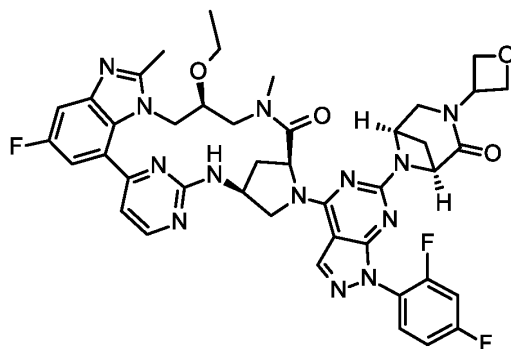
A solution of compound **62b** (20.0 mg, 0.02 mmol), 3-(iodomethyl)oxetane (7 mg, 0.03 mmol), CsF (10 mg, 0.07 mmol) and DIEA (0.01 mL, 0.07 mmol) in DMA (0.5 mL) was stirred

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at 60 °C for 3 h. Then the reaction mixture was purified by prep-HPLC to give Example **113** (12 mg) as a white solid. LCMS (M+H⁺): 865. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.27 (s, 1H), 7.87 - 7.78 (m, 1H), 7.67 - 7.55 (m, 1H), 7.34 - 7.28 (m, 1H), 7.27 - 7.19 (m, 1H), 7.19 - 7.13 (m, 2H), 7.12 - 7.08 (m, 1H), 6.73 - 6.65 (m, 1H), 5.89 - 5.64 (m, 1H), 5.40 - 5.30 (m, 1H), 4.84 - 4.76 (m, 2H), 4.68 - 4.59 (m, 1H), 4.55 - 4.41 (m, 4H), 4.29 - 4.09 (m, 3H), 4.00 - 3.90 (m, 2H), 3.88 - 3.75 (m, 3H), 3.12 (s, 1H), 3.05 - 3.00 (m, 3H), 2.98 - 2.90 (m, 1H), 2.88 - 2.83 (m, 3H), 2.81 - 2.73 (m, 2H), 2.57 (d, *J* = 3.6 Hz, 3H), 2.53 - 2.45 (m, 2H), 2.24 - 1.98 (m, 1H), 1.39 - 1.29 (m, 4H).

Example 114

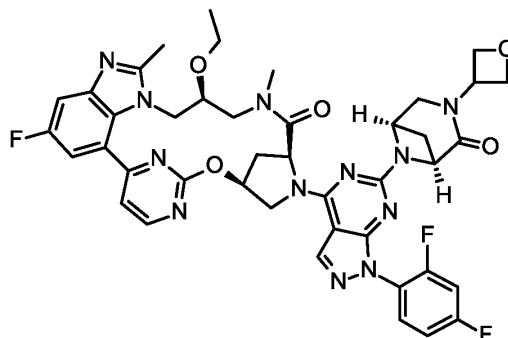
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **114** was prepared in analogy to the preparation of Example **60** by using compound **61b** instead of compound **60h** and Intermediate **E2** instead of Intermediate **E4**. LCMS (M+H⁺): 850. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.54 (s, 1H), 8.31 (s, 1H), 7.68 - 7.61 (m, 1H), 7.46 - 7.38 (m, 1H), 7.33 - 7.28 (m, 1H), 7.27 - 7.21 (m, 1H), 7.21 - 7.14 (m, 1H), 7.11 (s, 1H), 5.67 - 5.45 (m, 1H), 5.43 - 5.25 (m, 1H), 5.22 - 5.05 (m, 1H), 4.73 (br d, *J* = 7.2 Hz, 4H), 4.59 (br s, 5H), 4.27 (s, 2H), 4.17 (br s, 3H), 3.12 - 2.99 (m, 3H), 2.97 - 2.90 (m, 1H), 2.87 - 2.79 (m, 1H), 2.63 (s, 3H), 2.58 (s, 2H), 2.51 - 2.37 (m, 1H), 2.04 (s, 1H), 1.88 - 1.66 (m, 1H), 0.59 (t, *J* = 6.8 Hz, 3H).

Example 115

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-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

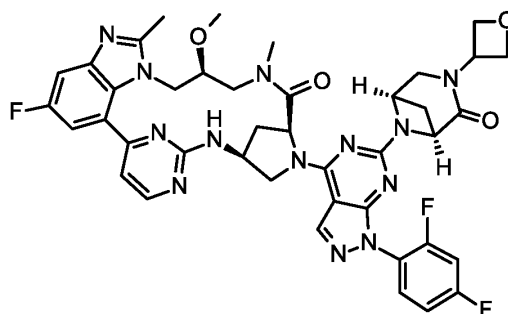
Example **115** was prepared in analogy to the preparation of Example **60** by using compound **61b** instead of compound **60h** and Intermediate **E11** instead of Intermediate **E4**.

- 5 LCMS (M+H⁺): 851. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.82 - 8.73 (m, 1H), 8.38 - 8.28 (m, 1H), 7.71 - 7.59 (m, 2H), 7.52 - 7.41 (m, 2H), 7.32 - 7.10 (m, 2H), 5.93 - 5.63 (m, 2H), 5.54 - 5.31 (m, 1H), 5.22 - 5.06 (m, 2H), 4.78 - 4.69 (m, 3H), 4.60 (br s, 5H), 4.50 - 4.41 (m, 1H), 4.17 (br s, 3H), 2.98 (s, 3H), 2.89 - 2.77 (m, 3H), 2.66 (s, 5H), 2.04 (s, 1H), 1.87 - 1.64 (m, 1H), 0.59 (s, 3H).

10

Example 116

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-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(23),2(26),3,5,18,20(24),21-heptaen-12-one



15

Example **116** was prepared in analogy to the preparation of Example **60** by using compound **61b** instead of compound **60h** and Intermediate **E3** instead of Intermediate **E4**.

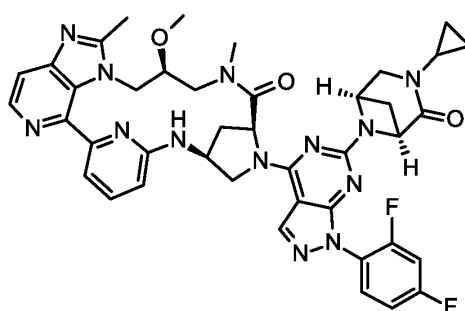
- LCMS (M+H⁺): 836. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.61 - 8.49 (m, 1H), 8.32 (s, 1H), 7.70 - 7.58 (m, 1H), 7.44 - 7.36 (m, 1H), 7.34 - 7.25 (m, 2H), 7.22 - 7.16 (m, 1H), 7.15 - 7.05 (m, 1H), 5.70 - 5.45 (m, 1H), 5.41 (br d, *J* = 8.8 Hz, 1H), 5.13 - 5.03 (m, 1H), 4.76 - 4.71
- 20

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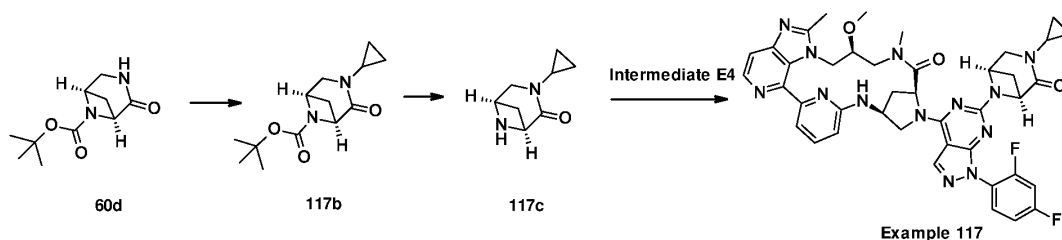
(m, 4H), 4.59 (s, 3H), 4.34 (br d, $J = 6.5$ Hz, 1H), 4.28 - 4.22 (m, 1H), 4.21 - 4.18 (m, 1H), 4.18 - 4.14 (m, 2H), 4.12 (br s, 1H), 3.14 - 3.02 (m, 3H), 2.98 - 2.87 (m, 2H), 2.84 (s, 3H), 2.82 (s, 1H), 2.63 - 2.55 (m, 3H), 2.53 - 2.38 (m, 2H), 1.74 (d, $J = 9.0$ Hz, 1H).

Example 117

- 5 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 10 The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl (1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 117b)

- To a solution of compound **60d** (500.0 mg, 2.36 mmol) in DCE (8 mL) was added
 15 cyclopropylboronic acid (1 g, 11.78 mmol), sodium carbonate (499 mg, 4.71 mmol), Cu(OAc)₂ (642 mg, 3.53 mmol) and [2,2]bipyridinyl (552 mg, 3.53 mmol) at 25 °C. The mixture was stirred at 80 °C for 16 h under O₂ atmosphere. Then the reaction mixture was poured into water and extracted with DCM. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give compound **117b** (200.0 mg) as colorless oil. LCMS
 20 (M-56+H⁺): 197.

Step 2: preparation of (1*S*,5*R*)-3-cyclopropyl-3,6-diazabicyclo[3.1.1]heptan-2-one (compound 117c)

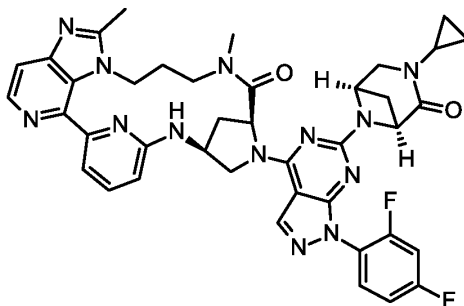
To a solution of compound **117b** (180.0 mg, 0.71 mmol) in DCM (2 mL) was added TFA (1.0 mL) at 0 °C. The mixture was stirred at 25 °C for 3 h and then concentrated to give compound **117c** (180.0 mg) as yellow oil. LCMS (M+H⁺): 153.

Step 3: preparation of (8S,11S,15R)-10-[6-[(1S,5R)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 117)

A solution of Intermediate **E4** (40.0 mg, 0.05 mmol), compound **117c** (44 mg, 0.16 mol), CsF (38 mg, 0.25 mmol) and DIEA (0.05 mL, 0.3 mmol) in DMA (1 mL) was stirred at 120 °C for 16 h. Then the reaction mixture was purified by prep-HPLC to give Example **117** (10 mg) as a white solid. LCMS (M+H⁺): 802. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.40 - 8.34 (m, 1H), 8.31 (s, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.57 (m, 2H), 7.50 - 7.37 (m, 1H), 7.34 - 7.09 (m, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.08 - 5.83 (m, 1H), 5.45 - 5.31 (m, 1H), 5.17 (br d, *J* = 0.8 Hz, 1H), 4.65 (br d, *J* = 1.0 Hz, 1H), 4.56 - 4.52 (m, 1H), 4.47 - 4.39 (m, 1H), 4.30 - 4.20 (m, 3H), 4.17 - 4.08 (m, 1H), 4.04 - 3.92 (m, 1H), 3.14 - 3.04 (m, 3H), 2.91 (br d, *J* = 13.4 Hz, 1H), 2.88 - 2.81 (m, 3H), 2.81 - 2.76 (m, 1H), 2.70 (br d, *J* = 13.9 Hz, 1H), 2.67 - 2.62 (m, 3H), 2.58 - 2.43 (m, 3H), 1.72 (d, *J* = 8.8 Hz, 1H), 1.07 - 0.86 (m, 1H), 0.81 - 0.52 (m, 2H), 0.20 - 0.02 (m, 1H).

Example 118

(8S,11S)-10-[6-[(1S,5R)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



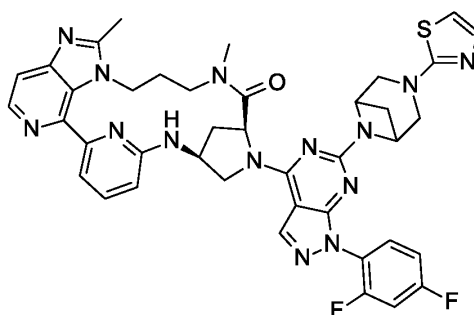
Example **118** was prepared in analogy to the preparation of Example **117** by using Intermediate **E12** instead of Intermediate **E4**. LCMS (M+H⁺): 772. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 - 8.29 (m, 2H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.35 -

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7.11 (m, 3H), 6.79 (d, $J = 8.1$ Hz, 1H), 5.52 - 5.31 (m, 2H), 4.59 - 4.58 (m, 2H), 4.53 - 4.43 (m, 2H), 4.31 - 4.26 (m, 1H), 4.22 (d, $J = 11.6$ Hz, 1H), 4.17 - 4.05 (m, 2H), 4.02 - 3.95 (m, 1H), 3.27 (br s, 1H), 3.11 - 3.04 (m, 3H), 2.94 - 2.76 (m, 2H), 2.73 - 2.66 (m, 3H), 2.60 - 2.40 (m, 3H), 2.09 - 1.94 (m, 1H), 1.83 - 1.68 (m, 1H), 1.45 - 1.20 (m, 1H), 0.78 - 0.50 (m, 2H), 0.22 - 0.02 (m, 1H).

Example 119

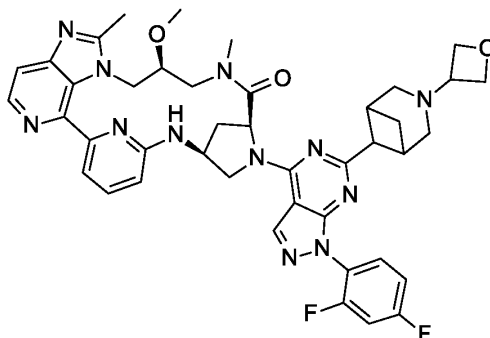
(8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



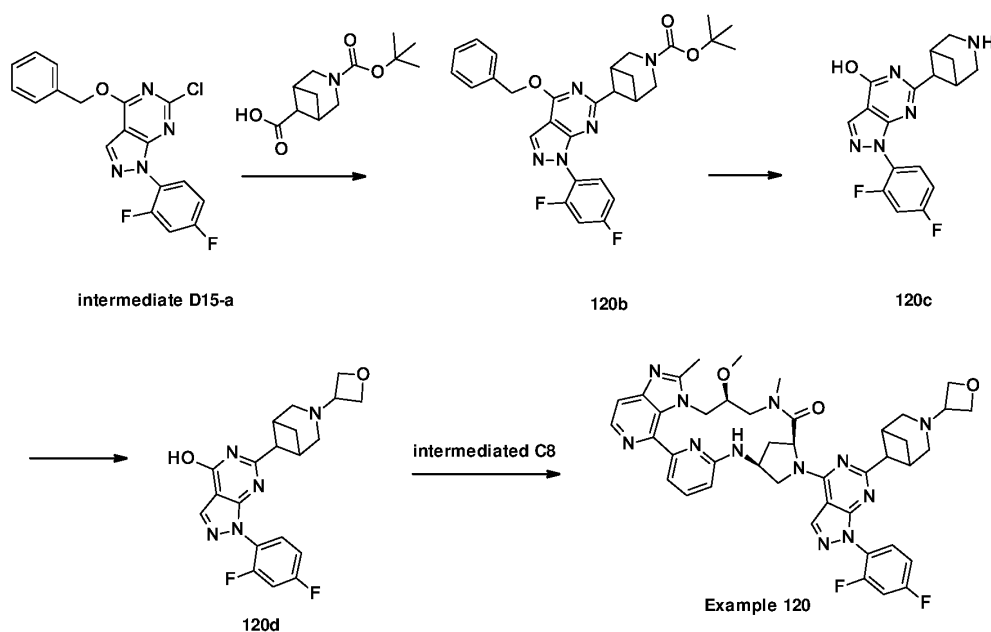
Example **119** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c** and intermediate **E12** instead of intermediate **E4**.
LCMS (M+H⁺):801. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.47 (d, $J = 6.3$ Hz, 1H), 8.28 (s, 1H), 8.14 - 8.04 (m, 1H), 7.98 (t, $J = 7.9$ Hz, 1H), 7.65 - 7.56 (m, 1H), 7.31 (d, $J = 4.3$ Hz, 1H), 7.28 - 7.21 (m, 2H), 7.20 - 7.13 (m, 1H), 7.06 - 7.01 (m, 1H), 6.95 - 6.86 (m, 1H), 5.60 - 5.48 (m, 1H), 5.46 - 5.33 (m, 1H), 4.62 - 4.57 (m, 1H), 4.50 - 4.43 (m, 2H), 4.39 - 4.29 (m, 2H), 4.26 - 4.14 (m, 3H), 4.13 - 4.06 (m, 1H), 3.67 - 3.47 (m, 3H), 3.16 - 3.06 (m, 4H), 2.94 - 2.85 (m, 3H), 2.82 - 2.78 (m, 1H), 2.62 - 2.54 (m, 1H), 2.19 - 2.10 (m, 1H), 1.83 - 1.68 (m, 1H), 1.46 - 1.31 (m, 1H).

Example 120

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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(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 *tert*-butyl 3-oxazol-2-yl-3,6-diazabicyclo[3.1.1] heptane-6-
5 carboxylate (compound 120b)

To a 40 mL vial equipped with a stir bar was added compound **D15-a** (500.0 mg, 1.3 mmol), 3-*tert*-butoxycarbonyl-3-azabicyclo[3.1.1]heptane-6-carboxylic acid (420 mg, 1.7 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)(PF₆) (15 mg, 0.01 mmol), NiCl₂.dtbbpy (3 mg, 0.01 mmol) in DME (20 mL) was added cesium carbonate (874 mg, 2.7 mmol). 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 a cooling fan to keep the reaction temperature at 25 °C for 14 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography to give compound **120b** (420 mg) as colorless oil. LCMS (M+H⁺): 534.

Step 2: preparation of 6-(3-azabicyclo[3.1.1]heptan-6-yl)-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-ol (compound 120c)

To a solution of compound **120b** (150.0 mg, 0.28 mmol) in DCM (1 mL) was added TFA (1 mL) at 0 °C. The reaction was stirred at 20°C for 12 h and then concentrated to give

5 compound **120c** (40.0 mg) as a white solid. LCMS (M+H⁺): 344.

Step 3: preparation of 1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-ol (compound 120d)

To a solution of compound **120c** (40 mg, 0.12 mmol) and oxetan-3-one (63 mg, 0.87 mmol) in DCE (1 mL) was added sodium triacetoxymethylborohydride (93 mg, 0.44 mmol) at 0 °C.

10 The mixture was stirred at 25 °C for 2 h and then concentrated. The residue was purified by prep-HPLC to give compound **120d** (23 mg) as a white solid. LCMS (M+H⁺): 400.

Step 4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetan-3-yl)-3-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo [15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

15 **1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 120)**

To a solution of compound **120d** (60.0 mg, 0.12 mmol), PyBOP (60.0 mg, 0.12 mmol), *N,N*-diisopropylethylamine (0.05 mL, 0.29 mmol) in DMF (0.5 mL) was added a solution of intermediated **E4** (26 mg, 0.06 mmol), *N,N*-diisopropylethylamine (0.06 mL, 0.35 mmol) in DMF (0.5 mL). The reaction mixture was stirred at 20 °C for 2 h and then concentrated. The

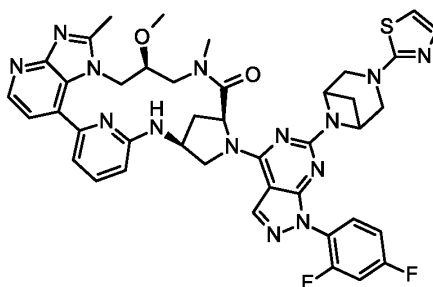
20 residue was purified by prep-HPLC to give Example **120** (9 mg) as a white solid. LCMS (M+H⁺): 803. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.46 (s, 1H), 8.37 (d, *J* = 5.5 Hz, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.69 - 7.60 (m, 2H), 7.49 - 7.39 (m, 1H), 7.32 - 7.23 (m, 1H), 7.21 - 7.14 (m, 1H), 6.81 - 6.71 (m, 1H), 6.04 (dd, *J* = 4.2, 15.4 Hz, 1H), 5.55 (br d, *J* = 8.8 Hz, 1H), 4.77 (t, *J* = 6.6 Hz, 2H), 4.74 - 4.69 (m, 3H), 4.56 - 4.48 (m, 1H), 4.41 - 4.16 (m, 3H), 4.06 - 3.80 (m, 3H), 3.14
25 (s, 1H), 3.06 (s, 4H), 2.99 (br d, *J* = 6.3 Hz, 2H), 2.93 (br d, *J* = 14.9 Hz, 1H), 2.86 - 2.81 (m, 3H), 2.66 - 2.61 (m, 4H), 2.59 - 2.45 (m, 3H), 1.63 - 1.52 (m, 1H), 1.38 - 1.27 (m, 1H).

Example 121

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1] heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-

30 **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**

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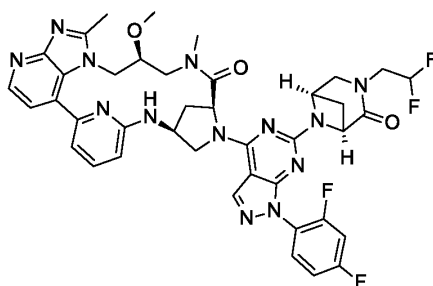


Example **121** was prepared in analogy to the preparation of Example **46** by using compound **47d** instead of compound **46c** and intermediate **E13** instead of intermediate **E4**.

LCMS (M+H⁺): 831. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 (d, *J* = 5.1 Hz, 1H), 8.12 (s, 1H), 7.87 - 7.80 (m, 1H), 7.60 - 7.51 (m, 1H), 7.38 (d, *J* = 5.3 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.15 - 7.05 (m, 2H), 6.73 - 6.66 (m, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 5.89 - 5.63 (m, 1H), 5.34 - 5.21 (m, 1H), 4.54 (br s, 1H), 4.38 (br d, *J* = 2.3 Hz, 1H), 4.34 - 4.25 (m, 2H), 4.24 - 4.12 (m, 3H), 4.09 - 3.94 (m, 2H), 3.51 - 3.33 (m, 2H), 3.08 - 3.03 (m, 3H), 2.99 (br d, *J* = 13.6 Hz, 1H), 2.89 - 2.81 (m, 3H), 2.68 (s, 3H), 2.63 (br d, *J* = 19.4 Hz, 2H), 2.51 (tt, *J* = 4.5, 8.9 Hz, 2H), 1.70 - 1.52 (m, 1H).

Example 122

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one



Example **122** was prepared in analogy to the preparation of Example **60** by using 1,1-difluoro-2-iodo-ethane instead of compound **60b** and intermediate **E13** instead of intermediate **E4**. LCMS (M+H⁺): 826. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.44 - 7.37 (m, 1H), 7.27 - 7.20 (m, 2H), 7.19 - 7.13 (m, 1H), 6.75 - 6.66 (m, 1H), 5.88 - 5.79 (m, 1H), 5.44 (d, *J* = 8.8 Hz, 1H), 4.64

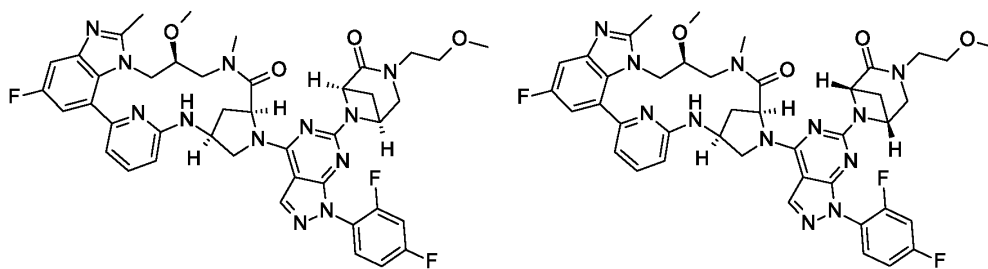
-201-

- 4.59 (m, 2H), 4.40 (br dd, $J = 6.2, 11.3$ Hz, 1H), 4.27 (br d, $J = 11.3$ Hz, 1H), 4.21 - 4.14 (m, 2H), 4.14 - 4.02 (m, 3H), 3.40 (br d, $J = 11.5$ Hz, 1H), 3.10 (s, 1H), 3.04 (s, 3H), 2.88 (br d, $J = 14.6$ Hz, 2H), 2.85 (s, 3H), 2.83 - 2.80 (m, 1H), 2.74 (br d, $J = 13.5$ Hz, 1H), 2.64 - 2.59 (m, 3H), 2.55 - 2.41 (m, 2H), 1.86 - 1.74 (m, 1H).

