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(54) Title: BICYCLIC INHIBITORS OF PAD4

(57) Abstract: The present invention provides compounds useful as inhibitors of PAD4, compositions thereof, and methods of treating PAD4-related disorders.

BICYCLIC INHIBITORS OF PAD4

BACKGROUND OF THE INVENTION

[0001] PAD4 is a member of the peptidylarginine deiminase (PAD) family of enzymes capable of catalysing the citrullination of arginine into citrulline within peptide sequences. PAD4 is responsible for the deimination or citrullination of a variety of proteins *in vitro* and *in vivo*, with consequences of diverse functional responses in a variety of diseases (*Jones J.E. et al, Curr. Opin. Drug Discov. Devel., 12(5), (2009),616-627*). Examples of exemplar diseases include rheumatoid arthritis, diseases with neutrophilic contributions to pathogenesis (for example vasculitis, systemic lupus erythematosus, ulcerative colitis) in addition to oncology indications. PAD4 inhibitors also have wider applicability as tools and therapeutics for human disease through epigenetic mechanisms.

[0002] Inhibitors of PAD4 have utility against Rheumatoid Arthritis (RA). RA is an auto-immune disease affecting approximately 1% of the population *(Wegner N. et al, Immunol. Rev., 233(1) (2010), 34-54)*. It is characterised by inflammation of articular joints leading to debilitating destruction of bone and cartilage. A weak genetic association between PAD4 polymorphisms and susceptibility to RA has been suggested, albeit inconsistently, in a number of population studies (*Kochi Y. et al, Ann. Rheum. Dis., 70, (2011),512-515*). PAD4 (along with family member PAD2) has been detected in synovial tissue where it is responsible for the deimination of a variety of joint proteins. This process is presumed to lead to a break of tolerance to, and initiation of immune responses to, citrullinated substrates such as fibrinogen, vimentin and collagen in RA joints. These anti-citrullinated protein antibodies (ACPA) contribute to disease pathogenesis and may also be used as a diagnostic test for RA (e.g. the commercially available CCP2 or cyclic citrullinated protein 2 test). In addition, increased citrullination may also offer additional direct contributions to disease pathogenesis through its ability to affect directly the function of several joint and inflammatory mediators (e.g. fibrinogen, anti-thrombin, multiple chemokines). In a smaller subset of RA patients, anti-PAD4 antibodies can be measured and may correlate with a more erosive form of the disease.

[0003] PAD4 inhibitors are also useful for the reduction of pathological neutrophil activity in a variety of diseases. Studies suggest that the process of Neutrophil Extracellular Trap (NET) formation, an innate defence mechanism by which neutrophils are able to immobilise and kill pathogens, is associated with histone citrulllination and is deficient in PAD4 knockout mice (*Neeli I. et al, J. Immunol., 180, (2008), 1895-1902* and *Li P. et al, J.*

Exp. Med., 207(9), (2010), 1853-1862). PAD4 inhibitors may therefore have applicability for diseases where NET formation in tissues contributes to local injury and disease pathology. Such diseases include, but are not limited to, small vessel vasculitis (*Kessenbrock K. et al, Nat. Med., 15(6), (2009), 623-625)*, systemic lupus erythematosus (*Hakkim A. et al, Proc. Natl. Acad. Sci. USA, 107(21), (2010), 9813-9818* and *Villanueva E. et al, J. Immunol., 187(1), (2011), 538-52),* ulcerative colitis *(Savchenko A. et al, Pathol. Int., 61(5), (2011), 290-7)*, cystic fibrosis, asthma *(Dworski R. et al, J. Allergy Clin. Immunol., 127(5), (2011), 1260-6)*, deep vein thrombosis *(Fuchs T. et al, Proc. Natl. Acad. Sci. USA, 107(36), (2010), 15880-5)*, periodontitis *(Vitkov L. et al, Ultrastructural Pathol., 34(1), (2010), 25-30)*, sepsis *(Clark S.R. et al, Nat. Med., 13(4), (2007), 463-9)*, appendicitis *(Brinkmann V. et al, Science, 303, (2004), 1532-5)*, and stroke. In addition, there is evidence that NETs may contribute to pathology in diseases affecting the skin, eg in cutaneous lupus erythematosis (*Villanueva E. et al, J. Immunol., 187(1), (2011), 538-52)* and psoriasis (*Lin A.M. et al., J. Immunol., 187(1), (2011), 490-500*), so a PAD4 inhibitor may show benefit to tackle NET skin diseases, when administered by a systemic or cutaneous route. PAD4 inhibitors may affect additional functions within neutrophils and have wider applicability to neutrophilic diseases.

[0004] Studies have demonstrated efficacy of tool PAD inhibitors (for example chloro-amidine) in a number of animal models of disease, including collagen-induced arthritis (*Willis V.C. et al, J. Immunol., 186(7), (2011), 4396-4404*), dextran sulfate sodium (DSS)-induced experimental colitis (*Chumanevich A.A. et al, Am. J. Physiol. Gastrointest. Liver Physiol., 300(6), (2011), G929–G938*), spinal cord repair *(Lange S. et al, Dev. Biol., 355(2), (2011), 205-14)*, and experimental autoimmune encephalomyelitis (EAE). The DSS colitis report also demonstrates that chloro-amidine drives apoptosis of inflammatory cells both *in vitro* and *in vivo*, suggesting that PAD4 inhibitors may be effective more generally in widespread inflammatory diseases.

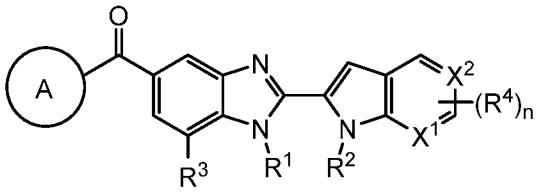
[0005] PAD4 inhibitors are also useful in the treatment of cancers (*Slack.J.L. et al, Cell. Mol. Life Sci., 68(4), (2011), 709-720*). Over-expression of PAD4 has been demonstrated in numerous cancers (*Chang X. et al, BMC Cancer, 9, (2009), 40*). An anti-proliferative role has been suggested for PAD4 inhibitors from the observation that PAD4 citrullinates arginine residues in histones at the promoters of p53-target genes such as p21, which are involved in cell cycle arrest and induction of apoptosis (*Li P. et al, Mol. Cell Biol., 28(15), (2008), 4745-4758*).

[0006] The aforementioned role of PAD4 in deiminating arginine residues in histones may be indicative of a role for PAD4 in epigenetic regulation of gene expression. PAD4 is

the primary PAD family member observed to be resident in the nucleus as well as the cytoplasm. Early evidence that PAD4 may act as a histone demethyliminase as well as a deiminase is inconsistent and unproven. However, it may reduce histone arginine methylation (and hence epigenetic regulation associated with this mark) indirectly *via* depletion of available arginine residues by conversion to citrulline. PAD4 inhibitors are useful as epigenetic tools or therapeutics for affecting expression of varied target genes in additional disease settings. Through such mechanisms, PAD4 inhibitors may also be effective in controlling citrullination levels in stem cells and may therefore therapeutically affect the pluripotency status and differentiation potential of diverse stem cells including, but not limited to, embryonic stem cells, neural stem cells, haematopoietic stem cells and cancer stem cells. Accordingly, there remains an unmet need to identify and develop PAD4 inhibitors for the treatment of PAD4-mediated disorders.

SUMMARY OF THE INVENTION

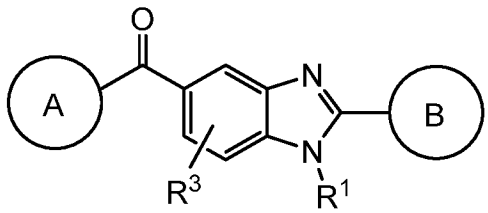
[0007] It has now been found that compounds of formula **I** are useful as inhibitors of PAD4:



I

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, R^4, X^1, and X^2 is as defined herein.

[0008] It has also been found that compounds of formula **I'** are useful as inhibitors of PAD4:



I'

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, and R^3 is as defined herein.

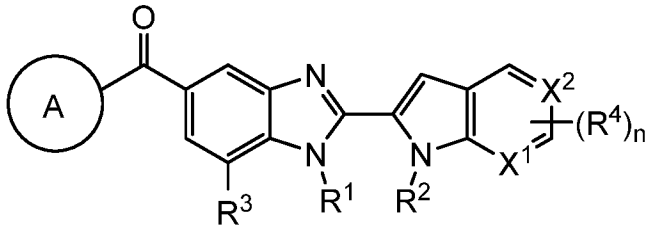
[0009] In some embodiments, a provided compound demonstrates selectivity for PAD4 with respect to PAD2. The present invention also provides pharmaceutically acceptable compositions comprising a provided compound. Provided compounds are useful in treatment

of various disorders associated with PAD4. Such disorders are described in detail, herein, and include, for example rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, and psoriasis.

DETAILED DESCRIPTION OF THE INVENTION

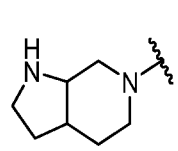
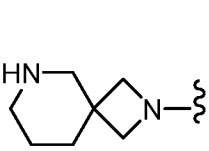
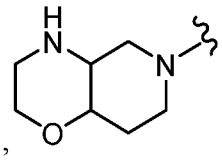
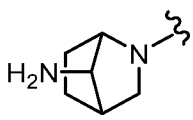
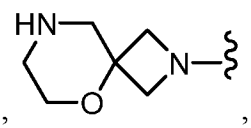
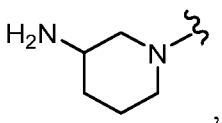
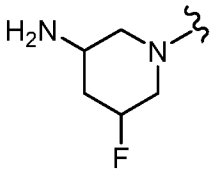
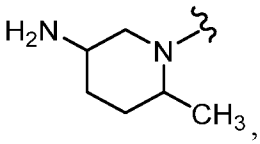
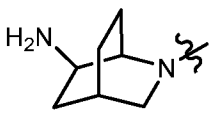
1. General Description of Certain Aspects of the Invention

[0010] In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined herein and described in embodiments. Such compounds have the structure of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  ,  ,  ,  ,  ,  ,  ,  , or  , wherein Ring A is optionally substituted with 1-4 groups selected from fluorine, -CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms;

R^1 is hydrogen, –CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or OR;

R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR;

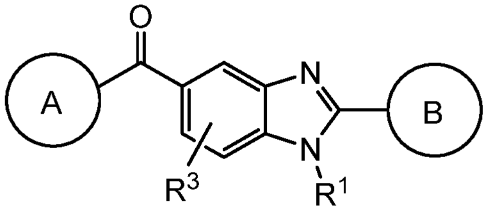
each of X^1 and X^2 is independently selected from N or $C(R^4)$;

each of R^3 and R^4 is independently halogen, -CN, –R, or –OR;

n is 0-4; and

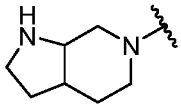
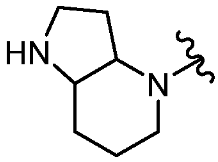
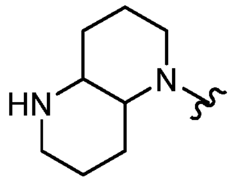
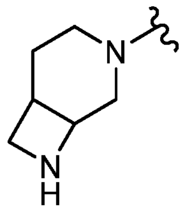
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

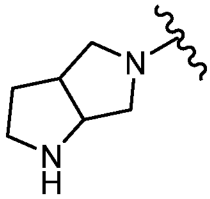
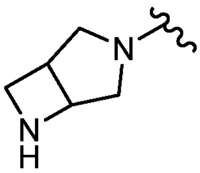
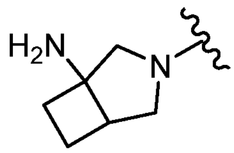
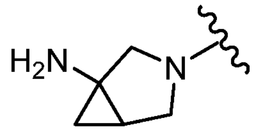
[0011] In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined herein and described in embodiments. Such compounds have the structure of formula **I'**:

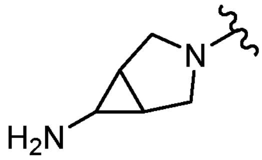
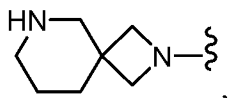
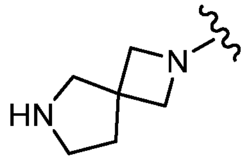
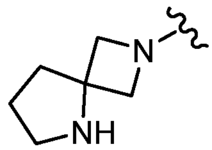


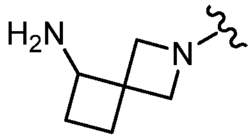
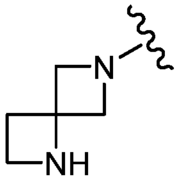
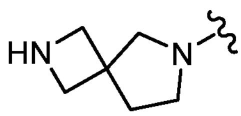
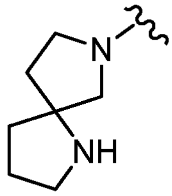
I'

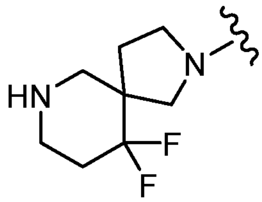
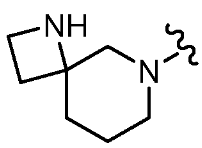
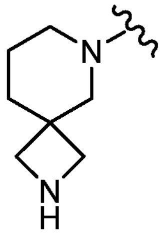
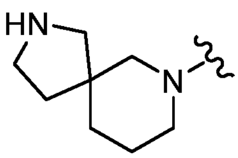
or a pharmaceutically acceptable salt thereof, wherein:

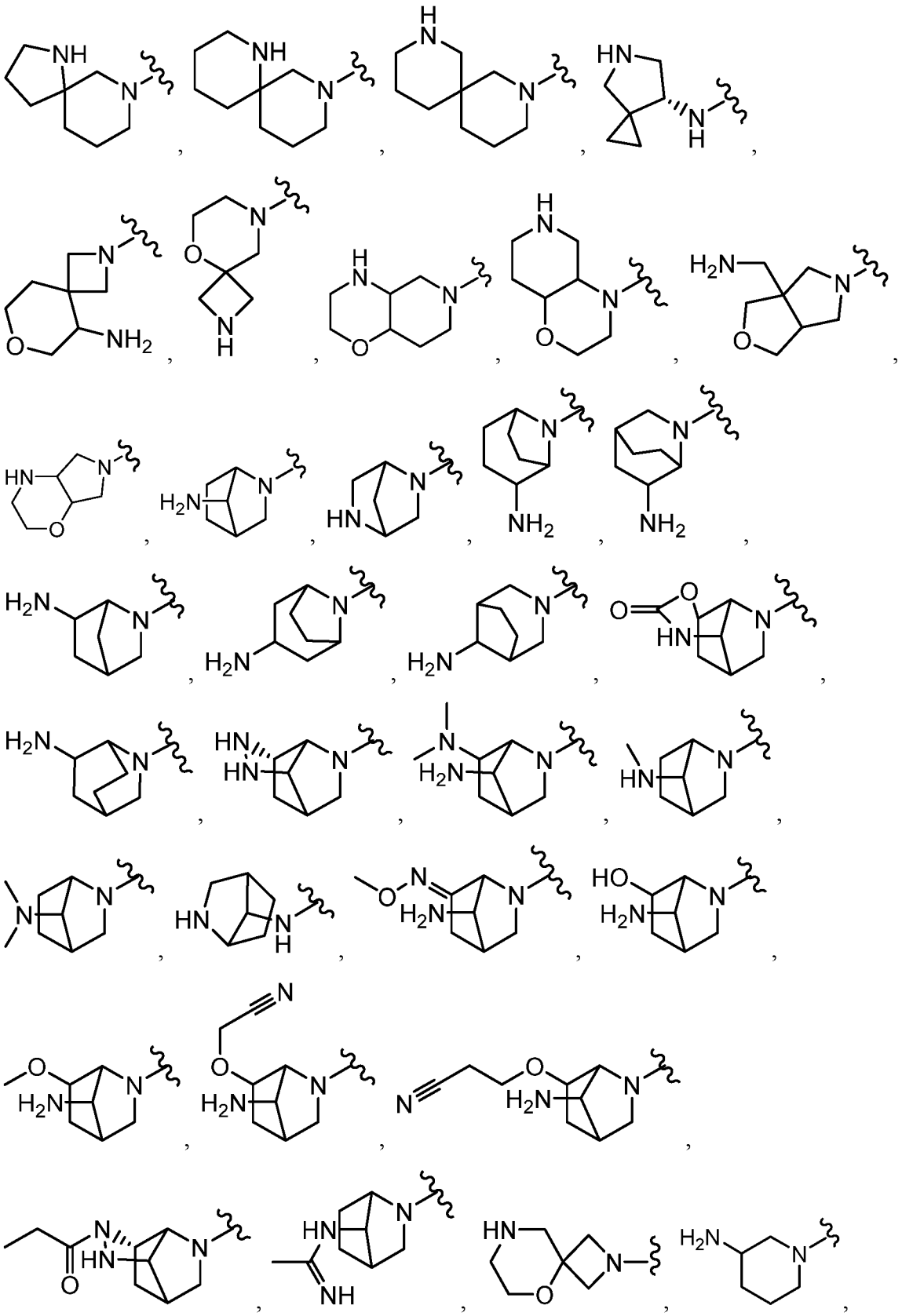
Ring A is  ,  ,  ,  ,

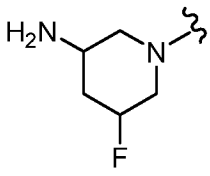
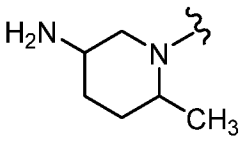
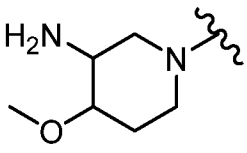
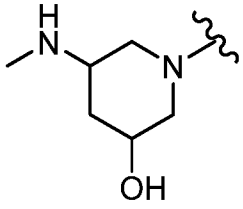
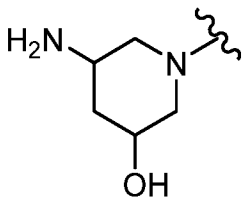
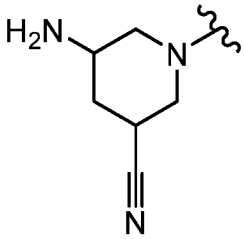
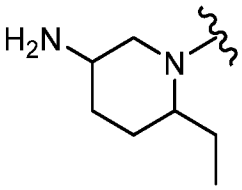
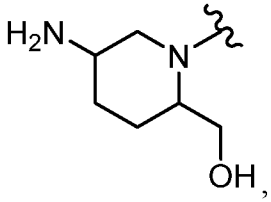
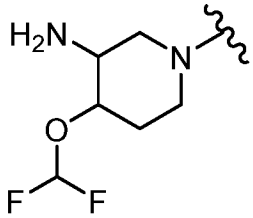
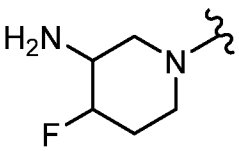
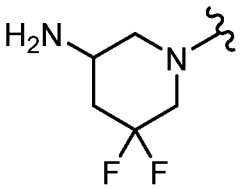
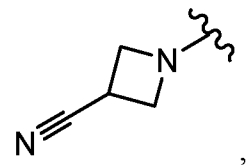
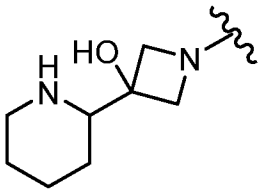
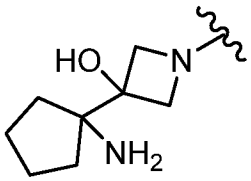
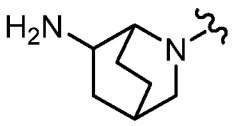
 ,  ,  ,  ,

 ,  ,  ,  ,

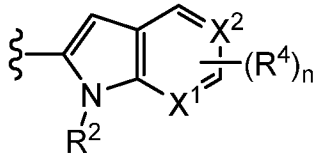
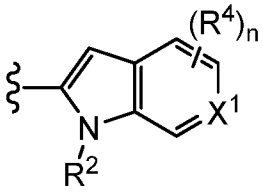
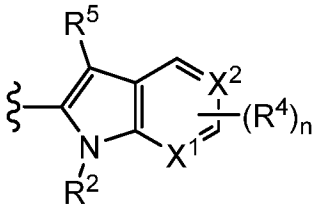
 ,  ,  ,  ,

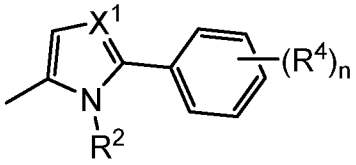
 ,  ,  ,  ,

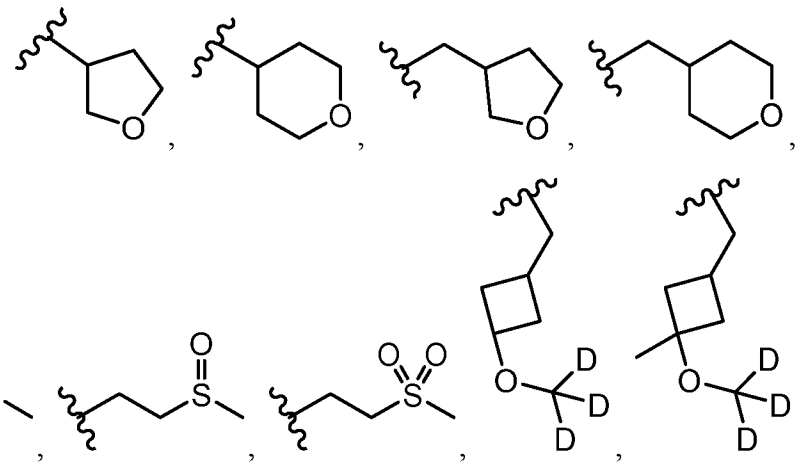


, wherein Ring A is optionally substituted with 1-4 groups selected from fluorine, -CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms;

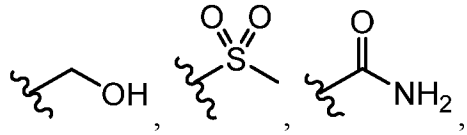
Ring B is 


or

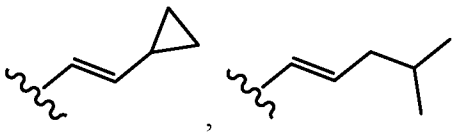
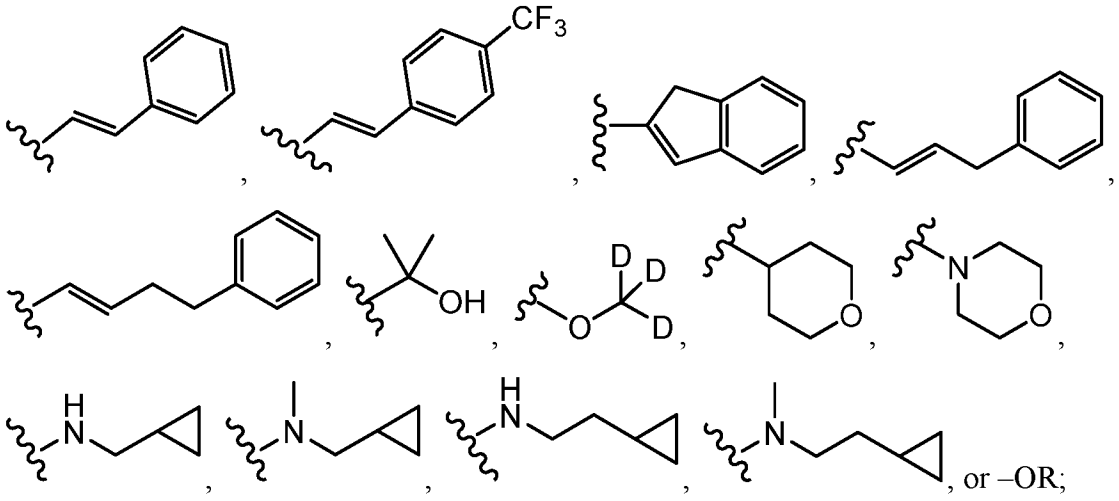

;

R^1 is hydrogen, –CN, -OR,  , C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or -OR;

R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR;

each of X^1 and X^2 is independently selected from N or $C(R^4)$;

R^3 is halogen, -CN, –R,  , or –OR;

each R^4 is independently halogen, -CN, –R,  ,  , or –OR;

R^5 is hydrogen or halogen;

n is 0-4; and

each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

2. Definitions

[0012] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0013] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0014] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases.

Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

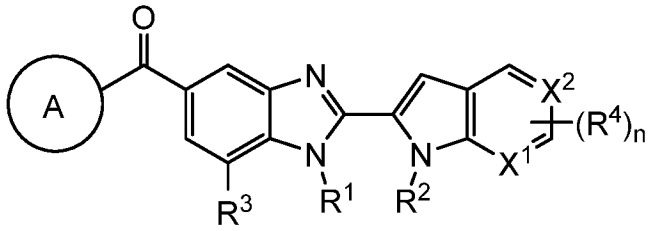
[0015] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0016] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0017] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in PAD4 activity between a sample comprising a compound of the present invention, or composition thereof, and PAD4, and an equivalent sample comprising PAD4 in the absence of said compound, or composition thereof.

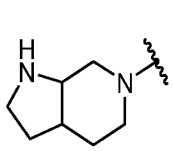
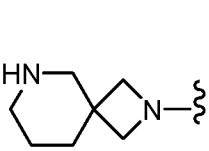
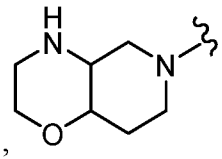
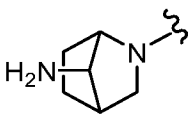
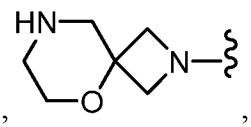
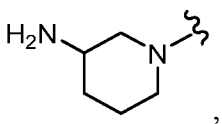
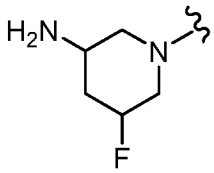
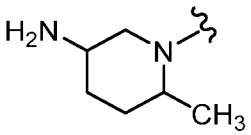
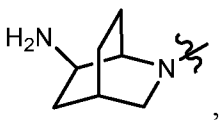
3. Description of Exemplary Compounds

[0018] According to one aspect, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  ,  ,  ,  ,  ,  ,  ,  , or  , wherein Ring A is optionally substituted with 1-4 groups selected from fluorine, -CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms;

R^1 is hydrogen, –CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or -OR;

R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR;

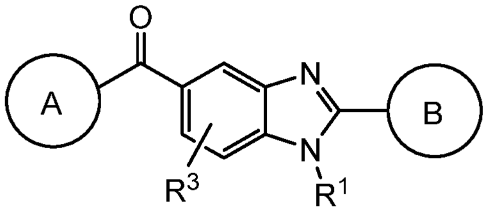
each of X^1 and X^2 is independently selected from N or $C(R^4)$;

each of R^3 and R^4 is independently halogen, -CN, –R, or –OR;

n is 0-4; and

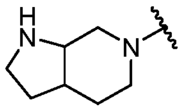
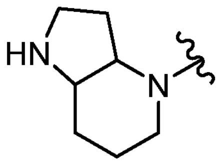
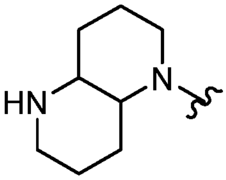
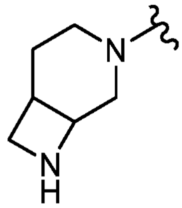
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

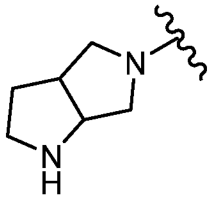
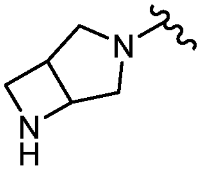
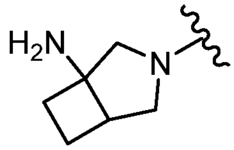
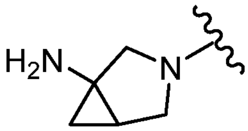
[0019] According to another aspect, the present invention provides a compound of formula **I'**:

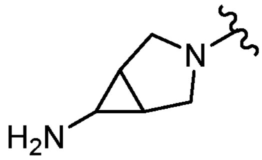
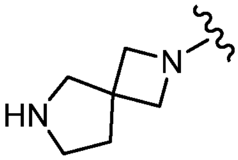
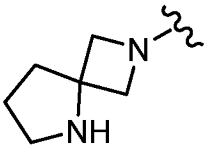


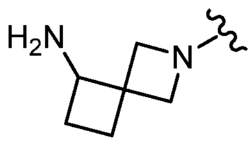
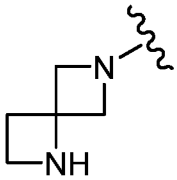
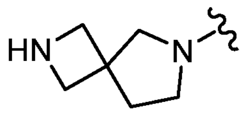
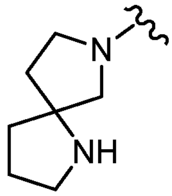
I'

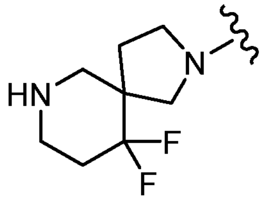
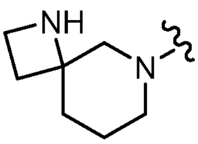
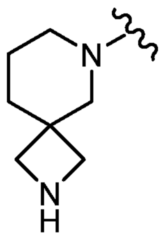
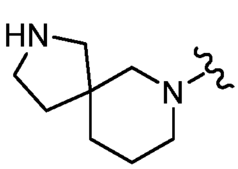
or a pharmaceutically acceptable salt thereof, wherein:

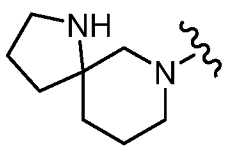
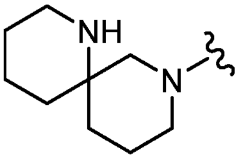
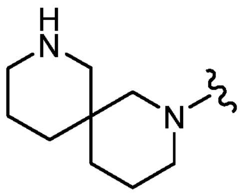
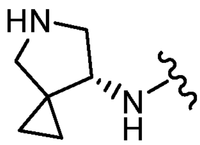
Ring A is  ,  ,  ,  ,

