(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2018 (18.01.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/011160 A1

(51) International Patent Classification:
C07D 471/08 (2006.01) *C07D 498/08* (2006.01)
C07D 487/04 (2006.01) *A61K 31/4985* (2006.01)
C07D 487/08 (2006.01) *A61K 31/506* (2006.01)
C07D 487/10 (2006.01) *A61P 31/12* (2006.01)
C07D 491/048 (2006.01)

(21) International Application Number:
PCT/EP2017/067315

(22) International Filing Date:
11 July 2017 (11.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2016/090043
14 July 2016 (14.07.2016) CN

(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road, 8th Floor, Suite 8 - Legal Department, Little Falls, New Jersey 07424 (US).

(72) Inventors: **HU, Taishan**; c/o Roche R&D Center (China) Ltd., Building 5, No. 720, Cailun Road, Shanghai 201203 (CN). **KOU, Buyu**; c/o Roche R&D Center (China) Ltd., Building 5, No. 720, Cailun Road, Shanghai 201203 (CN). **LIN, Xianfeng**; c/o Roche R&D Center (China) Ltd., Building 5, No. 720, Cailun Road, Shanghai 201203 (CN). **LIU, Haixia**; c/o Roche R&D Center (China) Ltd., Building 5, No. 720, Cailun Road, Shanghai 201203 (CN). **ZHANG, Zhisen**; c/o Roche R&D Center (China) Ltd., Building 5, No. 720, Cailun Road, Shanghai 201203 (CN).

(74) Agent: **HALBIG, Dirk**; F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

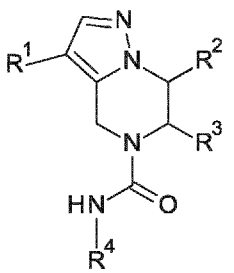
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

WO 2018/011160 A1

(54) Title: 6,7-DIHYDRO-4H-PYRAZOLO[1,5-A]PYRAZINE COMPOUNDS FOR THE TREATMENT OF INFECTIOUS DISEASES



(I)

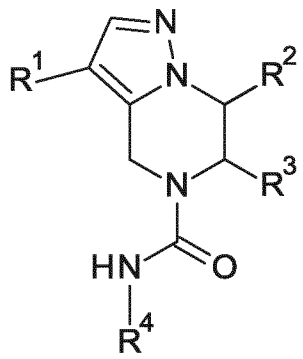
(57) Abstract: The present invention relates to compounds of the formula (I) or pharmaceutically acceptable salts, enantiomer or diastereomer thereof, wherein R^1 to R^4 are as described above. The compounds may be useful for the treatment or prophylaxis of hepatitis B virus infection.

6,7-DIHYDRO-4H-PYRAZOLO[1,5-A]PYRAZINE COMPOUNDS FOR THE TREATMENT OF INFECTIOUS DISEASES

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular for treating hepatitis B virus infection, and their pharmaceutical activity, manufacture, pharmaceutical compositions containing them and their potential use as medicaments.

FIELD OF THE INVENTION

The present invention relates to compounds of the formula (I),



(I),

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof, wherein R^1 to R^4 are as described below.The compounds of this invention are useful for the treatment or prophylaxis of hepatitis B virus infection.

Hepatitis B virus (HBV) infection is a major public health problem worldwide, roughly 30% of the world's population show serological evidence of current or past infection. Despite the introduction of a safe and effective prophylactic vaccine against the virus in the early 1980s, it is estimated that there are still more than 240 million chronic HBV carriers worldwide, a high percentage of whom will eventually develop liver cirrhosis or hepatocellular carcinoma (HCC) (WHO Hepatitis B. Fact Sheet N°204). In the 2010 Global Burden of Disease study (R Lozano, et al. Lancet, 380 (2012), 2095–2128), HBV infection ranked in the top health priorities in the world, and was the tenth leading cause of death (780,000 deaths per year). Recent studies have shown that progression to liver cirrhosis and HCC in patients with chronic HBV infection is

significantly associated with circulating HBV DNA levels. Thus, antiviral therapy against HBV is critical to prevent the progression to cirrhosis or development of HCC.

HBV is a small, enveloped virus that belongs to the Hepadnaviridae family. It contains a partly double-stranded DNA genome with approximately 3200 base pairs. HBV have a strong preference for infecting human hepatocytes. The life cycle begins when HBV attaches to the host cell membrane via its envelope proteins. The precise mechanism of viral entry has not been fully elucidated. The viral relaxed circular DNA (rcDNA) containing nucleocapsids are released into the cytoplasm and transported to the nucleus. In the nucleus, the rcDNA is repaired by both viral and cellular enzymes to form covalently closed circular DNA (cccDNA). There is evidence that each infected cell contains 1-50 cccDNA molecules as unique episomal minichromosomes. Both subgenomic RNA (sgRNA) and pregenomic RNA (pgRNA) are transcribed from the cccDNA using the cellular transcriptional machinery. After nuclear export, the pgRNA is translated into the core protein and the viral polymerase. The sgRNA is translated into the regulatory X protein and the three envelope proteins. Self-assembly of the RNA-containing viral nucleocapsid takes place via complex formation of the pgRNA with the core protein and the polymerase. Inside the nucleocapsid, the pgRNA is reverse transcribed into negative-strand DNA. rcDNA is then generated by plus-strand synthesis from the negative-strand DNA. The nucleocapsids are either re-imported to the nucleus for cccDNA amplification or enveloped and released via the endoplasmic reticulum (ER). The reverse transcriptase lacks proofreading activity; thus, mutations of the viral genome are frequent and result in the coexistence of genetically distinct viral species in infected individuals (quasispecies).

Currently, seven treatments are approved for chronic hepatitis B (CHB), including two formulations of interferon (IFN) (conventional IFN and PEG-IFN) and five nucleos(t)ide analogues (NUCs: lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil). The main difference between immunomodulatory agents and NUCs is that PEG-IFN has the advantage of a finite duration of use, whereas the use of NUCs is indefinite. The major drawback of PEG-IFN is its high frequency of adverse events. Some viral genotypes do not show good responses to interferon therapy. Long-term use of NUCs, on the other hand, poses the risk of drug resistance. The ultimate goal of antiviral therapy for CHB is to prevent progression to cirrhosis or HCC via eradication of HBV or persistent viral suppression. The majority of currently treated patients fail to achieve this goal. As indicated above, nucleocapsid assembly is a critical step for HBV genome replication. As the synthesis of viral DNA takes place

exclusively within the nucleocapsid, the assembly and disassembly of nucleocapsid must be precisely regulated to ensure correct packaging and release of the viral genome. Nucleocapsid assembly is an evolutionary constraint process that limits the diversity of HBV, and it is highly sensitive to even subtle molecular disturbances. Both assembly and disassembly of nucleocapsid make the process an attractive therapeutic target for the development of new antiviral therapies against various HBV genotypes and drug resistance isolates. A few capsid related anti-HBV compounds have been reported. For example, heteroaryldihydropyrimidines (HAP), including compounds named Bay 41-4109, Bay 38-7690 and Bay 39-5493 (Deres K. et al. Science 2003, 893), and phenylpropenamide derivatives such as AT-61 and AT-130 (Feld J. et al. Antiviral Research 2007, 168-177). Capsid has become a promising drug target with several molecules under clinical stage. There is still a need to develop new treatments for the prophylaxis and treatment of hepatitis B virus infection.

SUMMARY OF THE INVENTION

Objects of the present invention are novel compounds of formula (I), 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) as HBV inhibitors and for the treatment or prophylaxis of HBV infection. The compounds of formula (I) show superior anti-HBV activity.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term "C_{1-6}alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. In particular embodiments, C_{1-6}alkyl has 1 to 6 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of C_{1-6}alkyl include, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

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

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

The term "oxo" denotes a divalent oxygen atom =O.

The term "pyrimidinyloxy" denotes pyrimidinyl-O-.

The term "diastereomer" denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, activities and reactivities.

The term "enantiomers" denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

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

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

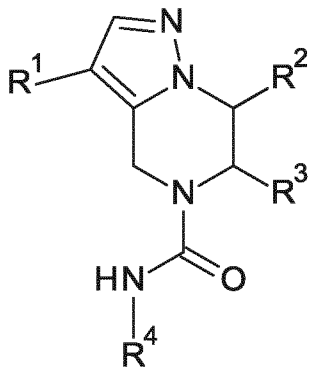
The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts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

Compounds of the general formula (I) which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the enantiomers. Particularly,

diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

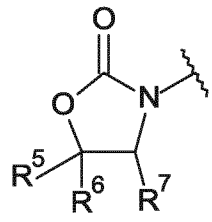
INHIBITOR OF HBV

The present invention provides (i) novel compounds having the general formula (I):



(I),

wherein

R^1 is , wherein R^5, R^6 and R^7 are independently selected from H or C_{1-6}alkyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

with the proviso that R^5, R^6 and R^7 are not H simultaneously, and

(6S)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

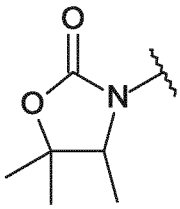
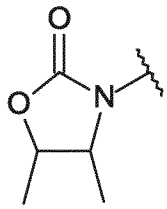
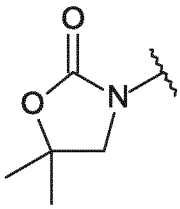
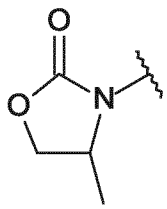
(6S)-N-[6-(difluoromethyl)-5-fluoro-2-pyridyl]-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2-chloro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-N-[2-(trifluoromethyl)-4-pyridyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

and their enantiomers or diastereomers are excluded.

A further embodiment of present invention is (ii) a compound of formula (I), wherein

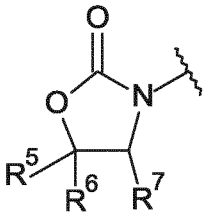
R^1 is  ,  ,  or  ;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl, chloropyridinyl, difluoropyridinyl, fluorochloropyridinyl, difluoromethylpyridinyl or trifluoromethylpyridinyl.

A further embodiment of present invention is (iii) a compound of formula (I), wherein

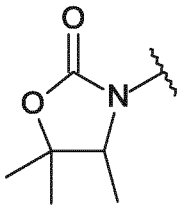
R^1 is  , wherein R^5, R^6 and R^7 are $C_{1\text{-}6}$alkyl;

R^2 is H;

R^3 is $C_{1\text{-}6}$alkyl;

R^4 is phenyl three times substituted by halogen, or pyridinyl substituted by halo$C_{1\text{-}6}$alkyl.

A further embodiment of present invention is (iv) a compound of formula (I), wherein



R^1 is ;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl or difluoromethylpyridinyl.

In another embodiment of the present invention, particular compounds of the present invention are (v) selected from:

(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4R)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(6-chloro-5-fluoro-3-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-N-[2-(trifluoromethyl)-4-pyridyl]-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(4S)-4-methyl-2-oxo-oxazolidin-3-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

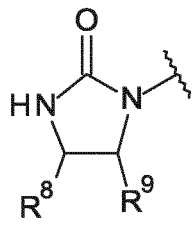
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-(2,6-difluoro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

In another embodiment of the present invention, more particular compounds of the present invention are (vi) selected from:
(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

Another embodiment of the present invention is (vii) a compound of formula (I), wherein

R^1 is , wherein R^8 is H, pyridinyl or haloC_{1-6}alkyl; R^9 is H, pyridinyl or C_{1-6}alkyl;

R^2 is H;

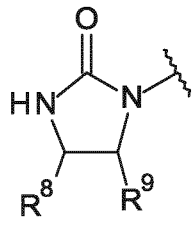
R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

with the proviso that R^8 and R^9 are not H simultaneously.

A further embodiment of the present invention is (viii) a compound of formula (I), wherein

R^1 is  , wherein R^8 is H, pyridinyl or trifluoromethyl; R^9 is H, pyridinyl or methyl;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl.

In another embodiment of the present invention, particular compounds of the present invention are (ix) selected from:

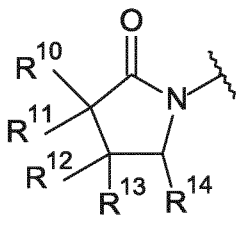
(6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(5S)-5-methyl-2-oxo-imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and

(6S)-6-methyl-3-[2-oxo-5-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

Another embodiment of the present invention is (x) a compound of formula (I), wherein

R^1 is  , wherein R^{10} is H, halogen or hydroxy; R^{11} is H or halogen; R^{12} is H, cyano, hydroxy, pyridinyl or pyrimidinyloxy; R^{13} is H, C_{1-6}alkyl or morpholinylcarbonyl; R^{14} is H, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl or $(C_{1-6}alkyl)_2aminoC_{1-6}alkyl$;

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

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

with the proviso that R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are not H simultaneously, and

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4R)-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4S)-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-[2-oxo-4-(trifluoromethyl)pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3R)-3-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(3-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(4-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4R)-4-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4S)-4-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(4S)-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[4-(morpholine-4-carbonyl)-2-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(4R)-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3R,4R)-3,4-dihydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

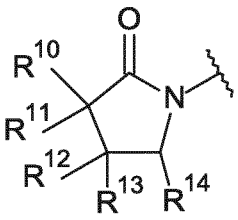
(6S)-3-[(3S,4R)-3,4-dihydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3S,4R)-3-hydroxy-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2R,3R,4S)-4-hydroxy-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

and their enantiomers or diastereomers are excluded.

A further embodiment of the present invention is (xi) a compound of formula (I), wherein

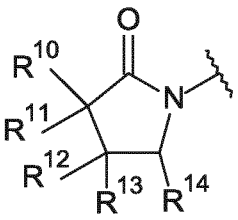
R^1 is , wherein R^{10} is H, fluoro or hydroxy; R^{11} is H or fluoro; R^{12} is H, cyano, hydroxy, pyridinyl or pyrimidinyloxy; R^{13} is H, methyl or morpholinylcarbonyl; R^{14} is H, methyl, methylaminocarbonyl or dimethylaminomethyl;

R^2 is H or methyl;

R^3 is methyl;

R^4 is trifluorophenyl, difluoropyridinyl or difluoromethylpyridinyl.

A further embodiment of the present invention is (xii) a compound of formula (I), wherein

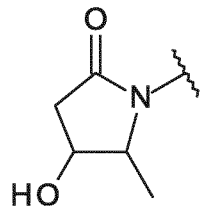
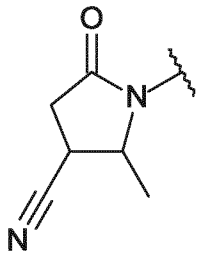
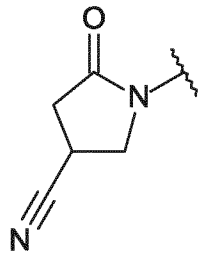
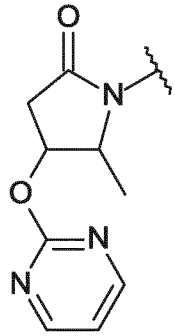
R^1 is , wherein R^{10} is H; R^{11} is H; R^{12} is cyano, hydroxy or pyrimidinyloxy; R^{13} is H; R^{14} is H or $C_{1\text{-}6}$alkyl;

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

R^3 is $C_{1\text{-}6}$alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl.

A further embodiment of the present invention is (xiii) a compound of formula (I), wherein

R^1 is , ,  or ;

R^2 is H or methyl;

R^3 is methyl;

R^4 is trifluorophenyl, difluoropyridinyl or difluoromethylpyridinyl.

In another embodiment of the present invention, particular compounds of the present invention are (xiv) selected from:

(6S)-3-[3-hydroxy-2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3R)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,4-trans-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,4-cis-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S,4R)-3-cyano-4-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S)-2-(methylcarbamoyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and

(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

In another embodiment of the present invention, particular compounds of the present invention are (xv) selected from:
(6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

Another embodiment of the present invention is (xvi) a compound of formula (I), wherein R^1 is
oxoazaspiro[2.4]heptanyl;
oxobenzimidazolyl;
oxodiazabicyclo[3.1.1]heptanyl;
oxodiazabicyclo[3.2.1]octanyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or C_{1-6}alkyl;
oxodiazabicyclo[3.3.1]nonanyl unsubstituted or substituted by C_{1-6}alkylcarbonyl;
oxodiazaspiro[3.4]octanyl substituted by C_{1-6}alkoxycarbonyl;
oxohexahydrobenzimidazolyl;
oxohexahydrocyclopenta[d]imidazolyl unsubstituted or substituted by hydroxy;
oxooxaazabicyclo[3.2.1]octanyl;
oxooxaazaspiro[2.4]heptanyl unsubstituted or substituted by C_{1-6}alkyl;
oxooxadiazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkylcarbonyl;
oxooxazinanyl which is twice substituted by C_{1-6}alkyl and cyano;
oxopyridinyl;
oxotetrahydrocyclopenta[d]oxazolyl;

oxotetrahydrofuro[3,4-d]imidazolyl; or
oxotetrahydrofuro[3,4-d]oxazolyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

with the proviso that

(6S)-6-methyl-3-(6-oxo-5-azaspiro[2.4]heptan-5-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

Methyl 6-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

Ethyl 6-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

(6S)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

and their enantiomers or diastereomers are excluded.

A further embodiment of the present invention is (xvii) a compound of formula (I), wherein

R^1 is 5-oxo-4-azaspiro[2.4]heptan-4-yl; 2-oxo-3H-benzimidazol-1-yl; 6-acetyl-4-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl; 8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 8-ethylsulfonyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 8-methyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl; 7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl; 2-tert-butylcarbonyl-7-oxo-2,6-diazaspiro[3.4]octanyl; 2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl; 2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl; 5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl; 4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl; 5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl; 7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl; 9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl; cyano(methyl)oxooxazinanyl; oxopyridinyl, 2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl; 2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl or 2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl, chloropyridinyl, difluoropyridinyl, difluoromethylpyridinyl or trifluoromethylpyridinyl.

A further embodiment of the present invention is (xviii) a compound of formula (I), wherein

R^1 is oxooxaazaspiro[2.4]heptanyl substituted by C_{1-6}alkyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl.

A further embodiment of the present invention is (xix) a compound of formula (I), wherein

R^1 is 7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl;

R^2 is H;

R^3 is methyl;

R^4 is difluoropyridinyl or difluoromethylpyridinyl.

In another embodiment of the present invention, particular compounds of the present invention are (xx) selected from:

(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-N-[2-(trifluoromethyl)-4-pyridyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3ar,7ar)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3ar,6as)-2-oxo-4,5,6,6a-tetrahydro-3ah-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3as,6ar)-2-oxo-4,5,6,6a-tetrahydro-3ah-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(5-oxo-4-azaspiro[2.4]heptan-4-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

Tert-butyl 6-[(6S)-5-[[2-(difluoromethyl)-4-pyridyl]carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

Tert-butyl 6-[(6S)-5-[(2,6-difluoro-4-pyridyl)carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

(6S)-6-methyl-3-(4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(8-ethylsulfonyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(8-methyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

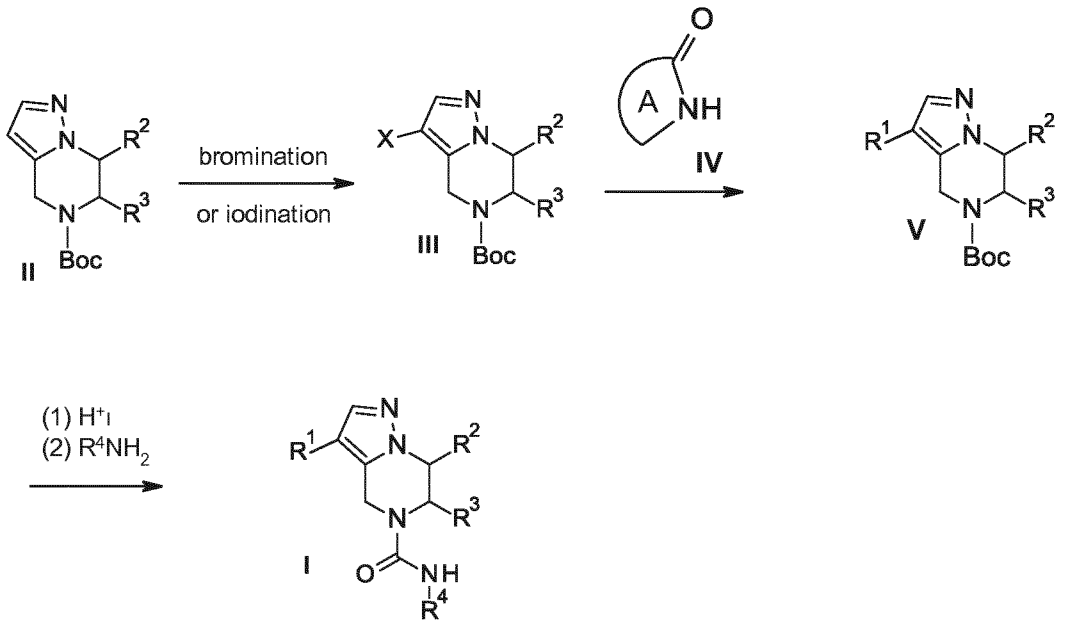
(6S)-3-(7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6R)-3-(7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(6-acetyl-4-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-6-methyl-3-(2-oxo-1-pyridyl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

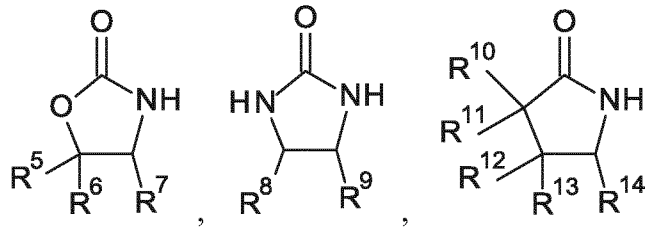
In another embodiment of the present invention, more particular compounds of the present invention are (xxi) selected from:
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

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^4 are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

Scheme 1:



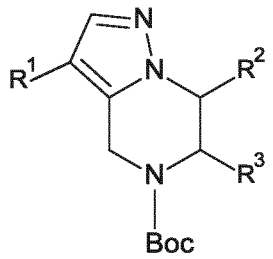
Compound of formula **IV** (ring A) is  or any one selected from unsubstituted or substituted ring of oxoazaspiro[2.4]heptane, oxobenzimidazole, oxodiazabicyclo[3.1.1]heptane, oxodiazabicyclo[3.2.1]octane, oxodiazabicyclo[3.3.1]nonane, oxodiazaspiro[3.4]octane, oxohexahydrobenzimidazole, oxohexahydrocyclopenta[d]imidazole, oxooxaazabicyclo[3.2.1]octane, oxooxaazaspiro[2.4]heptane, oxooxadiazabicyclo[3.3.1]nonane, oxooxazinane, oxopyridine, oxotetrahydrocyclopenta[d]oxazole, oxotetrahydrofuro[3,4-d]imidazole and oxotetrahydrofuro[3,4-d]oxazole. X is Br or I.

As depicted in **Scheme 1**, the synthesis of compounds of the present invention could be started from bicyclic compound of formula **(II)**, which was treated with halogenating agents, such as *N*-iodosuccinimide or *N*-bromosuccinimide, to give compound of formula **(III)**. Coupling reaction between compound of formula **(III)** and compound of formula **(IV)** in the presence of copper catalyst, such as CuI, afforded compound of formula **(V)**. The following Boc-deprotection in an acidic condition such as HCl/EtOAc or TFA/DCM and urea formation with amine R^4NH_2 in the presence of a phosgene equivalent, such as triphosgene and carbonyldiimidazole, could afford final compound of formula **(I)**. In the aforementioned urea

formation reaction, a suitable isocyanate or phenyl carbamate was also applied (Padiya, K. J. et al. *Org Lett.* 2012, 14, 2814 and references cited therein).

This invention also relates to a process for the preparation of a compound of formula (I) comprising the reaction of:

(a) the reaction of a compound of formula (IV),



(IV),

with an acid followed by urea formation with amine R^4NH_2 in the presence of a phosgene equivalent;

wherein R^1 to R^4 are defined above;

In step (a), the acid can be, for example, HCl in EtOAc and TFA in DCM; phosgene equivalent can be, for example, triphosgene and carbonyldiimidazole.

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

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (I) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to the suppression of serum HBV DNA levels, or HBeAg seroconversion to HBeAb, or HBsAg loss, or normalization of alanine aminotransferase levels and improvement in liver histology. 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 0.01 to 100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain from about 0.1 to about 1000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical

Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 0.1 mg to 1000 mg of the compound of the invention compounded with about 30 mg to 90 mg anhydrous lactose, about 5 mg to 40 mg sodium croscarmellose, about 5 mg to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 mg to 10 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 5 mg to 400 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.

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention can inhibit HBV's DNA synthesis and reduce HBV DNA levels. Accordingly, the compounds of the invention are useful for the treatment or prophylaxis of HBV infection.

The invention relates to the use of a compound of formula (I) for the treatment or prophylaxis of HBV infection.

The use of a compound of formula (I) for the preparation of medicaments useful in the treatment or prophylaxis diseases that are related to HBV infection is an object of the invention.

The invention relates in particular to the use of a compound of formula (I) for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

Another embodiment includes a method for the treatment or prophylaxis of HBV infection which method comprises administering an effective amount of a compound of formula (I), a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

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 used herein are as follows:

DCE:	1,2-dichloroethylene
DIAD:	diisopropyl azodicarboxylate
DIPEA:	*N,N*-diisopropylethylamine
DMAc:	*N,N*-dimethylacetamide
DMAP:	4-dimethylaminopyridine
EA or EtOAc:	ethyl acetate
EC_{50}:	half maximal effective concentration
HATU:	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HPLC:	high performance liquid chromatography
IPA:	isopropanol
LCMS	liquid chromatography–mass spectrometry
mCPBA:	meta-chloroperoxybenzoic acid
min(s):	minute(s)
MS:	mass spectrometry
MsCl:	methanesulfonyl chloride
NCS:	*N*-chlorosuccinimide
NIS:	*N*-iodosuccinimide
PE:	petroleum ether
prep-HPLC:	preparative high performance liquid chromatography
prep-TLC:	preparative thin layer chromatography

psi:	pounds per square inch
SFC:	supercritical fluid chromatography
TEA:	trimethylamine
TBSCl:	tert-butyldimethylsilyl chloride
t- BuXPhos:	2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TMG:	1,1,3,3-tetramethylguanidine
$Pd_2(dba)_3$:	Tris(dibenzylideneacetone)dipalladium(0)
pgRNA:	pre-genomic RNA
qPCR:	quantitative polymerase chain reaction
v/v	volume ratio

General Experimental Conditions

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 μm; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using XBridge™ Prep-C18 (5 μm, OBDTM 30 × 100 mm) column or SunFire™ Prep-C18 (5 μm, OBD™ 30 × 100 mm) column. Waters AutoP purification System (Column: XBridge™ Prep-C18, 30 × 100 mm, Sample Manager 2767, Pump 2525, Detector: Micromass ZQ and UV 2487, solvent system: acetonitrile and 0.1% ammonium hydroxide in water). LC/MS spectra of compounds were obtained using a LC/MS (Waters™ Alliance 2795- Micromass ZQ), LC/MS conditions were as follows (running time 6 mins):

Acidic condition: A: 0.1% formic acid in H_2O; B: 0.1% formic acid in acetonitrile;

Basic condition: A: 0.1% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Neutral condition: A: H_2O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion $(MH)^+$.

NMR Spectra were obtained using Bruker Avance 400 MHz.

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 atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

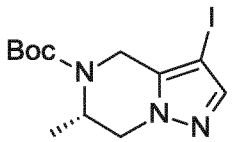
The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

PREPARATIVE EXAMPLES

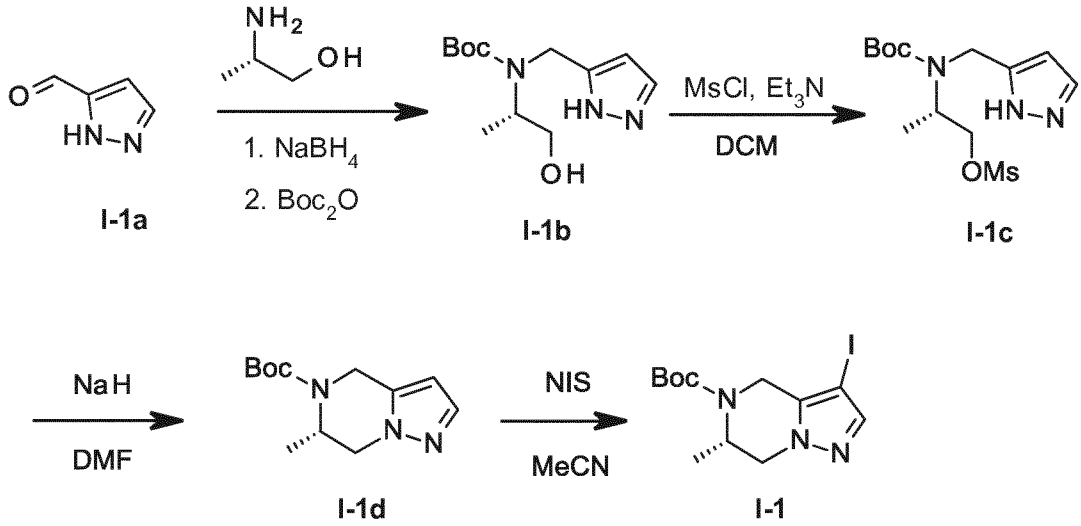
The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Intermediate I-1

tert-Butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate



Intermediate **I-1** was prepared according to the following scheme:



Step 1: preparation of tert-butyl N-[(1S)-2-hydroxy-1-methyl-ethyl]-N-(1H-pyrazol-5-ylmethyl)carbamate (compound I-1b)

To a solution of 1H-pyrazole-5-carbaldehyde (compound **I-1a**, 54.0 g, 562.5 mmol) in MeOH (300 mL) was added (2S)-2-aminopropan-1-ol (41.2 g, 675 mmol) and the reaction mixture was stirred at 25 °C for 1 hour. $NaBH_4$ (25.9 g, 675.0 mmol) was added at 0 °C and the reaction mixture was stirred for another hour followed by the addition of H_2O (300 mL) and Boc_2O (147.1 g, 675.0 mmol). The resulting mixture was stirred at room temperature for 12 hours, and extracted with EtOAc (600 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (eluting with 0%~5% MeOH in DCM) to afford compound **I-1b** (80 g) as a colorless oil. LCMS ($M+H^+$): 334.

Step 2: preparation of [(2S)-2-[tert-butoxycarbonyl(1H-pyrazol-5-ylmethyl)amino]propyl] methanesulfonate (compound I-1c)

To a mixture of tert-butyl N-[(1S)-2-hydroxy-1-methyl-ethyl]-N-(1H-pyrazol-5-ylmethyl)carbamate (compound **I-1b**, 80.0 g, 117.2 mmol) and Et_3N (100.5 g, 995.6 mmol) in DCM (800 mL) was added MsCl (57.3 g, 497.8 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature for 2 hours, then washed with water (500 mL), brine (500 mL), and dried over Na_2SO_4. The organic layer was concentrated to afford compound **I-1c** (100 g, crude), which was used directly in next step.

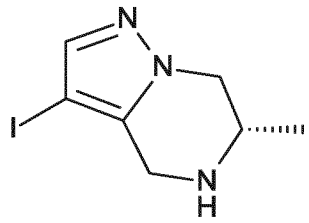
Step 3: preparation of tert-butyl (6S)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound I-1d)

To a solution of [(2S)-2-[tert-butoxycarbonyl(1H-pyrazol-5-ylmethyl)amino]propyl] methanesulfonate (compound **I-1c**, 100.0 g, 313.4 mmol) in DMF (1000 mL) was added NaH (15.0 g, 376.2 mmol) in portions at 0 °C. The reaction mixture was then stirred at room temperature for 12 hours, poured into water (2000 mL) and extracted with EtOAc (1000 mL) twice. The organic layers were combined and concentrated. The residue was purified by column chromatography (eluting with 10%~80% EtOAc in petroleum ether) to afford compound **I-1d** (18.0 g) as a colorless oil. LCMS ($M+H^+$): 238.

Step 4: preparation of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound I-1): To a solution of tert-butyl 6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **53c**, 3.3 g, 14.8 mmol) in CH_3CN (40 mL) was added NIS (5.0 g, 22.1 mmol) slowly. The reaction mixture was stirred at room temperature for 16 hours and then extracted with EtOAc (50 mL), washed with brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography (eluting with 10%~80% EtOAc in petroleum ether) to afford compound **I-1** (4.8 g) as a white solid.

Intermediate I-1-1

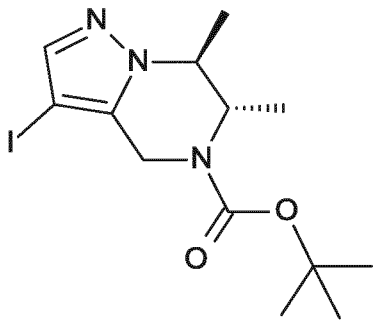
(6S)-3-iodo-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



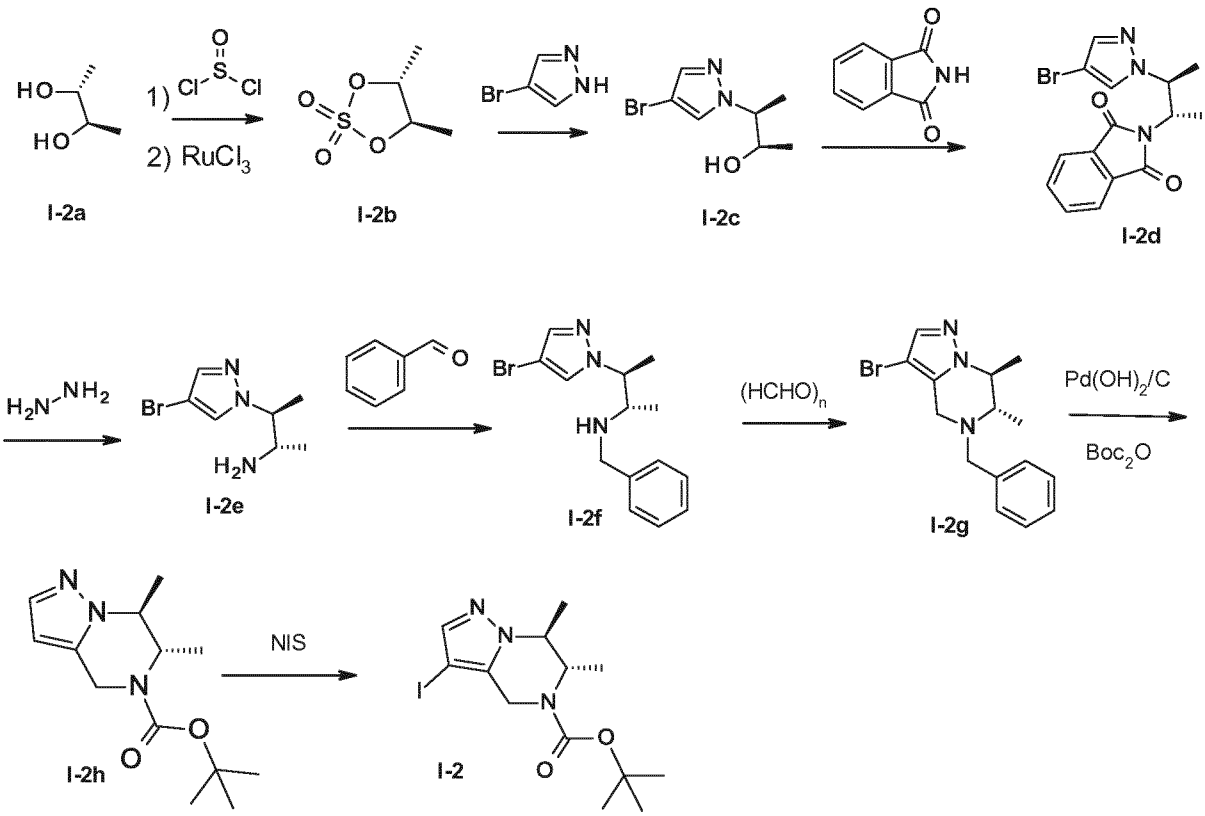
A mixture of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **I-1**, 2.0 g, 5.5 mmol) in HCl/EA (4 N, 50 mL) was stirred for 1 hour at room temperature, and then concentrated under reduced pressure. The residue was dissolved in DCM (100 mL), and basified with K_2CO_3. The solid was filtered off and organic layer was evaporated to give **Intermediate I-1-1** (1.3 g). LCMS ($M+H^+$): 264.

Intermediate I-2

tert-Butyl (6S,7S)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate



Intermediate **I-2** was prepared according to the following scheme:



Step 1: Preparation of (4R,5R)-4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (compound I-2b)

A solution of $SOCl_2$ (7.26 g, 4.45 mL, 61 mmol) in DCM (50 mL) was added dropwise to a stirred mixture of (2R,3R)-butane-2,3-diol (5 g, 55.5 mmol), imidazole (18.9 g, 277 mmol) and triethylamine (19.6 g, 27.1 mL, 194 mmol) in DCM (200 mL) at 0 °C, and the reaction mixture was stirred for 1 hour at 0 °C. The reaction mixture was quenched with H_2O and extracted twice with DCM. The combined organic layer was washed with H_2O, dried over $MgSO_4$, filtered and concentrated to give a residue. To a stirred solution of the crude residue in acetonitrile (200 mL) at 0 °C were added sodium periodate (17.8 g, 83.2 mmol), water (150 mL) and rhodium (III) chloride (1.16 g, 5.55 mmol) sequentially and the reaction mixture was stirred at 0 °C for 3 hours. The two layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$, filtered and concentrated to give compound **I-2b** as a colorless oil (8 g).

Step 2: Preparation of (2R,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-ol (compound I-2c)

A mixture of (4R,5R)-4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (compound **I-2b**, 8 g, 52.6 mmol), 4-bromo-1H-pyrazole (11.6 g, 78.9 mmol) and Cs_2CO_3 (34.3 g, 105 mmol) in DMF

(50 mL) was stirred at room temperature for 16 hours. The reaction mixture was filtered and concentrated. The resulting residue was taken up in 400 mL of THF/50% aq. H_2SO_4 (v/v 1/2), and stirred vigorously for 48 hours. The reaction mixture was then carefully basified with 10 M aqueous NaOH solution, and the layers were separated. The aqueous layer was extracted twice with DCM, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **I-2c** as a colorless oil (8 g). LCMS ($M+H^+$): 219.

Step 3: Preparation of 2-((2S,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-yl)isoindoline-1,3-dione (compound I-2d)

To a mixture of (2R,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-ol (compound **I-2c**, 8 g, 36.5 mmol), isoindoline-1,3-dione (5.91 g, 40.2 mmol) and triphenylphosphine (12.5 g, 47.5 mmol) in THF (75 mL) was added DIAD (11.1 g, 54.8 mmol) dropwise at room temperature. Then the reaction mixture was stirred at room temperature for 2 hours, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give compound **I-2d** as a white solid (5 g). LCMS ($M+H^+$): 348.

Step 4: Preparation of (2S,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound I-2e)

A mixture of 2-((2S,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-yl)isoindoline-1,3-dione (compound **I-2d**, 5 g, 14.4 mmol) and Hydrazine hydrate (7.19 g, 144 mmol) in MeOH (50 mL) was stirred at 80 °C for 15 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DCM, the solid was filtered off and the filtrate was concentrated to give compound **I-2e** as a slight yellow oil (3 g). LCMS ($M+H^+$): 218.

Step 5: Preparation of (2S,3S)-N-benzyl-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound I-2f)

A mixture of (2S,3S)-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound **I-2e**, 3 g, 13.8 mmol) and benzaldehyde (1.61 g, 15.1 mmol) in MeOH (50 mL) was stirred for 2 hours at room temperature. Then sodium borohydride (624 mg, 16.5 mmol) was added slowly at 0 °C in 30 mins and the reaction mixture was stirred at room temperature for another 30 mins. The reaction mixture was poured into 100 mL of H_2O and extracted with EtOAc (100 mL) twice. The combined organic layer was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give compound **I-2f** as light yellow oil (4 g). LCMS ($M+H^+$): 308.

Step 6: Preparation of (6S,7S)-5-benzyl-3-bromo-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (compound I-2g)

To a stirred solution of (2S,3S)-N-benzyl-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound **I-2f**, 4 g, 13 mmol) in acetonitrile (50 mL) was added paraformaldehyde (1.95 g, 64.9 mmol) and 2,2,2-trifluoroacetic acid (296 mg, 2.6 mmol), and the reaction mixture was stirred at 70 °C for 6 hours. The reaction mixture was concentrated and the residue was then taken up in EtOAc, and washed with $NaHCO_3$ aq. solution and brine. The organic layer was concentrated and the residue was purified on a silica gel column (heptane: EtOAc 1:0 to 9:1) to give compound **I-2g** as a colorless oil (2.3 g). LCMS ($M+H^+$): 320.

Step 7: Preparation of tert-butyl (6S,7S)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound I-2h)

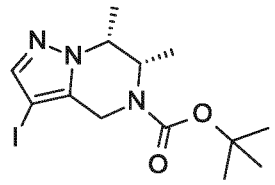
A mixture of (6S,7S)-5-benzyl-3-bromo-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (compound **I-2g**, 1.5 g, 4.68 mmol), di-tert-butyl dicarbonate (2.18 mL, 9.37 mmol) and $Pd(OH)_2/C$ (329 mg) in MeOH (50 mL) was heated to 50 °C and stirred for 15 h under hydrogen. Then the solid was filtered off and the filtrate was concentrated. The residue was dissolved in THF/MeOH (v/v 5:1, 50 ml), di-tert-butyl dicarbonate (2.18 ml, 9.37 mmol) and Na_2CO_3 (496 mg, 4.68 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours and then filtered through celite, the filtrate was concentrated and the crude material was purified by flash chromatography (silica gel, 10% to 50% EtOAc in hexanes, EtOAc contain 10% MeOH). LCMS ($M+H^+$): 252.

Step 8: Preparation of tert-butyl (6S,7S)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound I-2)

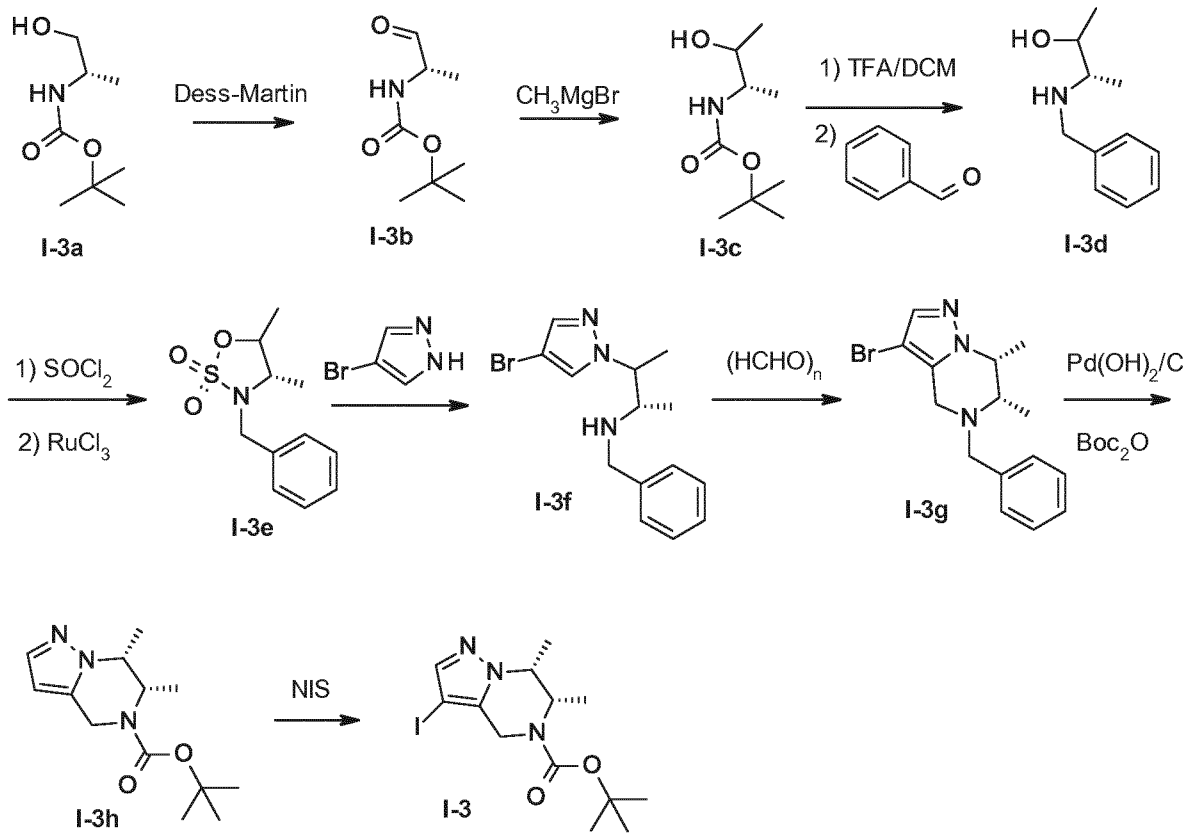
To a solution of (6S,7S)-tert-butyl 6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (compound **I-2**, 1.2 g, 4.77 mmol) in MeCN (20 mL) was added NIS (1.61 g, 7.16 mmol) and then stirred at room temperature for 16 hours. The reaction mixture was quenched with aq. $NaHSO_3$, extracted with EtOAc, dried and concentrated, The crude material was purified by flash chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give compound **I-2** as colorless oil, 1.2 g. LCMS ($M+H^+$): 378.