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Example 123 and Example 124

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(2-methoxyethyl)-2-oxo-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 and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(2-methoxyethyl)-2-oxo-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 **123** and Example **124** were prepared in analogy to the preparation of Example **3** and Example **4** by using 1-iodo-2-methoxy-ethane instead of 2,2-difluoroethyl trifluoromethanesulfonate in step 1. The mixture was separated via SFC to give Example **123** (7 mg, faster eluted) and Example **124** (10 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 80; Column: OD 250 × 30 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 45%; Flow rate: «Flow_Rate» mL/min; Back pressure: 100 bar; Column temperature: 35 °C)

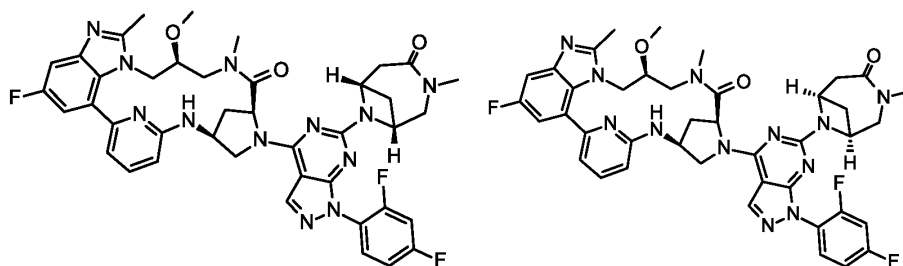
Example **123**, LCMS (M+H)⁺: 837, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.32 (s, 1H), 7.85 - 7.77 (m, 1H), 7.69 - 7.58 (m, 1H), 7.30 (dd, $J = 2.5, 8.5$ Hz, 1H), 7.27 - 7.21 (m, 1H), 7.20 - 7.12 (m, 2H), 7.09 (d, $J = 7.4$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 5.84 (br dd, $J = 4.2, 15.3$ Hz, 1H), 5.41 (d, $J = 9.0$ Hz, 1H), 4.67 - 4.63 (m, 1H), 4.59 - 4.50 (m, 1H), 4.49 - 4.38 (m, 1H), 4.25 (d, $J = 11.3$ Hz, 1H), 4.22 - 4.07 (m, 2H), 4.04 (br dd, $J = 2.5, 11.9$ Hz, 1H), 3.93 (br dd, $J = 9.1, 14.1$ Hz, 1H), 3.78 - 3.66 (m, 1H), 3.44 - 3.32 (m, 3H), 3.29 - 3.18 (m, 1H), 3.16 - 3.04 (m, 4H), 2.95 - 2.88 (m, 2H), 2.85 (s, 3H), 2.84 - 2.75 (m, 3H), 2.64 - 2.53 (m, 3H), 2.53 - 2.39 (m, 2H), 1.74 (br d, $J = 8.8$ Hz, 1H).

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Example **124**, LCMS (M+H)⁺: 837, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.31 (s, 1H), 7.84 - 7.78 (m, 1H), 7.68 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.20 - 7.13 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.84 (dd, *J* = 4.3, 15.4 Hz, 1H), 5.46 (br d, *J* = 8.6 Hz, 1H), 4.69 - 4.61 (m, 1H), 4.59 - 4.51 (m, 1H), 4.49 - 4.39 (m, 1H), 4.36 - 4.18 (m, 2H), 4.18 - 4.08 (m, 3H), 4.07 - 3.89 (m, 1H), 3.70 - 3.61 (m, 1H), 3.45 - 3.32 (m, 3H), 3.11 - 3.03 (m, 4H), 3.02 - 2.95 (m, 2H), 2.93 - 2.88 (m, 1H), 2.87 - 2.81 (m, 4H), 2.81 - 2.74 (m, 1H), 2.58 (s, 3H), 2.54 - 2.39 (m, 2H), 1.73 (d, *J* = 8.8 Hz, 1H).

Example 125 and Example 126

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,6*S*)-3-methyl-4-oxo-3,7-diazabicyclo[4.1.1]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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,6*R*)-3-methyl-4-oxo-3,7-diazabicyclo[4.1.1]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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



Example **125** and Example **126** were prepared in analogy to the preparation of Example **3** and Example **4** by using compound **125d** instead of compound **3b** in step 3. The mixture was separated via SFC to give Example **125** (9 mg, faster eluted) and Example **126** (11 mg slower eluted) as a white powder. (SFC condition: Instrument: SFC-150 Mgm; Column: (S,S) whelk-O1 250 × 30 mm I.D., 5 μ m; Mobile phase: A for CO₂ and B for methanol «Mobile_phasePrep»; Gradient: B 40%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column temperature: 35 °C)

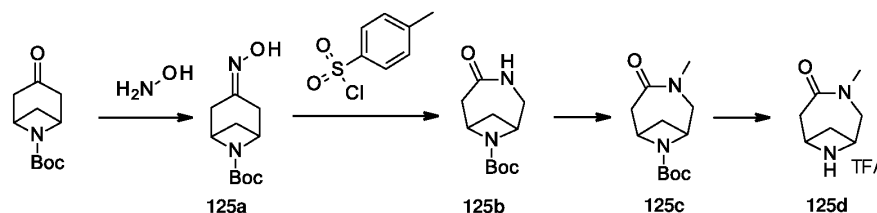
Example **125**, LCMS (M+H)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.23 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.60 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.30 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.23 (ddd, *J* = 2.7, 8.8, 10.2 Hz, 1H), 7.19 - 7.11 (m, 2H), 7.10 - 7.05 (m, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.83 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.34 (d, *J* = 8.9 Hz, 1H), 4.64 - 4.59 (m, 1H), 4.58 - 4.52 (m, 1H), 4.48 - 4.37 (m, 1H), 4.27 - 4.08 (m, 4H), 3.92 (br dd, *J* = 9.1, 14.1 Hz, 1H), 3.75 - 3.64 (m,

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1H), 3.38 (dd, $J = 2.2, 13.8$ Hz, 1H), 3.11 - 3.03 (m, 3H), 3.02 - 2.91 (m, 4H), 2.86 - 2.80 (m, 4H), 2.80 - 2.70 (m, 2H), 2.58 - 2.53 (m, 3H), 2.53 - 2.42 (m, 2H), 1.80 - 1.68 (m, 1H).

Example **126**, LCMS ($M+H$)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.21 (s, 1H), 7.83 - 7.77 (m, 1H), 7.64 - 7.55 (m, 1H), 7.29 (dd, $J = 2.5, 8.5$ Hz, 1H), 7.24 (ddd, $J = 2.7, 8.8, 10.3$ Hz, 1H), 7.18 - 7.11 (m, 2H), 7.07 (d, $J = 7.4$ Hz, 1H), 6.65 (br d, $J = 8.4$ Hz, 1H), 5.80 (dd, $J = 4.5, 15.5$ Hz, 1H), 5.35 (d, $J = 8.9$ Hz, 1H), 4.66 - 4.59 (m, 1H), 4.57 - 4.51 (m, 1H), 4.46 - 4.32 (m, 2H), 4.27 - 4.11 (m, 3H), 4.11 - 4.02 (m, 1H), 3.96 - 3.71 (m, 1H), 3.52 - 3.41 (m, 1H), 3.38 - 3.32 (m, 1H), 3.11 - 3.02 (m, 3H), 2.95 (s, 3H), 2.93 (br s, 1H), 2.87 - 2.83 (m, 3H), 2.78 (br d, $J = 10.3$ Hz, 1H), 2.74 - 2.66 (m, 1H), 2.60 (s, 3H), 2.52 - 2.41 (m, 2H), 1.77 - 1.68 (m, 1H).

Compound **125d** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-hydroxyimino-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound **125a)**

To a flask was added *tert*-butyl 3-oxo-6-azabicyclo[3.1.1]heptane-6-carboxylate (300 mg, 1.42 mmol), hydroxylamine hydrochloride (250 mg, 3.6 mmol), methanol (4 mL) and water (4 mL). The solution was stirred at r.t. for 16 h and diluted with 20 mL DCM and 20 mL water. The water layer was extracted with 15 mL DCM twice. The combined organic layer was dried and concentrated to give compound **125a** (340 mg) as a solid. LCMS ($M+H$)⁺: 227, ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.59 (s, 1H), 4.08 (dt, $J = 1.7, 3.0$ Hz, 1H), 4.04 - 3.99 (m, 1H), 2.96 (br d, $J = 15.9$ Hz, 2H), 2.55 (br d, $J = 18.3$ Hz, 1H), 2.48 - 2.42 (m, 1H), 1.38 (br t, $J = 2.8$ Hz, 1H), 1.35 (s, 9H), 1.16 (d, $J = 9.1$ Hz, 1H).

Step 2: preparation of *tert*-butyl 4-oxo-3,7-diazabicyclo[4.1.1]octane-7-carboxylate (compound **125b)**

To the flask containing compound **125a** (316 mg, 1.4 mmol) was added sodium carbonate (650 mg, 6.13 mmol), acetone (6 mL) and water (4 mL). The suspension was stirred at r.t. and *p*-toluenesulfonyl chloride (550 mg, 2.88 mmol) was added portion-wise. The resulted mixture was heated to 65 °C and stirred for 16 hrs. The mixture was diluted with some water and extracted with 30 mL DCM for three times. The organic layer was dried over Na₂O₄ and concentrated to give compound **125b** (297 mg) as a light yellow solid. LCMS ($M+H$)⁺: 227.

Step 3: preparation of *tert*-butyl 3-methyl-4-oxo-3,7-diazabicyclo[4.1.1]octane-7-carboxylate (compound 125c)

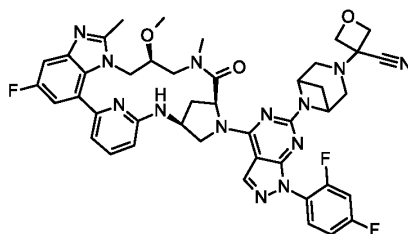
To a flask was added compound **125b** (150 mg, 662.92 μ mol), DMF (1.5 mL) and iodomethane (227 mg, 100 μ L, 1.6 mmol). The suspension was stirred at r.t. for a while and NaH (80 mg, 2 mmol) was added. The reaction was stirred for 4 hrs. and quenched with water. The mixture was extracted with some EA. The organic layer was dried and concentrated to give compound **125c** (150 mg) as an oil, which was used directly in the next step. LCMS (M+H)⁺: 241.

Step 4: preparation of 3-methyl-3,7-diazabicyclo[4.1.1]octan-4-one (compound 125d)

To a flask was added compound **125c** (150 mg, 624.22 μ mol), DCM (1.5 mL) and TFA (1.5 mL, 19.47 mmol). The brown solution was stirred at r.t. for 1 hr and concentrated to give compound **125d** (158 mg) as an oil, which was used directly in the next step. LCMS (M+H)⁺: 141.

Example 127

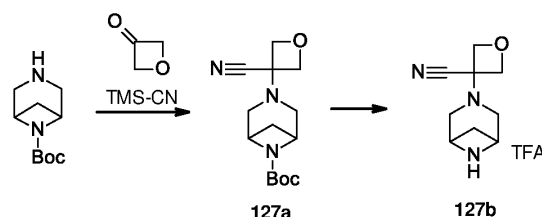
3-[-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]oxetane-3-carbonitrile



Example **127** was prepared in analogy to the preparation of Example **2** by using compound **127b** instead of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine;hydrochloride. Example **127** (3 mg), LCMS (M+H)⁺: 846, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.29 (s, 1H), 7.81 - 7.78 (m, 1H), 7.84 - 7.76 (m, 1H), 7.68 - 7.58 (m, 1H), 7.32 - 7.27 (m, 1H), 7.23 (ddd, *J* = 2.8, 8.8, 10.2 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.10 - 7.03 (m, 1H), 6.71 - 6.63 (m, 1H), 5.77 (br dd, *J* = 4.2, 15.4 Hz, 1H), 5.34 (d, *J* = 8.9 Hz, 1H), 4.69 - 4.62 (m, 2H), 4.59 - 4.53 (m, 2H), 4.49 - 4.39 (m, 2H), 4.34 - 4.19 (m, 3H), 3.99 - 3.89 (m, 1H), 3.66 - 3.57 (m, 1H), 3.45 - 3.36 (m, 1H), 3.12 - 2.97 (m, 4H), 2.97 - 2.87 (m, 2H), 2.86 - 2.81 (m, 4H), 2.78 (br d, *J* = 14.1 Hz, 1H), 2.65 - 2.57 (m, 3H), 2.56 - 2.41 (m, 3H).

The compound **127b** was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 3-(3-cyanooxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 127a)

To a tube was added *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (200 mg, 1.01 mmol) and acetic acid (2 mL). The solution was cooled with ice bath, oxetan-3-one (100 mg, 1.39 mmol) and TMS-CN (251 mg, 340 μ L, 2.54 mmol) were added. The reaction was warmed to r.t. and stirred for 16 hrs. The mixture was poured into 20 mL sat. NaHCO_3 aq. and extracted with 20 mL EA twice. The organic layer was concentrated and purified via silica gel chromatography to give compound **127a** (280 mg) as a white solid. LCMS ($\text{M}+\text{H}^+$): 280, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 4.72 (d, J = 7.1 Hz, 2H), 4.63 (br d, J = 7.5 Hz, 2H), 4.05 (d, J = 6.0 Hz, 2H), 3.01 - 2.85 (m, 2H), 2.85 - 2.71 (m, 2H), 2.40 - 2.32 (m, 1H), 1.64 (d, J = 8.1 Hz, 1H), 1.40 (s, 9H).

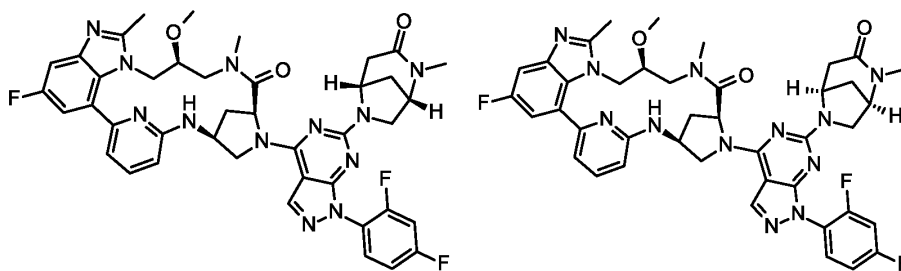
Step 2: preparation of 3-(3,6-diazabicyclo[3.1.1]heptan-3-yl)oxetane-3-carbonitrile (compound 127b)

To a flask was added compound **127a** (100 mg, 358. μ mol), DCM (1 mL) and TFA (1 mL, 12.98 mmol). The solution was stirred at r.t. for 1 hr and concentrated to give compound **127b** (175 mg) as a crude oil, which was used in the next step directly. LCMS ($\text{M}+\text{H}^+$): 180.

Example 128 and Example 129

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*S*)-2-methyl-3-oxo-2,6-diazabicyclo[3.2.1]octan-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one and (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*R*)-2-methyl-3-oxo-2,6-diazabicyclo[3.2.1]octan-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one

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Example **128** and Example **129** were prepared in analogy to the preparation of Example **3** and Example **4** by using compound *tert*-butyl 3-oxo-2,6-diazabicyclo[3.2.1]octane-6-carboxylate instead of compound *tert*-butyl 2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate and using compound iodoethane instead of compound 2,2-difluoroethyl trifluoromethanesulfonate in step 1. The mixture was separated via SFC to give Example **128** (18 mg, faster eluted) and Example **129** (12 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC-150 Mgm; Column: OJ 250 × 30 mm I.D., 5 μm; Mobile phase: A for CO₂ and B for Methanol «Mobile_phasePrep»; Gradient: B 20%; Flow rate: «Flow_Rate» mL /min; Back pressure: 100 bar; Column temperature: 35 °C).

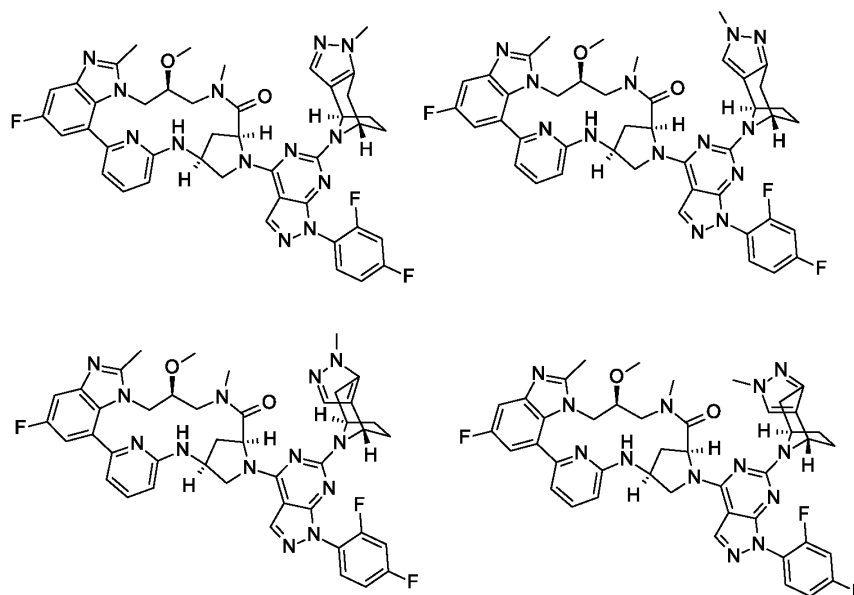
Example **128**, LCMS (M+H)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.22 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.58 (m, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 7.09 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.70 - 6.62 (m, 1H), 5.83 (dd, *J* = 4.4, 15.6 Hz, 1H), 5.34 (d, *J* = 9.0 Hz, 1H), 4.61 (br t, *J* = 4.9 Hz, 1H), 4.44 - 4.36 (m, 1H), 4.28 - 4.02 (m, 3H), 4.02 - 3.96 (m, 1H), 3.95 - 3.86 (m, 1H), 3.71 - 3.59 (m, 1H), 3.57 - 3.43 (m, 1H), 3.05 (s, 3H), 2.98 (s, 3H), 2.96 - 2.89 (m, 1H), 2.85 (s, 3H), 2.83 - 2.71 (m, 2H), 2.57 (s, 3H), 2.55 - 2.39 (m, 3H), 2.22 - 2.01 (m, 2H).

Example **129**, LCMS (M+H)⁺: 807, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.22 (s, 1H), 7.84 - 7.76 (m, 1H), 7.68 - 7.58 (m, 1H), 7.29 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.21 (ddd, *J* = 2.7, 8.8, 10.3 Hz, 1H), 7.14 (br dd, *J* = 2.5, 10.5 Hz, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.83 (dd, *J* = 4.5, 15.6 Hz, 1H), 5.43 (d, *J* = 8.9 Hz, 1H), 4.66 - 4.61 (m, 1H), 4.61 - 4.54 (m, 1H), 4.43 (dd, *J* = 6.1, 11.2 Hz, 1H), 4.29 - 4.17 (m, 2H), 4.08 - 3.94 (m, 2H), 3.82 - 3.66 (m, 1H), 3.48 - 3.41 (m, 1H), 3.06 (s, 3H), 2.99 (s, 3H), 2.96 - 2.89 (m, 1H), 2.85 (s, 3H), 2.76 (br d, *J* = 13.5 Hz, 1H), 2.70 - 2.61 (m, 1H), 2.60 - 2.53 (m, 3H), 2.48 (tt, *J* = 4.6, 9.1 Hz, 2H), 2.44 - 2.36 (m, 1H), 2.21 - 2.12 (m, 1H), 2.10 - 2.04 (m, 1H).

Example 131, 132, 133 and 134

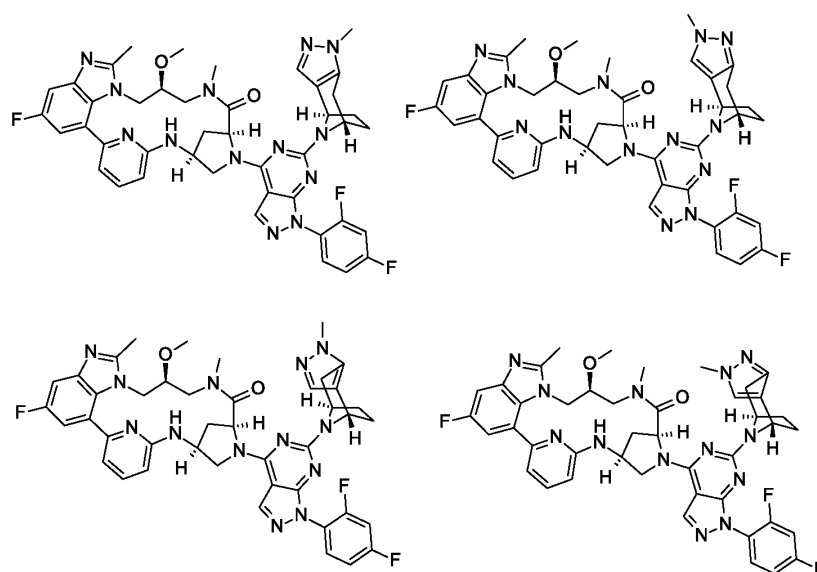
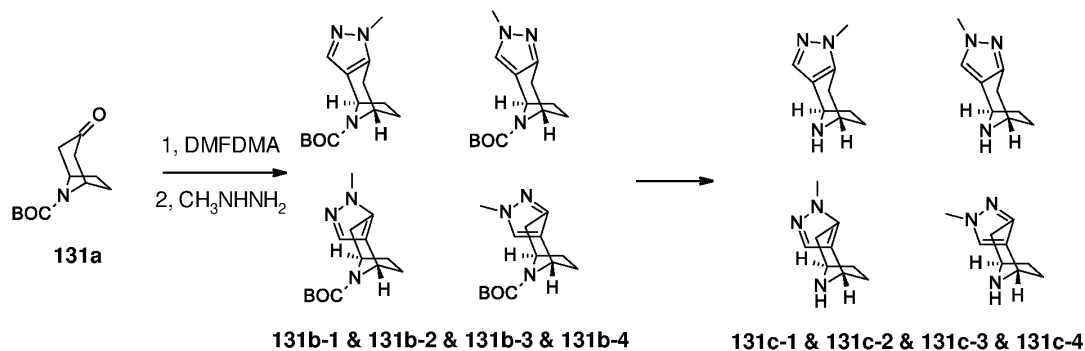
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-4-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-

- 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*S*,8*R*)-4-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-
- 5 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,8*S*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-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*S*,8*R*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-
- 10 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 15 The title compound was prepared according to the following scheme:

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Example **131** & **132** & **133** & **134**

Examples **131**, **132**, **133** and **134** were prepared in analogy to the preparation of Examples **103**, **104**, **105** and **106** by using compound **131a** instead of compound **103a** and intermediate **E1** instead of intermediate **E5**.