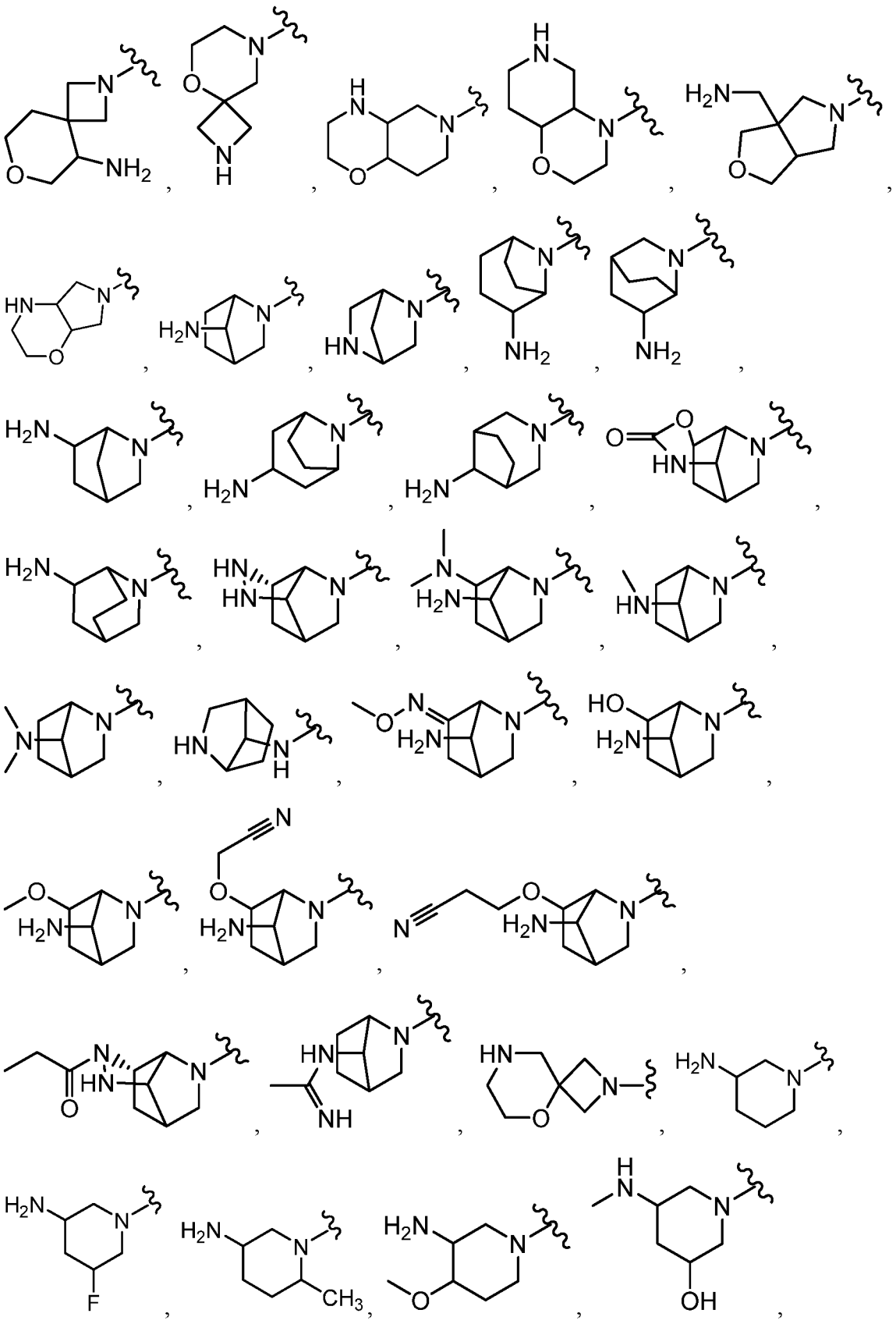
 ,  ,  ,  ,

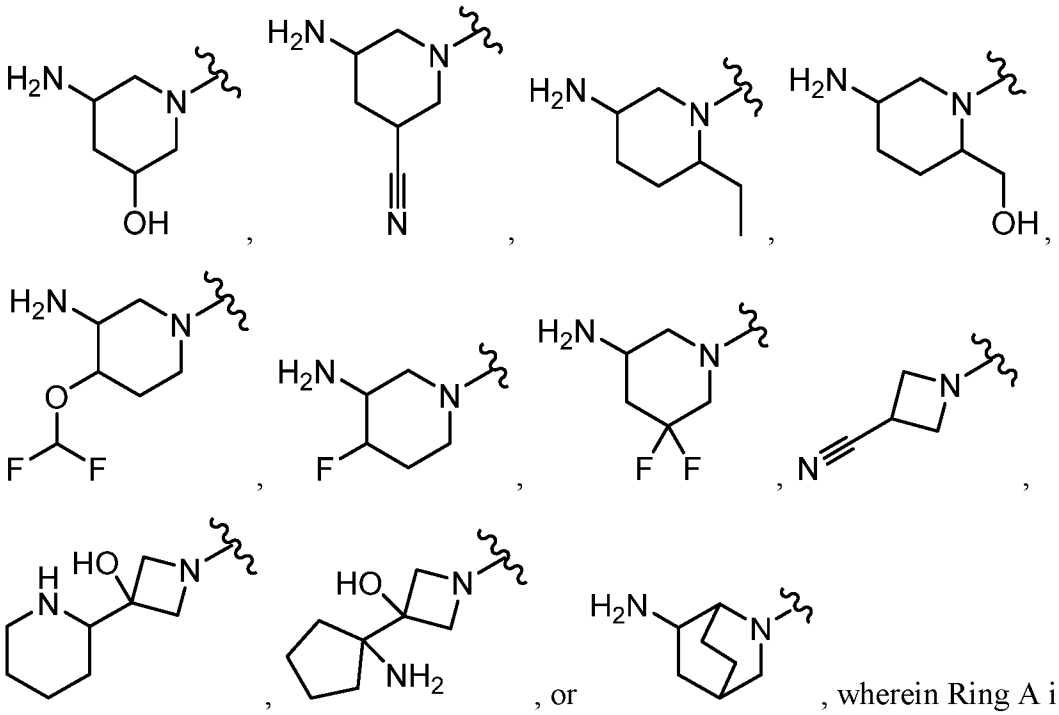
 ,  ,  ,  ,

 ,  ,  ,  ,

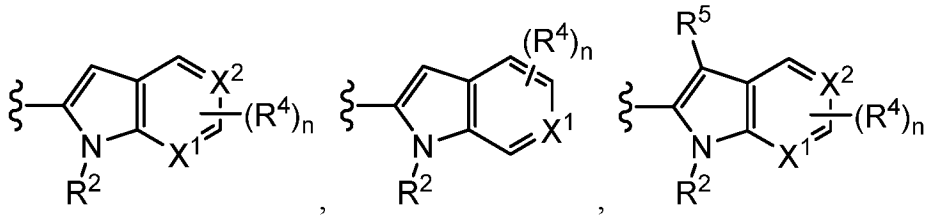
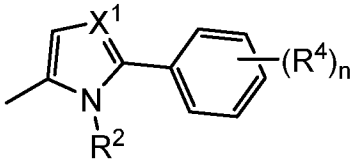
 ,  ,  ,  ,

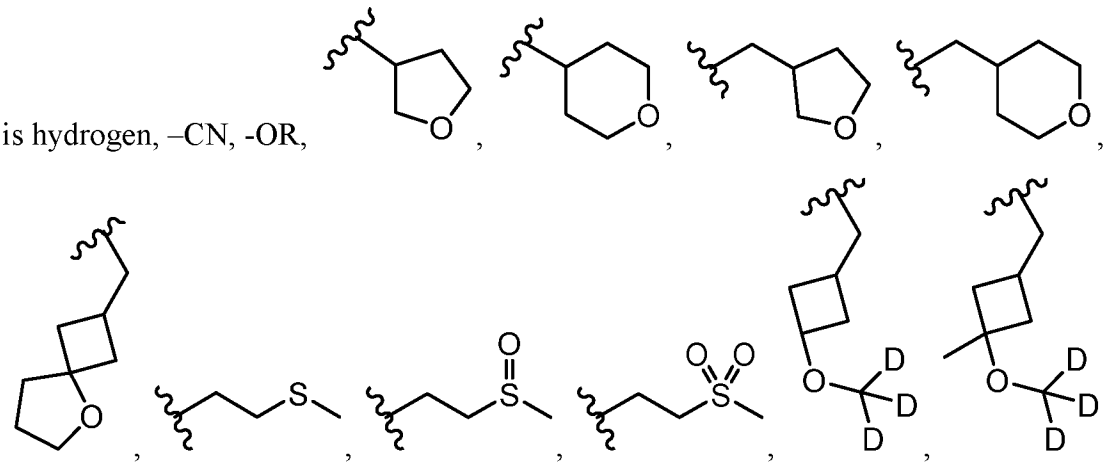
 ,  ,  ,  ,





optionally substituted with 1-4 groups selected from fluorine, -CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms;

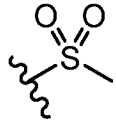
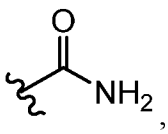
Ring B is  or  ;

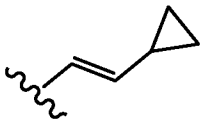
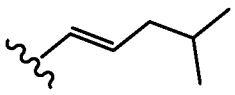
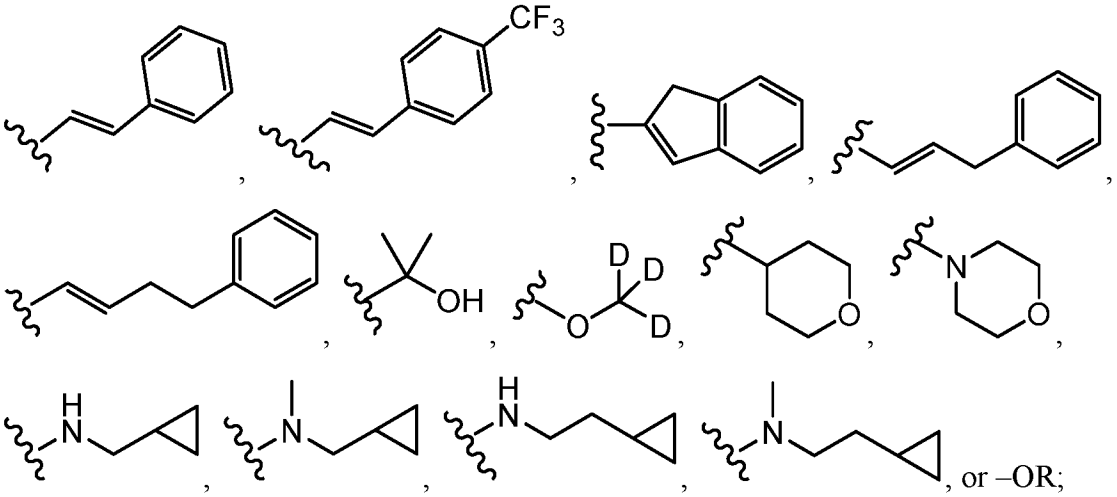
R^1 is hydrogen, –CN, -OR, 

C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or -OR;

R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR;

each of X^1 and X^2 is independently selected from N or $C(R^4)$;

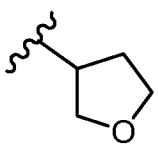
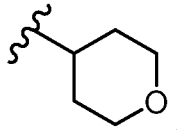
R^3 is halogen, -CN, –R,  ,  ,  , or –OR;

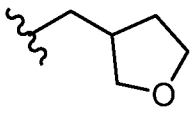
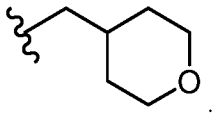
each R^4 is independently halogen, -CN, –R,  ,  , 

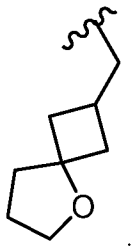
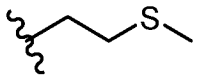
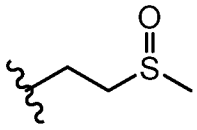
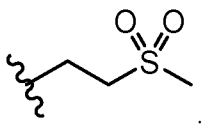
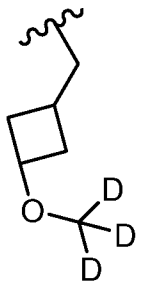
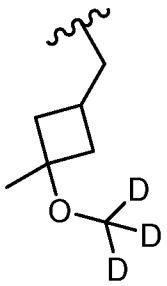
R^5 is hydrogen or halogen;

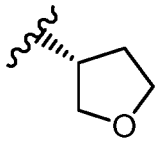
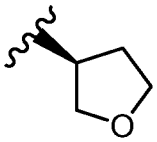
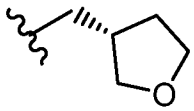
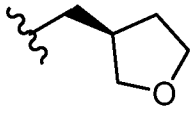
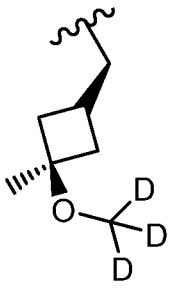
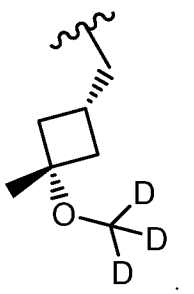
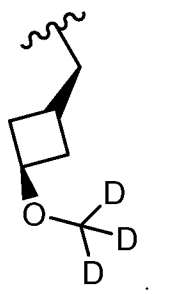
n is 0-4; and

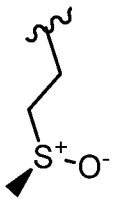
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

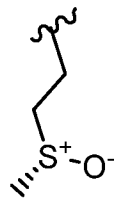
[0020] As defined above and described herein, R^1 is hydrogen, –CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or -OR. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is –CN. In some embodiments, R^1 is –OR. In some embodiments, R^1 is C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or OR. In some embodiments, R^1 is C_{1-3} aliphatic. In some embodiments, R^1 is methyl. In some embodiments, R^1 is ethyl. In some embodiments, R^1 is propyl. In some embodiments, R^1 is $–CH_2$-cyclobutyl optionally substituted with methyl and –OH. In some embodiments, R^1 is  . In some embodiments, R^1 is  .

In some embodiments, R^1 is  . In some embodiments, R^1 is  .

In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  .

[0021] In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is



. In some embodiments, R^1 is 

. In certain embodiments, R^1 is selected from those depicted in Table 1, below.

[0022] As defined above and described herein, R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is propyl. In some embodiments, R^2 is butyl. In some embodiments, R^2 is pentyl. In some embodiments, R^2 is hexyl. In some embodiments, R^2 is cyclopropyl. In some embodiments, R^2 is cyclobutyl. In some embodiments, R^2 is cyclopentyl. In some embodiments, R^2 is cyclohexyl. In some embodiments, R^2 is cyclopropylmethyl. In some embodiments, R^2 is cyclobutylmethyl. In some embodiments, R^2 is cyclopentylmethyl. In some embodiments, R^2 is cyclohexylmethyl. In some embodiments, R^2 is cyclopropylethyl. In some embodiments, R^2 is cyclobutylethyl. In some embodiments, R^2 is cyclopentylethyl. In some embodiments, R^2 is cyclohexylethyl. In some embodiments, R^2 is $–CH_2$-cyclopropyl or $–CH_2$-cyclobutyl. In some embodiments, R^1 is $–CH_2$-cyclobutyl optionally substituted with methyl and –OH.

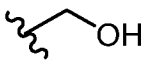
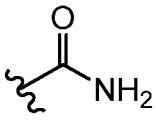
[0023] In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 1 fluorine atom. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 2 fluorine atoms. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 3 fluorine atoms. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 4 fluorine atoms. In some embodiments, R^2 is C_{1-10} aliphatic, substituted with 5 fluorine atoms. In some embodiments, R^2 is methyl, substituted with 1-3 fluorine atoms. In some embodiments, R^2 is trifluoromethyl. In some embodiments, R^2 is ethyl, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is 2,2,2-trifluoroethyl. In some embodiments, R^2 is propyl, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is 3,3,3-trifluoropropyl. In some embodiments, R^2 is butyl, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is 4,4,4-trifluorobutyl. In some embodiments, R^2 is pentyl, substituted with 1-5 fluorine atoms. In some embodiments, R^2 is 5,5,5-trifluoropentyl. In some embodiments, R^2 is hexyl, substituted with 1-5 fluorine atoms. In some embodiments,

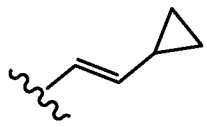
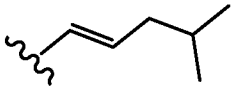
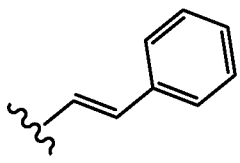
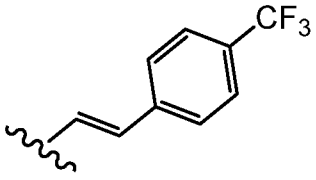
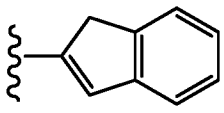
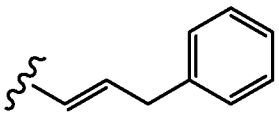
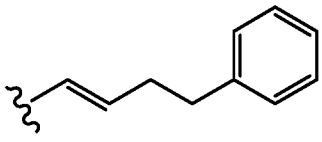
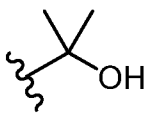
R^2 is 6,6,6-trifluorohexyl. In certain embodiments, R^2 is selected from those depicted in Table 1, below.

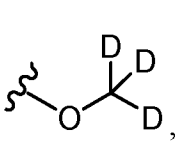
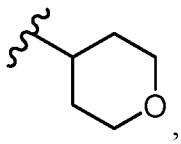
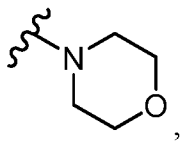
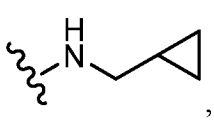
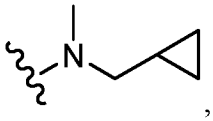
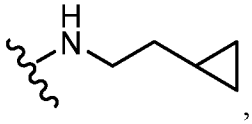
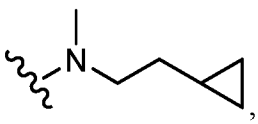
[0024] As defined above and described herein, each X^1 and X^2 is independently selected from N or $C(R^4)$. In some embodiments, both of X^1 and X^2 are N. In some embodiments, X^1 is N, and X^2 is CH. In some embodiments, X^1 is CH, and X^2 is N. In some embodiments, both of X^1 and X^2 are CH. In some embodiments, X^1 is N, and X^2 is $C(R^4)$. In some embodiments, X^1 is $C(R^4)$, and X^2 is N. In some embodiments, both of X^1 and X^2 are $C(R^4)$. In certain embodiments, X^1 and X^2 are selected from those depicted in Table 1, below.

[0025] As defined above and described herein, R^3 is halogen, -CN, –R, or –OR and each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

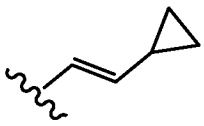
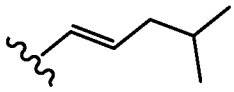
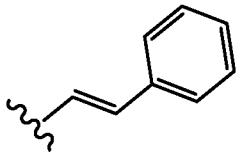
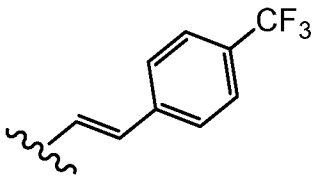
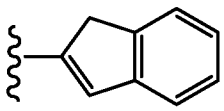
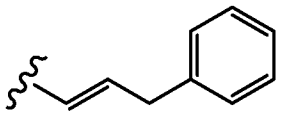
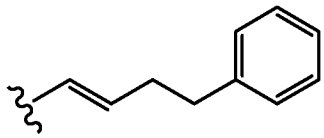
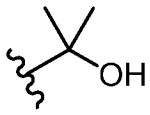
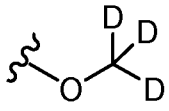
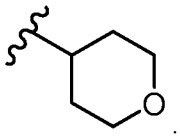
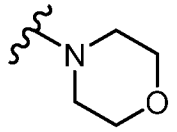
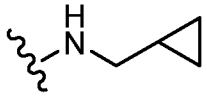
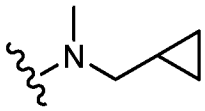
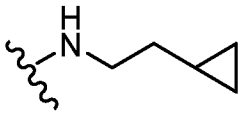
[0026] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is halogen. In some embodiments, R^3 is –CN. In some embodiments, R^3 is C_{1-3} aliphatic. In some embodiments, R^3 is methyl. In some embodiments, R^3 is ethyl. In some embodiments, R^3 is propyl. In some embodiments, R^3 is □OR. In some embodiments, R^3 is $–OCH_3$. In some embodiments, R^3 is $–OCH_2CH_3$. In some embodiments, R^3 is $-OCH_2CH_2CH_3$. In certain embodiments, R^3 is $-OCH(F)_2$.

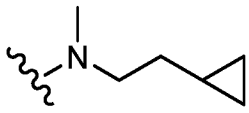
[0027] In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In certain embodiments, R^3 is selected from those depicted in Table 1, below.

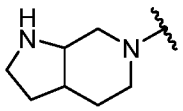
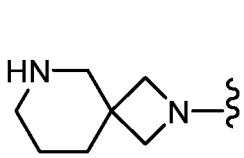
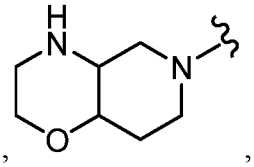
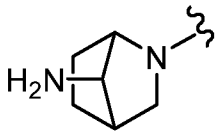
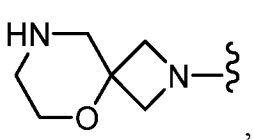
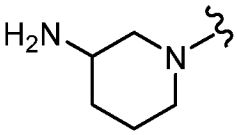
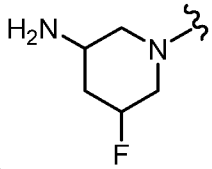
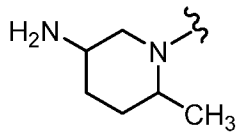
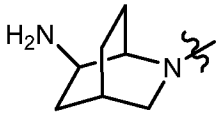
[0028] As defined above and described herein, each R^4 is independently halogen, -CN, –R,  ,  ,  ,  ,  ,  ,  ,  ,

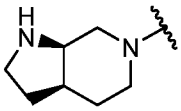
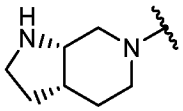
 ,  ,  ,  ,  ,  ,  , or –OR.

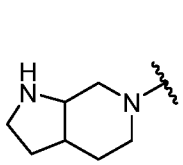
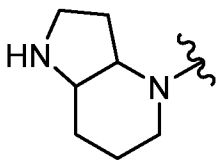
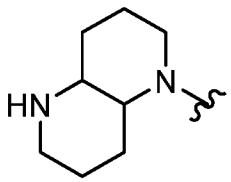
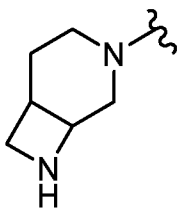
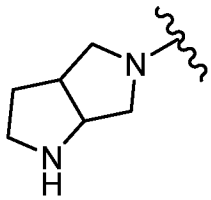
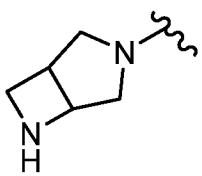
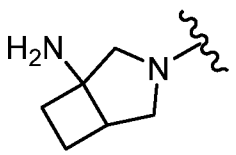
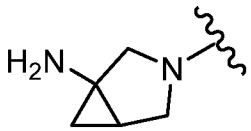
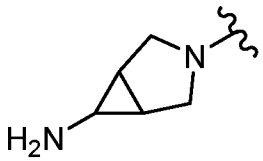
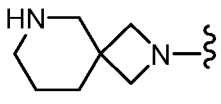
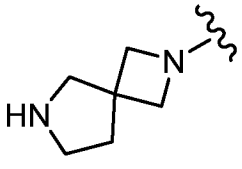
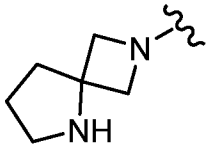
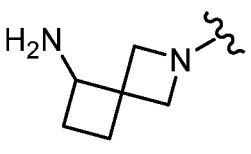
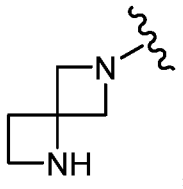
[0029] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is halogen. In some embodiments, R^4 is –CN. In some embodiments, R^4 is C_{1-6} aliphatic or –OR. In some embodiments, R^4 is $–OCH_3$. In some embodiments, R^4 is ethyl.

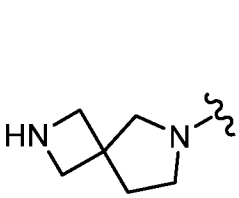
[0030] In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4 is  . In some embodiments, R^4

is  . In certain embodiments, R^4 is selected from those depicted in Table 1, below.

[0031] As defined above, Ring A is  ,  ,  ,  ,  ,  ,  ,  ,  , or wherein Ring A is optionally substituted with 1-4 groups selected from fluorine or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

[0032] In some embodiments, Ring A is  . In some embodiments, Ring A is  .

[0033] In some embodiments, Ring A is  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, Ring A is  ,  ,  ,  ,  ,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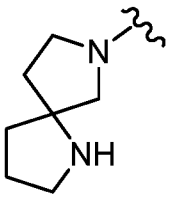
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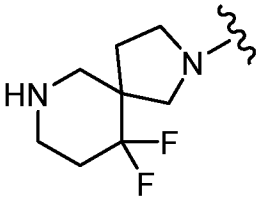
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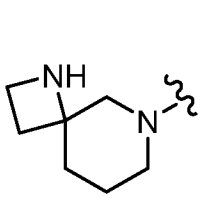
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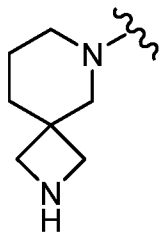
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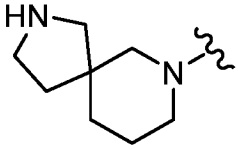
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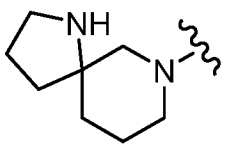
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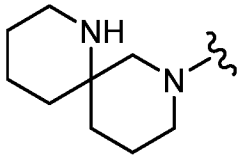
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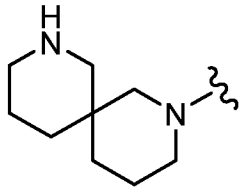
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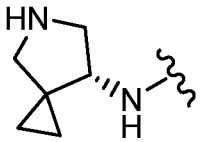
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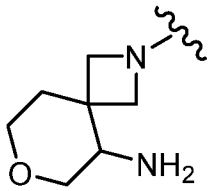
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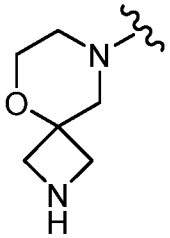
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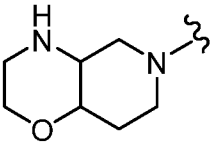
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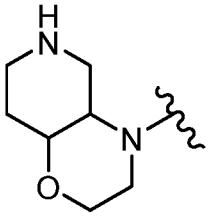
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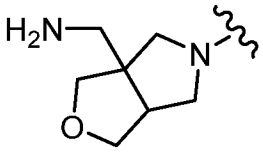
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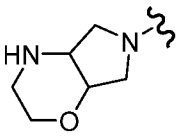
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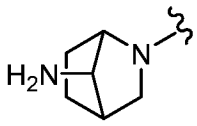
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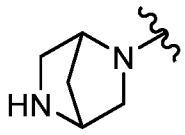
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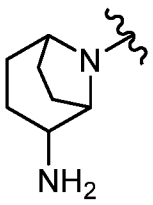
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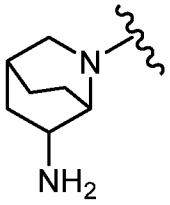
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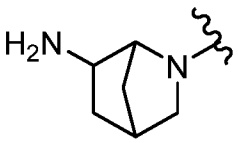
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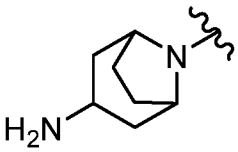
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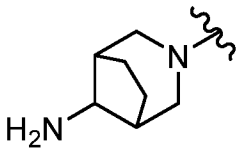
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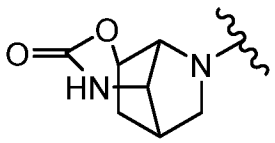
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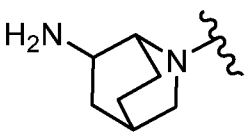
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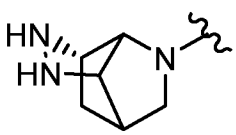
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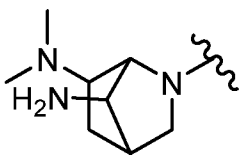
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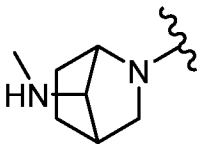
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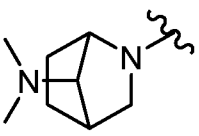
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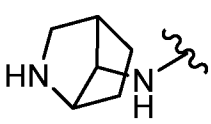
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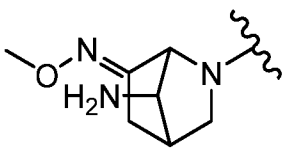
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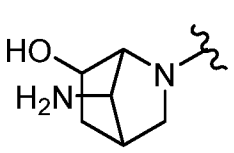
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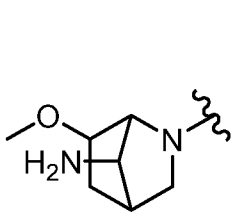
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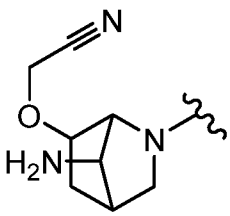
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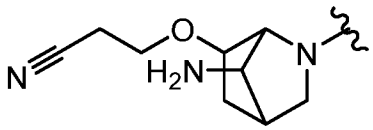
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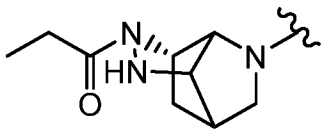
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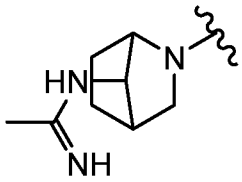
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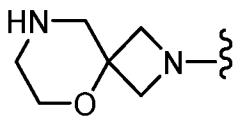
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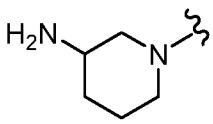
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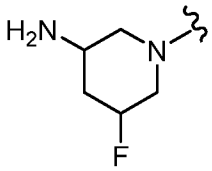
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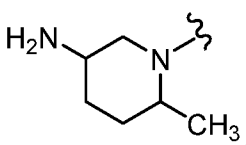
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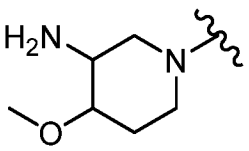
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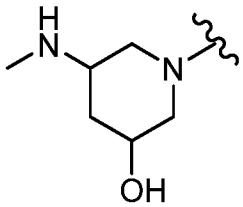
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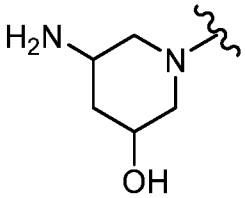
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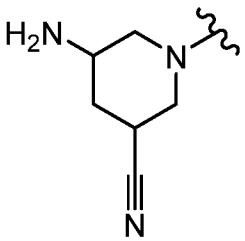
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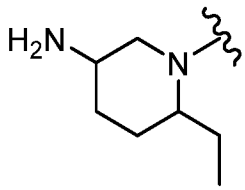
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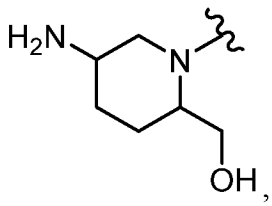
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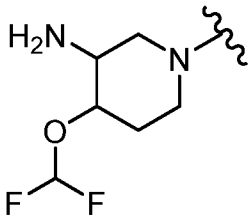
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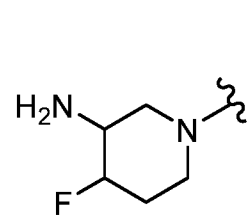
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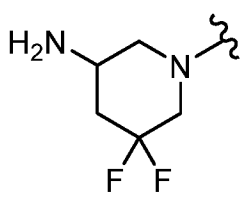
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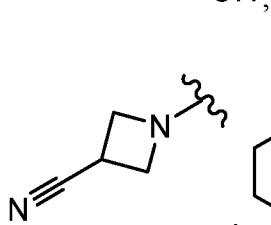
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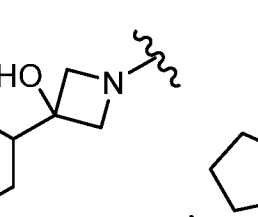
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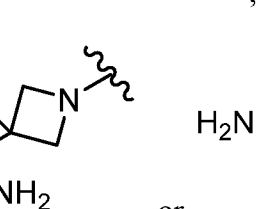
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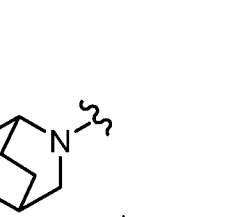
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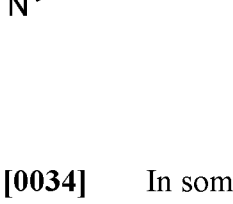
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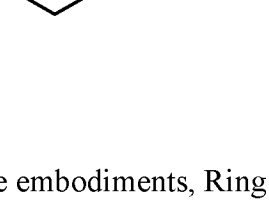
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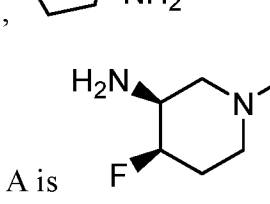
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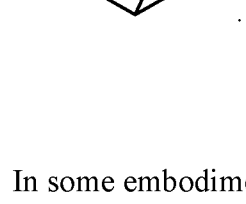
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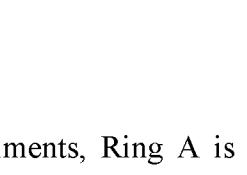
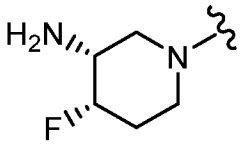
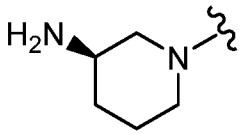
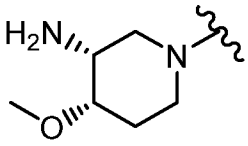
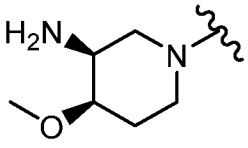
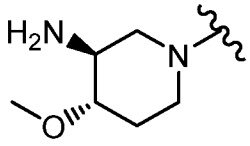
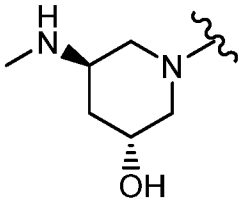
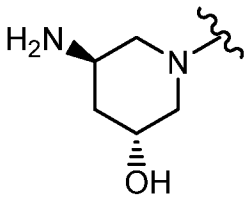
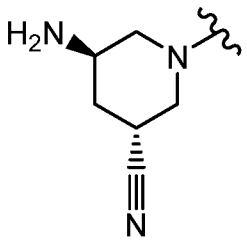
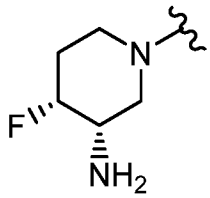
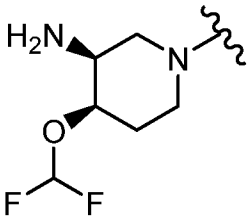
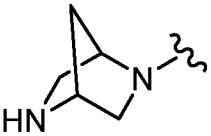
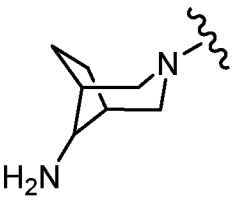


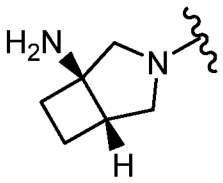
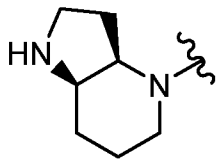
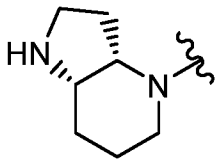
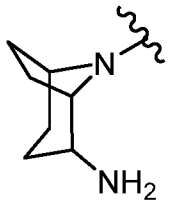
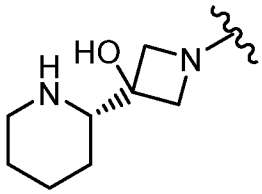
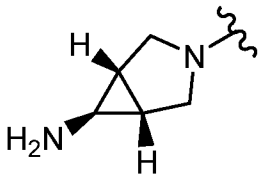
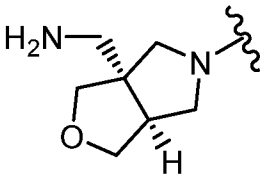
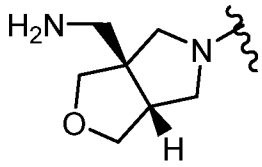
[0034] In some embodiments, Ring A is . In some embodiments, Ring A is

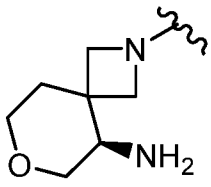
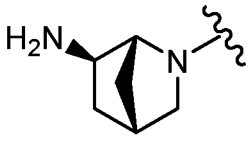
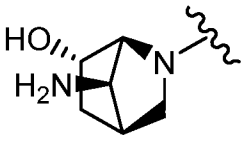
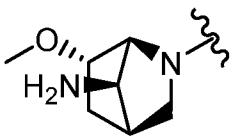
. In some embodiments, Ring A is

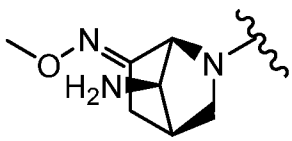
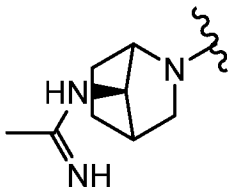
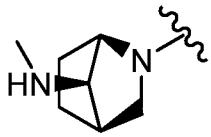
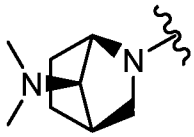
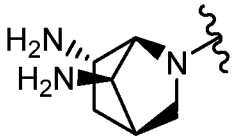
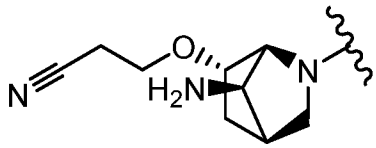
. In some

embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  .