Intermediate I-3

tert-Butyl (6S,7R)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate



Intermediate **I-3** was prepared according to the following scheme:



Step 1: preparation of (S)-tert-butyl (1-oxopropan-2-yl)carbamate (compound I-3b)

To a solution of (S)-tert-butyl (1-hydroxypropan-2-yl)carbamate (compound **I-3a**, 8.76 g, 50 mmol) in DCM (200 mL) was added Dess-Martin periodinane (31.8 g, 75 mmol) slowly. After stirred at room temperature for 2 hours, the reaction mixture was filtered through silica gel. The filtrate was concentrated *in vacuo* to give compound **I-3b** as a colorless oil (10 g).

Step 2: preparation of tert-butyl N-[(1S)-2-hydroxy-1-methyl-propyl]carbamate (compound I-3c)

To a solution of (S)-tert-butyl (1-oxopropan-2-yl)carbamate (compound **I-3b**, 8.66 g, 50 mmol) in THF (100 mL) at -78 °C was added methylmagnesium bromide (150 mL, 150 mmol) slowly. The reaction mixture was stirred at -78 °C for 2 hours and then quenched with water. The reaction mixture was poured into 200 mL of brine and extracted with EtOAc (100 mL) twice.

The combined organic layer was dried and concentrated *in vacuo* to give crude compound **I-3c** as a colorless oil (9 g). LCMS ($M+H^+$): 190

Step 3: preparation of tert-butyl (3S)-3-(benzylamino)butan-2-ol (compound I-3d)

A mixture of tert-butyl ((2S)-3-hydroxybutan-2-yl)carbamate (compound **I-3c**, 8 g, 25.4 mmol) and trifluoroacetic acid (28.9 g, 19.5 mL, 254 mmol) in DCM (40 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM (100 mL), to which benzaldehyde (2.69 g, 25.4 mmol) and sodium triacetoxyborohydride (10.8 g, 50.7 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours, then poured into 250 mL saturated aqueous $NaHCO_3$ and extracted with EtOAc (200 mL) twice. The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 20% to 80% EtOAc in hexanes) to give compound **I-3d** as a light yellow oil (2 g). LCMS ($M+H^+$): 180.

Step 4: preparation of (5S)-3-benzyl-4,5-dimethyl-1,2,3-oxathiazolidine 2,2-dioxide (compound I-3e)

A solution of $SOCl_2$ (1.46 g, 896 µL, 12.3 mmol) in DCM (10 mL) was added dropwise to a stirred mixture of (3S)-3-(benzylamino)butan-2-ol (compound **I-3d**, 2 g, 11.2 mmol), imidazole (3.8 g, 55.8 mmol) and triethylamine (3.95 g, 39 mmol) in DCM (50 mL) at 0 °C, and the reaction mixture was allowed to stirred at 0 °C for 1 hour. The reaction mixture was quenched with H_2O and extracted twice with DCM. The combined organic layer was washed with H_2O, dried over $MgSO_4$, filtered and concentrated. To a stirred solution of the crude residue in acetonitrile (100 mL) at 0 °C were added sodium periodate (3.82 g, 17.9 mmol), water (75 mL) and rhodium (III) chloride (233 mg, 1.12 mmol) sequentially and the reaction mixture was stirred at 0 °C for 3 hours. The two layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, the organic layer was dried over $MgSO_4$, filtered and concentrated to give compound **I-3e** as a colorless oil (3 g), LCMS ($M+H^+$): 242.

Step 5: preparation of (2S)-N-benzyl-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound I-3f)

A mixture of (5S)-3-benzyl-4,5-dimethyl-1,2,3-oxathiazolidine 2,2-dioxide (compound **I-3e**, 3 g, 10.6 mmol), 4-bromo-1H-pyrazole (3.11 g, 21.1 mmol) and Cs_2CO_3 (6.89 g, 21.1 mmol) in DMF (50 mL) was stirred at room temperature for 16 hours. The reaction mixture was filtered and concentrated. The residue was dissolved in DCM and 20% aq. H_2SO_4 (150 mL, v/v 1:1) and

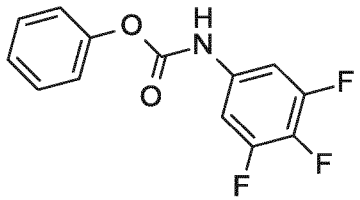
stirred vigorously for 12 hours. The reaction mixture was then carefully basified with 10 M aqueous NaOH solution, the layers were separated. The aqueous layer was extracted twice with DCM, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 20% to 60% EtOAc in hexanes) to give compound **I-3f** as a colorless oil (1 g). LCMS ($M+H^+$): 308

Preparation of tert-butyl (6S,7R)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-3)

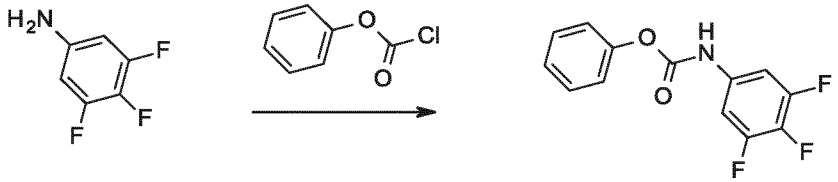
The compound **I-3** was prepared in analogy to compound **I-2** by using (2S)-N-benzyl-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound **I-3f**) instead of (2S,3S)-N-benzyl-3-(4-bromo-1H-pyrazol-1-yl)butan-2-amine (compound **I-2f**). Intermediate **I-3** was obtained as colorless oil (550 mg). LCMS ($M+H^+$): 378.

Intermediate I-4

Phenyl N-(3,4,5-trifluorophenyl)carbamate



Intermediate **I-4** was prepared according to the following scheme:

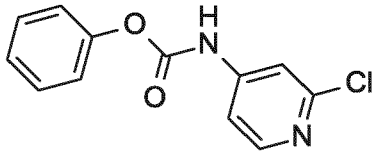


I-4

To a solution of 3,4,5-trifluoroaniline (1.47 g, 10 mmol) in DCM (30 mL) was added DIPEA (2.06 mL, 12 mmol), followed by adding phenyl chloroformate (1.38 mL, 11 mmol) dropwise at 0 °C. After addition the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with DCM, washed with water. The organic phase was seperated, dried over Na_2SO_4 and concentrated. The residue was purified by column to give Intermediate **I-4** as a white solid, 1.87 g. LCMS ($M+H^+$): 268.

Intermediate I-5

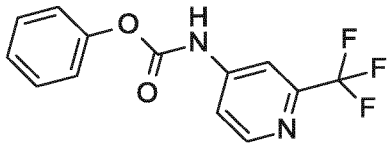
Phenyl N-(2-chloro-4-pyridyl)carbamate



Intermediae **I-5** was prepared in analogy to **Intermediate I-4** by using 2-chloropyridin-4-amine instead of 3,4,5-trifluoroaniline. Intermediae **I-5** was obtained as a white solid. LCMS ($M+H^+$): 249.

Intermediate I-6

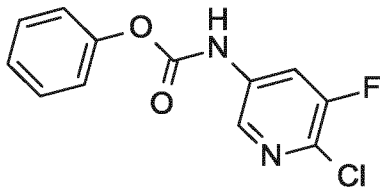
Phenyl N-(2-trifluoromethyl-4-pyridyl)carbamate



Intermediate **I-6** was prepared in analogy to Intermediate **I-4** by using 2-(trifluoromethyl)pyridin-4-amine instead of 3,4,5-trifluoroaniline. Intermediae **I-6** was obtained as a white solid. LCMS ($M+H^+$): 283.

Intermediate I-7

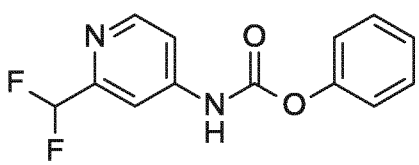
Phenyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate



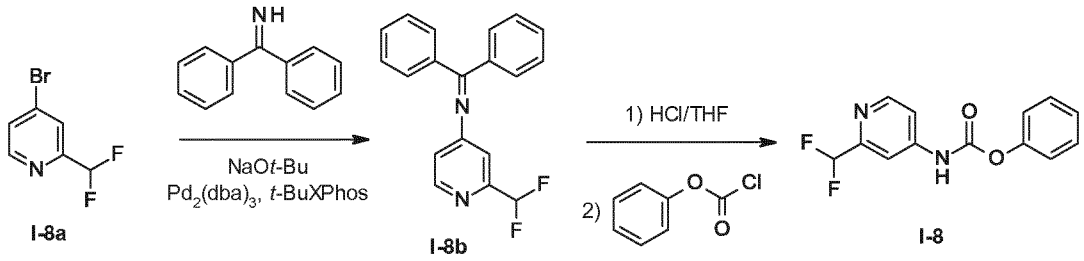
Intermediate **I-7** was prepared in analogy to Intermediate **I-4** by using 6-chloro-5-fluoro-pyridin-3-amine instead of 3,4,5-trifluoroaniline. Intermediae **I-7** was obtained as a white solid. LCMS ($M+H^+$): 267.

Intermediate I-8

Phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate



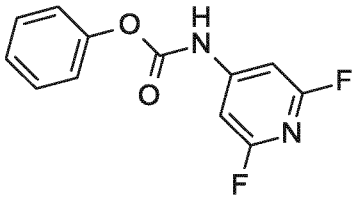
Intermediate **I-8** was prepared according to the following scheme:



To a mixture of 4-bromo-2-(difluoromethyl)pyridine (compound **I-8a**, 416 mg, 2.0 mmol), diphenylmethanimine (725 mg, 4.0 mmol) in toluene (15 mL) were added $Pd_2(dba)_3$ (92 mg, 0.1 mmol), *t*-BuXPhos (85 mg, 0.2 mmol) and NaO*t*-Bu (577 mg, 6 mmol). The reaction mixture was flushed with nitrogen and heated to 100 °C for 2 hours under nitrogen. The reaction mixture was cooled down, diluted with EtOAc (30 mL), and washed with water. The organic layer was separated and concentrated to give crude compound **I-8b** (617 mg). LCMS ($M+H^+$): 309. Compound **I-8b** (617 mg, 2.0 mmol) was dissolved in THF (10 mL) and hydrochloride acid (2 mL, 12 M). The reaction mixture was stirred at room temperature for 2 hours, and then concentrated. The residue was dissolved in DCM (5.0 mL), to which was added DIPEA (1.0 mL, 5.8 mmol) followed by phenyl carbonochloridate (251 μL, 2.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 hours, poured into water (20 mL), and extracted with EtOAc (20 mL) twice. The combined organic layer was concentrated, the residue was purified by column chromatography (eluting with 0%~20% EtOAc in petroleum ether) to afford compound **I-8** (264 mg), as white solid. LCMS ($M+H^+$): 265.

Intermediate I-9

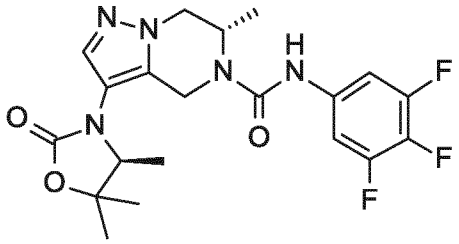
Phenyl N-(2,6-difluoro-4-pyridyl)carbamate



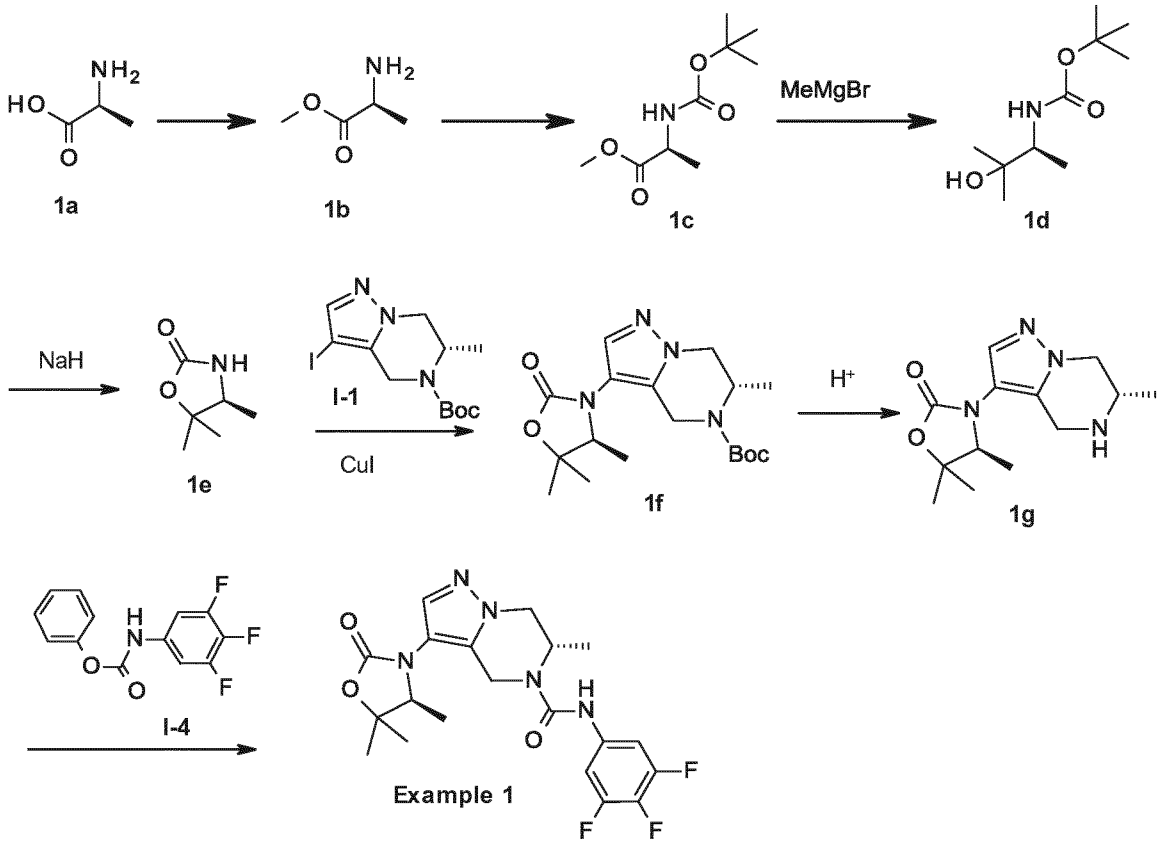
To a solution of 2,6-difluoropyridin-4-amine (550 mg, 4.23 mmol) and pyridine (1.71 ml, 21.1 mmol) in THF (15 mL) was added phenyl carbonochloridate (993 mg, 6.34 mmol) slowly at room temperature, then the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with EtOAc, washed with H_2O (20 mL), 1 M HCl (20 mL) and sat $NaHCO_3$ (2 x 25 mL). The organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Intermediate **I-9** was obtained as a white solid. LCMS ($M+H^+$): 251.

Example 1

(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of methyl (2S)-2-aminopropanoate (compound 1b)

To the mixture of (2S)-2-aminopropanoic acid (compound **1a**, 20.0 g, 224.5 mmol) in MeOH (300.0 mL) was added $SOCl_2$ (20.0 mL) at room temperature, then the mixture was stirred at 60 °C for 3 hours and then concentrated to give compound **1b** (23.0 g, crude) which was used in next step directly.

Step 2: preparation of methyl (2S)-2-(tert-butoxycarbonylamino)propanoate (compound 1c)

To a mixture of methyl (2S)-2-aminopropanoate (compound **1b**, 23.0 g, 223 mmol) in dioxane (200 mL) was added Boc_2O (48.7 g, 223.1 mmol) and $NaHCO_3$ aq. solution (200 mL) at room temperature, then the mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered, the filtrate was extracted with EtOAc twice (200 mL), the combined organic layer was dried over Na_2SO_4, filtered and concentrated to give compound **1c** (45.0 g) as colorless oil which was used in next step directly. ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 5.06 (br. s., 1H), 4.42 - 4.24 (m, 1H), 3.76 (s, 3H), 1.46 (s, 9H), 1.39 (d, *J*=7.2 Hz, 4H).

Step 3: preparation of methyl tert-butyl N-[(1S)-2-hydroxy-1,2-dimethyl-propyl]carbamate (compound 1d)

To a mixture of methyl (2S)-2-(tert-butoxycarbonylamino)propanoate (compound **1c**, 30.0 g, 147.6 mmol) in THF (500.0 mL) was added MeMgBr (147.6 mL, 443.0 mmol) at 0 °C, then the mixture was stirred at room temperature for 6 hours. The mixture was quenched with sat. aqueous NH_4Cl solution and extracted with EtOAc (200 mL) three times, the combined organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by chromatograph (PE/EtOAc=3/1) to give compound **1d** (11.0 g) as colorless oil . ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 4.70 (br. s., 1H), 3.60 (br. s., 1H), 1.45 (s, 9H), 1.23 (s, 3H), 1.18 (s, 3H), 1.14 (d, *J*=6.8 Hz, 3H).

Step 4: preparation of (4S)-4,5,5-trimethyloxazolidin-2-one (compound 1e)

To a solution of methyl tert-butyl N-[(1S)-2-hydroxy-1,2-dimethyl-propyl]carbamate (compound **1d**, 5.0 g, 24.6 mmol) in toluene (5 mL) was added NaH (2.0 g, 49.2 mmol) at 0 °C, then the mixture was stirred at room temperature for 16 hours. The mixture was quenched with sat. aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (20 mL) twice. The organic layer was separated and concentrated. The residue was dissolved in THF (50 mL) and stirred for 1 hour. Then the mixture was filtered, and the filtrate was concentrated to give compound **1e** (1.5 g) as colorless oil which was used in next step directly. LCMS ($M+H^+$): 130.1

Step 5: preparation of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 1f)

A mixture of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**, 1.5 g, 11.6 mmol), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **I-1**, 4.2 g, 11.6 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (156.4 mg, 1.1 mmol), CuI (208.8 mg, 1.1 mmol) and K_3PO_4 (4.9 g, 23.2 mmol) in dioxane (30.0 mL) was degassed and refilled with N_2, and stirred at 100 °C under N_2 for 16 hours. The mixture was filtered, the filtrate was concentrated and the crude product was purified by prep-HPLC to give compound **1f**

(1.2 g) as a colorless solid. LCMS ($M+H^+$): 365.2, ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 7.48 (s, 1H), 4.98 (d, *J*=17.4 Hz, 1H), 4.83 (br. s., 1H), 4.27 - 4.16 (m, 2H), 4.14 - 4.06 (m, 1H), 3.81 - 3.71 (m, 1H), 1.50 (s, 3H),1.41 (s, 9H), 1.40 (s, 3H), 1.18 (t, *J*=7.1 Hz, 6H).

Step 6: preparation of (4S)-4,5,5-trimethyl-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]oxazolidin-2-one (compound 1g)

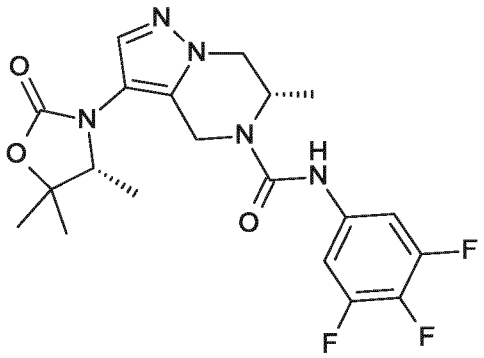
A solution of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**, 45.0 mg, 0.12 mmol) in HCl in EtOAc (4 N, 5.0 mL) was stirred at room temperature for 1 hour, then the mixture was concentrated to give crude compound **1g** (40.0 mg, crude) as a colorless oil.

Step 7: preparation of (6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 1)

To a mixture of (4S)-4,5,5-trimethyl-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]oxazolidin-2-one (compound **1g**, 40.0 mg, 0.13 mmol) and TEA (40.5 mg, 0.40 mmol) in DMF (5.0 mL) was added phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 35.5 mg, 0.13 mmol). The mixture was stirred at room temperature for 2 hours. Then the mixture was purified by prep-HPLC to give Example **1** (41.2 mg) as a colorless oil. LCMS ($M+H^+$): 438.2, ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 7.79 (s, 1H), 7.39 (s, 1H), 7.25 - 7.13 (m, 2H), 5.18 - 4.96 (m, 2H), 4.37 - 4.16 (m, 2H), 4.07 - 3.92 (m, 2H), 1.60 (s, 3H), 1.44 (s, 3H), 1.34 (d, *J*=7.0 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H).

Example 2

(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4R)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

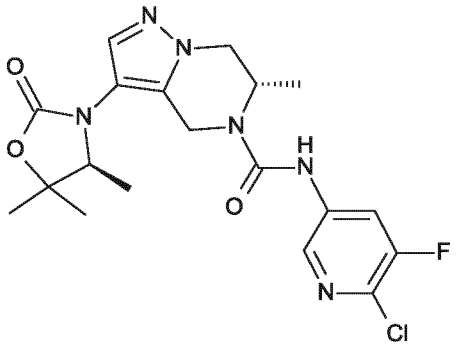


The Example **2** was prepared in analogy to Example **1** by using (2R)-2-aminopropanoic acid instead of (2S)-2-aminopropanoic acid (compound **1a**). Example **2** (37 mg) was obtained as a colorless oil. LCMS ($M+H^+$): 438.2, ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 7.52 (s,

1H), 7.41 (s, 1H), 7.23 - 7.13 (m, 2H), 5.12 – 5.02 (m, 1H), 4.79 (d, *J*=16.4 Hz, 1H), 4.53 (d, *J*=16.4 Hz, 1H), 4.29 - 4.25 (m, 1H), 4.08 (d, *J*=13.2 Hz, 1H), 3.88-3.85 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 1.32 (d, *J*=6.8 Hz, 3H), 1.27 (d, *J*=6.4 Hz, 3H).

Example 3

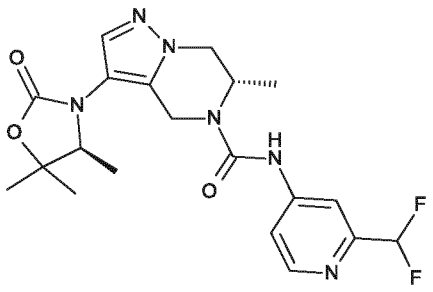
(6S)-N-(6-chloro-5-fluoro-3-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The Example **3** was prepared in analogy to Example **1** by using phenyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (Intermediate **I-7**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). Example **3** (30 mg) was obtained as a white solid. LCMS ($M+H^+$): 437.1, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.30 (d, *J*=2.2 Hz, 1H), 8.03 (dd, *J*=2.3, 10.6 Hz, 1H), 7.61 (s, 1H), 5.14 - 4.95 (m, 2H), 4.46 (d, *J*=16.8 Hz, 1H), 4.34 (dd, *J*=4.3, 12.8 Hz, 1H), 4.19 (dd, *J*=1.1, 12.8 Hz, 1H), 4.03 (q, *J*=6.6 Hz, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 1.24 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.6 Hz, 3H).

Example 4

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

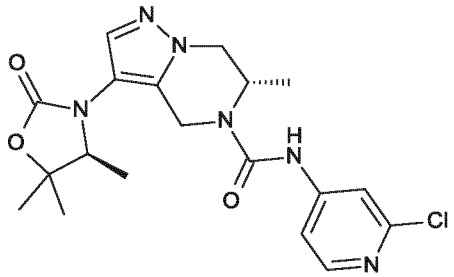


The Example **4** was prepared in analogy to Example **1** by using phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**) instead of phenyl N-(3,4,5-

trifluorophenyl)carbamate (Intermediate **I-4**). Example **4** (25 mg) was obtained as a white solid. LCMS ($M+H^+$): 435.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.43 (d, *J*=5.7 Hz, 1H), 7.88 (s, 1H), 7.68 (dd, *J*=2.0, 5.7 Hz, 1H), 7.61 (s, 1H), 6.67 (t, *J*=56.0 Hz, 1H), 5.17 - 4.97 (m, 2H), 4.47 (d, *J*=16.8 Hz, 1H), 4.35 (dd, *J*=4.3, 12.8 Hz, 1H), 4.20 (d, *J*=12.2 Hz, 1H), 4.03 (q, *J*=6.6 Hz, 1H), 1.58 (s, 3H), 1.45 (s, 3H), 1.25 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.6 Hz, 3H).

Example 5

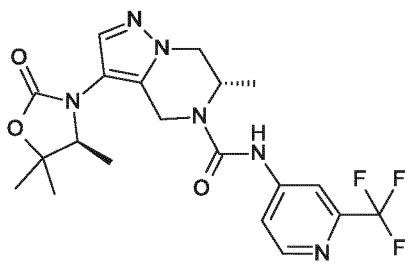
(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The Example **5** was prepared in analogy to Example **1** by using phenyl N-(2-chloro-4-pyridyl)carbamate (Intermediates **I-5**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). Example **5** (15 mg) was obtained as a white solid. LCMS ($M+H^+$): 419.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.16 (d, *J*=5.9 Hz, 1H), 7.70 (d, *J*=1.8 Hz, 1H), 7.61 (s, 1H), 7.49 (dd, *J*=1.9, 5.8 Hz, 1H), 5.08 (d, *J*=16.8 Hz, 1H), 5.03 - 4.97 (m, 1H), 4.46 (d, *J*=16.9 Hz, 1H), 4.34 (dd, *J*=4.4, 13.0 Hz, 1H), 4.19 (d, *J*=12.1 Hz, 1H), 4.03 (q, *J*=6.6 Hz, 1H), 1.58 (s, 3H), 1.45 (s, 3H), 1.25 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.6 Hz, 3H).

Example 6

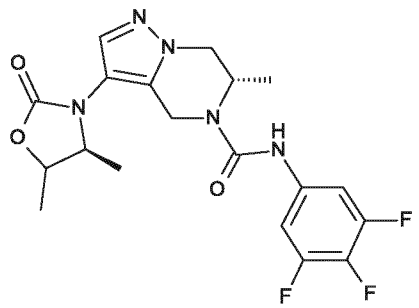
(6S)-6-methyl-N-[2-(trifluoromethyl)-4-pyridyl]-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



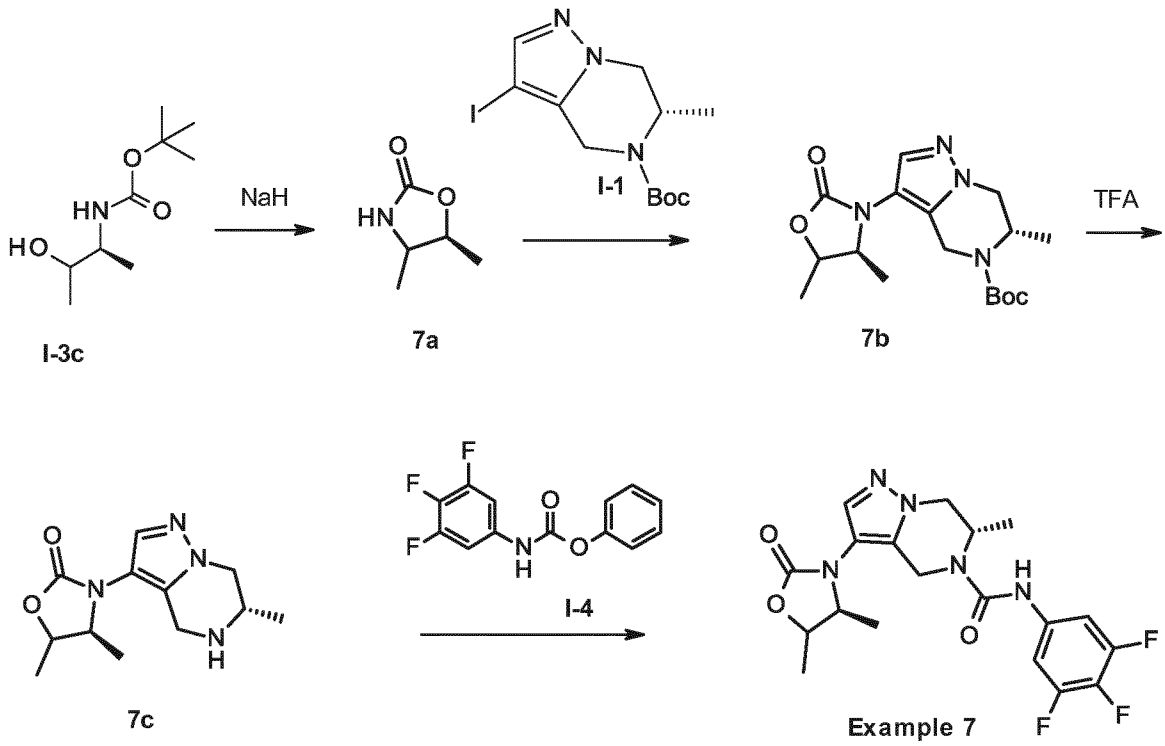
The Example **6** was prepared in analogy to Example **1** by using phenyl N-(2-trifluoromethyl-4-pyridyl)carbamate (Intermediate **I-6**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). Example **6** (15 mg) was obtained as a white solid. LCMS ($M+H^+$): 453.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.49 (d, *J*=5.6 Hz, 1H), 8.03 (d, *J*=2.0 Hz, 1H), 7.76 (dd, *J*=2.0, 5.7 Hz, 1H), 7.61 (s, 1H), 5.11 (d, *J*=16.9 Hz, 1H), 5.06 - 4.99 (m, 1H), 4.48 (d, *J*=16.8 Hz, 1H), 4.35 (dd, *J*=4.3, 12.8 Hz, 1H), 4.20 (dd, *J*=1.1, 12.8 Hz, 1H), 4.03 (q, *J*=6.5 Hz, 1H), 1.59 (s, 3H), 1.45 (s, 3H), 1.26 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H).

Example 7

(6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of (6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 7)

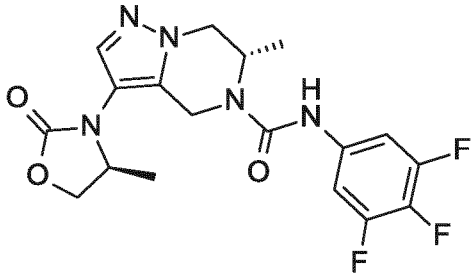
The title compound was prepared in analogy to Example **1** by using tert-butyl N-[(1S)-2-hydroxy-1-methyl-propyl]carbamate (compound **I-3c**) instead of methyl tert-butyl N-[(1S)-2-hydroxy-1,2-dimethyl-propyl]carbamate (compound **1d**). Final separation by SFC (Column: Chiralpak AD-3 100×4.6 mm I.D., 3um; Mobile phase: ethanol (0.05% DEA) in CO_2 from 5% to 40%; Wavelength: 220nm) gave **Example 7** as two separated isomers, **Example 7-1** and **Example 7-2**.

Example 7-1: 8 mg, white solid, LCMS ($M+H^+$): 424.2, ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 7.71 (s, 1H), 7.43 (s, 1H), 7.25 - 7.14 (m, 2H), 5.16 - 4.89 (m, 3H), 4.38 - 4.20 (m, 3H), 4.03 (dd, *J*=1.6, 12.9 Hz, 1H), 1.46 (d, *J*=6.7 Hz, 3H), 1.34 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.7 Hz, 3H).

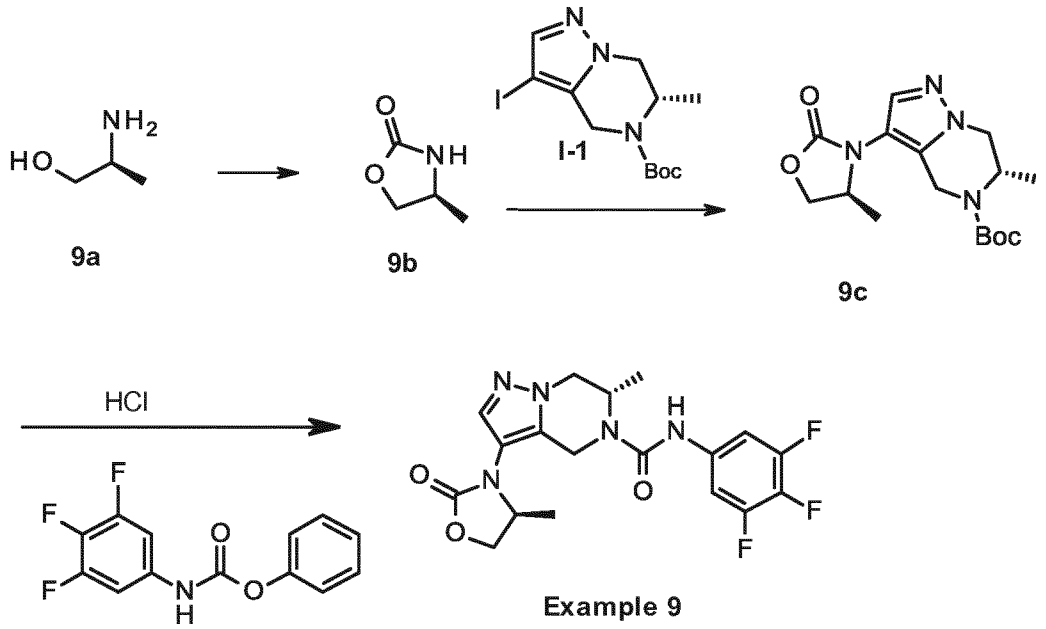
Example 7-2: 40 mg, white solid, LCMS ($M+H^+$): 424.2, ^1H NMR (400MHz, CHLOROFORM-d) δ ppm 7.76 (s, 1H), 7.41 (s, 1H), 7.23 - 7.11 (m, 2H), 5.16 - 5.08 (m, 1H), 5.04 (d, *J*=16.7 Hz, 1H), 4.44 - 4.35 (m, 1H), 4.31 (d, *J*=16.7 Hz, 1H), 4.22 (dd, *J*=5.1, 12.9 Hz, 1H), 4.03 (dd, *J*=1.6, 12.9 Hz, 1H), 3.96 - 3.86 (m, 1H), 1.59 (d, *J*=6.3 Hz, 3H), 1.38 - 1.26 (m, 6H)

Example 9

(6S)-6-methyl-3-[(4S)-4-methyl-2-oxo-oxazolidin-3-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of (4S)-4-methyloxazolidin-2-one (compound 9b)

To a mixture of (2S)-2-aminopropan-1-ol (compound **9a**, 5 g, 66.57 mmol) and TEA (20.21 g, 199.71 mmol) in DCM (50 mL) at 0 °C was added a solution of triphosgene (7.90 g, 26.63 mmol) in DCM (20 mL) dropwise. The mixture was then stirred at room temperature for 18 hours and then concentrated and purified by silica gel column chromatography (DCM: MeOH=20:1) to give compound **9b** (1.5 g, crude) as a colorless oil. ^{1}H NMR: (400MHz, $CDCl_3$) δ ppm 4.52 - 4.47 (m, 1H), 4.04 - 3.98 (m, 1H), 3.96 - 3.92 (m, 1H), 1.29 (d, *J*=6.0 Hz, 3H).

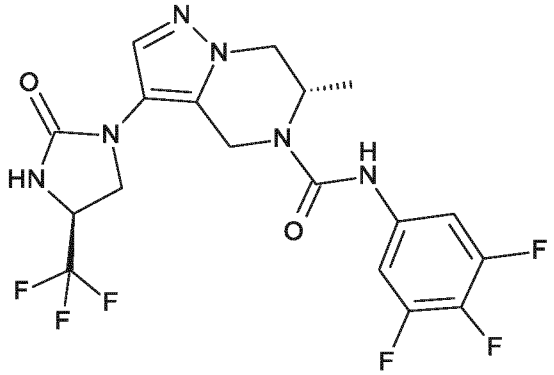
Preparation of (6S)-6-methyl-3-[(4S)-4-methyl-2-oxo-oxazolidin-3-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 9)

The **Example 9** was prepared in analogy to Example **1** by using (4S)-4-methyloxazolidin-2-one (compound **9b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**). **Example 9** (56 mg) was obtained as a white solid, LCMS (M+H$^+$): 410.1, ^{1}H NMR (400MHz, $CDCl_3$) δ

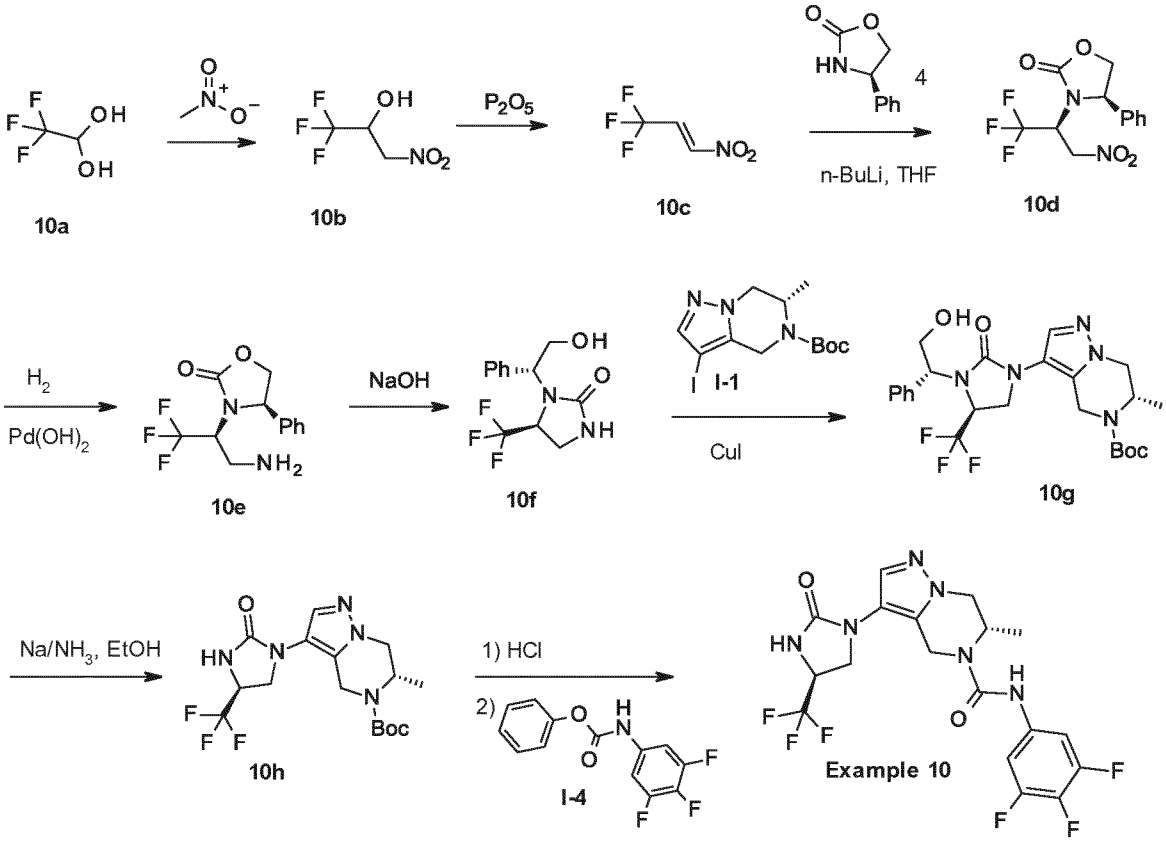
ppm 7.47 - 7.42 (m, 1H), 7.17 - 7.08 (m, 2H), 5.10 (m, *J*=6.2 Hz, 1H), 5.00 (d, *J*=16.6 Hz, 1H), 4.69 (t, *J*=8.5 Hz, 1H), 4.40 - 4.29 (m, 2H), 4.17 (dd, *J*=5.0, 12.9 Hz, 1H), 4.10 (dd, *J*=7.1, 8.5 Hz, 1H), 4.04 (d, *J*=12.9 Hz, 1H), 1.35 (d, *J*=6.1 Hz, 3H), 1.28 (d, *J*=7.0 Hz, 3H).

Example 10

(6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of 1,1,1-trifluoro-3-nitro-propan-2-ol (compound 10b)

To a mixture of 2,2,2-trifluoroethane-1,1-diol (compound **10a**, 25.0 g, 161.6 mmol) in CH_3NO_2 (29.5 g, 484.7 mmol) was added Na_2CO_3 (1.8 g, 16.2 mmol), the reaction mixture was stirred at 60°C for 3 hours, then cooled to room temperature and stirred for 12 hours. The reaction mixture was partitioned between EtOAc (400 mL) and H_2O (200 mL). The organic phase was washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give compound **10b** (35.0 g, crude) as green-yellow liquid which was used in next step directly.

Step 2: preparation of (E)-3,3,3-trifluoro-1-nitro-prop-1-ene (compound 10c)

A mixture of 1,1,1-trifluoro-3-nitro-propan-2-ol (compound **10b,** 35.0 g, crude) and P_2O_5 (22.9 g, 161.6 mmol) was stirred at 90 °C for 1 hour. The mixture was submitted to fractional distillation at atmospheric pressure (distilled at 83-85°C), and compound **10c** (5.2 g) was obtained as a green-yellow liquid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.45 - 7.34 (m, 1H), 7.04 (qd, *J*=6.5, 13.2 Hz, 1H).

Step 3: preparation of (4R)-4-phenyl-3-[(1S)-2,2,2-trifluoro-1-(nitromethyl)ethyl]oxazolidin-2-one (compound 10d)

A solution of (E)-3,3,3-trifluoro-1-nitro-prop-1-ene(compound **10c**, 5.0 g, 35.4 mmol) in THF (80 mL) was cooled to -75 °C, n-BuLi (12.7 mL, 31.9 mmol) was added dropwise, the reaction mixture was stirred at the same temperature for 1 hour. Then (4R)-4-phenyloxazolidin-2-one (4.6 g, 28.4 mmol) dissolved in THF (20 mL) was added dropwise. After being stirred for further 0.5 hour, the reaction was quenched by saturated aqueous NH_4Cl solution, and the mixture was allowed to warm to room temperature slowly and stirred for 12 h, and then partitioned between EtOAc (200 mL) and H_2O (200 mL). Organic phase was washed with brine (100 mL) and concentrated to give compound **10d** (12.3 g, crude) as light yellow solid. ^{1}H NMR (300MHz, CHLOROFORM-d) δ ppm 7.45 - 7.38 (m, 3H), 7.29 - 7.24 (m, 2H), 5.44 (dd, *J*=8.5, 14.3 Hz, 1H), 4.94 - 4.88 (m, 1H), 4.74 - 4.66 (m, 2H), 4.36 - 4.28 (m, 1H), 4.27 - 4.19 (m, 1H).

Step 4: preparation of (4R)-3-[(1S)-1-(aminomethyl)-2,2,2-trifluoro-ethyl]-4-phenyl-oxazolidin-2-one (compound 10e)

A mixture of (4R)-4-phenyl-3-[(1S)-2,2,2-trifluoro-1-(nitromethyl)ethyl]oxazolidin-2-one (compound **10d**, 12.3 g, 40.4 mmol) and $Pd(OH)_2$ (2.8 g, 4.0 mmol) in MeOH (200 ml) was stirred for 12 hours under H_2 (50 psi) atmosphere at room temperature. The reaction mixture was filtered and the filtrate was concentrated to give compound **10e** (11.5 g, crude) as a brown solid.

Step 5: preparation of (5S)-1-[(1R)-2-hydroxy-1-phenyl-ethyl]-5-(trifluoromethyl)imidazolidin-2-one (compound 10f)

To a solution of (4R)-3-[(1S)-1-(aminomethyl)-2,2,2-trifluoro-ethyl]-4-phenyl-oxazolidin-2-one (compound **10e**, 11.5 g, 41.95 mmol) in MeOH (120 ml) was added NaOH (10.1 g, 251.74 mmol). The reaction mixture was stirred for 2 hours at 80 °C. After cooled to 0 °C, the mixture was neutralized by careful addition of aqueous solution of HCl (3M), and then extracted twice with EtOAc (500 mL). The combined organic layer was concentrated and the residue was purified by column chromatography (PE/EtOAc=1/1) to give a crude product (2.0 g). The crude product was further purified by prep-HPLC to give compound **10f** (0.6 g) as a colorless oil. LCMS ($M+H^+$): 275.0

Step 6: preparation of tert-butyl (6S)-3-[(4S)-3-[(1R)-2-hydroxy-1-phenyl-ethyl]-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 10g)

Compound **10g** was prepared in analogy to tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) by using (5S)-1-[(1R)-2-hydroxy-1-phenyl-ethyl]-5-(trifluoromethyl)imidazolidin-2-one (compound **10f**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**). Compound **10g** was obtained as a brown solid (0.42 g). LCMS: ($M+H^+$): 510.1.

Step 7: preparation of tert-butyl (6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 10h)

NH_3 gas was bubbled into THF (40 mL) at -70 °C for 5 mins, then Na (45.1 mg, 1.96 mmol) was added slowly, and five drops of EtOH was added. After 10 minutes, tert-butyl (6S)-3-[(4S)-3-[(1R)-2-hydroxy-1-phenyl-ethyl]-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **10g**, 200.0 mg, 0.39 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -70 °C for 20 mins and then poured into saturated aqueous solution of NH_4Cl (100 mL), and extracted with EtOAc three times (100 mL). The organic layer was concentrated and the residue was purified by prep-TLC (DCM/MeOH=10/1) to give compound **10h** as a brown solid, (145.0 mg). LCMS: ($M+H^+$): 390.1.

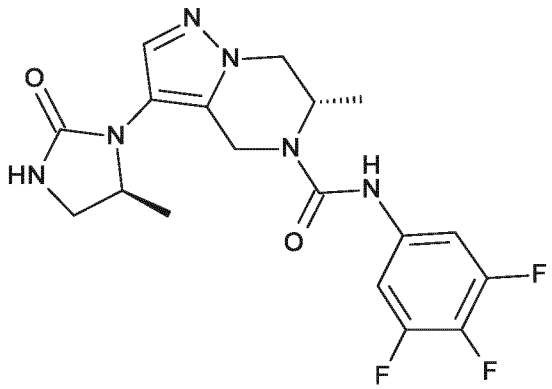
Preparation of (6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 10)

The Example **10** was prepared in analogy to Example **1** by using tert-butyl (6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **10h**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**).