5 SFC condition of step 1: Instrument: SFC 150 Mgm; Column: REGIS (S,S) Whelk-01, 250×30 mm I.D., 5 μm ; Mobile phase: A for CO_2 and B for Methanol (0.1% $\text{NH}_3\text{H}_2\text{O}$); Gradient: B 8%; Flow rate: 80 mL /min; Back pressure: 100bar; Column temperature: 35 $^\circ\text{C}$. Compound **131b-1** (first eluted), **131b-2** (second eluted), **131b-3** (third eluted) and **131b-4** (forth eluted).

10 Example **131**, LCMS ($\text{M}+\text{H}^+$): 830. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ = 8.30 - 8.17 (m, 1H), 7.90 - 7.76 (m, 1H), 7.68 - 7.56 (m, 1H), 7.41 - 7.04 (m, 6H), 6.76 - 6.64 (m, 1H), 5.90 - 5.69 (m, 1H), 5.58 - 5.43 (m, 1H), 5.42 - 5.23 (m, 1H), 4.71 - 4.56 (m, 2H), 4.49 - 4.35 (m, 1H), 4.27 - 4.11 (m, 2H), 4.02 - 3.73 (m, 4H), 3.18 - 2.94 (m, 5H), 2.92 - 2.76 (m, 4H), 2.66 - 2.42 (m, 6H), 2.39 - 2.28 (m, 1H), 2.26 - 2.07 (m, 1H), 1.94 - 1.64 (m, 2H).

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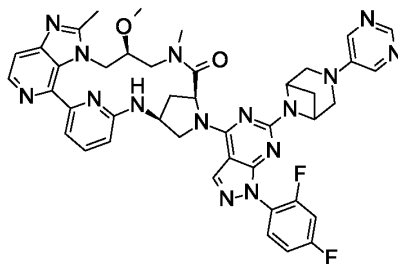
Example **132**, LCMS (M+H⁺): 830. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.26 - 8.16 (m, 1H), 7.92 - 7.78 (m, 1H), 7.70 - 7.57 (m, 1H), 7.39 - 7.02 (m, 6H), 6.76 - 6.65 (m, 1H), 5.88 - 5.68 (m, 1H), 5.57 - 5.48 (m, 1H), 5.41 - 5.17 (m, 1H), 5.10 - 4.90 (m, 1H), 4.69 - 4.54 (m, 1H), 4.53 - 4.33 (m, 1H), 4.30 - 4.06 (m, 2H), 4.01 - 3.79 (m, 1H), 3.72 - 3.57 (m, 3H), 3.20 - 2.93 (m, 5H), 2.93 - 2.75 (m, 4H), 2.70 - 2.45 (m, 6H), 2.41 - 2.08 (m, 2H), 1.99 - 1.82 (m, 1H), 1.83 - 1.62 (m, 1H).

Example **133**, LCMS (M+H⁺): 830. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.28 - 8.13 (m, 1H), 7.94 - 7.77 (m, 1H), 7.67 - 7.56 (m, 1H), 7.39 - 7.03 (m, 6H), 6.77 - 6.66 (m, 1H), 5.99 - 5.80 (m, 1H), 5.70 - 5.38 (m, 1H), 5.35 - 5.24 (m, 1H), 4.72 - 4.54 (m, 1H), 4.53 - 4.35 (m, 1H), 4.33 - 4.10 (m, 2H), 4.08 - 3.88 (m, 1H), 3.79 - 3.68 (m, 3H), 3.27 - 3.18 (m, 1H), 3.16 - 2.95 (m, 4H), 2.94 - 2.74 (m, 4H), 2.73 - 2.29 (m, 8H), 2.26 - 2.09 (m, 1H), 1.97 - 1.60 (m, 2H).

Example **134**, LCMS (M+H⁺): 830. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.29 - 8.17 (m, 1H), 7.88 - 7.78 (m, 1H), 7.64 - 7.55 (m, 1H), 7.35 - 7.06 (m, 6H), 6.74 - 6.63 (m, 1H), 5.93 - 5.63 (m, 1H), 5.51 - 5.35 (m, 1H), 5.31 - 5.17 (m, 1H), 4.97 - 4.91 (m, 1H), 4.69 - 4.54 (m, 1H), 4.53 - 4.35 (m, 1H), 4.27 - 4.09 (m, 2H), 4.01 - 3.84 (m, 1H), 3.74 - 3.59 (m, 3H), 3.39 - 3.35 (m, 1H), 3.27 - 2.91 (m, 5H), 2.90 - 2.77 (m, 3H), 2.74 - 2.43 (m, 6H), 2.40 - 2.30 (m, 1H), 2.28 - 2.09 (m, 1H), 1.99 - 1.82 (m, 1H), 1.80 - 1.64 (m, 1H).

Example 135

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-5-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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



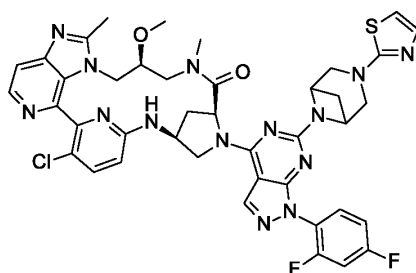
Example **135** was prepared in analogy to the preparation of Example **53** by using 5-iodopyrimidine instead of 3-iodo-1-methyl-pyrazole **53a**. LCMS (M+H⁺): 826. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.46 - 8.41 (m, 1H), 8.37 (d, *J* = 5.4 Hz, 1H), 8.25 (s, 2H), 8.21 (s, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 5.4 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.31 - 7.22 (m, 1H), 7.16 (br d, *J* = 0.8 Hz, 1H), 6.73 (br d, *J* = 8.5 Hz, 1H), 6.04 - 5.78 (m, 1H), 5.39 (br d, *J* = 9.5 Hz, 1H), 4.50 - 4.42 (m, 2H), 4.41 - 4.31 (m, 2H), 4.21 - 4.02 (m, 4H),

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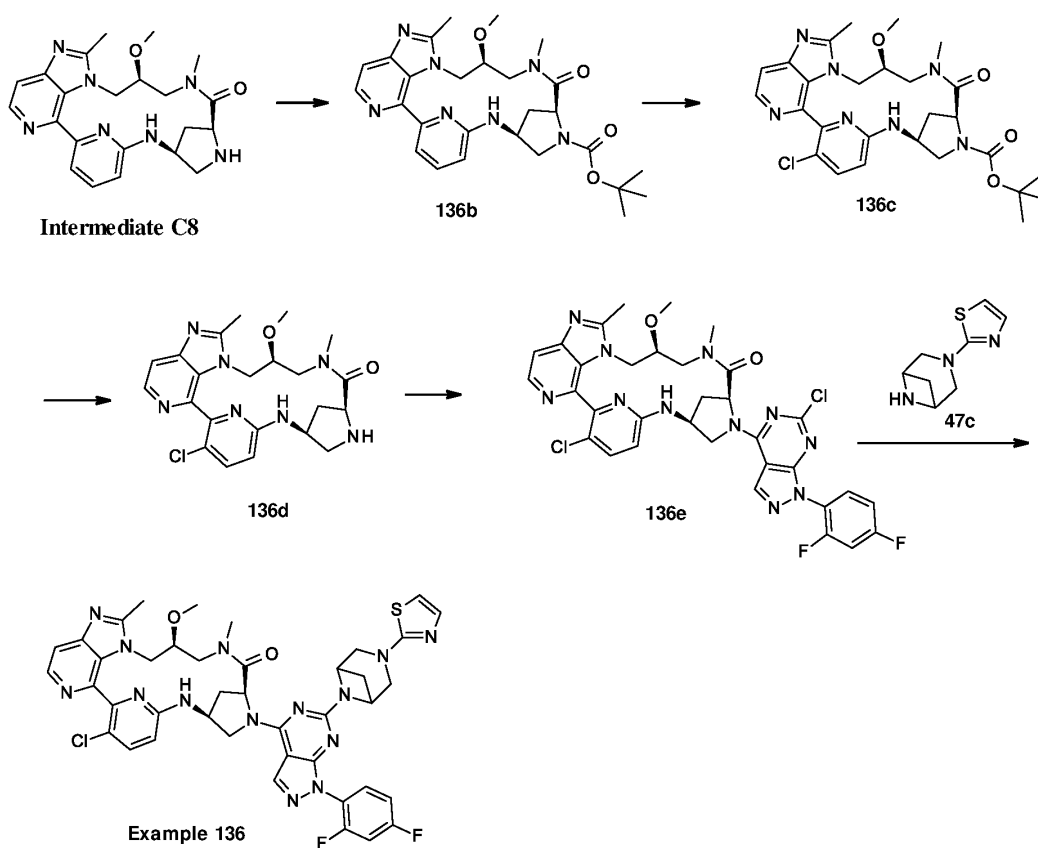
3.68 - 3.55 (m, 2H), 3.09 (s, 3H), 3.06 (br s, 1H), 2.87 (s, 3H), 2.85 - 2.80 (m, 2H), 2.79 - 2.72 (m, 2H), 2.65 - 2.46 (m, 3H), 1.66 (d, $J = 9.1$ Hz, 1H), 1.18 (t, $J = 7.1$ Hz, 1H).

Example 136

(8*S*,11*S*,15*R*)-3-chloro-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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 tert-butyl (8*S*,11*S*,15*R*)-15-methoxy-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(24),2(26),3,5,18,20,22-heptaene-10-carboxylate (compound 136b)

To a solution of Intermediate **C8** (100.0 mg, 0.22 mmol) in methanol (1.5 mL) was added DIEA (85.0 mg, 0.66 mmol) and Boc₂O (70.0 mg, 0.32 mmol) at 0 °C. The reaction was stirred at 25 °C for 1 h. Then the reaction mixture was concentrated, the residue was purified by prep-TLC to give compound **136b** (50.0 mg) as a white solid. LCMS (M+H⁺): 522.

Step 2: preparation of tert-butyl (8*S*,11*S*,15*R*)-3-chloro-15-methoxy-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(24),2(26),3,5,18,20,22-heptaene-10-carboxylate (compound 136c)

To a solution of compound **136b** (20.0 mg, 0.04 mmol) in ACN (0.5 mL) was added a solution of *N*-chlorosuccinimide (8 mg, 0.06 mmol) at 70 °C. After being stirred at 70 °C for 8 h, the reaction mixture was concentrated, the residue was purified by prep-TLC to give compound **136c** (8.0 mg) as a yellow solid. LCMS (M+H⁺): 556.

Step 3: preparation of (8*S*,11*S*,15*R*)-3-chloro-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-12-one (compound 136d)

A solution of compound **136c** (8.0 mg, 0.01 mmol) in DCM (0.5 mL) and TFA (0.5 mL) was stirred at 20 °C for 1 h. Then the reaction mixture was concentrated to give compound **136d** (8.0 mg) as yellow oil. LCMS (M+H⁺): 456.

Step 4: preparation of (8*S*,11*S*,15*R*)-3-chloro-10-[6-chloro-1-(2,4-difluorophenyl)pyrazolo[5,4-*d*]pyrimidin-4-yl]-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-12-one (compound 136e)

A mixture of compound **136d** (8.0 mg, 0.01 mmol), Intermediate **D1** (4 mg, 0.01 mmol) and DIEA (0.01 mL, 0.07 mmol) in ACN (0.5 mL) was stirred at 80 °C for 1 h. Then the reaction mixture was concentrated to give compound **136e** (10.0 mg) as a yellow solid. LCMS (M+H⁺): 720.

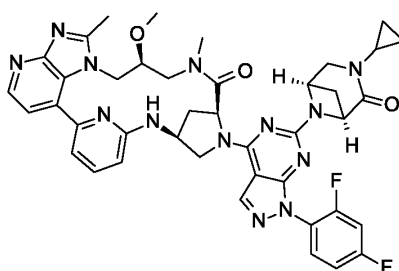
Step 5: preparation of (8*S*,11*S*,15*R*)-3-chloro-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 136)

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A mixture of compound **136e** (10.0 mg, 0.01 mmol), compound **47c** (14 mg, 0.05 mmol), CsF (11 mg, 0.07 mmol) and DIEA (0.01 mL, 0.07 mmol) in DMA (0.5 mL) was stirred at 120 °C for 15 hrs. Then the reaction mixture was concentrated and the residue was purified by prep-HPLC to give Example **136** (0.5 mg) as a white solid. LCMS (M+H⁺): 865. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.50 (d, *J* = 6.0 Hz, 1H), 8.29 - 8.24 (m, 1H), 8.02 - 7.96 (m, 2H), 7.63 - 7.55 (m, 2H), 7.25 - 7.22 (m, 2H), 6.92 (d, *J* = 9.5 Hz, 1H), 6.81 - 6.78 (m, 1H), 5.42 - 5.34 (m, 2H), 4.69 - 4.63 (m, 3H), 4.45 - 4.44 (m, 1H), 4.33 - 4.26 (m, 4H), 4.11 - 4.05 (m, 2H), 3.88 - 3.82 (m, 1H), 3.19 (s, 1H), 3.14 (s, 2H), 3.05 (s, 3H), 3.02 - 2.96 (m, 2H), 2.82 - 2.80 (m, 3H), 2.77 - 2.68 (m, 2H), 2.04 (s, 1H), 1.73 - 1.68 (m, 1H).

Example 137

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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

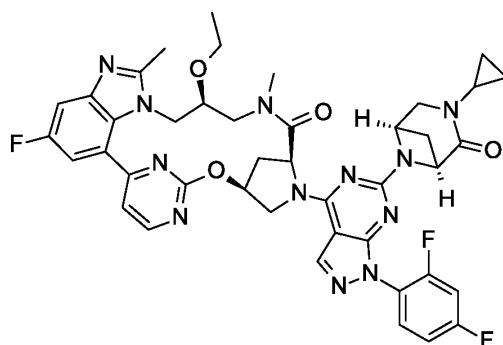


Example **137** was prepared in analogy to the preparation of Example **117** by using Intermediate **E13** instead of Intermediate **E4**. LCMS (M+H⁺): 802. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.56 (m, 1H), 7.43 - 7.36 (m, 1H), 7.30 - 7.13 (m, 3H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.96 - 5.71 (m, 1H), 5.43 - 5.29 (m, 1H), 4.61 (br d, *J* = 4.9 Hz, 1H), 4.56 - 4.50 (m, 1H), 4.39 (br s, 1H), 4.32 - 4.17 (m, 3H), 4.16 - 4.10 (m, 1H), 4.05 - 3.94 (m, 1H), 3.12 - 3.02 (m, 3H), 3.01 - 2.91 (m, 1H), 2.88 (s, 3H), 2.85 (s, 1H), 2.83 - 2.76 (m, 1H), 2.66 (s, 3H), 2.63 (s, 1H), 2.56 - 2.39 (m, 3H), 1.83 - 1.66 (m, 1H), 1.02 - 0.86 (m, 1H), 0.82 - 0.50 (m, 2H), 0.29 - 0.05 (m, 1H).

Example 138

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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

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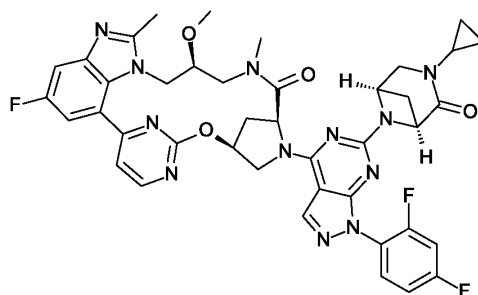


Example **138** was prepared in analogy to the preparation of Example **117** by using Intermediate **E11** instead of Intermediate **E4**. LCMS ($M+H^+$): 835. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.81 - 8.72 (m, 1H), 8.31 (s, 1H), 7.71 - 7.58 (m, 2H), 7.50 - 7.36 (m, 2H),
 5 7.31 - 7.13 (m, 2H), 5.92 - 5.83 (m, 1H), 5.81 - 5.66 (m, 1H), 5.52 - 5.32 (m, 1H), 4.58 (s, 4H),
 4.51 - 4.37 (m, 2H), 4.32 - 4.23 (m, 1H), 4.22 - 4.16 (m, 1H), 4.15 - 4.11 (m, 1H), 4.06 - 3.92 (m,
 1H), 3.07 - 2.96 (m, 3H), 2.91 - 2.85 (m, 1H), 2.84 - 2.78 (m, 2H), 2.67 (br d, J = 4.8 Hz, 1H),
 2.64 - 2.61 (m, 3H), 2.61 - 2.56 (m, 1H), 2.53 - 2.45 (m, 1H), 1.71 (d, J = 8.8 Hz, 1H), 1.07 -
 0.95 (m, 1H), 0.84 - 0.65 (m, 1H), 0.63 - 0.54 (m, 4H), 0.26 - 0.13 (m, 1H).

10

Example 139

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



15

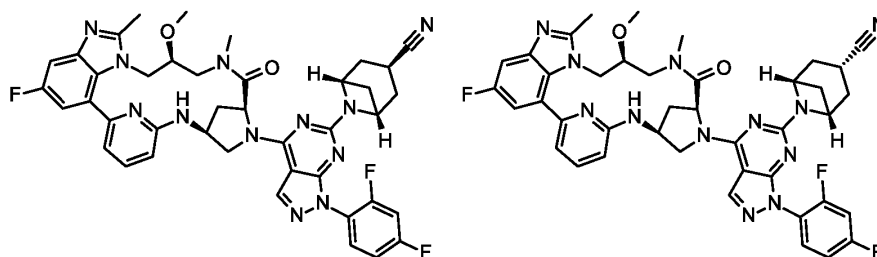
Example **139** was prepared in analogy to the preparation of Example **117** by using Intermediate **E14** instead of Intermediate **E4**. LCMS ($M+H^+$): 821. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.89 - 8.85 (m, 1H), 8.33 (s, 1H), 7.80 - 7.76 (m, 1H), 7.74 - 7.69 (m, 2H),
 7.68 - 7.59 (m, 1H), 7.30 - 7.22 (m, 1H), 7.19 (dt, J = 2.4, 8.0 Hz, 1H), 6.19 - 5.99 (m, 1H), 5.87
 20 - 5.70 (m, 1H), 5.52 - 5.39 (m, 1H), 4.59 - 4.40 (m, 3H), 4.33 - 4.24 (m, 2H), 4.15 (dd, J = 3.7,
 5.8 Hz, 1H), 4.02 - 3.94 (m, 1H), 3.10 (s, 1H), 3.04 (s, 3H), 2.99 - 2.92 (m, 4H), 2.86 - 2.81 (m,

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4H), 2.79 (br s, 1H), 2.75 - 2.59 (m, 2H), 2.54 - 2.47 (m, 1H), 1.80 - 1.69 (m, 1H), 1.33 - 1.23 (m, 2H), 0.79 - 0.53 (m, 2H).

Example 140 and Example 141

(1*S*,5*R*)-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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile and (1*R*,5*S*)-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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile



Example **140** and Example **141** were prepared in analogy to the preparation of Example **3** and Example **4** by using compound **140b** instead of compound **3b** in step 3. The mixture was purified and separated via prep-HPLC to give Example **140** (9 mg, faster eluted) and Example **141** (3 mg, slower eluted) as a white powder.

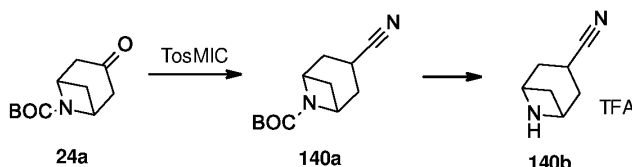
Example **140**, LCMS (M+H)⁺: 789, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.27 (s, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.64 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.32 - 7.25 (m, 1H), 7.25 - 7.17 (m, 1H), 7.17 - 7.11 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.83 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.37 (d, *J* = 8.9 Hz, 1H), 4.66 - 4.61 (m, 1H), 4.59 - 4.55 (m, 1H), 4.47 (dd, *J* = 6.1, 11.2 Hz, 1H), 4.29 - 4.11 (m, 4H), 4.01 - 3.91 (m, 1H), 3.55 - 3.43 (m, 1H), 3.12 - 3.00 (m, 3H), 2.92 - 2.86 (m, 1H), 2.83 (s, 3H), 2.81 - 2.77 (m, 1H), 2.69 - 2.60 (m, 1H), 2.59 - 2.53 (m, 3H), 2.53 - 2.43 (m, 3H), 2.24 - 2.00 (m, 2H), 1.68 (d, *J* = 9.3 Hz, 1H).

Example **141**, LCMS (M+H)⁺: 789, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.29 (s, 1H), 7.81 (dd, *J* = 7.6, 8.3 Hz, 1H), 7.64 (dt, *J* = 5.9, 8.6 Hz, 1H), 7.30 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.24 (ddd, *J* = 2.8, 8.8, 10.3 Hz, 1H), 7.15 (dd, *J* = 2.5, 10.5 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.81 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.41 (d, *J* = 8.8 Hz, 1H), 4.67 - 4.63 (m, 1H), 4.58 - 4.56 (m, 1H), 4.51 - 4.43 (m, 1H), 4.31 - 4.09 (m, 4H), 3.96 - 3.85 (m, 1H), 3.13 -

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3.02 (m, 3H), 2.96 - 2.89 (m, 1H), 2.88 - 2.83 (m, 3H), 2.83 - 2.78 (m, 1H), 2.76 - 2.61 (m, 3H), 2.60 - 2.54 (m, 3H), 2.54 - 2.44 (m, 2H), 2.02 - 1.88 (m, 2H), 1.56 (d, $J = 9.1$ Hz, 1H).

The compound **140b** was prepared according to the following scheme:



5 **Step 1: preparation of *tert*-butyl 3-cyano-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound 140a)**

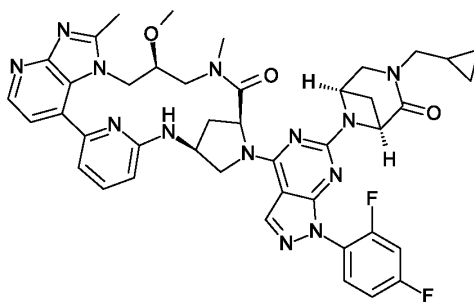
To a flask was added *tert*-butyl 3-oxo-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound **24a**, 100 mg, 473.35 μ mol), diethylene glycol dimethyl ether (2 mL) and ethanol (500 μ L). The solution was cooled with ice bath and *p*-toluenesulfonylmethyl isocyanate (130 mg, 665.85 μ mol) was added, followed by potassium *tert*-butanolate (150 mg, 1.34 mmol). The final mixture was warmed to r.t. slowly and stirred for 16 hrs. The reaction mixture diluted with 10 mL DCM and 10 mL water. The water layer was extracted with 10 DCM twice. The combined organic layer was dried and concentrated. The crude oil was purified via silica gel chromatography to give compound **140a** (20 mg) as an oil. LCMS (M+H)⁺: 223.

15 **Step 2: preparation of 6-azabicyclo[3.1.1]heptane-3-carbonitrile (compound 140b)**

To the flask containing compound 140a (20 mg, 89.98 μ mol) was added TFA (1 mL, 12.98 mmol) and DCM (1 mL). The solution was stirred at r.t. for 2 hrs and concentrated to give compound **140b** (20 mg) as a crude oil, which was used in the next directly. LCMS (M+H)⁺: 123.

Example 142

20 **(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one**

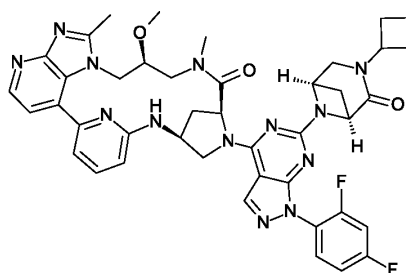


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Example **142** was prepared in analogy to the preparation of Example **60** by using iodomethylcyclopropane instead of compound **60b** and intermediate **E13** instead of intermediate **E4**. LCMS (M+H⁺): 816. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.38 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 7.91 - 7.79 (m, 1H), 7.64 - 7.57 (m, 1H), 7.50 - 7.36 (m, 1H), 7.34 - 7.09 (m, 3H), 6.82 - 6.69 (m, 1H), 5.93 - 5.73 (m, 1H), 5.55 - 5.24 (m, 1H), 4.70 - 4.40 (m, 6H), 4.33 - 4.07 (m, 5H), 3.12 - 3.02 (m, 3H), 2.91 - 2.83 (m, 4H), 2.75 - 2.70 (m, 1H), 2.69 - 2.61 (m, 3H), 2.60 - 2.39 (m, 2H), 1.86 - 1.68 (m, 1H), 1.46 - 1.19 (m, 1H), 1.05 - 0.75 (m, 1H), 0.38 - 0.12 (m, 4H).