[0035] In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some

embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  .

[0036] In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is


. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
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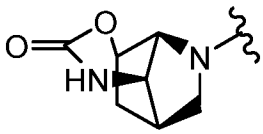
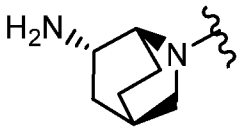
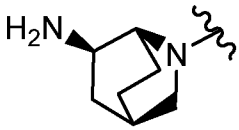
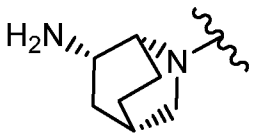
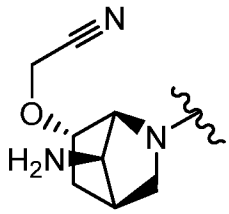
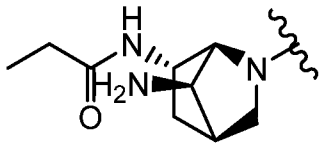
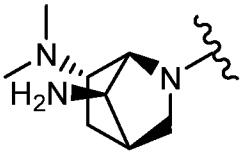
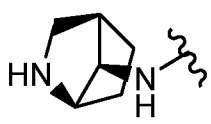
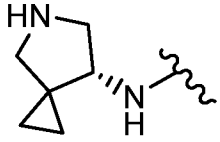
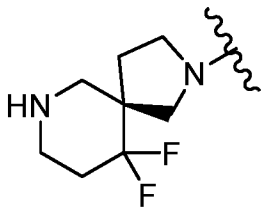
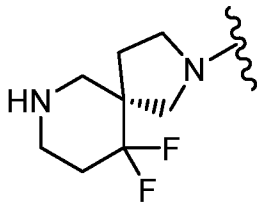
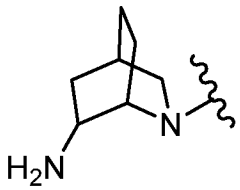
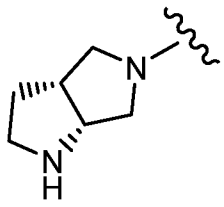
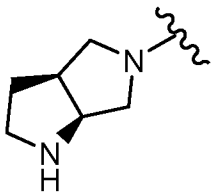
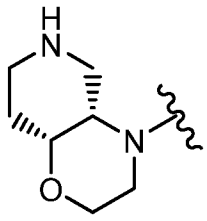
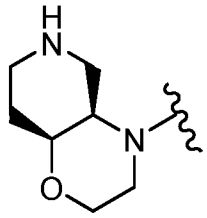
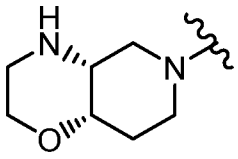
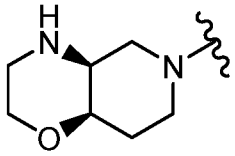
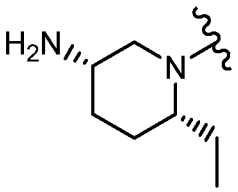
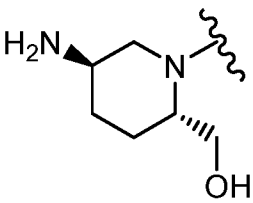
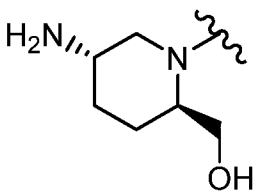
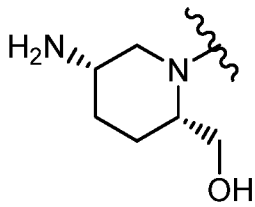
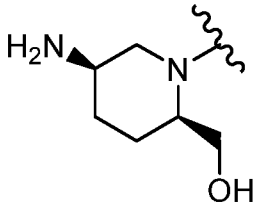
[0037] In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
. In some embodiments, Ring A is 
.

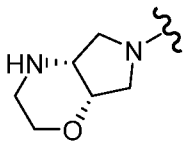
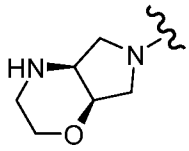
[0038] In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  .

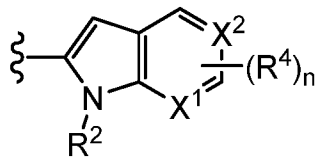
[0039] In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some embodiments, Ring A is  . In some

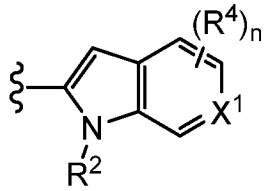
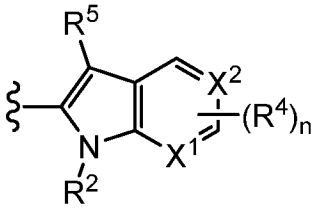
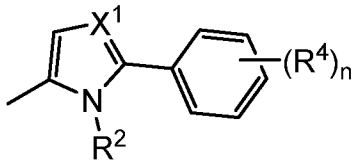
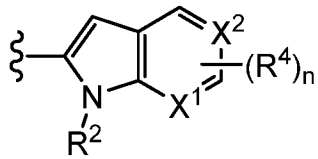


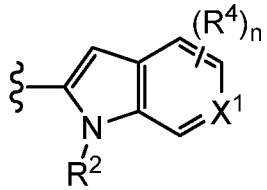
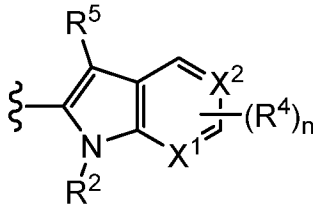
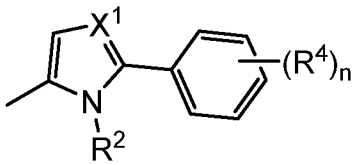
embodiments, Ring A is . In some embodiments, Ring A is



. In some embodiments, Ring A is  . In some embodiments, Ring A is  . In certain embodiments, Ring A is selected from those depicted in Table 1, below.

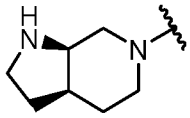
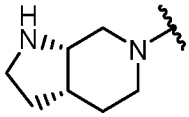
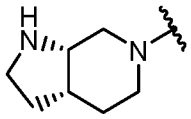
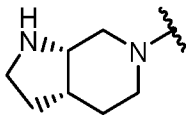
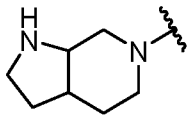
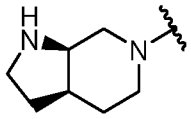
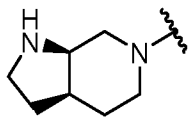
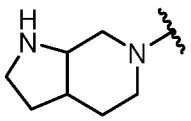
[0040] As defined above and described herein, Ring B is  ,

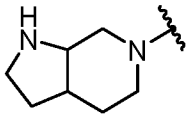
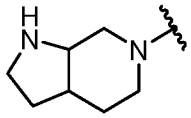
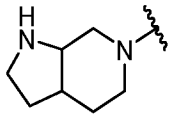
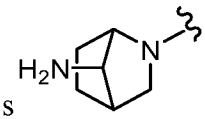
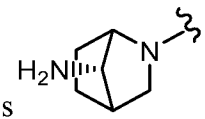
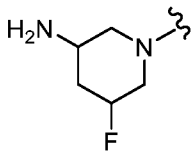
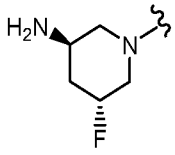
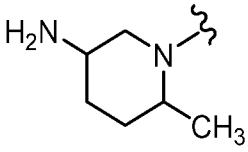
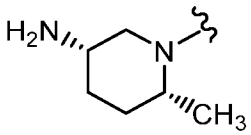
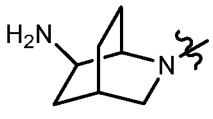
 ,  or  . In some embodiments, Ring B is  . In some embodiments, Ring B is

 . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In certain embodiments, Ring B is selected from those depicted in Table 1, below.

[0041] As defined above and described herein, R^5 is hydrogen or halogen. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is halogen. In some embodiments, R^5 is fluoro. In certain embodiments, R^5 is selected from those depicted in Table 1, below.

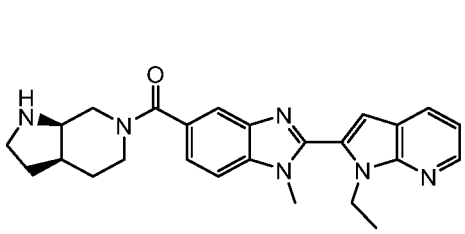
[0042] As defined above and described herein, n is 0-4. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In certain embodiments, n is selected from those depicted in Table 1, below.

[0043] In some embodiments, R^1 is methyl, R^2 is ethyl, X^1 is N, X^2 is CH, R^3 is hydrogen, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is 2,2,2-trifluoroethyl, X^1 is N, X^2 is CH, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is N, R^3 is $-OCH_3$, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is ethyl, X^1 is N, X^2 is CH, R^3 is hydrogen, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is N, R^3 is hydrogen, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is 2,2,2-trifluoroethyl, X^1 is N, X^2 is CH, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is N, R^3 is $-OCH_3$, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is 2,2,2-trifluoroethyl, X^1 is N, X^2 is CH, and Ring A is  . In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is N, R^3 is $-OCH_3$, and Ring A is

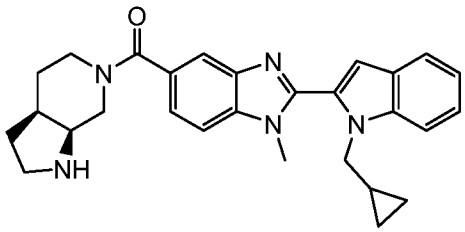

. In some embodiments R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is ethyl, X^1 is N, X^2 is CH, R^3 is hydrogen, and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$, and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$, and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$ and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$ and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$, and Ring A is 
. In some embodiments, R^1 is methyl, R^2 is cyclopropylmethyl, X^1 is N, X^2 is CH, R^3 is $-OCH_3$, and Ring A is 
. In some embodiments, Ring A is 
.

[0044] In some embodiments, the compound of formula **I** is selected from those depicted below in Table 1.

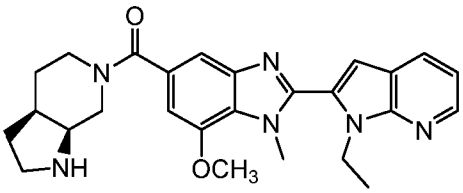
Table 1. Exemplary Compounds of Formula I



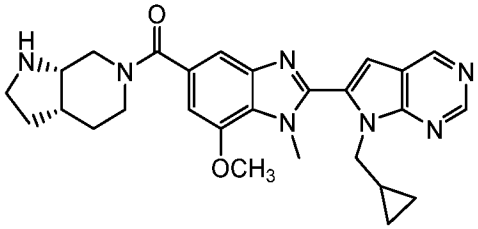
I-1



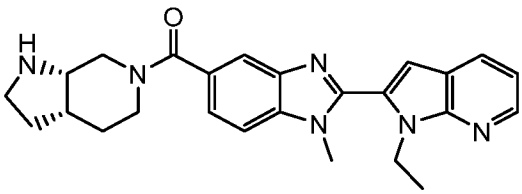
I-2



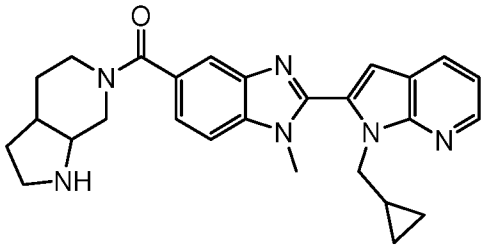
I-3



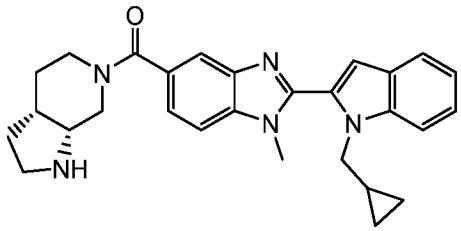
I-4



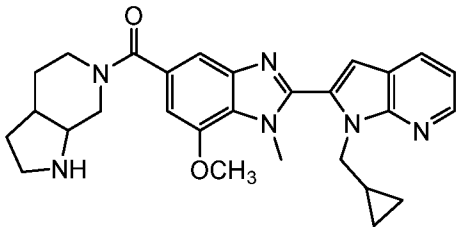
I-5



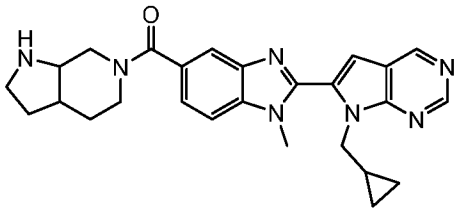
I-6



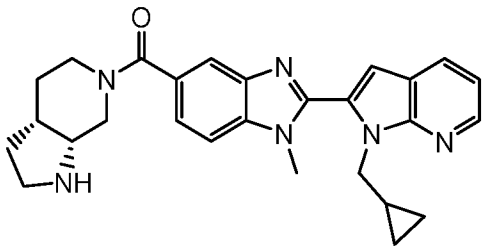
I-7



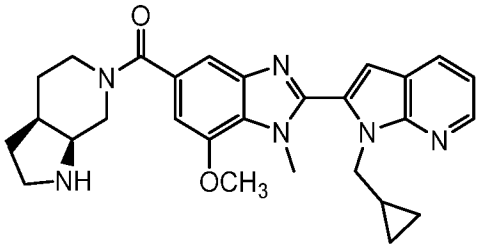
I-8

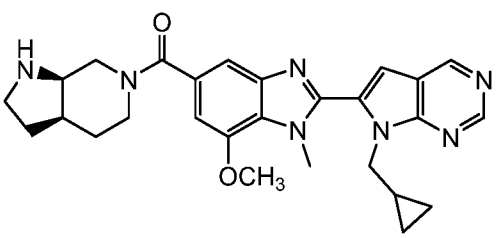


I-9

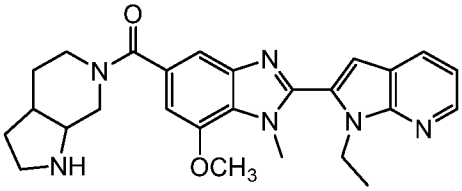


I-10

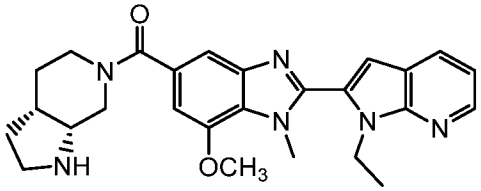




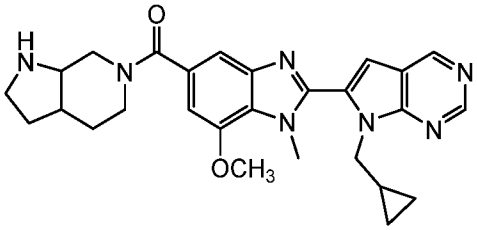
I-11



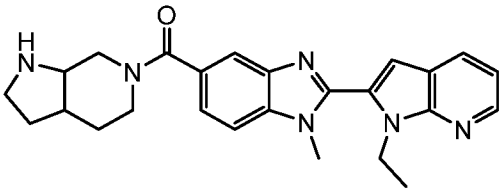
I-12



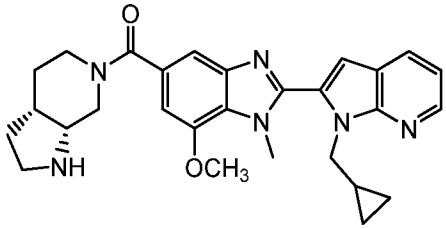
I-13



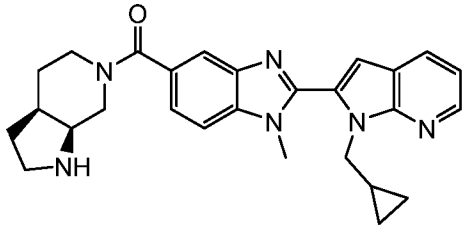
I-14



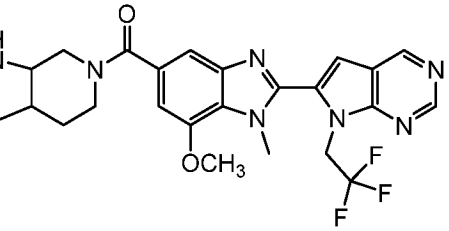
I-15



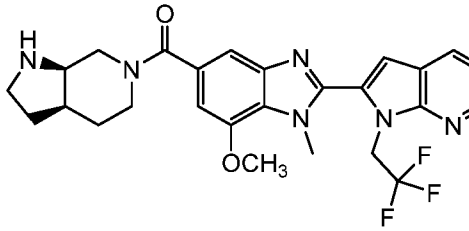
I-16



I-17



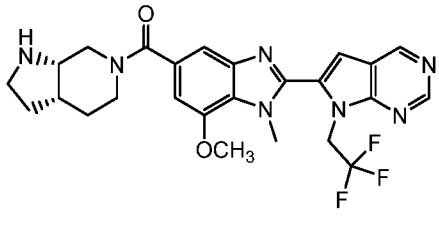
I-18



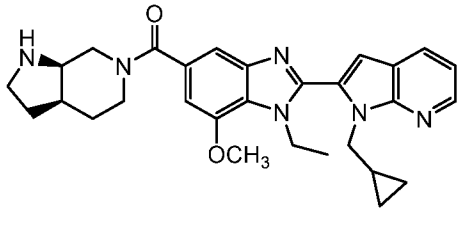
I-19

I-20

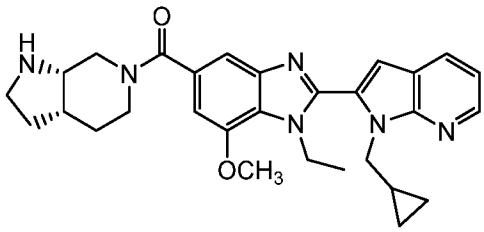
I-21



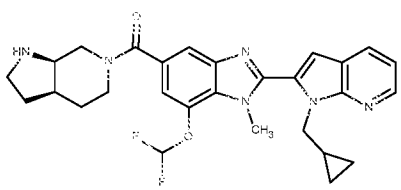
I-22

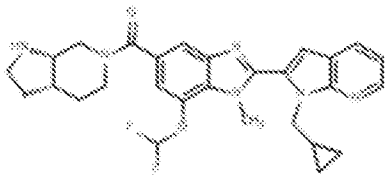


I-23

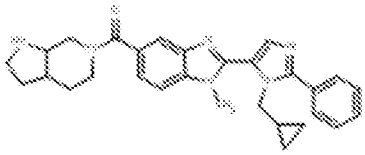


I-24





I-25



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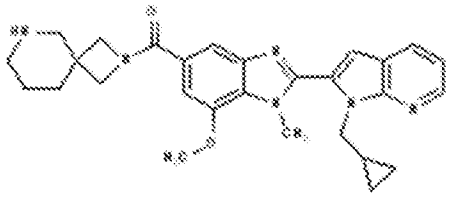

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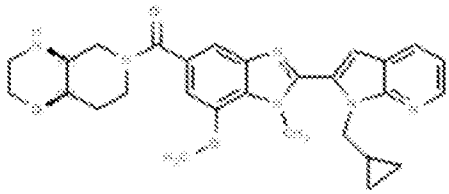

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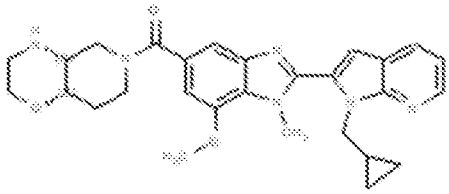

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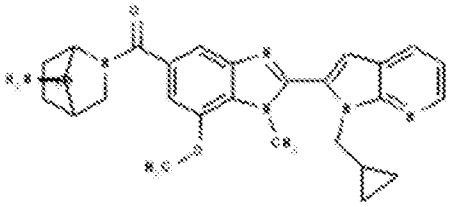

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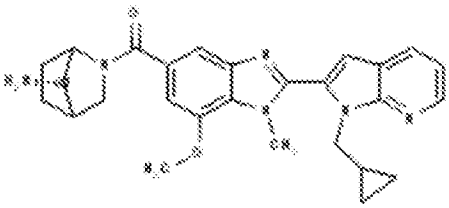

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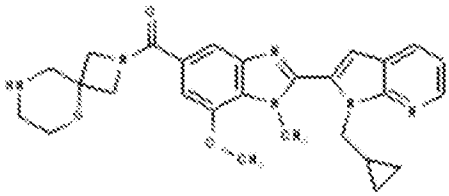

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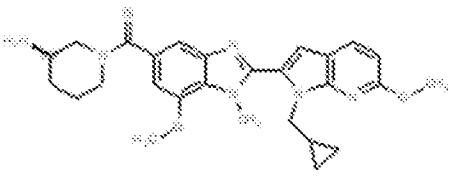

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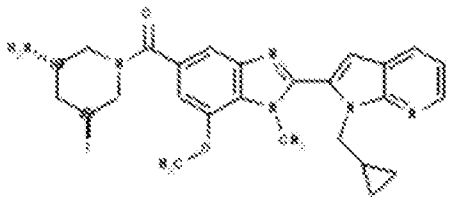

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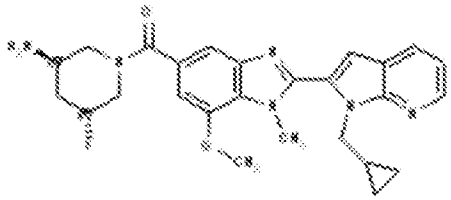

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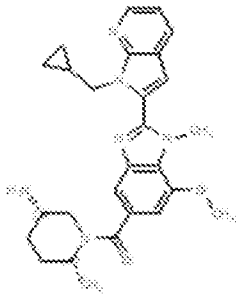

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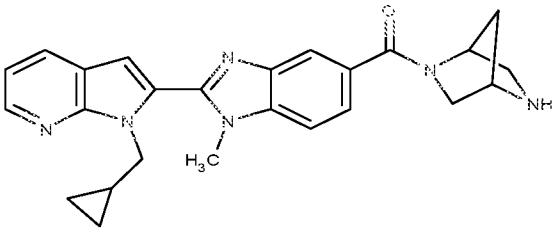

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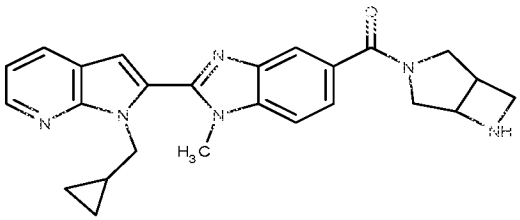

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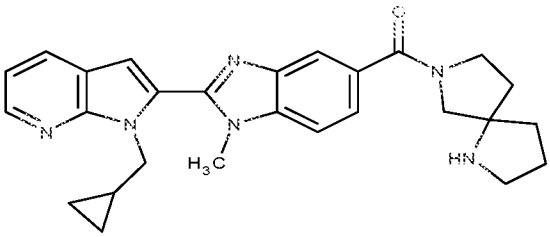

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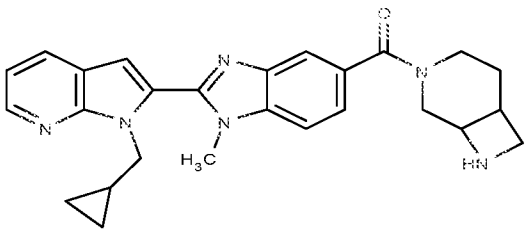

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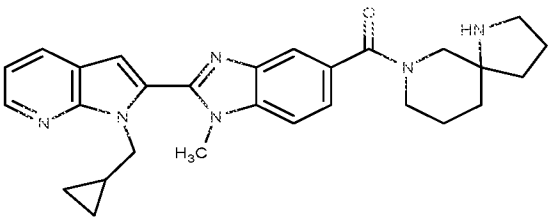

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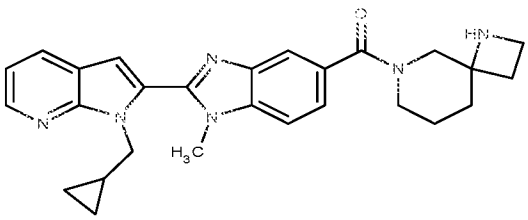

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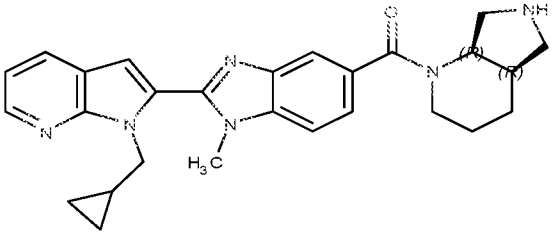

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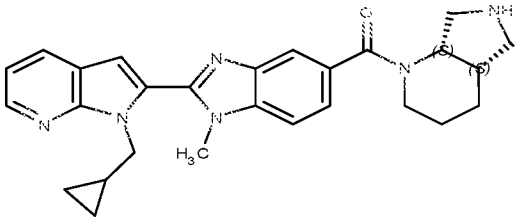

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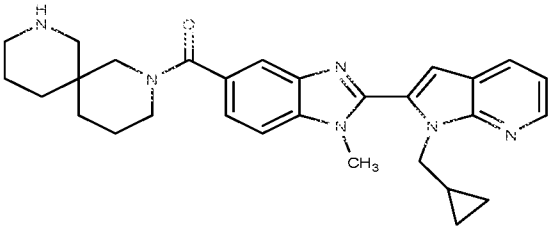

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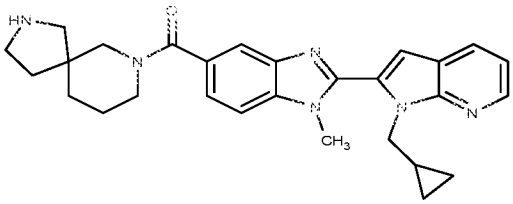

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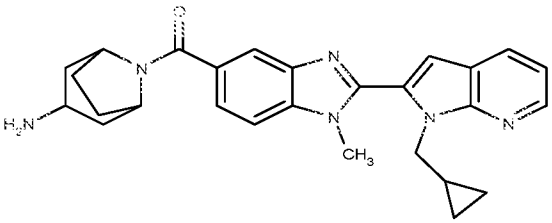

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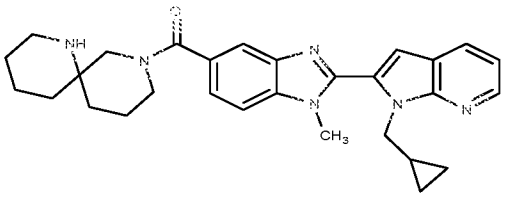

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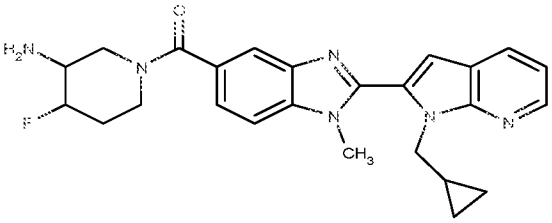

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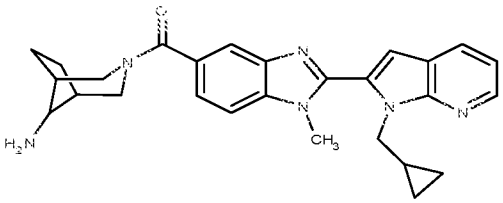

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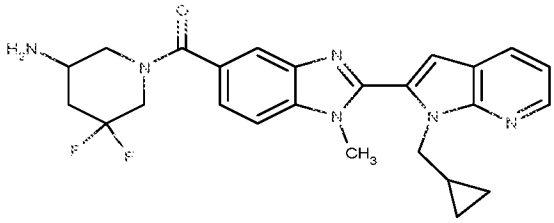