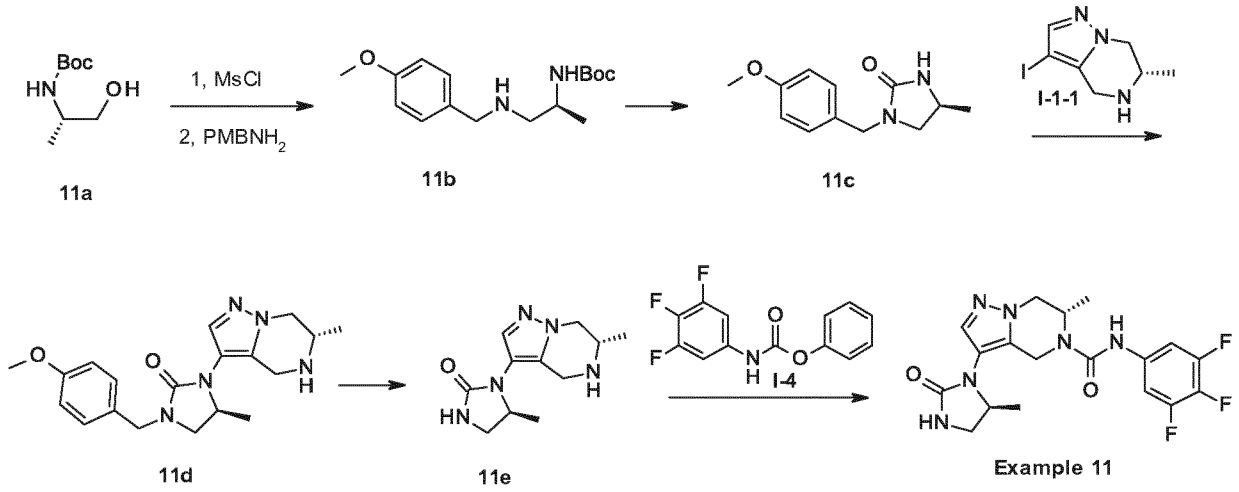
Example **10** (41 mg) was obtained as a white solid. LCMS: ($M+H^+$): 463.0, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.61 (s, 1H), 7.35 - 7.24 (m, 2H), 5.08 (d, *J*=16.8 Hz, 1H), 4.99 - 4.95 (m, 1H), 4.55 - 4.44 (m, 2H), 4.29 (dd, *J*=4.4, 12.8 Hz, 1H), 4.23 - 4.11 (m, 2H), 3.93 (dd, *J*=4.3, 10.1 Hz, 1H), 1.26 (d, *J*=6.8 Hz, 1H).

Example 11

(6S)-6-methyl-3-[(5S)-5-methyl-2-oxo-imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl N-[(1S)-2-[(4-methoxyphenyl)methylamino]-1-methyl-ethyl]carbamate (compound 11b)

To a solution of tert-butyl N-[(1S)-2-hydroxy-1-methyl-ethyl]carbamate (compound **11a**, 4.0 g, 22.8 mmol) and Et_3N (6.9 g, 68.4 mmol) in DCM (150 mL) was added MsCl (3.2 g, 27.4 mmol) at 0 °C. The reaction was stirred at 0~10 °C for 2 hours and then quenched with $NaHCO_3$ (50 mL), washed with brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_3CN (150 mL), to which were added K_2CO_3 (6.3 g, 45.6 mmol) and $PMBNH_2$ (3.2 g, 22.8 mmol). The reaction was stirred at 50 °C for 16 hours. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatograph (PE: EtOAc= 1:3) to give compound **11b** (1.7 g) as a yellow oil, LCMS $(M+H)^+$: 295.2.

Step 2: preparation of (4S)-1-[(4-methoxyphenyl)methyl]-4-methyl-imidazolidin-2-one (compound 11c)

To a solution of tert-butyl N-[(1S)-2-[(4-methoxyphenyl)methylamino]-1-methyl-ethyl]carbamate (compound **11b**, 1.7 g, 5.8 mmol) in THF (50 mL) was added KOtBu (1.9 g, 17.3 mmol) at room temperature in portions. The reaction was stirred at 80 °C for 3 hours. After cooled to room temperature, the reaction was quenched with aqueous solution of HCl (11.5 mL, 1 M) and extracted with EtOAc twice (15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give compound **11c** (250.0 mg,) as a white solid, LCMS $(M+Na)^+$: 243.1.

Step 3: preparation of(4S)-1-[(4-methoxyphenyl)methyl]-4-methyl-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]imidazolidin-2-one (compound 11d)

A mixture of (4S)-1-[(4-methoxyphenyl)methyl]-4-methyl-imidazolidin-2-one (compound **11c**, 125.0 mg, 0.57 mmol), (6S)-3-iodo-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (**Intermediate I-1-1**, 164.2 mg, 0.62 mmol,) K_3PO_4 (242.0 mg, 1.14 mmol), CuI (28.6 mg, 0.15 mmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (21.3 mg, 0.15 mmol) in dioxane (5.0 mL) was stirred at 110 °C for 16 hours under N_2. The reaction mixture was filtered, and the filtrate was concentrated, the residue was purified by prep-HPLC to give compound **11d** (10.0 mg) as a green solid, LCMS $(M+H)^+$ = 356.2.

Step 4: preparation of (5S)-5-methyl-1-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]imidazolidin-2-one (compound 11e)

To a mixture of (4S)-1-[(4-methoxyphenyl)methyl]-4-methyl-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]imidazolidin-2-one (compound **11d**, 10.0 mg, 0.03 mol) in THF (1.0 mL) and MeOH (1.0 mL) was added $Pd(OH)_2$ (1.0 mg) and a drop of HCl aqueous solution at room temperature. The reaction mixture was stirred at 40 °C under 50 psi of H_2 for 24

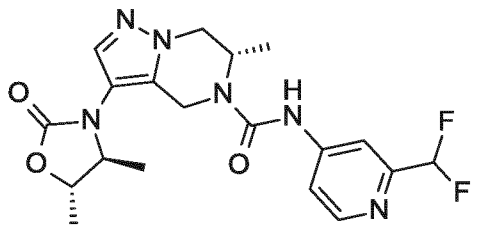
hours. The reaction mixture was filtered, and the filtrate was concentrated to give compound **11e** (8.3 mg, crude) as a yellow solid, which was used in the next step directly.

Step 5: preparation of (6S)-6-methyl-3-[(5S)-5-methyl-2-oxo-imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 11)

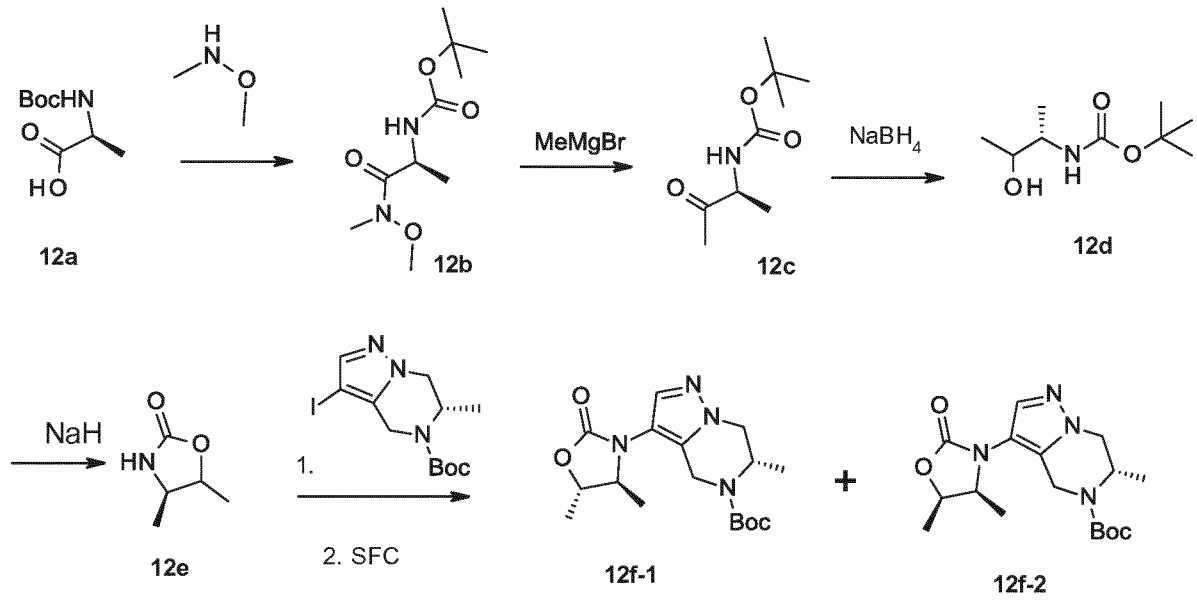
To a mixture of (5S)-5-methyl-1-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]imidazolidin-2-one (compound **11e**, 8.3 mg, 0.04 mmol) and DIPEA (18.1 mg, 0.14 mmol) in DMF (1.0 mL) was added phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 13.4 mg, 0.05 mmol). The mixture was stirred at room temperature for 2 hours, and then purified by prep-HPLC to give Example **11** (7 mg) as a colorless oil. LCMS ($M+H^+$): 409.2. ^1H NMR (400MHz, DMSO-d_6) δ ppm 9.14 (br. s., 1H), 7.47 - 7.42 (m, 3H), 6.73 (s, 1H), 4.94 (d, *J*=16.9 Hz, 1H), 4.90 - 4.82 (m, 1H), 4.27 - 4.18 (m, 2H), 4.15 - 4.08 (m, 1H), 4.04 - 3.95 (m, 1H), 3.55 (t, *J*=8.7 Hz, 1H), 2.98 (t, *J*=8.3 Hz, 1H), 1.14 (d, *J*=6.1 Hz, 3H), 1.09 (d, *J*=6.7 Hz, 3H).

Example 12

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



Preparation of tert-butyl (6S)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 12f-1) and tert-butyl (6S)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 12f-2)



Step 1: preparation of tert-butyl N-[(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxo-ethyl]carbamate (compound 12b)

To a stirred solution of (2S)-2-(tert-butoxycarbonylamino)propanoic acid (compound **12a**, 20.0 g, 105.7 mmol) in THF (300 mL) were added HATU (60.3 g, 158.5 mmol), TEA (26.7 g, 264.2 mmol) and N-methoxymethanamine (15.5 g, 158.5 mmol) at 0 °C. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 15 hours, and then diluted with EA (200 mL), was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (PE: EtOAc=1:1) to give compound **12b** (21.0 g) as a white solid.

Step 2: preparation of tert-butyl N-[(1S)-1-methyl-2-oxo-propyl]carbamate (compound 12c)

To a solution of tert-butyl N-[(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxo-ethyl]carbamate (compound **12b**, 16.0 g, 68.88 mmol) in THF (200 ml) was added dropwise MeMgBr (48.2 ml, 144.65 mmol) at 0 °C. The reaction mixture was stirred at room temperature under N_2 for 18 hours. The reaction mixture was cautiously quenched by adding NH_4Cl aqueous solution (200 mL) and extracted with EtOAc three times (200 mL), the organic layer was washed with brine (200.0 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (PE: EtOAc=5:1) to give compound **12c** (8.9 g) as a white solid.

Step 3: preparation of tert-butyl N-[(1S)-2-hydroxy-1-methyl-propyl]carbamate (compound 12d)

To a solution of tert-butyl N-[(1S)-1-methyl-2-oxo-propyl]carbamate (compound **12c**, 2.0 g, 10.7 mmol) in THF (20 mL) and MeOH (5 mL) was added $NaBH_4$ (444.5 mg, 11.7 mmol) in

one portion at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc 3 times (10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give compound **12d** (2.25 g, crude) as a color less oil.

Step 4: preparation of (4R)-4,5-dimethyloxazolidin-2-one (compound 12e)

To a solution of tert-butyl N-[(1S)-2-hydroxy-1-methyl-propyl]carbamate (1.25 g, 6.6 mmol) in toluene (40.0 mL) was added NaH (660.5 mg, 16.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, and then quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc three times (20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give compound **12e** (800.0 mg, crude) as a yellow oil, which was used in the next step directly.

Step 4: Preparation of tert-butyl (6S)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 12f-1) and tert-butyl (6S)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 12f-2)

An oven-dried resealable Schlenk tube was charged with (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (187.8 mg, 1.32 mmol), K_3PO_4 (2.8 g, 13.2 mmol), CuI (251.4 mg, 1.32 mmol), (4R)-4,5-dimethyloxazolidin-2-one (800.0 mg, 6.6 mmol), tert-butyl (6S)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (**compound I-1d**, 2.4 g, 6.6 mmol) and dioxane (25 mL) under N_2. The mixture was stirred at 110 °C for 16 hours. After cooled to room temperature, the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel chromatograph (PE: EtOAc= 1:1) and then Prep-HPLC to give tert-butyl (6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate as a yellow oil (1.3 g), which was submitted to chiral SFC (Column: Chiralpak AD-3 100×4.6 mm I.D., 3um; Mobile phase: ethanol (0.05% DEA) in CO_2 from 5% to 40%; Wavelength: 220 nm) to give compound **12f-1** (Peak 1) and compound **12f-2** (Peak 2) as white solids.

Compound **12f-1** (326 mg, Peak 1), LCMS $(M+Na)^+$: 373.2, ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.56 - 7.50 (m, 1H), 4.80 (d, *J*=17.2 Hz, 1H), 4.72 - 4.61 (m, 1H), 4.32 (quin, *J*=6.4 Hz, 1H), 4.22 - 4.15 (m, 1H), 4.15 - 4.03 (m, 2H), 3.80 (quin, *J*=6.4 Hz, 1H), 1.44 (s, 9H), 1.41 (d, *J*=6.1 Hz, 3H), 1.14 (d, *J*=6.1 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H)

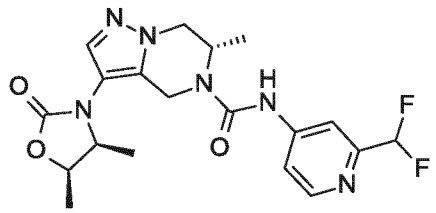
Compound **12f-2** (592 mg, Peak 2), LCMS $(M+Na)^+$: 373.2, ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.54 (s, 1H), 4.91 - 4.76 (m, 2H), 4.66 (br. s., 1H), 4.29 - 3.98 (m, 4H), 1.43 (s, 9H), 1.29 (d, *J*=6.5 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 6H), 1.01 (d, *J*=6.6 Hz, 3H).

Preparation of (6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 12)

The Example **12** was prepared in analogy to Example **1** by using tert-butyl (6S)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **12f-1**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) and phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). Example **12** (30 mg) was obtained as white solid. LCMS: $(M+H^+)$: 421.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.31 (d, *J*=5.7 Hz, 1H), 7.77 (d, *J*=2.1 Hz, 1H), 7.56 (dd, *J*=2.1, 5.7 Hz, 1H), 7.48 (s, 1H), 6.55 (t, *J*=56 Hz, 1H), 5.05 - 4.84 (m, 2H), 4.40 - 4.18 (m, 3H), 4.08 (dd, *J*=1.3, 12.8 Hz, 1H), 3.82 - 3.69 (m, 1H), 1.42 (d, *J*=6.2 Hz, 3H), 1.18 (d, *J*=6.1 Hz, 3H), 1.13 (d, *J*=6.8 Hz, 3H).

Example 13

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

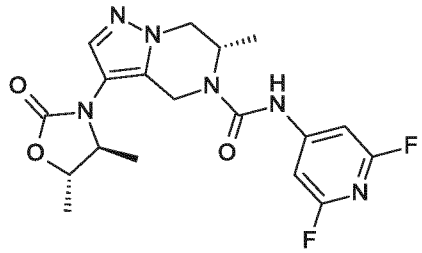


The **Example 13** was prepared in analogy to **Example 1** by using tert-butyl (6S)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **12f-2**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) and phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 13** (22 mg) was obtained as white solid. LCMS: $(M+H^+)$: 421.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.31 (d, *J*=5.7 Hz, 1H), 7.77 (d, *J*=2.2 Hz, 1H), 7.57 (dd, *J*=2.1, 5.7 Hz, 1H), 7.49 (s, 1H), 6.55 (t,

J=56 Hz, 1H), 5.03 - 4.80 (m, 3H), 4.35 (d, *J*=16.8 Hz, 1H), 4.27 - 4.14 (m, 2H), 4.08 (dd, *J*=1.3, 12.8 Hz, 1H), 1.32 (d, *J*=6.6 Hz, 3H), 1.13 (d, *J*=7.0 Hz, 3H), 1.08 (d, *J*=6.6 Hz, 3H).

Example 16

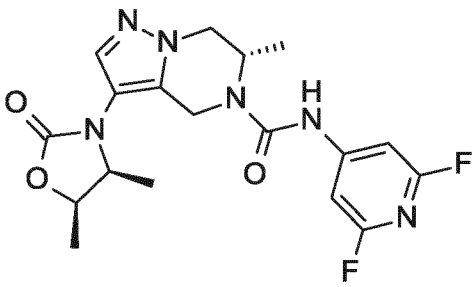
(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The **Example 16** was prepared in analogy to Example **1** by using tert-butyl (6S)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **12f-1**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) and phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 16** (22 mg) was obtained as white solid. LCMS: ($M+H^+$): 407.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.60 (s, 1H), 7.12 (s, 2H), 5.08 (d, *J*=16.9 Hz, 1H), 5.03 - 4.96 (m, 1H), 4.51 - 4.29 (m, 3H), 4.24 - 4.15 (m, 1H), 3.98 - 3.82 (m, 1H), 1.54 (d, *J*=6.2 Hz, 3H), 1.30 (d, *J*=6.1 Hz, 3H), 1.25 (d, *J*=6.8 Hz, 3H)

Example 17

(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

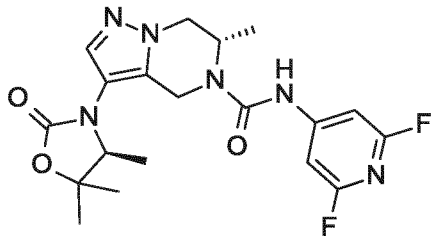


The **Example 17** was prepared in analogy to Example **1** by using tert-butyl (6S)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **12f-2**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-

trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) and phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 17** (28 mg) was obtained as white solid. LCMS: ($M+H^+$): 407.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.61 (s, 1H), 7.12 (s, 2H), 5.09 (d, *J*=16.8 Hz, 1H), 5.05 - 4.93 (m, 2H), 4.45 (d, *J*=16.9 Hz, 1H), 4.39 - 4.28 (m, 2H), 4.19 (dd, *J*=1.3, 12.8 Hz, 1H), 1.44 (d, *J*=6.6 Hz, 3H), 1.25 (d, *J*=6.8 Hz, 3H), 1.20 (d, *J*=6.6 Hz, 3H).

Example 18

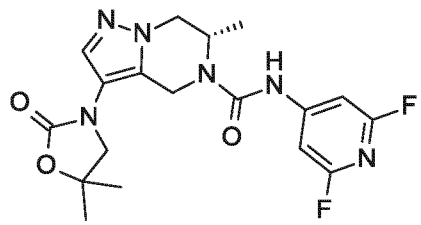
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



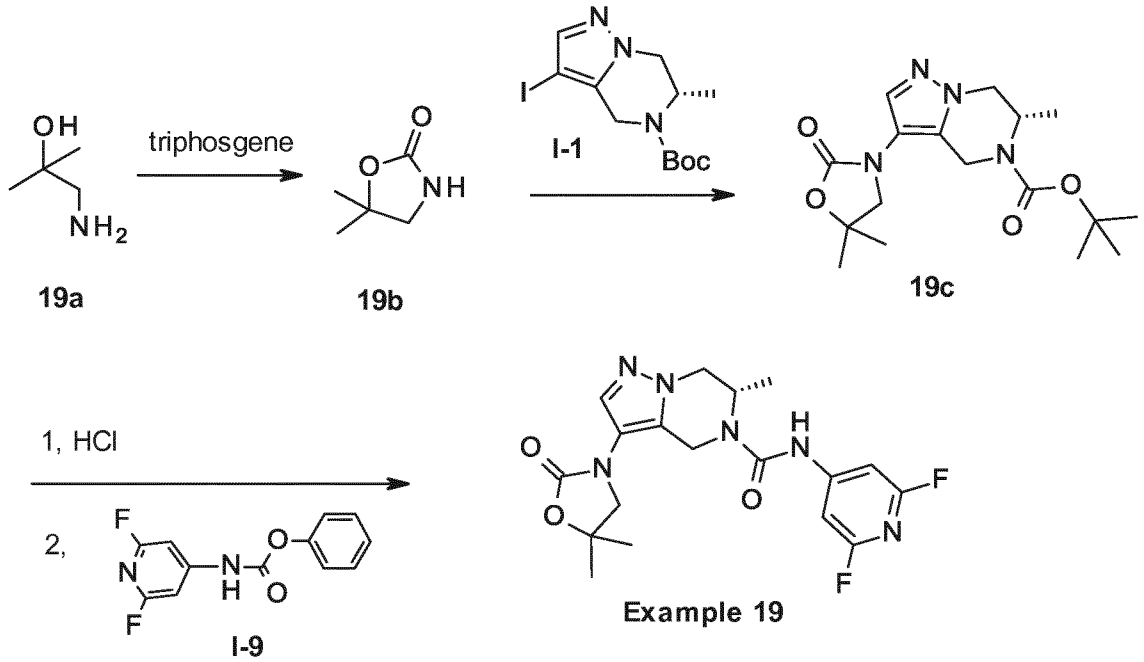
The **Example 18** was prepared in analogy to **Example 1** by using phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 18** (34 mg) was obtained as a white solid. LCMS ($M+H^+$): 421.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.61 (s, 1H), 7.11 (s, 2H), 5.08 (d, *J*=16.9 Hz, 1H), 5.04 - 4.96 (m, 1H), 4.46 (d, *J*=16.9 Hz, 1H), 4.34 (dd, *J*=4.3, 12.8 Hz, 1H), 4.19 (dd, *J*=1.2, 12.8 Hz, 1H), 4.03 (q, *J*=6.6 Hz, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 1.25 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H).

Example 19

(6S)-N-(2,6-difluoro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of 5,5-dimethyloxazolidin-2-one (compound 19b)

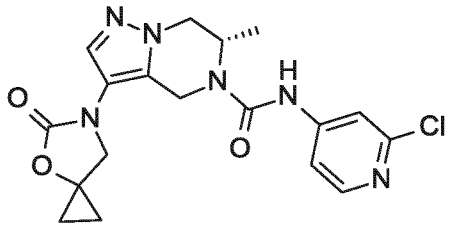
To a mixture of 1-amino-2-methyl-propan-2-ol (40.0 g, 448.9 mmol) and TEA (136.3 g, 1.35 mmol) in DCM (500.0 mL) was added a solution of triphosgene (53.1 g, 179.6 mmol) in DCM (100.0 mmol) at 0 °C during 1 hour, then the mixture was warmed to room temperature and stirred for 1 hour. The mixture was concentrated and the residue was purified by chromatograph (DCM/MeOH=10/1) to give compound **19b** (38.3 g) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 7.55 - 7.23 (m, 1H), 3.20 (d, *J*=0.6 Hz, 2H), 1.34 (s, 6H).

Preparation of (6S)-N-(2,6-difluoro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 19)

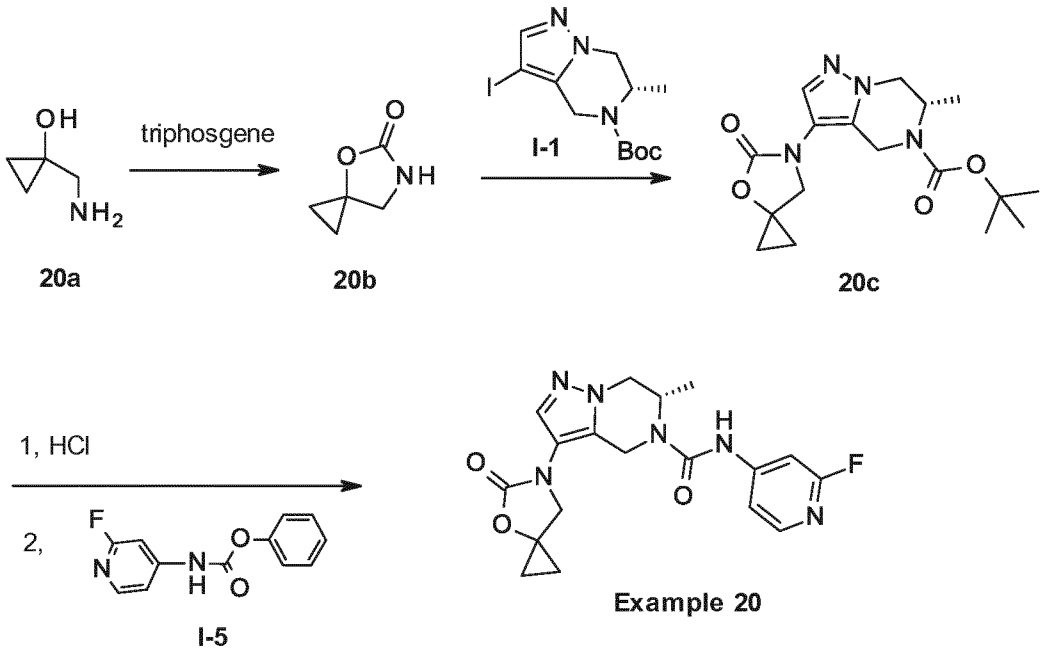
The **Example 19** was prepared in analogy to **Example 1** by using 5,5-dimethyloxazolidin-2-one (compound **19b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 19** (44 mg) was obtained as a white solid. LCMS (M+H$^+$): 407.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.64 (s, 1H), 7.10 (s, 2H), 5.12 (d, *J*=16.9 Hz, 1H), 5.05 - 4.94 (m, 1H), 4.58 (d, *J*=16.9 Hz, 1H), 4.31 (dd, *J*=4.4, 12.7 Hz, 1H), 4.17 (dd, *J*=1.0, 12.8 Hz, 1H), 3.89 - 3.75 (m, 2H), 1.58 (s, 6H), 1.28 (d, *J*=6.8 Hz, 3H).

Example 20

(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of 4-oxa-6-azaspiro[2.4]heptan-5-one (compound 20b)

The compound **20b** was prepared in analogy to 5,5-dimethyloxazolidin-2-one (compound **19b**) by using 1-(aminomethyl)cyclopropanol instead of 1-amino-2-methyl-propan-2-ol(compound **19a**) and The compound **20b** (330.0 mg) was obtained as a white solid. ^{1}H NMR (400MHz, Chloroform-d) δ ppm 6.09 - 5.69 (m, 1H), 3.70 (s, 2H), 1.29 - 1.21 (m, 2H), 0.78 - 0.70 (m, 2H), 0.78 - 0.70 (m, 1H).

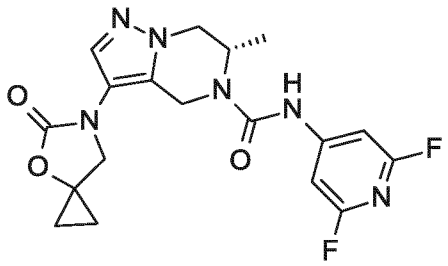
Preparation of (6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 20)

The **Example 20** was prepared in analogy to **Example 1** by using 4-oxa-6-azaspiro[2.4]heptan-5-one (compound **20b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-(2-chloro-4-pyridyl)carbamate (Intermediate **I-5**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 20** (15 mg) was obtained as a white solid. LCMS (M+H$^+$): 403.1, ^{1}H NMR (400MHz, METHANOL-d$_4$) δ ppm 8.15 (d, *J*=5.9 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.48 (dd, *J*=2.0, 5.8 Hz, 1H), 5.15 (d, *J*=17.0 Hz, 1H), 5.06 - 4.98

(m, 1H), 4.61 (d, *J*=17.0 Hz, 1H), 4.32 (dd, *J*=4.5, 12.8 Hz, 1H), 4.23 - 4.07 (m, 3H), 1.34 - 1.23 (m, 5H), 1.00 - 0.87 (m, 2H).

Example 21

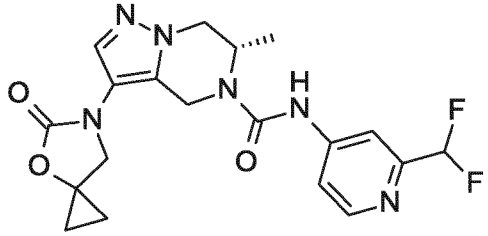
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The **Example 21** was prepared in analogy to **Example 1** by using 4-oxa-6-azaspiro[2.4]heptan-5-one (compound **20b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 21**(34 mg) was obtained as a white solid. LCMS ($M+H^+$): 405.1, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.68 (s, 1H), 7.12 (s, 2H), 5.15 (d, *J*=16.9 Hz, 1H), 5.06 - 4.96 (m, 1H), 4.60 (d, *J*=16.9 Hz, 1H), 4.32 (dd, *J*=4.4, 12.8 Hz, 1H), 4.23 - 4.07 (m, 3H), 1.36 - 1.20 (m, 5H), 0.96 - 0.88 (m, 2H).

Example 22

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

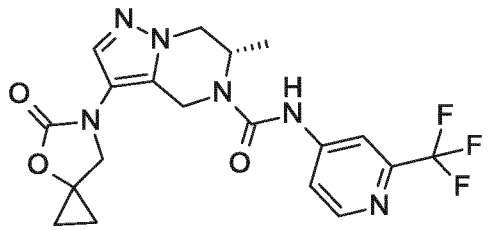


The **Example 22** was prepared in analogy to **Example 1** by using 4-oxa-6-azaspiro[2.4]heptan-5-one (compound **20b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 22** (40 mg) was obtained as a white solid. LCMS ($M+H^+$): 419.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 8.43 (d, *J*=5.7 Hz, 1H), 7.89 (d, *J*=2.1 Hz, 1H), 7.73 - 7.63 (m, 2H), 6.88 - 6.42 (m, 1H), 5.17 (d,

J=16.9 Hz, 1H), 5.05-5.02 (m, 1H), 4.61 (d, *J*=16.9 Hz, 1H), 4.33 (dd, *J*=4.4, 12.7 Hz, 1H), 4.26 - 4.07 (m, 3H), 1.41 - 1.17 (m, 5H), 1.01 - 0.83 (m, 2H).

Example 23

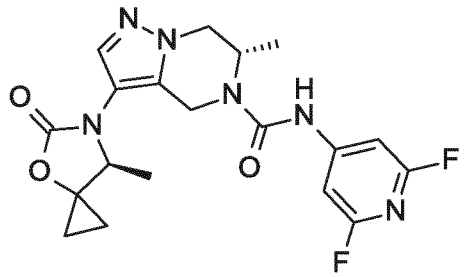
(6S)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-N-[2-(trifluoromethyl)-4-pyridyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



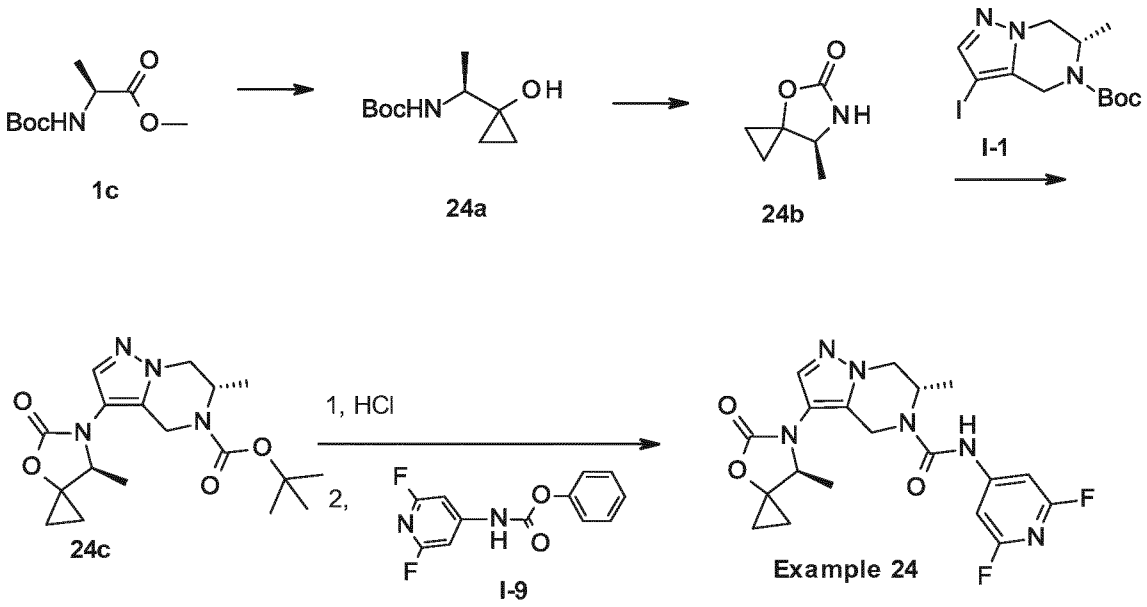
The **Example 23** was prepared in analogy to **Example 1** by using 4-oxa-6-azaspiro[2.4]heptan-5-one (compound **20b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-(2-trifluoromethyl-4-pyridyl)carbamate (Intermediate **I-6**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 22** (40 mg) was obtained as white solid. LCMS ($M+H^+$): 437.1, ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.49 (d, *J*=5.6 Hz, 1H), 8.04 (d, *J*=2.1 Hz, 1H), 7.76 (dd, *J*=2.1, 5.6 Hz, 1H), 7.68 (s, 1H), 5.17 (d, *J*=16.9 Hz, 1H), 5.07 - 5.00 (m, 1H), 4.62 (d, *J*=16.9 Hz, 1H), 4.33 (dd, *J*=4.5, 12.8 Hz, 1H), 4.24 - 4.06 (m, 3H), 1.35 - 1.20 (m, 5H), 0.97 - 0.88 (m, 2H).

Example 24

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of tert-butyl N-[(1S)-1-(1-hydroxycyclopropyl)ethyl]carbamate (compound 24a)

To a solution of methyl (2S)-2-(tert-butoxycarbonylamino)propanoate (compound **1c**, 2.0 g, 9.84 mmol) and Titanium(IV) isopropoxide (559.38 mg, 1.97 mmol) in THF (30 mL) was added ethylmagnesium bromide (9.84 mL, 29.52 mmol) dropwise over 1 hour at 0 °C. The mixture was stirred at room temperature for 17 hours, and then quenched with HCl (1.0 N, 20 mL). Water (50 mL) was added, and the mixture was extracted with EtOAc (50 mL). The organic phase was concentrated, and the residue was purified by column chromatography (PE:EtOAc=3:1) to afford compound **24a** (350 mg) as yellow oil. LCMS: ($M+H^+$): 202.1.

Preparation of (7S)-7-methyl-4-oxa-6-azaspiro[2.4]heptan-5-one (compound 24b)

To a solution of tert-butyl N-[(1S)-1-(1-hydroxycyclopropyl)ethyl]carbamate (compound **24a**, 350.0 mg, 1.74 mmol) in toluene (15 mL) was added sodium hydride (84 mg, 3.48 mmol), and the mixture was stirred at 80 °C for 2 hours. After cooled to room temperature, the mixture was quenched with ammonium chloride solution (20 mL) and extracted with EtOAc three times (20 mL). The combine organic phase was concentrated to afford compound **24b** (400 mg) as yellow oil. LCMS: ($M+H^+$): 128.1.

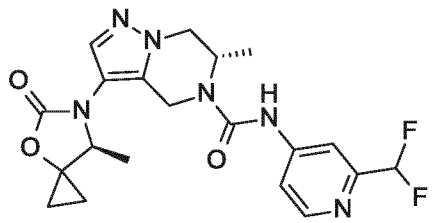
Preparation of (6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 24)

The **Example 24** was prepared in analogy to **Example 1** by using (7S)-7-methyl-4-oxa-6-azaspiro[2.4]heptan-5-one (compound **24b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of

phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 24** (15 mg) was obtained as a white solid. LCMS ($M+H^+$): 419.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.53 (s, 1H), 7.00 (s, 2H), 5.00 (d, *J*=16.9 Hz, 1H), 4.94 - 4.86 (m, 1H), 4.37 (d, *J*=16.9 Hz, 1H), 4.28 - 4.18 (m, 2H), 4.12 - 4.05 (m, 1H), 1.30 - 1.05 (m, 7H), 1.01 - 0.90 (m, 2H), 0.84 - 0.72 (m, 1H).

Example 25

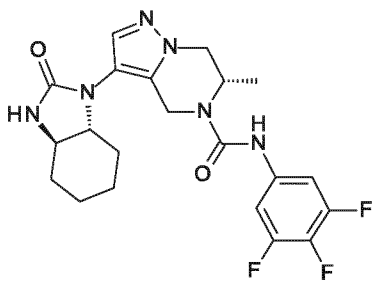
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



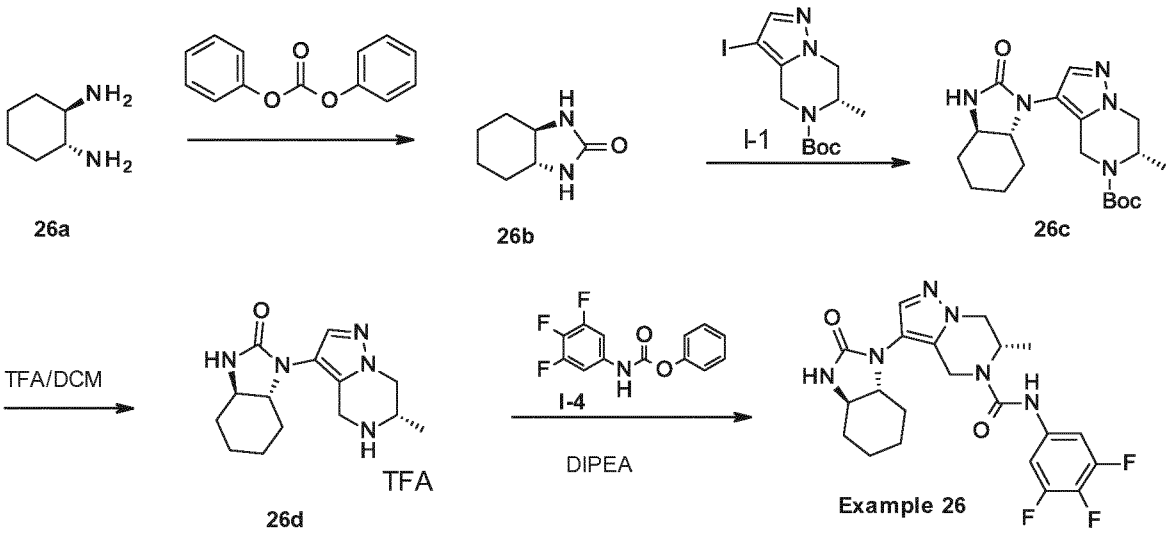
The **Example 25** was prepared in analogy to **Example 1** by using (7S)-7-methyl-4-oxa-6-azaspiro[2.4]heptan-5-one (compound **24b**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**) and phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**) instead of phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**). **Example 25** (20 mg) was obtained as a white solid. LCMS ($M+H^+$): 433.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.31 (d, *J*=5.7 Hz, 1H), 7.78 (d, *J*=2.1 Hz, 1H), 7.63 - 7.47 (m, 2H), 6.55 (d, *J*=56 Hz, 1H),, 5.01 (d, *J*=16.9 Hz, 1H), 4.96 - 4.87 (m, 1H), 4.39 (d, *J*=16.8 Hz, 1H), 4.29 - 4.19 (m, 2H), 4.09 (dd, *J*=1.2, 12.8 Hz, 1H), 1.21 - 1.08 (m, 7H), 1.02 - 0.92 (m, 2H), 0.84 - 0.72 (m, 1H).

Example 26

(6S)-3-[(3aR,7aR)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of (3aR,7aR)-1,3,3a,4,5,6,7,7a-octahydrobenzimidazol-2-one (compound 26b)

The mixture of diphenyl carbonate (7.5 g, 35.0 mmol) and (1R,2R)-cyclohexane-1,2-diamine (4.0 g, 35.0 mmol) in 2-propanol (40 mL) was refluxed overnight. The solvent was removed and the residue was purified by column chromatography (eluting with 50% EtOAc in petroleum ether) to afford compound **26b** (2.4 g). LCMS ($M+H^+$): 127.

Step 2: preparation of tert-butyl (6S)-3-[(3aR,7aR)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 26c)

An oven-dried re-sealable Schlenk tube was charged with (S)-tert-butyl 3-iodo-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (Intermediate **I-1**, 400 mg, 1.1 mmol), K_3PO_4 (468 mg, 2.2 mmol), CuI (83.9 mg, 0.44 mmol), and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (62.7 mg, 0.44 mmol), evacuated and backfilled with argon. Methyl (3aR,7aR)-hexahydro-1H-benzo[d]imidazol-2(3H)-one (compound **26b**, 201 mg, 1.43 mmol) in DMSO (5 ml) were added under nitrogen. The mixture was stirred at 110 °C for 2 hours under microwave, quenched with sat. aqueous solution of NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with sat. NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph to afford the product compound **26c** (260 mg). LCMS ($M+H^+$): 376.

Step 3: preparation of (3aR,7aR)-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-one 2,2,2-trifluoroacetic acid (compound 26d)

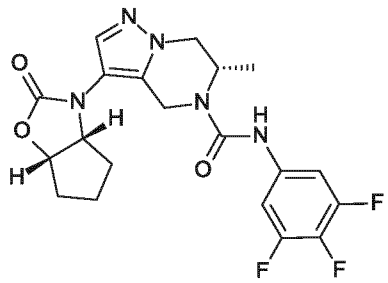
The mixture of tert-butyl (6S)-3-[(3aR,7aR)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **26c**, 260 mg, 692 μmol), 2,2,2-trifluoroacetic acid (2.0 mL) in DCM (5.0 mL) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to afford crude compound **26d** (283 mg). LCMS ($M+H^+$): 276.

Step 4: (6S)-3-[(3aR,7aR)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 26)

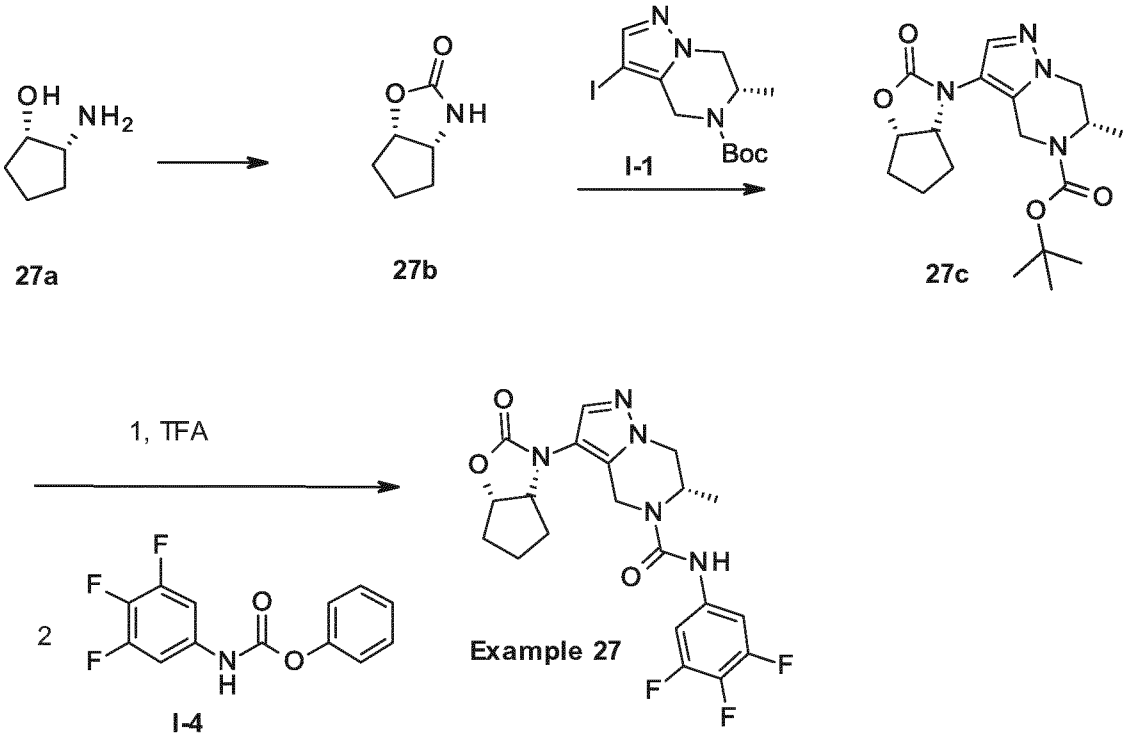
The crude compound **26d** (100 mg, 0.25 mmol) was dissolved in DCM (3 ml), to which were added DIPEA (0.5 mL), and phenyl (3,4,5-trifluorophenyl)carbamate (intermediate **I-4**, 80.0 mg, 0.30 mol). The reaction mixture was stirred at 50°C for 1 hour. The reaction mixture was cooled down, washed with ice-water, extracted with DCM twice. The combined organic phase was concentrated. The residue was purified by prepare-HPLC to afford **Example 26** (39 mg). LCMS ($M+H^+$): 449; ^1H NMR (400MHz, METHANOL-d_4) δ = 7.38 (s, 1H), 7.17 (dd, *J*=6.4, 10.3 Hz, 2H), 4.87 - 4.79 (m, 2H), 4.41 (d, *J*=16.8 Hz, 1H), 4.20 - 4.13 (m, 1H), 4.06 - 4.00 (m, 1H), 3.25 (br d, *J*=3.1 Hz, 1H), 3.15 (br d, *J*=10.9 Hz, 1H), 2.02 - 1.72 (m, 4H), 1.45 - 1.29 (m, 4H), 1.17 (d, *J*=7.0 Hz, 3H).