Example 143

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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

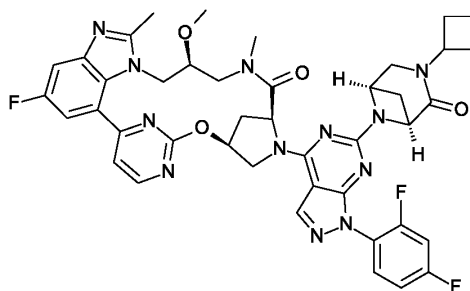


Example **143** was prepared in analogy to the preparation of Example **60** by using iodocyclobutane instead of compound **60b** and intermediate **E13** instead of intermediate **E4**. LCMS (M+H⁺): 816. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.42 - 8.35 (m, 1H), 8.26 (s, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.52 (m, 1H), 7.46 - 7.33 (m, 1H), 7.31 - 7.13 (m, 3H), 6.69 (d, *J* = 8.6 Hz, 1H), 5.92 - 5.66 (m, 1H), 5.44 - 5.25 (m, 1H), 4.83 (br s, 2H), 4.64 - 4.59 (m, 2H), 4.46 - 4.32 (m, 1H), 4.24 - 4.08 (m, 4H), 4.05 - 3.89 (m, 1H), 3.12 - 3.01 (m, 3H), 2.99 - 2.89 (m, 1H), 2.88 - 2.84 (m, 3H), 2.81 - 2.74 (m, 1H), 2.68 (br d, *J* = 13.5 Hz, 1H), 2.66 - 2.61 (m, 3H), 2.55 - 2.42 (m, 2H), 2.16 - 2.02 (m, 3H), 1.73 (br d, *J* = 9.0 Hz, 1H), 1.70 - 1.55 (m, 3H).

Example 144

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-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

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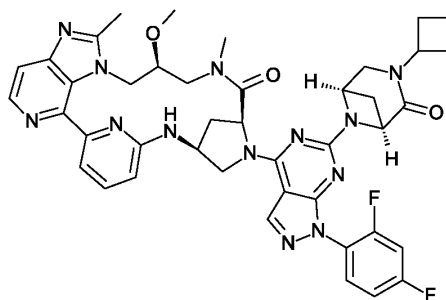


Example **144** was prepared in analogy to the preparation of Example **60** by using iodocyclobutane instead of compound **60b** and intermediate **E14** instead of intermediate **E4**.

LCMS (M+H⁺): 835. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.81 - 8.71 (m, 1H), 8.30 (s, 1H), 7.72 - 7.55 (m, 2H), 7.50 - 7.38 (m, 2H), 7.32 - 7.10 (m, 2H), 5.89 - 5.79 (m, 1H), 5.78 - 5.63 (m, 1H), 5.53 - 5.30 (m, 1H), 4.67 - 4.62 (m, 1H), 4.59 (br s, 1H), 4.55 (br s, 1H), 4.49 - 4.35 (m, 2H), 4.27 (br s, 1H), 4.19 - 4.09 (m, 3H), 4.04 - 3.92 (m, 1H), 3.06 - 2.97 (m, 3H), 2.94 - 2.85 (m, 1H), 2.82 (s, 3H), 2.81 - 2.76 (m, 2H), 2.63 - 2.57 (m, 3H), 2.55 - 2.44 (m, 1H), 2.17 - 2.09 (m, 1H), 2.09 - 1.99 (m, 2H), 1.80 - 1.69 (m, 1H), 1.68 - 1.54 (m, 3H).

Example 145

(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



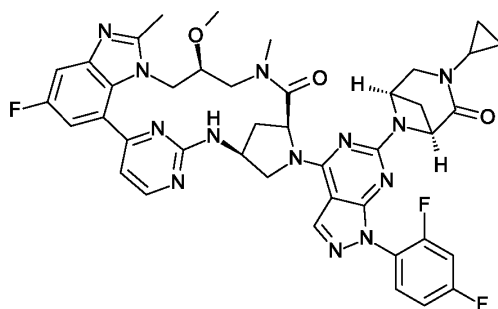
Example **145** was prepared in analogy to the preparation of Example **60** by using iodocyclobutane instead of compound **60b**. LCMS (M+H⁺): 816. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.40 - 8.35 (m, 1H), 8.30 (s, 1H), 7.89 - 7.83 (m, 1H), 7.66 - 7.60 (m, 2H), 7.48 - 7.40 (m, 1H), 7.28 - 7.13 (m, 2H), 6.78 - 6.69 (m, 1H), 6.05 - 5.83 (m, 1H), 5.46 - 5.30 (m, 1H), 4.62 (br d, *J* = 4.5 Hz, 2H), 4.51 - 4.37 (m, 2H), 4.29 - 4.16 (m, 3H), 4.12 (br dd, *J* = 3.8, 5.8 Hz, 1H), 4.04 - 3.92 (m, 1H), 3.11 (s, 1H), 3.04 (s, 2H), 2.97 (br dd, *J* = 4.8, 13.3 Hz, 1H), 2.90 (br d, *J* = 14.3 Hz, 1H), 2.85 - 2.82 (m, 3H), 2.81 - 2.74 (m, 1H), 2.71 (br d, *J* = 13.6 Hz,

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1H), 2.67 - 2.62 (m, 3H), 2.58 - 2.51 (m, 1H), 2.49 - 2.42 (m, 1H), 2.15 - 2.02 (m, 3H), 1.73 (br d, $J = 8.6$ Hz, 1H), 1.70 - 1.57 (m, 3H).

Example 146

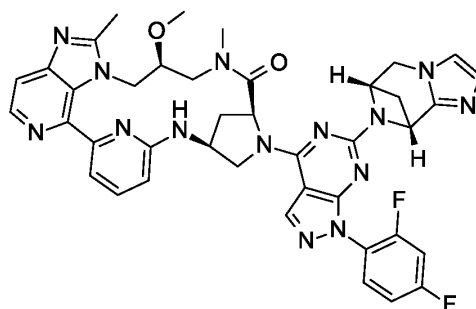
(8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



Example **146** was prepared in analogy to the preparation of Example **117** by using Intermediate **E3** instead of Intermediate **E4**. LCMS ($M+H^+$): 820. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.59 - 8.55 (m, 1H), 8.30 (s, 1H), 7.68 - 7.59 (m, 1H), 7.41 (dd, $J = 2.5$, 8.5 Hz, 1H), 7.33 - 7.22 (m, 2H), 7.18 (br t, $J = 7.7$ Hz, 1H), 7.14 - 7.10 (m, 1H), 5.70 - 5.48 (m, 1H), 5.40 - 5.28 (m, 1H), 4.59 (s, 3H), 4.56 (br d, $J = 2.3$ Hz, 1H), 4.36 - 4.30 (m, 1H), 4.29 - 4.24 (m, 1H), 4.23 - 4.18 (m, 1H), 4.17 - 4.11 (m, 2H), 4.04 - 3.95 (m, 1H), 3.13 - 3.04 (m, 3H), 2.99 - 2.89 (m, 1H), 2.90 - 2.85 (m, 3H), 2.85 - 2.77 (m, 2H), 2.63 - 2.56 (m, 3H), 2.55 - 2.41 (m, 3H), 1.81 - 1.70 (m, 1H), 0.81 - 0.53 (m, 2H), 0.24 - 0.07 (m, 1H).

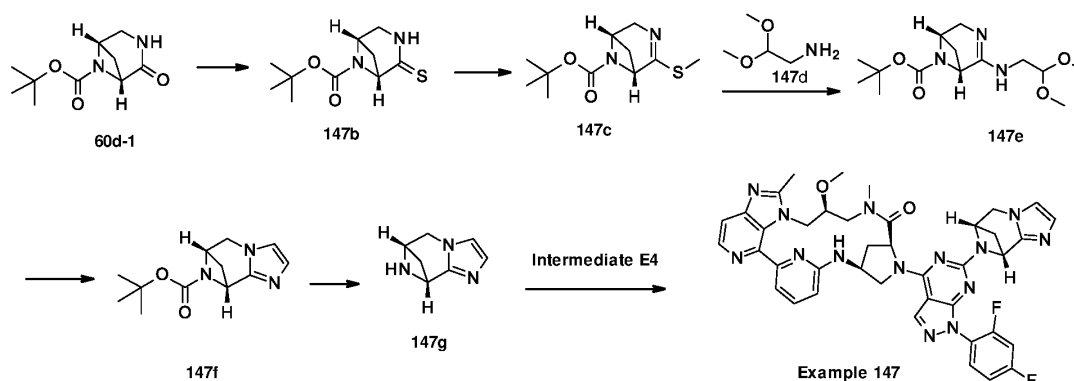
Example 147

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-12-one



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The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl (1*R*, 5*S*)-2-thioxo-3, 6-diazabicyclo [3.1.1] heptane-6-carboxylate (compound 147b)

To a stirred solution of compound **60d-1** (6 g, 17 mmol) in toluene (80 mL) was added Lawesson's Reagent (4.1 g, 10.2 mmol) portion wise at 20 °C. The mixture was stirred at 95 °C for 1 h, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography to give compound **147b** (3.8 g) as a light yellow solid. LCMS ($M+H^+$): 229.

Step 2: preparation of *tert*-butyl (1*R*, 5*S*)-2-methylsulfanyl-3, 6-diazabicyclo [3.1.1] hept-2-ene-6-carboxylate (compound 147c)

A mixture of compound **147b** (4.2 g, 18.4 mmol) and MeI (11.5 mL, 184 mmol) in DCM (60 mL) was stirred at 20 °C for 16 h. Then the reaction mixture was washed with brine and then concentrated to give compound **147c** (4.1g) as a yellow solid. LCMS ($M+H^+$): 243.

Step 3: preparation of *tert*-butyl (1*R*, 5*S*)-2-(2, 2-dimethoxyethylamino)-3, 6-diazabicyclo [3.1.1] hept-2-ene-6-carboxylate (compound 147e)

A mixture of compound **147c** (3.6 g, 14.9 mmol) and compound **147d** (1.87 g, 17.8 mmol) in ethanol (50 mL) was stirred at 70 °C for 16 h. Then the reaction mixture was purified by prep-HPLC to afford compound **147e** (3.6 g) as light yellow oil. LCMS ($M+H^+$): 300.

Step 4: preparation of *tert*-butyl (1*R*, 8*S*)-3, 6, 9-triazatricyclo [6.1.1.02, 6] deca-2, 4-diene-9-carboxylate (compound 147f)

To a solution of compound **147e** (1 g, 3.34 mmol) in toluene (20 mL) was added *p*-toluenesulfonic acid (86 mg, 0.5 mmol). The mixture was stirred at 110 °C for 16 h and then concentrated. The residue was purified by prep-HPLC to afford compound **147f** (120.0 mg) as light brown oil. LCMS ($M+H^+$): 236.

Step 5: preparation of (1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.02,6]deca-2,4-diene

(compound 147g)

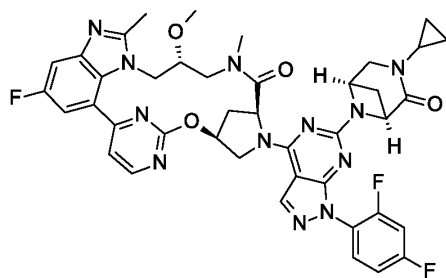
To a solution of compound **147f** (60.0 mg, 0.26 mmol) in DCM (3 mL) was added TFA (1.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at 25 °C and then concentrated to give compound **147g** (60.0 mg) as light yellow oil. LCMS (M+H⁺): 136.

5 **Step 6: preparation of (8*S*, 11*S*, 15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-12-one (Example 147)**

A mixture of Intermediate **E4** (30.0 mg, 0.04 mmol), CsF (28 mg, 0.19 mmol), compound
10 **147g** (11 mg, 0.04 mmol) and DIPEA (0.07 mL, 0.4 mmol) in DMA (2 mL) was stirred at 120 °C for 18 h. The reaction mixture was purified by prep-HPLC to give the product Example **147** (5 mg) as a white solid. LCMS (M+H⁺): 785. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.43 - 8.37 (m, 1H), 8.31 (s, 1H), 7.90 (t, *J* = 7.9 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.61 - 7.52 (m, 1H), 7.49 - 7.42 (m, 1H), 7.31 - 7.19 (m, 4H), 6.84 - 6.77 (m, 1H), 6.10 - 5.86 (m, 1H), 5.51 - 5.31 (m,
15 1H), 4.55 - 4.44 (m, 1H), 4.35 - 4.17 (m, 4H), 4.05 - 3.89 (m, 1H), 3.68 - 3.56 (m, 1H), 3.22 - 2.99 (m, 6H), 2.93 - 2.82 (m, 4H), 2.78 - 2.51 (m, 5H), 2.06 - 1.96 (m, 1H), 1.38 - 1.18 (m, 1H).

Example 148

**(8*S*,11*S*,15*S*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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-
20 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**



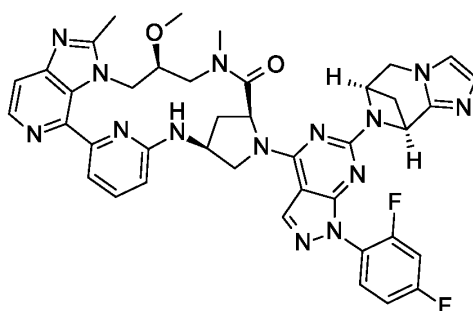
Example **148** was prepared in analogy to the preparation of Example **117** by using Intermediate **E16** instead of Intermediate **E4**. LCMS (M+H⁺): 821. ¹H NMR (400 MHz,
25 METHANOL-*d*₄) δ = 8.74 - 8.64 (m, 1H), 8.32 (s, 1H), 7.68 - 7.55 (m, 1H), 7.45 (br d, *J* = 5.3 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.34 - 7.14 (m, 3H), 5.89 - 5.80 (m, 1H), 5.75 - 5.66 (m, 1H), 5.55 - 5.37 (m, 1H), 4.55 - 4.49 (m, 2H), 4.45 - 4.39 (m, 1H), 4.36 - 4.26 (m, 1H), 4.21 - 4.12 (m, 2H), 4.01 - 3.92 (m, 1H), 3.56 - 3.44 (m, 1H), 3.16 - 3.08 (m, 2H), 3.05 (s, 3H), 2.91 - 2.85 (m, 1H),

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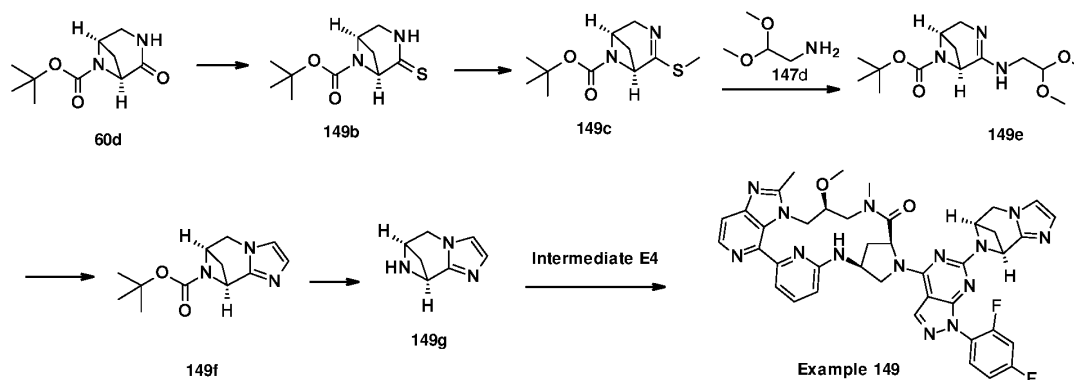
2.84 - 2.81 (m, 3H), 2.81 - 2.79 (m, 1H), 2.78 - 2.76 (m, 1H), 2.73 - 2.65 (m, 1H), 2.64 - 2.59 (m, 3H), 2.55 - 2.43 (m, 1H), 1.71 (d, $J = 8.5$ Hz, 1H), 0.77 - 0.50 (m, 2H), 0.15 (br d, $J = 4.5$ Hz, 1H).

Example 149

- 5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-tdien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one



- 10 The title compound was prepared according to the following scheme:

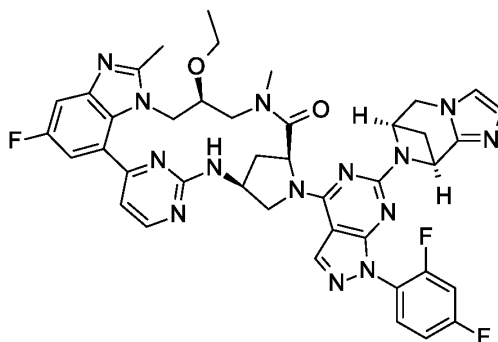


- Example **149** was prepared in analogy to the preparation of Example **147** by using compound **60d** instead of compound **60d-1**. LCMS ($M+H^+$): 785. ¹H NMR (400 MHz, METHANOL-*d*₄) $\delta = 8.28 - 8.25$ (m, 1H), 8.17 - 8.14 (m, 1H), 7.79 - 7.74 (m, 1H), 7.55 - 7.52 (m, 1H), 7.48 - 7.43 (m, 1H), 7.37 - 7.29 (m, 1H), 7.16 - 7.04 (m, 2H), 6.79 (d, $J = 6.4$ Hz, 1H), 6.68 - 6.62 (m, 2H), 5.94 - 5.74 (m, 1H), 5.43 - 5.15 (m, 1H), 4.61 - 4.54 (m, 1H), 4.49 - 4.43 (m, 1H), 4.39 - 4.32 (m, 1H), 4.16 - 4.04 (m, 3H), 4.00 - 3.94 (m, 1H), 3.87 - 3.78 (m, 1H), 3.06 - 2.95 (m, 4H), 2.91 - 2.84 (m, 1H), 2.74 (d, $J = 17.1$ Hz, 4H), 2.60 - 2.50 (m, 5H), 1.77 - 1.63 (m, 1H), 1.26 - 1.12 (m, 1H).

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Example 150

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-
 5 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

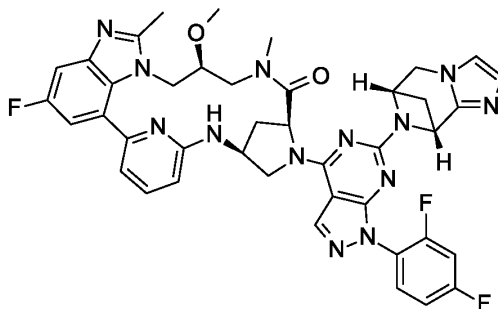


Example **150** was prepared in analogy to the preparation of Example **147** by using compound **60d** instead of compound **60d-1** and intermediate **E2** instead of intermediate **E4**.

- 10 LCMS (M+H⁺): 817. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.62 - 8.51 (m, 1H), 8.26 (s, 1H), 7.61 - 7.53 (m, 1H), 7.46 - 7.38 (m, 1H), 7.35 - 7.17 (m, 3H), 7.12 (dd, *J* = 5.2, 7.6 Hz, 1H), 6.94 - 6.87 (m, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 5.65 - 5.45 (m, 2H), 5.20 (br s, 4H), 4.34 - 3.93 (m, 5H), 3.17 - 3.13 (m, 1H), 3.09 (d, *J* = 5.6 Hz, 3H), 3.04 - 2.88 (m, 2H), 2.73 - 2.54 (m, 6H), 1.88 - 1.72 (m, 1H), 1.36 - 1.27 (m, 1H), 0.66 - 0.55 (m, 3H).

15 Example 151

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-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

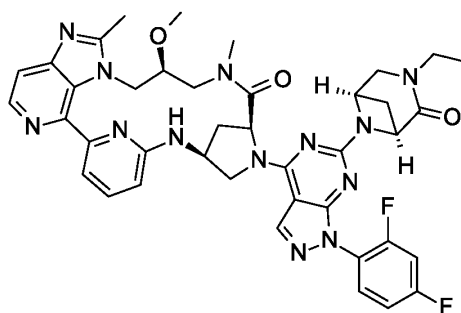


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Example **151** was prepared in analogy to the preparation of Example **147** by using intermediate **E2** instead of intermediate **E4**. LCMS (M+H⁺): 802. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.25 (s, 1H), 7.83 (t, *J* = 8.1 Hz, 1H), 7.61 - 7.54 (m, 1H), 7.34 - 7.30 (m, 1H), 7.28 - 7.20 (m, 1H), 7.20 - 7.15 (m, 2H), 7.14 - 7.09 (m, 1H), 6.92 - 6.89 (m, 1H), 6.80 - 6.76 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.86 - 5.78 (m, 1H), 5.46 - 5.40 (m, 1H), 4.74 - 4.64 (m, 2H), 4.49 - 4.37 (m, 1H), 4.30 - 4.13 (m, 3H), 4.09 - 3.92 (m, 1H), 3.18 - 3.06 (m, 4H), 3.01 - 2.96 (m, 1H), 2.90 - 2.81 (m, 4H), 2.67 - 2.44 (m, 6H), 1.87 - 1.77 (m, 1H), 1.45 - 0.96 (m, 1H).

Example 152

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one

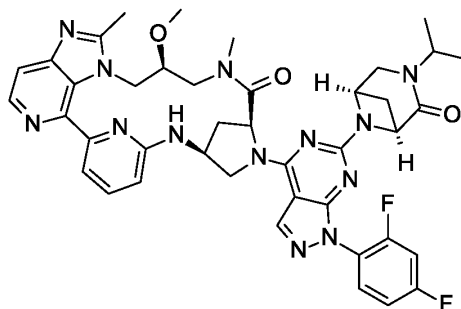


Example **152** was prepared in analogy to the preparation of Example **60** by using bromoethane instead of compound **60b** and compound **60d** instead of compound **60f**. LCMS (M+H⁺): 790. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.50 (d, *J* = 6.3 Hz, 1H), 8.31 (s, 1H), 8.08 (d, *J* = 6.4 Hz, 1H), 8.00 (t, *J* = 7.9 Hz, 1H), 7.62 (dt, *J* = 2.4, 8.4 Hz, 1H), 7.42 - 7.33 (m, 1H), 7.29 - 7.21 (m, 1H), 7.18 (br t, *J* = 7.8 Hz, 1H), 7.00 - 6.90 (m, 1H), 6.03 (dd, *J* = 4.3, 15.6 Hz, 1H), 5.49 (d, *J* = 8.6 Hz, 1H), 4.73 - 4.69 (m, 1H), 4.65 - 4.50 (m, 2H), 4.46 (br dd, *J* = 6.4, 11.3 Hz, 1H), 4.41 - 4.19 (m, 3H), 4.16 (br dd, *J* = 3.7, 5.8 Hz, 1H), 4.01 (br dd, *J* = 2.3, 11.7 Hz, 1H), 3.45 - 3.35 (m, 1H), 3.15 - 3.05 (m, 4H), 2.95 (s, 4H), 2.86 - 2.74 (m, 4H), 2.66 (br d, *J* = 13.5 Hz, 1H), 2.58 - 2.45 (m, 2H), 1.83 - 1.68 (m, 1H), 0.97 - 0.72 (m, 3H).