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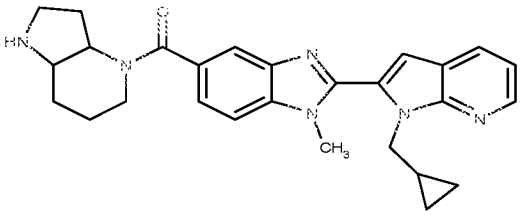

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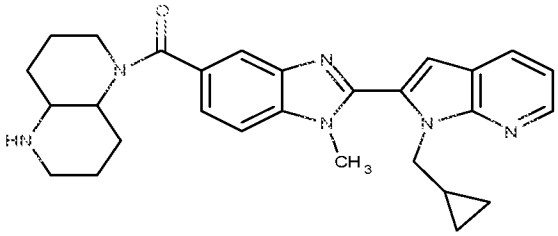

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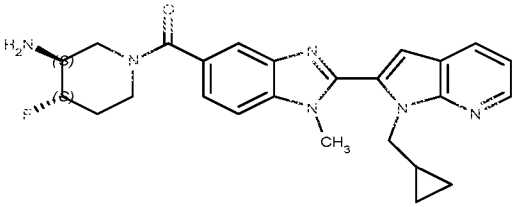

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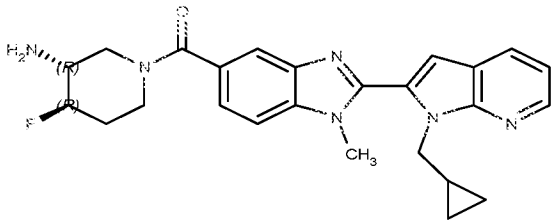

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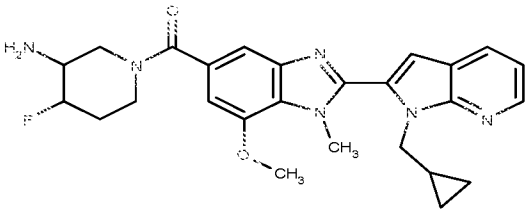

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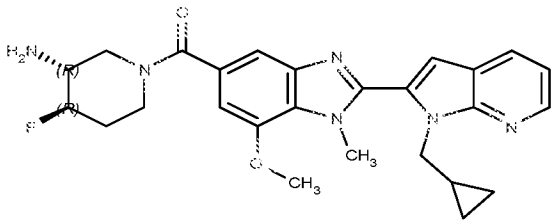

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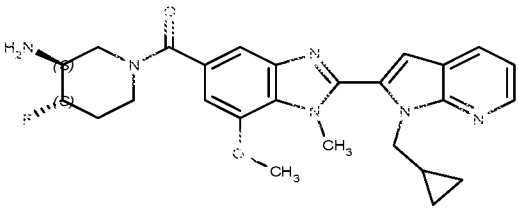

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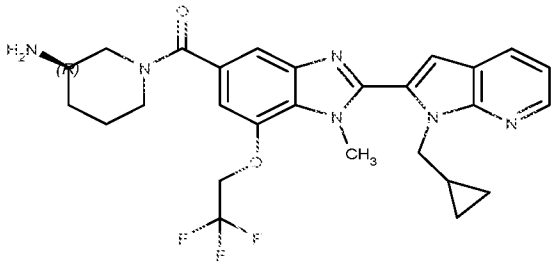

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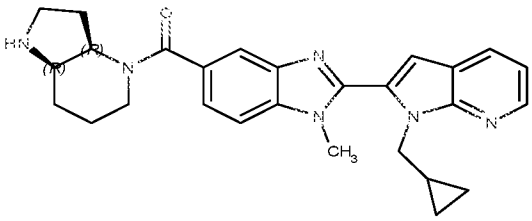

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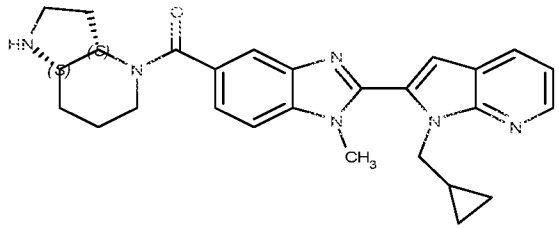

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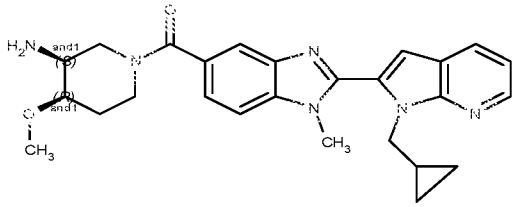

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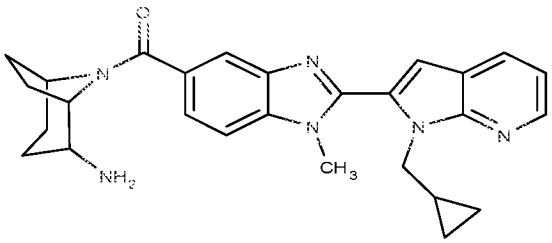

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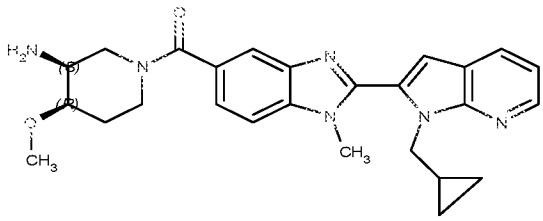

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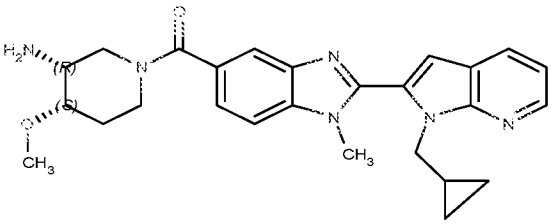

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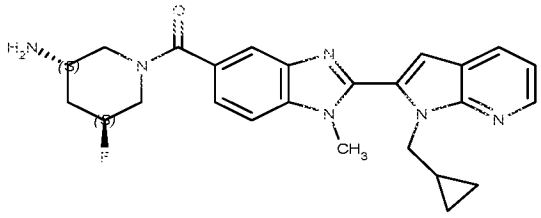

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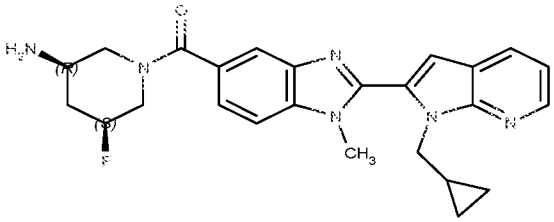

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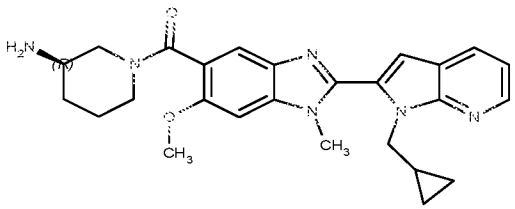

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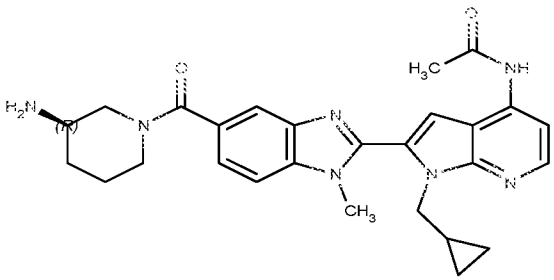

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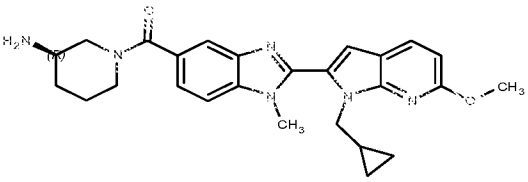

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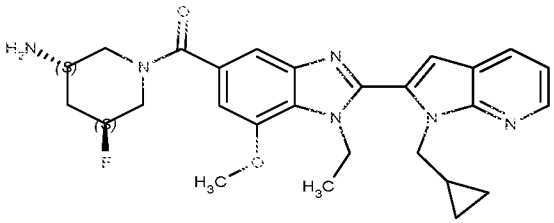

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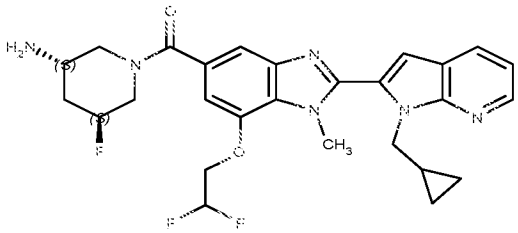

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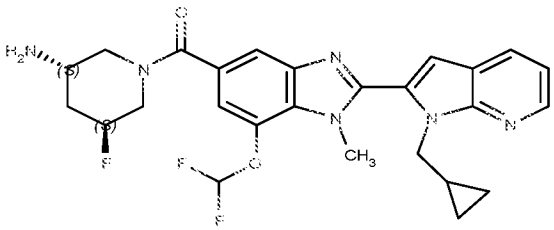

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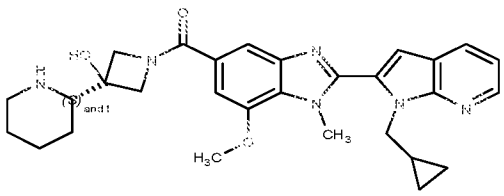

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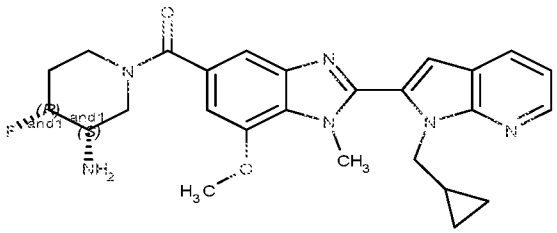

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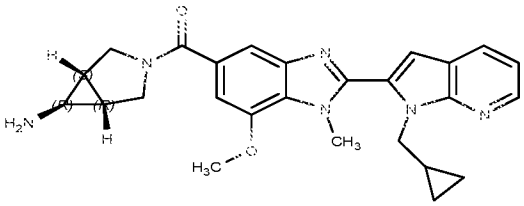

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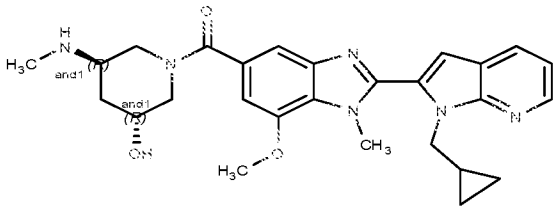

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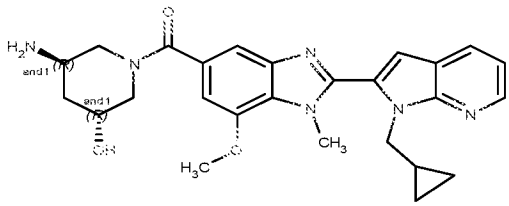

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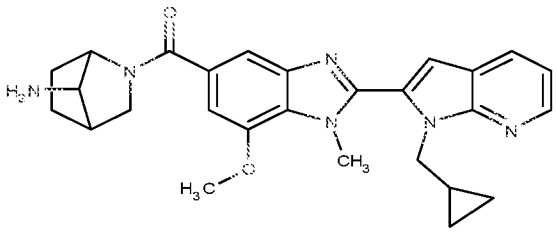

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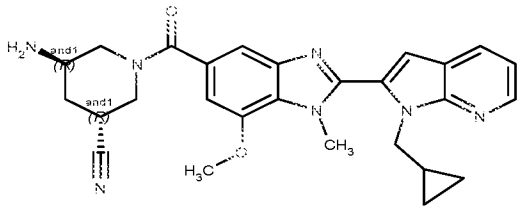

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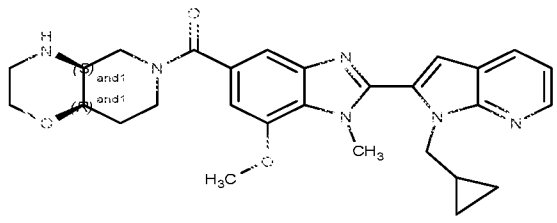

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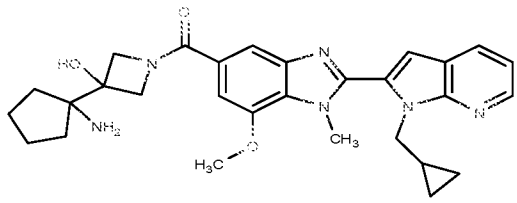

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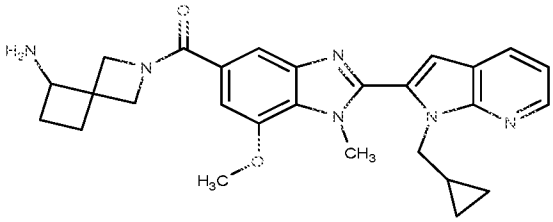
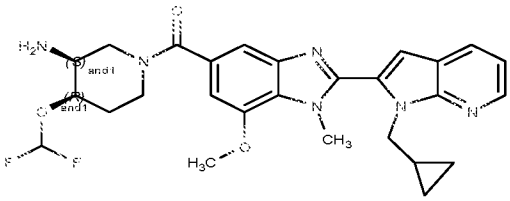


I-85



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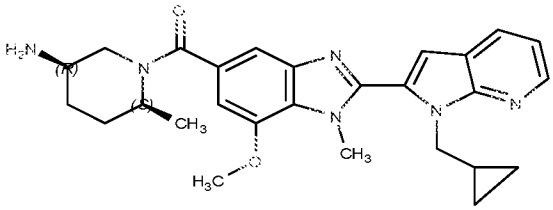

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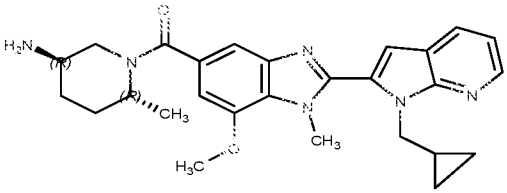

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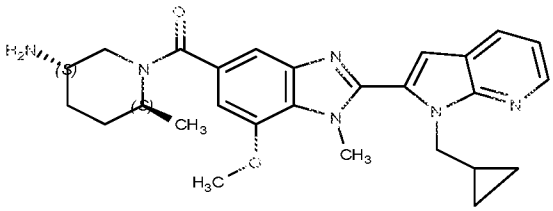

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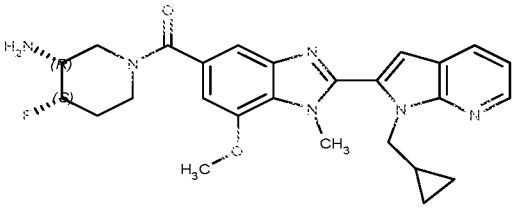

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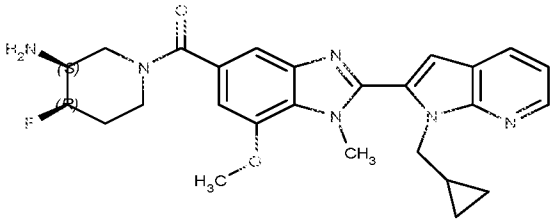

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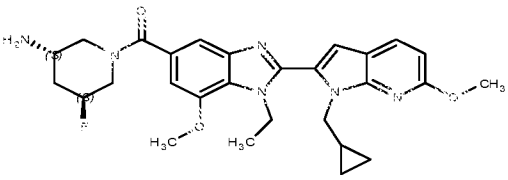

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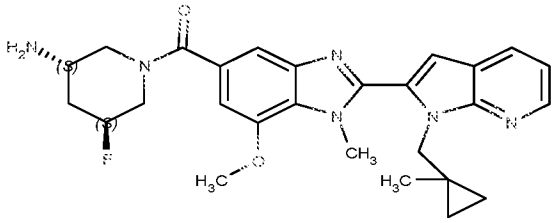

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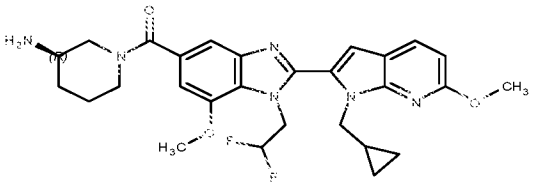

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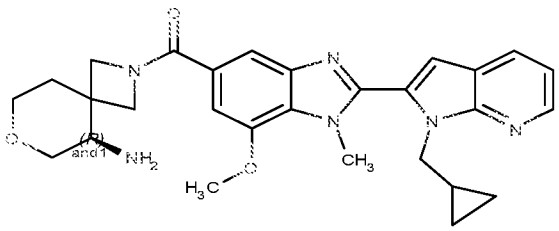

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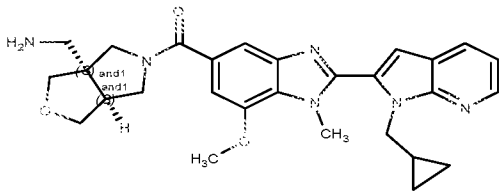

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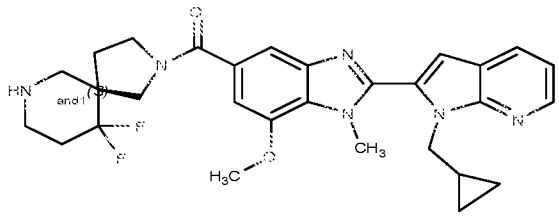

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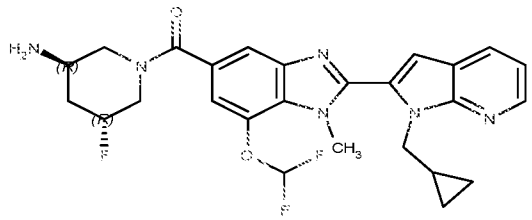

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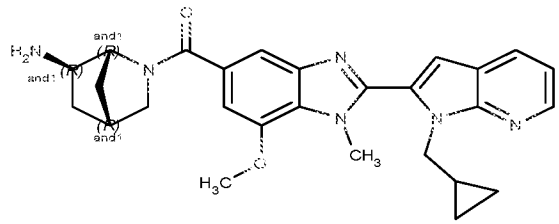

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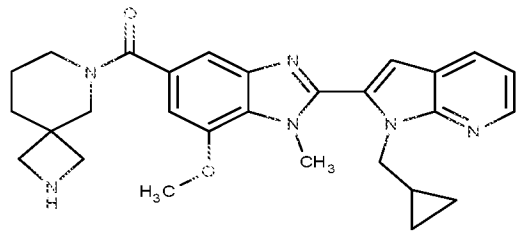

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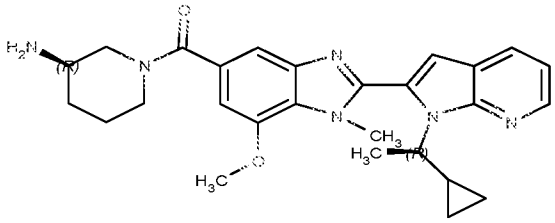

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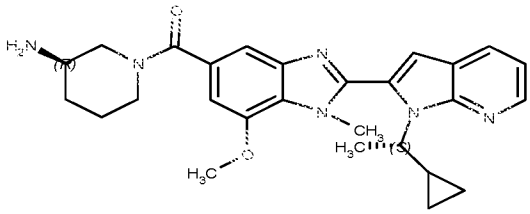

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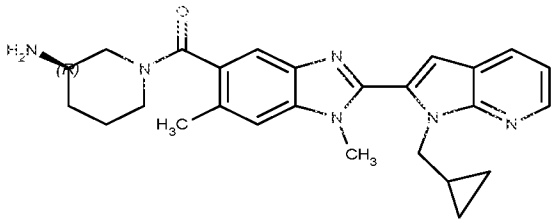

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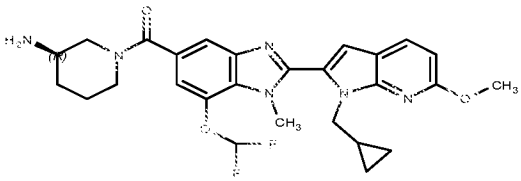

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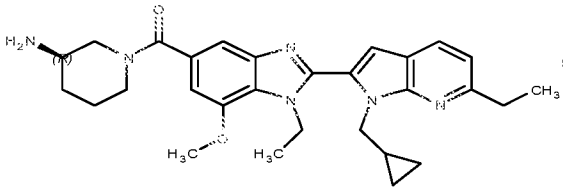

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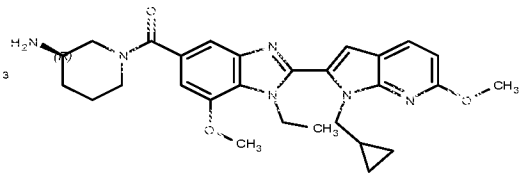

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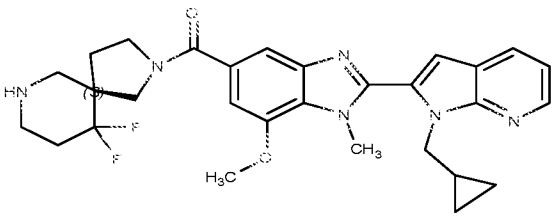

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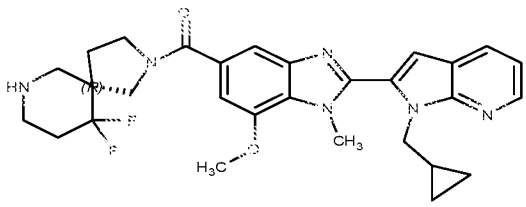

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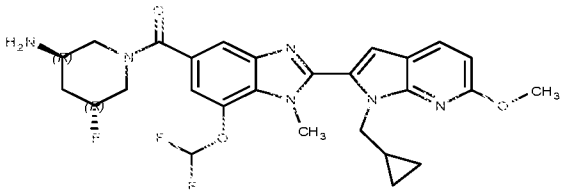

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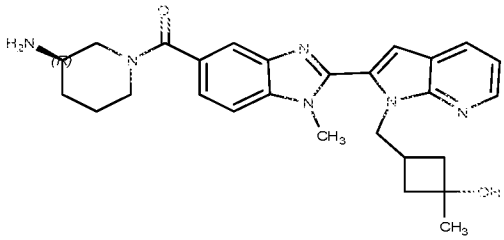

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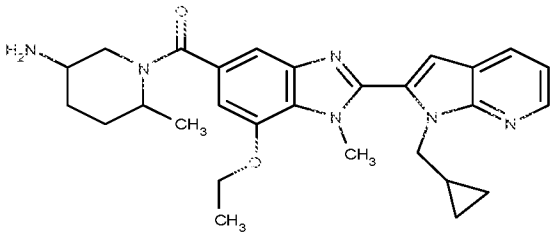

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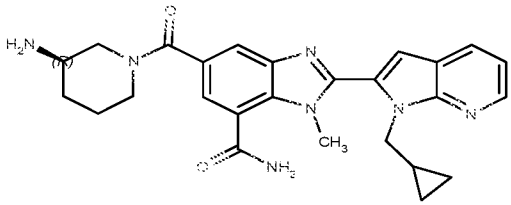

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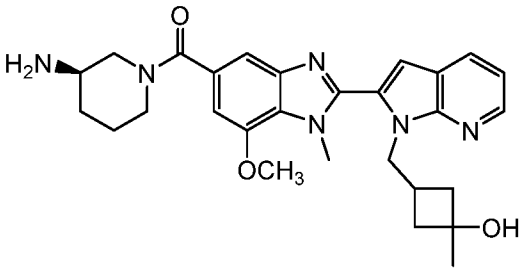

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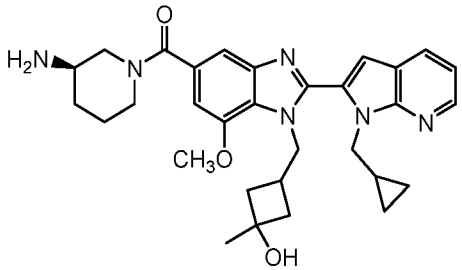

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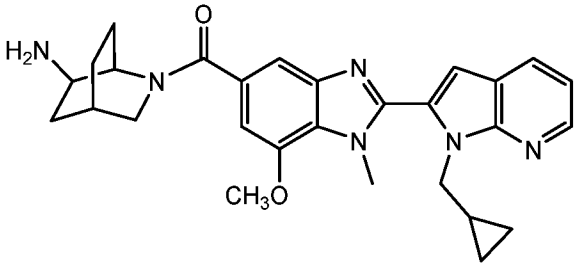

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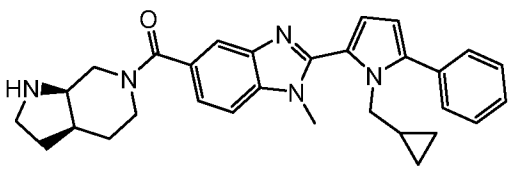

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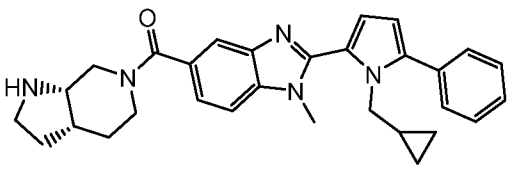

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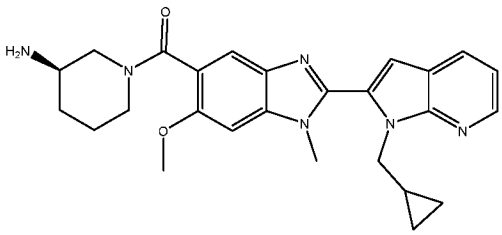

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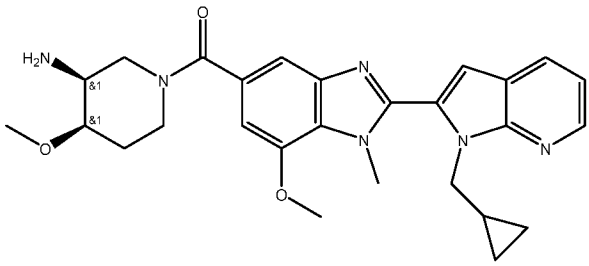

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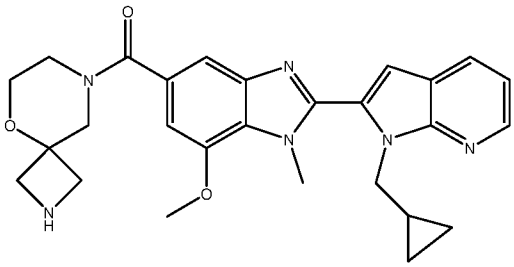

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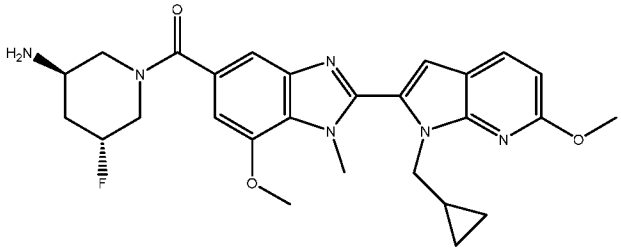

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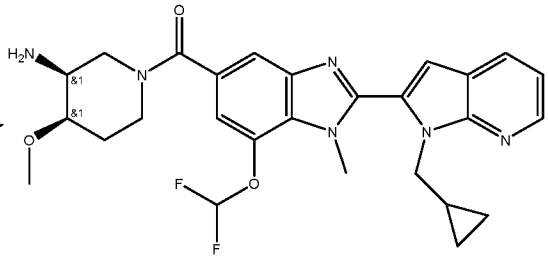

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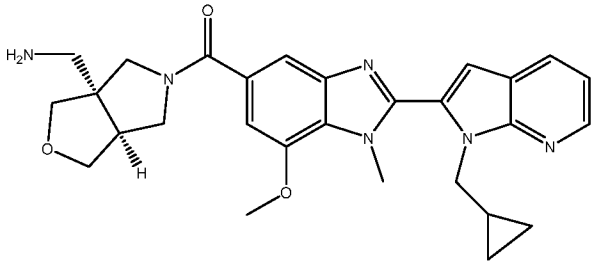

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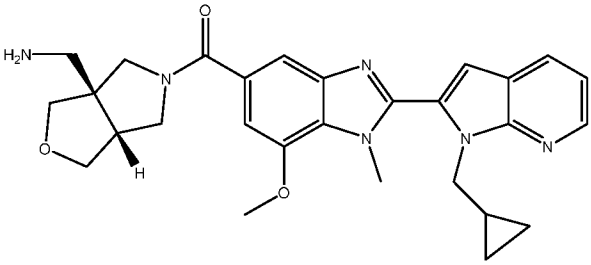

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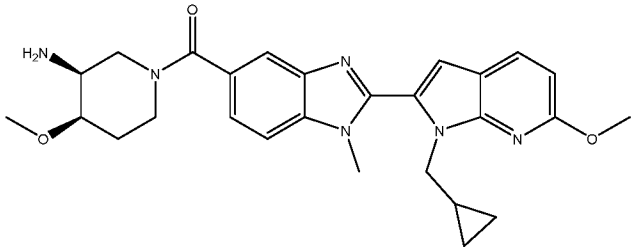

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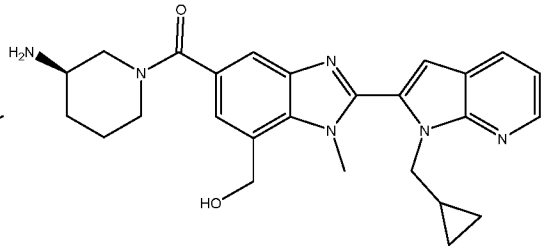

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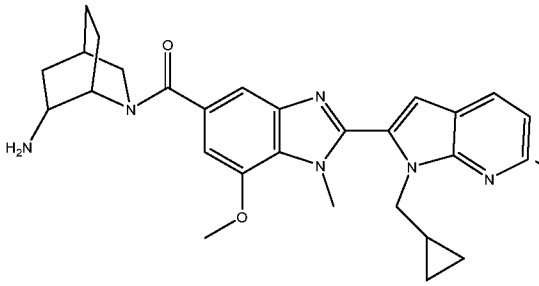

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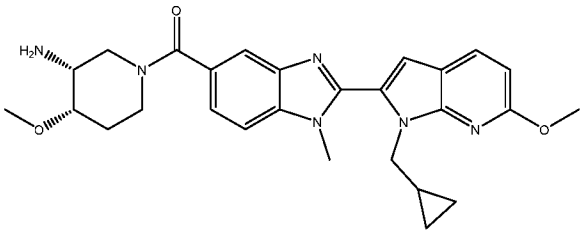

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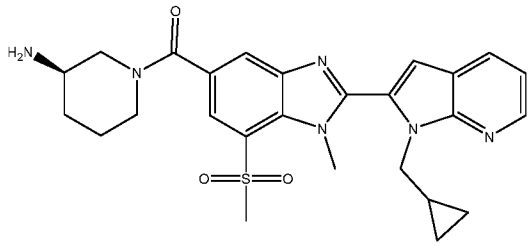

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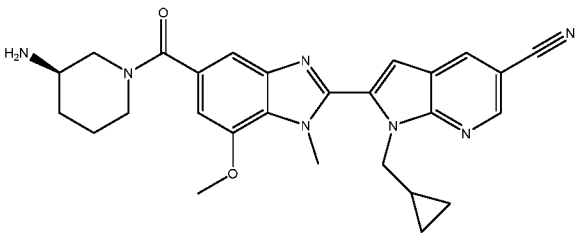

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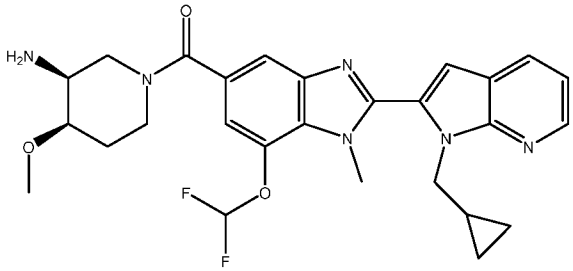