Example 27

(6S)-3-[(3aR,6aS)-2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of (3aR,6aS)-3,3a,4,5,6,6a-hexahydrocyclopenta[d]oxazol-2-one (compound 27b)

A mixture of (1S,2R)-2-aminocyclopentanol hydrochloride (compound **27a**, 500 mg, 3.63 mmol) and potassium hydroxide (1.83 g, 32.7 mmol) in water (25 mL) was stirred at 0 °C for 2 hours, then THF (50 mL) and triphosgene (2.16 g, 7.27 mmol) was added slowly, the reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was poured into 20 mL H_2O and extracted with EtOAc twice (50 mL). The combined organic layer was washed with sat. aqueous sloution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The residue was washed with n-heptane to give compound **27b** (260 mg) as a white solid. LCMS ($M+H^+$): 128.1.

Step 2: preparation of tert-butyl (6S)-3-[(3S,6aS)-2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 27c)

To a 10 mL microwave vial was added (3aR,6aS)-3,3a,4,5,6,6a-hexahydrocyclopenta[d]oxazol-2-one (compound **27b**, 52.5 mg, 0.41 mmol), (S)-tert-butyl 3-iodo-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (Intermediate **I-1**, 100 mg, 0.27 mmol), potassium phosphate (117 mg, 0.55 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (15.7 mg, 0.11 mmol) and copper (I) iodide (10.5 mg, 0.055 mmol) and DMSO (5 mL), the vial was capped and heated in the microwave at 105 °C for 2 hours. The reaction

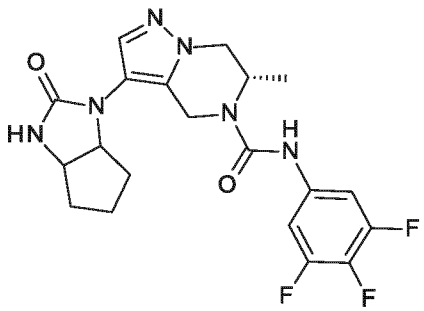
mixture was poured into EtOAc (50 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **27c** (100 mg) as a light brown oil. LCMS ($M+H^+$): 363.4.

Step 3: preparation of (6S)-3-[(3aR,6aS)-2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 27)

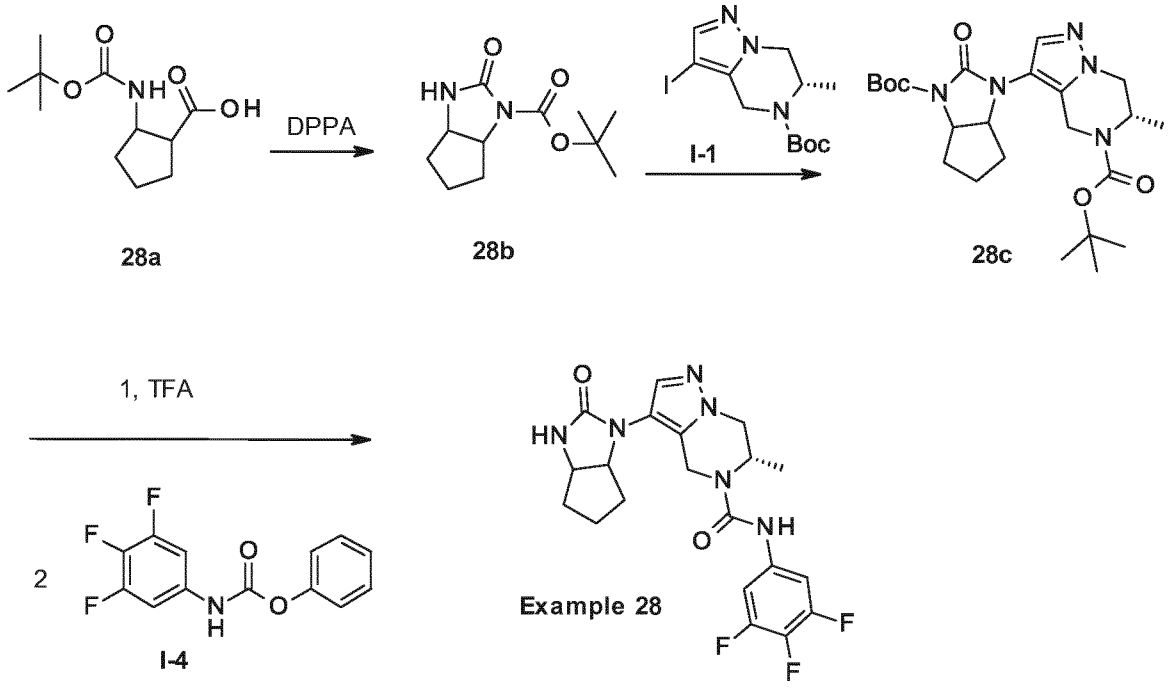
A mixture of tert-butyl (6S)-3-[(3S,6aS)-2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **27c**, 80 mg, 221 μmol) in DCM/TFA(2 mL, 1:1) was stirred at room temperature for 30 mins. The reaction mixture was concentrated and the residue was disolved in DMF (2 mL), then N-ethyl-N-isopropylpropan-2-amine (143 mg, 1.1 mmol), phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 70.8 mg, 265 μmol) were added. The reaction mixture was stirred at 70 °C for 1 hour, then purified by prep-HPLC to give **Example 27** (65 mg) as a white solid, LCMS ($M+H^+$): 436.2. ^1H NMR (400MHz, METHANOL-d4) δ ppm 7.53 (s, 1H), 7.19-7.13 (m, 2H), 5.07 (dd, *J*=5.3, 7.1 Hz, 1H), 4.87 - 4.78 (m, 2H), 4.61 - 4.54 (m, 1H), 4.42 (d, *J*=16.9 Hz, 1H), 4.20 (dd, *J*=4.5, 12.8 Hz, 1H), 4.05 (dd, *J*=0.9, 12.7 Hz, 1H), 2.05 - 1.94 (m, 1H), 1.80 - 1.64 (m, 4H), 1.60 - 1.47 (m, 1H), 1.16 (d, *J*=7.0 Hz, 3H).

Example 28

(6S)-6-methyl-3-(2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of tert-butyl 2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazole-3-carboxylate (compound 28b)

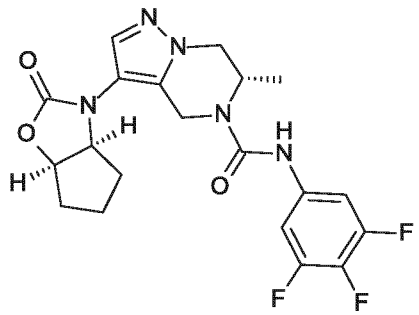
A mixture of cis 2-((tert-butoxycarbonyl)amino)cyclopentanecarboxylic acid (compound **28a**, 500 mg, 2.18 mmol) and 4-methylmorpholine (243 mg, 2.4 mmol) in DCE (10 mL) was stirred at room temperature for 10 mins, then diphenyl phosphorazidate (660 mg, 2.4 mmol) was added. After stirred at room temperature for 2 hours, the reaction mixture was heated to 75 °C for 6 hours, then diluted with H_2O and extracted with DCM (20 mL) two times. The combined organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The crude material was triturated in heptane (10 mL) to give compound **28b** (300 mg) as a white solid. LCMS ($M+H^+$): 227.1.

Preparation of (6S)-6-methyl-3-(2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 28)

The **Example 28** was prepared in analogy to **Example 27** by using tert-butyl 2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazole-3-carboxylate (compound **28b**) instead of (3aR,6aS)-3,3a,4,5,6,6a-hexahydrocyclopenta[d]oxazol-2-one (compound **27b**). **Example 28** (120 mg) was obtained as a white solid, LCMS (M+H+): 435.2, ^{1}H NMR (400MHz, METHANOL-d4) δ ppm 7.56 (d, *J*=3.3 Hz, 1H), 7.31-7.26 (m, 2H), 5.06 (d, *J*=16.6 Hz, 0.5H), 5.01 - 4.91 (m, 1.5H), 4.64 - 4.50 (m, 1.5H), 4.39 (d, *J*=16.6 Hz, 0.5H), 4.33 - 4.26 (m, 2H), 4.26 - 4.11 (m, 1H), 1.89 - 1.58 (m, 6H), 1.29 (d, *J*=6.8 Hz, 1.5H), 1.22 (d, *J*=6.8 Hz, 1.5H).

Example 29

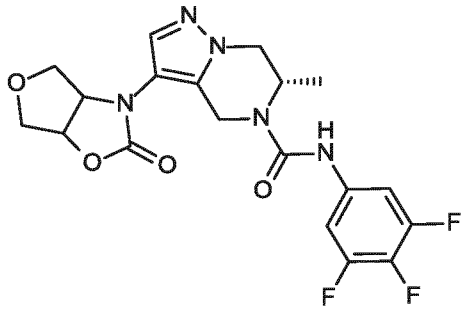
(6S)-3-[(3aS,6aR)-2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



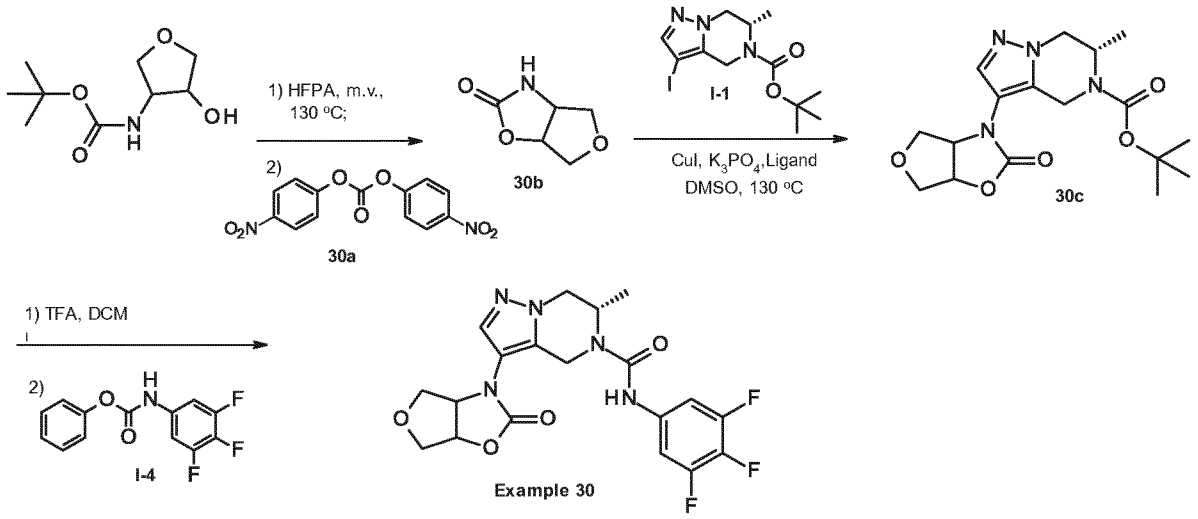
The **Example 29** was prepared in analogy to **Example 27** by using (1R,2S)-2-aminocyclopentanol hydrochloride instead of (1S,2R)-2-aminocyclopentanol hydrochloride (compound **27a**). **Example 29** (80 mg) was obtained as a white solid. LCMS ($M+H^+$): 436.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.52 (s, 1H), 7.19-7.12 (m, 2H), 5.11 - 5.03 (m, 1H), 4.95 (d, *J*=16.8 Hz, 1H), 4.90 - 4.83 (m, 1H), 4.54 (t, *J*=6.5 Hz, 1H), 4.28 (d, *J*=16.8 Hz, 1H), 4.23 - 4.14 (m, 1H), 4.11 - 4.00 (m, 1H), 2.05 - 1.95 (m, 1H), 1.84 - 1.65 (m, 4H), 1.63 - 1.51 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H).

Example 30

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: Preparation of 3a,4,6,6a-tetrahydro-3H-furo[3,4-d]oxazol-2-one (compound 30b)

The solution of tert-butyl N-(cis-4-hydroxytetrahydrofuran-3-yl)carbamate (CAS: 1631070-69-3, Pharmablock catalog PBLL8008, 220 mg, 1.08 mmol) in hexanfluoroisopropanol (5 mL) was heated under microwave at 130 °C for 3h. The solvent was removed, and the residue was dissolved in DCM (10 mL). To the solution was added DIEA (140 mg, 189 μl, 1.08 mmol) and bis(4-nitrophenyl) carbonate (compound **30a**, 329 mg, 1.08 mmol). The mixture was stirred at room temperature overnight. The solvent was removed to give crude compound **30b** (430mg, purity 30%) which was directly used for next step.

Step 2: Preparation of tert-butyl (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 30c)

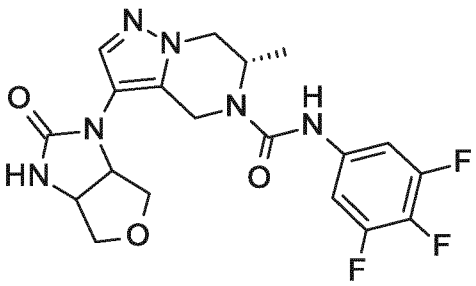
To a solution of (S)-tert-butyl 3-iodo-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (compound **30b**, 300 mg, 826 μmol), CuI (31.5 mg, 165 μmol), K_3PO_4 (351 mg, 1.65 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (47 mg, 330 μmol,) in DMSO (10 mL) was added 3a,4,6,6a-tetrahydro-3H-furo[3,4-d]oxazol-2-one (compound **30b**, 430mg, purity 30%) under argon. The mixture was stirred at 110 °C for 2h, quenched with sat. aqueous solution of NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with sat. NH_4Cl and brine, dried over Na_2SO_4 and concentrated to give crude compound **30c** (420 mg) which was directly used in next step. LCMS (M+1): 365.

Step 3: Preparation of (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

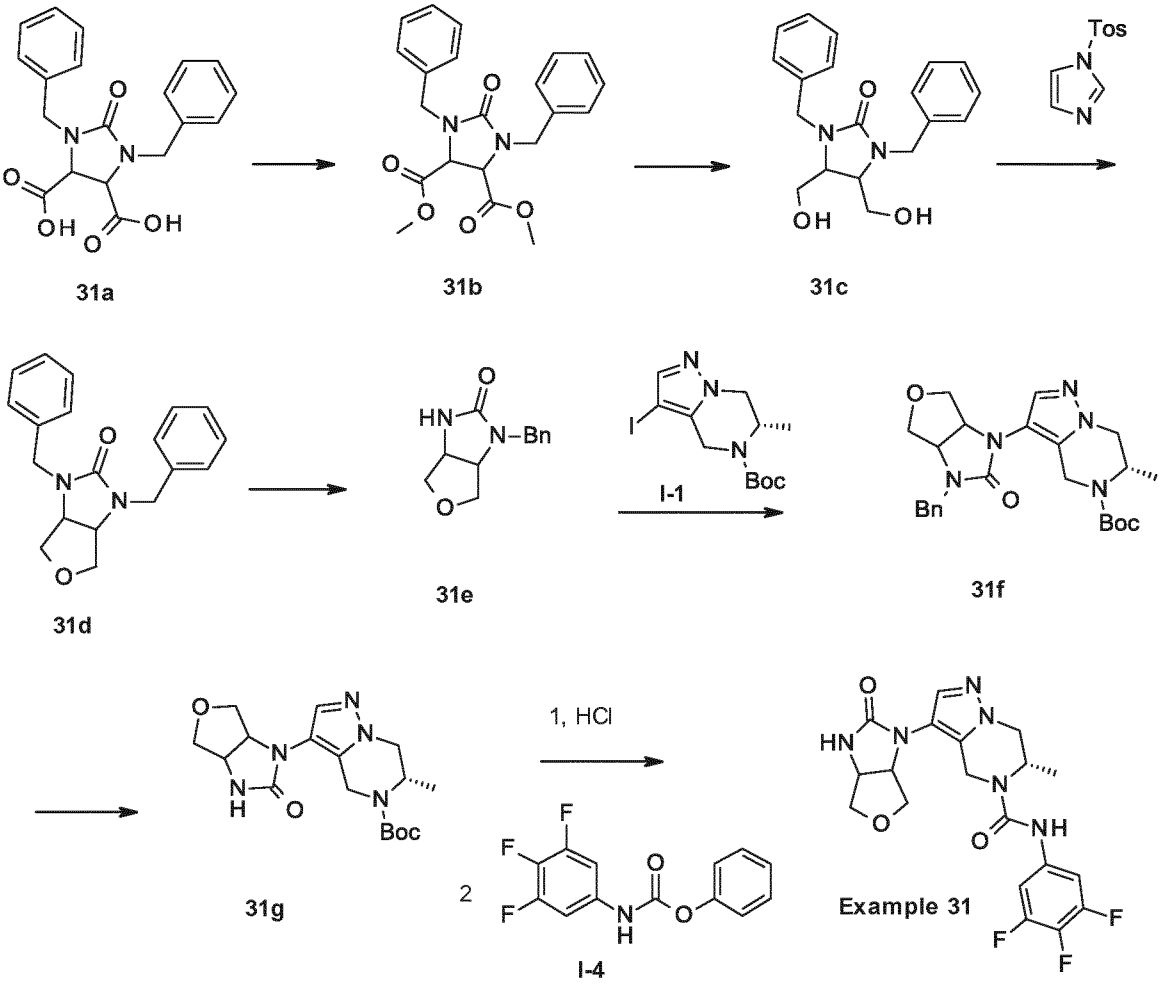
To a solution of tert-butyl (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **30c**, 420 mg, 1.15 mmol) in DCM (10 mL) was added TFA (3 mL), the mixture was stirred at room temperature for 30 min, then concentrated. The residue was further dried under high vacuum, and then dissolved in DCM (10 mL). To the solution was added DIEA (715 mg, 966 µl, 5.53 mmol) and phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 250 mg, 936 µmol). The mixture was stirred at room temperature overnight, then the solvent was removed to give a crude product, which was purified by prep-HPLC to give **Example 30** (30 mg) as a white powder. LCMS (M+1): 438. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.66 (s, 0.5H), 7.65 (s, 0.5 H), 7.29 (dd, *J*=6.4, 10.3 Hz, 2H), 5.34 - 5.29 (m, 1H), 5.07 (d, *J*=16.9 Hz, 0.5H), 5.02 - 4.95 (m, 1H), 4.95 (d, *J*=16.9 Hz, 0.5H), 4.85 - 4.76 (m, 1H), 4.53 (d, *J*=16.9 Hz, 0.5H), 4.43 (d, *J*=16.9 Hz, 0.5H), 4.36 - 4.26 (m, 1H), 4.25 - 4.13 (m, 2H), 4.01 (d, *J*=4.6 Hz, 0.5H), 3.98 (d, *J*=4.3 Hz, 0.5H), 3.71 (d, *J*=3.9 Hz, 0.5H), 3.68 (d, *J*=3.8 Hz, 0.5H), 3.55 - 3.47 (m, 1H), 1.28 (d, *J*=6.8 Hz, 1.5H), 1.24 (d, *J*=6.8 Hz, 1.5H).

Example 31

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of dimethyl 1,3-dibenzyl-2-oxo-imidazolidine-4,5-dicarboxylate (compound 31b)

To the mixture of 1,3-dibenzyl-2-oxo-imidazolidine-4,5-dicarboxylic acid (compound **31a**, 2.0 g, 5.6 mmol) in MeOH (20.0 mL) was added $SOCl_2$ (2.0 mL), the reaction mixture was stirred at 60 °C for 16 hours, and then concentrated. The residue was dissolved in EtOAc (20 mL) and the organic layer was washed with sat.$NaHCO_3$ twice (5 mL), dried over Na_2SO_4, filtered and concentrated to give compound **31b** (2.1 g) as a yellow solid. LCMS ($M+H^+$): 383.1

Step 2: preparation of 1,3-dibenzyl-4,5-bis(hydroxymethyl)imidazolidin-2-one (compound 31c)

To the mixture of dimethyl 1,3-dibenzyl-2-oxo-imidazolidine-4,5-dicarboxylate (compound **31b**, 2.1 g, 5.5 mmol) in THF (20.0 mL) was added $LiAlH_4$ (0.2 g, 5.5 mmol) at 0 °C, the mixture was then warmed to room temperature and stirred for 2 hours. The mixture was quenched carefully with H_2O (1.0 mL), concentrated and the residue was purified by chromatograph (EtOAc) to give compound **31c** (1.6 g) as yellow solid. LCMS ($M+H^+$): 327.1.

Step 3: preparation of 1,3-dibenzyl-3a,4,6,6a-tetrahydrofuro[3,4-d]imidazol-2-one (compound 31d)

To the mixture of 1,3-dibenzyl-4,5-bis(hydroxymethyl)imidazolidin-2-one (compound **31c**, 1.5 g, 4.60 mmol) in THF (20 mL) was added NaH (275.7 mg, 6.89 mmol) and 1-(p-tolylsulfonyl)imidazole (222.3 mg, 3.22 mmol) at 0 °C, the reaction mixture was stirred at room temperature for 16 hours and then concentrated. The residue was purified by prep-TLC (PE/EtOAc=3/1) to give compound **31d** (1.1 g) as a white solid, LCMS ($M+H^+$): 309.1.

Step 4: preparation of 3-benzyl-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-2-one (compound 31e)

To the mixture of 1,3-dibenzyl-3a,4,6,6a-tetrahydrofuro[3,4-d]imidazol-2-one (compound **31d**, 1.10 g, 3.57 mmol) in THF (20 mL) was bubbled in NH_3 for 10 minutes at -78 °C, then Na (856.0 mg, 35.67 mmol) and EtOH (1.0 mL) was added to the mixture. The resulting mixture was stirred at -78 °C for 30 mins and quenched with sat. NH_4Cl (5 mL). Then the reaction mixture was concentrated and the residue was suspended and stirred in THF (20 mL). After 30 mins, the mixture was filtered and the filtrate was concentrated to give compound **31e** (0.60 g) as a white solid. LCMS ($M+H^+$): 219.1.

Step 5: preparation of tert-butyl (6S)-3-(1-benzyl-2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]imidazol-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 31f)

A mixture of 3-benzyl-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-2-one (compound **31e**, 0.6 g, 2.7 mmol), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**,1.0 g, 2.7 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (38.4 mg, 0. 3 mmol), CuI (51.4 mg, 0.3 mmol) and K_3PO_4 (1.2 g, 5.5 mmol) in NMP (30 mL) was stirred at 100 °C for 6 hours under N_2. The reaction mixture was filtered, and the filtrate was diluted with brine (20 mL) and extracted with EtOAc three times (20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated, the residue was purified by chromatograph (EtOAc) to give compound **31f** (0.7 g) as a yellow solid. LCMS ($M+H^+$): 454.1.

Step 6: preparation of tert-butyl (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 31g)

To the mixture of tert-butyl (6S)-3-(1-benzyl-2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]imidazol-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound

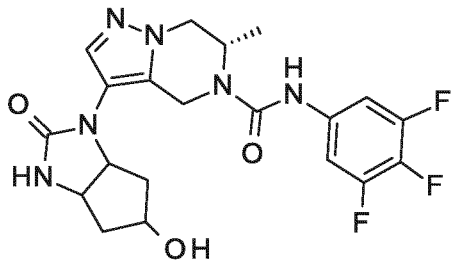
31f, 100.0 mg, 0.22 mmol) in THF (10 mL) was bubbled in NH_3 for 10 mins at - 78 °C, then Na (50.7 mg, 2.20 mmol) and EtOH (0.1 mL) was added and the mixture was stirred at -78 °C for 30 mins. The reaction was quenched with sat. NH_4Cl and then concentrated in *vacuo*. The residue was suspended in THF (20 mL) and stirred for 30 minutes, then the solid was filtered and filtrate was concentrated to give compound **31g** (55.0 mg) as a yellow solid. LCMS ($M+H^+$): 364.1

Step 7: preparation of (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 31)

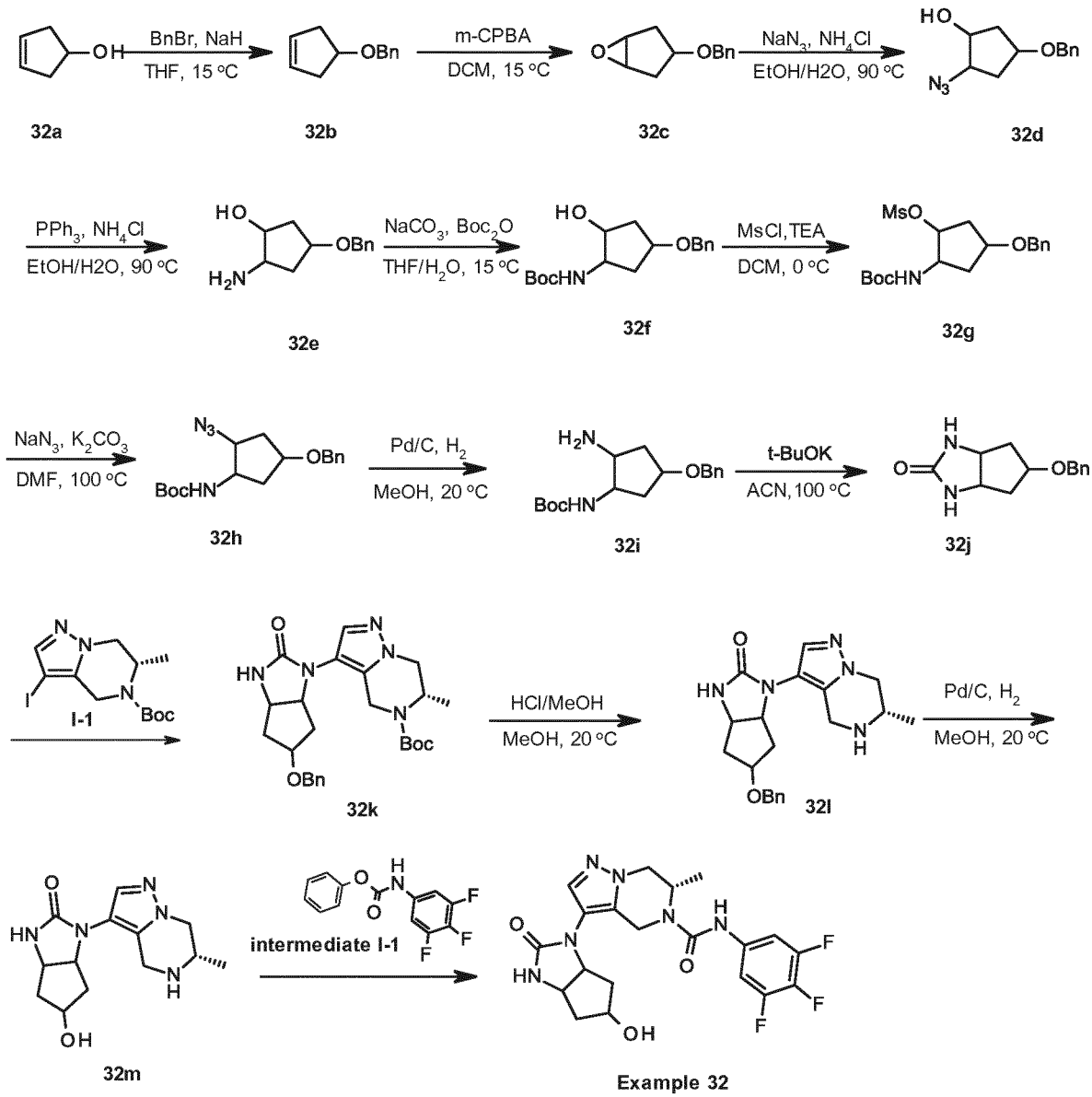
The **Example 31** was prepared in analogy to **Example 1** by using tert-butyl (6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **31g**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**). **Example 31** (6.2 mg) was obtained as white solid. LCMS ($M+H^+$): 437.1, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.59 (d, *J*=3.6 Hz, 1H), 7.39 - 7.20 (m, 2H), 5.11 - 4.94 (m, 2H), 4.78 - 4.72 (m, 1H), 4.55 (d, *J*=16.8 Hz, 1H), 4.47 - 4.39 (m, 1H), 4.29 (td, *J*=4.1, 12.7 Hz, 1H), 4.21 - 4.13 (m, 1H), 4.00 - 3.89 (m, 2H), 3.64 (dd, *J*=4.6, 9.4 Hz, 1H), 3.56 - 3.47 (m, 1H), 1.33 - 1.17 (m, 3H).

Example 32

(6S)-3-(5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of cyclopent-3-en-1-yloxymethylbenzene (compound 32b)

To a solution of cyclopent-3-en-1-ol (compound **32a**, 5.0 g, 59.4 mmol) in THF (100.0 ml) was added NaH (3.1 g, 77.2 mmol) in portions at 0 °C. The reaction was stirred at the same temperature for 30 minutes, then BnBr (10.2 g, 59.4 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 12 hours. The reaction was quenched with H_2O (300 mL) and extracted with EtOAc twice (200 mL). The combined organic layer was dried over Na_2SO_4, concentrated to give compound **32b** (12.5 g, crude) as a brown oil.

Step 2: preparation of 3-benzyloxy-6-oxabicyclo[3.1.0]hexane (compound 32c)

To a solution of cyclopent-3-en-1-yloxymethylbenzene (compound **32b**, 0.3 g, crude) in DCM (200 mL) was added m-CPBA (25.6 g, 118.8 mmol). The reaction was stirred for 12 hours at room temperature. The reaction was quenched with saturated aqueous Na_2SO_3, diluted with H_2O (200 mL) and adjusted to pH=10 with Na_2CO_3. Then the mixture was extracted with DCM

(200.0 mL) two times, dried and concentrated *in vacuo*, the residue was purified by column chromatography (EtOAc/PE=1/10) to give compound **32c** (4.0 g) as a brown oil. **LCMS:** ($M+Na^+$): 213.2

Step 3: preparation of 2-azido-4-benzyloxy-cyclopentanol (compound 32d)

To a solution of 3-benzyloxy-6-oxabicyclo[3.1.0]hexane (compound **32c**, 3.0 g, 15.7 mmol) in EtOH/H_2O (40/10 mL) was added NH_4Cl (2.5 g, 47.1 mmol) and NaN_3 (3.0 g, 47.1mmol). The reaction mixture was stirred at 90 °C for 12 hours and then cooled to room temperature, H_2O (100 mL) was added, then EtOH was removed under reduced pressure. The obtained solution (70 mL), which contained compound **32d**, was used for next step without further purification.

Step 4: preparation of 2-amino-4-benzyloxy-cyclopentanol (compound 32e)

To a solution of (1S,2S)-2-azido-4-benzyloxy-cyclopentanol (compound **32d** in 70 mL H_2O from previous step) in THF (100.0 mL) was added PPh_3 (5.7 g, 21.9 mmol). The reaction was stirred at 80 °C for 5 hours. Then the reaction was diluted with H_2O (200 mL), and extracted with EtOAc twice (200 mL). The combined organic phase was dried and concentrated to give compound **32e** (10.6 g, crude) as a brown oil which was used for next step without further purification.

Step 5: preparation of tert-butyl N-[4-benzyloxy-2-hydroxy-cyclopentyl]carbamate (compound 32f)

To a solution of (1S,2S)-2-amino-4-benzyloxy-cyclopentanol (compound **32e**, 10.6 g, 14.6 mmol, crude) in THF (100 mL) was added Na_2CO_3 (3.1 g, 29.2 mmol) and Boc_2O (4.8 g, 21.9 mmol). The reaction was stirred at room temperature for 3 hours. Then the reaction mixture was partitioned between H_2O (200 mL) and EtOAc (400 mL). Organic layer was separated and concentrated, the residue was purified by column chromatography (PE/EtOAc=5/1) to give a crude product (10.0 g), which was further purified by prep-HPLC to give compound **32f** (3.8 g) as a white solid. LCMS: ($M+H^+$): 308.1

Step 6: preparation of [4-benzyloxy-2-(tert-butoxycarbonylamino)cyclopentyl] methanesulfonate (compound 32g)

To a solution of tert-butyl N-[4-benzyloxy-2-hydroxy-cyclopentyl]carbamate (compound **32f**, 2.0 g, 6.51 mmol) in DCM (50.0 mL) were added TEA (1.3 g, 13.02 mmol) and then MsCl (0.9 g, 7.81 mmol) slowly at 0 °C. The reaction was stirred for 0.5 hour at 0 °C. The reaction mixture was poured into H_2O (200 mL), and extracted with DCM (400 mL). The organic layer was dried over Na_2SO_4 and then concentrated to give compound **32g** (2.9 g, crude) as a brown oil.

Step 7: preparation of tert-butyl N-(2-azido-4-benzyloxy-cyclopentyl)carbamate (compound 32h)

To a solution of [4-benzyloxy-2-(tert-butoxycarbonylamino)cyclopentyl] methanesulfonate (compound **32g**, 2 90 g, 6.51 mmol, crude) in DMF (50.0 mL) was added K_2CO_3 (1.17 g, 8.46 mmol) and NaN_3 (0.55 g, 8.46 mmol). The reaction was stirred for 12 hours at 90 °C, then poured into H_2O (200 mL), extracted with EtOAc (400 mL). The organic layer was dried over Na_2SO_4 and then concentrated to give compound **32h** (2.6 g, crude) as a brown oil.

Step 8: preparation of tert-butyl N-[2-amino-4-benzyloxy-cyclopentyl]carbamate (compound 32i)

To a solution of tert-butyl N-(2-azido-4-benzyloxy-cyclopentyl)carbamate (compound **32h**, 2.6 g, 6.51 mmol, crude) in MeOH (50.0 mL) was added Pd (2.7 g, 2.60 mmol, 10% on carbon). The reaction was stirred for 2 hours at room temperature under 1 atm. of H_2. The reaction mixture was filtered and the filtrate was concentrated, the residue was purified by column chromatography (DCM/MeOH=10/1) to give compound **32i** (1.2 g) as a white solid. LCMS: ($M+H^+$): 307.2

Step 9: preparation of 5-benzyloxy-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[d]imidazol-2-one (compound 32j)

To a solution of tert-butyl N-[2-amino-4-benzyloxy-cyclopentyl]carbamate (compound **32i**, 800.0 mg, 2.61 mmol) in CH_3CN (20.0 mL) was added t-BuOK (586.0 mg, 5.22 mmol). The reaction was stirred for 12 hours at 80 °C. Then the reaction mixture was concentrated and the residue was treated with H_2O (200 mL), extracted with EtOAc (200 mL) three times. The combined organic layer was concentrated and the residue was purified by prep-TLC (DCM/MeOH=10/1) to give compound **32j** (0.3 g) as a white solid.

Step 10: preparation of tert-butyl (6S)-3-(5-benzyloxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 32k)

Compound **32k** was prepared in analogy to tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**) by using 5-benzyloxy-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[d]imidazol-2-one (compound **32j**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**). Compound **32k** was obtained as a brown solid (115.0 mg). LCMS ($M+H^+$): 468.2.

Step 11: preparation of 5-benzyloxy-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-2-one (compound 32l)

To a solution of tert-butyl (6S)-3-(5-benzyloxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **32k**, 115.0 mg, 0.25 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.0 mmol), the reaction mixture was stirred at room temperature for 2 hours under N_2 atmosphere, then concentrated to give compound **32l** (124.0 mg, crude) as a brown solid. LCMS ($M+H^+$): 368.3.

Step 12: preparation of 5-hydroxy-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-2-one (compound 32m)

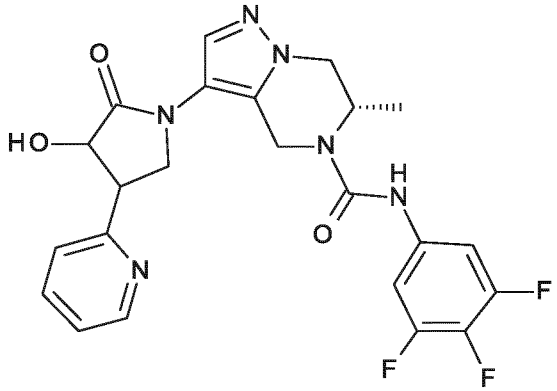
To a mixture of 5-benzyloxy-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-2-one (compound **32l**, 115.0 mg, 0.28 mmol) in MeOH (20.0 mL) was added $Pd(OH)_2$ (40.0 mg, 0.057 mmol), the reaction mixture was stirred at room temperature for 12 hours under H_2 (50Psi) atmosphere, then adjust to pH=8 by $NaHCO_3$ and filtered, the filtrate was concentrated and the residue was purified by prep-HPLC (DCM/MeOH=5/1) to give compound **32m** (24.0 mg) as brown solid. LCMS ($M+H^+$): 278.0.

Step 13: preparation of (6S)-3-(5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 32)

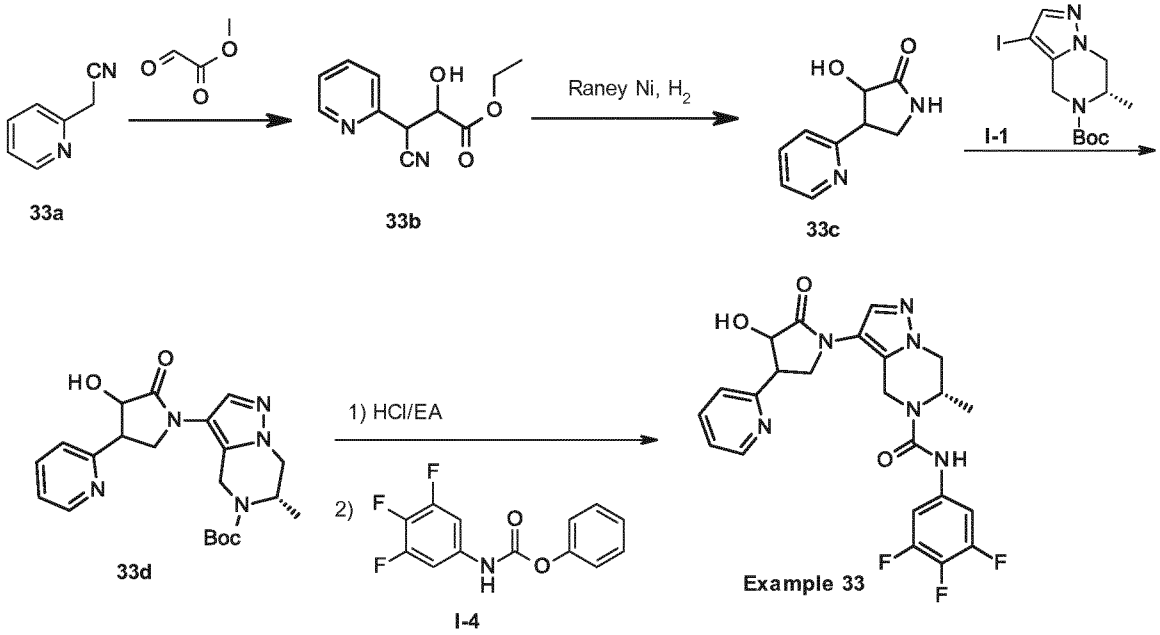
To a mixture of 5-hydroxy-3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-2-one (compound **32m**, 24.0 mg, 0.087 mmol) in DMF (2.0 mL) was added DIPEA (22.5 mg, 0.174 mmol) and phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 25.4 mg, 0.095 mmol), the reaction mixture was stirred at room temperature for 12 hours, then filtered and the filtrate was purified by prep-HPLC to give **Example 32** (3.8 mg) as a white solid. LCMS ($M+H^+$): 451.0. ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.62 - 7.54 (m, 1H), 7.36 - 7.21 (m, 2H), 5.08 - 4.95 (m, 1H), 4.69 - 4.61 (m, 1H), 4.58 - 4.39 (m, 2H), 4.38 - 4.26 (m, 2H), 4.20 - 4.10 (m, 1H), 2.06 - 1.97 (m, 2H), 1.97 - 1.88 (m, 1H), 1.81 (td, *J*=6.8, 14.0 Hz, 1H), 1.86 - 1.76 (m, 1H), 1.36 - 1.19 (m, 3H).

Example 33

(6S)-3-[3-hydroxy-2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of ethyl 3-cyano-2-hydroxy-3-(2-pyridyl)propanoate (compound 33b)

To a solution of 2-(2-pyridyl)acetonitrile (compound **33a**, 2.0 g, 17.0 mmol) and $NaHCO_3$ (1.4 g, 17.0 mmol) in MeCN (20 mL) was added ethyl 2-oxoacetate (3.8 g, 18.6 mmol). The reaction mixture was stirred at 25 °C for 5 hours, then filtered and the filtrate was concentrated to afford compound **33b** (4.0 g, crude) as a yellow oil. LCMS ($M+H^+$): 221.1.

Preparation of 3-hydroxy-4-(2-pyridyl)pyrrolidin-2-one (compound 33c):

To a solution of ethyl 3-cyano-2-hydroxy-3-(2-pyridyl)propanoate (compound **33b**, 3.0 g, 13.6 mmol) and $NH_3.H_2O$ (0.5 ml) in MeOH (50.0 ml) was added Raney Ni (2.0 g), then the mixture was stirred at 30 °C for 34 hours under H_2 (50 psi). The mixture was concentrated and the residue was purified by column chromatography (DCM:MeOH=10:1) and then prep-HPLC to afford cis- isomer **33c-1** (50 mg) and trans- isomer **33c-2** (300 mg) as yellow solids. LCMS ($M+H^+$): 179.1.

Preparation of ((6S)-3-[3-hydroxy-2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 33):

The **Example 33** was prepared in analogy to **Example 1** by using 3-hydroxy-4-(2-pyridyl)pyrrolidin-2-one (compound **33c-1** or **33c-2**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**).

Cis-isomer **33c-1** gave two isomers of **Example 33**, **Example 33-1** and **Example 33-2**, after SFC separation (Chiralcel OD-3 100×4.6 mm ID, 3um; mobile phase, methanol (0.05% DEA) in CO_2 from 5% to 40%).

Example 33-1 (6 mg), white solid. LCMS ($M+H^+$): 487.3. ^1H NMR (400MHz, MeOD) δ ppm 8.60 (d, *J*=4.5 Hz, 1H), 7.94 (t, *J*=7.7 Hz, 1H), 7.71 (s, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 7.46 - 7.38 (m, 1H), 7.30 (dd, *J*=6.4, 10.3 Hz, 2H), 5.16 (d, *J*=17.1 Hz, 1H), 4.97 (d, *J*=5.6 Hz, 1H), 4.81 (d, *J*=7.3 Hz, 1H), 4.59 (d, *J*=17.2 Hz, 1H), 4.33 (dd, *J*=4.5, 12.7 Hz, 1H), 4.27 - 4.09 (m, 4H), 1.32 (d, *J*=6.9 Hz, 3H).

Example 33-2 (6 mg), white solid, LCMS ($M+H^+$): 487.3. ^1H NMR (400MHz, MeOD) δ ppm 8.44 (d, *J*=4.9 Hz, 1H), 7.77 - 7.68 (m, 1H), 7.58 (s, 1H), 7.33 (d, *J*=7.8 Hz, 1H), 7.26 - 7.13 (m, 3H), 5.02 (d, *J*=16.9 Hz, 1H), 4.90 - 4.84 (m, 1H), 4.69 (d, *J*=7.5 Hz, 1H), 4.47 (d, *J*=17.1 Hz, 1H), 4.21 (dd, *J*=4.5, 12.7 Hz, 1H), 4.13 - 3.86 (m, 4H), 1.16 (d, *J*=6.9 Hz, 3H).

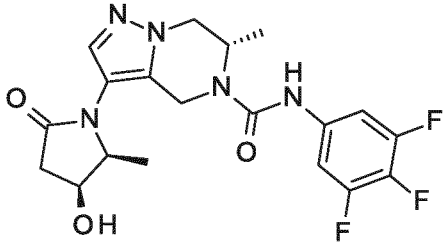
Trans-isomer **33c-2** gave another two isomers of **Example 33**, **Example 33-3** and **Example 33-4**, after SFC separation (Chiralpak AS-3 100×4.6mm ID, 3um; mobile phase, ethanol (0.05% DEA) in CO_2 from 5% to 40%)

Example 33-3 (7 mg), white solid. LCMS ($M+H^+$): 487.3. ^1H NMR (400MHz, DMSO-d_6) δ ppm 9.29 (br. s., 1H), 8.66 (d, *J*=4.8 Hz, 1H), 7.87 (t, *J*=7.6 Hz, 1H), 7.75 (s, 1H), 7.60 - 7.48 (m, 3H), 7.39 (dd, *J*=4.8, 7.5 Hz, 1H), 6.03 (d, *J*=6.7 Hz, 1H), 5.18 (d, *J*=17.2 Hz, 1H), 5.00 - 4.89 (m, 1H), 4.64 (dd, *J*=6.4, 9.5 Hz, 1H), 4.44 (d, *J*=17.3 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.21 (s, 1H), 4.11 - 4.02 (m, 1H), 3.93 (t, *J*=9.4 Hz, 1H), 3.75 - 3.65 (m, 1H), 1.20 (d, *J*=6.7 Hz, 3H).