Example 153

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-12-one

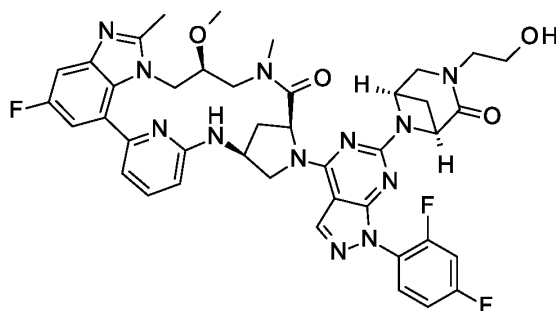
-224-



Example **153** was prepared in analogy to the preparation of Example **60** by using 2-bromopropane instead of compound **60b** and compound **60d** instead of compound **60f**. LCMS (M+H⁺): 804. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.50 (d, *J* = 6.4 Hz, 1H), 8.32 (s, 1H), 8.09 (d, *J* = 6.4 Hz, 1H), 8.00 (t, *J* = 8.0 Hz, 1H), 7.68 - 7.59 (m, 1H), 7.45 - 7.34 (m, 1H), 7.31 - 7.23 (m, 1H), 7.21 - 7.12 (m, 1H), 7.01 - 6.90 (m, 1H), 6.04 (dd, *J* = 4.1, 15.4 Hz, 1H), 5.56 - 5.31 (m, 1H), 4.73 - 4.68 (m, 1H), 4.66 - 4.59 (m, 1H), 4.53 - 4.39 (m, 2H), 4.36 - 4.24 (m, 2H), 4.22 - 4.09 (m, 2H), 3.93 (br dd, *J* = 2.7, 11.7 Hz, 1H), 3.24 (br d, *J* = 11.4 Hz, 1H), 3.08 (s, 3H), 3.00 - 2.91 (m, 4H), 2.82 (s, 4H), 2.69 - 2.61 (m, 1H), 2.59 - 2.47 (m, 2H), 1.81 - 1.65 (m, 1H), 1.12 (dd, *J* = 6.9, 13.0 Hz, 3H), 0.83 (br d, *J* = 1.1 Hz, 3H).

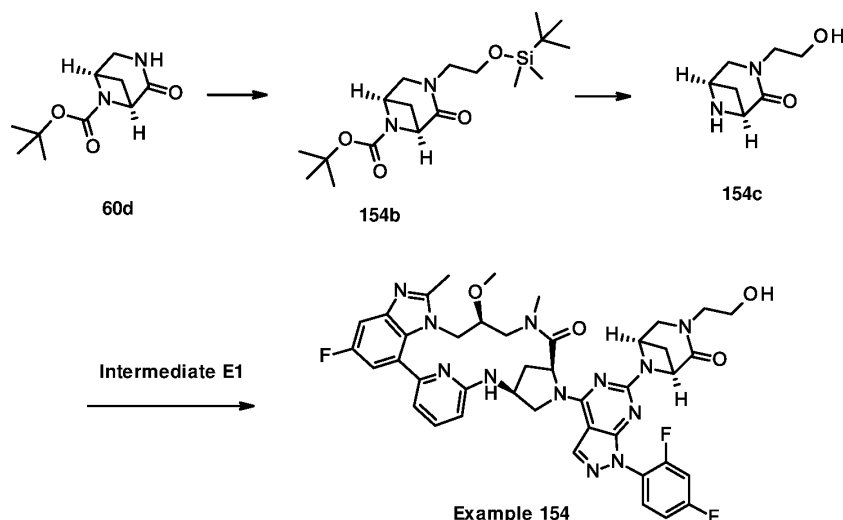
Example 154

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(2-hydroxyethyl)-2-oxo-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-15 **1(24),2(26),3,5,18,20,22-heptaen-12-one**



The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl (1*S*,5*R*)-3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound **154b)**

To a solution of compound **60d** (200 mg, 0.94 mmol) in DMF (2 mL) was added sodium hydride (113 mg, 2.83 mmol) at 0 °C and then stirred for 1 h. *Tert*-butyl-(2-iodoethoxy)-dimethyl-silane (1.08 g, 3.77 mmol) in DMF (1 mL) was added to the reaction mixture at 0 °C, then the reaction mixture was stirred at 0 °C for another 2 h. The reaction mixture was poured into sat.aq. NH₄Cl (10 mL) and extracted with EA. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography to give compound **154b** (130 mg) as yellow oil. LCMS (M+H⁺-56): 315.

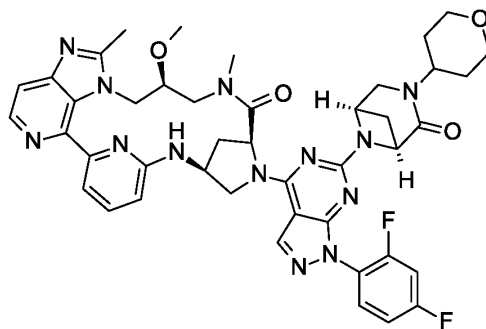
Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(2-hydroxyethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20,22-heptaen-12-one (Example **154)**

Example **154** was prepared in analogy to the preparation of Example **147** by using compound **154b** instead of compound **147f** and Intermediate **E1** instead of Intermediate **E4**. LCMS (M+H⁺): 823. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.41 - 8.30 (m, 1H), 7.90 - 7.83 (m, 1H), 7.69 - 7.60 (m, 1H), 7.58 - 7.48 (m, 2H), 7.29 - 7.20 (m, 1H), 7.19 - 7.12 (m, 2H), 6.76 (t, *J* = 8.3 Hz, 1H), 6.17 - 5.98 (m, 1H), 5.47 - 5.31 (m, 1H), 4.70 - 4.60 (m, 2H), 4.60 - 4.53 (m, 1H), 4.51 - 4.42 (m, 1H), 4.21 (br s, 3H), 4.16 (dd, *J* = 3.7, 5.7 Hz, 1H), 3.99 - 3.89 (m, 1H), 3.88 - 3.76 (m, 1H), 3.56 - 3.34 (m, 3H), 3.15 - 3.11 (m, 1H), 3.08 - 3.00 (m, 3H), 3.00 - 2.91 (m, 4H), 2.85 (br s, 3H), 2.79 - 2.73 (m, 1H), 2.64 - 2.45 (m, 2H), 1.91 - 1.73 (m, 1H).

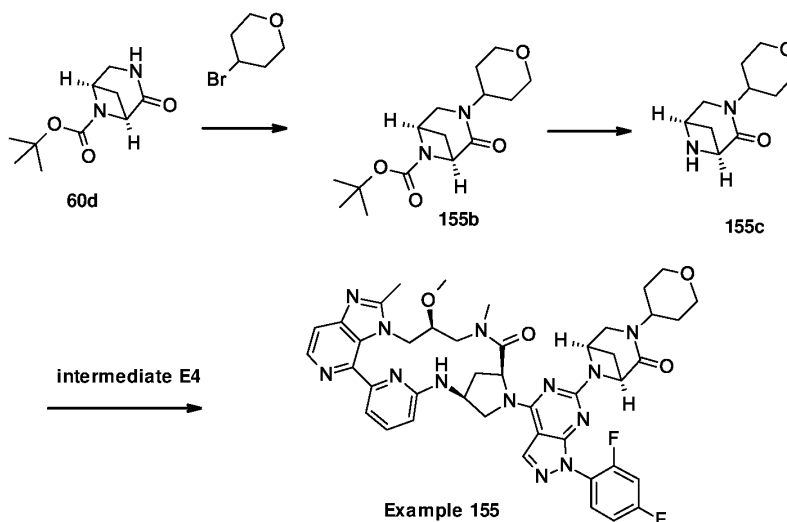
Example 155

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-2-oxo-3-tetrahydropyran-4-yl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-

5 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*S*, 5*R*)-2-oxo-3-tetrahydropyran-4-yl-3, 6-diazabicyclo [3.1.1] heptane-6-carboxylate (compound 155b)

To a solution of compound **60d** (100.0 mg, 0.47 mmol), lithium *tert*-butoxide (75 mg, 0.94 mmol), copper iodide (9.0 mg, 0.05 mmol) in DMF (0.8 mL) and ACN (5.4 mL) was added 4-bromo-tetrahydropyran (155 mg, 0.94 mmol) under N₂ and then stirred at 25°C for 1 h under *hν* (254 nm). Then the reaction mixture was filtered and the filtrate was concentrated, the residue

15 was poured into water (50 mL) and extracted with EA. The organic layer was dried and

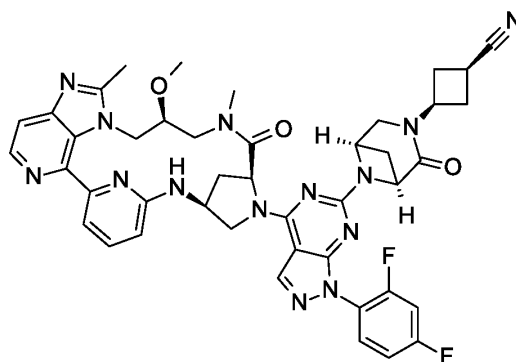
concentrated, the residue was purified by prep-HPLC to give compound **155b** (44 mg) as yellow oil. LCMS ($M+H^+$ -56): 241.

Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20,22-heptaen-12-one (Example 155)

Example 155 was prepared in analogy to the preparation of Example 147 by using compound **155b** instead of compound **147f**. LCMS ($M+H^+$): 846. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.49 (d, *J* = 6.3 Hz, 1H), 8.33 (s, 1H), 8.06 (d, *J* = 6.3 Hz, 1H), 7.99 (t, *J* = 8.0 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.31 - 7.22 (m, 1H), 7.21 - 7.12 (m, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.10 - 5.83 (m, 1H), 5.52 (d, *J* = 8.4 Hz, 1H), 4.65 - 4.59 (m, 2H), 4.34 - 4.20 (m, 4H), 4.17 (br dd, *J* = 3.7, 5.8 Hz, 2H), 4.07 - 3.99 (m, 1H), 3.99 - 3.87 (m, 3H), 3.50 - 3.41 (m, 2H), 3.16 - 3.05 (m, 4H), 2.99 (br d, *J* = 15.3 Hz, 1H), 2.96 - 2.91 (m, 3H), 2.82 (s, 4H), 2.73 - 2.63 (m, 1H), 2.61 - 2.43 (m, 2H), 1.88 - 1.75 (m, 1H), 1.73 (d, *J* = 8.9 Hz, 1H), 1.62 - 1.48 (m, 2H).

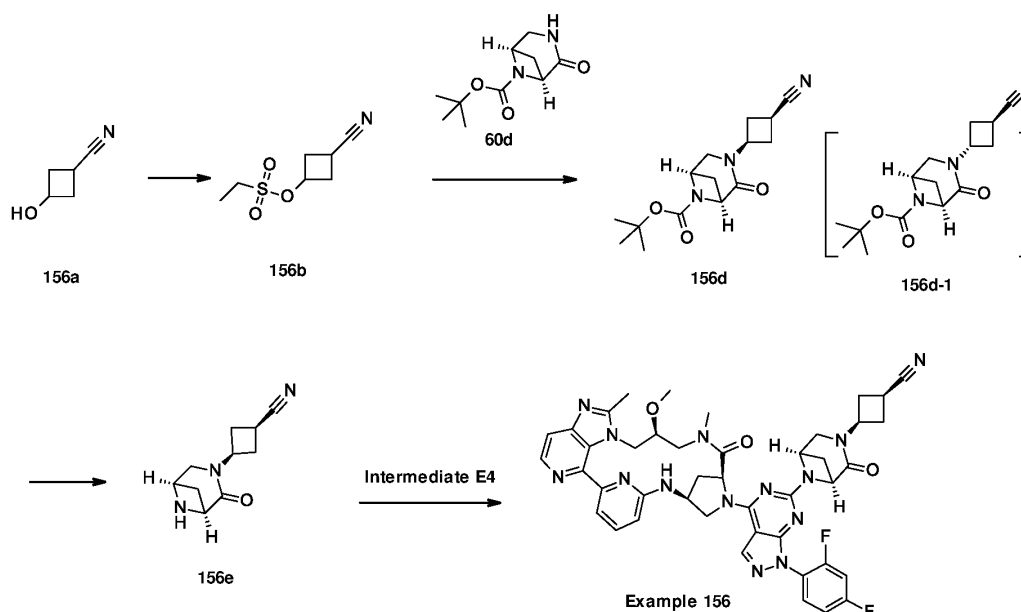
Example 156

Cis-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile



The title compound was prepared according to the following scheme:

-228-



Step 1: preparation of (3-cyanocyclobutyl) ethanesulfonate (compound 156b)

To a solution of compound **156a** (200 mg, 2.06 mmol) and triethylamine (0.57 mL, 4.12 mmol) in DCM (4 mL) was added ethanesulfonyl chloride (0.29 mL, 3.09 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h and then poured into water (10 mL), extracted with DCM. The organic layer was dried and concentrated to give compound **156b** (350.0 mg) as brown oil.

Step 2: preparation of *cis-tert*-butyl (1*S*, 5*R*)-3-(3-cyanocyclobutyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate and *trans-tert*-butyl (1*S*, 5*R*)-3-(3-cyanocyclobutyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 156d and 156d-1)

To a solution of compound **60d** (200 mg, 0.94 mmol) in DMF (3 mL) was added sodium hydride (113 mg, 2.83 mmol) at 0 °C, after 0.5 h, compound **156c** (357 mg, 1.88 mmol) was added and the reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by silica gel column chromatography and SFC to give compound **156d** (faster eluted, 160.0 mg) as a yellow solid and compound **156d-1** (slower eluted, 90.0 mg) as a yellow solid. LCMS ($M+H^+$ -56): 236. The configurations of compounds **156d** and **156d-1** were confirmed by 2D NMR.

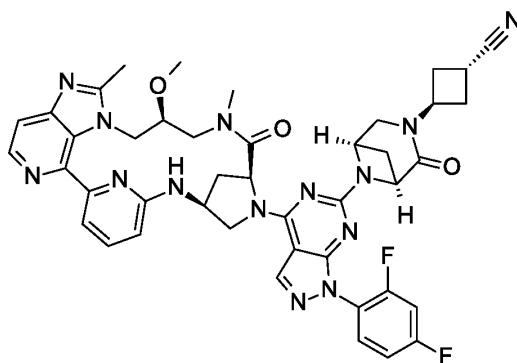
SFC condition: Instrument CASWH-Prep-SFC-I; Method Column DAICEL CHIRALPAK IG (250mm×30mm,10μm); Condition CO₂-EtOH(0.1%NH₃H₂O); Begin B 15; End B 15; Gradient Time(min) 3; 100% B Hold Time(min) 0; Flowrate(mL/min) 150.

Step 3~4: preparation of *cis*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile (Example 156)

Example **156** was prepared in analogy to the preparation of Example **147** by using compound **156d** instead of compound **147f**. LCMS (M+H⁺): 841. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.53 - 8.43 (m, 1H), 8.34 (s, 1H), 8.09 - 7.94 (m, 2H), 7.64 (s, 1H), 7.42 - 7.35 (m, 1H), 7.31 - 7.16 (m, 2H), 6.95 (br d, *J* = 9.0 Hz, 1H), 6.15 - 5.88 (m, 1H), 5.58 - 5.38 (m, 1H), 4.93 - 4.92 (m, 1H), 4.78 - 4.76 (m, 2H), 4.70 (br s, 1H), 4.65 - 4.51 (m, 3H), 4.45 - 4.33 (m, 2H), 4.27 - 4.13 (m, 2H), 4.08 - 3.97 (m, 1H), 3.18 - 3.06 (m, 3H), 2.99 (br d, *J* = 1.5 Hz, 1H), 2.97 - 2.92 (m, 4H), 2.91 - 2.86 (m, 1H), 2.84 - 2.81 (m, 2H), 2.77 (s, 1H), 2.70 - 2.63 (m, 1H), 2.58 - 2.47 (m, 4H), 1.82 - 1.69 (m, 1H).

Example 157

***Trans*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile**



Example **157** was prepared in analogy to the preparation of Example **147** by using compound **156d-1** instead of compound **147f**. LCMS (M+H⁺): 841. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.50 (d, *J* = 6.3 Hz, 1H), 8.33 (s, 1H), 8.15 - 7.90 (m, 2H), 7.73 - 7.57 (m, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.32 - 7.15 (m, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.13 - 5.94 (m, 1H),

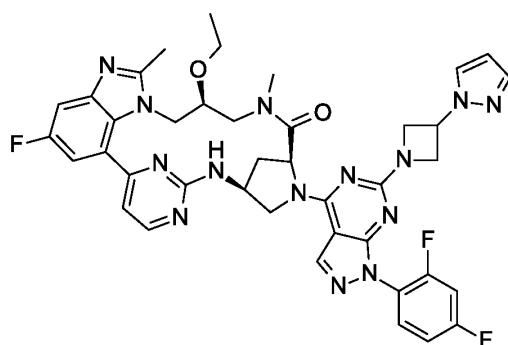
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5.53 (d, $J = 8.4$ Hz, 1H), 5.09 - 4.97 (m, 1H), 4.74 - 4.58 (m, 3H), 4.55 - 4.36 (m, 2H), 4.28 (br d, $J = 11.0$ Hz, 2H), 4.19 - 4.08 (m, 1H), 4.00 - 3.91 (m, 1H), 3.34 (br s, 1H), 3.16 - 3.07 (m, 3H), 3.02 (s, 1H), 2.98 (s, 3H), 2.94 (s, 1H), 2.85 (s, 3H), 2.82 - 2.77 (m, 1H), 2.71 - 2.60 (m, 2H), 2.57 - 2.48 (m, 1H), 2.46 - 2.35 (m, 1H), 2.31 - 2.21 (m, 2H), 1.73 (d, $J = 8.9$ Hz, 1H).

5

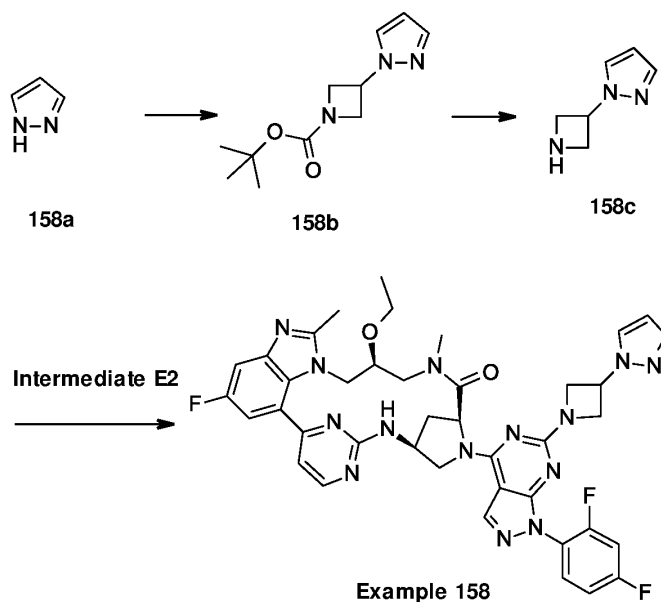
Example 158

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrazol-1-ylazetidin-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



10

The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-pyrazol-1-ylazetidine-1-carboxylate (compound 158b)

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To a solution of compound **158a** (200 mg, 2.94 mmol) and 1-BOC-3-iodoazetidine (1.66 g, 5.88 mmol) in DMF (4 mL) was added cesium carbonate (2.87 g, 8.81 mmol) and then stirred at 90 °C for 16 h. The reaction mixture was diluted with H₂O and extracted with ethyl acetate. The organic layer was dried and concentrated, the residue was purified by silica gel column

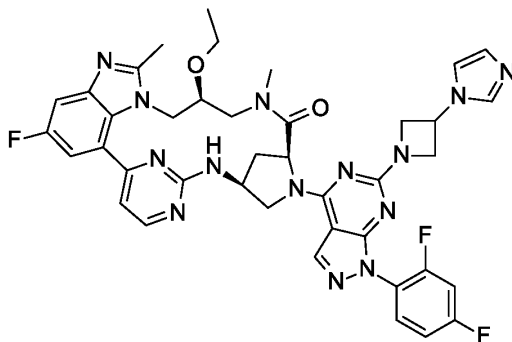
5 chromatography to give compound **158b** (300.0 mg) as yellow oil. LCMS (M+H⁺-56): 168.

Step 2~3: preparation of (8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(3-pyrazol-1-ylazetididin-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 158)

10 Example **158** was prepared in analogy to the preparation of Example **147** by using compound **158b** instead of compound **147f** and Intermediate **E2** instead of Intermediate **E4**.
LCMS (M+H⁺): 805. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.65 (d, *J* = 5.3 Hz, 1H), 8.32 (s, 1H), 7.79 - 7.75 (m, 1H), 7.73 - 7.67 (m, 2H), 7.67 - 7.58 (m, 3H), 7.24 (ddd, *J* = 2.8, 8.8, 10.2 Hz, 1H), 7.19 - 7.13 (m, 2H), 6.34 (t, *J* = 2.1 Hz, 1H), 6.04 - 5.80 (m, 1H), 5.43 - 5.26 (m, 2H),
15 4.64 - 4.56 (m, 1H), 4.54 - 4.47 (m, 1H), 4.45 - 4.40 (m, 1H), 4.39 - 4.29 (m, 3H), 4.05 - 3.91 (m, 1H), 3.49 - 3.39 (m, 1H), 3.14 (s, 1H), 3.08 - 2.97 (m, 3H), 2.97 - 2.90 (m, 2H), 2.90 - 2.85 (m, 3H), 2.82 - 2.77 (m, 1H), 2.75 - 2.69 (m, 1H), 2.67 - 2.47 (m, 1H), 0.69 - 0.60 (m, 3H).

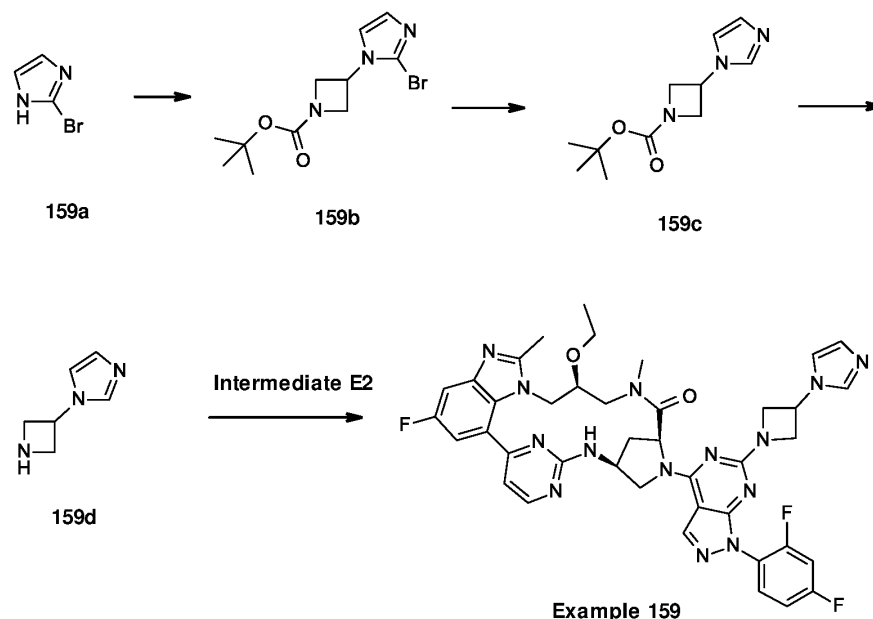
Example 159

(8S,11S,15R)-10-[1-(2,4-difluorophenyl)-6-(3-imidazol-1-ylazetididin-1-yl)pyrazolo[3,4-
20 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



The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 3-(2-bromoimidazol-1-yl)azetidine-1-carboxylate (compound 159b)

A mixture of compound **159a** (100.0 mg, 0.68 mmol), potassium carbonate (282 mg, 2.04 mmol) and 1-BOC-3-iodoazetidine (963 mg, 3.4 mmol) in DMF (2 mL) was stirred at 120 °C for 16 h. Then the reaction mixture was concentrated, the residue was purified by prep-HPLC to give compound **159b** (120 mg) as a white solid. LCMS ($M+2+H^+$): 304.