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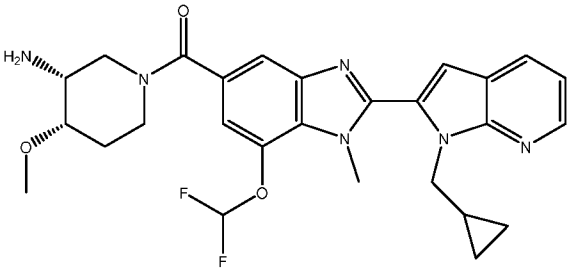

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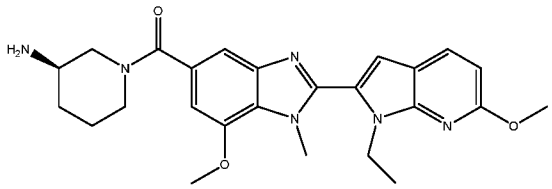

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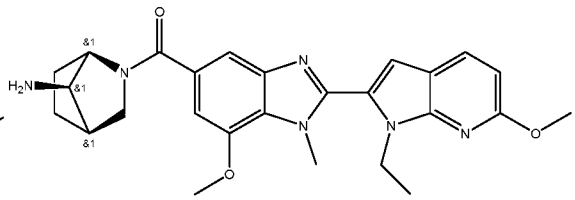

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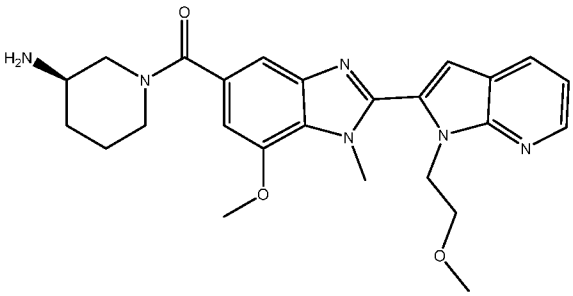

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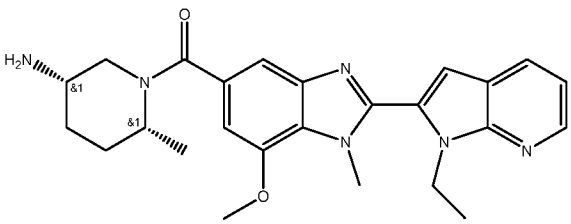

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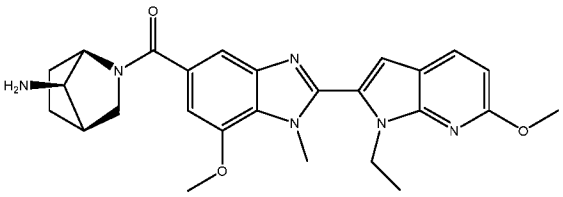

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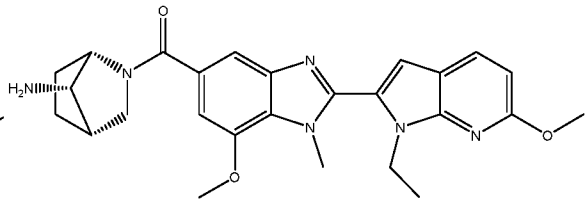

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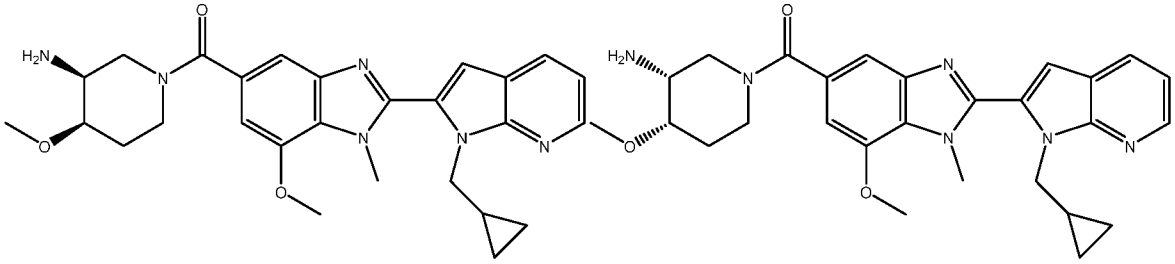

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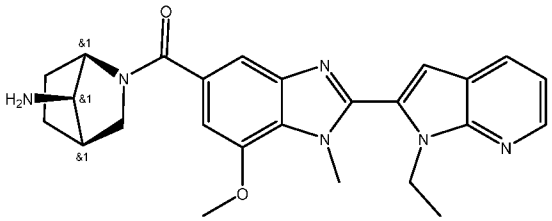

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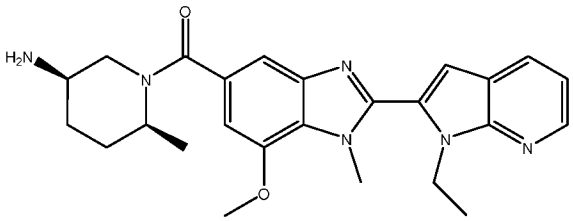

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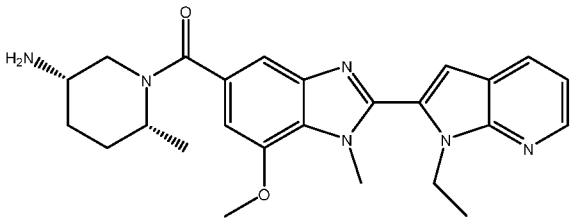

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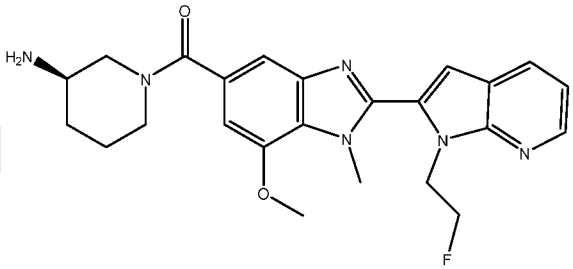
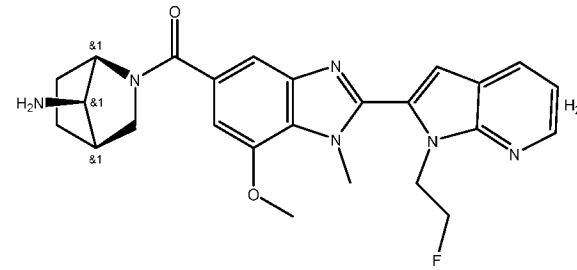


I-145



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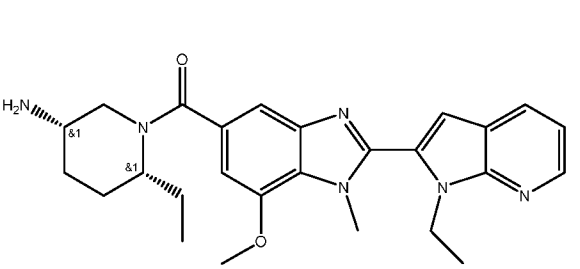

I-147

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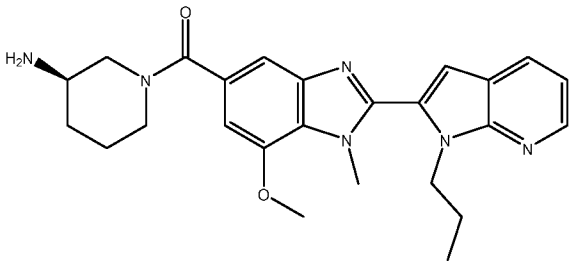
I-149



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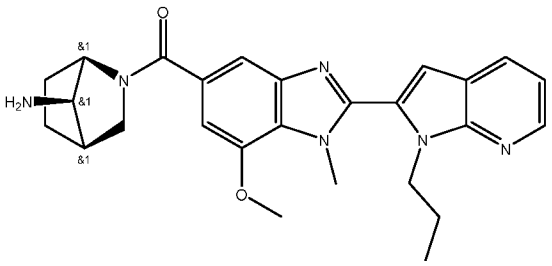

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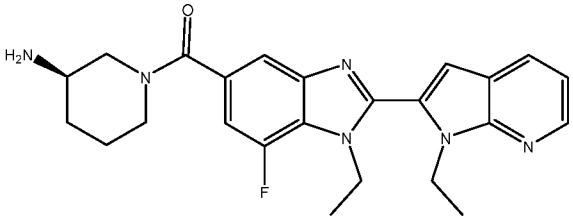

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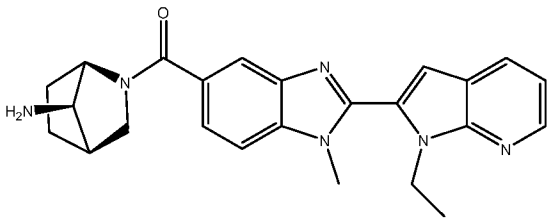

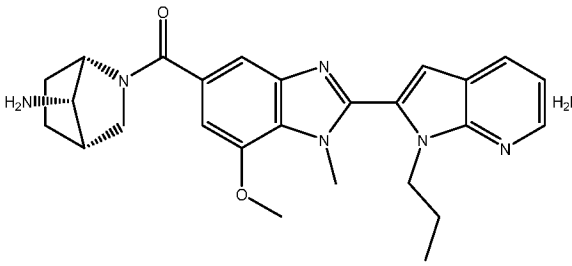

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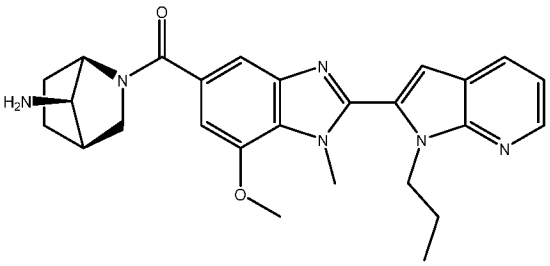

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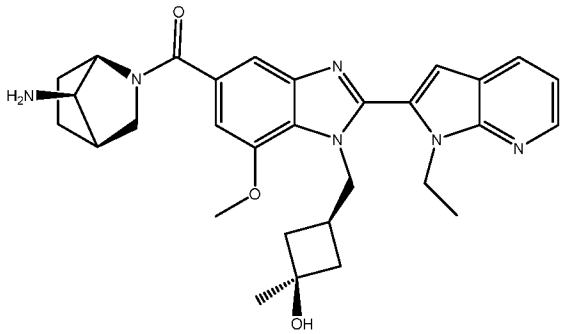

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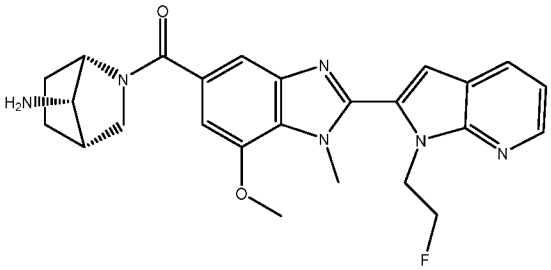

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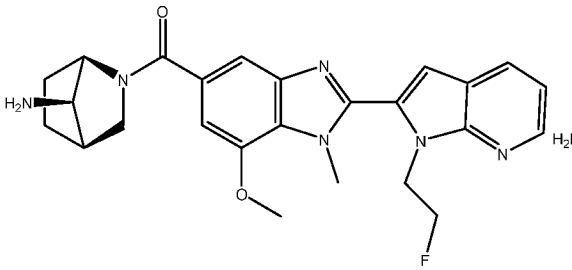

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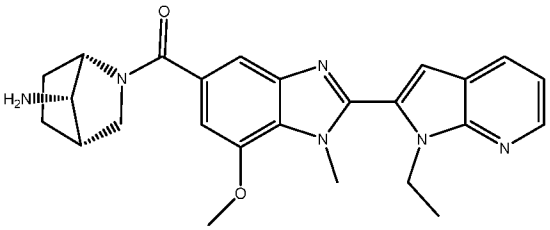

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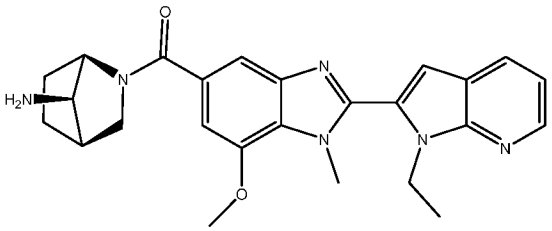

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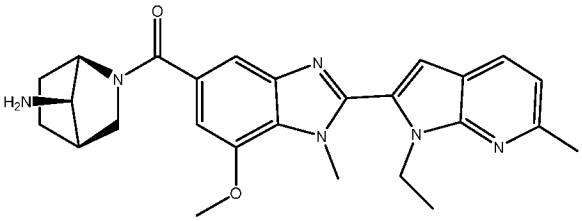

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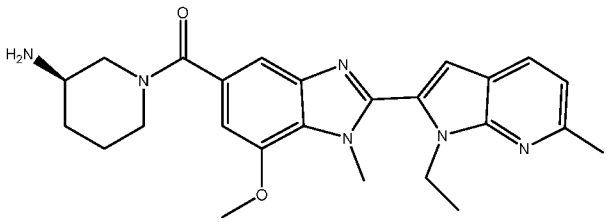

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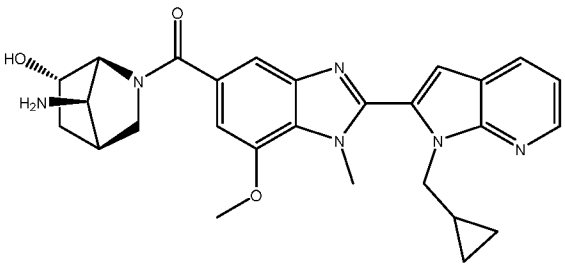

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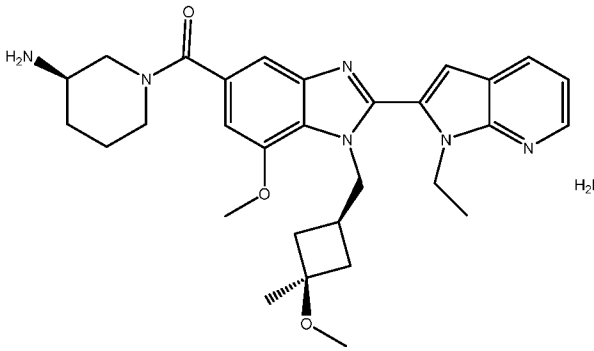

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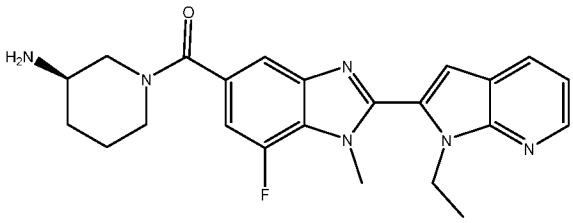

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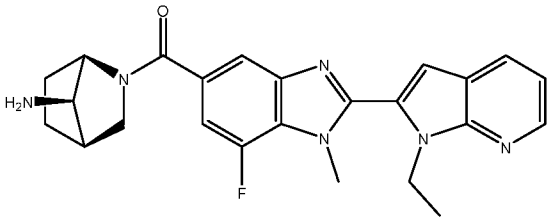

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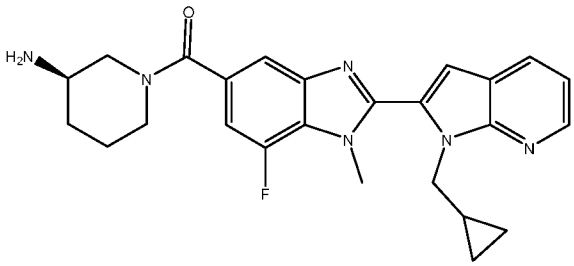

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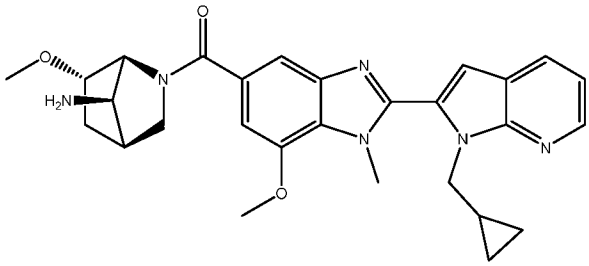

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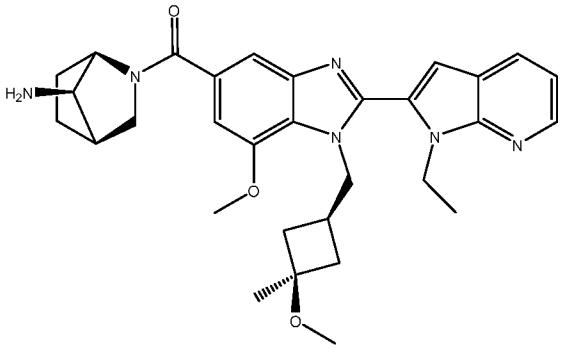

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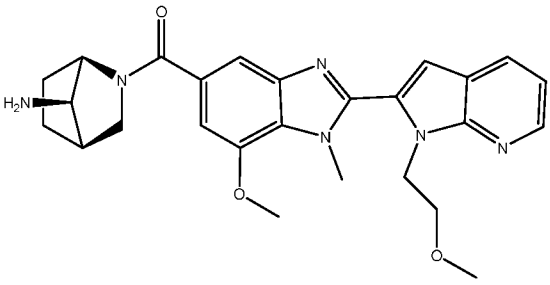

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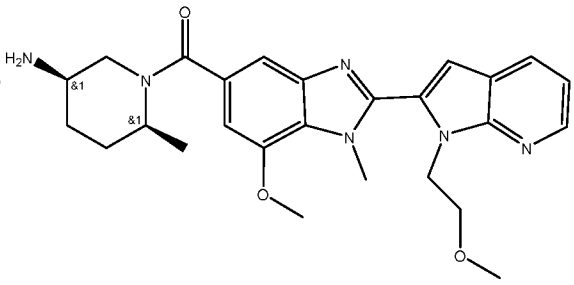

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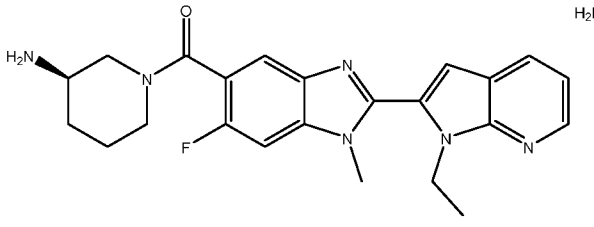

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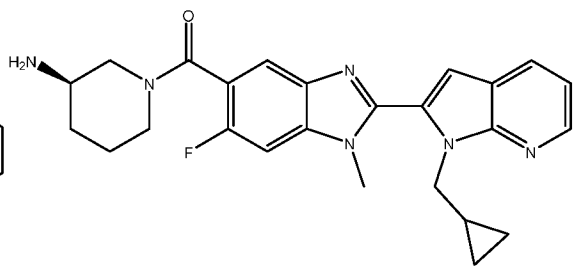

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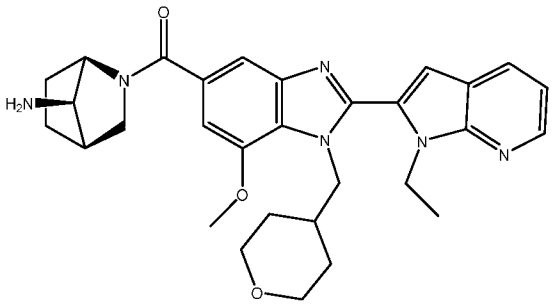

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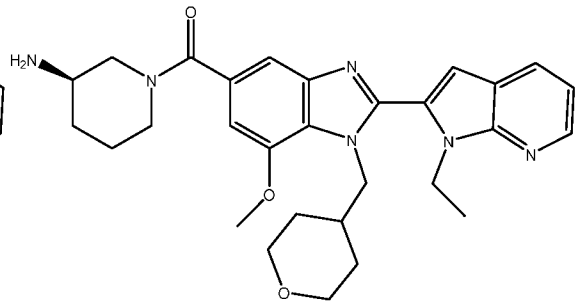

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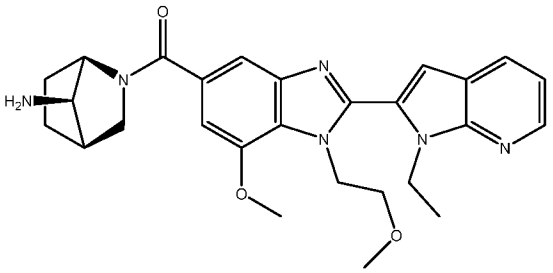

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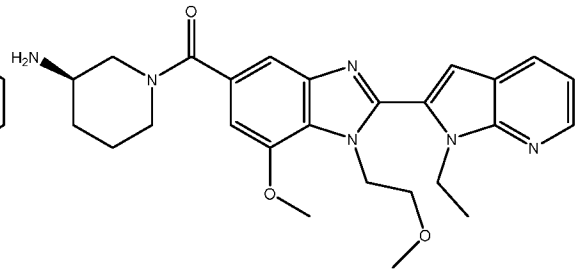

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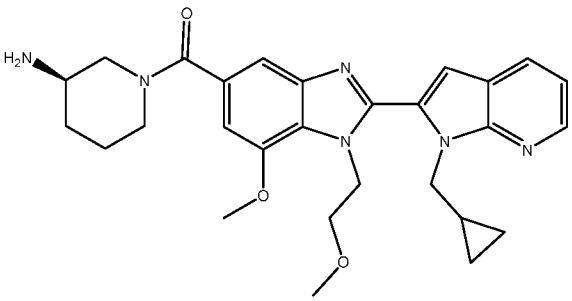

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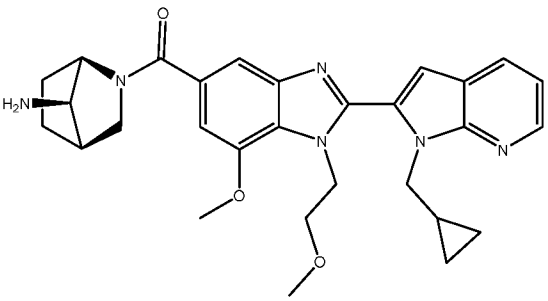

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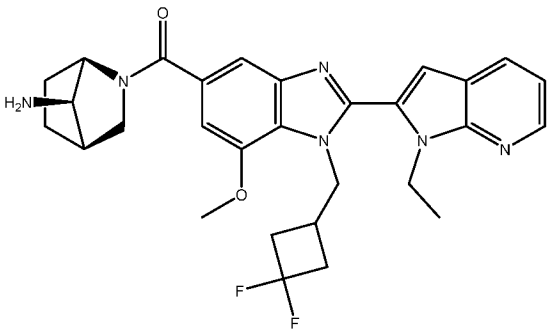

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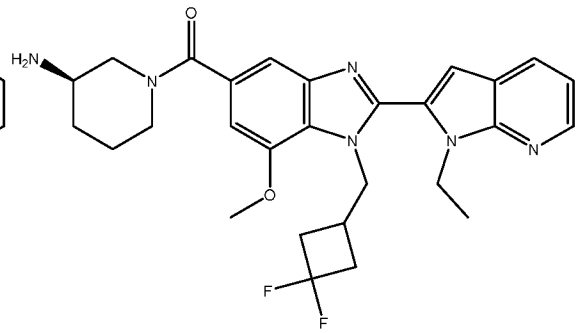

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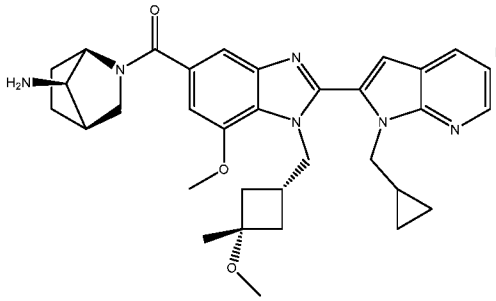

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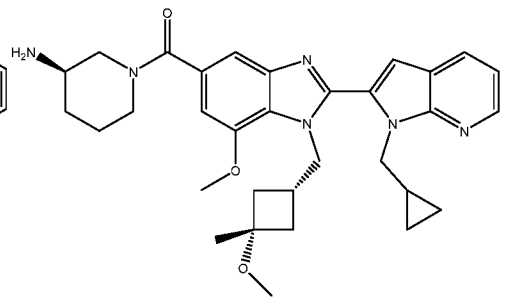

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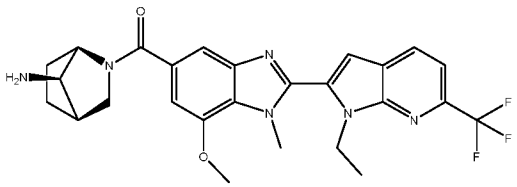

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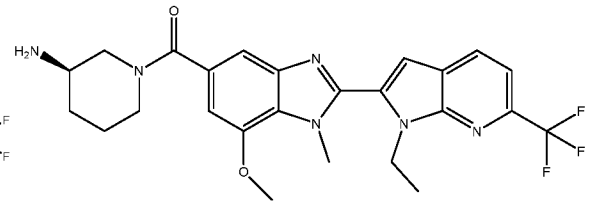

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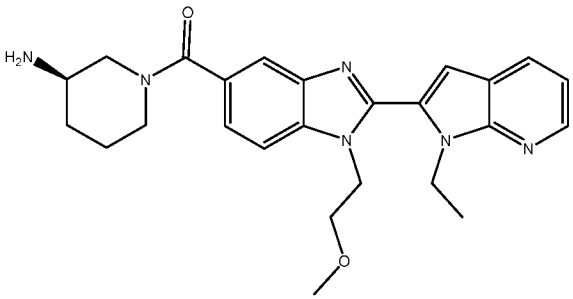

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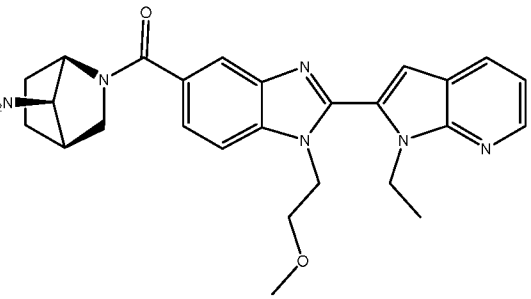

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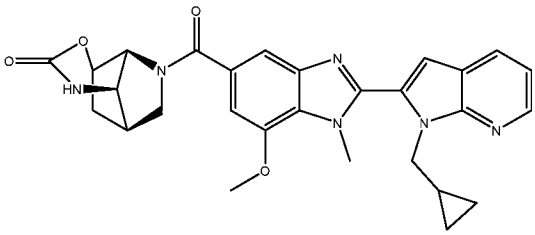

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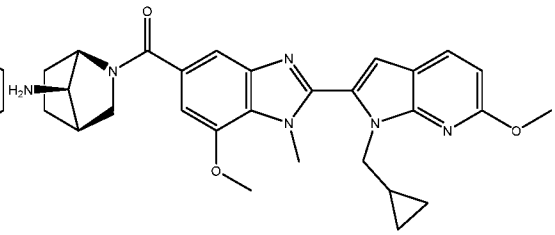

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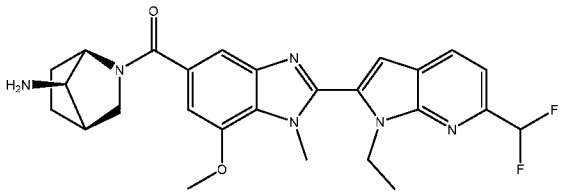

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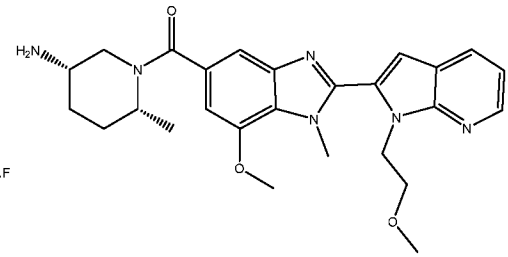

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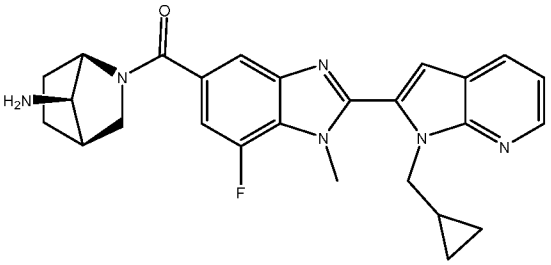

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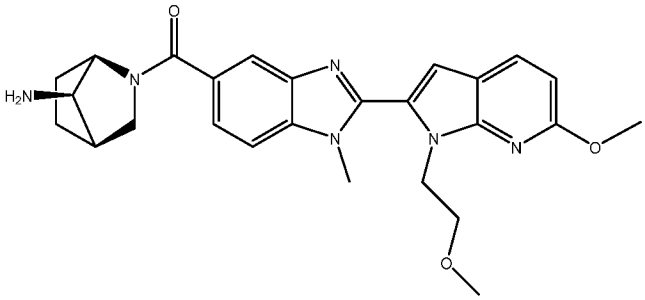

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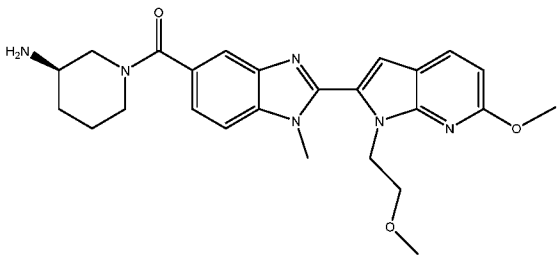

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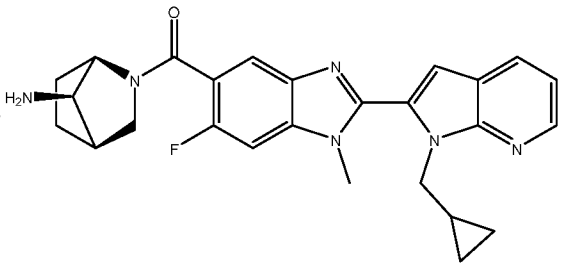

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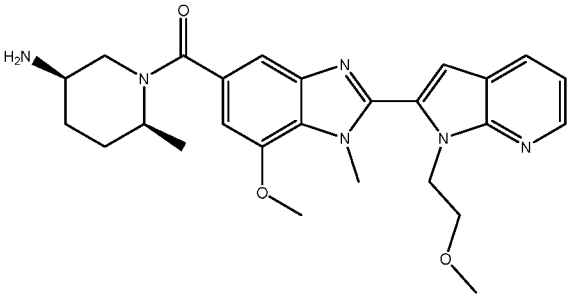

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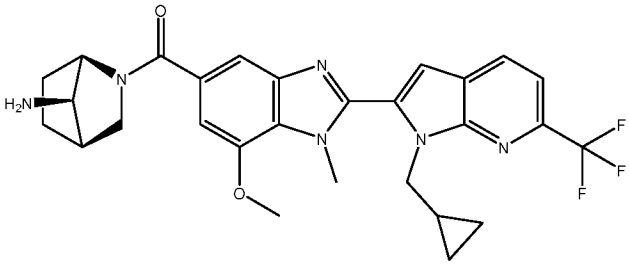

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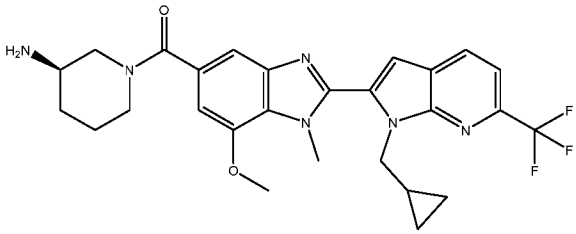

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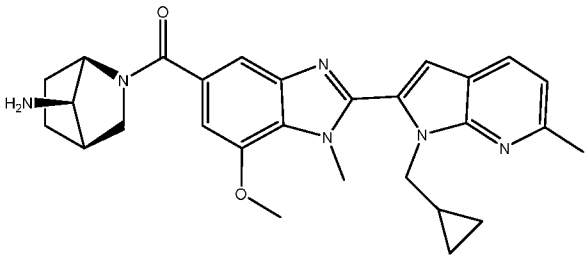