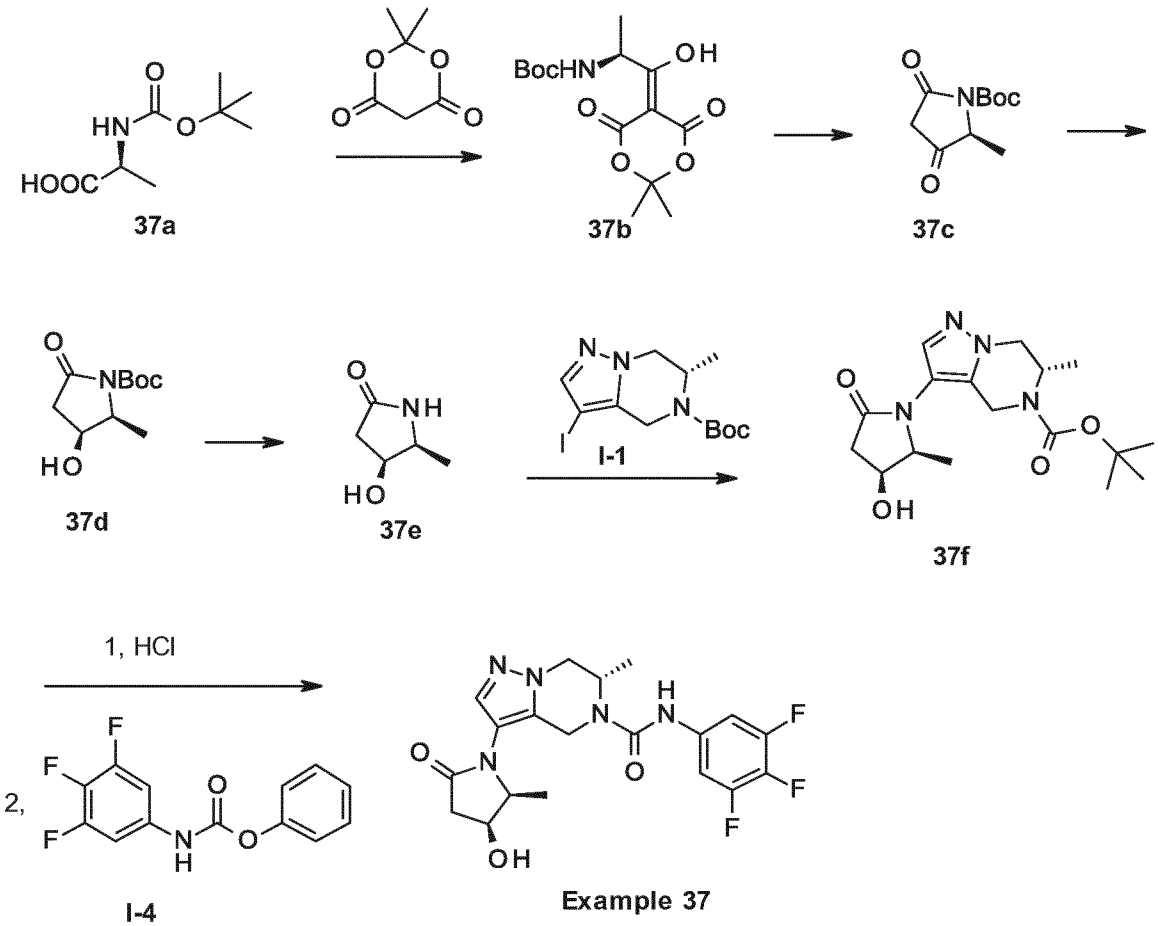
Example 33-4 (7 mg), white solid, LCMS ($M+H^+$): 487.3. ^1H NMR (400MHz, DMSO-d_6) δ ppm 9.37 (br. s., 1H), 8.66 (d, *J*=3.9 Hz, 1H), 7.87 (dt, *J*=1.8, 7.7 Hz, 1H), 7.73 (s, 1H), 7.59 - 7.48 (m, 3H), 7.39 (dt, *J*=0.9, 6.2 Hz, 1H), 6.06 (d, *J*=5.9 Hz, 1H), 5.12 (d, *J*=17.2 Hz, 1H), 5.02 - 4.93 (m, 1H), 4.61 (dd, *J*=5.5, 9.4 Hz, 1H), 4.54 (d, *J*=17.2 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.22 - 4.15 (m, 1H), 3.99 (d, *J*=9.2 Hz, 2H), 3.71 (q, *J*=9.3 Hz, 1H), 1.23 (d, *J*=6.8 Hz, 3H).

Example 37

(6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl N-[(1S)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-hydroxy-1-methyl-ethyl]carbamate (compound 37b)

To a stirred solution of (2S)-2-(tert-butoxycarbonylamino)propanoic acid (compound **37a**, 1.7 g, 11.63 mmol) and DMAP (2.0 g, 15.86 mmol) in DCM (50 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (2.0 g, 10.57 mmol) at 0 °C. EDCI (4.9 g, 25.37 mmol) was then added. The reaction mixture was stirred at room temperature for 15 hours. The yellow reaction mixture was cooled to 0°C and washed with cold 5% $KHSO_4$ (100 mL) three times and brine. The

organic layer was dried over Na_2SO_4, filtered and concentrated to afford crude compound **37b** (11.4 g), which was used directly in the next step. LCMS: ($M+Na^+$): 338.2

Step 2: preparation of tert-butyl (2S)-2-methyl-3,5-dioxo-pyrrolidine-1-carboxylate (compound 37c)

A stirred solution of tert-butyl N-[(1S)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-hydroxy-1-methyl-ethyl]carbamate (compound **37b**, 10.0 g, 31.7 mmol) in EtOAc (150 mL) was refluxed for 0.5 hour. The reaction mixture was concentrated to afford compound **37c** (6.7 g, crude) as a yellow solid. LCMS ($M+Na^+$): 236.2.

Step 3: preparation of tert-butyl (2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidine-1-carboxylate (compound 37d)

To a stirred solution of tert-butyl (2S)-2-methyl-3,5-dioxo-pyrrolidine-1-carboxylate (compound **37c**, 6.2 g, 29.08 mmol) in DCM (300 mL) was added HOAc (30 mL) at 0 °C. Then $NaBH_4$ (2.2 g, 58.15 mmol) was added slowly in three portions. After being stirred at 0°C for 5 hours, the reaction mixture was quenched with cold 5% $NaHCO_3$ aqueous solution at 0°C. The reaction mixture was extracted with DCM (100 mL) three times. The combined organic layer was washed with 5% $NaHCO_3$ aqueous solution, brine and then concentration. The residue was purified by flash chromatography (DCM/MeOH=10:1) to afford compound **37d** (2.7 g) as a white solid. LCMS ($2M+Na^+$): 453.1.

Step 4: preparation of (4S,5S)-4-hydroxy-5-methyl-pyrrolidin-2-one (compound 37e)

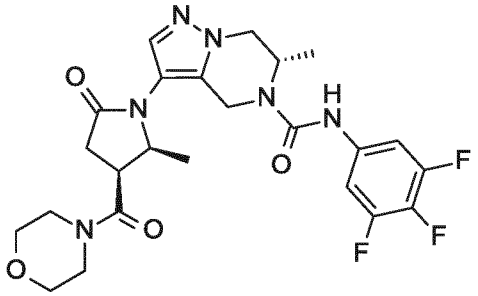
To a stirred solution of tert-butyl (2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidine-1-carboxylate (compound **37d**, 1.8 g, 8.36 mmol) in DCM (60 mL) was added TFA (6 mL) dropwise at 0°C. The reaction was stirred at 0°C for 1 hour and then stirred at room temperature for 14 hours. The reaction was concentrated and then toluene (50mL) was added to the residue, and the solution was concentrated to afford crude compound **37e** (1.0 g) as a brown oil.

Preparation of (6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 37)

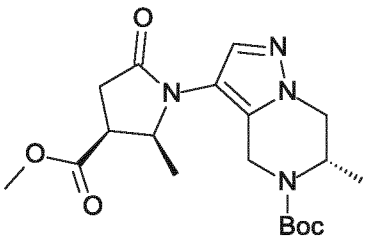
The title compound was prepared in analogy to **Example 1** by using (4S,5S)-4-hydroxy-5-methyl-pyrrolidin-2-one (compound **37e**) instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**). **Example 37** was obtained (628.0 mg) as a yellow solid. LCMS ($M+H)^+$: 424.3, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.53 (s, 1H), 7.36 - 7.23 (m, 2H), 5.04 - 4.94 (m, 2H), 4.52 - 4.45 (m, 1H), 4.40 - 4.28 (m, 2H), 4.21 - 4.12 (m, 2H), 2.88 (dd, *J*=6.3, 17.3 Hz, 1H), 2.52 - 2.39 (m, 1H), 1.22 (d, *J*=6.7 Hz, 3H), 1.20 (d, *J*=6.7 Hz, 3H).

Example 38

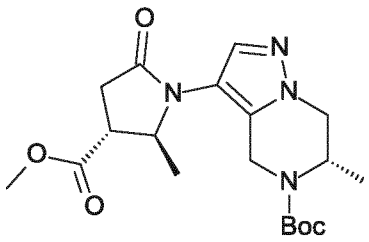
(6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



Preparation of tert-butyl (6S)-3-[(2S,3S)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-38) and tert-butyl (6S)-3-[(2S,3R)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-39)

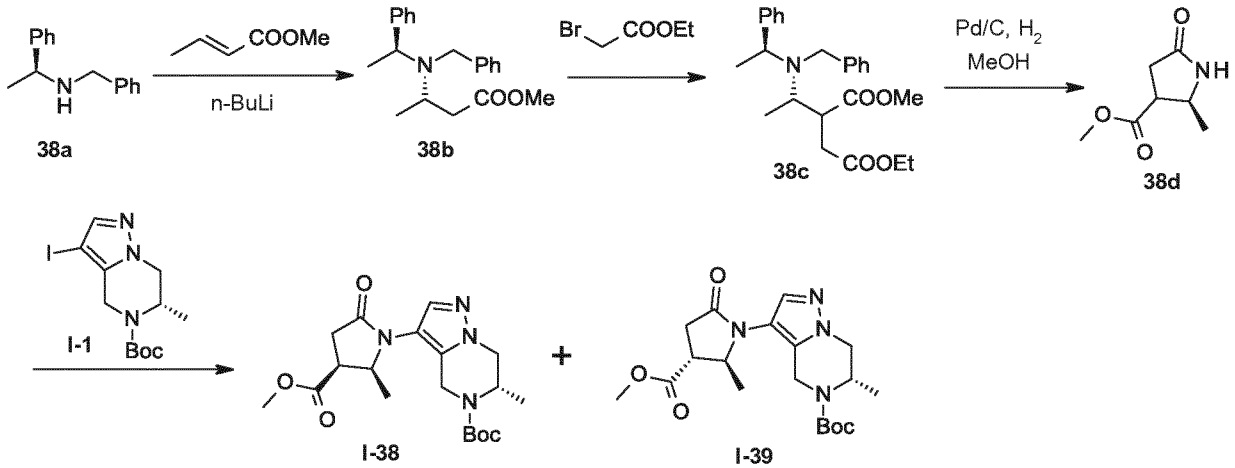


I-38



I-39

Intermediate I-38 and **Intermediate I-39** were prepared according to the following scheme:



Step 1: preparation of methyl 3-[benzyl-[(1S)-1-phenylethyl]amino]butanoate (compound 38b)

n-Butyllithium solution (46.0 mL, 115.0 mmol) was added dropwise to a solution of (1S)-N-benzyl-1-phenyl-ethanamine (compound **38a**, 25.0 g, 118.3 mmol) in THF (270 mL) at -10 °C under nitrogen. The resulting red solution of lithium amide was cooled to -78 °C and a solution of methyl (E)-but-2-enoate (10.7 g, 106.5 mmol) in THF (30 mL) was added by cannula. The reaction mixture was stirred at -78 °C for 1 hour, then quenched with saturated ammonium chloride solution, and extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph (eluting with 5% EtOAc in petroleum ether) to give compound **38b** (25.6 g) as a yellow oil. LCMS ($M+H^+$): 312.

Step 2: preparation of O4-ethyl O1-methyl 2-[1-[benzyl-[(1S)-1-phenylethyl]amino]ethyl]butanedioate (compound 38c)

To a stirred solution of methyl 3-[benzyl-[(1S)-1-phenylethyl]amino]butanoate (compound **38b**, 25.0 g, 80.3 mmol) in THF (250.0 mL) was added LDA (120 mL, 240.8 mmol) dropwise at -78 °C. After 1 hour, trimethyl borate (25.0 g, 240.8 mmol) was added and the reaction mixture was stirred for 30 minutes at the same temperature. Then a solution of ethyl 2-bromoacetate (26.8 g, 160.6 mmol) in THF (50.0 mL) was added dropwise at -78 °C, the temperature was maintained for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution and extracted by EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph (eluting with 10% EtOAc in petroleum ether) to give compound **38c** (22.0 g, crude) as a yellow oil. LCMS ($M+H^+$): 398.

Step 3: preparation of methyl (2S)-2-methyl-5-oxo-pyrrolidine-3-carboxylate (compound 38d)

A mixture of O4-ethyl O1-methyl 2-[1-[benzyl-[(1S)-1-phenylethyl]amino]ethyl]butanedioate (compound **38c**, 22.0 g, 55.3 mmol) and palladium on carbon (2.2 g) in MeOH (500 mL) was stirred at room temperature under hydrogen (50 psi) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatograph (eluting with 5% methanol in dichloromethane) to give compound **38d** (5.5 g, crude) as a yellow oil. LCMS ($M+H^+$): 158.

Step 4: preparation of tert-butyl (6S)-3-[(2S,3S)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-38) and tert-butyl (6S)-3-[(2S,3R)-3-methoxycarbonyl-2-methyl-5-oxo-

pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-39)

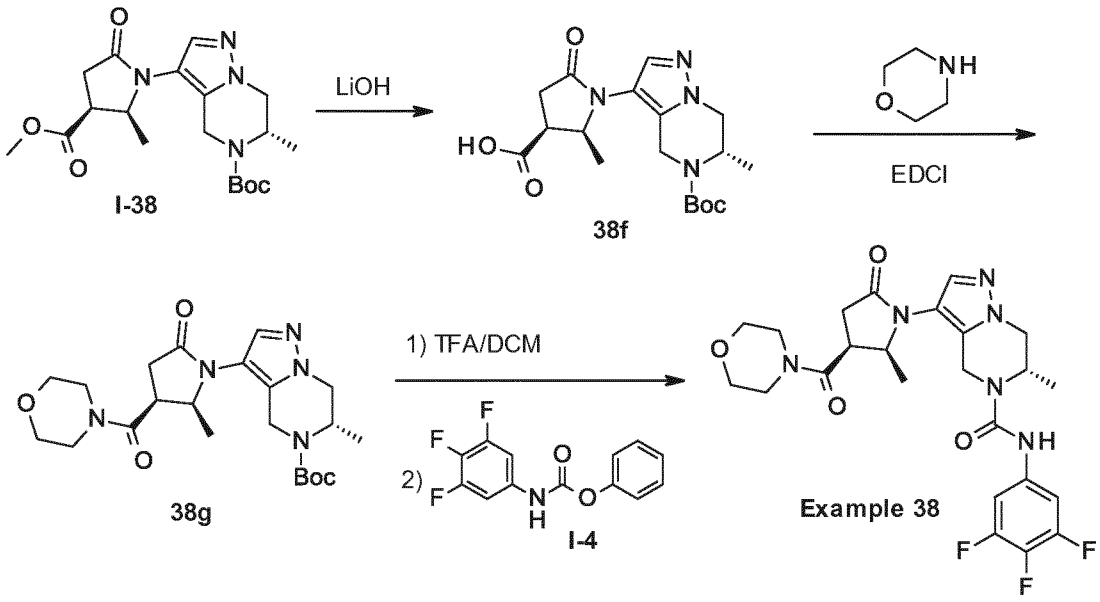
An oven-dried re-sealable Schlenk tube was charged with tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 2.9 g, 8.0 mmol), K_3PO_4 (3.4 g, 16.0 mmol), CuI (304.7 mg, 1.6 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (227.6 mg, 1.6 mmol), evacuated and backfilled with argon. Methyl (2S)-2-methyl-5-oxo-pyrrolidine-3-carboxylate (compound **38d**,1.25 g, 8.0 mmol) in dioxane (40.0 ml) were added under nitrogen. The mixture was stirred at 110 °C for 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified first by silica gel chromatograph, and then by SFC (Column: Chiralcel OD-3 100×4.6 mm, I.D. 3um, mobile phase: ethanol (0.05% DEA) in CO_2 from 5% to 40%, Wavelength: 220 nm) to give two isomers, Intermediate **I-38** (520 mg) as a yellow solid and Intermediate **I-39** (594 mg) as a yellow solid.

Intermediate **I-38**, LCMS ($M+H^+$): 393. ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.53 (s, 1H), 4.81 (d, *J*=17.4 Hz, 1H), 4.64 (d, *J*=5.1 Hz, 1H), 4.36 - 4.27 (m, 1H), 4.22 - 4.14 (m, 1H), 4.09 - 3.96 (m, 2H), 3.70 - 3.67 (m, 3H), 3.62 (q, *J*=8.4 Hz, 1H), 2.72 (dd, *J*=8.3, 16.8 Hz, 1H), 2.54 (d, *J*=8.7 Hz, 1H), 1.45 (s, 9H), 1.00 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H).

Intermediate **I-39**, LCMS ($M+H^+$): 393. ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.53 - 7.45 (m, 1H), 4.78 (d, *J*=17.5 Hz, 1H), 4.65 (br. s., 1H), 4.21 - 4.14 (m, 1H), 4.11 (t, *J*=6.1 Hz, 1H), 4.08 - 3.99 (m, 2H), 3.70 (s, 3H), 3.10 - 3.02 (m, 1H), 2.81 - 2.72 (m, 1H), 2.65 - 2.57 (m, 1H), 1.44 (s, 9H), 1.20 (d, *J*=6.2 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H).

Preparation of (6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 38)

Example 38 was prepared according to the following scheme:



Step 1: preparation of (2S,3S)-1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-2-methyl-5-oxo-pyrrolidine-3-carboxylic acid (compound 38f)

To a solution of tert-butyl (6S)-3-[(2S,3S)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-38**, 110 mg, 280 μmol) in tetrahydrofuran (280 μL) was added a solution of lithium hydroxide monohydrate in water (2.0 M, 280 μL, 561 μmol). The reaction mixture was stirred at room temperature for 2 hours and then diluted with DCM/i-PrOH (V/V=5/1), acidified to pH=4-5 with 1N aqueous solution of HCl, and washed with water. The organic phase was dried and concentrated to give crude compound **38f** (106 mg). LCMS ($M+H^+$): 379.

Step 6: preparation of tert-butyl (6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 38g)

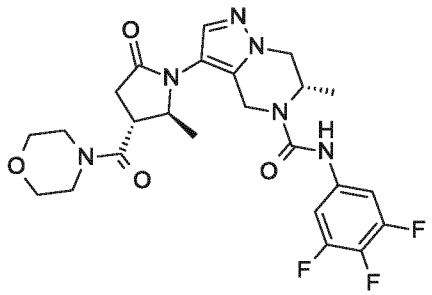
To a solution of (2S,3S)-1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-2-methyl-5-oxo-pyrrolidine-3-carboxylic acid (compound **38f**, 106 mg, 0.28 mmol) in dry DMF (5.0 ml) were added morpholine (36.6 mg, 420 μmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (69.8 mg, 364 μmol), 1H-benzo[d][1,2,3]triazol-1-ol (11.4 mg, 84 μmol) and DIPEA (1.0 ml, 5.83 mmol). The reaction mixture was heated to 50 °C and stirred for 2 hours, then cooled down, washed with ice-water, and extracted with DCM twice. The organic phase was concentrated. The residue was purified by column chromatography to give compound **38g** (80 mg). LCMS ($M+H^+$): 448.

Step 7: preparation of (6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 38)

The mixture of tert-butyl (6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **38g**, 80 mg, 179 μmol), 2,2,2-trifluoroacetic acid (2.0 mL) and solvent DCM (1.0 mL) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, the residue was dissolved in DCE (3.0 ml), then added DIPEA (0.5 mL), phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 52.5 mg, 197 μmol). The reaction mixture was stirred at 50°C for 1 hour and then cooled down, washed with ice-water, extracted with DCM twice. The combined organic phase was concentrated. The residue was purified sequentially by column chromatography, and then pre-HPLC to give **Example 38** (38 mg). LCMS ($M+H^+$): 521. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.60 (s, 1H), 7.34 - 7.26 (m, 2H), 5.05 - 4.96 (m, 2H), 4.48 - 4.38 (m, 1H), 4.36 - 4.29 (m, 2H), 4.21 - 4.15 (m, 1H), 4.02 (q, *J*=8.5 Hz, 1H), 3.77 - 3.63 (m, 8H), 3.21 - 3.11 (m, 1H), 2.57 (dd, *J*=8.7, 17.2 Hz, 1H), 1.20 (d, *J*=6.8 Hz, 3H), 1.10 (d, *J*=6.6 Hz, 3H)

Example 39

(6S)-6-methyl-3-[(2S,3R)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

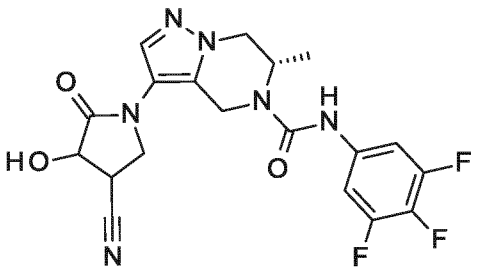


The title compound was prepared in analogy to **Example 38** by using tert-butyl (6S)-3-[(2S,3R)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-39**) instead of tert-butyl (6S)-3-[(2S,3S)-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-38**). **Example 39** was obtained as a solid (38.6 mg). LCMS ($M+H^+$): 521. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.58 (s, 1H), 7.34 - 7.26 (m, 2H), 5.04 - 4.93 (m, 2H), 4.39 - 4.26 (m, 3H), 4.20 - 4.14 (m, 1H), 3.76 - 3.59 (m, 8H), 3.48 - 3.41 (m,

1H), 2.95 (dd, *J*=9.3, 17.1 Hz, 1H), 2.65 (dd, *J*=6.1, 17.1 Hz, 1H), 1.33 (d, *J*=6.4 Hz, 3H), 1.24 (d, *J*=6.8 Hz, 3H)

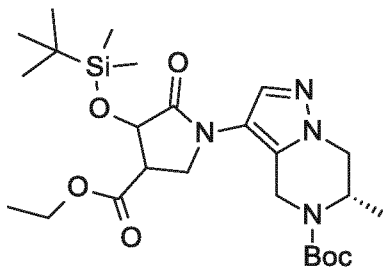
Example 40

(6S)-3-(3,4-trans-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

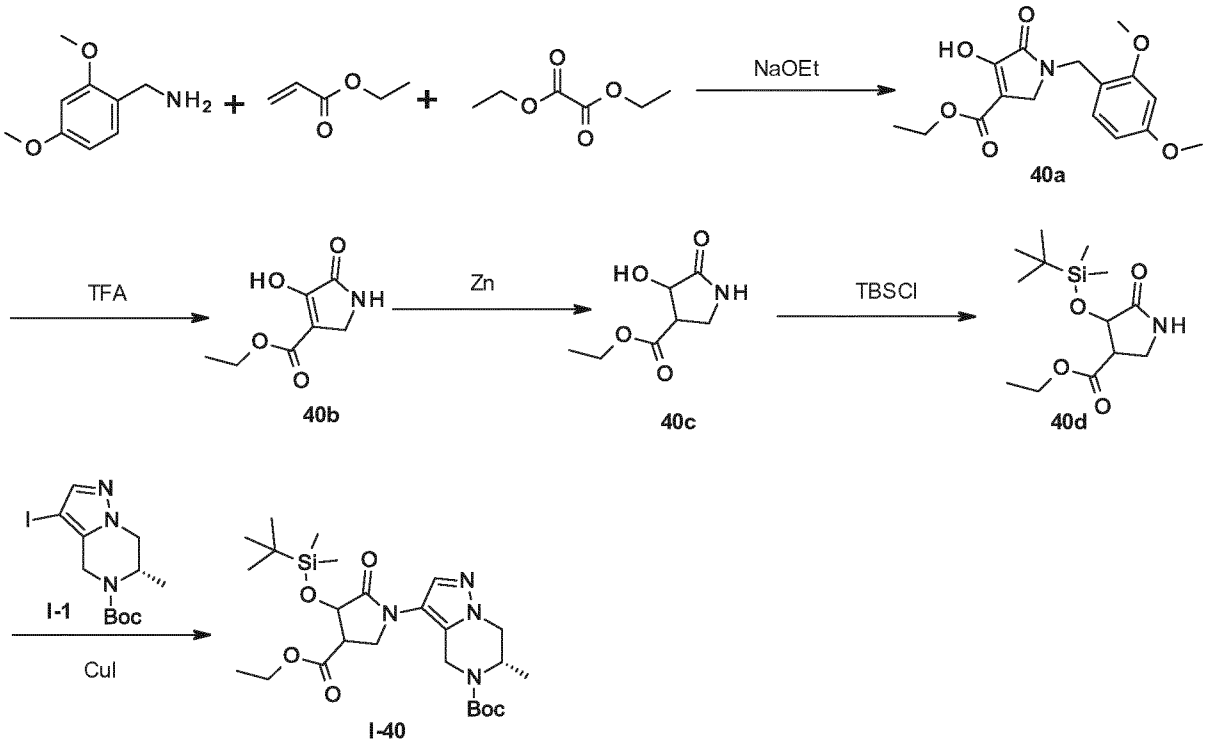


trans-isomers

Preparation of tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate I-40)



Intermediate **I-40** was prepared according to the following scheme:



Step 1: preparation of ethyl 1-[(2,4-dimethoxyphenyl)methyl]-4-hydroxy-5-oxo-2H-pyrrole-3-carboxylate (compound 40a)

To a solution of (2,4-dimethoxyphenyl)methanamine (33.4 g, 199.8 mmol) in EtOH(100 mL) was added ethyl prop-2-enoate (20.0 g, 199.8 mmol) in portions at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, and then EtOH was removed to give a residue. A solution of NaOEt in EtOH (fresh prepared by dissolving Na (5.51 g, 239.71 mmol) in EtOH (50.0 ml)) was added to a mixture of above residue and diethyl oxalate (29.2 g, 199.8 mmol). The resulting reaction mixture was heated to 80 °C for 2 hours. After cooled to room temperature, the reaction mixture was concentrated, and treated with saturated NH_4Cl aqueous solution (200 mL) and extracted with DCM three times. The organic layer was dried over Na_2SO_4, filtered and concentrated to give compound **40a** (60.0g) as a yellow solid. LCMS ($M+H^+$): 322.

Step 2: preparation of ethyl 4-hydroxy-5-oxo-1,2-dihydropyrrole-3-carboxylate (compound 40b)

The mixture of ethyl 1-[(2,4-dimethoxyphenyl)methyl]-4-hydroxy-5-oxo-2H-pyrrole-3-carboxylate (compound **40a**, 60.0 g, 186.7 mmol) and 2,2,2-trifluoroacetic acid (400 mL) was stirred at 80 °C for 4 hours under nitrogen. The solvent was removed under vacuum to give compound **40b** (35.0 g, crude) which was used in next step directly. LCMS ($M+H^+$): 172.

Step 3: preparation of ethyl 4-hydroxy-5-oxo-pyrrolidine-3-carboxylate (compound 40c)

To a solution of ethyl 4-hydroxy-5-oxo-1,2-dihydropyrrole-3-carboxylate (compound **40b**, 15.0 g, 87.7 mmol) in EtOH (200 mL) were added water (20 mL) and ammonium chloride (23.4 g, 438.2 mmol) and zinc powder (28.6 g, 438.2 mmol). The mixture was stirred at 80 °C for 18 hours and filtered. The filtrate was concentrated and purified by reversed-phase column chromatography to give compound **40c** (63.0 g, crude) as a yellow oil. LCMS ($M+H^+$): 174.

Step 4: preparation of ethyl 4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-3-carboxylate (compound 40d)

To a solution of ethyl 4-hydroxy-5-oxo-pyrrolidine-3-carboxylate (compound **40c**, 30.0 g, 174.0 mmol) and imidazole (36.0 g, 261.0 mmol) in DMF (150 ml) was added tert-butyldimethylsilyl chloride (36.0 g, 192.0 mmol). The reaction mixture was stirred at room temperature for 24 hours, and then concentrated, treated with water (50 ml) and extracted with EtOAc twice. The combine organic phase was dried over Na_2SO_4 and concentrated to afford compound **40d** (10.0 g, crude) as a yellow oil. LCMS ($M+H^+$): 288.

Step 5: tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (I-40)

An oven-dried sealable Schlenk tube was charged with (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.42 g, 3.0 mmol), K_3PO_4 (7.0 g, 33.0 mmol), evacuated and backfilled with argon. Then CuI (0.45 g, 3.0 mmol), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 6.0 g, 16.5 mmol), ethyl 4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-3-carboxylate (compound **40d**, 4.8 g, 16.5 mmol) and toluene (60.0 ml) were added under nitrogen. The mixture was stirred at 100 °C for 15 hours. The mixture was filtered and the filtrated was concentrated. The residue was purified by column chromatography (eluting with 50% EtOAc in petroleum ether) to afford trans-isomers (Intermediate *trans*-**I-40**, 1.77 g) and cis-isomers (Intermediate *cis*-**I-40**, 0.56 g).

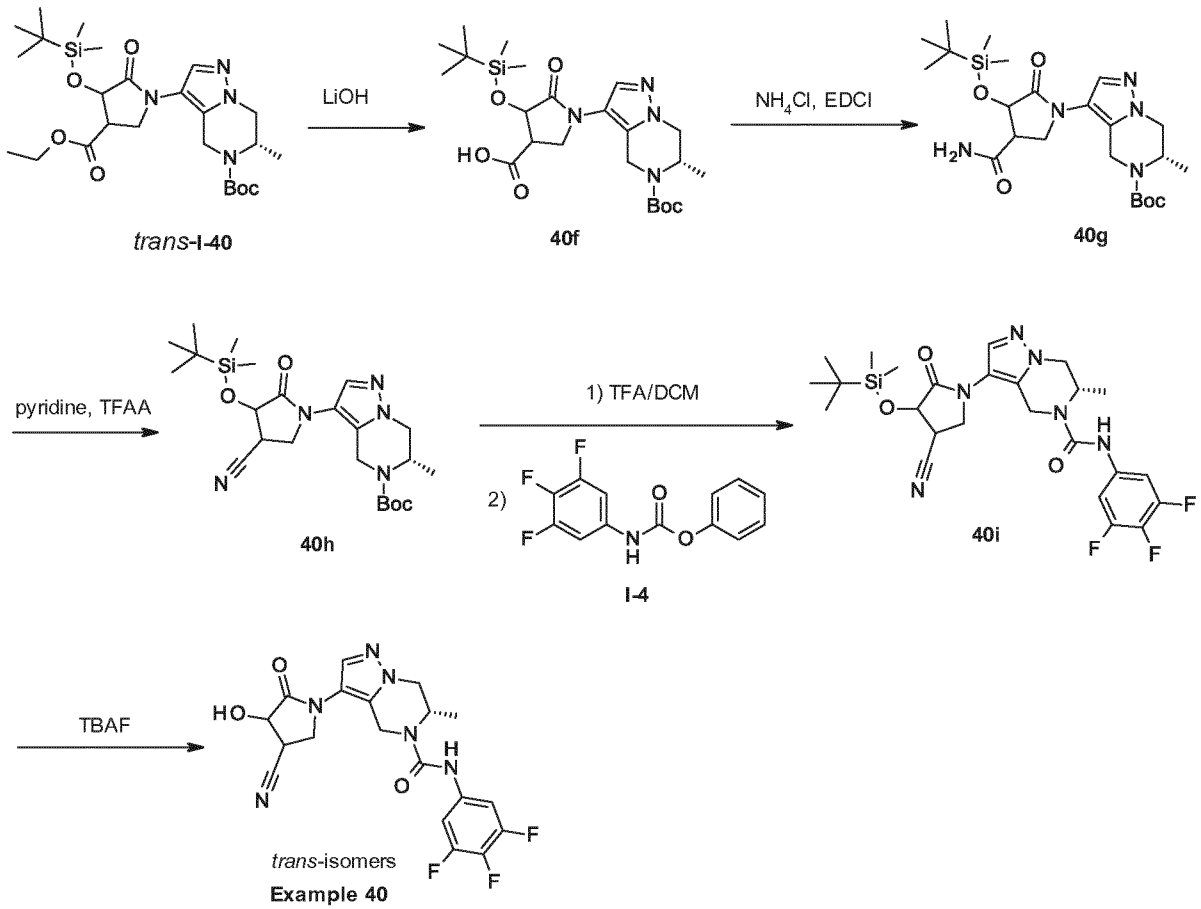
tert-butyl (6S)-3-[3,4-trans-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *trans*-**I-40**,): LCMS ($M+H^+$): 523. ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.59 (d, *J*=1.4 Hz, 1H), 4.98 - 4.78 (m, 1H), 4.73 - 4.58 (m, 2H), 4.36 - 4.12 (m, 3H), 4.10 - 3.93 (m, 2H), 3.82 - 3.79 (m, 1H), 3.57 - 3.51 (m, 1H), 3.46 - 3.37 (m, 1H), 1.44 (s, 9H), 1.21 (dt, *J*=1.1, 6.5 Hz, 3H), 1.11 - 1.02 (m, 3H), 0.86 (d, *J*=1.1 Hz, 9H), 0.18 - 0.10 (m, 6H).

tert-butyl (6S)-3-[3,4-cis-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *cis*-**I-40**,): LCMS ($M+H^+$): 523. ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.61 (s, 1H), 5.02 - 4.76

(m, 1H), 4.66 (dd, *J*=1.4, 8.8 Hz, 2H), 4.46 - 4.27 (m, 1H), 4.20 - 4.13 (m, 3H), 4.08 - 4.02 (m, 1H), 3.86 - 3.76 (m, 1H), 3.41 (d, *J*=2.8 Hz, 1H), 3.30 - 3.27 (m, 1H), 3.22 - 3.05 (m, 1H), 1.44 (s, 9H), 1.26 - 1.21 (m, 3H), 1.06 (dd, *J*=6.9, 9.9 Hz, 3H), 0.89 (s, 9H), 0.14 (d, *J*=9.7 Hz, 6H).

Preparation of (6S)-3-(3,4-trans-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 40)

Example 40 was prepared according to the following scheme.



Step 1: preparation of 1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-3-carboxylic acid (compound 40f)

To a solution of tert-butyl (6S)-3-[3,4-trans-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *trans*-**I-40**, 250 mg, 0.49 mmol) in THF (1.0 mL) was added lithium hydroxide solution in water (1.0 ml, 2 M). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc, and acidified to pH=4-5 with 1N

hydrogen chloride solution. The organic phase was dried and concentrated to give compound **40f** (200 mg). LCMS ($M+H^+$): 495.

Step 2: preparation of tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-carbamoyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 40g)

To a solution of 1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-3-carboxylic acid (compound **40f**, 200 mg, 0.40 mmol) in DCE (5 ml) was added ammonium chloride (216 mg, 4.0 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (101 mg, 0.53 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (16.4 mg, 0.12 mmol and DIPEA (2.0 mL). The reaction mixture was heated to 50 °C and stirred at for 2 hours, and then cooled down, washed with brine, extracted with DCM twice. The combined organic phase was dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography to give compound **40g** (110 mg). LCMS ($M+H^+$): 494.

Step 3: preparation of tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 40h)

To a solution of tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-carbamoyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **40g**, 110 mg, 223 μmol) in dry THF (3.0 mL) was added pyridine (0.2 mL). The mixture was flushed with nitrogen and cooled to 0°C, then to which was added dropwise trifluoroacetic anhydride (0.2 mL). The reaction mixture was stirred at 0 °C for another 30 minutes. The reaction mixture was quenched with ice-water, extracted with EtOAc twice. The organic phase was dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography to give compound **40h** (95 mg). LCMS ($M+H^+$): 476.

Step 4: preparation of (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (compound 40i)

The mixture of tert-butyl (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **40h**, 95 mg, 200 μmol), 2,2,2-trifluoroacetic acid (3.0 mL) and DCM (1.5 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated, and the residue was dissolved in DMF (3 mL), to which were then added DIPEA (1.0 mL), phenyl (3,4,5-

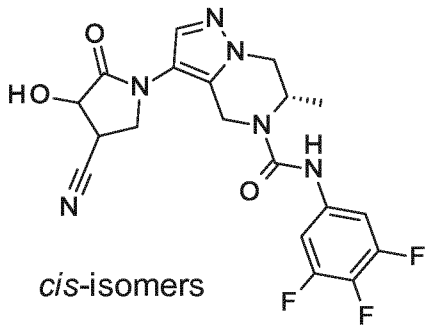
trifluorophenyl)carbamate (Intermediate **I-4**, 58.7 mg, 220 μmol). The reaction mixture was stirred at 50°C for 1 hour, and then cooled down, directly purified by column chromatography to give compound **40i** (95 mg). LCMS ($M+H^+$): 549.

Step 5: preparation of (6S)-3-(3,4-trans-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 40)

A mixture of (6S)-3-[3-[tert-butyl(dimethyl)silyl]oxy-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (compound **40i**, 88 mg, 160 μmol) and tetrabutylammonium fluoride 1.0 M solution in tetrahydrofuran (1.0 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated and the residue was purified by column chromatography to give **Example 40** (40.0 mg). LCMS ($M+H^+$): 435. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.66 (s, 1H), 7.33 - 7.24 (m, 2H), 5.12 - 4.93 (m, 2H), 4.75 - 4.70 (m, 1H), 4.59 - 4.43 (m, 1H), 4.30 (td, *J*=4.6, 12.8 Hz, 1H), 4.20 - 4.14 (m, 1H), 4.09 - 3.94 (m, 2H), 3.50 (dq, *J*=4.7, 9.2 Hz, 1H), 1.27 (dd, *J*=6.8, 16.1 Hz, 3H).

Example 41

(6S)-3-(3,4-cis-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



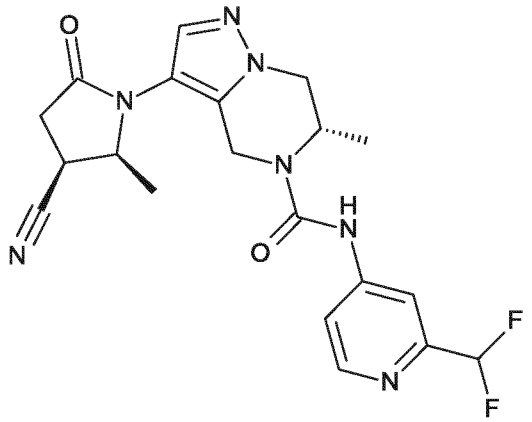
cis-isomers

The title compound was prepared in analogy to **Example 40** by using tert-butyl (6S)-3-[3,4-cis-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *cis*-**I-40**) instead of tert-butyl (6S)-3-[3,4-trans-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *trans*-**I-40**). **Example 41** was obtained as a solid (9.7 mg). LCMS ($M+H^+$): 435. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.66 (s, 1H), 7.33 - 7.24 (m, 2H), 5.12 - 4.92 (m, 2H), 4.76 - 4.71 (m, 1H),

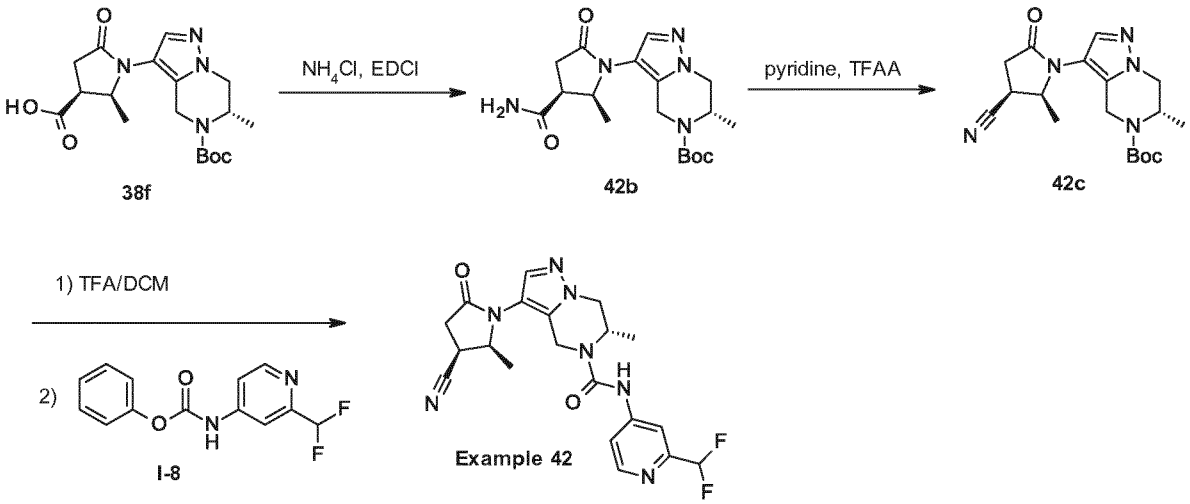
4.59 - 4.42 (m, 1H), 4.30 (td, *J*=4.6, 12.7 Hz, 1H), 4.21 - 4.13 (m, 1H), 4.09 - 3.95 (m, 2H), 3.50 (dq, *J*=5.0, 9.2 Hz, 1H), 1.30 - 1.22 (m, 3H).

Example 42

(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl (6S)-3-[(2S,3S)-3-carbamoyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 42b)

To a solution of (2S,3S)-1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-2-methyl-5-oxo-pyrrolidine-3-carboxylic acid (compound **38f**, 193.0 mg, 0.51 mmol) in DCE (5.0 ml) was added ammonium chloride (81.8 mg, 1.53 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (127.0 mg, 0.66 mmol), DIPEA (0.5 mL) and 1H-benzo[d][1,2,3]triazol-1-ol (20.7 mg, 0.15 mmol). The

reaction mixture was stirred at 45°C for 2 hours and then washed with ice-water, extracted with DCM twice. The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give compound **42b** (173 mg, crude), which was used directly in next step. LCMS ($M+H^+$): 378.

Step 2: preparation of tert-butyl (6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 42c)

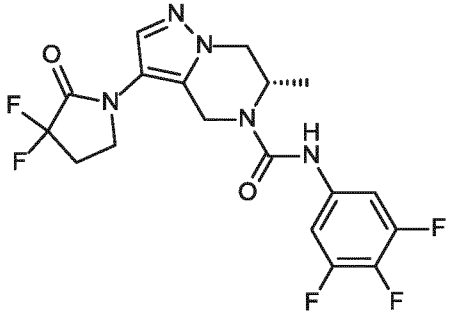
To a solution of tert-butyl (6S)-3-[(2S,3S)-3-carbamoyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **42b**, 1.2 g, 3.18 mmol) in dry THF (8.0 mL) was added pyridine (1.2 ml, 14.8 mmol). The mixture was flushed with nitrogen and cooled to 0°C, to which was then added dropwise of trifluoroacetic anhydride (1.2 mL, 8.59 mmol). The reaction mixture was stirred at 0°C for another 3 hours. The reaction mixture was quenched by adding ice-water, extracted with EtOAc twice. The organic phase was dried over Na_2SO_4, concentrated. The residue was purified by column chromatography {eluting with 60% EtOAc (containing 10% MeOH) in petroleum ether} to afford compound **42c** (670.0 mg). LCMS ($M+H^+$): 360.

Step 3: preparation of (6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 42)

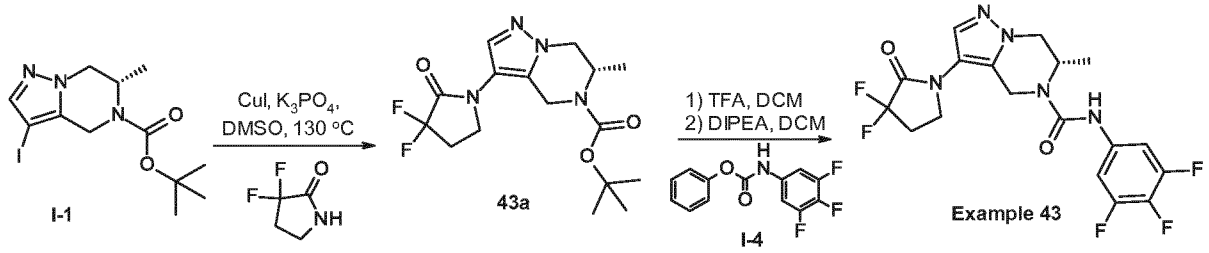
The mixture of tert-butyl (6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **41c**, 40.0 mg, 111 μmol), 2,2,2-trifluoroacetic acid (2.0 mL) and DCM (1.0 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated, the residue was dissolved in DCE (3.0 mL), to which were then added DIPEA (0.5 mL), and phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**, 44.1 mg, 167 μmol). The reaction mixture was stirred at 50°C for 2 hours, then cooled down, washed with water, extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column and then preparative HPLC to give **Example 42** (26.6 mg). LCMS ($M+H^+$): 430. ^1H NMR (400MHz, METHANOL-d_4) δ = 8.43 (d, *J*=5.7 Hz, 1H), 7.87 (d, *J*=2.1 Hz, 1H), 7.68 (dd, *J*=2.1, 5.7 Hz, 1H), 7.59 (s, 1H), 6.84 - 6.51 (m, 1H), 5.10 - 4.97 (m, 2H), 4.42 - 4.32 (m, 3H), 4.20 (dd, *J*=1.2, 12.8 Hz, 1H), 3.92 (td, *J*=7.0, 9.0 Hz, 1H), 3.04 - 2.88 (m, 2H), 1.43 (d, *J*=6.5 Hz, 3H), 1.25 (d, *J*=6.8 Hz, 3H).

Example 43

(6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: Preparation of tert-butyl (6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 43a)

To a solution of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 300 mg, 826 μmol), K_3PO_4 (526 mg, 2.48 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (47 mg, 330 μmol), CuI (31.5 mg, 165 μmol) in DMSO (10 mL) was added 3,3-difluoropyrrolidin-2-one (150 mg, 1.24 mmol) under argon. The mixture was stirred at 110 °C for 6h, then quenched with sat. aqueous solution of NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with sat NH_4Cl and brine, dried over Na_2SO_4 and concentrated to give the crude compound **43a** (280 mg) which was directly used in next step. LCMS (M+1): 357.