Step 2: preparation of *tert*-butyl 3-imidazol-1-ylazetidine-1-carboxylate (compound 159c)

To a solution of compound **159b** (120 mg, 0.4 mmol) in methanol (3 mL) was added wet Pd/C (60.0 mg) under N_2 at 25 °C. The mixture was stirred under H_2 (balloon) at 50 °C for 2 h, then the reaction mixture was filtered, the filtrate was concentrated to give compound **159c** (85 mg) as colorless oil. LCMS ($M+H^+$): 224.

Step 3~4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-imidazol-1-ylazetidin-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 159)

Example **159** was prepared in analogy to the preparation of Example **147** by using compound **159c** instead of compound **147f** and Intermediate **E2** instead of Intermediate **E4**. LCMS ($M+H^+$): 805. 1H NMR (400 MHz, METHANOL- d_4) δ = 8.55 (d, J = 5.3 Hz, 1H), 8.27 (s, 1H), 7.87 - 7.80 (m, 1H), 7.67 - 7.56 (m, 1H), 7.44 - 7.38 (m, 2H), 7.32 - 7.17 (m, 2H), 7.16 -

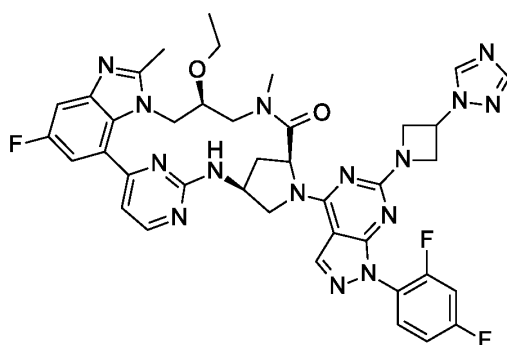
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7.08 (m, 2H), 7.05 (s, 1H), 5.72 - 5.46 (m, 1H), 5.40 - 5.26 (m, 1H), 5.16 (br s, 1H), 4.76 - 4.70 (m, 1H), 4.55 - 4.43 (m, 2H), 4.39 - 4.31 (m, 1H), 4.29 - 4.23 (m, 1H), 4.22 - 4.09 (m, 3H), 4.03 - 3.88 (m, 1H), 3.27 - 3.21 (m, 1H), 3.14 - 2.98 (m, 3H), 2.96 - 2.80 (m, 2H), 2.67 - 2.55 (m, 5H), 2.53 - 2.42 (m, 1H), 0.63 - 0.54 (m, 3H).

5

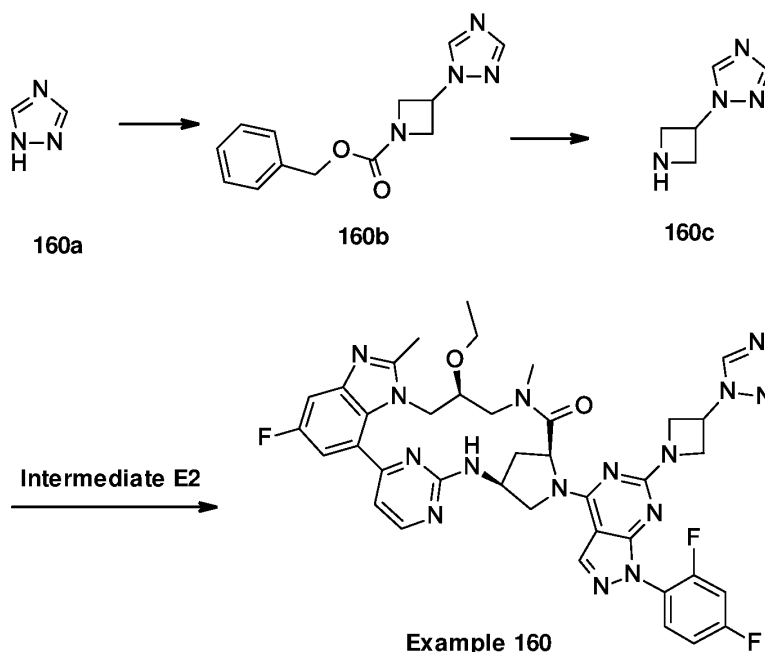
Example 160

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1,2,4-triazol-1-yl)azetidin-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one



10

The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl 3-(1,2,4-triazol-1-yl)azetidine-1-carboxylate (compound 160b)

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To a solution of 1-*N*-Cbz-3-hydroxyazetidine (1.2 g, 5.79 mmol) and compound **160a** (200.0 mg, 2.9 mmol), triphenylphosphane (1139 mg, 4.34 mmol) in toluene (4 mL) was added diisopropyl azodicarboxylate (0.68 mL, 3.47 mmol) at 0 °C under N₂. The reaction mixture was stirred at 100 °C for 16 h and then poured into ice water, extracted with EA. The organic layer was concentrated, the residue was purified by prep-HPLC to give compound **160b** (400.0 mg) as colorless oil. LCMS (M+H): 259.

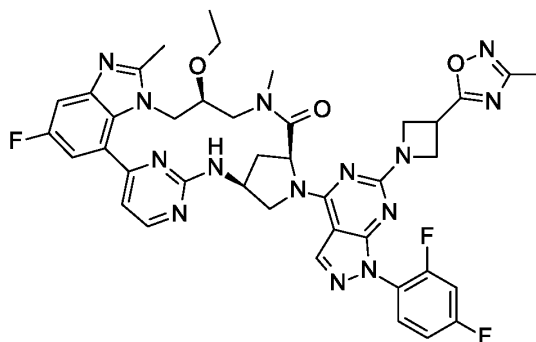
Step 2~3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1,2,4-triazol-1-yl)azetidin-1-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one (Example 160)

Example **160** was prepared in analogy to the preparation of Example **60** by using compound **160b** instead of compound **60g** and Intermediate **E2** instead of Intermediate **E4**. LCMS (M+H⁺): 806. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.60 - 8.56 (m, 2H), 8.30 (s, 1H), 8.07 (s, 1H), 7.69 - 7.60 (m, 1H), 7.42 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.27 - 7.20 (m, 1H), 7.19 - 7.15 (m, 1H), 7.15 - 7.10 (m, 1H), 5.74 - 5.50 (m, 1H), 5.47 - 5.29 (m, 2H), 4.53 (br d, *J* = 8.8 Hz, 1H), 4.49 (br d, *J* = 6.1 Hz, 1H), 4.47 - 4.42 (m, 1H), 4.41 - 4.37 (m, 1H), 4.34 (dd, *J* = 3.7, 8.9 Hz, 1H), 4.32 - 4.27 (m, 1H), 4.25 - 4.15 (m, 2H), 4.05 - 3.93 (m, 1H), 3.13 (s, 1H), 3.03 (s, 2H), 2.97 - 2.91 (m, 1H), 2.86 (br d, *J* = 13.3 Hz, 1H), 2.70 - 2.57 (m, 6H), 2.56 - 2.46 (m, 1H), 0.64 - 0.56 (m, 3H).

20

Example 161

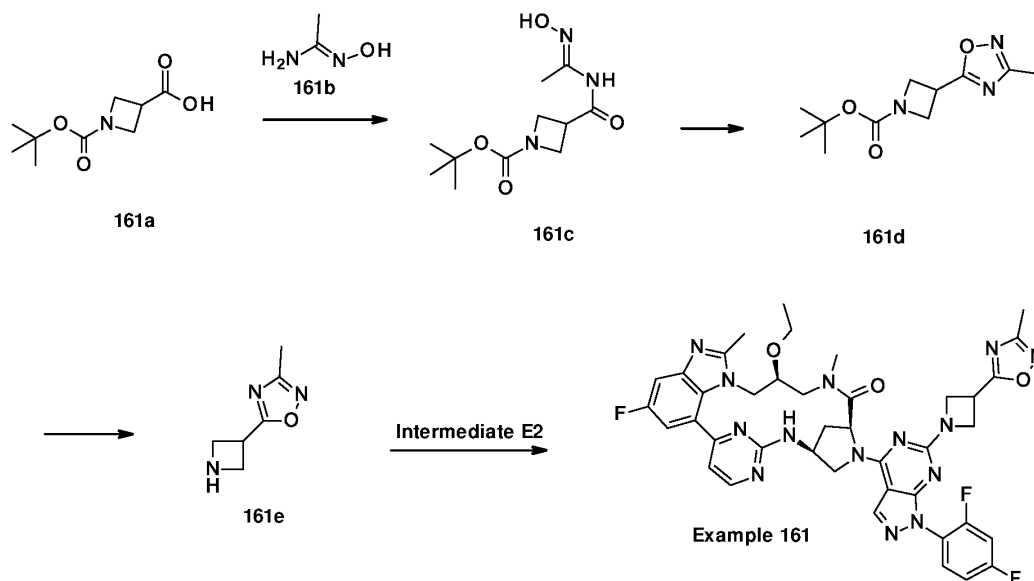
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyl-1,2,4-oxadiazol-5-yl)azetidin-1-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one



25

The title compound was prepared according to the following scheme:

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Step 1: preparation of *tert*-butyl 3-[[*(E)*-*N*-hydroxy-*C*-methyl-carbonimidoyl]carbamoyl]azetidine-1-carboxylate (compound **161c)**

To a solution of compound **161b** (500.0 mg, 6.75 mmol) and compound **161a** (1.36 g, 6.75 mmol) in DCM (20 mL) was added TEA (2.81 mL, 20.25 mmol), EDCI (1.94 g, 10.12 mmol) and HOBT (1.37 g, 10.12 mmol) at 0 °C under N₂. The reaction mixture was stirred at 25 °C for 16 h and then poured into water, extracted with DCM. The organic layer was dried and concentrated to give compound **161c** (1 g) as light yellow oil. LCMS (M+H⁺): 258.

Step 2: preparation of *tert*-butyl 3-(3-methyl-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (compound **161d)**

A solution of compound **161c** (100.0 mg, 0.39 mmol) in toluene (2 mL) was heated to 100 °C and for 16 h. Then the reaction mixture was concentrated to give compound **161d** (60.0 mg) as light yellow oil.

Step 3~4: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyl-1,2,4-oxadiazol-5-yl)azetidin-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 **161)**

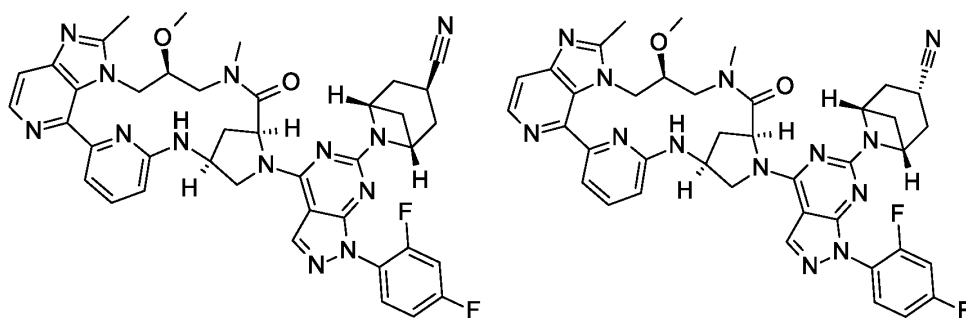
Example **161** was prepared in analogy to the preparation of Example **147** by using compound **161d** instead of compound **147f** and Intermediate **E2** instead of Intermediate **E4**. LCMS (M+H⁺): 821. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.57 (d, *J* = 5.3 Hz, 1H), 8.29 (s, 1H), 7.68 - 7.59 (m, 1H), 7.44 - 7.40 (m, 1H), 7.33 - 7.28 (m, 1H), 7.27 - 7.21 (m, 1H), 7.20 - 7.15 (m, 1H), 7.14 - 7.10 (m, 1H), 5.73 - 5.51 (m, 1H), 5.44 - 5.27 (m, 1H), 4.79 - 4.73 (m, 2H),

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4.47 - 4.34 (m, 3H), 4.31 - 4.15 (m, 5H), 4.04 - 3.94 (m, 1H), 3.12 (s, 1H), 3.04 (s, 2H), 2.96 - 2.84 (m, 2H), 2.70 - 2.57 (m, 5H), 2.55 - 2.49 (m, 1H), 2.44 - 2.36 (m, 3H), 0.66 - 0.56 (m, 3H).

Example 162A and Example 162B

(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-
 5 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-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-
 azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile and (1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-
 [(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-
 10 yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile



Example 162A and Example 162B were prepared in analogy to the preparation of Example 3 and Example 4 by using 140b instead of compound 3b and using intermediate E4 instead of intermediate E1 in step 3. The mixture was purified and separated via prep-HPLC to give
 15 Example 162A (8.4 mg, faster eluted) and Example 162B (3.6 mg, slower eluted) as a white powder.

Example 162A, LCMS (M+H)⁺: 772, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.36 (d, *J* = 5.5 Hz, 1H), 8.28 (s, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.67 - 7.58 (m, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.24 (ddd, *J* = 2.8, 8.8, 10.2 Hz, 1H), 7.19 - 7.13 (m, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.03 (dd, *J* =
 20 4.4, 15.4 Hz, 1H), 5.40 (d, *J* = 8.9 Hz, 1H), 4.70 - 4.64 (m, 1H), 4.49 (dd, *J* = 6.1, 11.1 Hz, 1H), 4.35 - 4.12 (m, 4H), 4.04 - 3.93 (m, 1H), 3.56 - 3.43 (m, 1H), 3.15 - 3.02 (m, 3H), 3.01 - 2.87 (m, 1H), 2.83 (s, 3H), 2.77 - 2.65 (m, 2H), 2.65 - 2.61 (m, 3H), 2.61 - 2.46 (m, 4H), 2.22 - 2.01 (m, 2H), 1.68 (d, *J* = 9.3 Hz, 1H).

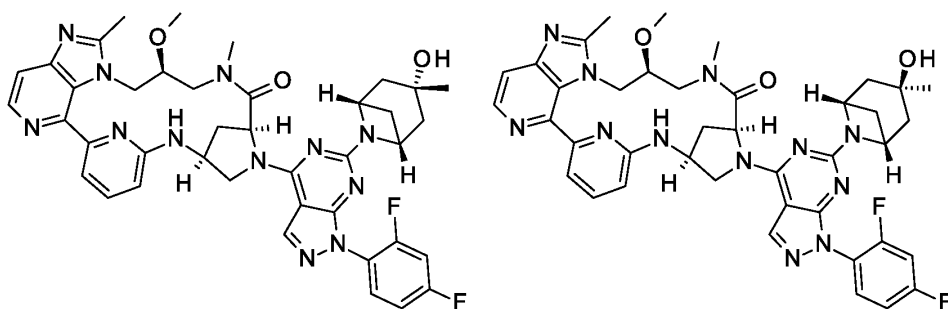
Example 162B, LCMS (M+H)⁺: 772, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.39 -
 25 8.35 (m, 1H), 8.30 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 5.5 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.20 - 7.14 (m, 1H), 6.79 - 6.74 (m, 1H), 6.02 (dd, *J* = 4.4, 15.5 Hz, 1H), 5.44 (br d, *J* = 8.6 Hz, 1H), 4.71 - 4.67 (m, 1H), 4.65 - 4.55 (m, 2H), 4.50 (br dd, *J* = 6.1,

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11.5 Hz, 1H), 4.30 - 4.21 (m, 3H), 3.93 (dd, $J = 9.1, 13.9$ Hz, 1H), 3.16 - 3.04 (m, 3H), 2.99 - 2.91 (m, 1H), 2.87 - 2.80 (m, 4H), 2.77 - 2.67 (m, 3H), 2.66 - 2.62 (m, 3H), 2.60 - 2.47 (m, 2H), 2.03 - 1.89 (m, 2H), 1.57 (d, $J = 9.3$ Hz, 1H).

Example 164A and Example 164B

5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-*exo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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)-6-[(1*R*,5*S*)-3-*endo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-
10 *d*]pyrimidin-4-yl]-15-methoxy-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

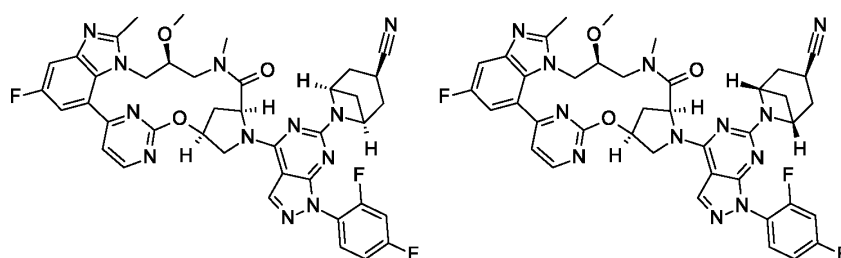


Example **164A** and Example **164B** were prepared in analogy to the preparation of Example **24** by using intermediate **E4** instead of intermediate **E1** in step 3. The mixture was purified via prep-HPLC and separated via SFC to give Example **164B** (faster eluted) and Example **164A** (16 mg, slower eluted) as a white powder. (SFC condition: Instrument: SFC 150 Mgm Column: GS Ethyl Pyridine II, 50 × 20 mm I.D., 5 μm Mobile phase: A for CO₂ and B for IPA (0.1% NH₃-H₂O) Gradient: B 40% Flow rate: 80 mL /min Back pressure: 100 bar Column temperature: 35 °C).

Example **164A**, LCMS (M+H)⁺: 777, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.44 (d, $J = 5.9$ Hz, 1H), 8.26 (s, 1H), 7.94 (t, $J = 8.0$ Hz, 1H), 7.91 - 7.87 (m, 1H), 7.66 - 7.59 (m, 1H), 7.42 (d, $J = 7.4$ Hz, 1H), 7.23 (ddd, $J = 2.8, 8.8, 10.2$ Hz, 1H), 7.20 - 7.13 (m, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.10 (dd, $J = 4.4, 15.4$ Hz, 1H), 5.41 (d, $J = 8.8$ Hz, 1H), 4.73 - 4.68 (m, 1H), 4.49 (dd, $J = 6.1, 11.2$ Hz, 1H), 4.39 - 4.20 (m, 4H), 4.02 - 3.93 (m, 1H), 3.16 - 3.05 (m, 3H), 3.03 - 2.96 (m, 1H), 2.94 - 2.88 (m, 3H), 2.76 - 2.72 (m, 3H), 2.71 - 2.63 (m, 1H), 2.63 - 2.48 (m, 4H), 2.45 - 2.34 (m, 1H), 2.22 (d, $J = 8.3$ Hz, 1H), 1.88 - 1.70 (m, 2H), 1.07 (s, 3H).

Example 165A and Example 165B

(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile and (1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile



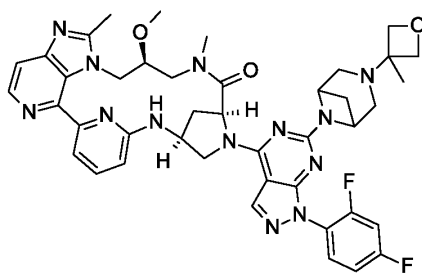
Example **165A** and Example **165B** were prepared in analogy to the preparation of Example **3** and Example **4** by using **140b** instead of compound **3b** and using intermediate **E15** instead of intermediate **E1** in step 3. The mixture was purified and separated via prep-HPLC to give Example **165A** (4.3 mg, slower eluted) and Example **165B** (10.9 mg, faster eluted) as a white powder.

Example **165A**, LCMS (M+H)⁺: 791, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.78 (d, *J* = 5.3 Hz, 1H), 8.31 - 8.27 (m, 1H), 7.70 - 7.60 (m, 2H), 7.49 - 7.41 (m, 2H), 7.27 - 7.20 (m, 1H), 7.20 - 7.13 (m, 1H), 5.89 (dd, *J* = 4.0, 15.8 Hz, 1H), 5.83 (br t, *J* = 3.5 Hz, 1H), 5.48 (d, *J* = 8.8 Hz, 1H), 4.52 - 4.46 (m, 1H), 4.41 - 4.19 (m, 4H), 4.08 - 3.97 (m, 1H), 3.56 - 3.46 (m, 1H), 3.10 - 2.98 (m, 3H), 2.97 - 2.87 (m, 1H), 2.87 - 2.81 (m, 4H), 2.79 - 2.72 (m, 1H), 2.71 - 2.63 (m, 1H), 2.63 - 2.55 (m, 3H), 2.55 - 2.46 (m, 2H), 2.45 - 2.36 (m, 1H), 2.22 - 1.98 (m, 2H), 1.74 - 1.67 (m, 1H).

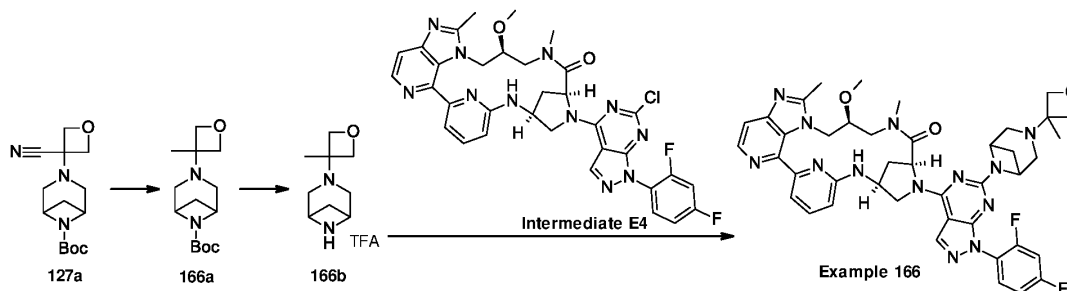
Example **165B**, LCMS (M+H)⁺: 791, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.81 - 8.77 (m, 1H), 8.30 (s, 1H), 7.67 - 7.61 (m, 2H), 7.51 - 7.44 (m, 2H), 7.28 - 7.20 (m, 1H), 7.20 - 7.13 (m, 1H), 5.90 - 5.66 (m, 2H), 5.49 (d, *J* = 8.8 Hz, 1H), 4.50 - 4.34 (m, 2H), 4.33 - 4.16 (m, 3H), 4.03 - 3.91 (m, 1H), 3.10 - 2.99 (m, 3H), 2.95 - 2.85 (m, 2H), 2.85 - 2.81 (m, 4H), 2.81 - 2.65 (m, 4H), 2.65 - 2.61 (m, 3H), 2.59 - 2.49 (m, 1H), 2.04 - 1.87 (m, 2H), 1.55 (d, *J* = 9.0 Hz, 1H).

Example 166

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
 5 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 compound was prepared according to the following scheme:



10 **Step 1: preparation of *tert*-butyl 3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (compound 166a)**

To a solution of compound **127a** (100 mg, 0.357 mmol) in dry THF (2 ml) was added MeMgBr (1.8 mL, 1 mol/L in THF) dropwise under N₂ atmosphere at 25 °C. The reaction mixture was stirred at 60 °C for 48 h. The reaction was quenched with H₂O (20 mL). The
 15 mixture was extracted with DCM (30 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via silica gel column chromatography to give compound **166a** (30 mg) as a colorless oil. LCMS (M+H)⁺: 269.

Step 2: preparation of 3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptane;2,2,2-trifluoroacetic acid (compound 166b)

20 To a flask contained compound **166a** (30 mg, 111.79 μmol) was added DCM (1 mL) and TFA (592 mg, 400 μL, 5.19 mmol). The solution was stirred at r.t. for 1 hr and then concentrated to give compound **166b** (31 mg) as a crude oil, which was used directly in the next

step. LCMS (M+H)⁺: 169.