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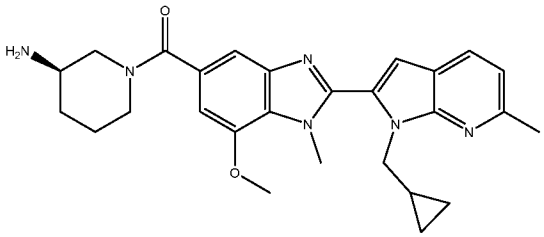
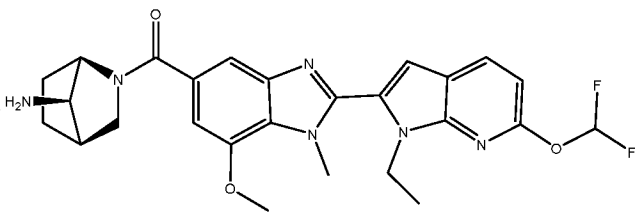


I-199



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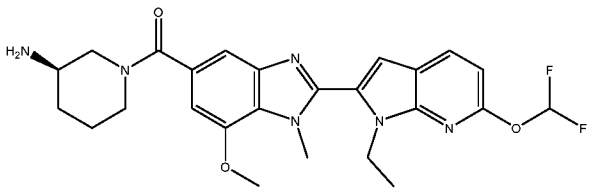

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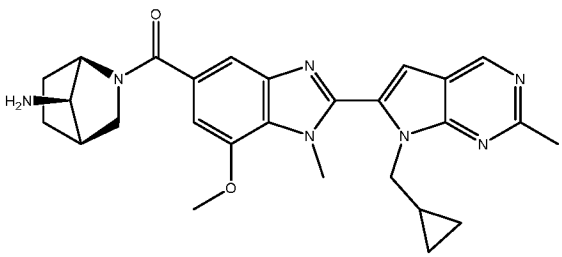

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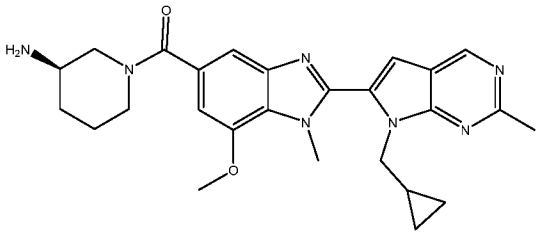

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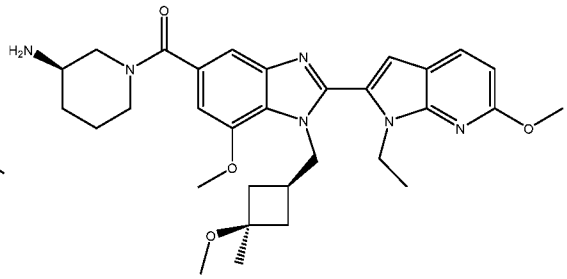

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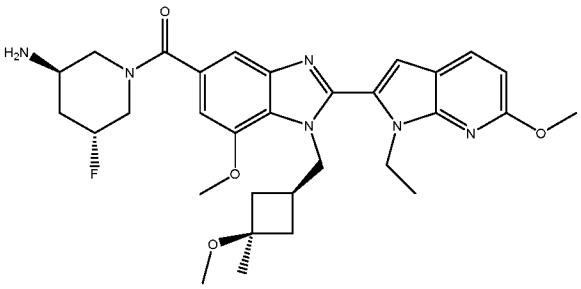

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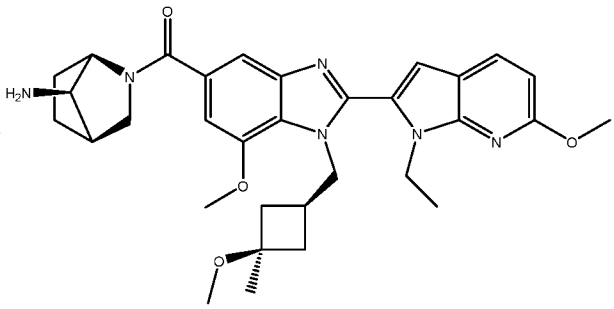

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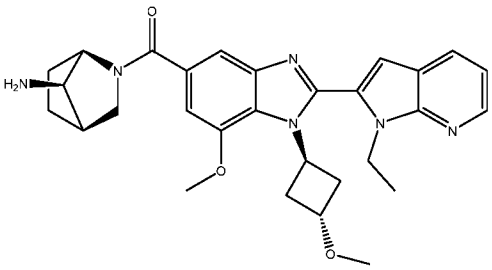

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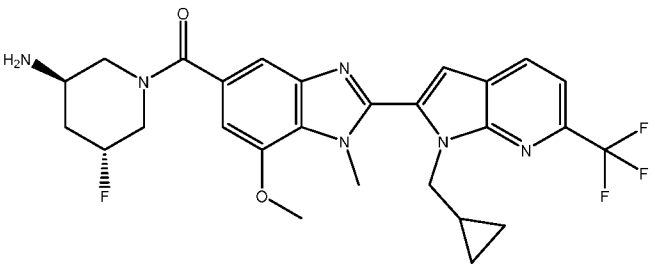

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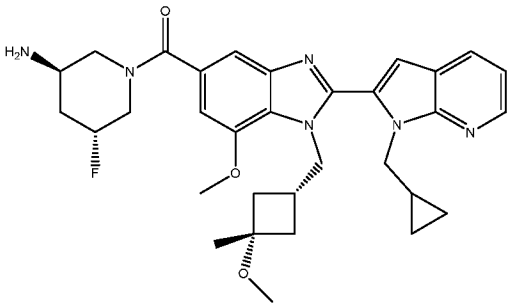

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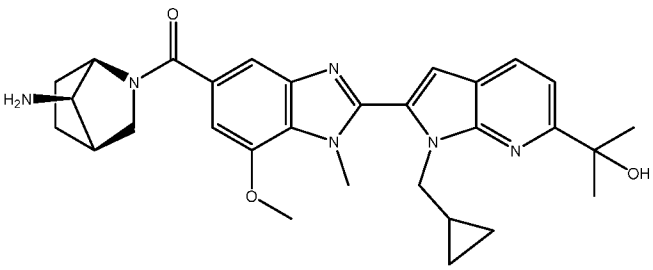

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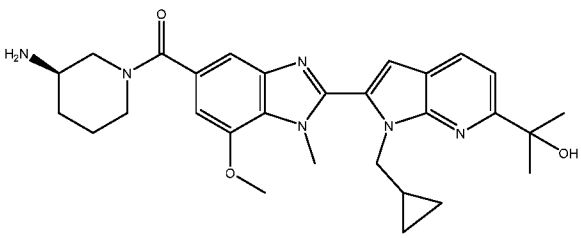

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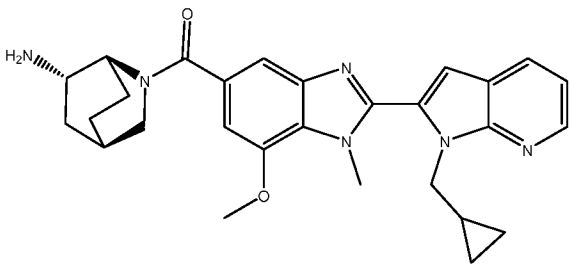

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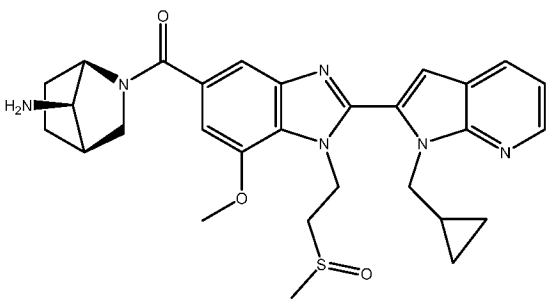

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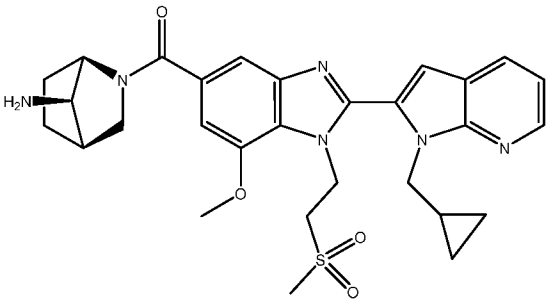

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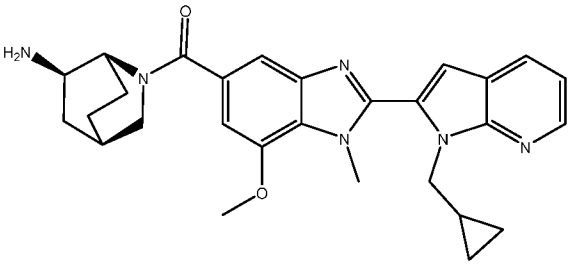

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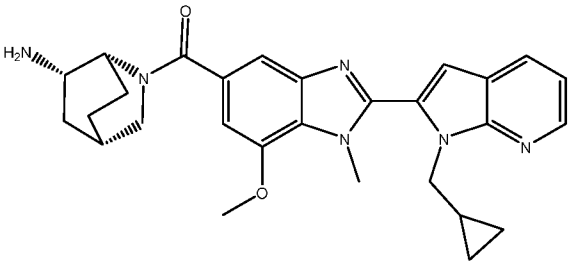

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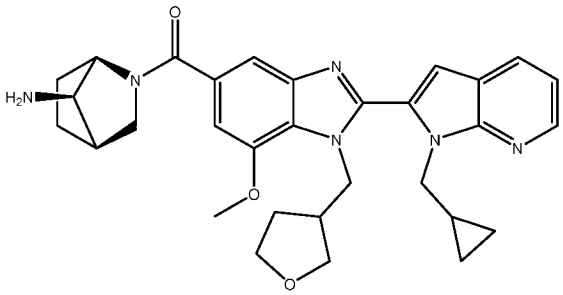

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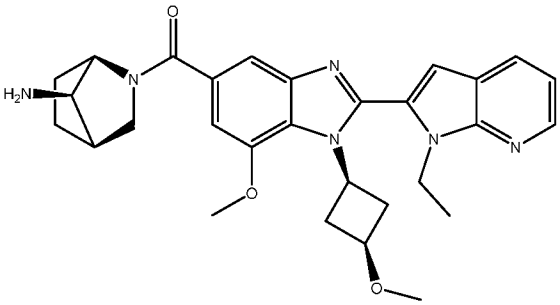

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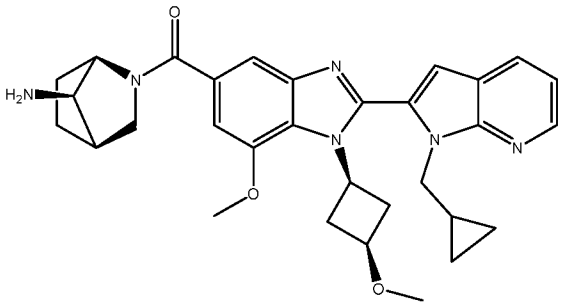

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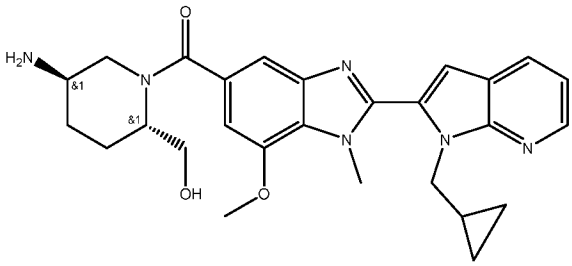

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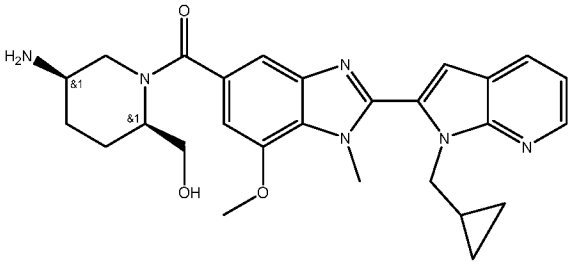

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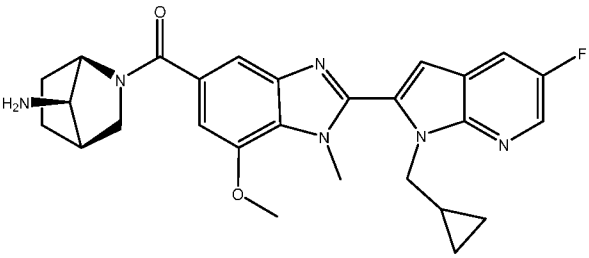

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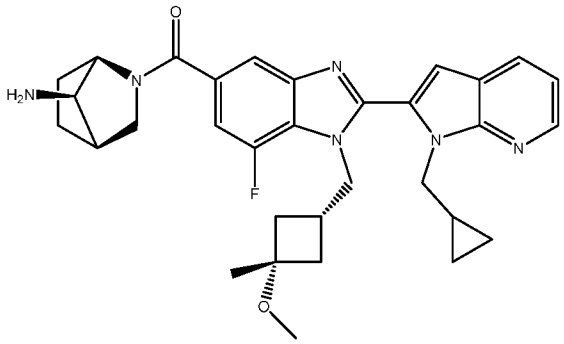

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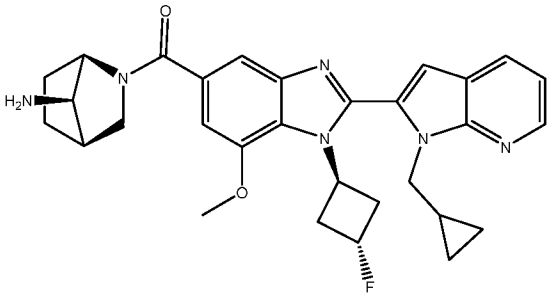

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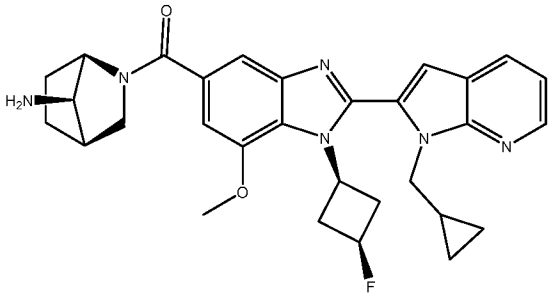

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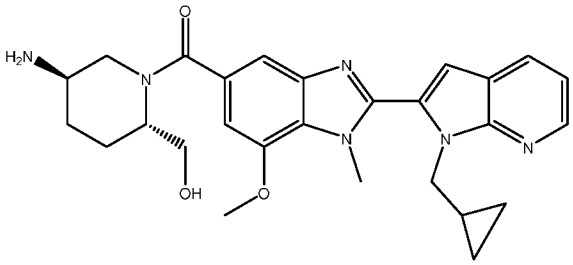

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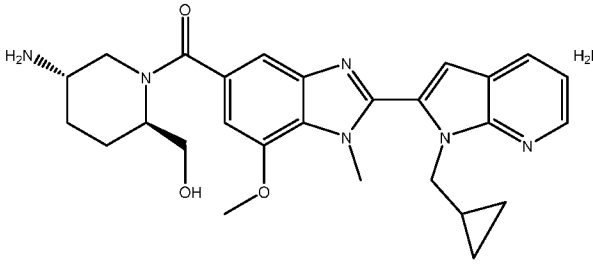

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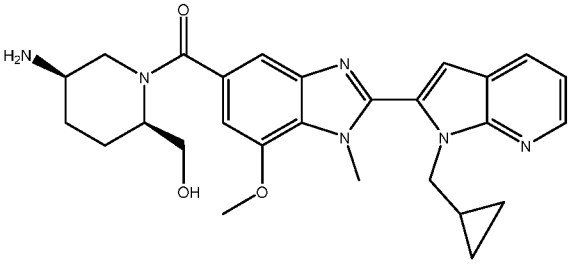

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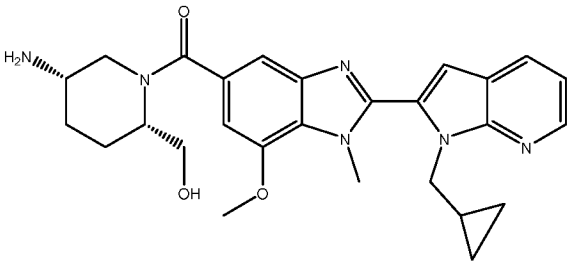

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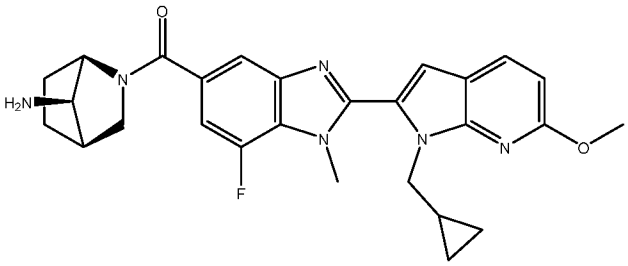

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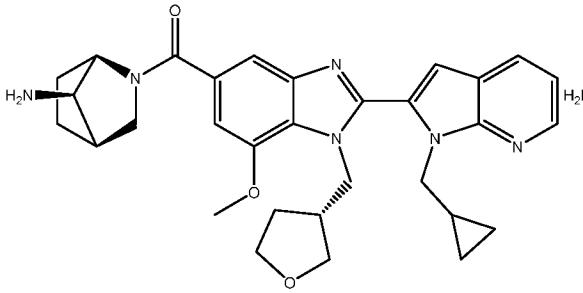

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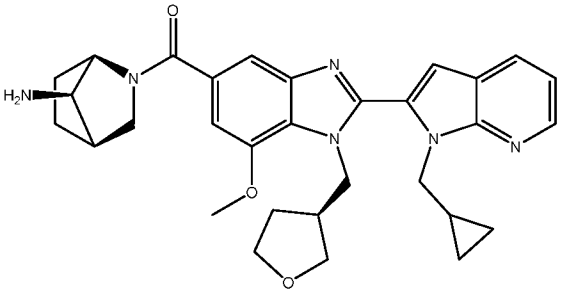

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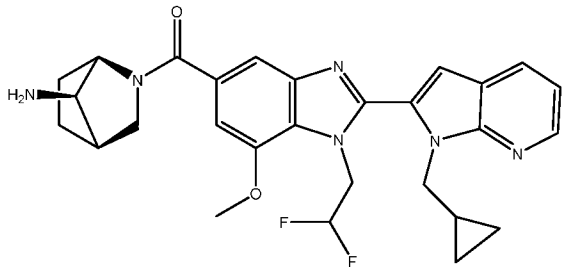

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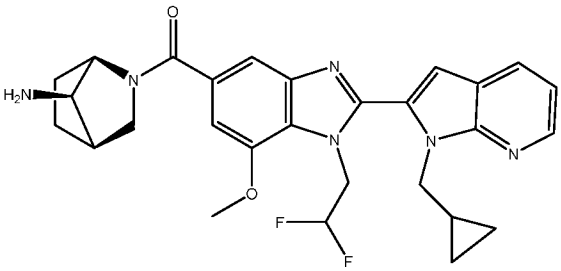

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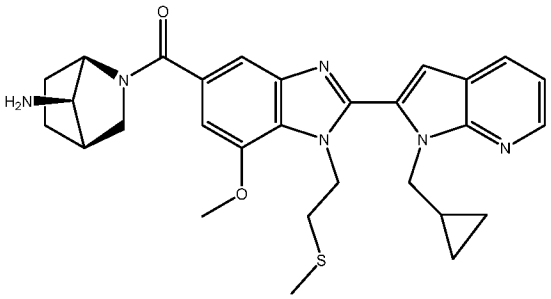

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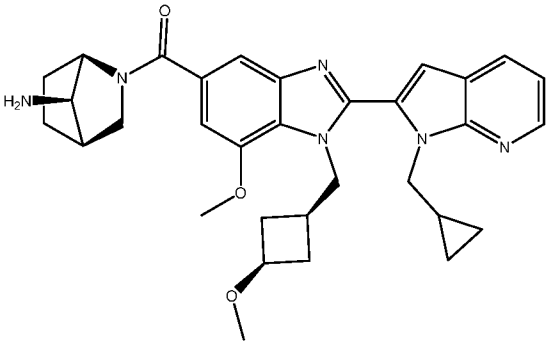

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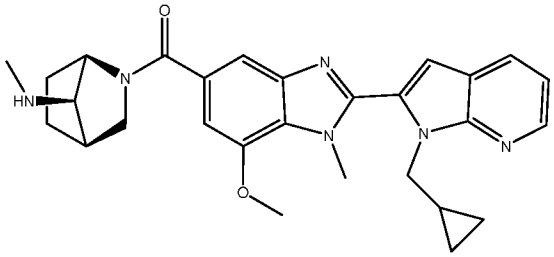

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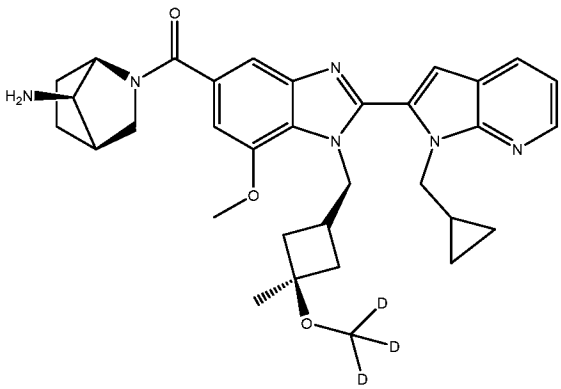

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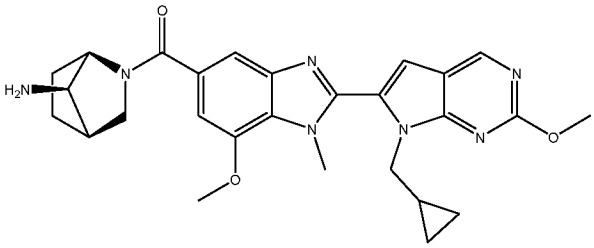

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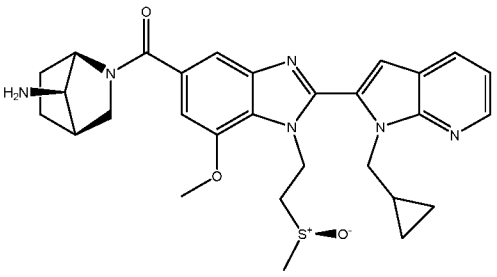

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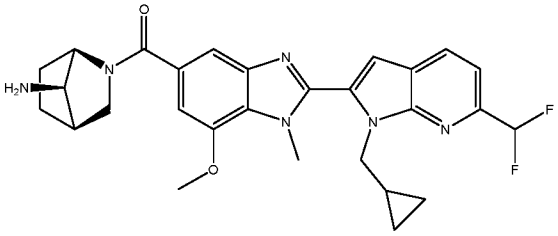

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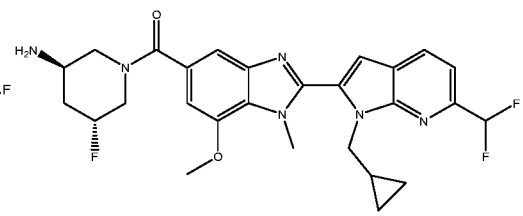

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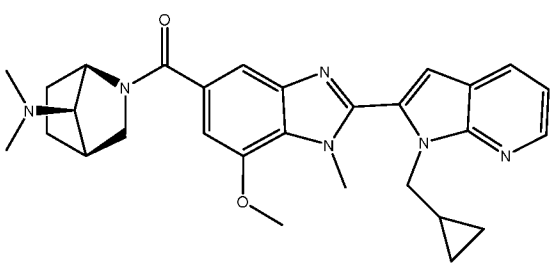

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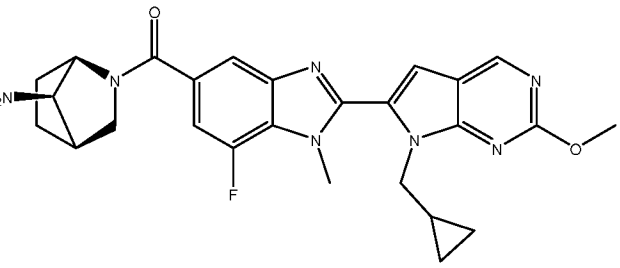

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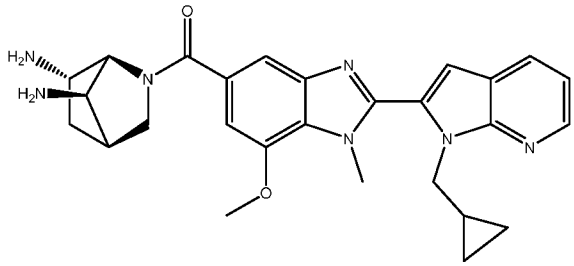

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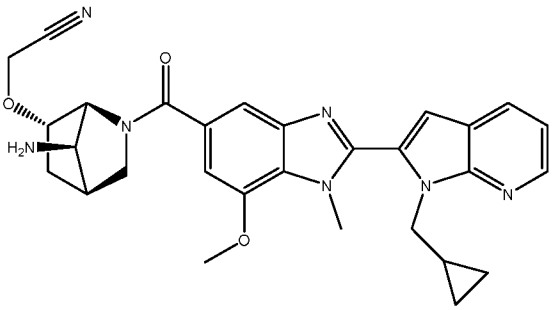

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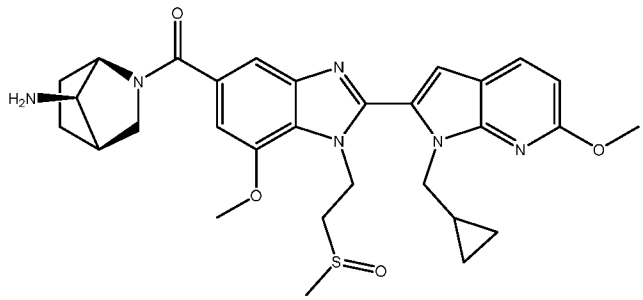

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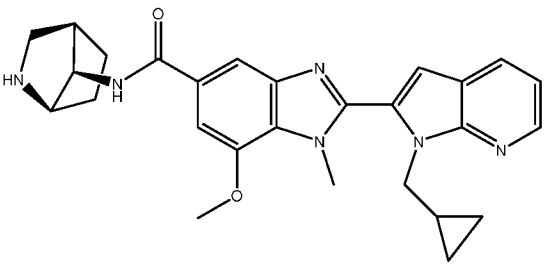

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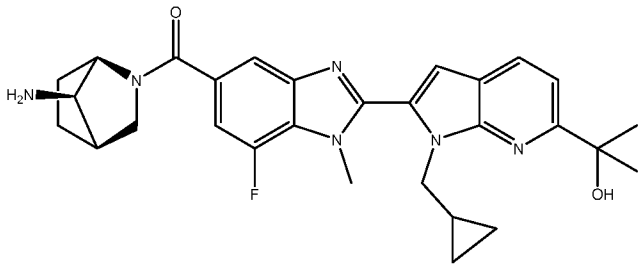

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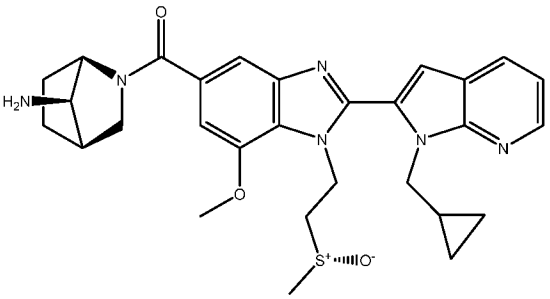

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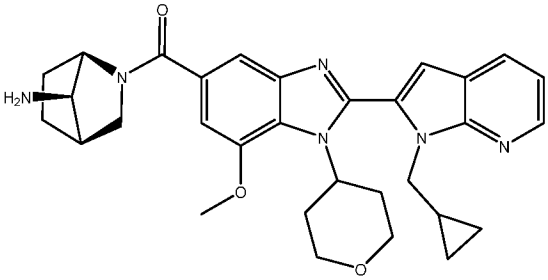

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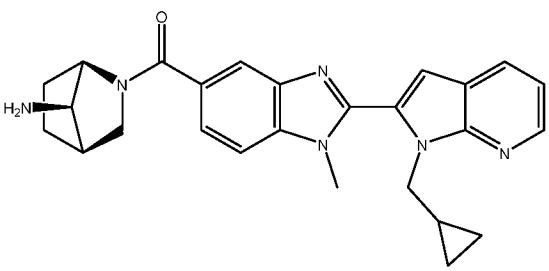

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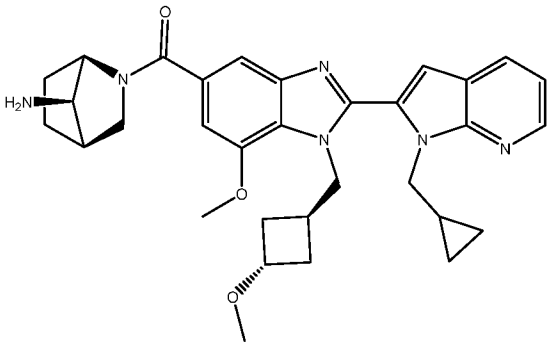

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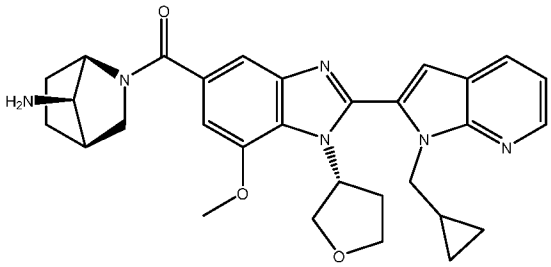

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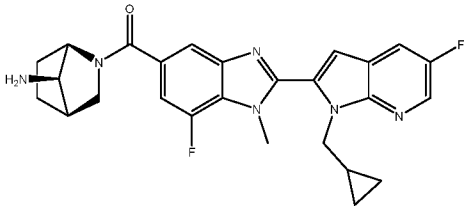

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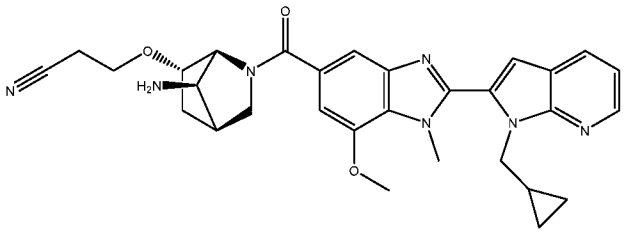

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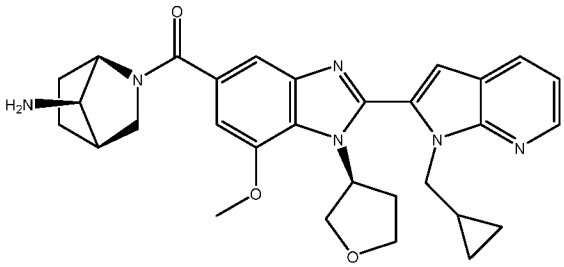

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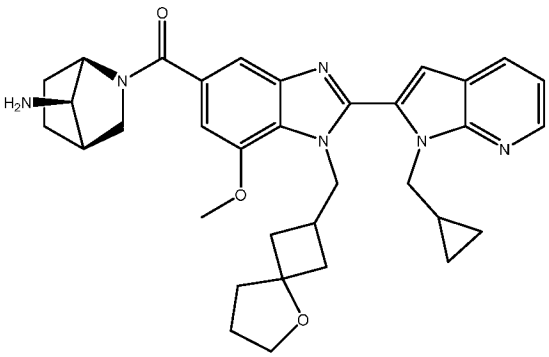

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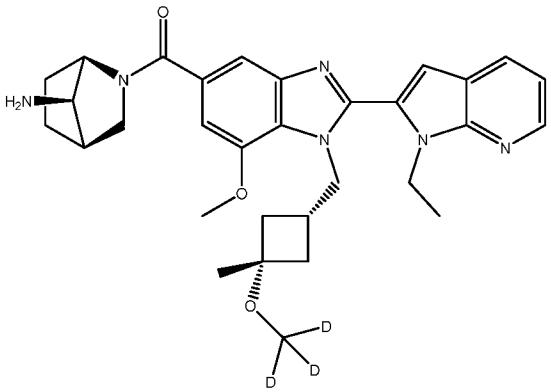