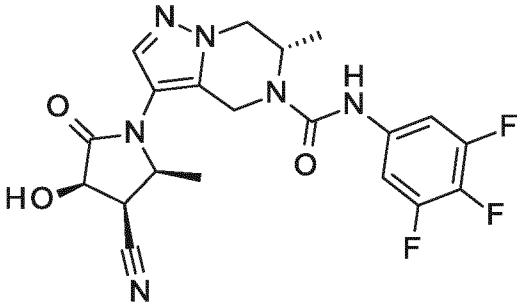
Step 2: Preparation of (6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 43)

To a solution of tert-butyl (6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **43a**, 280 mg, 786 μmol) in DCM (10 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 30 mins, then solvent was removed under reduced pressure. The residue was dissolved in DCM (10 mL), to which were added DIEA (508 mg, 686 μL, 3.93 mmol), and phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 252 mg, 943 μmol). The mixture was stirred at room temperature overnight, and then concentrated. The residue was purified by prep-HPLC to

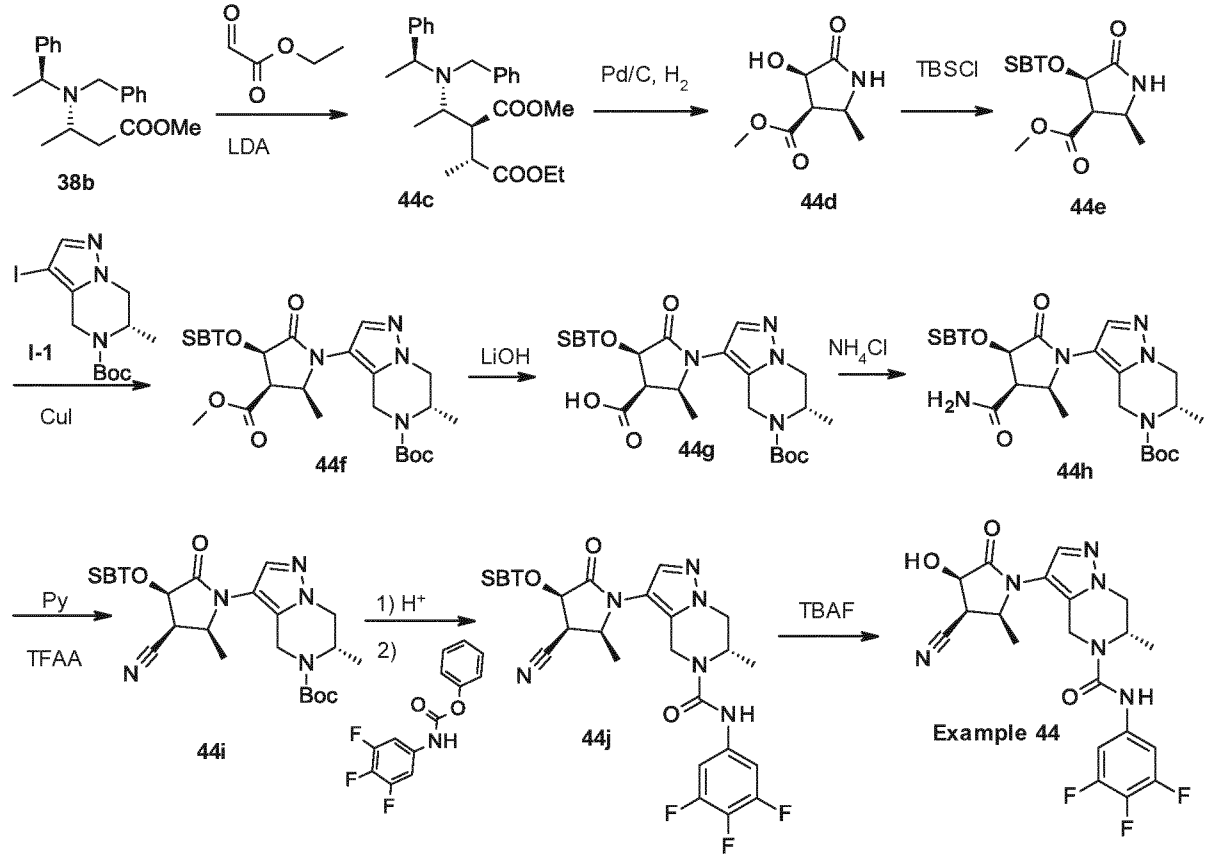
give **Example 43** (38 mg) as a white powder. LCMS (M+1): 430. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.75 (s, 1H), 7.28 (dd, *J*=6.4, 10.3 Hz, 2H), 5.09 (d, *J*=17.0 Hz, 1H), 5.02 - 4.92 (m, 1H), 4.56 (d, *J*=17.1 Hz, 1H), 4.38 - 4.27 (m, 1H), 4.19 (dd, *J*=1.0, 12.8 Hz, 1H), 4.02 - 3.85 (m, 2H), 2.77 (tt, *J*=6.7, 15.5 Hz, 2H), 1.28 (d, *J*=7.0 Hz, 3H).

Example 44

(6S)-3-[(2S,3S,4R)-3-cyano-4-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to following scheme:



Preparation of O1-ethyl O4-methyl (2R,3S)-3-[1-[benzyl-[(1S)-1-phenylethyl]amino]ethyl]-2-methyl-butanedioate (compound 44c)

To a stirring solution of methyl 3-[benzyl-[(1S)-1-phenylethyl]amino]butanoate (compound **38b**, 5.0 g, 16.1 mmol) in THF (100.0 mL) was added dropwise of LDA (24.1 mL, 48.2 mmol) at -78 °C. After being stirred for 1 hour, trimethyl borate (5.0 g, 48.2 mmol) was added and the mixture was stirred for another 30 minutes. Then a solution of ethyl 2-oxoacetate (3.3 g, 32.1 mmol) in THF (20 mL) was added dropwise at -78 °C, the temperature was maintained for 1 hour. The reaction was quenched by saturated aqueous ammonium chloride solution and extracted by EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (eluting with 10% EtOAc in petroleum ether) to give compound **44c** (3.6 g) as a yellow oil. LCMS ($M+H^+$): 414.

Preparation of methyl (2S,3R,4R)-4-hydroxy-2-methyl-5-oxo-pyrrolidine-3-carboxylate (compound 44d)

To a solution of O1-ethyl O4-methyl (2R,3S)-3-[1-[benzyl-[(1S)-1-phenylethyl]amino]ethyl]-2-methyl-butanedioate (compound **44c**, 4.8 g, 11.6 mmol) in MeOH (100.0 mL) was added palladium on carbon (0.5 g) in one portion under nitrogen. Then hydrogen (50 psi) was introduced to the system, the reaction mixture was stirred at room temperature for 16 hours, then filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (eluting with 5% methanol in dichloromethane) to give compound **44d** (1.7 g). LCMS ($M+H^+$): 174.

Preparation of methyl (2S,3R,4R)-4-[tert-butyl(dimethyl)silyl]oxy-2-methyl-5-oxo-pyrrolidine-3-carboxylate (compound 44e)

To a mixture of methyl (2S,3R,4R)-4-hydroxy-2-methyl-5-oxo-pyrrolidine-3-carboxylate (1.8 g, 10.4 mmol) and imidazole (1.4 g, 20.8 mmol) in DMF (20 mL) was added TBSCl (1.9 g, 12.5 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph (DCM: MeOH= 40:1) to give compound **44e** (2.8 g, 93.3% yield) as colorless oil. LCMS ($M+H^+$): 288.2

Preparation of tert-butyl (6S)-3-[(2S,3R,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 44f)

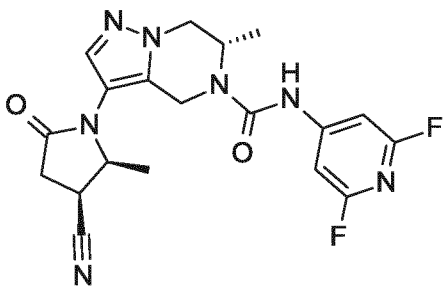
An oven-dried Schlenk tube were charged with (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (64.0 mg, 0.45 mmol), K_3PO_4 (959.5 mg, 4.52 mmol, 2.0 eq), CuI (85.7 mg, 0.45 mmol), (2S,3R,4R)-4-[tert-butyl(dimethyl)silyl]oxy-2-methyl-5-oxo-pyrrolidine-3-carboxylate (compound **44e**, 650.0 mg, 2.26 mmol), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (820.8 mg, 2.26 mmol, 1.0 eq) and toluene (15 mL). The mixture was stirred at 90 °C for 72 hours under N_2. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel chromatograph (PE: EtOAc= 1: 1). To give compound **44f** (177.5 mg, 15.0% yield) as a yellow oil. LCMS ($M+H^+$) = 523.3, ^1H NMR (400MHz, DMSO-d6) δ = 7.45 (s, 1H), 4.83 (d, J=17.3 Hz, 1H), 4.75 - 4.60 (m, 2H), 4.25 - 4.12 (m, 2H), 4.11 - 3.98 (m, 2H), 3.62 (s, 3H), 3.57 (t, J=6.4 Hz, 1H), 1.45 (s, 9H), 1.06 (d, J=6.3 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 0.86 (s, 9H), 0.13 (d, J=12.3 Hz, 6H)

Preparation of (6S)-3-[(2S,3S,4R)-3-cyano-4-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 44)

The title compound was prepared in analogy to **Example 40** by using tert-butyl (6S)-3-[(2S,3R,4R)-4-[tert-butyl(dimethyl)silyl]oxy-3-methoxycarbonyl-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **44f**) instead of tert-butyl (6S)-3-[3,4-trans-3-[tert-butyl(dimethyl)silyl]oxy-4-ethoxycarbonyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate *trans*-**I-40**. **Example 44** was obtained as a solid (14.6 mg). LCMS ($M+H^+$): 449. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.57 (s, 1H), 7.31 - 7.22 (m, 2H), 5.07 - 4.93 (m, 2H), 4.76 (d, *J*=9.8 Hz, 1H), 4.37 (d, *J*=16.9 Hz, 1H), 4.33 - 4.27 (m, 1H), 4.25 - 4.15 (m, 2H), 3.09 (t, *J*=9.5 Hz, 1H), 1.37 (d, *J*=6.2 Hz, 3H), 1.21 (d, *J*=6.8 Hz, 3H).

Example 45

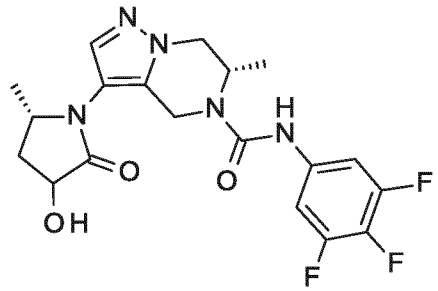
(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



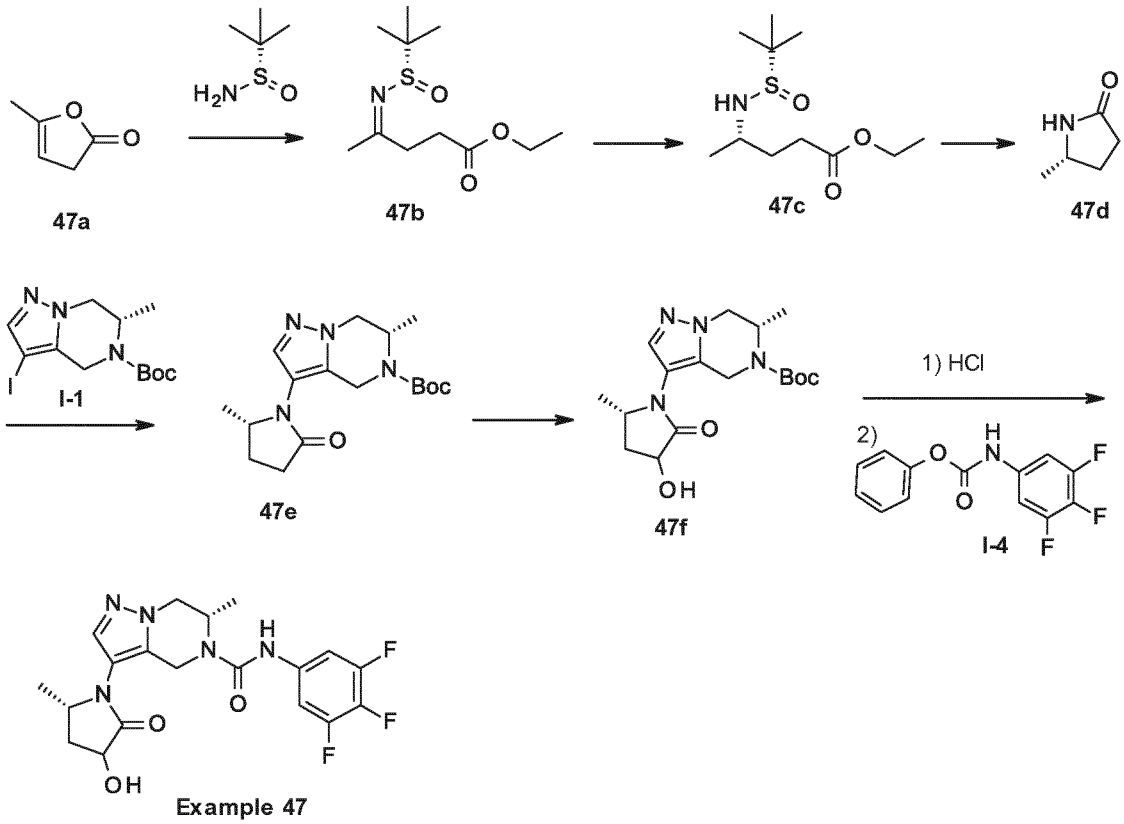
The **Example 45** was prepared in analogy to **Example 42** by using phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**). **Example 52** (50 mg) was obtained as white solid. LCMS $(M+H)^+$: 416.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.59 (s, 1H), 7.11 (s, 2H), 5.12 - 4.93 (m, 2H), 4.45 - 4.30 (m, 3H), 4.20 (dd, *J*=1.3, 12.9 Hz, 1H), 3.91 (td, *J*=6.9, 9.0 Hz, 1H), 3.06 - 2.85 (m, 2H), 1.42 (d, *J*=6.5 Hz, 3H), 1.25 (d, *J*=6.8 Hz, 3H).

Example 47

(6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 4-[(S)-tert-butylsulfinyl]iminopentanoate (compound 47b)

A mixture of 5-methyl-3H-furan-2-one (compound **47a**, 2.0 g, 20.4 mmol), (*S*)-2-methylpropane-2-sulfinamide (2.7 g, 22.4 mmol), EtOH (940.0 mg, 20.4 mmol) and $Ti(OEt)_4$ (9.3 g, 40.8 mmol) in THF (150.0 mL) was stirred at 60 °C for 16 hours under N_2. The reaction was quenched with saturated aqueous $NaHCO_3$ (60.0 mL) and then filtered. The filtrate was extracted with EtOAc (40 mL) three times. The organic layer was concentrated, and the residue was purified by column chromatography (PE: EtOAc=5: 1~2: 1) to give compound **47b** (3.3 g) as yellow oil. LCMS ($M+H^+$): 248.3.

Step 2: preparation of ethyl (4S)-4-[[(S)-tert-butylsulfinyl]amino]pentanoate (compound 47c)

To a solution of ethyl (4Z)-4-[(S)-tert-butylsulfinyl]iminopentanoate (compound **47b**, 3.3 g, 13.3 mmol) in THF (60 mL) was added L-selectride (16 mL, 16.0 mmol) dropwise at -78 °C under N_2. Then the mixture was stirred at -78 °C for 6 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) and filtered. The filtrate was diluted with water (40 mL) and extracted with EtOAc (30 mL) three times. The organic layer was concentrated, and the residue was purified by column chromatography (PE: EtOAc=5: 1~1: 1) to give compound **47c** (1.0 g) as yellow oil.

Step 3: preparation of (5S)-5-methylpyrrolidin-2-one (compound 47d)

To a solution of ethyl (4S)-4-[[(S)-tert-butylsulfinyl]amino]pentanoate (compound **47c**, 1.0 g, 4.0 mmol) in THF (15 mL) was added 1 N HCl (10 mL). The mixture was stirred at room temperature for 16 hours. The reaction was basified to pH=12 with saturated aqueous K_2CO_3 and then washed with EtOAc (10 mL) three times. The aqueous layer was concentrated to dryness. The residue was suspended in THF (50 mL) and filtered. The filtrate was concentrated to give compound **47d** (200 mg) as a light yellow oil.

Step 4: preparation of tert-butyl (6S)-6-methyl-3-[(2S)-2-methyl-5-oxo-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 47e)

A mixture of (5S)-5-methylpyrrolidin-2-one (compound **47d**, 70.0 mg, 0.7 mmol), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 254.2 mg, 0.7 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (10.0 mg, 0.07 mmol), CuI (13.3 mg, 0.07 mmol) and K_3PO_4 (297.0 mg, 1.4 mmol) in dioxane (3 mL) was stirred at 100 °C for 16 hours under N_2. The reaction solution was filtered, and the filtrate was concentrated. The residue was purified by prep-TLC to give compound **47e** (60.0 mg), LCMS ($M+H^+$): 335.2

Step 5: preparation of tert-butyl (6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 47f)

To a solution of tert-butyl (6S)-6-methyl-3-[(2S)-2-methyl-5-oxo-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **47e**, 40.0 mg, 0.12 mmol) in THF (2 mL) was added LiHMDS (0.48 mL, 0.48 mmol) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 30 mins. A solution of 2-(phenylsulfonyl)-3-phenyl-oxaziridine(Davis reagent, 48.0 mg, 0.18 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred at -78 °C-20 °C for 16 hours. The reaction was quenched with water (0.5 mL) and then concentrated, the residue was purified by prep-TLC (EtOAc as the eluent) to give compound **47f** (25.0 mg) as a yellow oil. LCMS ($M+H^+$): 351.1.

Step 6: preparation of (6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 47)

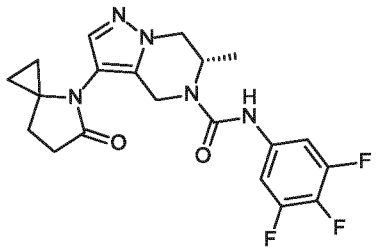
To a solution of tert-butyl (6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **47f**, 40.0 mg, 0.11 mmol) in DCM (2.0 mL) was added HCl/dioxane (0.5 mL, 2.0 mmol). The mixture was stirred at room temperature for 1h, and then concentrated to a yellow solid (30.0 mg, crude). The crude solid (27.5 mg, 0.11 mmol) was dissolved in DMF (2 mL), to which were added Et_3N (33.0 mg, 0.33 mmol) and phenyl N-(3,4,5-trifluorophenyl)carbamate (30.0 mg, 0.11 mmol). The mixture was stirred at room temperature for 2 hours, and then filtered. The filtrate was purified by prep-HPLC to give (6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (20.0 mg, 42.9%) as a white solid. The product was further separated by SFC to give two isomers: **Example 47-1** and **Example 47-2**.

Example 47-1 (7.1 mg), white solid; LCMS ($M+H^+$): 424.1, ^1H NMR: (400MHz, MeOD) δ ppm 7.60 (s, 1H), 7.28 - 7.25 (m, 2H), 5.01 - 4.94 (m, 1H), 4.85 (d, *J*=17.1 Hz, 1H), 4.56 - 4.42 (m, 2H), 4.33 - 4.25 (m, 1H), 4.20 - 4.09 (m, 2H), 2.35 - 2.18 (m, 2H), 1.28 (d, *J*=7.0 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 3H).

Example 47-2 (1.8 mg), white solid; LCMS ($M+H^+$): 424.1, ^1H NMR: (400MHz, MeOD) δ ppm 7.58 (s, 1H), 7.37 - 7.25 (m, 2H), 5.03-4.95 (m, 1H), 4.60 - 4.48 (m, 2H), 4.38 - 4.26 (m, 2H), 4.21 - 4.07 (m, 2H), 2.32 - 2.20 (m, 2H), 1.25 (d, *J*=6.6 Hz, 3H), 1.21 (d, *J*=6.8 Hz, 3H).

Example 49

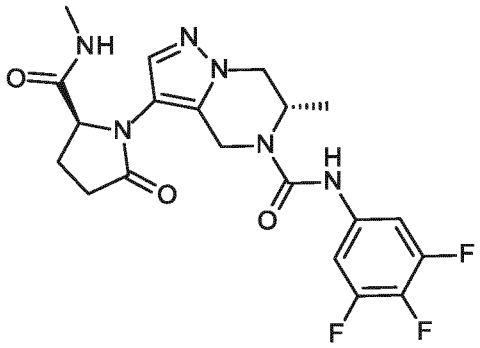
(6S)-6-methyl-3-(5-oxo-4-azaspiro[2.4]heptan-4-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



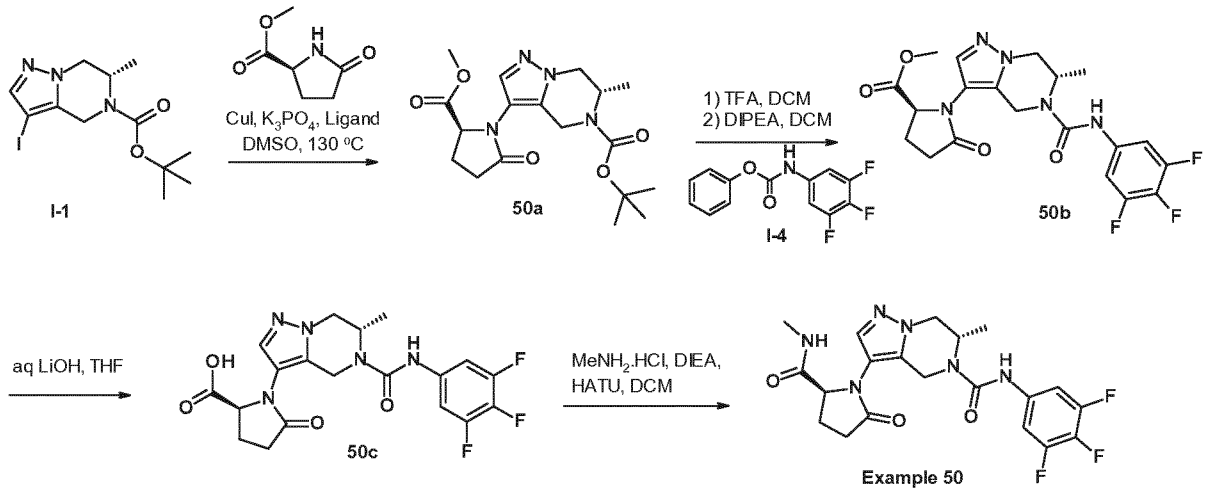
The title compound was prepared in analogy to the preparation of **Example 43** by using 4-azaspiro[2.4]heptan-5-one instead of 3,3-difluoropyrrolidin-2-one. **Example 49** was obtained as a a white solid (32 mg). LCMS (M+1): 420. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.44 (s, 1H), 7.29 (dd, *J*=6.4, 10.3 Hz, 2H), 5.01 - 4.92 (m, 1H), 4.84 (d, *J*=17.0 Hz, 1H), 4.33 (d, *J*=17.0 Hz, 1H), 4.34 - 4.28 (m, 1H), 4.22 - 4.07 (m, 1H), 2.78 - 2.62 (m, 2H), 2.41 - 2.25 (m, 2H), 1.24 (d, *J*=6.8 Hz, 3H), 0.72 (m, 4H).

Example 50

(6S)-6-methyl-3-[(2S)-2-(methylcarbamoyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of methyl (2S)-1-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-2-carboxylate (compound 50b)

Compound **50b** was prepared in analogy to the preparation of **Example 43** by using methyl (2S)-5-oxopyrrolidine-2-carboxylate instead of 3,3-difluoropyrrolidin-2-one. Crude compound **50b** (350 mg) was obtained, 100mg of which was purified by prep-HPLC to give compound **50b** (35 mg) as a white powder. LCMS (M+1): 452.

Preparation of (2S)-1-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-2-carboxylic acid (compound 50c)

To the solution of methyl (2S)-1-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-2-carboxylate (compound **50b**, 250 mg crude, 554 µmol) in THF (5 mL) was added aq. LiOH solution (0.5 M, 5 mL). The mixture was stirred at room temperature overnight, then neutralized with aq. HCl and concentrated. The residue was purified by prep-HPLC to give compound **50c** (110 mg) as a white powder. LCMS (M+1): 438.

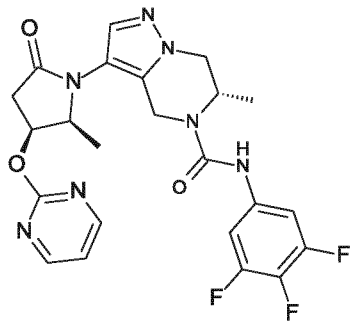
Preparation of (6S)-6-methyl-3-[(2S)-2-(methylcarbamoyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 50)

To a solution of (2S)-1-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-2-carboxylic acid (compound **50c**, 20 mg, 45.7 µmol), methylamine hydrochloride (6.17 mg, 91.5 µmol) in DCM (5 mL) was added DIEA (17.7 mg, 24 µl, 137 µmol) and HATU (34.8 mg, 91.5 µmol). The resulting mixture was stirred overnight at room temperature, and then concentrated. The residue was purified by prep-HPLC to give **Example 50** (6 mg) as a white powder. LCMS (M+1): 451. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.51 (s, 1H), 7.32 (dd, *J*=6.4, 10.3 Hz, 2H), 4.99 (d, *J*=17.1 Hz, 1H), 5.03 - 4.95 (m, 1H), 4.56 (dd, *J*=3.7, 8.3 Hz, 1H), 4.50 (d, *J*=17.0 Hz, 1H), 4.27 (dd, *J*=4.5, 12.5

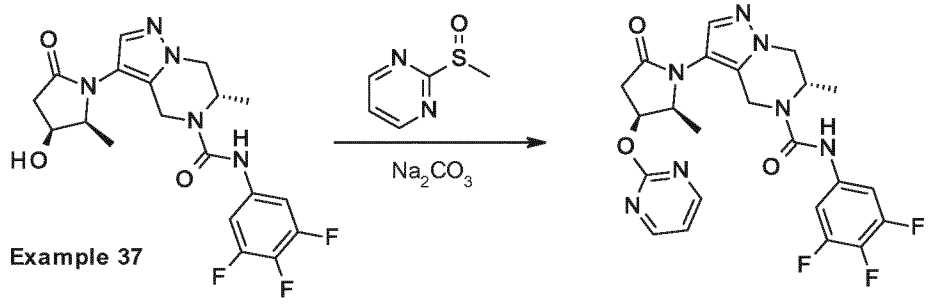
Hz, 1H), 4.16 - 4.08 (m, 1H), 2.73 - 2.65 (m, 1H), 2.69 (s, 3H), 2.61 - 2.47 (m, 2H), 2.19 - 2.09 (m, 1H), 1.29 (d, *J*=7.0 Hz, 3H).

Example 51

(6S)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The tittle compound was prepared according to following scheme:

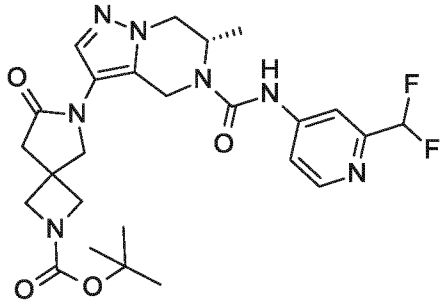


Example 37 Example 51

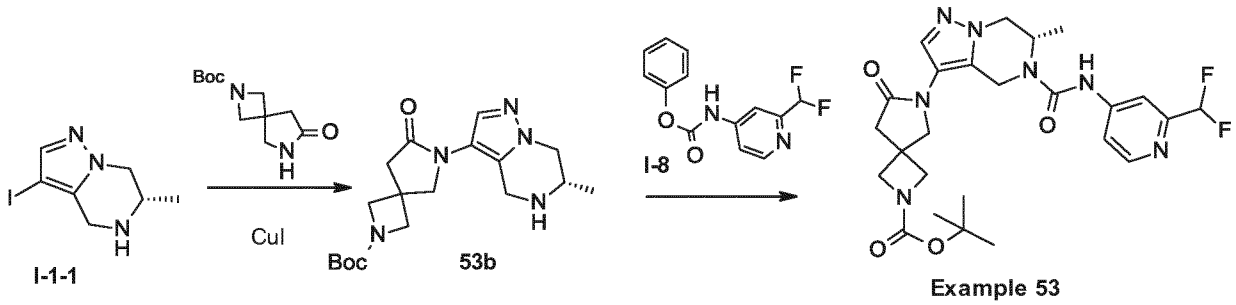
To a microwave vial was added (6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (**Example 37**, 151.0 mg, 1.06 mmol) and sodium carbonate (67.6 mg, 638 µmol) in dioxane (8 mL). The vial was capped and heated to 110 °C for 3hours. The reaction mixture was cooled down, washed with ice-water, extracted with EtOAc twice. The combined organic phase was concentrated and the residue was purified by prep-HPLC to give **Example 51** (29.7 mg). LCMS ($M+H^+$): 502. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.64 (d, *J*=4.8 Hz, 2H), 7.59 (s, 1H), 7.34 - 7.26 (m, 2H), 7.19 (t, *J*=4.9 Hz, 1H), 5.92 - 5.87 (m, 1H), 5.06 - 4.97 (m, 2H), 4.59 - 4.49 (m, 1H), 4.43 (d, *J*=16.8 Hz, 1H), 4.34 (dd, *J*=4.3, 12.8 Hz, 1H), 4.19 (dd, *J*=1.3, 12.8 Hz, 1H), 3.13 (dd, *J*=6.5, 17.7 Hz, 1H), 2.73 (dd, *J*=3.1, 17.6 Hz, 1H), 1.26 (d, *J*=6.7 Hz, 3H), 1.23 (d, *J*=6.8 Hz, 3H).

Example 53

tert-butyl 6-[(6S)-5-[[2-(difluoromethyl)-4-pyridyl]carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl 6-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate (compound 53b)

To a solution of tert-butyl 6-oxo-2,7-diazaspiro[3.4]octane-2-carboxylate (271.5 mg, 1.2 mmol) in dioxane (15 mL) were added (6S)-3-iodo-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine(Intermediate **I-1-1**, 263.0 mg, 1.0 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (14.2 mg, 0.1 mmol), K_3PO_4 (637.0 mg, 3.0 mmol) and CuI (19.0 mg, 0.1 mmol) under N_2, and the mixture was stirred at room temperature for 12 hours and then filtered and concentrated under reduced pressure, the residue was purified by column chromatograph on silica gel (DCM/MeOH=50/1 to 20/1) to give compound **53b** (200 mg) as a white oil. LCMS ($M+H^+$): 362.

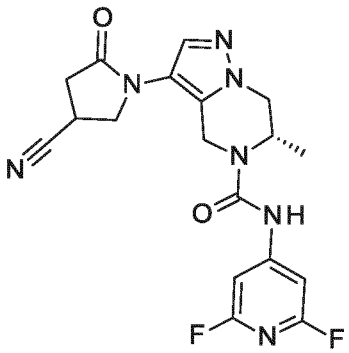
Step 2: preparation of tert-butyl 6-[(6S)-5-[(3-chloro-4-fluoro-phenyl)carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate (Example 53)

To a solution of tert-butyl 6-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate (compound **53b**, 150 mg, 332 μmol) and DIPEA (290 μl, 1.66 mmol) in DCE (5 mL) was added phenyl (2-(difluoromethyl)pyridin-4-yl)carbamate (105 mg, 398 μmol) at 20 °C, and then the mixture was stirred at 60 °C for 1 hour.

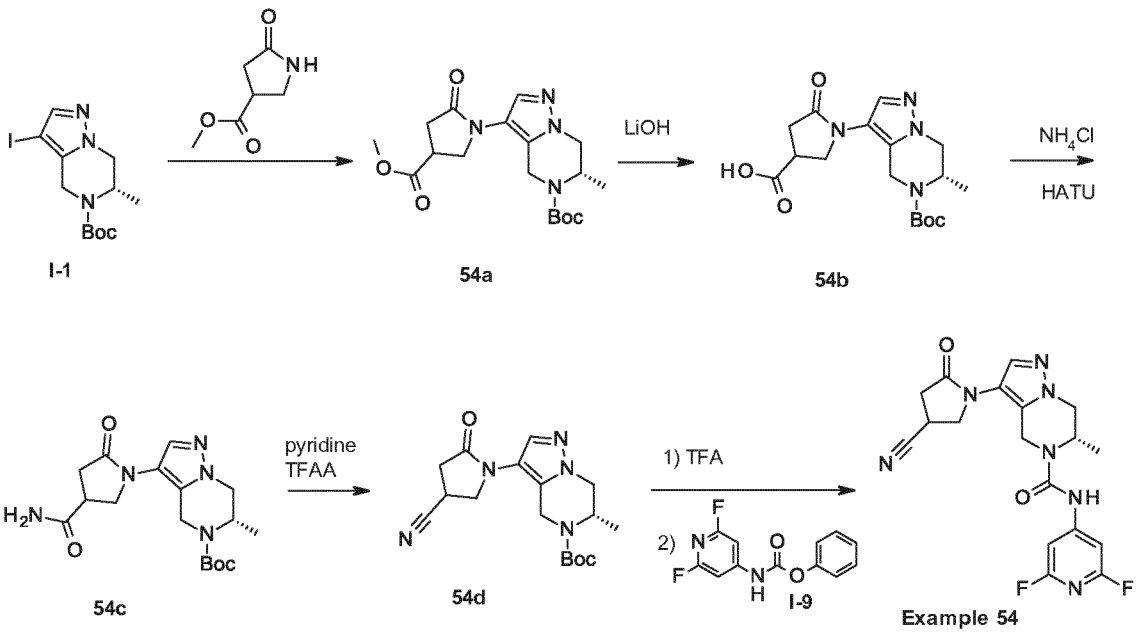
The crude reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 12 g, 10% to 80% EtOAc in hexanes, EtOAc contain 10% MeOH) to give **Example 53** (53 mg) as a white solid. LCMS ($M+H^+$): 532.2. ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.43 (d, *J*=5.7 Hz, 1H), 7.87 (d, *J*=2.1 Hz, 1H), 7.73 - 7.61 (m, 2H), 6.67 (d, *J*=56.0 Hz, 1H), 5.09 (d, *J*=17.0 Hz, 1H), 5.02 - 4.96 (m, 1H), 4.55 (d, *J*=17.0 Hz, 1H), 4.32 (dd, *J*=4.4, 12.8 Hz, 1H), 4.17 (dd, *J*=1.1, 12.8 Hz, 1H), 4.12 - 3.98 (m, 6H), 2.88 (s, 2H), 1.47 (s, 9H), 1.29 (d, *J*=6.8 Hz, 3H).

Example 54

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl (6S)-3-(4-methoxycarbonyl-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 54a)

A mixture of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 364 mg, 1.0 mmol), methyl 5-oxopyrrolidine-3-carboxylate (286 mg, 2.0 mmol), (1S,2S)-cyclohexane-1,2-diamine (46 mg, 0.4 mmol), CuI (38 mg, 0.2 mmol) and K_3PO_4 (636 mg, 3 mmol) in DMSO (10 mL) under N_2 was stirred at microwave for 2 hours at room temperature. The reaction mixture was diluted with EtOAc (20 mL) and washed with water and brine. The organic layer was concentrated to afford compound **54a** (200 mg) as a slight yellow oil. LCMS ($M+H^+$): 379.

Step 2: preparation of 1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-3-carboxylic acid (compound 54b)

A mixture of tert-butyl (6S)-3-(4-methoxycarbonyl-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **54a**, 200 mg,0.53 mmol) and $LiOH \cdot H_2O$ (110 mg, 2.62 mmol) in THF/H_2O (10 mL, 5:1) was stirred at room temperature for 2 hours. Then the reaction was adjusted to pH = 4, extracted with DCM (20 mL) two times, the organic layer was dried and concentrated to compound **54b** (183 mg) as slight yellow solid LCMS ($M+H^+$): 365.

Step 3: preparation of tert-butyl (6S)-3-(4-carbamoyl-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 54c)

A mixture of 1-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-5-oxo-pyrrolidine-3-carboxylic acid (compound **54b**, 183 mg, 0.5 mmol), HATU (210 mg, 0.6 mmol), NH_4Cl (138 mg, 2.5 mmol) and DIPEA (770 mg, 6 mmol) in THF (10 mL) was stirred at 60 °C for 2 hours. The reaction mixture was diluted with hydrochloride acid (0.5 M, 15 mL), and extracted with EtOAc (20 mL) twice. The organic layer was concentrated to afford compound **54c** (150 mg) as a slight yellow solid. LCMS ($M+H^+$): 364.

Step 4: preparation of tert-butyl (6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 54d)

To a solution of tert-butyl (6S)-3-(4-carbamoyl-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **54c**, 150 mg, 0.41 mmol) in dry tetrahydrofuran (5.0 mL) at 0 °C under nitrogen was added pyridine (0.5 mL, 6.2 mmol) followed by dropwise addition of a solution of trifluoroacetic anhydride (0.5 mL, 3.5 mmol) in dry tetrahydrofuran (1.0 mL). The resulting reaction mixture was allowed to warm slowly to room temperature, and stirred overnight, then quenched with ice-water, and extracted with EtOAc (20 mL) twice. The organic layer was concentrated to afford compound **54d** (138 mg) as a slight yellow solid. LCMS ($M+H^+$): 346.

Step 5: preparation of (6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 54)

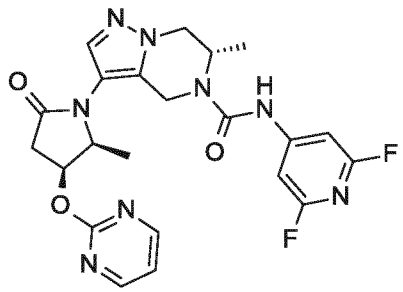
A mixture of tert-butyl (6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **54d**, 200 mg, 579 μmol) and 2,2,2-trifluoroacetic acid (446 μL, 5.79 mmol) in isopropyl acetate (1 mL) was stirred at 70 °C for 2 hours. The reaction mixture was concentrated to remove most of the TFA, the residue was dissolved in isopropyl acetate (1 mL), then added DIPEA (374 mg, 2.9 mmol) and phenyl (2,6-difluoropyridin-4-yl)carbamate (Intermediate **I-9**, 174 mg, 695 μmol). The reaction mixture was stirred at 70 °C for 1 hour. The reaction mixture was concentrated in *vacuo* and the residue was purified by flash chromatography (silica gel, 40 g, 10% to 70% EtOAc in hexanes, EtOAc contain 10% MeOH), and then by SFC to give **Example 54** as two isomers, **Example 54-1** and **Example 54-2**.

Example 54-1, 70 mg, white solid. LCMS ($M+H^+$): 402.1. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.65 (s, 1H), 7.10 (s, 2H), 5.09 (d, *J*=17.1 Hz, 1H), 5.04 - 4.94 (m, 1H), 4.53 (d, *J*=17.0 Hz, 1H), 4.32 (dd, *J*=4.5, 12.8 Hz, 1H), 4.24 - 4.14 (m, 2H), 4.05 (dd, *J*=6.1, 9.8 Hz, 1H), 3.84 - 3.72 (m, 1H), 3.05 - 2.94 (m, 1H), 2.93 - 2.83 (m, 1H), 1.29 (d, *J*=7.0 Hz, 3H).

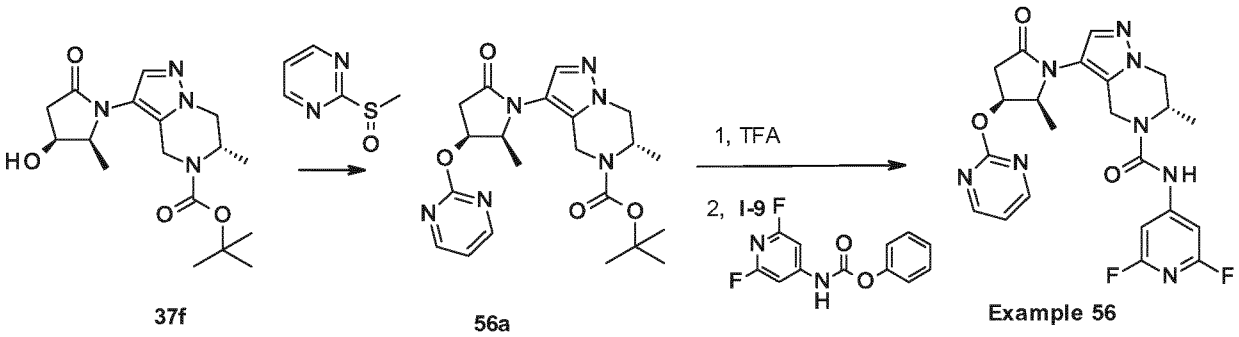
Example 54-2, 70 mg, white solid. LCMS ($M+H^+$): 402.1. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 9.77 (s, 1H), 7.62 (s, 1H), 7.16 (s, 2H), 4.99 (d, *J*=17.2 Hz, 1H), 4.91 - 4.81 (m, 1H), 4.42 (d, *J*=17.1 Hz, 1H), 4.31 - 3.96 (m, 4H), 3.81 (quin, *J*=7.9 Hz, 1H), 2.96 - 2.70 (m, 2H), 1.16 (d, *J*=6.7 Hz, 3H).

Example 56

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



37f 56a Example 56

Step 1: preparation of tert-butyl (6S)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 56a)

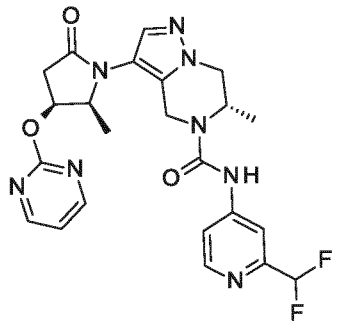
A mixture of tert-butyl (6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **37f**, 70 mg, 200 μmol), 2-(methylsulfinyl)pyrimidine (56.8 mg, 400 μmol) and sodium carbonate (63.5 mg, 599 μmol,) in dioxane (2 mL) was heated at 110 °C for16 hours. The crude reaction mixture was concentrated in *vacuo*. The residue was purified by flash chromatography (silica gel, 12 g, 20% to 80% EtOAc in hexanes, EtOAc contain 10% MeOH) to give compound **56a** (50 mg) as light yellow oil, LCMS ($M+H^+$): 429.2.

Step 2: preparation of (6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 56)

A mixture of (S)-tert-butyl 6-methyl-3-((2S,3S)-2-methyl-5-oxo-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (compound **56a**, 20 mg, 46.7 μmol) and 2,2,2-trifluoroacetic acid (121 μl) in DCM (2 mL) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, the residue was dissolved in DMF (2 mL), to which were then added DIPEA (30.2 mg, 233 μmol) and phenyl (2,6-difluoropyridin-4-yl)carbamate (Intermediate **I-9**, 14 mg, 56 μmol). The reaction mixture was stirred at 60 °C for 1 hour. The reaction mixture was purified by prep-HPLC to give **Example 56** (7 mg) as white solid. LCMS ($M+H^+$): 485.2. ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.65 (d, *J*=4.9 Hz, 2H), 7.60 (s, 1H), 7.19 (t, *J*=4.8 Hz, 1H), 7.13 (s, 2H), 5.94 - 5.85 (m, 1H), 5.13 - 5.00 (m, 2H), 4.54 (dd, *J*=5.4, 6.6 Hz, 1H), 4.47 (d, *J*=16.9 Hz, 1H), 4.36 (dd, *J*=4.2, 12.8 Hz, 1H), 4.21 (dd, *J*=1.3, 12.8 Hz, 1H), 3.14 (dd, *J*=6.5, 17.7 Hz, 1H), 2.73 (dd, *J*=3.0, 17.7 Hz, 1H), 1.26 (d, *J*=6.7 Hz, 3H), 1.24 (d, *J*=6.7 Hz, 3H).