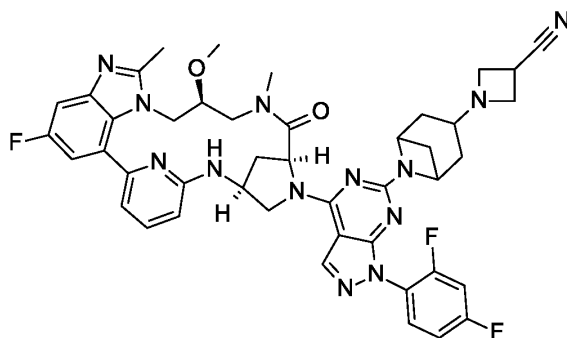
Step 3: preparation of (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-

5 1(23),2(26),3,5,18,20(24),21-heptaen-12-one (Example 166)

To a tube was added intermediate **E4** (30 mg, 43.72 μmol), DIEA (37 mg, 50 μL, 286 μmol), compound **166b** (30 mg, 106 μmol), cesium fluoride (20 mg, 131 μmol) and acetonitrile (2 mL). The solution was stirred at 90 °C for 16 h, then the reaction mixture was filtered and the filtrate was purified via pre-HPLC to give Example **166** (24.2 mg) as a white powder. LCMS
 10 (M+H)⁺: 818, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.36 (d, *J* = 5.4 Hz, 1H), 8.28 (s, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.66 - 7.58 (m, 2H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.23 (ddd, *J* = 2.8, 8.8, 10.2 Hz, 1H), 7.19 - 7.12 (m, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.04 (dd, *J* = 4.4, 15.5 Hz, 1H), 5.36 (d, *J* = 8.9 Hz, 1H), 4.74 - 4.55 (m, 3H), 4.45 (br dd, *J* = 5.9, 11.1 Hz, 1H), 4.32 - 4.20 (m, 4H), 4.20 - 4.11 (m, 2H), 3.91 (dd, *J* = 9.3, 14.0 Hz, 1H), 3.43 - 3.34 (m, 2H), 3.13 - 3.00 (m, 3H),
 15 2.96 - 2.89 (m, 1H), 2.83 (s, 3H), 2.80 (br d, *J* = 10.5 Hz, 2H), 2.70 (d, *J* = 13.6 Hz, 1H), 2.63 (s, 3H), 2.59 - 2.44 (m, 3H), 1.86 - 1.72 (m, 1H), 1.41 - 1.28 (m, 3H).

Example 167

1-[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),2,4,6(26),18,20,22-
 20 **heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptan-3-yl]azetidine-3-carbonitrile**

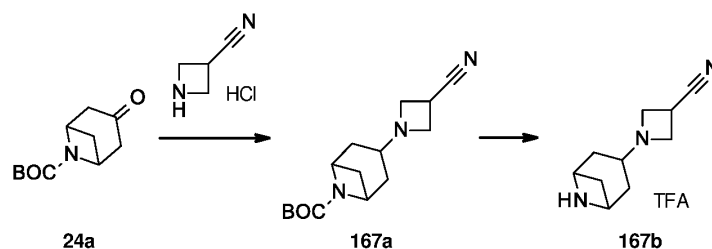


Example **167** was prepared in analogy to the preparation of Example **2** by using compound **167b** instead of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine. Example
 25 **167** was obtained as a white powder, LCMS (M+H)⁺: 844, ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 8.33 (s, 1H), 7.91 - 7.84 (m, 1H), 7.70 - 7.59 (m, 1H), 7.54 (dd, *J* = 2.5, 7.5 Hz, 1H), 7.47 (dd,

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$J = 2.4, 10.2$ Hz, 1H), 7.29 - 7.21 (m, 1H), 7.20 - 7.13 (m, 2H), 6.81 - 6.75 (m, 1H), 6.13 (br dd, $J = 4.6, 15.2$ Hz, 1H), 5.43 (d, $J = 8.9$ Hz, 1H), 4.73 - 4.67 (m, 1H), 4.54 - 4.39 (m, 2H), 4.38 - 4.12 (m, 8H), 4.09 - 4.01 (m, 1H), 3.96 - 3.78 (m, 2H), 3.18 - 3.15 (m, 1H), 3.09 - 3.03 (m, 3H), 2.96 (s, 3H), 2.83 - 2.77 (m, 3H), 2.77 - 2.73 (m, 1H), 2.70 - 2.48 (m, 3H), 2.38 - 2.19 (m, 2H), 2.19 - 2.07 (m, 1H), 1.61 (d, $J = 9.6$ Hz, 1H).

The compound **167b** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 3-(3-cyanoazetidin-1-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound 167a)

To a tube was added *tert*-butyl 3-oxo-6-azabicyclo[3.1.1]heptane-6-carboxylate (compound **24a**, 20 mg, 94.67 μ mol), DIEA (22 mg, 171.77 μ mol), azetidine-3-carbonitrile;hydrochloride (20 mg, 168.69 μ mol) and ethanol (2 mL). The solution was at r.t. for 1 hr and then sodium triacetoxyborohydride (50 mg, 235.92 μ mol) was added. The final mixture was stirred at r.t. for 2 days, then the reaction mixture was diluted with water and extracted with DCM. The organic layer was dried and concentrated to give compound **167a** (30 mg) as a crude oil, which was used in the next step directly. LCMS (M+H)⁺: 278.

Step 2: preparation of 1-(6-azabicyclo[3.1.1]heptan-3-yl)azetidine-3-carbonitrile; 2,2,2-trifluoroacetic acid (compound 167b)

To the flask contained compound **167a** (30 mg, 108.16 μ mol) was added TFA (1.48 g, 1 mL, 12.98 mmol) and DCM (2 mL). The mixture was stirred at r.t. for 1 hr and concentrated. The compound **167b** (30 mg) was obtained as a yellow oil and used directly in the next step. LCMS (M+H)⁺: 178.

Example 168

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. coli) 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) binds 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, 5 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 10 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).

Table 1. The test results in TR-FRET assay

Example NO.	FRET_IC50 (nM)	Example NO.	FRET_IC50 (nM)	Example NO.	FRET_IC50 (nM)
1	0.9	55	0.7	117	0.4
2	2.8	56	1	118	0.4
3	0.5	57	2	119	1.5
4	1.2	59	0.7	120	1.8
5	1.6	60	1.1	121	1.7
6	1.5	61	0.6	122	1.3
7	1.2	62	2.1	123	1.1
8	0.5	63	0.5	124	1
9	0.8	64	5.2	125	0.3
10	0.7	65	3.3	126	0.9
11	1	66	2.3	127	1.9
12	0.5	67	3.9	128	2.8
13	2.1	68	3.5	129	3.2
14	0.5	69	3.1	131	3.7
15	3.8	70	0.8	132	3.9
16	0.8	71	1.2	133	3.4
17	2.8	72	0.9	134	3.8
18	2.2	73	1	135	0.5
19	0.6	76	1.8	136	3.1
20	0.8	77	0.7	137	0.5
21	1.3	78	1	138	0.3
22	1	79	0.8	139	0.8
23	0.7	80	0.8	140	1.6
24	1.3	81	0.7	141	1.1
26	2.5	82	1.6	142	0.7
27	5.9	83	0.7	143	0.7
28	1	84	0.7	144	0.9

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29	1.1	85	1.6	145	0.8
30	0.7	87	0.9	146	1.1
31	1.5	88	1.2	147	1.5
32	3.7	89	1.3	148	0.8
33	0.9	90	1.2	149	1.8
34	1.5	91	1.5	150	1.7
35	0.9	92	0.7	151	1.5
36	1.2	93	1.6	152	1.6
37	1.6	94	1	153	1.2
38	1.5	95	0.6	154	2
39	1.9	100	1.7	155	1.1
40	2.2	101	0.9	156	0.9
42	0.7	102	1	157	1
43	1	103	2.9	158	1.8
44	2.2	104	2.8	159	1.3
45	1.4	105	2.7	160	1.7
46	0.6	106	5	161	6.7
47	3.3	107	1.2	162A	1.2
48	1.9	108	1.2	162B	1.4
49	1	109	3.8	164A	1.4
50	1.1	112	1.6	165A	1.1
51	2.4	113	2.4	165B	0.9
52	1.4	114	1.1	166	1.4
53	0.8	115	0.8	167	1.5
54	1.5	116	0.6		

Example 169

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.: 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 THP1-Dual™ cells was co-incubated 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 μ L 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 μ L of stimulator (final concentration is 20 μ M of 2'3'cGAMP, or final concentration is 10 MOI baculovirus virus,) was added before 6 μ L of compound solution per well (final 1% DMSO) was transferred by Agilent Bravo. Then 30 μ L of cell suspension ($\sim$ 33,000 cells, 1.1×10^6 cells/mL) per well was added immediately by thermo multidrop combi dispenser for incubation 20-24 h at 37 $^{\circ}$ C, 5% CO₂. At the end of the incubation, 10 μ L of cellular supernatant was transferred to proxiplate 384-plus plate for IRF detection, and then 10 μ L of QUANTI-Luc™ Gold solution was added to the plate that proceeded with the measurement immediately. To detect cell viability, 30 μ L 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.

Table 2. The test results in THP1 cellular assay

Example NO.	THP1_IC50 (nM)	Example NO.	THP1_IC50 (nM)	Example NO.	THP1_IC50 (nM)
1	6	59	5	119	13
2	8	61	51	121	3
3	8	63	29	122	8
4	2	64	29	123	53
5	4	67	48	124	8
6	13	68	29	125	14
7	49	69	12	126	7
8	3	70	2	127	54
9	28	71	86	129	69
10	14	72	13	131	23
11	68	73	30	132	18
12	14	76	23	133	11
14	13	78	17	134	15
16	70	79	27	135	18
19	19	80	18	136	46
20	3	82	73	137	5
21	30	83	40	138	1
23	8	84	94	139	9
24	7	85	19	140	2
28	16	87	21	141	6
31	5	88	32	142	8
32	2	89	32	143	2
33	10	90	18	144	5
34	10	91	18	145	3
35	7	92	67	146	2

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36	64	93	6	148	14
37	10	94	51	150	8
38	34	95	3	151	69
39	18	100	14	152	49
40	6	101	2	153	28
42	39	102	95	154	20
43	48	103	45	155	32
44	76	104	12	156	78
46	45	105	33	157	37
47	8	106	74	158	28
48	6	107	36	161	35
49	1	109	50	162A	51
50	83	112	15	165A	64
51	9	113	51	165B	40
52	3	114	4	166	78
53	4	115	20	167	20
54	17	116	13		
55	28	117	4		
56	32	118	35		

Example 170

Single dose pharmacokinetics (SDPK) study in Male C57BL/6J Mice

Pharmacokinetic properties of compounds were assessed by single dose PK studies in Male C57BL/6J Mice (vendor: WTLH-BJ). Briefly, two groups of animals were administered a single dose of respective compound intravenously (IV, bolus) at 1 mg/kg or orally (PO, by gavage) at 10 mg/kg. Blood samples were collected via Jugular vein at 5 min (only for IV), 15 min, 30 min, 1 h, 2 h, 4 h, 7 h and 24 h post-dose. Blood samples were placed into pre-chilled commercial EDTA-K2 tubes (vendor: Jiangsu Kangjian medical supplies co., LTD) and centrifuged at 3,200 g for 10 min at 4°C to separate plasma from the samples. After centrifugation, the resulting plasma was transferred to clean tubes for bioanalysis with LC/MS/MS. The pharmacokinetic parameters were calculated using noncompartmental analysis. The volume of distribution (V_{ss}), half-life (T_{1/2}) and clearance (CL) were obtained based on the plasma concentration-time curve after IV dose. The peak concentration (C_{max}) was recorded directly from experimental observations after PO dose. The area under the plasma concentration-time curve (AUC_{0-last}) was calculated using the linear trapezoidal linear interpolation rule up to the last detectable concentration. The bioavailability (F) was calculated based on the dose normalized AUC_{0-last} after IV and PO dose. Results of PK parameters following IV and PO administration are given in Table 3.

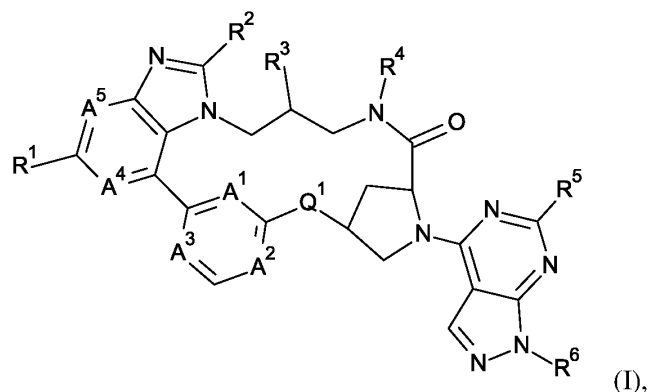
Table 3. PK results for the compounds of this invention

Example NO.	PO C _{max} (ng/mL)	PO AUC _{0-last} (h×ng/mL)	IV AUC _{0-last} (h×ng/mL)	CL (mL/min/kg)	V _{ss} (L/kg)	T _{1/2} (h)	F (%)
91	2453	18986	484	33.7	2.64	1.57	383

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CLAIMS

1. A compound of formula (I),

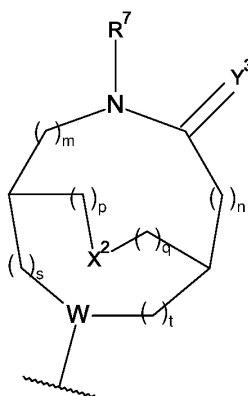
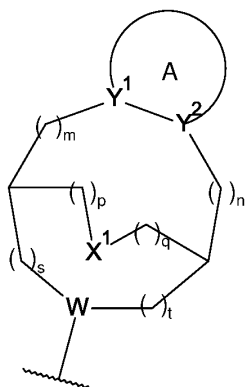


wherein

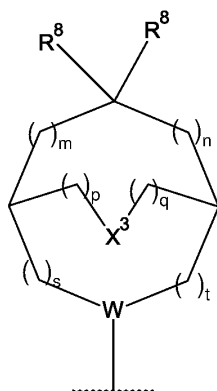
- 5 A^1 is CH or N;
 A^2 is CH or N;
 A^3 is CR^7 or N; wherein R^7 is H or halogen;
 A^4 is CH or N;
 A^5 is CH or N;
- 10 R^1 is H or halogen;
 R^2 is C_{1-6} alkyl;
 R^3 is H or C_{1-6} alkoxy;
 R^4 is C_{1-6} alkyl;
 R^5 is (cyano C_{3-7} cycloalkyl) C_{1-6} alkyl,
- 15 1,1-dioxothietanyl,
 1,7-diazaspiro[3.4]octanyl substituted by halo C_{1-6} alkylcarbonyl,
 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C_{1-6} alkyl, oxetanyl or
 oxetanyl C_{1-6} alkyl,
 3,3-dioxo-3 λ^6 -thia-6-azabicyclo[3.1.1]heptanyl,
- 20 3-oxo-3 λ^4 -thia-6-azabicyclo[3.1.1]heptanyl,
 3-thia-6-azabicyclo[3.1.1]heptanyl,
 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by halo C_{1-6} alkyl,
 6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C_{1-6} alkyl,
 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
- 25 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by halo C_{1-6} alkyl,
 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C_{1-6} alkyl,

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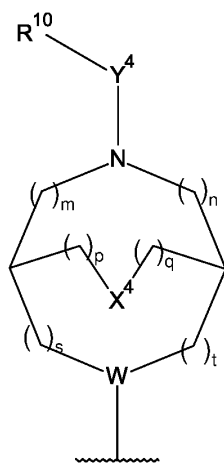
- azetidinyI which is once or twice substituted by substituents independently selected from
 cyano, halogen, hydroxy, amino, C₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl,
 aminoC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇
 cycloalkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl,
 5 cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxy, heterocyclyl, heteroaryl, heteroarylcarbonyl
 and heterocyclcarbonyl,
 cyanoC₁₋₆alkyl,
 C₃₋₇cycloalkyl substituted by cyano,
 morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
 10 oxetanyl substituted by cyanoC₁₋₆alkyl,
 oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl,
 pyrrolidinyl substituted by hydroxyC₁₋₆alkyl,



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, or



; wherein

Y¹ is CH, C or N;Y² is CH, C or N;5 Y³ is O or S;Y⁴ is a bond, C₁₋₆alkylene, -COO- or sulfonyl;

W is CH or N;

X¹, X², X³ and X⁴ are independently selected from C(R⁸)₂, O, S, SO₂, SO, NR⁹,N(CON(R⁹)₂) and N(COOR⁹);10 wherein each R⁸ is independently H, deuterio, halogen, hydroxy, cyano, C₁₋₆alkyl,C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₃₋7cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋7cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl,N(R⁹)₂, OR⁹, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl,15 heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋

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alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl or heterocyclisulfonyl;

each R⁹ is independently H, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋

5 alkyl, haloC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₁₋₆alkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heteroaryl, aryl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, haloC₃₋₇cycloalkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylsulfonyl, haloC₁₋₆alkylsulfonyl, haloC₃₋₇cycloalkylsulfonyl or heterocyclisulfonyl;

R⁷ is C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, haloC₃₋₇cycloalkyl, haloC₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₃₋₇cycloalkyl, C₁₋₆alkoxyC₃₋₇cycloalkylC₁₋₆alkyl, haloC₁₋₆alkyl, haloC₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkoxyC₃₋₇cycloalkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, cyanoC₁₋₆alkoxyC₃₋₇cycloalkyl, hydroxyC₃₋₇cycloalkyl, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxyC₃₋₇cycloalkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heteroaryl or heteroarylC₁₋₆alkyl;

R¹⁰ is (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋₆alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, heterocyclylC₁₋₆alkyl, heteroarylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylcarbonyl, haloC₁₋₆alkoxycarbonyl, haloC₁₋₆alkylsulfonyl, heterocyclylC₁₋₆alkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, heteroarylC₁₋₆alkylcarbonyl, arylcarbonyl, aryl, heterocyclyl or heteroaryl;

30 Ring A is a aryl ring, heteroaryl ring or heterocyclyl ring, each of which is unsubstituted or substituted by C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, halogen, cyano or nitro;

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m, n, p, q, s, t are independently 0, 1 or 2, with the proviso that m, n, p, q, s, t are not 0 simultaneously;

R⁶ is phenyl twice or three times substituted by substituents independently selected from halogen, cyano, hydroxy and C₁₋₆alkoxy;

5 Q¹ is NH or O;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1, wherein

R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,

10 1,1-dioxothietanyl,

1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dienyl substituted by C₁₋₆alkyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dienyl substituted by C₁₋₆alkyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or

15 oxetanylC₁₋₆alkyl,

2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C₁₋₆alkyl, C₁₋

6alkoxyC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl,

cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, oxetanyl, oxetanylC₁₋₆alkyl or

tetrahydropyranyl,

20 2-oxo-3,8-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

3,6-diazabicyclo[3.1.1]heptanyl substituted by (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋

6alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, (oxopyrrolidinyl)C₁₋

25 6alkyl, 1,3,4-thiadiazolyl, 1H-pyrazolylC₁₋₆alkyl, 2-oxaspiro[3.3]heptanylcarbonyl,

C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋

6alkyloxetanyl, C₁₋₆alkylpyrazolyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylC₁₋

6alkylcarbonyl, cyanooxetanyl, haloC₁₋₆alkoxycarbonyl, oxazolyl, oxetanylC₁₋

6alkylcarbonyl, oxetanylcarbonyl, pyrimidinyl, thiazolyl, thiazolylC₁₋₆alkyl or

30 thiazolylcarbonyl,

3-azabicyclo[3.1.1]heptanyl substituted by oxetanyl,

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by oxetanyl or oxetanylC₁₋₆alkyl,

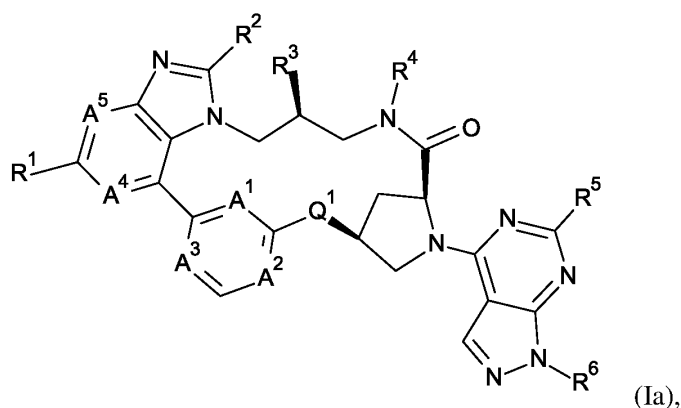
3-oxo-2,6-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

3-oxo-3λ⁴-thia-6-azabicyclo[3.1.1]heptanyl,

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- 3-thia-6-azabicyclo[3.1.1]heptanyl,
 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dienyl substituted by C₁₋₆alkyl,
 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dienyl substituted by C₁₋₆alkyl,
 4-oxo-3,7-diazabicyclo[4.1.1]octanyl substituted by C₁₋₆alkyl,
 5 4-oxo-8-oxa-3,10-diazabicyclo[4.3.1]decanyl substituted by C₁₋₆alkyl,
 5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decanyl,
 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,
 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently
 selected from hydroxy, cyano, C₁₋₆alkyl and cyanoC₃₋₇cycloalkyl,
 10 6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,
 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,
 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,
 azetidiny which is once substituted by pyrazolyl, 1,2,4-triazolyl or C₁₋₆alkyl-1,2,4-
 15 oxadiazolyl, or twice substituted by substituents independently selected from cyano,
 C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl and
 haloazetidiny carbonyl,
 cyanoC₁₋₆alkyl,
 C₃₋₇cycloalkyl substituted by cyano,
 20 morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
 oxetanyl substituted by cyanoC₁₋₆alkyl,
 oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl, or
 pyrrolidinyl substituted by hydroxyC₁₋₆alkyl.