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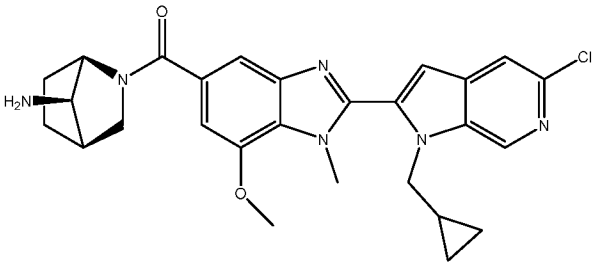

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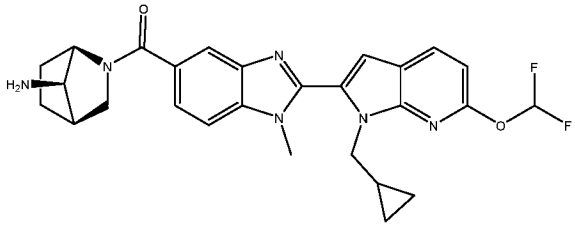

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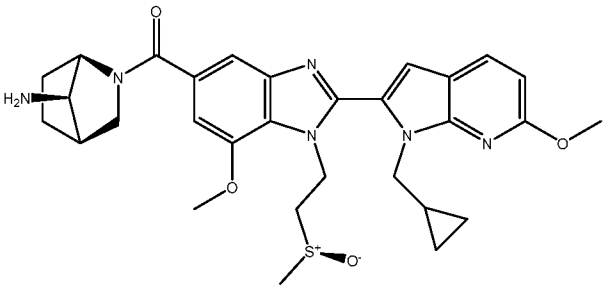
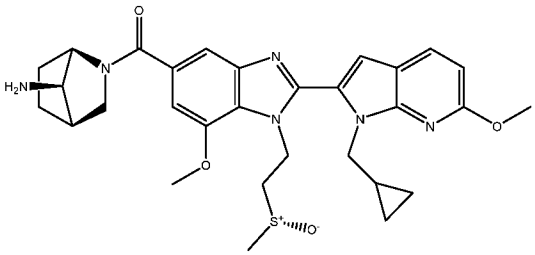


I-262



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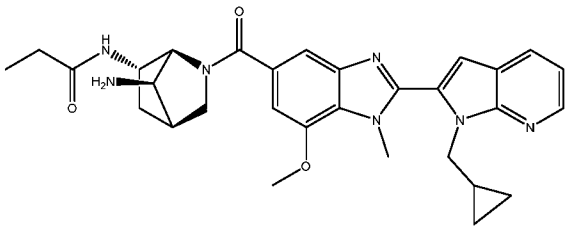

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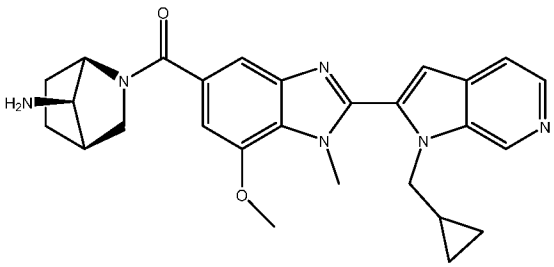

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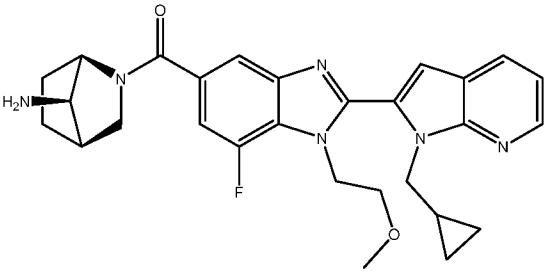

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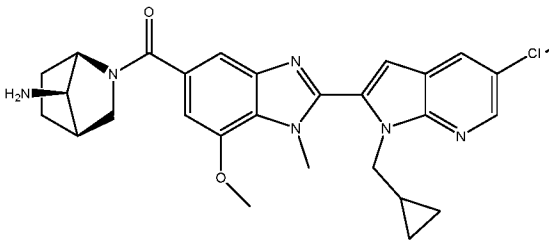

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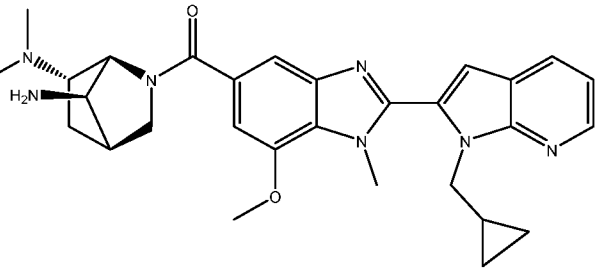

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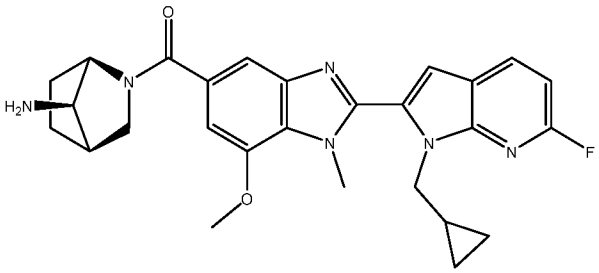

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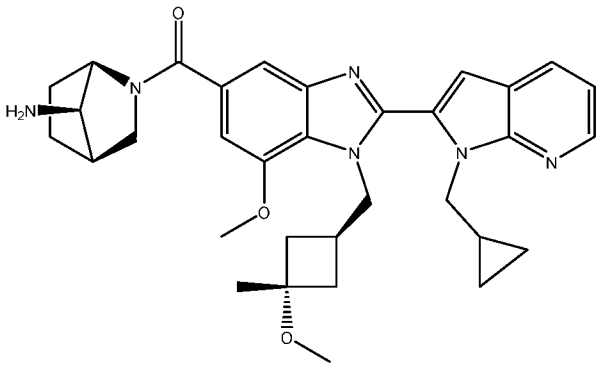

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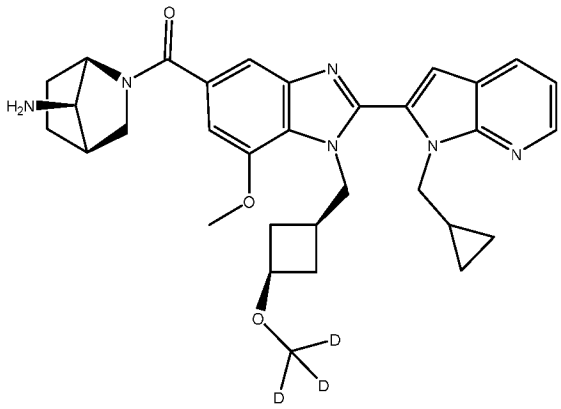

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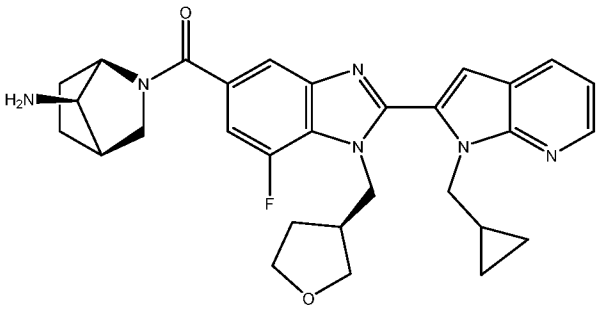

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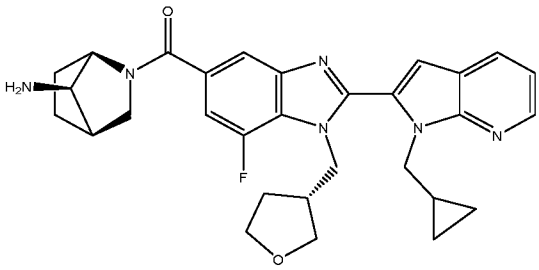

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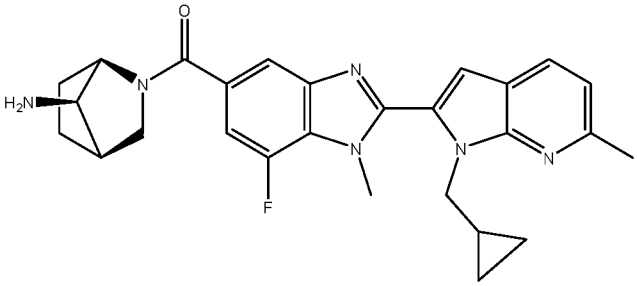

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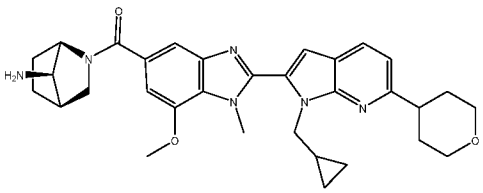

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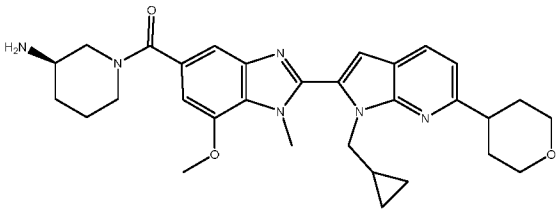

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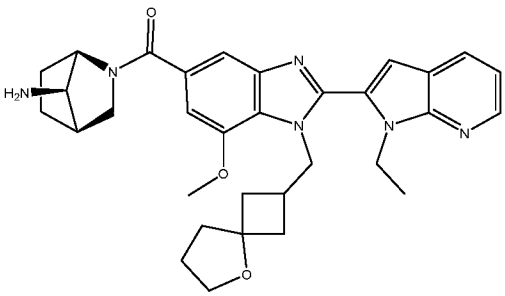

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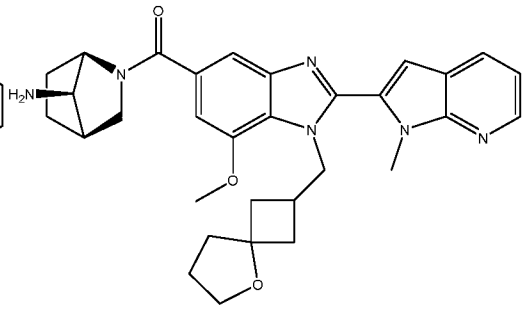

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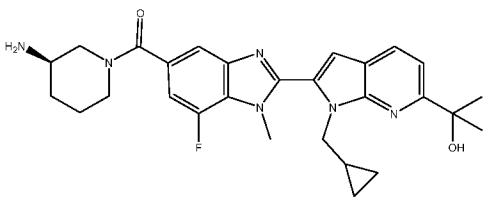

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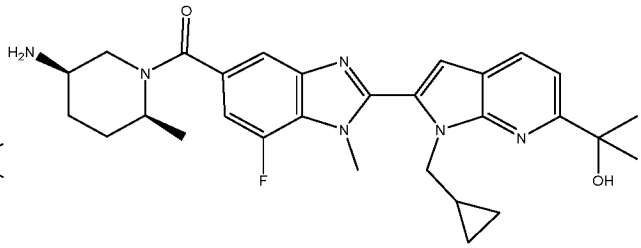

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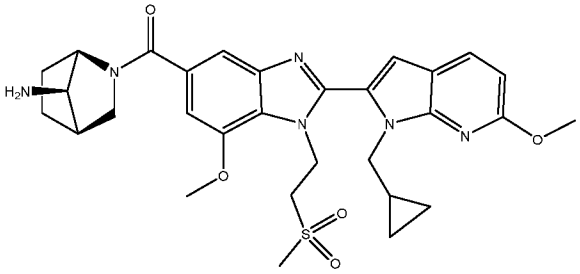

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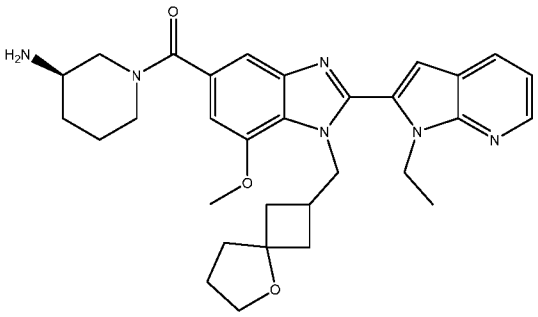

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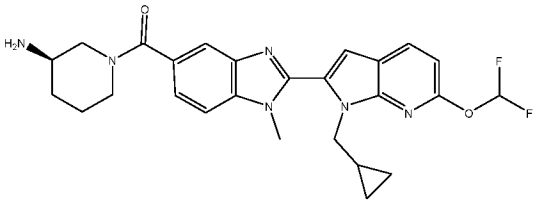

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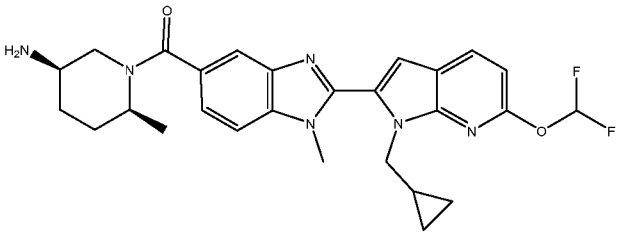

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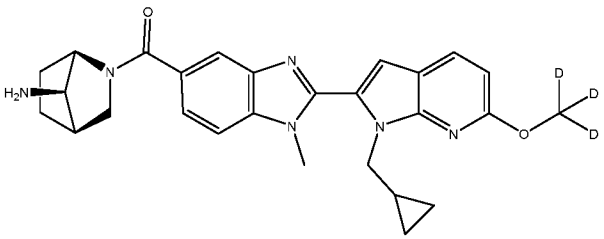

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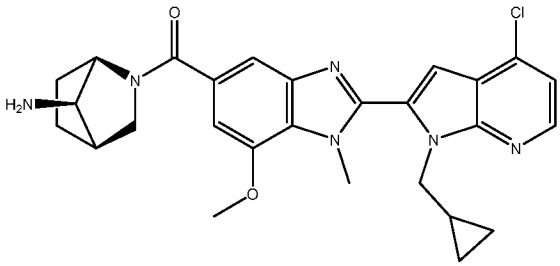

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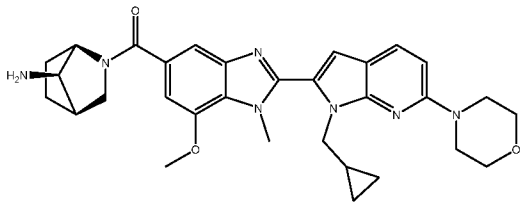

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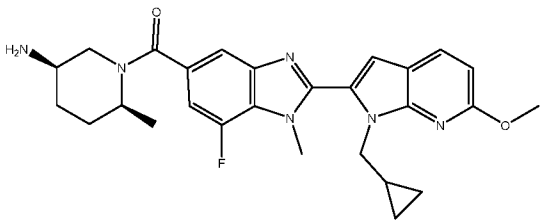

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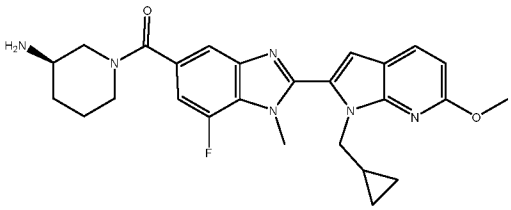

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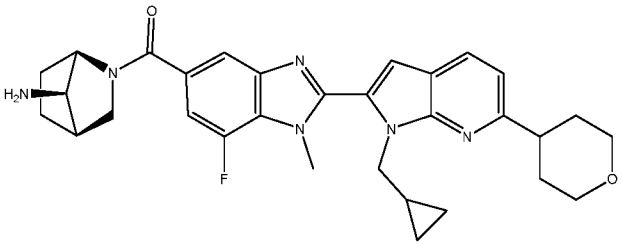

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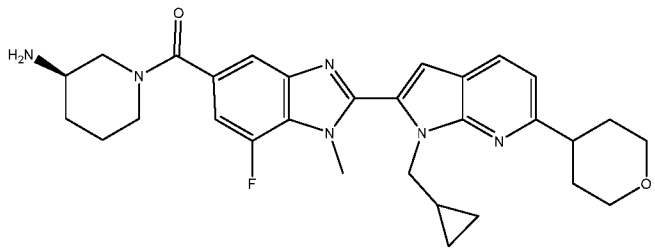

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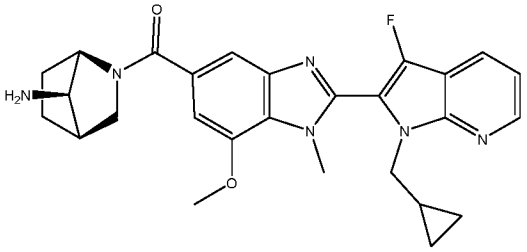

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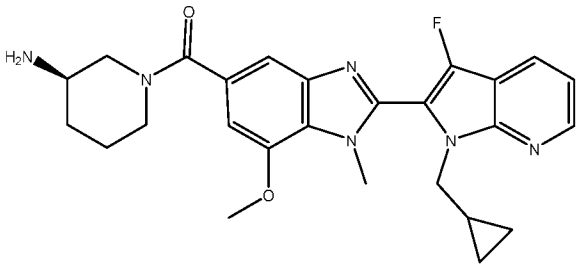

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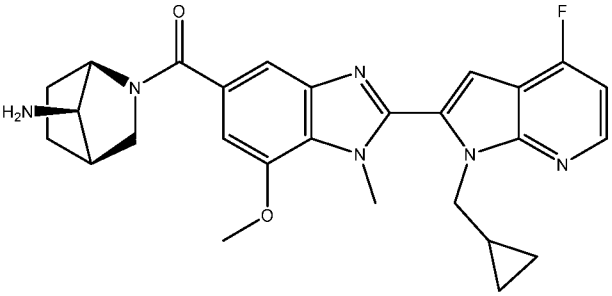

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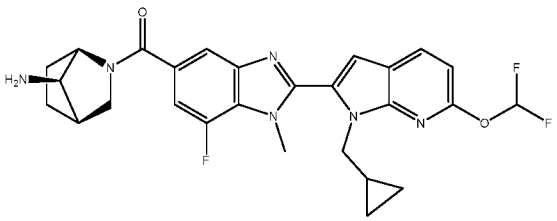

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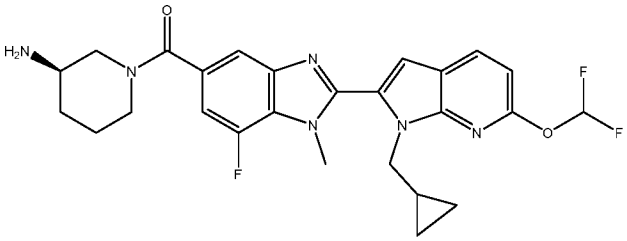

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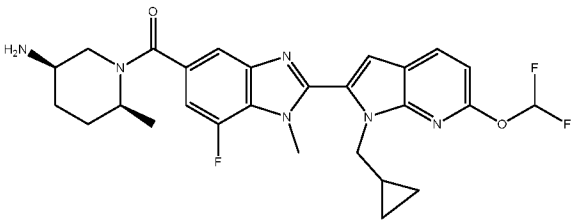

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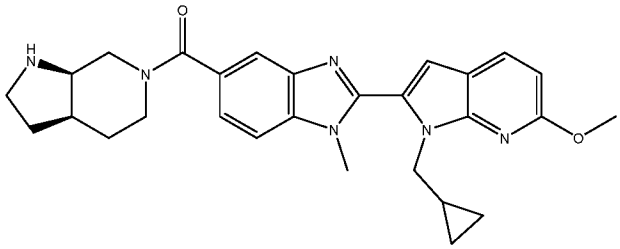

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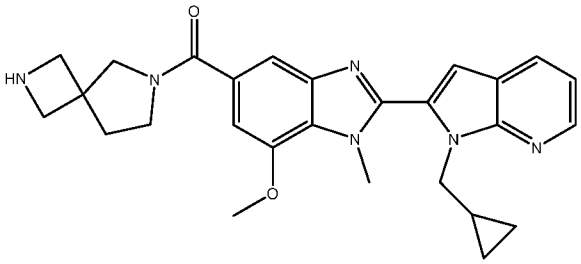

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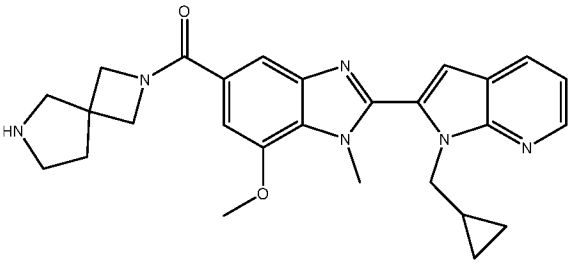

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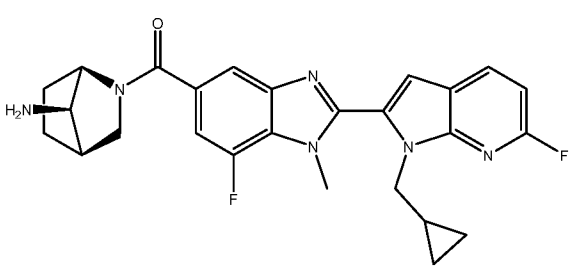

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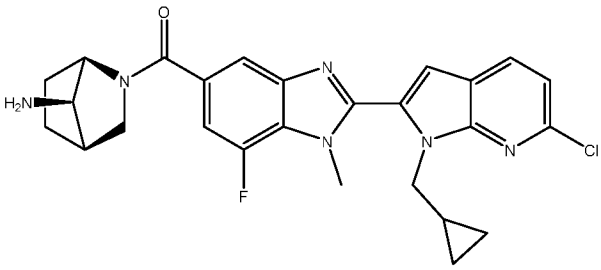

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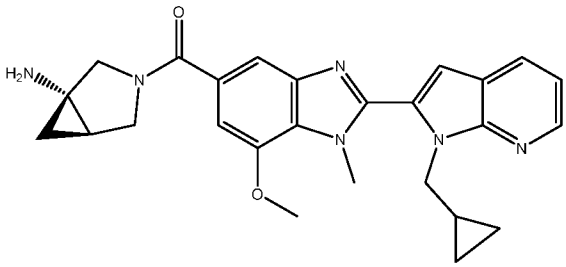

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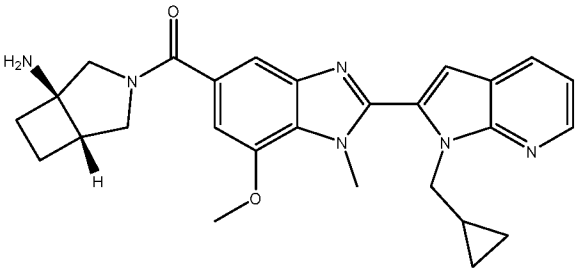

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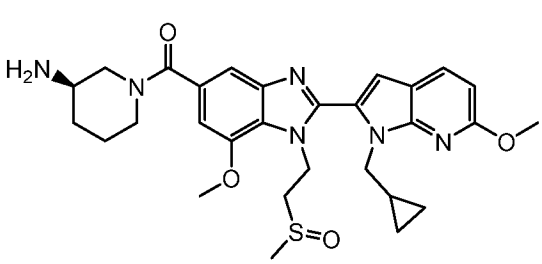

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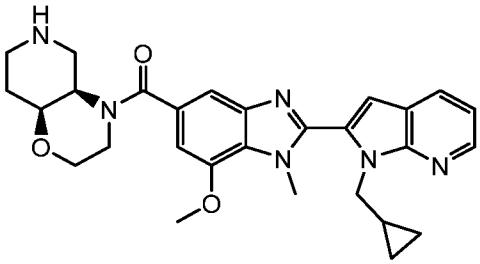

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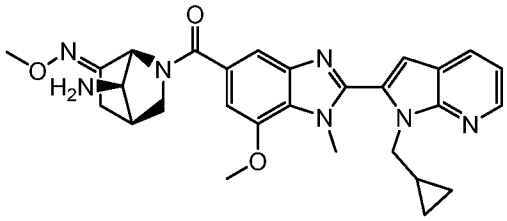

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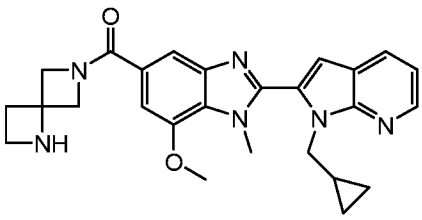

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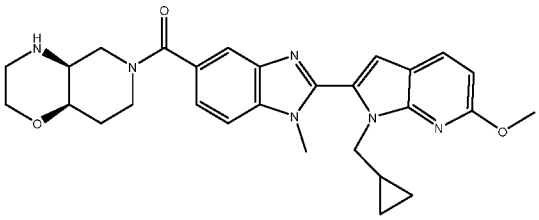

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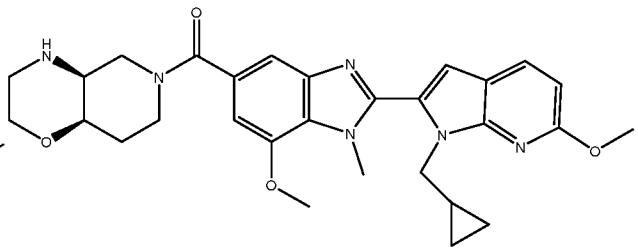

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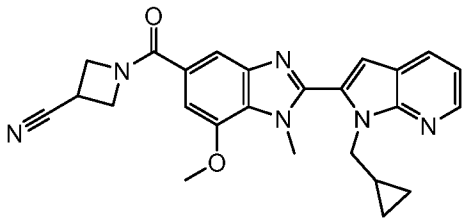

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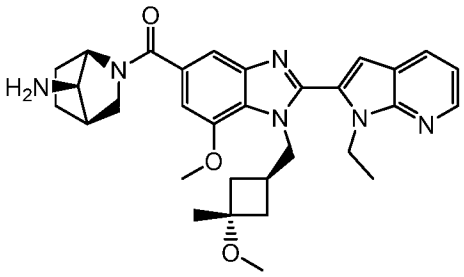

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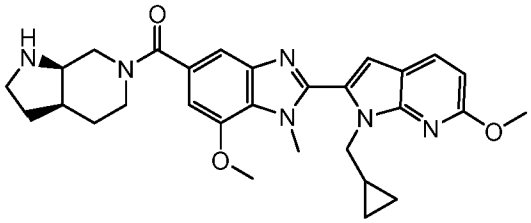

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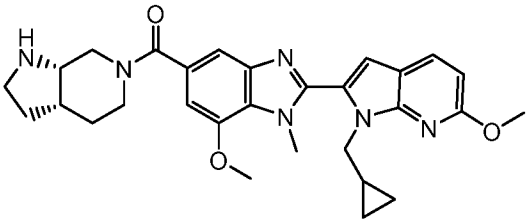

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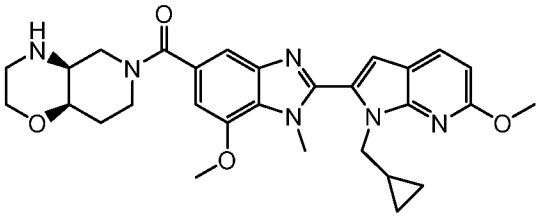

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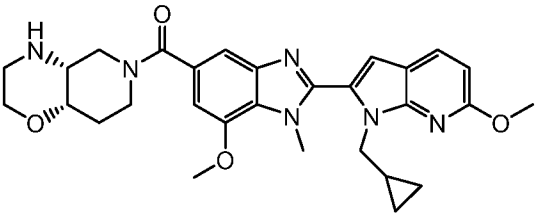

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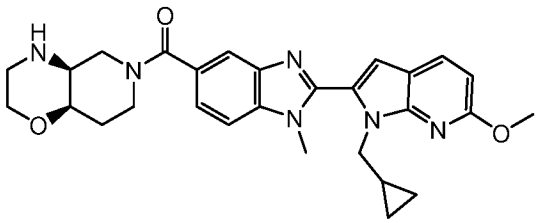
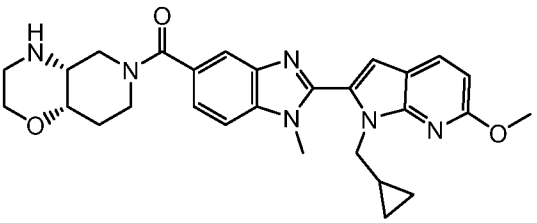


I-317



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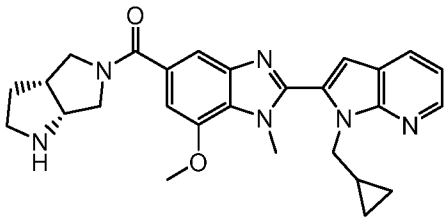

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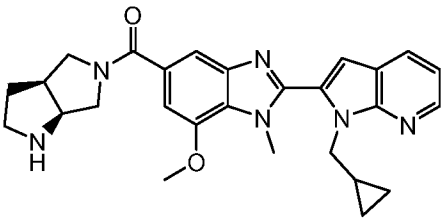
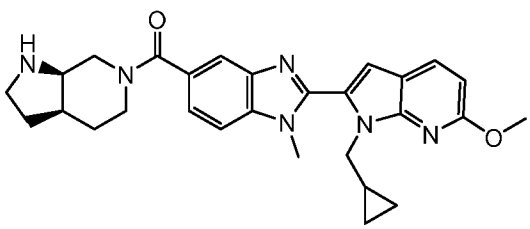


I-320



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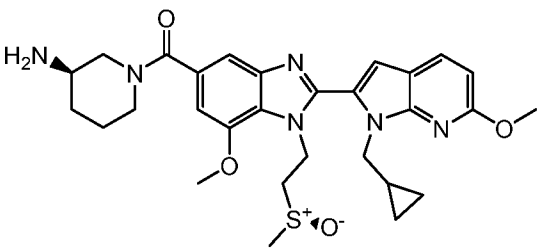

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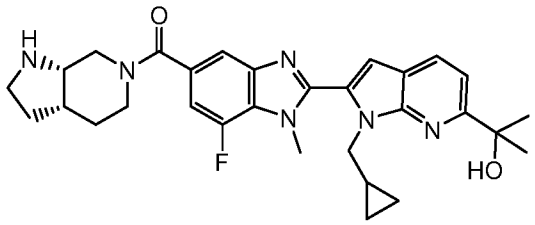

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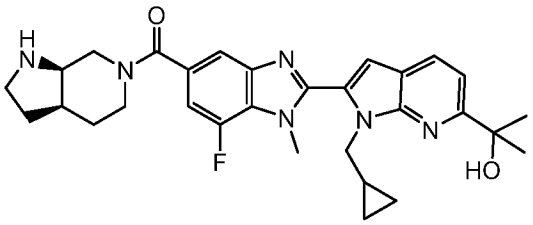

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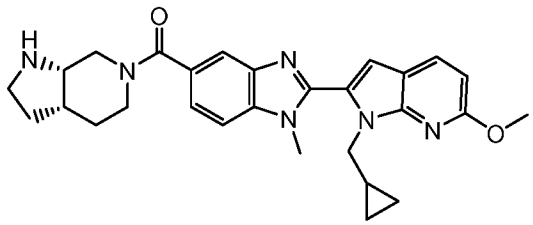

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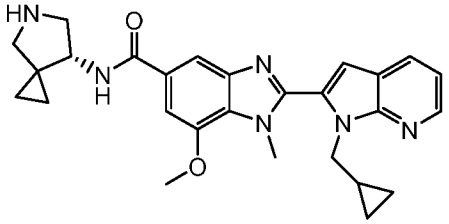

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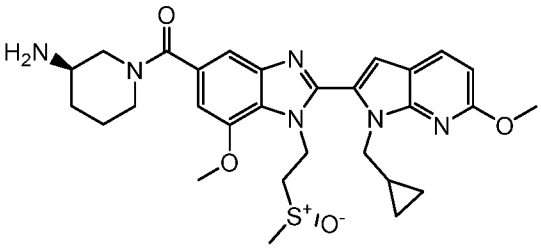