Example 57

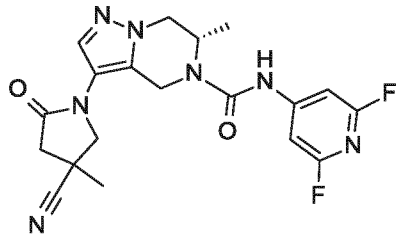
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



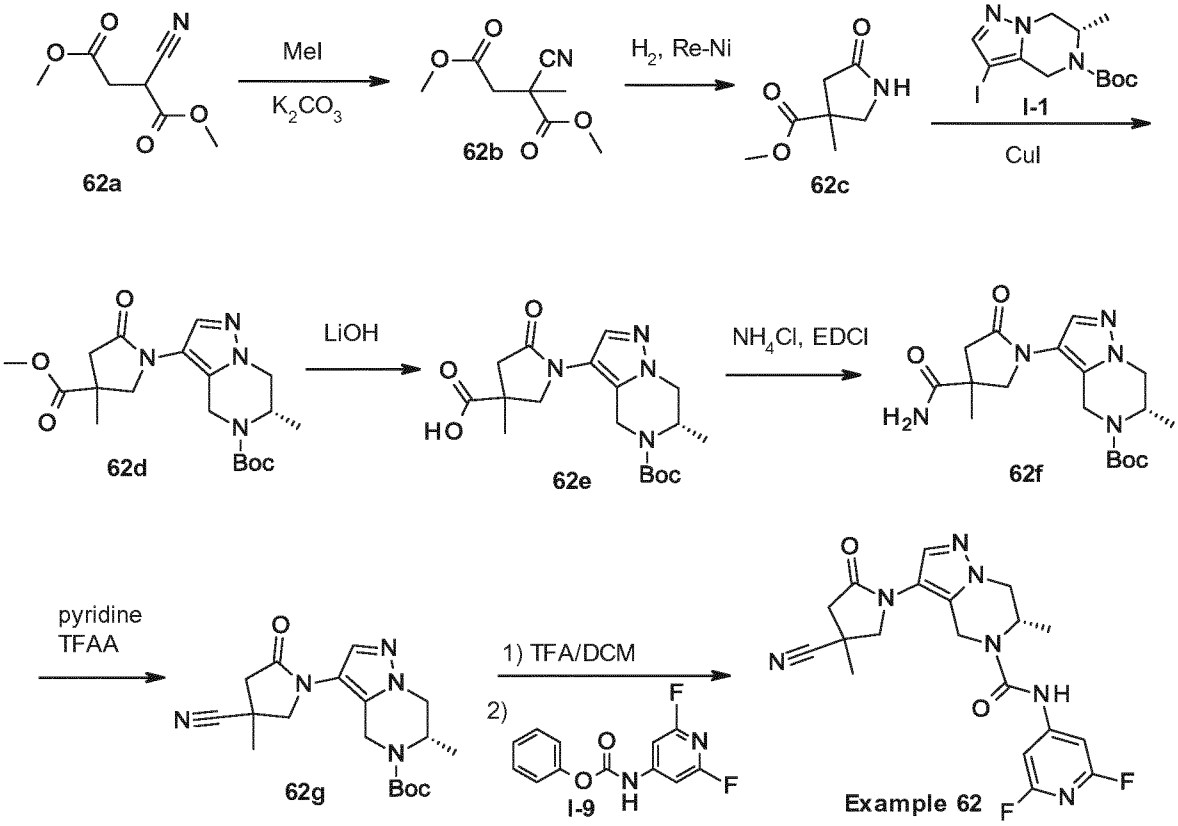
A mixture of (S)-tert-butyl 6-methyl-3-((2S,3S)-2-methyl-5-oxo-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (compound **56a**, 20 mg, 46.7 μmol) and 2,2,2-trifluoroacetic acid (121 μL) in DCM (2 mL) was stirred at room temperature for 30 mins. The reaction mixture was concentrated, the residue was dissolved in DMF (2 mL), to which were then then added DIPEA (30.2 mg, 233 μmol) and phenyl (2,6-difluoropyridin-4-yl)carbamate (Intermediate **I-8**, 14.8 mg, 56 μmol). The reaction mixture was stirred at 60 °C for 1 hour. The reaction mixture was purified by prep-HPLC to give **Example 57** (7 mg) as a white solid. LCMS ($M+H^+$): 499.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.53 (d, *J*=4.9 Hz, 2H), 8.31 (d, *J*=5.7 Hz, 1H), 7.77 (d, *J*=2.2 Hz, 1H), 7.58 (dd, *J*=2.1, 5.7 Hz, 1H), 7.48 (s, 1H), 7.07 (t, *J*=4.8 Hz, 1H), 6.74 - 6.37 (m, 1H), 5.83 - 5.70 (m, 1H), 5.05 - 4.85 (m, 2H), 4.52 - 4.33 (m, 2H), 4.25 (dd, *J*=4.3, 12.8 Hz, 1H), 4.09 (d, *J*=12.8 Hz, 1H), 3.02 (dd, *J*=6.5, 17.7 Hz, 1H), 2.62 (dd, *J*=3.1, 17.7 Hz, 1H), 1.15 (d, *J*=6.7 Hz, 3H), 1.13 (d, *J*=6.7 Hz, 3H).

Example 62

(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Preparation of dimethyl 2-cyano-2-methyl-butanedioate (compound 62b)

To a solution of dimethyl 2-cyanobutanedioate (compound **62a**, 513 mg, 3 mmol) in acetone (5 mL) was added iodomethane (639 mg, 4.5 mmol) and potassium carbonate (829 mg, 6 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was extracted with EtOAc twice, washed with water. The combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give compound **62b** (556 mg, crude). LCMS ($M+H^+$): 186.

Preparation of methyl 3-methyl-5-oxo-pyrrolidine-3-carboxylate (compound 62c)

To a suspension of Raney nickel (85.7 mg, 1.0 mmol) (pre-washed with methanol) in solvent MeOH (10 mL) was added dimethyl 2-cyano-2-methyl-butanedioate (compound **46b**, 185.0 mg, 1.0 mmol) in MeOH (5 mL). The reaction mixture was heated at 40 °C under 1 atmosphere of H_2 overnight. The reaction mixture was filtered and concentrated to give compound **62c** (157.1 mg, crude). LCMS ($M+H^+$): 158.

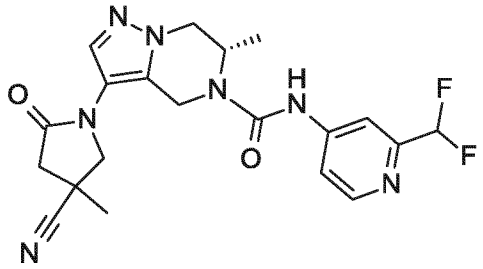
Preparation of (6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 62)

The title compound was prepared in analogy to **Example 54** by using methyl 3-methyl-5-oxo-pyrrolidine-3-carboxylate (compound **62c**) instead of methyl 5-oxopyrrolidine-3-carboxylate. **Example 62** was obtained as a solid (25.0 mg). LCMS ($M+H^+$): 416. ^1H NMR

(400MHz, METHANOL-d_4) δ = 7.64 (s, 1H), 7.10 (s, 2H), 5.16 - 5.04 (m, 1H), 5.02 - 4.93 (m, 1H), 4.60 - 4.50 (m, 1H), 4.32 (dd, *J*=4.4, 12.7 Hz, 1H), 4.26 - 4.15 (m, 2H), 3.93 - 3.85 (m, 1H), 3.13 - 3.05 (m, 1H), 2.79 - 2.72 (m, 1H), 1.69 (s, 3H), 1.29 (d, *J*=6.8 Hz, 3H).

Example 63

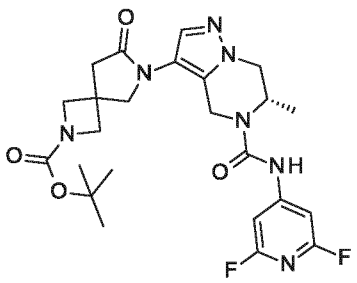
(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared in analogy to **Example 62** by using phenyl N-(2-difluoromethyl-4-pyridyl)carbamate (Intermediate **I-8**) instead of phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**). **Example** 62 (35 mg) was obtained. LCMS ($M+H^+$): 430. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.42 (d, *J*=5.6 Hz, 1H), 7.87 (s, 1H), 7.70 - 7.63 (m, 2H), 6.67 (t, *J*=56 Hz, 1H), 5.13 (d, *J*=8.0 Hz, 0.5H), .5.09 (d, *J*=8.0 Hz, 0.5H), 5.05 - 4.96 (m, 1H), 4.58 (d, *J*=8.0 Hz, 0.5H), 4.54 (d, *J*=8.0 Hz, 0.5H), 4.33 (dd, *J*=4.5, 12.8 Hz, 1H), 4.27 - 4.15 (m, 2H), 3.93 - 3.84 (m, 1H), 3.13 - 3.05 (m, 1H), 2.79 - 2.71 (m, 1H), 1.69 (s, 3H), 1.30 (d, *J*=6.8 Hz, 3H).

Example 64

tert-butyl 6-[(6S)-5-[(2,6-difluoro-4-pyridyl)carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate

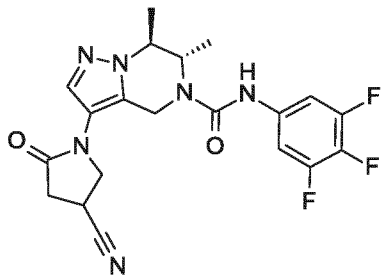


The **Example 64** was prepared in analogy to **Example 53** by using phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**) instead of phenyl N-[2-(difluoromethyl)-4-pyridyl]carbamate (Intermediate **I-8**). **Example 64** (60 mg) was obtained as a white solid. LCMS

$(M+H)^+$: 518.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.64 (s, 1H), 7.10 (s, 2H), 5.07 (d, *J*=17.0 Hz, 1H), 5.03 - 4.94 (m, 1H), 4.53 (d, *J*=17.0 Hz, 1H), 4.31 (dd, *J*=4.4, 12.8 Hz, 1H), 4.17 (dd, *J*=1.2, 12.8 Hz, 1H), 4.10 - 4.00 (m, 6H), 2.87 (s, 2H), 1.47 (s, 9H), 1.29 (d, *J*=6.8 Hz, 3H).

Example 65

(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



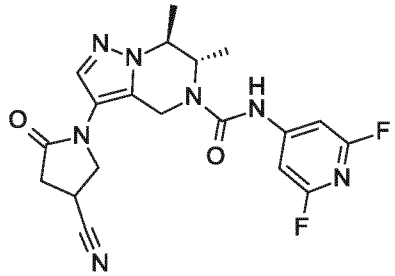
The **Example 65** and **66** was prepared in analogy to **Example 54** by using tert-butyl (6S,7S)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (intermediate **I-2**) instead of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (intermediate **I-1**) and phenyl N-(3,4,5-trifluorophenyl)carbamate (intermediate **I-4**) instead of phenyl N-(2,6-difluoro-4-pyridyl)carbamate (intermediate **I-9**). Separation of the final product by SFC (chiral column, chiralpak® IC, 5 μm, 30 × 250 mm; mobile phase, 60% CO_2 and 40% MeOH (MeOH+0.5% NH_3H_2O); flow rate 80 mL/min, back pressure 100 bar) gave **Example 65** as two isomers, **Example 65-1** and **Example 65-2.**

Example 65-1 was obtained (60 mg) as white solid. LCMS $(M+H)^+$: 433.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.66 (s, 1H), 7.32 - 7.28 (m, 2H), 5.06 (d, *J*=17.0 Hz, 1H), 4.76 (q, *J*=6.5 Hz, 1H), 4.49 (d, *J*=17.0 Hz, 1H), 4.43 - 4.33 (m, 1H), 4.20 - 4.04 (m, 2H), 3.77 (td, *J*=7.8, 15.6 Hz, 1H), 3.04 - 2.94 (m, 1H), 2.93 - 2.83 (m, 1H), 1.45 (d, *J*=6.6 Hz, 3H), 1.25 (d, *J*=6.8 Hz, 3H).

Example 65-2 was obtained (60 mg) as white solid. LCMS $(M+H)^+$: 433.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.66 (s, 1H), 7.38 - 7.24 (m, 2H), 5.07 (d, *J*=16.9 Hz, 1H), 4.77 (q, *J*=6.7 Hz, 1H), 4.49 (d, *J*=16.9 Hz, 1H), 4.38 (q, *J*=6.9 Hz, 1H), 4.18 (dd, *J*=8.3, 9.8 Hz, 1H), 4.05 (dd, *J*=6.2, 9.8 Hz, 1H), 3.85 - 3.71 (m, 1H), 3.05 - 2.94 (m, 1H), 2.93 - 2.82 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.24 (d, *J*=7.0 Hz, 3H).

Example 67

(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



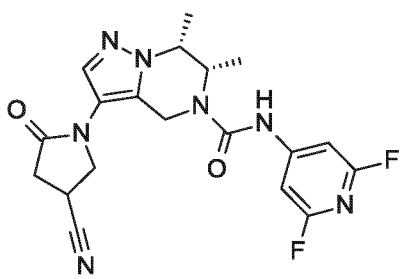
The **Example 67** was prepared in analogy to **Example 54** by using tert-butyl (6S,7S)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-2**) instead of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**). Separation of the final product with SFC (chiral column, chiralpak® IC, 5 μm, 30 × 250 mm; mobile phase, 60% CO_2 and 40% MeOH (MeOH+0.5% NH_3H_2O); flow rate 80 mL/min, back pressure 100 bar) gave **Example 67** as two isomers, **Example 67-1** and **Example 67-2.**

Example 67-1 was obtained (60 mg) as white solid. LCMS $(M+H)^+$: 416.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.66 (s, 1H), 7.13 (s, 2H), 5.12 (d, *J*=17.0 Hz, 1H), 4.79 (q, *J*=6.2 Hz, 1H), 4.53 (d, *J*=17.1 Hz, 1H), 4.44 - 4.35 (m, 1H), 4.21 - 4.02 (m, 2H), 3.87 - 3.70 (m, 1H), 3.05 - 2.95 (m, 1H), 2.92 - 2.83 (m, 1H), 1.45 (d, *J*=6.6 Hz, 3H), 1.27 (d, *J*=7.0 Hz, 3H).

Example 67-2 was obtained (40 mg) as white solid. LCMS $(M+H)^+$: 416.2, ^1H NMR (400MHz, METHANOL-d_4) δ = 7.66 (s, 1H), 7.13 (s, 2H), 5.12 (d, *J*=17.0 Hz, 1H), 4.80 (q, *J*=6.6 Hz, 1H), 4.54 (d, *J*=17.0 Hz, 1H), 4.40 (q, *J*=6.7 Hz, 1H), 4.19 (dd, *J*=8.4, 9.7 Hz, 1H), 4.05 (dd, *J*=6.2, 9.8 Hz, 1H), 3.78 (td, *J*=7.7, 15.5 Hz, 1H), 3.05 - 2.95 (m, 1H), 2.94 - 2.83 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H), 1.26 (d, *J*=6.8 Hz, 3H).

Example 68

(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



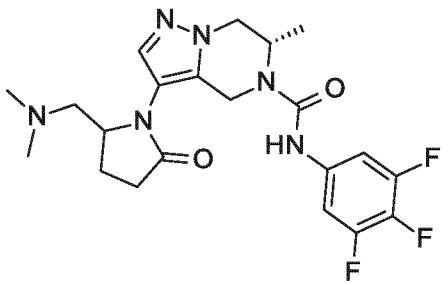
The **Example 68** was prepared in analogy to **Example 54** by using tert-butyl (6S,7R)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (intermediate **I-3**) instead of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**). Separation of the final product with SFC (chiral column, chiralpak® IC, 5 μm, 30 × 250 mm; mobile phase, 70% CO_2 and 30% MeOH (MeOH+0.5% NH_3H_2O); flow rate 80 mL/min, back pressure 100 bar) gave **Example 68** as two isomers, **Example 68-1** and **Example 68-2**.

Example 68-1 was obtained (48 mg) as white solid. LCMS $(M+H)^+$: 416.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.64 (s, 1H), 7.10 (s, 2H), 5.06 (d, *J*=17.1 Hz, 1H), 4.83 - 4.70 (m, 1H), 4.53 (d, *J*=17.2 Hz, 1H), 4.49 - 4.40 (m, 1H), 4.19 - 4.05 (m, 2H), 3.87 - 3.70 (m, 1H), 3.06 - 2.94 (m, 1H), 2.93 - 2.83 (m, 1H), 1.63 (d, *J*=6.7 Hz, 3H), 1.18 (d, *J*=7.0 Hz, 3H).

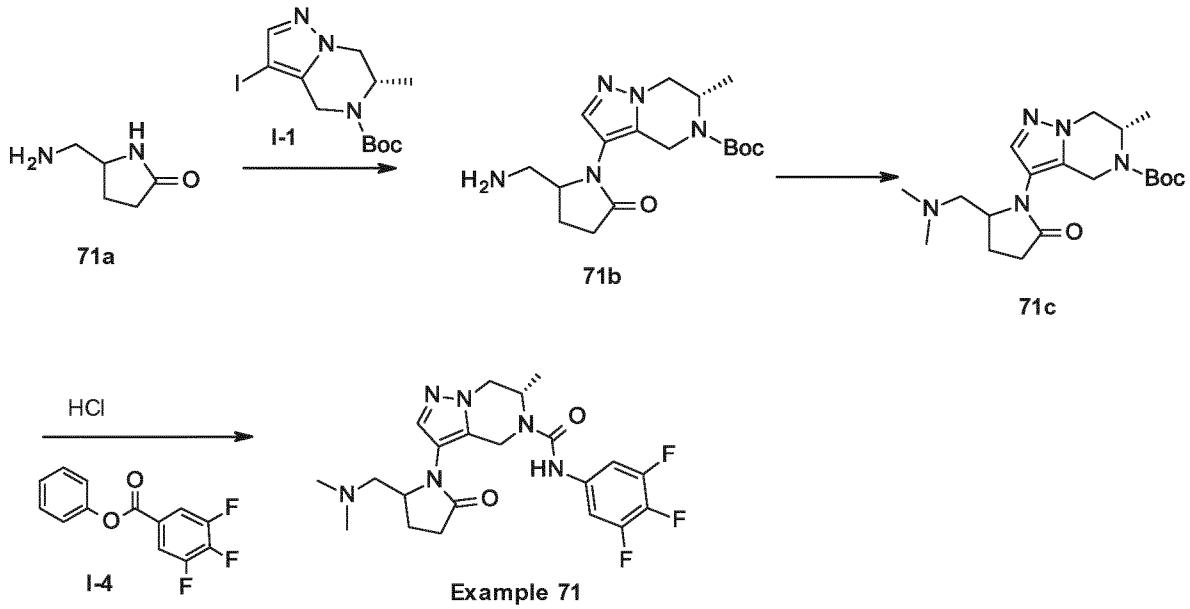
Example 68-2 was obtained (53 mg) as white solid. LCMS $(M+H)^+$: 416.2, ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.64 (s, 1H), 7.11 (s, 2H), 5.06 (d, *J*=17.0 Hz, 1H), 4.76 (dd, *J*=4.1, 6.8 Hz, 1H), 4.53 (d, *J*=17.1 Hz, 1H), 4.50 - 4.42 (m, 1H), 4.19 (dd, *J*=8.4, 9.8 Hz, 1H), 4.03 (dd, *J*=6.2, 9.8 Hz, 1H), 3.85 - 3.72 (m, 1H), 3.06 - 2.95 (m, 1H), 2.92 - 2.84 (m, 1H), 1.63 (d, *J*=6.7 Hz, 3H), 1.17 (d, *J*=6.8 Hz, 3H).

Example 71

(6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: **preparation of tert-butyl (6S)-3-[2-(aminomethyl)-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 71b)**

A mixture of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 636.34 mg, 1.75 mmol), 5-(aminomethyl)pyrrolidin-2-one (compound **71a**, 200.0 mg, 1.75 mmol, 1.0 eq), (1S,2S)-cyclohexane-1,2-diamine (99.69 mg, 0.700 mmol), CuI (66.4 mg, 0.35 mmol) and K_3PO_4 (1.11 g, 5.26 mmol, 3.0 eq) in DMSO (10 mL) was stirred at 110 °C for 12 hours under N_2 protection. Then the reaction mixture was filtered and the filtrate was purified by pre-HPLC to give compound **71b** (100.0 mg) as white solid.

Step 2: **preparation of tert-butyl (6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 71c)**

To a solution of tert-butyl (6S)-3-[2-(aminomethyl)-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **71b**, 90.0 mg, 0.26 mmol) and 1,3,5-trioxane (232.01 mg, 2.58 mmol) in methanol (10 mL) was added palladium under carbon (2.74 mg, 0.03 mmol) under H_2. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated to give crude compound **71c** (40.0 mg).

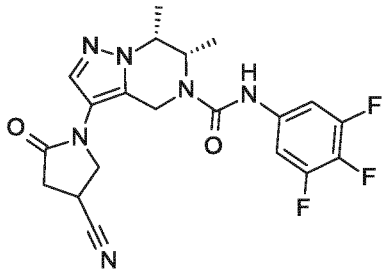
Step 3: **preparation of (6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 71)**

The **Example 71** was prepared in analogy to **Example 1** by using tert-butyl (6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-

a]pyrazine-5-carboxylate (compound **71c**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**). **Example 71** (6.1 mg) was obtained as a colorless oil. LCMS $(M+H)^+$: 451.0, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 8.43 (br s, 1H), 7.67 - 7.46 (m, 1H), 7.40 - 7.23 (m, 2H), 5.01 (br s, 2H), 4.48 (d, *J*=16.9 Hz, 1H), 4.39 - 4.26 (m, 2H), 4.23 - 4.10 (m, 1H), 2.87 - 2.62 (m, 3H), 2.60 - 2.53 (m, 1H), 2.52 - 2.40 (m, 6H), 2.16 - 2.06 (m, 2H), 1.40 - 1.13 (m, 3H).

Example 72

(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



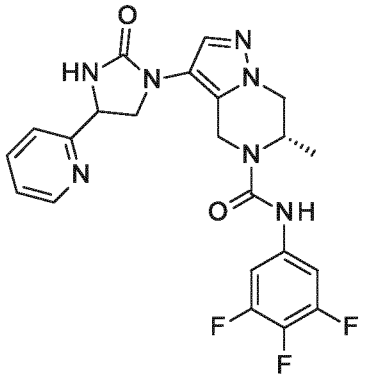
The **Example 72** was prepared in analogy to **Example 54** by using tert-butyl (6S,7R)-3-iodo-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-3**) instead of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**) and phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**) instead of phenyl N-(2,6-difluoro-4-pyridyl)carbamate (Intermediate **I-9**). Separation of the final product by SFC (chiral column, chiralpak® AD-H, 5 µm, 20 × 250 mm; mobile phase, 70% CO_2 and 30% MeOH (MeOH+0.5%NH_3H_2O); flow rate 65 mL/min, back pressure 100 bar) gave **Example 72** as two isomers, **Example 72-1** and **Example 72-2**.

Example 72-1 was obtained (40 mg) as a white solid. LCMS $(M+H)^+$: 433.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.51 (s, 1H), 7.24 - 7.09 (m, 2H), 4.89 (d, *J*=16.9 Hz, 1H), 4.68 - 4.56 (m, 1H), 4.45 - 4.28 (m, 2H), 4.07 (dd, *J*=8.4, 9.8 Hz, 1H), 3.91 (dd, *J*=6.2, 9.8 Hz, 1H), 3.74 - 3.58 (m, 1H), 2.93 - 2.82 (m, 1H), 2.81 - 2.69 (m, 1H), 1.51 (d, *J*=6.7 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H).

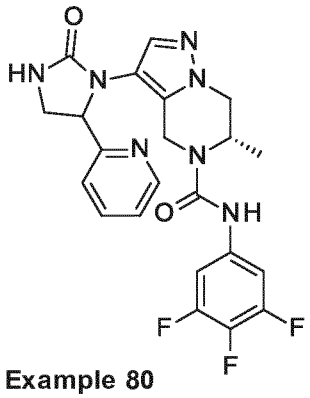
Example 72-2 was obtained (27 mg) as a white solid. LCMS $(M+H)^+$: 433.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.64 (s, 1H), 7.39 - 7.20 (m, 2H), 5.01 (d, *J*=17.0 Hz, 1H), 4.82 - 4.69 (m, 1H), 4.58 - 4.39 (m, 2H), 4.21 - 4.03 (m, 2H), 3.85 - 3.70 (m, 1H), 3.06 - 2.94 (m, 1H), 2.92 - 2.81 (m, 1H), 1.63 (d, *J*=6.7 Hz, 3H), 1.16 (d, *J*=6.8 Hz, 3H).

Examples 79 & 80

(6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide and (6S)-6-methyl-3-[2-oxo-5-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide

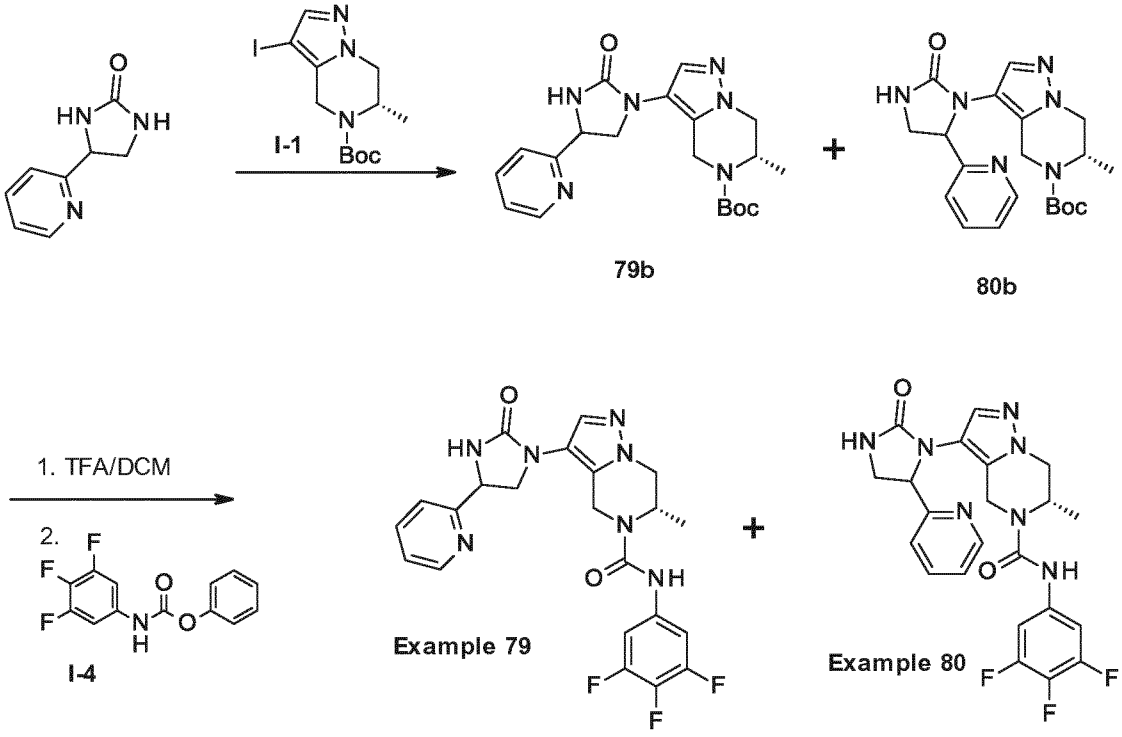


Example 79



Example 80

The title compounds were prepared according to the following scheme:



Step 1: preparation of tert-butyl (6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)imidazolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate & tert-butyl (6S)-6-methyl-3-[2-oxo-5-(2-pyridyl)imidazolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 79b & 80b)

An oven-dried sealable Schlenk tube were charged with (S)-tert-butyl 3-iodo-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (Intermediate **I-1**, 500 mg, 1.38 mmol), K_3PO_4 (584 mg, 2.75 mmol), CuI (78.7 mg, 0.41 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (78.3 mg, 0.55 mmol), 4-(2-pyridyl)imidazolidin-2-one (CAS: 503758-50-6, Accela ChemBio Co. Ltd. Cat. # SY0395182, 70 mg, 1.65 mmol) and DMSO (10 mL). The mixture was stirred at 110 °C for 2 hours under microwave under N_2, quenched with sat. aqueous solution of NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph to afford a mixture comprising compound **79b** and compound **80b** (236 mg). LCMS ($M+H^+$): 399.

Step 2: preparation of (6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 79) and (6S)-6-methyl-3-[2-oxo-5-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 80)

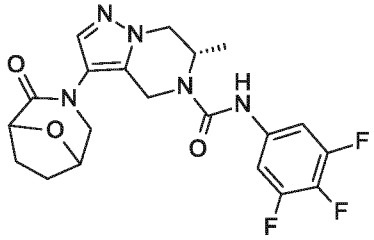
The mixture of compound **79b** and compound **80b** obtained above (236 mg, 592 μmol) was treated with 2,2,2-trifluoroacetic acid (2 mL) in DCM (1mL) at room temperature for 30 minutes. The reaction mixture was then concentrated. The resulting residue was dissolved in DCM (3 mL), to which were then added DIPEA (0.5 mL), phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 52.5 mg, 197 μmol). The reaction mixture was stirred at 50°C for 1 hour, then cooled down, washed with ice-water, extracted with DCM twice. The combined organic phase was dried and concentrated. The residue was purified by prep-HPLC to afford **Example 79** (49 mg) and **Example 80** (18 mg).

Example 79: ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.60 (dd, *J*=0.7, 4.2 Hz, 1H), 7.93 (dt, *J*=1.8, 7.7 Hz, 1H), 7.63 - 7.57 (m, 2H), 7.41 (ddd, *J*=1.1, 4.9, 7.6 Hz, 1H), 7.31 (ddd, *J*=2.3, 6.4, 10.2 Hz, 2H), 5.14 - 5.03 (m, 2H), 5.01 - 4.93 (m, 1H), 4.57 (dd, *J*=3.1, 16.7 Hz, 1H), 4.35 (dt, *J*=3.3, 9.3 Hz, 1H), 4.31 - 4.24 (m, 1H), 4.14 (dd, *J*=1.2, 12.7 Hz, 1H), 3.85 (ddd, *J*=3.3, 6.6, 9.0 Hz, 1H), 1.26 (t, *J*=7.2 Hz, 3H). LCMS ($M+H^+$): 472.

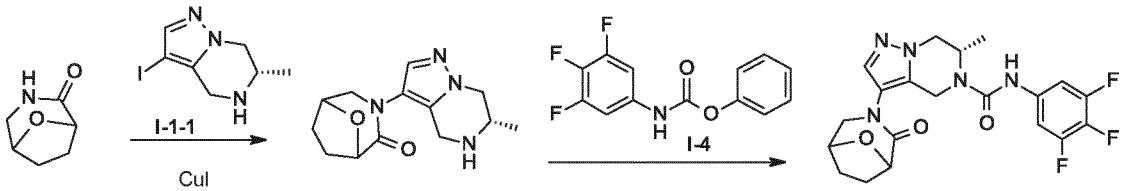
Example 80: ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.59 - 8.52 (m, 1H), 7.80 (ddt, *J*=1.8, 3.2, 7.7 Hz, 1H), 7.47 (dd, *J*=7.8, 12.5 Hz, 1H), 7.38 - 7.26 (m, 4H), 5.37 - 5.27 (m, 1H), 5.02 - 4.89 (m, 1H), 4.57 (d, *J*=16.9 Hz, 0.5H), 4.28 (d, *J*=16.6 Hz, 0.5H), 4.24 - 4.10 (m, 1H), 4.07 - 3.94 (m, 2H), 3.71 - 3.56 (m, 1H), 1.23 (d, *J*=7.0 Hz, 2H), 0.92 (d, *J*=6.8 Hz, 2H). LCMS ($M+H^+$): 472.

Example 83

(6S)-6-methyl-3-(4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of 3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-8-oxa-3-azabicyclo[3.2.1]octan-4-one (compound 83b)

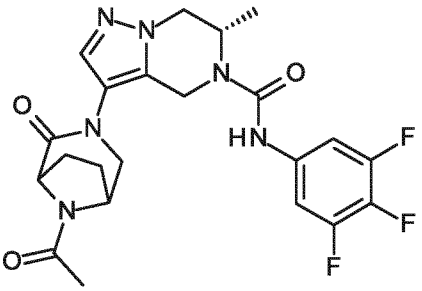
The compound **83b** was prepared in analogy to compound **11d** by using 8-oxa-3-azabicyclo[3.2.1]octan-4-one (compound **83a**, for its synthesis refer to *Synthesis*, ***2011***, *1113*) instead of (4S)-1-[(4-methoxyphenyl)methyl]-4-methyl-imidazolidin-2-one (compound **11c**). Compound **83b** (15 mg) was obtained as white solid.

Step 2: preparation of (6S)-6-methyl-3-(4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 83)

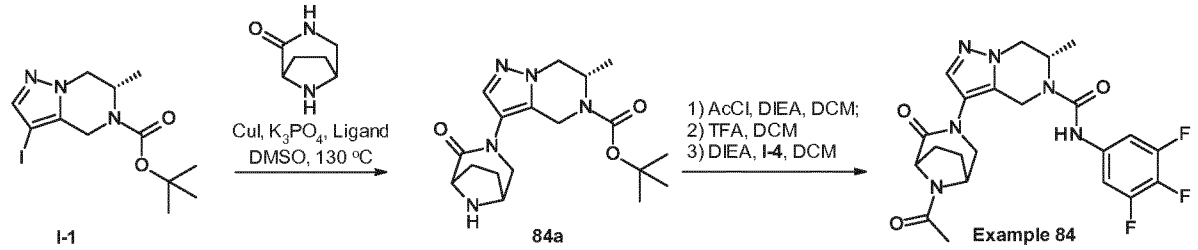
To a solution of 3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-8-oxa-3-azabicyclo[3.2.1]octan-4-one (compound **83b**, 15.0 mg, 0.06 mmol, 1.0 eq) and DIPEA (15.5 mg, 0.12 mmol) in DMF (2.0 mL) was added phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4,** 24.0 mg, 0.09 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and purified by prep-HPLC to give **Example 83** (5.2 mg) as a gray solid. LCMS $(M+H)^+$: 436.3, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.64 (d, *J*=2.3 Hz, 1H), 7.35 - 7.22 (m, 2H), 5.03 - 4.94 (m, 2H), 4.76 (d, *J*=4.5 Hz, 1H), 4.57 (d, *J*=5.8 Hz, 1H), 4.38 (d, *J*=16.8 Hz, 1H), 4.30 (d, *J*=12.8 Hz, 1H), 4.20 - 4.12 (m, 1H), 4.07 - 3.94 (m, 1H), 3.49 - 3.38 (m, 1H), 2.34 - 2.18 (m, 3H), 2.16 - 2.05 (m, 1H), 1.27 (t, *J*=5.9 Hz, 3H).

Example 84

(6S)-3-(8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



I-1 84a Example 84

Step 1: Preparation of tert-butyl (6S)-6-methyl-3-(4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 84a)

The mixture of tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**,1.15 g, 3.17 mmol), (1R,5S)-3,8-diazabicyclo[3.2.1]octan-2-one (CAS: 22315-17-9, PharmaBlock Sciences, Cat. # PB05912, 400 mg, 3.17 mmol), K_3PO_4 (2.02 g, 9.51 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (180 mg, 1.27 mmol) and CuI (121 mg, 634 µmol) in DMSO (5 mL) was heated at 110 °C for 5 hours. The mixture was diluted with EtOAc, washed with sat. aqueous solution of NH_4Cl and brine, dried over Na_2SO_4 and concentrated to give a crude product (1.0 g) which was directly used in next step. LCMS (M+1): 362.

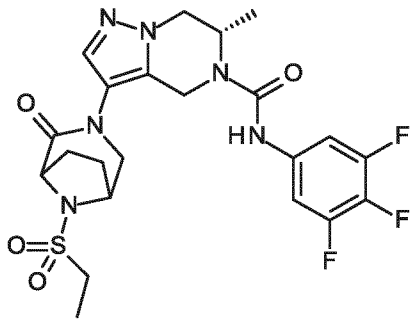
Step 2: Preparation of (6S)-3-(8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 84)

To a solution of tert-butyl (6S)-6-methyl-3-(4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **84a**, 100 mg, 277 µmol,) in DCM (5 mL) was added DIEA (107 mg, 145 µl, 830 µmol) and acetyl chloride (32.6 mg, 415 µmol) at room temperature. The mixture was stirred at room temperature for 30 min, then quenched with sat. NH_4Cl, diluted with EtOAc, washed with sat NH_4Cl and brine, dried over

Na_2SO_4, and then concentrated. The residue was dissolved in DCM (5 mL), and then TFA (5 mL) was added. After being stirred at room temperature for 30 min, the mixture was concentrated to give a crude product which was dissolved in DCM (5 mL), DIEA (0.5 mL) and phenyl (3,4,5-trifluorophenyl)carbamate (111 mg, 415 μmol) was added. The mixture was stirred at room temperature overnight, then concentrated to give a crude product which was purified by prep-HPLC to give **Example 84** (25 mg) as a white powder. LCMS (M+1): 477. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.67 - 7.63 (m, 1H), 7.33 - 7.19 (m, 2H), 5.02 - 4.94 (m, 2H), 4.91 - 4.83 (m, 1H), 4.79 - 4.64 (m, 1H), 4.43 - 4.25 (m, 2H), 4.21 - 4.11 (m, 1H), 4.10 - 3.95 (m, 1H), 3.64 - 3.42 (m, 1H), 2.50 - 2.03 (m, 7H), 1.34 - 1.19 (m, 3H).

Example 85

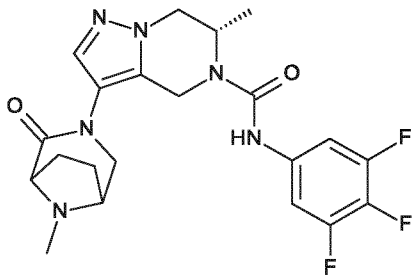
(6S)-3-(8-ethylsulfonyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



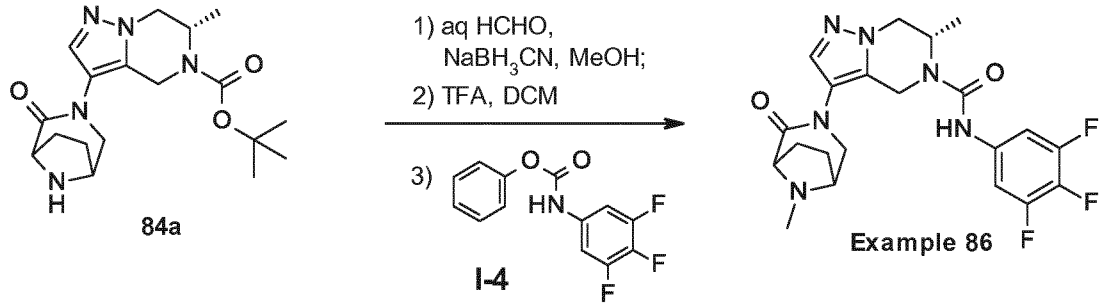
The title compound was prepared in analogy to the preparation of **Example 84** by using methanesulfonyl chloride instead of acetyl chloride. **Example 85** (5 mg) was obtained as a white solid. LCMS (M+1): 527. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.63 (s, 0.5H), 7.62 (s, 0.5H), 7.31 - 7.22 (m, 2H), 4.98 - 4.90 (m, 2H), 4.56 - 4.50 (m, 1H), 4.46 - 4.41 (m, 1H), 4.36 (d, *J*=16.9 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.16 (d, *J*=13.3 Hz, 1H), 4.09 - 3.97 (m, 1H), 3.61 - 3.52 (m, 1H), 3.31 - 3.25 (m, 2H), 2.41 - 2.32 (m, 2H), 2.31 - 2.22 (m, 1H), 2.12 - 2.07 (m, 1H), 1.40 (t, *J*=7.3 Hz, 3H), 1.29 (d, *J*=7.0 Hz, 1.5H), 1.25 (d, *J*=7.0 Hz, 1.5H).

Example 86

(6S)-6-methyl-3-(8-methyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



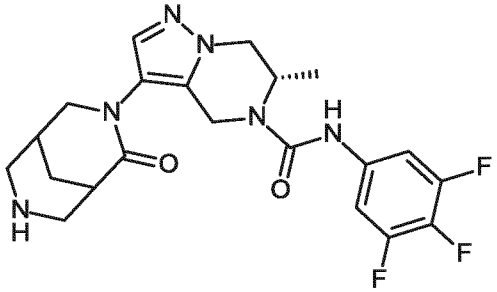
The title compound was prepared according to the following scheme:



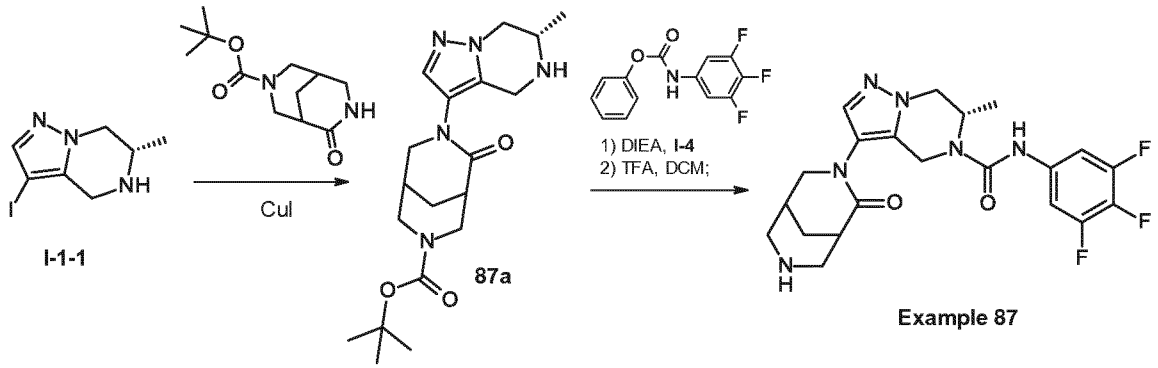
To a solution of tert-butyl (6S)-6-methyl-3-(4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **84a**, 150 mg, 415 μmol) in MeOH (5 mL) was added formaldehyde (35% solution, 0.1 mL) and $NaBH_3CN$ (52.2 mg, 830 μmol). The mixture was stirred at room temperature for 1h, then another portion of formaldehyde and $NaBH_3CN$ was added. After another hour, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with sat $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The crude product was dissolved in DCM (5 mL) and TFA (5 mL) was added. was After being stirred at room temperature for 30min, the solvent was removed. The residue was dissolved in DCM (5 mL) and DIEA (268 mg, 2.08 mmol) and phenyl (3,4,5-trifluorophenyl)carbamate (166 mg, 623 μmol) were added. The mixture was stirred at room temperature overnight, solvent was removed under reduced pressure to give a crude product which was purified by prep-HPLC to give **Example 86** (34 mg) as a white powder. LCMS (M+1): 449. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.62 (s, 1H), 7.27 (dd, *J*=6.4, 10.3 Hz, 2H), 4.98 - 4.90 (m, 2H), 4.36 (d, *J*=17.0 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.15 (d, *J*=12.5 Hz, 1H), 4.01 - 3.89 (m, 1H), 3.62 - 3.52 (m, 2H), 3.44 - 3.35 (m, 1H), 2.54 (s, 1.5H), 2.53 (s, 1.5H), 2.43 - 2.27 (m, 2H), 2.17 - 2.07 (m, 1H), 2.04 - 1.92 (m, 1H), 1.32 - 1.21 (m, 3H).

Example 87

(6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: Preparation of tert-butyl 3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-4-oxo-3,7-diazabicyclo[3.3.1]nonane-7-carboxylate (compound 87a)

The mixture of (6S)-3-iodo-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (Intermediate **I-1-1**, 219 mg, 832 μmol), tert-butyl 6-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (CAS: 183277-52-2, Wuxi, Cat. #: WX120011, 200 mg, 832 μmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (47.4 mg, 333 μmol), CuI (31.7 mg, 166 μmol) and potassium phosphate (530 mg, 2.5 mmol) in DMSO (5 mL) was stirred at 110 °C for 3 hours under argon. The mixture was cooled to room temperature and diluted with EtOAc (50 mL), washed with sat NH_4Cl and brine, dried over Na_2SO_4 and concentrated to give a crude compound **87a** (312 mg) which was used in next step directly. LCMS (M+1): 376.

Step 2: Preparation of (6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 87)

To a solution of tert-butyl 3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-4-oxo-3,7-diazabicyclo[3.3.1]nonane-7-carboxylate (compound **87a**, 312 mg, 0.832mmol) in DCM (5 mL) was added DIEA (215 mg, 290 μl, 1.66 mmol) and phenyl (3,4,5-trifluorophenyl)carbamate (289 mg, 1.08 mmol). The reaction mixture was stirred overnight at

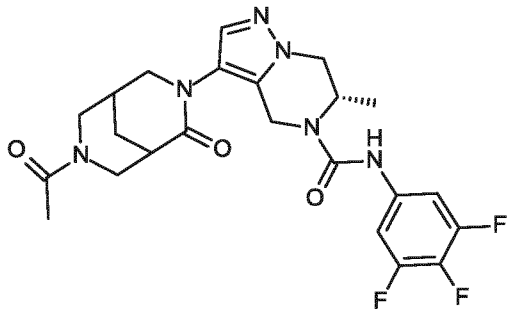
room temperature, then TFA (5 mL) was added at 0 °C. After being stirred at room temperature for 30 min, the solvent was removed under reduced pressure to give a crude product, 100 mg of which was purified by prep-HPLC to give **Example 87** as two isomers, **Example 87-1** (10 mg) and **Example 87-2** (8 mg) as white powders.

Example 87-1: LCMS (M+1): 449. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.72 (s, 1H), 7.28 (dd, *J*=6.4, 10.3 Hz, 2H), 4.96 (d, *J*=16.9 Hz, 1H), 4.99 - 4.90 (m, 1H), 4.37 (d, *J*=16.9 Hz, 1H), 4.35 - 4.28 (m, 1H), 4.21 - 4.14 (m, 1H), 4.00 (dd, *J*=5.9, 12.7 Hz, 1H), 3.73 (d, *J*=12.6 Hz, 1H), 3.31 - 3.23 (m, 2H), 3.20 - 3.10 (m, 2H), 2.79 - 2.71 (m, 1H), 2.40 - 2.24 (m, 2H), 2.12 - 2.06 (m, 1H), 1.27 (d, *J*=6.8 Hz, 3H).

Example 87-2: LCMS (M+1): 449. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.74 (s, 1H), 7.28 (dd, *J*=6.4, 10.3 Hz, 2H), 5.00 - 4.90 (m, 2H), 4.42 (d, *J*=16.9 Hz, 1H), 4.34 - 4.27 (m, 1H), 4.20 - 4.13 (m, 1H), 3.95 (dd, *J*=5.6, 12.5 Hz, 1H), 3.76 (d, *J*=12.8 Hz, 1H), 3.30 - 3.21 (m, 2H), 3.16 - 3.06 (m, 2H), 2.75 - 2.69 (m, 1H), 2.36 - 2.22 (m, 2H), 2.09 (d, *J*=12.5 Hz, 1H), 1.30 (d, *J*=6.8 Hz, 3H).

Example 88

(6S)-3-(7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



To a solution of (6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (**Example 87**, 200 mg crude, 446 μmol) in DCM (5 mL) was added DIEA (288 mg, 2.23 mmol) and AcCl (70 mg, 892

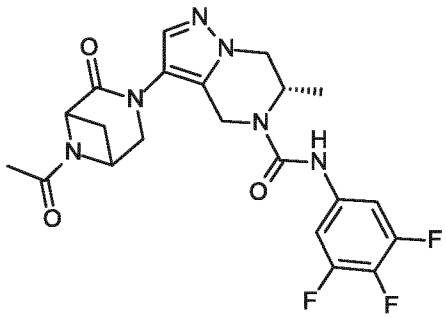
μmol). The reaction mixture was stirred at room temperature for 1h, then quenched with sat NH_4Cl, and solvent was removed. The crude product was purified by prep-HPLC to give **Example 88** as two isomers, **Example 88-1** (6 mg) and **Example 88-2** (5 mg), as white powders.