- 25 3. A compound of formula (Ia),



wherein

A¹ is CH or N;

A² is CH or N;

A³ is CR⁷ or N; wherein R⁷ is H or halogen;

5 A⁴ is CH or N;

A⁵ is CH or N;

R¹ is H or halogen;

R² is C₁₋₆alkyl;

R³ is H or C₁₋₆alkoxy;

10 R⁴ is C₁₋₆alkyl;

R⁵ is (cyanoC₃₋₇cycloalkyl)C₁₋₆alkyl,

1,1-dioxothietanyl,

1,7-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkylcarbonyl,

10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dienyl substituted by C₁₋₆alkyl,

15 10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dienyl substituted by C₁₋₆alkyl,

2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl substituted by C₁₋₆alkyl, oxetanyl or
oxetanylC₁₋₆alkyl,

2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by (halooxetanyl)C₁₋₆alkyl, C₁₋

6alkoxyC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl,

20 cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, oxetanyl, oxetanylC₁₋₆alkyl or
tetrahydropyranyl,

2-oxo-3,8-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,

3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,

3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,

25 3,6-diazabicyclo[3.1.1]heptanyl substituted by (C₁₋₆alkyl)₂aminocarbonyl, (C₁₋

6alkyl)₂aminosulfonyl, (C₁₋₆alkyl)oxopyrrolidinylcarbonyl, (oxopyrrolidinyl)C₁₋

6alkyl, 1,3,4-thiadiazolyl, 1H-pyrazolylC₁₋₆alkyl, 2-oxaspiro[3.3]heptanylcarbonyl,

C₁₋₆alkoxyC₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋

6alkyloxetanyl, C₁₋₆alkylpyrazolyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylC₁₋

30 6alkylcarbonyl, cyanooxetanyl, haloC₁₋₆alkoxycarbonyl, oxazolyl, oxetanylC₁₋
6alkylcarbonyl, oxetanylcarbonyl, pyrimidinyl, thiazolyl, thiazolylC₁₋₆alkyl or
thiazolylcarbonyl,

3-azabicyclo[3.1.1]heptanyl substituted by oxetanyl,

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- 3-oxa-7,9-diazabicyclo[3.3.1]nonanyl substituted by oxetanyl or oxetanylC₁₋₆alkyl,
 3-oxo-2,6-diazabicyclo[3.2.1]octanyl substituted by C₁₋₆alkyl,
 3-oxo-3λ⁴-thia-6-azabicyclo[3.1.1]heptanyl,
 3-thia-6-azabicyclo[3.1.1]heptanyl,
 5 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dienyl substituted by C₁₋₆alkyl,
 4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dienyl substituted by C₁₋₆alkyl,
 4-oxo-3,7-diazabicyclo[4.1.1]octanyl substituted by C₁₋₆alkyl,
 4-oxo-8-oxa-3,10-diazabicyclo[4.3.1]decanyl substituted by C₁₋₆alkyl,
 5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decanyl,
 10 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl substituted by haloC₁₋₆alkyl,
 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently
 selected from hydroxy, cyano, C₁₋₆alkyl and cyanoC₃₋₇cycloalkyl,
 6-oxo-1,7-diazaspiro[3.4]octanyl substituted by C₁₋₆alkyl,
 6-oxo-2-oxa-7-azaspiro[3.4]octanyl,
 15 7-oxo-2,6-diazaspiro[3.4]octanyl substituted by haloC₁₋₆alkyl,
 9-oxo-1,8-diazaspiro[3.5]nonanyl substituted by C₁₋₆alkyl,
 azetidiny which is once substituted by pyrazolyl, 1,2,4-triazolyl or C₁₋₆alkyl-1,2,4-
 oxadiazolyl, or twice substituted by substituents independently selected from cyano,
 C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl and
 20 haloazetidiny carbonyl,
 cyanoC₁₋₆alkyl,
 C₃₋₇cycloalkyl substituted by cyano,
 morpholinyl substituted by C₁₋₆alkoxyC₁₋₆alkyl or cyanoC₁₋₆alkyl,
 oxetanyl substituted by cyanoC₁₋₆alkyl,
 25 oxopyrrolidinyl substituted by cyano or hydroxyC₁₋₆alkyl, or
 pyrrolidinyl substituted by hydroxyC₁₋₆alkyl;
 R⁶ is phenyl twice substituted by substituents independently selected from halogen, cyano,
 hydroxy and C₁₋₆alkoxy;
 Q¹ is NH or O;
 30 or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1-3, wherein A³ is CH.

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5. A compound according to any one of claims 1-4, wherein R¹ is H or fluoro.
6. A compound according to any one of claims 1-5, wherein R² is methyl.
- 5 7. A compound according to any one of claims 1-6, wherein R³ is H, methoxy or ethoxy.
8. A compound according to any one of claims 1-7, wherein R⁴ is methyl.
9. A compound according to any one of claims 1-8, wherein
- 10 R⁵ is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, cyanoC₁₋₆alkyl, cyanoC₃₋₇cycloalkyl, haloC₁₋₆alkyl, oxetanyl or tetrahydropyranyl,
- 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,
- 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,
- 15 3,6-diazabicyclo[3.1.1]heptanyl substituted by C₁₋₆alkylpyrazolyl, thiazolylcarbonyl, 1,3,4-thiadiazolyl or thiazolyl,
- 3-thia-6-azabicyclo[3.1.1]heptanyl,
- 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently selected from hydroxy, cyano and C₁₋₆alkyl, or
- 20 azetidiny which is twice substituted by substituents independently selected from cyano, C₁₋₆alkyl and C₁₋₆alkoxy.
10. A compound according to any one of claims 1-9, wherein
- R⁵ is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by 2,2-difluoroethyl, 2-cyanoethyl, 2-
- 25 fluoroethyl, 3-cyanocyclobutyl, cyclobutyl, cyclopropyl, cyclopropylmethyl, ethyl, isopropyl, methyl, oxetan-3-yl or tetrahydropyran-4-yl,
- 3,3-dioxo-3λ⁶-thia-6-azabicyclo[3.1.1]heptanyl,
- 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,
- 3,6-diazabicyclo[3.1.1]heptanyl substituted by 1-methylpyrazol-3-yl, thiazole-2-carbonyl,
- 30 1,3,4-thiadiazol-2-yl or thiazol-2-yl,
- 3-thia-6-azabicyclo[3.1.1]heptanyl,
- 6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently selected from hydroxy, cyano and methyl, or

azetidiny which is twice substituted by substituents independently selected from cyano, methyl and methoxy.

11. A compound according to any one of claims 1-10, wherein R⁵ is 2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-cyanoethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(3-cyanocyclobutyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3,3-dioxo-3 λ^6 -thia-6-azabicyclo[3.1.1]heptan-6-yl, 3,6,9-triazatricyclo[6.1.1.02,6]deca-2,4-dien-9-yl, 3-cyano-3-methoxy-azetidin-1-yl, 3-cyano-3-methyl-azetidin-1-yl, 3-cyano-6-azabicyclo[3.1.1]heptan-6-yl, 3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl, 3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-thia-6-azabicyclo[3.1.1]heptan-6-yl or 3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl.
12. A compound according to any one of claims 1-11, wherein R⁶ is phenyl twice substituted by halogen.
13. A compound according to any one of claims 1-12, wherein R⁶ is phenyl twice substituted by fluoro.
14. A compound according to any one of claims 1-13, wherein R⁶ is 2,4-difluorophenyl.
15. A compound according to any one of claims 1-14, wherein
- A¹ is CH or N;
- A² is CH or N;
- A³ is CH;
- A⁴ is CH or N;
- A⁵ is CH or N;

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- R^1 is H or halogen;
 R^2 is C_{1-6} alkyl;
 R^3 is H or C_{1-6} alkoxy;
 R^4 is C_{1-6} alkyl;
5 R^5 is 2-oxo-3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, cyano C_{1-6} alkyl, cyano C_{3-7} cycloalkyl, halo C_{1-6} alkyl, oxetanyl or tetrahydropyranyl,
3,3-dioxo-3 λ^6 -thia-6-azabicyclo[3.1.1]heptanyl,
3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dienyl,
10 3,6-diazabicyclo[3.1.1]heptanyl substituted by C_{1-6} alkylpyrazolyl, thiazolylcarbonyl, 1,3,4-thiadiazolyl or thiazolyl,
3-thia-6-azabicyclo[3.1.1]heptanyl,
6-azabicyclo[3.1.1]heptanyl once or twice substituted by substituents independently selected from hydroxy, cyano and C_{1-6} alkyl, or
15 azetidiny which is twice substituted by substituents independently selected from cyano, C_{1-6} alkyl and C_{1-6} alkoxy;
 R^6 is phenyl twice substituted by halogen;
 Q^1 is NH or O;
or a pharmaceutically acceptable salt thereof.
20
16. A compound according to any one of claims 1-15, wherein
 A^1 is CH or N;
 A^2 is CH or N;
 A^3 is CH;
25 A^4 is CH or N;
 A^5 is CH or N;
 R^1 is H or fluoro;
 R^2 is methyl;
 R^3 is H, methoxy or ethoxy;
30 R^4 is methyl;
 R^5 is 2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(1-methylpyrazol-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-

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6-yl, 3-(2-cyanoethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(2-fluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(3-cyanocyclobutyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3,3-dioxo-3 λ^6 -thia-6-azabicyclo[3.1.1]heptan-6-yl, 3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl, 3-cyano-3-methoxy-azetidin-1-yl, 3-cyano-3-methyl-azetidin-1-yl, 3-cyano-6-azabicyclo[3.1.1]heptan-6-yl, 3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl, 3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl, 3-thia-6-azabicyclo[3.1.1]heptan-6-yl or 3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl;

R⁶ is 2,4-difluorophenyl;

Q¹ is NH or O;

or a pharmaceutically acceptable salt thereof.

17. A compound selected from:

(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(2-oxopyrrolidin-1-yl)ethyl]-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-[3-(trifluoromethyl)-6,8-dihydro-5*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-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-[6-[(1*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-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-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-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-(thiazol-2-ylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 5 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-oxaspiro[3.3]heptane-6-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 10 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*H*-pyrazol-5-ylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 15 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,5*R*)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 20 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 25 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,5*R*)-3-methyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-
- 30 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;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-methyl-2-oxo-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-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-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-
- 5 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-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-
6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
10 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[(1*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-
6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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;
15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
7,10,13,17,19,23,26-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*R*,5*S*)-3-methyl-2-oxo-3,6-
20 diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*R*,5*S*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-
yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
25 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*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-
yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
30 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*,5*R*)-3-ethyl-2-oxo-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-[(1*R*,5*S*)-3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 5 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
3-[(1*R*,5*S*)-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]-2-oxo-3,6-
- 10 diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;
3-[(1*S*,5*R*)-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]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]propanenitrile;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-hydroxy-3-methyl-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-[3-[(3-fluorooxetan-3-yl)methyl]-2-oxo-3,6-
- 20 diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*R*,5*S*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 25 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(3,5-difluoro-2-pyridyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
- 30 dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-hydroxyethyl)-5-oxo-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-[1-(2,4-difluorophenyl)-6-[1-(2-hydroxyethyl)-2-oxo-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;
- 5 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]-*N,N*-dimethyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide;
- 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]-*N,N*-dimethyl-3,6-diazabicyclo
- 10 [3.1.1]heptane-3-sulfonamide;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(2-methoxyacetyl)-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;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetane-2-carbonyl)-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(oxetane-3-carbonyl)-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-methylsulfonylacetyl)-3,6-diazabicyclo
- 25 [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;
- 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]-*N*-methyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxamide;
- 30 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-[2-(oxetan-3-yl)acetyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-

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- 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-(difluoromethoxy)acetyl]-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-methylsulfonyl-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-(8-methyl-9-oxo-1,8-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(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-methyl-6-oxo-1,7-diazaspiro[3.4]octan-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-[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(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]oxetan-3-yl]acetonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methyl-5-oxo-pyrrolidine-3-carbonyl)-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-pyrimidin-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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;
- 3-fluoro-4-[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]-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-1-yl]benzonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(4-fluoro-2-hydroxy-phenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

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- 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-(3-oxazol-2-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-
- 5 hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-(hydroxymethyl)-5-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(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*S*)-2-(hydroxymethyl)pyrrolidin-1-
- 10 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;
methyl 6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-15-methoxy-13,18-dimethyl-
- 15 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;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1-methylpyrazol-4-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;
- 3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-
- 25 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-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]propanenitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(1,1-dioxothietan-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;
- 30 (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-methyl-2-oxo-3,6-
- diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-13,18-dimethyl-

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- 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-(thiazole-2-carbonyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*S*,5*R*)-3-(oxetan-3-ylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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-(7-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-9-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-(1,3,4-thiadiazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*)-22-fluoro-10-[1-(2-fluoro-4-methoxy-phenyl)-6-(3-thiazol-2-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(24),2,4,6(26),18,20,22-heptaen-12-one;
Trans-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile;
Cis-3-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]cyclobutanecarbonitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(3*R*)-3-(methoxymethyl)morpholin-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[2-(hydroxymethyl)-2-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
(8*S*,11*S*,15*R*)-10-[6-[7-(2,2-difluoroacetyl)-1,7-diazaspiro[3.4]octan-1-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-dimethyl-
10 7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-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-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
15 (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-methyl-2-oxo-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrimidin-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
1-[[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-ethoxy-22-fluoro-13,18-dimethyl-12-oxo-
25 5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]methyl]cyclopropanecarbonitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-thia-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
30 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-oxo-3λ⁴-thia-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

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- 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}]]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-(methoxymethyl)azetidine-3-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3,3-dioxo-3λ⁶-thia-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}]]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 2-[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}]]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidin-3-yl]acetonitrile;
- 7-[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}]]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxa-7-azaspiro[3.4]octan-6-one;
- (8*S*,11*S*,15*R*)-10-[6-[2-(2,2-difluoroethyl)-7-oxo-2,6-diazaspiro[3.4]octan-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}]]hexacos-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-methyl-2-oxo-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}]]hexacos-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*,5*R*)-3-methyl-2-oxo-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}]]hexacos-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-(3-fluoroazetidine-1-carbonyl)-2-methylazetidin-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}]]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(4*aR*,7*aS*)-6-methyl-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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-[(4*aR*,7*aS*)-6-(oxetan-3-ylmethyl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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-[(4*aR*,7*aS*)-6-(oxetan-3-yl)-2,3,4*a*,5,7,7*a*-hexahydropyrrolo[3,4-*b*][1,4]oxazin-4-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(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methyl-azetidine-3-carbonitrile;
- 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(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3-methoxy-azetidine-3-carbonitrile;
- 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(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-5-oxo-pyrrolidine-3-carbonitrile;
- (8*S*,11*S*,15*R*)-10-[6-[3-(cyclopropylmethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(2-fluoroethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*S*)-3-(2-fluoroethyl)-2-oxo-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),2,4,6(26),18,20,22-heptaen-12-one;

- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-methyl-2-oxo-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(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-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-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(26),3,5,18,20(24),21-heptaen-12-one;
- 10 10-[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]-3-methyl-8-oxa-3,10-diazabicyclo[4.3.1]decan-4-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-4-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2,5-dien-12-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*S*,8*R*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-5-methyl-10-oxa-4,5,12-triazatricyclo[6.3.1.0^{2,6}]dodeca-2(6),3-dien-12-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;
- 25 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,2*S*,8*R*)-5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-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;
- 30 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,2*R*,8*S*)-5-oxo-6,9-diazatricyclo[6.1.1.0^{2,6}]decan-9-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-[(3*R*)-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-
5 1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]morpholin-3-
yl]acetonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-yl)-3-oxa-7,9-
diazabicyclo[3.3.1]nonan-9-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-
10 1(24),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[7-(oxetan-3-ylmethyl)-3-oxa-7,9-
diazabicyclo[3.3.1]nonan-9-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;
- 15 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-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*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-
20 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-[(1*S*,5*R*)-3-(oxetan-3-yl)-2-oxo-3,6-
diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-methoxy-13,18-
25 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-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-
(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
30 1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

- (8*S*,11*S*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*)-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-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-(oxetan-3-yl)-3-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-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-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(2,2-difluoroethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-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*,5*S*)-3-(2-methoxyethyl)-2-oxo-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}]hexacos-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*,5*R*)-3-(2-methoxyethyl)-2-oxo-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}]hexacos-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*,6*S*)-3-methyl-4-oxo-3,7-diazabicyclo[4.1.1]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}]hexacos-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*S*,6*R*)-3-methyl-4-oxo-3,7-diazabicyclo[4.1.1]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}]hexacos-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),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-3,6-diazabicyclo[3.1.1]heptan-3-yl]oxetane-3-carbonitrile;
- 5 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*S*)-2-methyl-3-oxo-2,6-diazabicyclo[3.2.1]octan-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),2,4,6(26),18,20,22-heptaen-12-one;
- 10 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,5*R*)-2-methyl-3-oxo-2,6-diazabicyclo[3.2.1]octan-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),2,4,6(26),18,20,22-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*R*,8*S*)-4-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-
- 15 methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,8*R*)-4-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-
- 20 methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,8*S*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-
- 25 methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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*,8*R*)-5-methyl-4,5,11-triazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-11-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-22-fluoro-15-
- 30 methoxy-13,18-dimethyl-7,10,13,17,19,26-hexazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.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-pyrimidin-5-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*)-3-chloro-10-[1-(2,4-difluorophenyl)-6-(3-thiazol-2-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-12-one;
- 5 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 10 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 15 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (1*S*,5*R*)-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
- 20 (1*R*,5*S*)-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}]hexacos-1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
- 25 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-(cyclopropylmethyl)-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;
- 30 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,21,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacos-1(23),2(26),3,5,18,20(24),21-heptaen-12-one;

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- (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-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;
- 5 (8*S*,11*S*,15*R*)-10-[6-[(1*S*,5*R*)-3-cyclobutyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-(2,4-difluorophenyl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*S*,5*R*)-3-cyclopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]-1-10 (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-[(1*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-15 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-[6-[(1*S*,5*R*)-3-cyclopropyl-2-oxo-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;
- 20 (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-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*S*,8*R*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-25 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*R*,8*S*)-3,6,9-triazatricyclo[6.1.1.0^{2,6}]deca-2,4-dien-9-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),21-30 heptaen-12-one;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-ethyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-

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- 7,10,13,17,19,23,26-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)-6-[(1*S*,5*R*)-3-isopropyl-2-oxo-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 5 7,10,13,17,19,23,26-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)-6-[(1*S*,5*R*)-3-(2-hydroxyethyl)-2-oxo-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-
- 10 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*S*,5*R*)-2-oxo-3-tetrahydropyran-4-yl-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-
- 7,10,13,17,19,23,26-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;
- 15 *Cis*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile;
- Trans*-3-[(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-
- 20 12-oxo-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-
- 1(24),2(26),3,5,18,20,22-heptaen-10-yl]pyrazolo[3,4-*d*]pyrimidin-6-yl]-2-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl]cyclobutanecarbonitrile;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-(3-pyrazol-1-ylazetidin-1-yl)pyrazolo[3,4-*d*]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-
- 25 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-imidazol-1-ylazetidin-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;
- (8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(1,2,4-triazol-1-yl)azetidin-1-
- 30 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-(3-methyl-1,2,4-oxadiazol-5-yl)azetidin-1-

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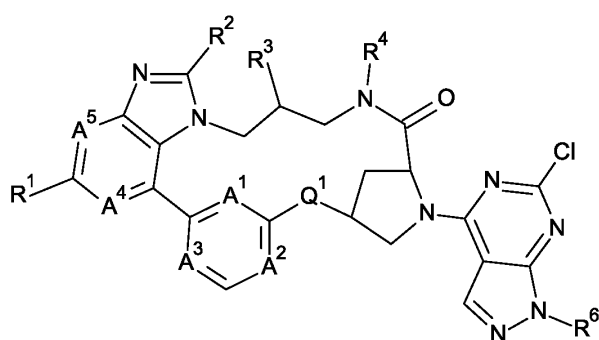
- yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-ethoxy-22-fluoro-13,18-dimethyl-5,7,10,13,17,19,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(24),2,4,6(26),18,20,22-heptaen-12-one;
(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-13,18-dimethyl-12-oxo-7,10,13,17,19,23,26-heptazapentacyclo[15.6.1.1^{2,6}.1^{8,11}.0^{20,24}]hexacosa-1(23),2(26),3,5,18,20(24),21-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
(1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-15-methoxy-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-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[(1*S*,5*R*)-3-*exo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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*R*,5*S*)-3-*endo*-hydroxy-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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;
(1*S*,5*R*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*exo*-carbonitrile;
(1*R*,5*S*)-6-[1-(2,4-difluorophenyl)-4-[(8*S*,11*S*,15*R*)-22-fluoro-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-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptane-3-*endo*-carbonitrile;
(8*S*,11*S*,15*R*)-10-[1-(2,4-difluorophenyl)-6-[3-(3-methyloxetan-3-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]pyrazolo[3,4-d]pyrimidin-4-yl]-15-methoxy-13,18-dimethyl-7,10,13,17,19,23,26-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
1-[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-

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1(24),2,4,6(26),18,20,22-heptaen-10-yl]pyrazolo[3,4-d]pyrimidin-6-yl]-6-azabicyclo[3.1.1]heptan-3-yl]azetidine-3-carbonitrile;
or a pharmaceutically acceptable salt thereof.

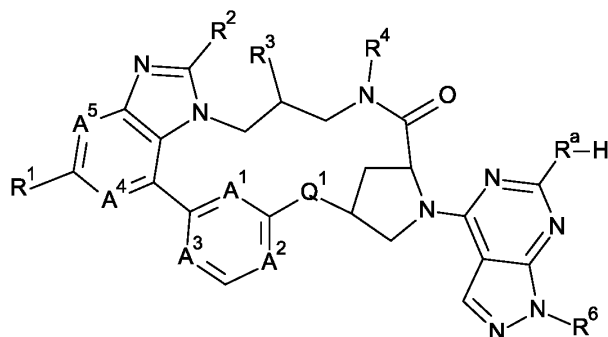
- 5 18. A process for the preparation of a compound according to any one of claims 1 to 17 comprising any one of the following steps:

- a) the formation of compound of formula (I) via nucleophilic substitution or Buchwald cross coupling between compound of formula (VIII),



(VIII), and HR⁵;

- 10 b) the formation of compound of formula (I) via nucleophilic substitution reaction

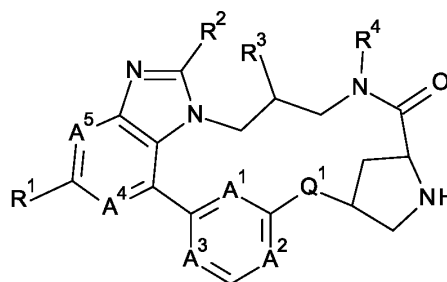


between compound of (IX),

(IX), and halide or acid anhydride; or condensation reaction between compound of formula (IX) and acid; or reductive amination between compound of formula (IX) and ketone or aldehyde;

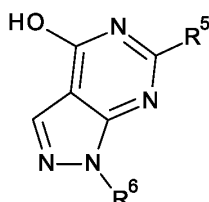
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c) the formation of compound of formula (I) via condensation reaction between



compound of formula (VII),

(VII), and



compound of formula (VIIb),

(VIIb), in the presence of coupling reagent;

wherein

the coupling reagent in step c) is PyBOP;

X is halogen; HR^a is heterocyclyl with reactive primary or secondary amino group;

R¹ to R⁶, Q¹ and A¹ to A⁶ are as defined as in any one of claim 1 to 16.

19. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 17 for use as therapeutically active substance.

20. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 30 and a pharmaceutically acceptable excipient.

21. The use of a compound according to any one of claims 1 to 17 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.

22. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 17 for the preparation of a medicament 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.

23. The use of a compound according to any one of claims 1 to 17 for the treatment to subjects
5 suffered from an inteferonopathy or auto-inflammatory diseases in which the STING activation are the root-cause of disease pathologies.

24. The use of a compound according to any one of claims 1 to 17 for the treatment or
prophylaxis of systemic lupus erythematosus (SLE), dermatomyositis, diabetic kidney disease
10 (DKD), diabetic retinopathy (DR), age-related macular degeneration (AMD), Anti-Neutrophilic
Cytoplasmic Autoantibodies (ANCA) vasculitis, STING-associated vasculopathy with onset in
infancy (SAVI), familial chilblain lupus (FCL), Niemann-Pick disease type C (NPC), Aicardi-
Goutières Syndrome (AGS), COPA syndrome or Wiskott-Aldrich syndrome.

15 25. The use of a compound according to any one of claims 1 to 17 for the preparation of a
medicament for the treatment or prophylaxis of systemic lupus erythematosus (SLE),
dermatomyositis, diabetic kidney disease (DKD), diabetic retinopathy (DR), age-related macular
degeneration (AMD), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) vasculitis,
STING-associated vasculopathy with onset in infancy (SAVI), familial chilblain lupus (FCL),
20 Niemann-Pick disease type C (NPC), Aicardi-Goutières Syndrome (AGS), COPA syndrome or
Wiskott-Aldrich syndrome.

26. The use of a compound according to any one of claims 1 to 17 for the inhibition of STING.

25 27. The use of a compound according to any one of claims 1 to 17 for the preparation of a
medicament for the inhibition of STING.

28. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 17,
when manufactured according to a process of claim 18.

30

29. 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 17.