Example 88-1: LCMS (M+1): 491. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.62 - 7.50 (m, 1H), 7.47 - 7.32 (m, 2H), 5.06 - 4.93 (m, 2H), 4.77 (d, *J*=16.9 Hz, 0.6H), 4.67 (d, *J*=16.9Hz, 0.4H), 4.39 - 4.25 (m, 2H), 4.23 - 4.07 (m, 2.6H), 3.86 (dd, *J*=5.0, 12.5 Hz, 0.4H), 3.62 (d, *J*=12.8 Hz, 1H), 3.56 - 3.50 (m, 1H), 3.04 - 2.95 (m, 1H), 2.85 - 2.75 (m, 1H), 2.42 - 2.31 (m, 2H), 2.20 - 2.12 (m, 1H), 2.09 - 1.88 (m, 3H), 1.30 - 1.17 (m, 3H).

Example 88-2: LCMS (M+1): 491. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.68 - 7.37 (m, 3H), 5.14 - 4.92 (m, 2H), 4.81 (d, *J*=16.3 Hz, 0.4H), 4.50 (d, *J*=16.5 Hz, 0.6H), 4.32 - 4.09 (m, 4.6H), 3.93 - 3.85 (m, 0.4H), 3.61 - 3.47 (m, 2H), 3.05 - 2.96 (m, 1H), 2.86 - 2.72 (m, 1H), 2.43 - 2.31 (m, 2H), 2.23 - 2.07 (m, 4H), 1.32 - 1.19 (m, 3H).

Example 91

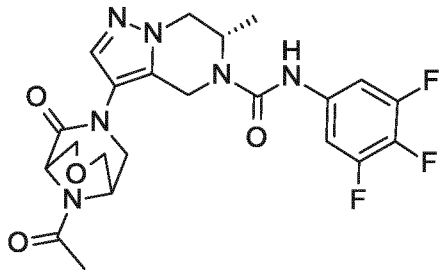
(6S)-3-(6-acetyl-4-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



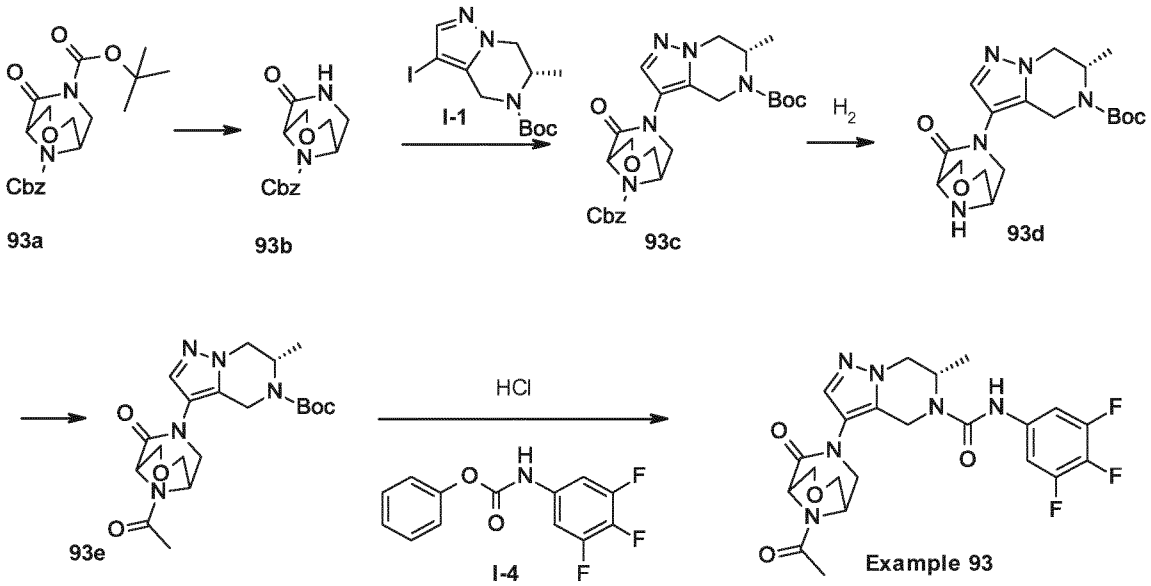
The title compound was prepared in analogy to the preparation of **Example 88** by using tert-butyl 4-oxo-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (CAS: 1273562-74-5, PharmaBlock, Cat.# PBN20111097) instead of tert-butyl 6-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate. **Example 91** was obtained as a white solid (60 mg). LCMS (M+1): 463. ^{1}H NMR (400MHz, METHANOL-d_4) δ ppm 7.67 - 7.59 (m, 1H), 7.38 - 7.22 (m, 2H), 5.04 - 4.91 (m, 2H), 4.76 - 4.57 (m, 2H), 4.55 - 4.35 (m, 1H), 4.34 - 4.25 (m, 1H), 4.20 - 4.11 (m, 1H), 3.89 - 3.79 (m, 1H), 3.71 - 3.52 (m, 2H), 2.44 - 2.31 (m, 1H), 2.26 (s, 1H), 2.24 (s, 1H), 2.20 - 2.12 (m, 0.6H), 2.13 (s, 0.5H), 2.12 (s, 0.5H), 2.07 - 2.00 (m, 0.4H), 1.31 - 1.20 (m, 3H).

Example 93

(6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (compound 93b)

To a solution of O9-benzyl O7-tert-butyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7,9-dicarboxylate (compound **93a**, 80.0 mg, the synthesis refer to PCT Int. Appl., 2014184328) in DCM (1mL) was added HCl/EtOAc (4N, 0.53 mL). The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed. The residue was dissolved in CH_3CN, basified with K_2CO_3, and then filtered and concentrated to give compound **93b** (50 mg) as colorless oil. LCMS$(M+H)^+$: 277.0

Step 2: preparation of benzyl 7-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (compound 93c)

The compound **93c** was prepared in analogy to compound **1f** by using benzyl 6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (compound **93b**) instead of(4S)-4,5,5-

trimethyloxazolidin-2-one (compound **1e**). Compound **93c** (30 mg) was obtained as a white solid. LCMS $(M+H)^+$:512.2.

Step 3: preparation of tert-butyl (6S)-6-methyl-3-(6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 93d)

To a solution of benzyl 7-[(6S)-5-tert-butoxycarbonyl-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (compound **93c**, 30.0 mg, 0.060 mmol) in methanol (10 mL) was added Pd/C(5 mg). The reaction mixture was stirred at room temperature for 16 hours under 50 psi of H_2. The mixture was filtered and the filtrate was concentrated to give crude compound **93d** (30.0 mg). LCMS $(M+H)^+$: 378.2.

Step 4: preparation of tert-butyl (6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 93e)

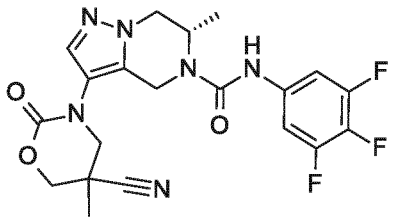
To a solution of tert-butyl (6S)-6-methyl-3-(6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **93d**, 30.0 mg, 0.040 mmol) and triethylamine (0.01 mL, 0.080 mmol, 2 eq) in DCM (5.0 mL) was added acetyl chloride (4.7 mg, 0.060 mmol). The reaction mixture was stirred at room temperature for 0.5 hour, and then the solvent was removed to give crude compound **93e** (20.0 mg). LCMS $(M+H)^+$: 420.2.

Step 5: preparation of (6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 93)

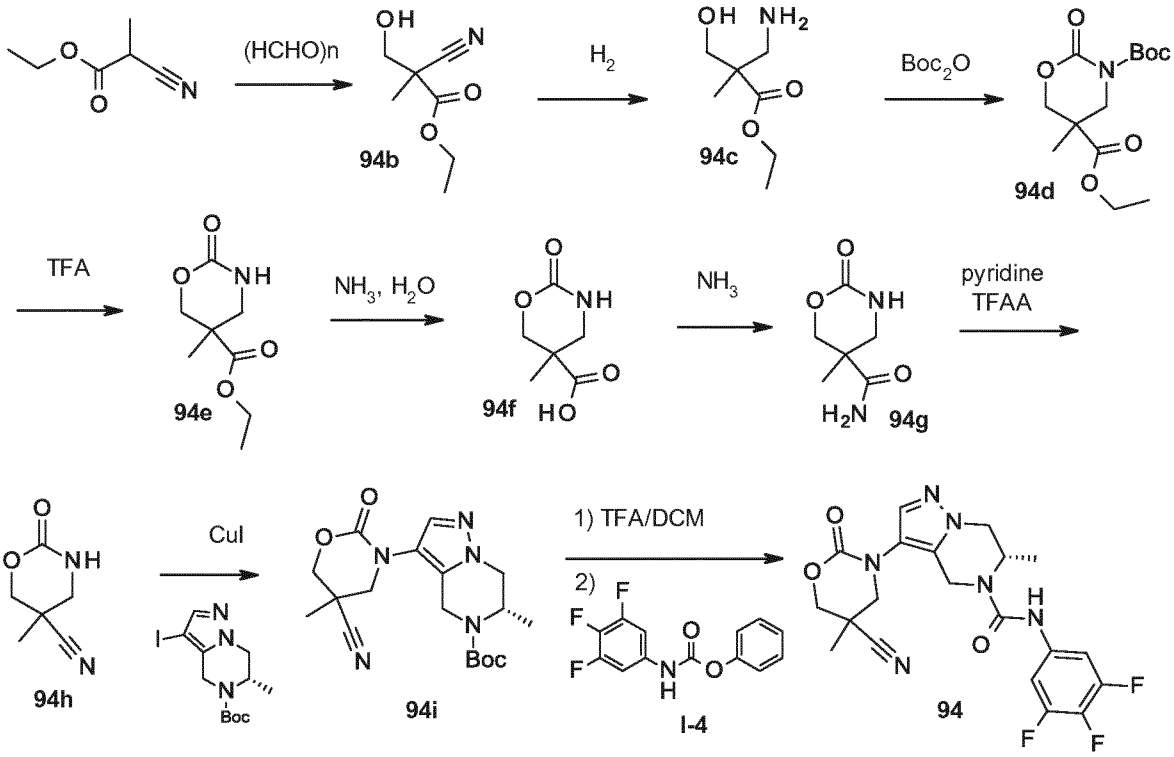
Example 93 was prepared in analogy to **Example 1** by using b tert-butyl (6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **93e**) instead of tert-butyl (6S)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **1f**). **Example 93** (4.0 mg) was obtained as white solid. LCMS $(M+H)^+$: 493.2, ^1H NMR (400MHz, METHANOL-d_4) δ ppm 7.72 - 7.67 (m, 1H), 7.30-7.24 (m, 2H), 5.07 (d, *J*=1.6 Hz, 1H), 5.00 - 4.94 (m, 1H), 4.87 - 4.83 (m, 1H), 4.68 - 4.06 (m, 7H), 4.24 - 4.06 (m, 3H), 3.93 - 3.71 (m, 3H), 2.27 - 2.20 (m, 3H).

Example 94

(6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of ethyl 2-cyano-3-hydroxy-2-methyl-propanoate (compound 94b)

To a solution of ethyl 2-cyanopropanoate (40.0 g, 314.6 mmol) in ethanol (400 mL) was added potassium carbonate (124.4 g, 943.8 mmol) and paraformaldehyde (14.2 g, 471.9 mmol). The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with brine. The organic phase was concentrated, then purified by column chromatography to give compound **94b** (16.0 g) as colorless oil. LCMS ($M+H^+$): 158.

Step 2: preparation of ethyl 2-(aminomethyl)-3-hydroxy-2-methyl-propanoate hydrochloride (compound 94c)

To a solution of ethyl 2-cyano-3-hydroxy-2-methyl-propanoate (compound **94b**, 16.0 g, 101.8 mmol) in ethanol (200 mL) was added platinum oxide (2.3 g, 10.2 mmol) and hydrogen chloride (4 M in dioxane, 50.9 mL, 203.6 mmol). The reaction mixture was stirred at 25 °C for 12 hours under hydrogen atmosphere (50 Psi). The reaction mixture was filtered and the filtrate was concentrated to give compound **94c** (19.4 g, crude) as a colorless oil. LCMS ($M+H^+$): 198.

Step 3: preparation of O3-tert-butyl O5-ethyl 5-methyl-2-oxo-1,3-oxazinane-3,5-dicarboxylate (compound 94d)

To a solution of ethyl 2-(aminomethyl)-3-hydroxy-2-methyl-propanoate hydrochloride (compound **94c**, 19.0 g, 96.1 mmol) in acetonitrile (200 mL) was added potassium carbonate (26.6 g, 192.2 mmol). After being stirred at 25 °C for 30 minutes, the mixture was added into a stirring mixture of di-tert-butyl dicarbonate (62.9 g, 288.4 mmol), triethylamine (29.2 g, 288.4 mmol) and 4-dimethylaminopyridine (2.4 g, 19.2 mmol) in acetonitrile (200 mL). The reaction mixture was stirred for 12 h at 25 °C. The reaction mixture was filtered and the filtrate was concentrated, the obtained residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, concentrated and the residue was purified by column chromatography to give compound **94d** (11.0 g) as a colorless oil. LCMS ($M+H^+$): 288.

Step 4: preparation of ethyl 5-methyl-2-oxo-1,3-oxazinane-5-carboxylate (compound 94e)

To a solution of O3-tert-butyl O5-ethyl 5-methyl-2-oxo-1,3-oxazinane-3,5-dicarboxylate (compound **94d**, 11.0 g, 38.3 mmol) in DCM (70 mL) was added 2,2,2-trifluoroacetic acid (14 mL), the reaction mixture was stirred at 25 °C for 2 hours, and basified carefully to pH=10 by adding sodium hydroxide solution (2M). The organic phase was separated, washed with brine, concentrated to give compound **94e** (4.2 g, crude) as an off white solid. LCMS ($M+H^+$): 188.

Step 5: preparation of 5-methyl-2-oxo-1,3-oxazinane-5-carboxylic acid (compound 94f)

To a solution of ethyl 5-methyl-2-oxo-1,3-oxazinane-5-carboxylate (compound **94e**, 560 mg, 3.0 mmol) in ethanol (10 mL) was added ammonia aqueous solution (25%- 28%, 10 mL). The reaction mixture was sealed and heated at 72°C overnight. The reaction mixture was concentrated, and then 2-methyltetrahydrofuran was added to co-evaporate water to give compound **94f** (428 mg, crude). LCMS ($M+H^+$): 160.

Step 6: preparation of 5-methyl-2-oxo-1,3-oxazinane-5-carboxamide (compound 94g)

To a mixture of 5-methyl-2-oxo-1,3-oxazinane-5-carboxylic acid (compound **94f**, 500 mg, 3.14 mmol) and 4-methylmorpholine (518 µL, 4.71 mmol) in dry THF (20 mL) and DCM (20

mL) at -10 °C was added dropwise isobutyl chloroformate (491 μL, 3.77 mmol). The reaction mixture was stirred at -10 °C for 2 hours, then slowly warmed to 0 °C for 30 minutes. The reaction mixture was cooled down to -10 °C again, to which was added ammonia solution (0.4 M in THF, 8.0 mL). The reaction mixture was stirred at room temperature for 3 hours and then filtered, and the solid was collected to give compound **94g** (300 mg). LCMS ($M+H^+$): 159.

Step 7: preparation of 5-methyl-2-oxo-1,3-oxazinane-5-carbonitrile (compound 94h)

To a mixture of 5-methyl-2-oxo-1,3-oxazinane-5-carboxamide (compound **94g**, 300.0 mg, 1.9 mmol) and pyridine (1 mL) in dry THF (8 mL) at 0°C was added dropwise trifluoroacetic anhydride (1 mL). After addition the reaction mixture was stirred at room temperature for 2 hours and then washed with ice-water, extracted with DCM/i-PrOH (V/V=5/1) twice, the organic phase was combined and concentrated. The residue was purified by column chromatography (eluting with 85%-100% EtOAc (containing 10% MeOH) in petroleum ether) to give compound **94h** (100.0 mg). LCMS ($M+H^+$): 141.

Step 8: preparation of tert-butyl (6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 94i)

The mixture of 5-methyl-2-oxo-1,3-oxazinane-5-carbonitrile (compound **94h**, 7.7 mg, 55 μmo), tert-butyl (6S)-3-iodo-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (Intermediate **I-1**, 20.0 mg, 55 μmol), K_3PO_4 (23.4 mg, 110 μmol), CuI (2.1 mg, 11 μmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (1.6 mg, 11 μmol) in DMSO (5 mL) was flushed with nitrogen and sealed. The reaction mixture was heated to 105 °C under microwave for 2 hours. The reaction mixture was cooled down, poured into ice-water and extracted with EtOAc twice. The combined organic phase was dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography to give compound **94i** (8.3 mg). LCMS ($M+H^+$): 376.

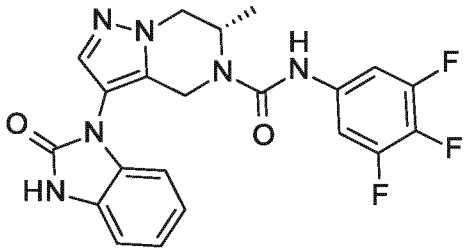
Step 9: preparation of (6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (Example 94)

The mixture of tert-butyl (6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **94i**, 60.0 mg, 160 μmol), 2,2,2-trifluoroacetic acid (2.0 mL) and DCM (1.0 mL) was stirred at room temperature for 30 minutes, and then concentrated. The residue was dissolved in DCE (3.0 mL), to which were added DIPEA (0.5 mL), and phenyl N-(3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 85.4 mg, 320 μmol). The reaction mixture was stirred at 50 °C for 1 hour and then cooled down,

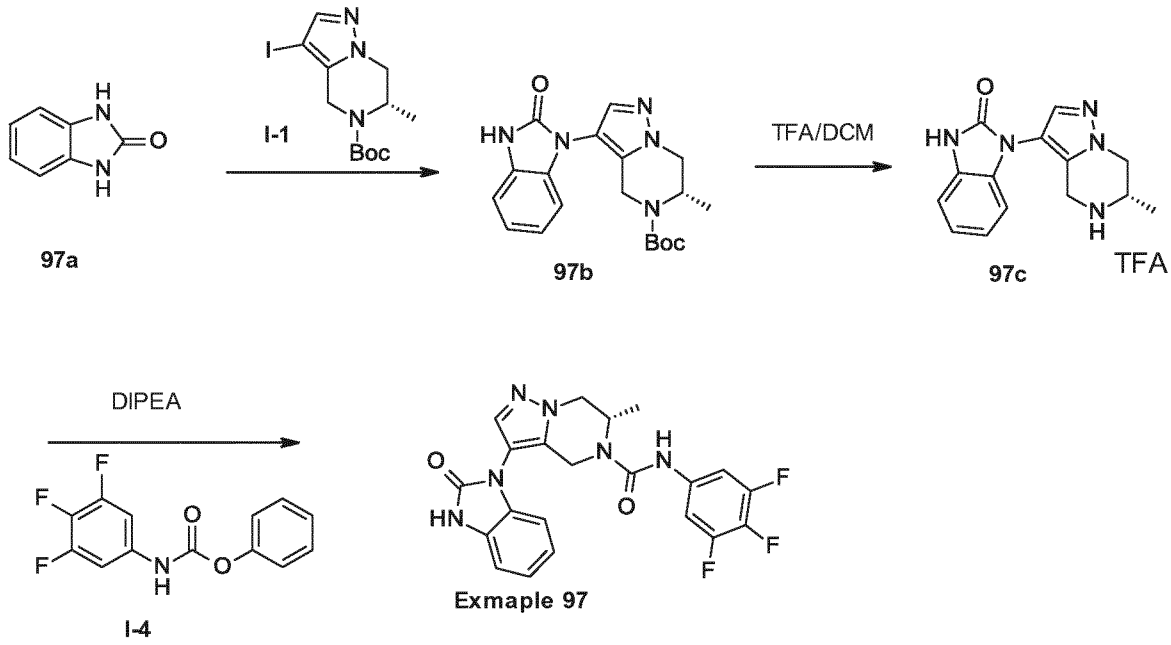
diluted with DCM, washed with ice-water, and brine. Organic phase was concentrated and the residue was purified by column chromatography (eluting with 80% EtOAc (containing 10% MeOH) in petroleum ether(to give **Example 94** (65.0 mg) as a white solid. LCMS ($M+H^+$): 449. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.64 (s, 1H), 7.32 - 7.23 (m, 2H), 5.07 - 4.92 (m, 2H), 4.60 - 4.54 (m, 1H), 4.50 - 4.37 (m, 2H), 4.34 - 4.26 (m, 1H), 4.17 (d, *J*=12.7 Hz, 1H), 3.97 - 3.86 (m, 2H), 1.52 (s, 3H), 1.29 - 1.24 (m, 3H).

Example 97

(6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The title compound was prepared according to the following scheme:



Step 1: preparation of tert-butyl (6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound 97b)

An oven-dried sealable Schlenk tube were charged with (S)-tert-butyl 3-iodo-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (Intermediate **I-1**, 400 mg, 1.1 mmol), K_3PO_4 (468 mg, 2.2 mmol), CuI (83.9 mg, 0.44 mmol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-

diamine (62.7 mg, 0.44 mmol), 1H-benzo[d]imidazol-2(3H)-one (591 mg, 4.41 mmol) and DMSO (5.0 ml) under nitrogen. The mixture was stirred at 110 °C for 2 hours under microwave, quenched with sat. aqueous solution of NH_4Cl and diluted with EtOAc. The organic layer was separated and washed with sat NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatograph to afford the product compound **97b** (230 mg). LCMS ($M+H^+$): 370.

Step 2: preparation of 3-[(6S)-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-1H-benzimidazol-2-one (compound 97c)

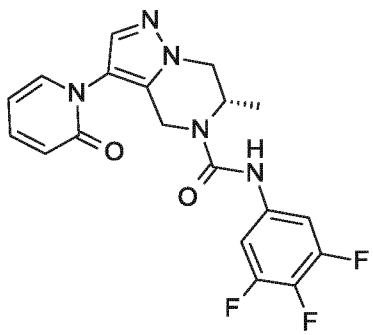
The mixture of tert-butyl (6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (compound **97b**, 230 mg, 623 μmol), 2,2,2-trifluoroacetic acid (2 mL) in DCM (5 mL) was stirred at room temperature for 30 minutes, and then concentrated to afford crude product **97c** (250 mg). LCMS ($M+H^+$): 270.

Step 3: preparation of (6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide (compound 97)

The mixture of crude compound **97c** (96 mg, 0.25 mmol), DIPEA (0.5 mL), and phenyl (3,4,5-trifluorophenyl)carbamate (Intermediate **I-4**, 80.0 mg, 0.30 mol) in DCM (3.0 mL) was stirred at 50°C for 1 hour. The reaction mixture was cooled down, diluted with DCM, washed with ice-water, and brine. The organic phase was separated and concentrated. The residue was purified by prepare-HPLC to afford product compound **97** (37 mg). LCMS ($M+H^+$): 443. ^1H NMR (400MHz, DMSO-d_6) δ ppm 7.00 (br d, *J*=2.6 Hz, 1H), 6.44 (br s, 2H), 6.34 (br s, 3H), 6.19 (br s, 1H), 4.41 - 4.14 (m, 2H), 3.84 - 3.54 (m, 2H), 3.47 (br s, 1H), 0.52 (br s, 3H).

Example 99

(6S)-6-methyl-3-(2-oxo-1-pyridyl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide



The **Example 99** was prepared in analogy to **Example 1** by using 1H-pyridin-2-one instead of (4S)-4,5,5-trimethyloxazolidin-2-one (compound **1e**). **Example 99** (47 mg) was obtained as

white solid. LCMS $(M+23)^+$: 426.1, ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 9.13 (s, 1H), 7.71 (s, 1H), 7.69 (dd, *J*=1.3, 6.8 Hz, 1H), 7.56 - 7.48 (m, 1H), 7.42 (dd, *J*=6.5, 10.8 Hz, 2H), 6.52 (d, *J*=9.3 Hz, 1H), 6.34 (t, *J*=6.7 Hz, 1H), 4.98 - 4.91 (m, 1H), 4.88 (d, *J*=17.1 Hz, 1H), 4.34 (d, *J*=16.8 Hz, 1H), 4.30 - 4.23 (m, 1H), 4.22 - 4.16 (m, 1H), 1.17 (d, *J*=6.8 Hz, 3H).

Example 100: HBV inhibition assays

Cell line and culture conditions:

HepG2.2.15 is a stably-transfected cell line containing the HBV genome. It is derived from the hepatoblastoma cell line Hep G2 (American Type Culture Collection, ATCC® HB-8065™) by the published procedures described in reference: MA Selles *et al.* Proc. Natl. Acad. Sci. USA 1987, 84, 1005-1009. The cell line was maintained in Dulbecco's modified Eagle's medium and nutrient mixture F-12 (DMEM/F-12, Gibco, Cat.#:11320-033) supplemented with 10% fetal bovine serum (Gibco, Cat.#:10099-141), 100 U/mL penicillin, 100 μg/mL streptomycin (Gibco, Cat.#:15140-122), and 0.3 mg/mL of G418 Sulfate (Gibco, Cat.#: 10131-027).

Anti-HBV activity in vitro:

HepG2.2.15 cells were seeded into 96-well plates at a density of 3×10^4 cells per well in culture media of 100 μL DMEM/F-12 supplemented with 2.5% fetal bovine serum, 100 U/mL penicillin, 100 μg/mL streptomycin and cultured overnight at 37 °C. The test compounds were serially half-log diluted in DMSO, then diluted 100 times in culture media. 100 μL culture media containing diluted compounds were added into the plates to reach 0.5% final concentration of DMSO in every well. Five days after compound treatment, culture supernatant was collected for further analysis.

For quantitative PCR detection of extracellular HBV DNA, culture supernatant was processed by 500 μg/mL Proteinase K (Sigma, Cat.#:P2308) digestion at 50 °C for 1 hour. After heat inactivation of the enzyme at 95 °C for 15 minutes, the samples were subjected to HBV DNA quantification by qPCR. The effective compound concentration at which HBV replication was inhibited by 50% (EC_{50}) was determined.

The Examples of the present invention were tested in the above assays as described herein and found to have EC_{50} less than 1 μM in HepG2.2.15 assay as shown in Table 1 below.

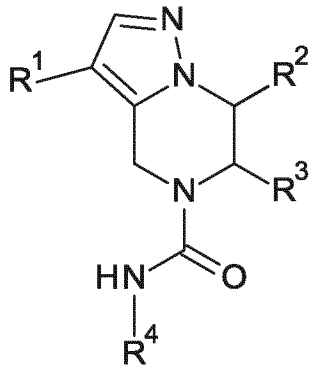
Table 1. Activity of compounds of this invention in HepG2.2.15 assay

Example No	EC_{50} (μM)	Example No	EC_{50} (μM)	Example No	EC_{50} (μM)	Example No	EC_{50} (μM)
1	0.003	**24**	0.018	**45**	0.020	**72-1**	0.047

2	0.016	**25**	0.041	**47-1**	0.432	**72-2**	0.008
3	0.195	**26**	0.117	**47-2**	0.379	**79**	0.007
4	0.036	**27**	0.031	**49**	0.055	**80**	0.147
5	0.084	**28**	0.049	**50**	0.161	**83**	0.015
6	0.051	**29**	0.012	**51**	0.016	**84**	0.208
7-1	0.012	**30**	0.036	**53**	0.111	**85**	0.133
7-2	0.016	**31**	0.281	**54-1**	0.094	**86**	0.081
9	0.041	**32**	0.240	**54-2**	0.301	**87-1**	0.141
10	0.349	**33-1**	0.025	**56**	0.031	**88-2**	0.025
11	0.051	**33-2**	0.135	**57**	0.055	**91**	0.110
12	0.208	**33-3**	0.021	**62**	0.119	**93**	0.291
13	0.259	**33-4**	0.008	**63**	0.302	**94**	0.018
16	0.086	**37**	0.061	**64**	0.060	**97**	0.088
17	0.079	**38**	0.137	**65-1**	0.009	**99**	0.147
18	0.020	**39**	0.100	**65-2**	0.046		
19	0.048	**40**	0.076	**67-1**	0.063		
20	0.266	**41**	0.052	**67-2**	0.413		
21	0.066	**42**	0.052	**68-1**	0.045		
22	0.146	**43**	0.043	**68-2**	0.272		
23	0.158	**44**	0.097	**71**	0.324		

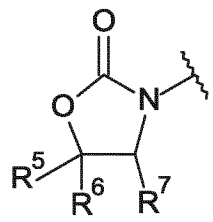
CLAIMS

1. A compound of formula (I),



(I),

wherein

R^1 is  , wherein R^5, R^6 and R^7 are independently selected from H or C_{1-6}alkyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

with the proviso that R^5, R^6 and R^7 are not H simultaneously, and

(6S)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

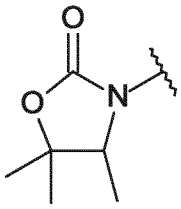
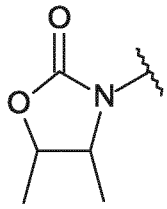
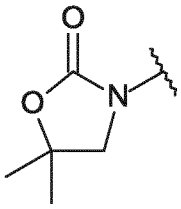
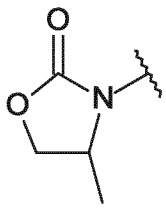
(6S)-N-[6-(difluoromethyl)-5-fluoro-2-pyridyl]-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2-chloro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-N-[2-(trifluoromethyl)-4-pyridyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

and their enantiomers or diastereomers are excluded.

2. A compound according to claim 1, wherein

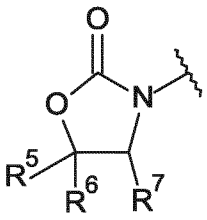
R^1 is  ,  ,  or  ;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl, chloropyridinyl, difluoropyridinyl, fluorochloropyridinyl, difluoromethylpyridinyl or trifluoromethylpyridinyl.

3. A compound according to claim 1, wherein

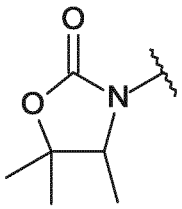
R^1 is  , wherein R^5, R^6 and R^7 are C_{1-6}alkyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is phenyl three times substituted by halogen, or pyridinyl substituted by haloC_{1-6}alkyl.

4. A compound according to claim 1 or 3, wherein

R^1 is  ;

R^2 is H;

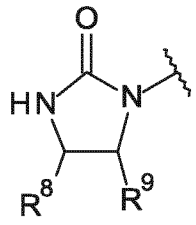
R^3 is methyl;

R^4 is trifluorophenyl or difluoromethylpyridinyl.

5. A compound selected from:
(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4R)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(6-chloro-5-fluoro-3-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-N-[2-(trifluoromethyl)-4-pyridyl]-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(4S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-[(4S)-4-methyl-2-oxo-oxazolidin-3-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5S)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-3-[(4S,5R)-4,5-dimethyl-2-oxo-oxazolidin-3-yl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-(2,6-difluoro-4-pyridyl)-3-(5,5-dimethyl-2-oxo-oxazolidin-3-yl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

6. A compound according to claim 3, selected from:
(6S)-6-methyl-N-(3,4,5-trifluorophenyl)-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(4S)-4,5,5-trimethyl-2-oxo-oxazolidin-3-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

7. A compound of formula (I), wherein

R^1 is , wherein R^8 is H, pyridinyl or haloC_{1-6}alkyl; R^9 is H, pyridinyl or C_{1-6}alkyl;

R^2 is H;

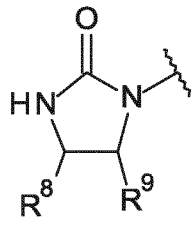
R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

with the proviso that R^8 and R^9 are not H simultaneously.

8. A compound according to claim 7, wherein

R^1 is , wherein R^8 is H, pyridinyl or trifluoromethyl; R^9 is H, pyridinyl or methyl;

R^2 is H;

R^3 is methyl;

R^4 is trifluorophenyl.

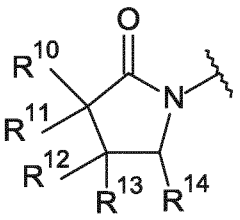
9. A compound selected from:
(6S)-6-methyl-3-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(5S)-5-methyl-2-oxo-imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and

(6S)-6-methyl-3-[2-oxo-5-(2-pyridyl)imidazolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

10. A compound of formula (I), wherein

R^1 is , wherein R^{10} is H, halogen or hydroxy; R^{11} is H or halogen; R^{12} is H, cyano, hydroxy, pyridinyl or pyrimidinyloxy; R^{13} is H, C_{1-6}alkyl or morpholinylcarbonyl; R^{14} is H, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl or $(C_{1-6}alkyl)_2aminoC_{1-6}alkyl$;

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

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

with the proviso that R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are not H simultaneously, and

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4R)-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(4S)-4-cyano-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

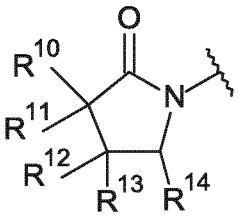
(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-[2-oxo-4-(trifluoromethyl)pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3R)-3-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(3-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-[2-oxo-4-(4-pyridyl)pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(4R)-4-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(4S)-4-hydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-[(4S)-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-[4-(morpholine-4-carbonyl)-2-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-[(4R)-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(3R,4R)-3,4-dihydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(3S,4R)-3,4-dihydroxy-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(3S,4R)-3-hydroxy-2-oxo-4-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(2R,3R,4S)-4-hydroxy-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
and their enantiomers or diastereomers are excluded.

11. A compound according to claim 10, wherein

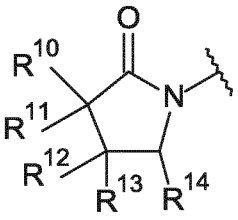
R^1 is , wherein R^{10} is H, fluoro or hydroxy; R^{11} is H or fluoro; R^{12} is H, cyano, hydroxy, pyridinyl or pyrimidinyloxy; R^{13} is H, methyl or morpholinylcarbonyl; R^{14} is H, methyl, methylaminocarbonyl or dimethylaminomethyl;

R^2 is H or methyl;

R^3 is methyl;

R^4 is trifluorophenyl, difluoropyridinyl or difluoromethylpyridinyl.

12. A compound according to claim 10, wherein

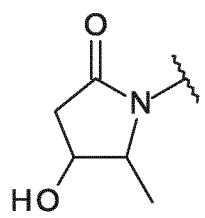
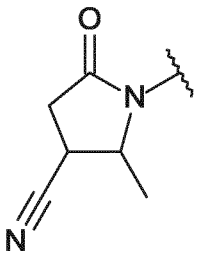
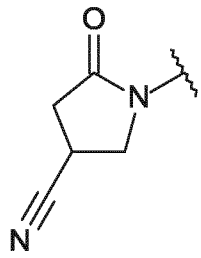
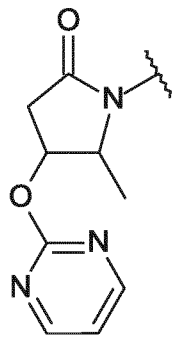
R^1 is , wherein R^{10} is H; R^{11} is H; R^{12} is cyano, hydroxy or pyrimidinyloxy; R^{13} is H; R^{14} is H or C_{1-6}alkyl;

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

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl.

13. A compound according to claim 12, wherein

R^1 is , ,  or ;

R^2 is H or methyl;

R^3 is methyl;

R^4 is trifluorophenyl, difluoropyridinyl or difluoromethylpyridinyl.

14. A compound selected from:

(6S)-3-[3-hydroxy-2-oxo-4-(2-pyridyl)pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3S)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3R)-2-methyl-3-(morpholine-4-carbonyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,4-trans-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,4-cis-4-cyano-3-hydroxy-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(3,3-difluoro-2-oxo-pyrrolidin-1-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S,4R)-3-cyano-4-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(5S)-3-hydroxy-5-methyl-2-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S)-2-(methylcarbamoyl)-5-oxo-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(4-cyano-4-methyl-2-oxo-pyrrolidin-1-yl)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-N-(2,6-difluoro-4-pyridyl)-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[2-[(dimethylamino)methyl]-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

15. A compound selected from:
(6S)-3-[(2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidin-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-[(2S,3S)-3-cyano-2-methyl-5-oxo-pyrrolidin-1-yl]-N-(2,6-difluoro-4-pyridyl)-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(2S,3S)-2-methyl-5-oxo-3-pyrimidin-2-yloxy-pyrrolidin-1-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S,7S)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and

(6S,7R)-3-(4-cyano-2-oxo-pyrrolidin-1-yl)-6,7-dimethyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

16. A compound of formula (I), wherein

R^1 is oxoazaspiro[2.4]heptanyl;
oxobenzimidazolyl;
oxodiazabicyclo[3.1.1]heptanyl;
oxodiazabicyclo[3.2.1]octanyl substituted by C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or C_{1-6}alkyl;
oxodiazabicyclo[3.3.1]nonanyl unsubstituted or substituted by C_{1-6}alkylcarbonyl;
oxodiazaspiro[3.4]octanyl substituted by C_{1-6}alkoxycarbonyl;
oxohexahydrobenzimidazolyl;
oxohexahydrocyclopenta[d]imidazolyl unsubstituted or substituted by hydroxy;
oxooxaazabicyclo[3.2.1]octanyl;
oxooxaazaspiro[2.4]heptanyl unsubstituted or substituted by C_{1-6}alkyl;
oxooxadiazabicyclo[3.3.1]nonanyl substituted by C_{1-6}alkylcarbonyl;
oxooxazinanyl which is twice substituted by C_{1-6}alkyl and cyano;
oxopyridinyl;
oxotetrahydrocyclopenta[d]oxazolyl;
oxotetrahydrofuro[3,4-d]imidazolyl; or
oxotetrahydrofuro[3,4-d]oxazolyl;

R^2 is H;

R^3 is C_{1-6}alkyl;

R^4 is phenyl which is three times substituted by halogen; or pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl;

with the proviso that

(6S)-6-methyl-3-(6-oxo-5-azaspiro[2.4]heptan-5-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

Methyl 6-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

Ethyl 6-[(6S)-6-methyl-5-[(3,4,5-trifluorophenyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;

(6S)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
and their enantiomers or diastereomers are excluded.

17. A compound according to claim 16, wherein
R^1 is 5-oxo-4-azaspiro[2.4]heptan-4-yl; 2-oxo-3H-benzimidazol-1-yl; 6-acetyl-4-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl; 8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 8-ethylsulfonyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 8-methyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl; 4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl; 7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl; 2-tert-butylcarbonyl-7-oxo-2,6-diazaspiro[3.4]octanyl; 2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl; 2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl; 5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl; 4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl; 5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl; 7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl; 9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl; cyano(methyl)oxooxazinanyl; oxopyridinyl, 2-oxo-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]oxazol-3-yl; 2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl or 2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl;
R^2 is H;
R^3 is methyl;
R^4 is trifluorophenyl, chloropyridinyl, difluoropyridinyl, difluoromethylpyridinyl or trifluoromethylpyridinyl.

18. A compound according to claim 16, wherein
R^1 is oxooxaazaspiro[2.4]heptanyl substituted by C_{1-6}alkyl;
R^2 is H;
R^3 is C_{1-6}alkyl;
R^4 is pyridinyl which is once or twice substituted by substituents independently selected from halogen and haloC_{1-6}alkyl.

19. A compound according to claim 18, wherein
R^1 is 7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl;
R^2 is H;

R^3 is methyl;

R^4 is difluoropyridinyl or difluoromethylpyridinyl.

20. A compound selected from:

(6S)-N-(2-chloro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl)-N-[2-(trifluoromethyl)-4-pyridyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3ar,7ar)-2-oxo-3a,4,5,6,7,7a-hexahydro-3H-benzimidazol-1-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3ar,6as)-2-oxo-4,5,6,6a-tetrahydro-3ah-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-[(3as,6ar)-2-oxo-4,5,6,6a-tetrahydro-3ah-cyclopenta[d]oxazol-3-yl]-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydrofuro[3,4-d]oxazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-6-methyl-3-(2-oxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d]imidazol-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

(6S)-3-(5-hydroxy-2-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[d]imidazol-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

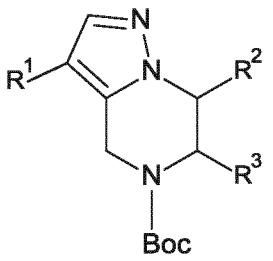
(6S)-6-methyl-3-(5-oxo-4-azaspiro[2.4]heptan-4-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;

Tert-butyl 6-[(6S)-5-[[2-(difluoromethyl)-4-pyridyl]carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;
Tert-butyl 6-[(6S)-5-[(2,6-difluoro-4-pyridyl)carbamoyl]-6-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-3-yl]-7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate;
(6S)-6-methyl-3-(4-oxo-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(8-acetyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(8-ethylsulfonyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-(8-methyl-4-oxo-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-(4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6R)-3-(7-acetyl-4-oxo-3,7-diazabicyclo[3.3.1]nonan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(6-acetyl-4-oxo-3,6-diazabicyclo[3.1.1]heptan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(9-acetyl-6-oxo-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-3-(5-cyano-5-methyl-2-oxo-1,3-oxazinan-3-yl)-6-methyl-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide;
(6S)-6-methyl-3-(2-oxo-3H-benzimidazol-1-yl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-6-methyl-3-(2-oxo-1-pyridyl)-N-(3,4,5-trifluorophenyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

21. A compound selected from:

(6S)-N-(2,6-difluoro-4-pyridyl)-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide; and
(6S)-N-[2-(difluoromethyl)-4-pyridyl]-6-methyl-3-[(7S)-7-methyl-5-oxo-4-oxa-6-azaspiro[2.4]heptan-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxamide.

22. A process for the preparation of a compound according to any one of claims 1 to 21 comprising the following step:
(a) the reaction of a compound of formula (IV),



(IV),

with an acid followed by urea formation with amine R^4NH_2 in the presence of a phosgene equivalent; wherein R^1 to R^4 are defined as in any one of claims 1 to 21.

23. A compound or pharmaceutically acceptable salts, enantiomers or diastereomers according to any one of claims 1 to 21 for use as therapeutically active substance.

24. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 21 and a therapeutically inert carrier.

25. The use of a compound according to any one of claims 1 to 21 for the treatment or prophylaxis of hepatitis B virus infection.

26. The use of a compound according to any one of claims 1 to 21 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

27. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 21 for the treatment or prophylaxis of hepatitis B virus infection.

28. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 21, when manufactured according to a process of claim 22.

29. A method for the treatment or prophylaxis of hepatitis B virus infection, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 21.

5

20. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/067315

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08 C07D487/04 C07D487/08 C07D487/10 C07D491/048
C07D498/08 A61K31/4985 A61K31/506 A61P31/12
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/109689 A2 (NOVIRA THERAPEUTICS INC [US]) 7 July 2016 (2016-07-07) the whole document	1-30
A	WO 2009/085983 A1 (GENENTECH INC [US]; PRICE STEPHEN [GB]; HEALD ROBERT [GB]; LEE WENDY [] 9 July 2009 (2009-07-09) paragraph [00141] Examples and claims	1-30

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2017	26/09/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PAUL A BARSANTI ET AL: "Structure-Based Drug Design of Novel Potent and Selective Tetrahydropyrazolo[1,5- a]pyrazines as ATR Inhibitors", ACS MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 1, 20 November 2014 (2014-11-20), pages 37-41, XP055349939, United States ISSN: 1948-5875, DOI: 10.1021/ml500353p compounds 3-7, 17-19, 20, 21, 23-26	1-30
X,P	WO 2016/113273 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 21 July 2016 (2016-07-21) the whole document	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/067315

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016109689 A2	07-07-2016	AU 2015373996 A1	13-07-2017
		US 2016185777 A1	30-06-2016
		US 2016185778 A1	30-06-2016
		US 2016185779 A1	30-06-2016
		US 2017121328 A1	04-05-2017
		US 2017121329 A1	04-05-2017
		US 2017158691 A1	08-06-2017
		WO 2016109663 A2	07-07-2016
		WO 2016109684 A2	07-07-2016
		WO 2016109689 A2	07-07-2016
WO 2009085983 A1	09-07-2009	AR 069803 A1	17-02-2010
		AU 2008343065 A1	09-07-2009
		BR PI0819529 A2	26-05-2015
		CA 2706571 A1	09-07-2009
		CN 101945870 A	12-01-2011
		CY 1114663 T1	05-10-2016
		CY 1116681 T1	15-03-2017
		DK 2222675 T3	04-11-2013
		DK 2690101 T3	28-09-2015
		EP 2222675 A1	01-09-2010
		EP 2690101 A1	29-01-2014
		ES 2437141 T3	09-01-2014
		ES 2546171 T3	21-09-2015
		HK 1147254 A1	28-03-2014
		HK 1188209 A1	27-05-2016
		HR P20151002 T1	23-10-2015
		HU E025192 T2	28-01-2016
		IL 205977 A	31-05-2015
		JP 5421925 B2	19-02-2014
		JP 2011507889 A	10-03-2011
		KR 20100093608 A	25-08-2010
		MY 158829 A	15-11-2016
		NZ 586802 A	30-03-2012
		PE 11582009 A1	28-08-2009
		PE 12102013 A1	31-10-2013
		PT 2222675 E	13-11-2013
		PT 2690101 E	08-10-2015
		SI EP2222675 T1	31-12-2013
		SI EP2690101 T1	30-10-2015
		TW 200932745 A	01-08-2009
		US 2010004269 A1	07-01-2010
		US 2011158990 A1	30-06-2011
		US 2012309765 A1	06-12-2012
		US 2013150584 A1	13-06-2013
		WO 2009085983 A1	09-07-2009
		ZA 201003625 B	31-08-2011
WO 2016113273 A1	21-07-2016	AU 2016208095 A1	13-07-2017
		TW 201629066 A	16-08-2016
		US 2016237090 A1	18-08-2016
		WO 2016113273 A1	21-07-2016