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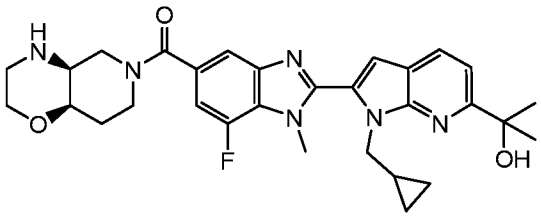

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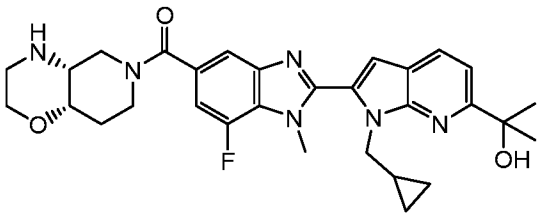

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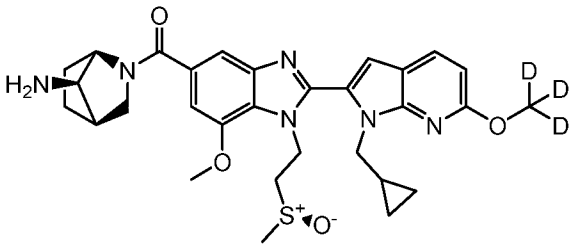

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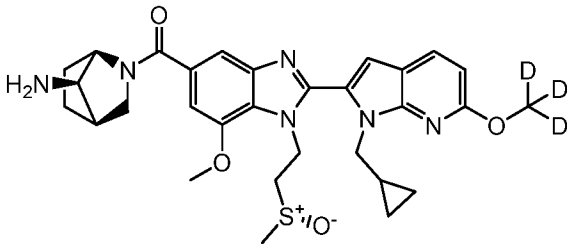

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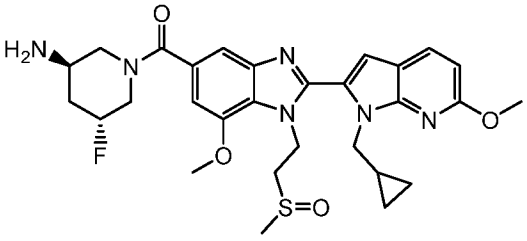

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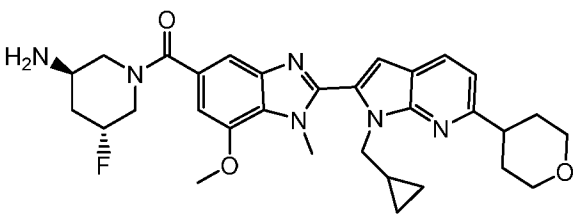

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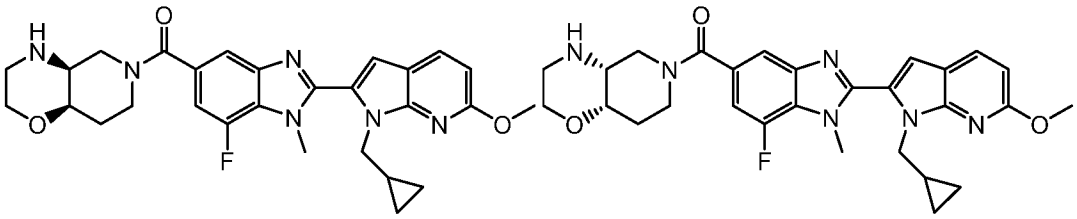

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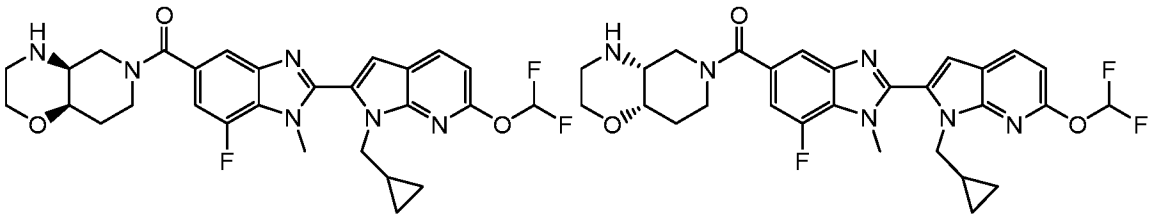
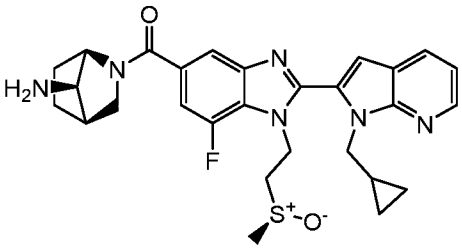


I-336 I-337



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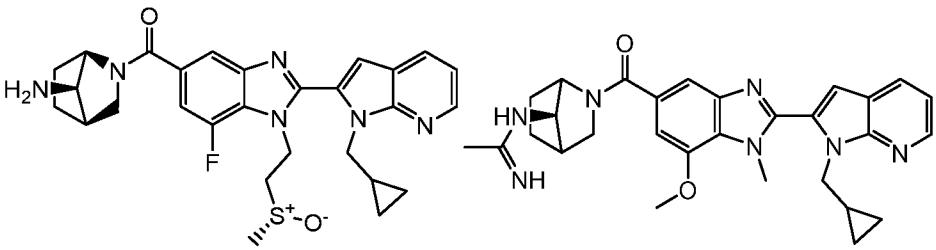

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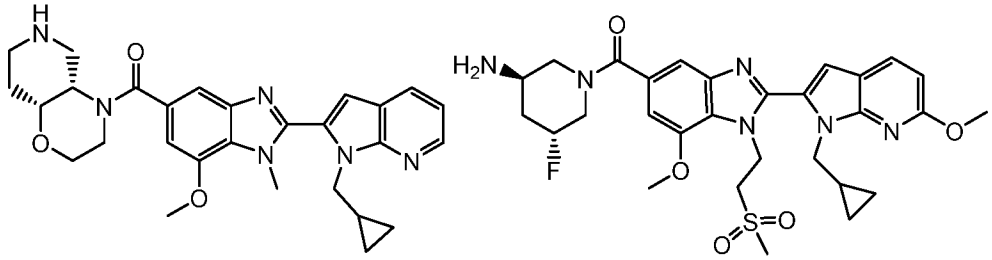

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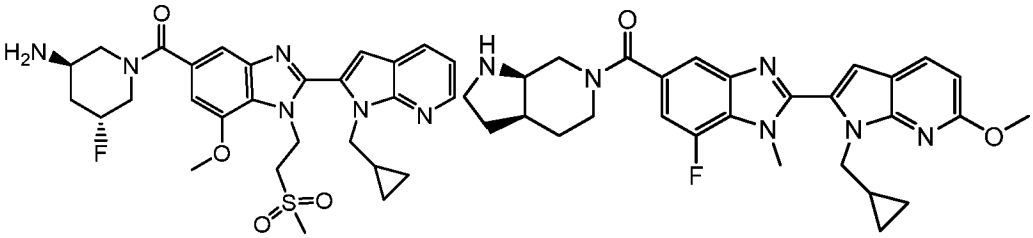

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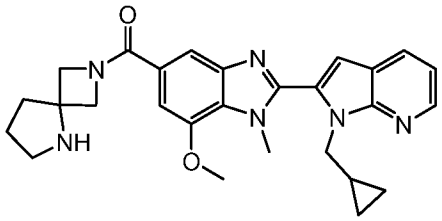

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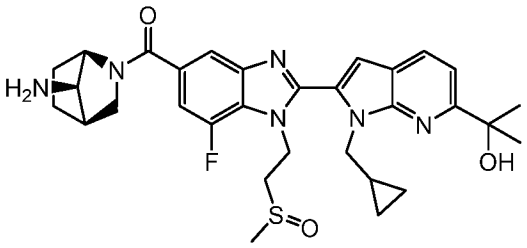

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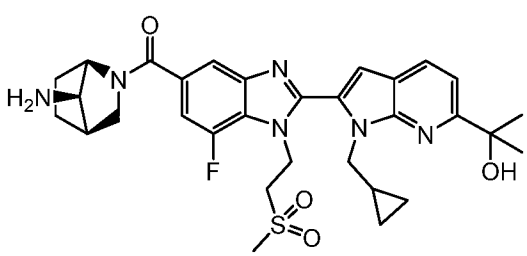

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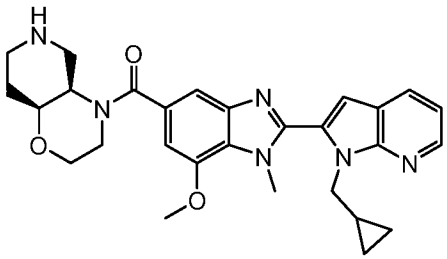

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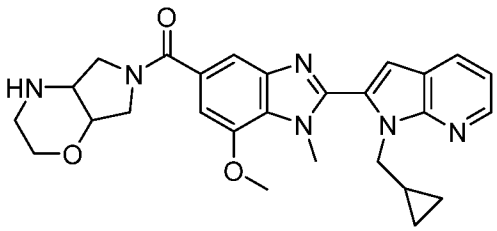

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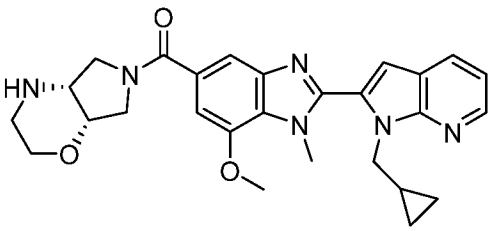

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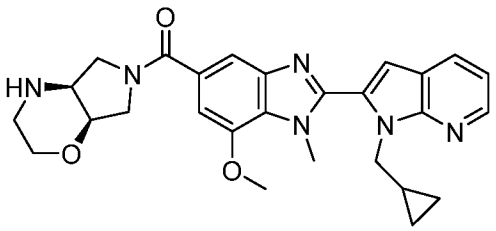

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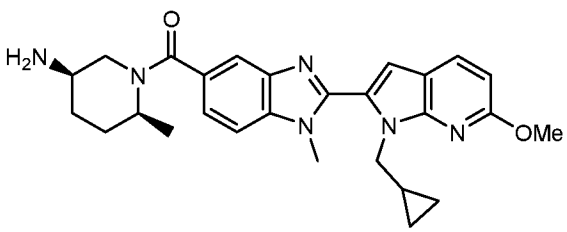

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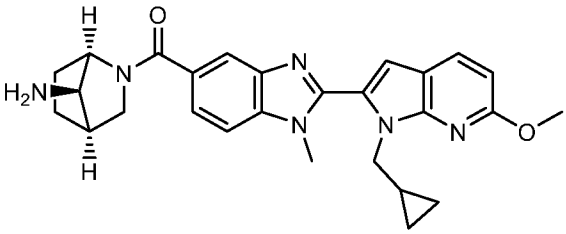

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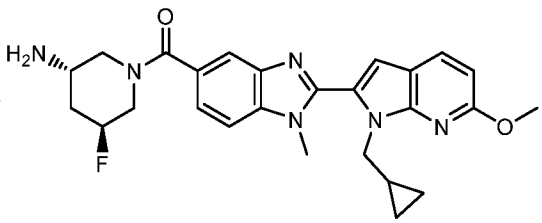

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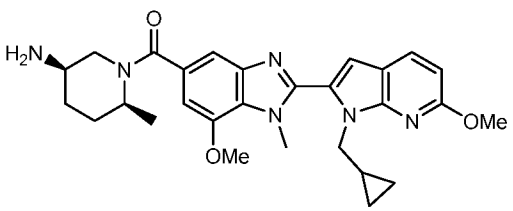

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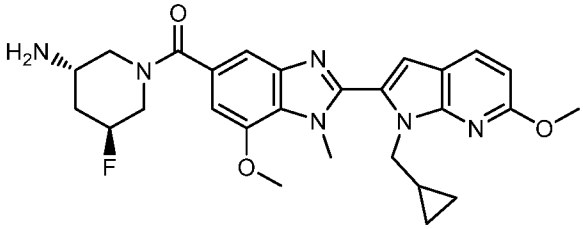

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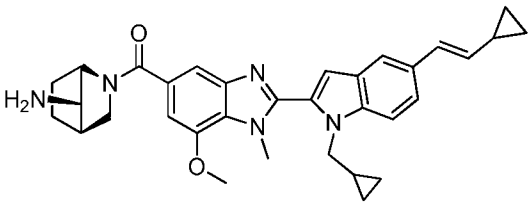

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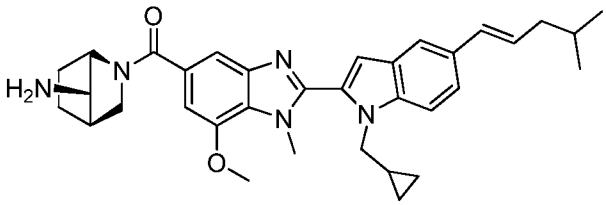

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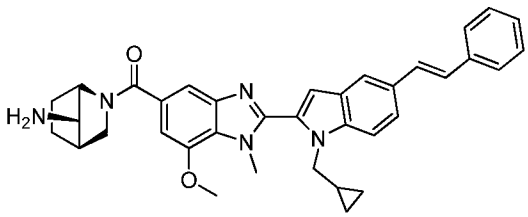

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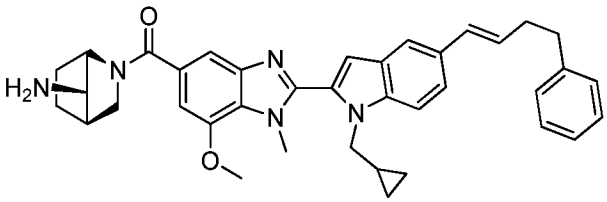

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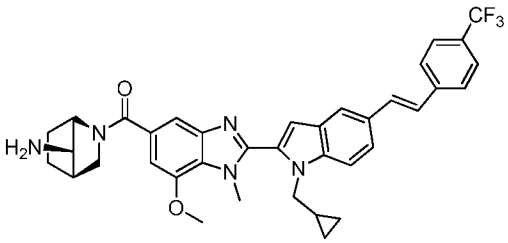

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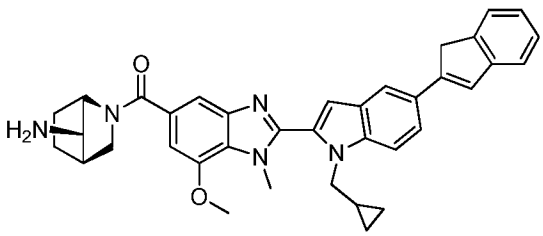

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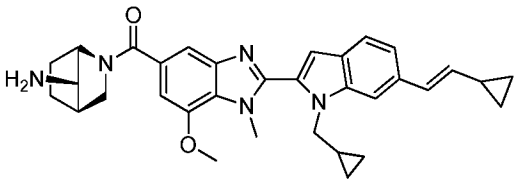

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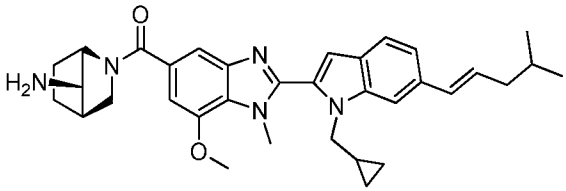

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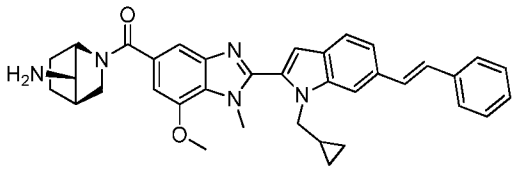

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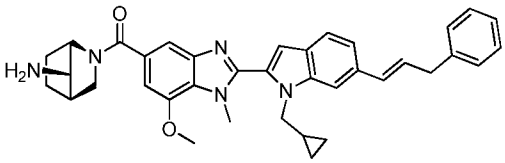

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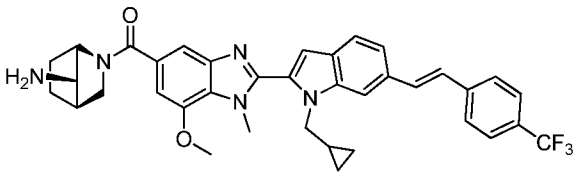

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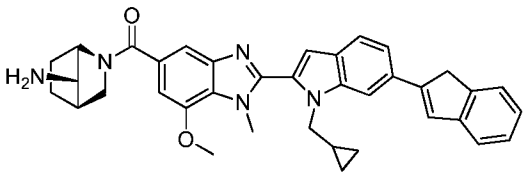

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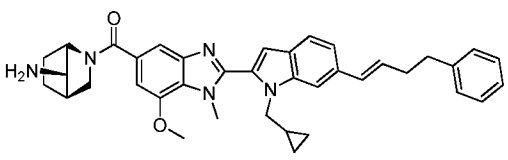

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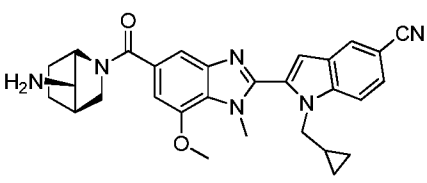

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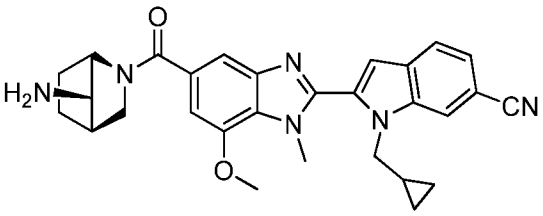

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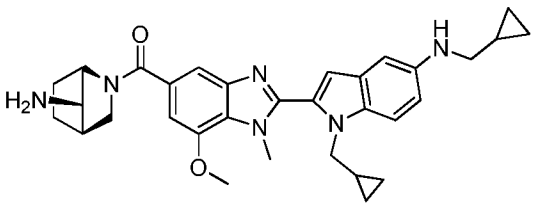

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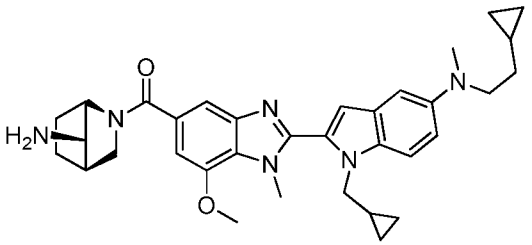

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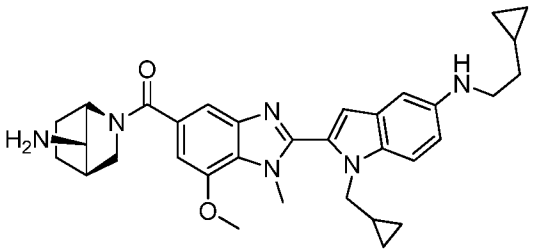

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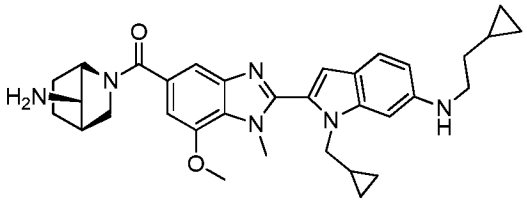
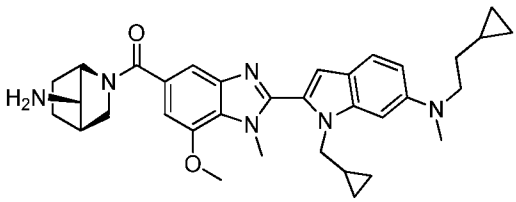


I-375



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[0045] In certain embodiments, the present invention provides any compound described above and herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the present invention provides a compound as depicted in Table 1, above, or a pharmaceutically acceptable salt thereof.

[0046] In some embodiments, the present invention provides any compound described above and herein in isolated form.

4. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[0047] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit PAD4, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit PAD4, in a biological sample or in a patient. In certain embodiments, a composition of this invention is

formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[0048] The term "subject," as used herein, is used interchangeably with the term "patient" and means an animal, preferably a mammal. In some embodiments, a subject or patient is a human. In other embodiments, a subject (or patient) is a veterinary subject (or patient). In some embodiments, a veterinary subject (or patient) is a canine, a feline, or an equine subject.

[0049] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0050] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0051] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or

castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0052] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0053] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0054] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0055] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0056] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a

suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0057] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0058] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0059] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[0060] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0061] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide,

oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0062] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0063] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0064] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0065] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating

excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0066] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0067] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0068] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting

aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0069] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0070] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0071] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[0072] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0073] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0074] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[0075] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent.

[0076] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0077] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present

invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[0078] Compounds and compositions described herein are generally useful for the inhibition of PAD4.

[0079] The activity of a compound utilized in this invention as an inhibitor of PAD4, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine the inhibition of PAD4. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of PAD4 are set forth in the Examples below. In some embodiments, a provided compound inhibits PAD4 selectively as compared to PAD2.

[0080] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0081] Provided compounds are inhibitors of PAD4and are therefore useful for treating one or more disorders associated with activity of PAD4. Thus, in certain embodiments, the present invention provides a method for treating a PAD4-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[0082] In one embodiment, a PAD4-mediated disorder is a disease, condition, or disorder mediated by inappropriate PAD4 activity. In some embodiments, a PAD4-mediated disorder is selected from the group consisting of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, and psoriasis. In a further embodiment, the disorder mediated by inappropriate PAD4 activity is rheumatoid arthritis. In a further embodiment, the disorder mediated by inappropriate PAD4 activity is systemic lupus. In a further embodiment, the disorder mediated by inappropriate PAD4 activity is vasculitis. In a further embodiment, the disorder mediated by inappropriate PAD4 activity is cutaneous lupus erythematosis. In a further embodiment, the disorder mediated by inappropriate PAD4 activity is psoriasis.

[0083] In one embodiment there is provided a method of treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, or psoriasis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound or a pharmaceutically acceptable salt thereof.

[0084] In one embodiment there is provided a method of treatment of rheumatoid arthritis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treatment of systemic lupus, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treatment of vasculitis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treatment of cutaneous lupus erythematosis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treatment of psoriasis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a provided compound, or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments, a PAD4-mediated disorder is selected from the group consisting of acid-induced lung injury, acne (PAPA), acute lymphocytic leukemia, acute, respiratory distress syndrome, Addison's disease, adrenal hyperplasia, adrenocortical insufficiency, ageing, AIDS, alcoholic hepatitis, alcoholic hepatitis, alcoholic liver disease, allergen induced asthma, allergic bronchopulmonary, aspergillosis, allergic conjunctivitis, alopecia, Alzheimer's disease, amyloidosis, amyotropic lateral sclerosis, and weight loss, angina pectoris, angioedema, anhidrotic ecodermal dysplasia-ID, ankylosing spondylitis, anterior segment, inflammation, antiphospholipid syndrome, aphthous stomatitis, appendicitis, arthritis, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, autoimmune hepatitis, bee sting-induced inflammation, behcet's disease, Behcet's syndrome, Bells Palsey, berylliosis, Blau syndrome, bone pain, bronchiolitis, burns, bursitis, cancer, cardiac hypertrophy, carpal tunnel syndrome, catabolic disorders, cataracts, cerebral aneurysm, chemical irritant-induced inflammation, chorioretinitis, chronic heart failure, chronic lung disease of prematurity, chronic lymphocytic leukemia, chronic obstructive

pulmonary disease, colitis, complex regional pain syndrome, connective tissue disease, corneal ulcer, crohn's disease, cryopyrin-associated periodic syndromes, cyrptococcosis, cystic fibrosis, deficiency of the interleukin-1–receptor antagonist (DIRA), dermatitis, dermatitis endotoxemia, dermatomyositis, diffuse intrinsic pontine glioma, endometriosis, endotoxemia, epicondylitis, erythroblastopenia, familial amyloidotic polyneuropathy, familial cold urticarial, familial mediterranean fever, fetal growth retardation, glaucoma, glomerular disease, glomerular nephritis, gout, gouty arthritis, graft-versus-host disease, gut diseases, head injury, headache, hearing loss, heart disease, hemolytic anemia, Henoch-Scholein purpura, hepatitis, hereditary periodic fever syndrome, herpes zoster and simplex, HIV-1, Hodgkin's disease, Huntington's disease, hyaline membrane disease, hyperammonemia, hypercalcemia, hypercholesterolemia, hyperimmunoglobulinemia D with recurrent fever (HIDS), hypoplastic and other anemias, hypoplastic anemia, idiopathic thrombocytopenic purpura, incontinentia pigmenti, infectious mononucleosis, inflammatory bowel disease, inflammatory lung disease, inflammatory neuropathy, inflammatory pain, insect bite-induced inflammation, iritis, irritant-induced inflammation, ischemia/reperfusion, juvenile rheumatoid arthritis, keratitis, kidney disease, kidney injury caused by parasitic infections, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, leptospiriosis, leukemia, Loeffler's syndrome, lung injury, lung injury, lupus, lupus, lupus nephritis, lymphoma, meningitis, mesothelioma, mixed connective tissue disease, Muckle-Wells syndrome (urticaria deafness amyloidosis), multiple sclerosis, muscle wasting, muscular dystrophy, myasthenia gravis, myocarditis, mycosis fungiodes, mycosis fungoides, myelodysplastic syndrome, myositis, nasal sinusitis, necrotizing enterocolitis, neonatal onset multisystem inflammatory disease (NOMID), nephrotic syndrome, neuritis, neuropathological diseases, non-allergen induced asthma, obesity, ocular allergy, optic neuritis, organ transplant, osterarthritis, otitis media, paget's disease, pain, pancreatitis, Parkinson's disease, pemphigus, pericarditis, periodic fever, periodontitis, peritoneal endometriosis, pertussis, pharyngitis and adenitis (PFAPA syndrome), plant irritant-induced inflammation, pneumonia, pneumonitis, pneumosysts infection, poison ivy/ urushiol oil-induced inflammation, polyarteritis nodosa, polychondritis, polycystic kidney disease, polymyositis, psoriasis, psoriasis, psoriasis, psoriasis, psychosocial stress diseases, pulmonary disease, pulmonary hypertension, pulmonayr fibrosis, pyoderma gangrenosum, pyogenic sterile arthritis, renal disease, retinal disease, rheumatic carditis, rheumatic disease, rheumatoid arthritis, sarcoidosis, seborrhea, sepsis, severe pain, sickle cell, sickle cell anemia, silica-induced disease, Sjogren's syndrome, skin diseases, sleep apnea, solid tumors, spinal

cord injury, Stevens-Johnson syndrome, stroke, subarachnoid hemorrhage, sunburn, temporal arteritis, tenosynovitis, thrombocytopenia, thyroiditis, tissue transplant, TNF receptor associated periodic syndrome (TRAPS), toxoplasmosis, transplant, traumatic brain injury, tuberculosis, type 1 diabetes, type 2 diabetes, ulcerative colitis, urticarial, uveitis, and Wegener's granulomatosis.

[0086] In one embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in therapy. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder mediated by inappropriate PAD4 activity. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, or psoriasis. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of rheumatoid arthritis. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of systemic lupus. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of vasculitis. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cutaneous lupus erythematosis. In another embodiment, the invention provides a provided compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of psoriasis. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate PAD4 activity. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, or psoriasis. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of systemic lupus. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for use in the treatment of vasculitis. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cutaneous lupus erythematosis. In another embodiment, the invention provides the use of a provided compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of psoriasis. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of a disorder mediated by inappropriate PAD4 activity comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, or psoriasis, comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of rheumatoid arthritis comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of systemic lupus comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of vasculitis comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of cutaneous lupus erythematosis comprising a provided compound, or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention provides a pharmaceutical composition for the treatment or prophylaxis of psoriasis comprising a provided compound, or a pharmaceutically acceptable salt thereof

[0087] All features of each of the aspects of the invention apply to all other aspects mutatis mutandis.

[0088] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXEMPLIFICATION

[0089] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of

the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[0090] Method A

MET/u-HPLC (low pH 7 min method)
Column: Phenomenex Kinetex-XB C18, 2.1 mm x 100 mm, 1.7 µm
Flow rate: 0.6 ml/min
Mobile Phase: A, Formic acid (aqueous) 0.1% and B, Formic acid (MeCN) 0.1%
Injection Vol: 3 µl
Temp.: 40 °C
Detection: 215 nm (nominal)
Gradient Time (minutes) - % B
0.00 - 5
5.30 - 100
5.80 - 100
5.82 - 5

[0091] Method B

MET/CR/1600 (high pH 7 min method)
Column: Phenomenex Gemini C18, 2.0mmx100mm, 3µm
Flow rate: 0.5ml/min
Mobile phase:
A: 2mM ammonium bicarbonate in HPLC grade water pH10
B: HPLC grade MeCN
Injection volume: 3 µl
Temperature: 50 °C
Detection: 215nm
Gradient time: (minutes) - %B
0.0 – 5
5.50 – 100
5.90 – 100
5.92 – 5
9.00 - 5

[0092] Method C

METCR 1416 (low pH Shimadzu 7min method)
Column: Waters Atlantis dC18, 2.1mmx100mm, 3µm column
Flow rate: 0.6 ml/min
Mobile Phase: A, Formic acid (aqueous) 0.1% and B, Formic acid (acetonitrile) 0.1%
Injection Vol: 3 µl
Temp.: 40 °C
Detection: 215 nm (nominal)
Gradient Time (minutes) - % B
0.00 - 5
5.00 - 100
5.40 - 100
5.42 – 5

[0093] Method D

METCR 1410 (low pH Shimadzu 2min method)
Column: Kinetex Core-Shell C18, 2.1mmx50mm, 5µm column
Flow rate: 1.2 ml/min
Mobile Phase: A, Formic acid (aqueous) 0.1% and B, Formic acid (acetonitrile) 0.1%
Injection Vol: 3 µl
Temp.: 40 °C
Detection: 215 nm (nominal)
Gradient Time (minutes) - % B

0.00 - 5
1.20 - 100
1.30 - 100
1.31 – 5

[0094] Method E:

Chiral HPLC preparative method
Column: Chiralpak IC 250mm x 4.6mm, 5µm column
Flow rate: 15 ml/min
Mobile Phase: 35% Ethanol: 65%CO2
Sample Diluent: Ethanol
Temp.: 40°C
Detection: 215 nm (nominal)

[0095] Method F:

Chiral purity analysis method
Column: Chiralpak IC 250mm x 4.6mm, 5µm column
Flow Rate: 4 ml/min
Injection Vol: 10 µL
Temp.: 40°C
Detection: 215 nm
Isocratic Conditions 40% Ethanol: 60%CO2

[0096] Method G

Chiral HPLC preparative method
Column: XSelect CSH C18 50x2.1 mm, 1.7um
Flow rate: 0.6 ml/min
Mobile Phase: Water (0.1% v/v TFA), MecN (0.1% v/v TFA)
Sample Diluent: Ethanol
Temp.: 40°C
Detection: 240 nm (nominal)

[0097] Method H

MET/u-HPLC (high pH MS16 7 min method)
Column: Waters UPLC CSH C18, 2.1mmx100mm 5µm column
Flow rate: 0.6 ml/min

Mobile Phase: A, 2mM Ammonium bicarbonate modified to pH 10 with Ammonium hydroxide (aqueous) and B, acetonitrile
Injection Vol: 3 µl
Temp.: 40 °C
Detection: 215 nm (nominal)
Gradient Time (minutes) - % B
0.00 - 5
5.30 - 100
5.80 - 100
5.82 - 5

[0098] Method I:

Chiral purity analysis method
Column: Lux C4 (21.2mm x 250mm, 5um)
Flow Rate: 21 ml/min
Injection Vol: 350 µL
Detection: 222 nm
Isocratic Conditions: MeOH (0.1% v/v NH3)

[0099] Method J

MET/CR/0990 (high pH 3min method)
Column: Phenomenex Gemini C18, 2.0mmx100mm, 3µm
Flow rate: 1ml/min
Mobile phase: A, 2mM ammonium bicarbonate in HPLC grade water pH10
B HPLC grade MeCN
Injection volume: 3 µl
Temperature: 60 °C
Detection: 215nm
Gradient time: (minutes) - %B
0.0– 1
1.80 – 100
2.10 – 100
2.30 – 1

[00100] Method K:

Chiral HPLC preparative method
Column: Amy-C 20mm x 250mm, 5um
Flow Rate: 21 ml/min
Mobile Phase: 4:6 heptane:ethanol (0.1% v/v ammonia)
Sample Diluent: Methanol
Temp.: Ambient
Detection: 254 nm

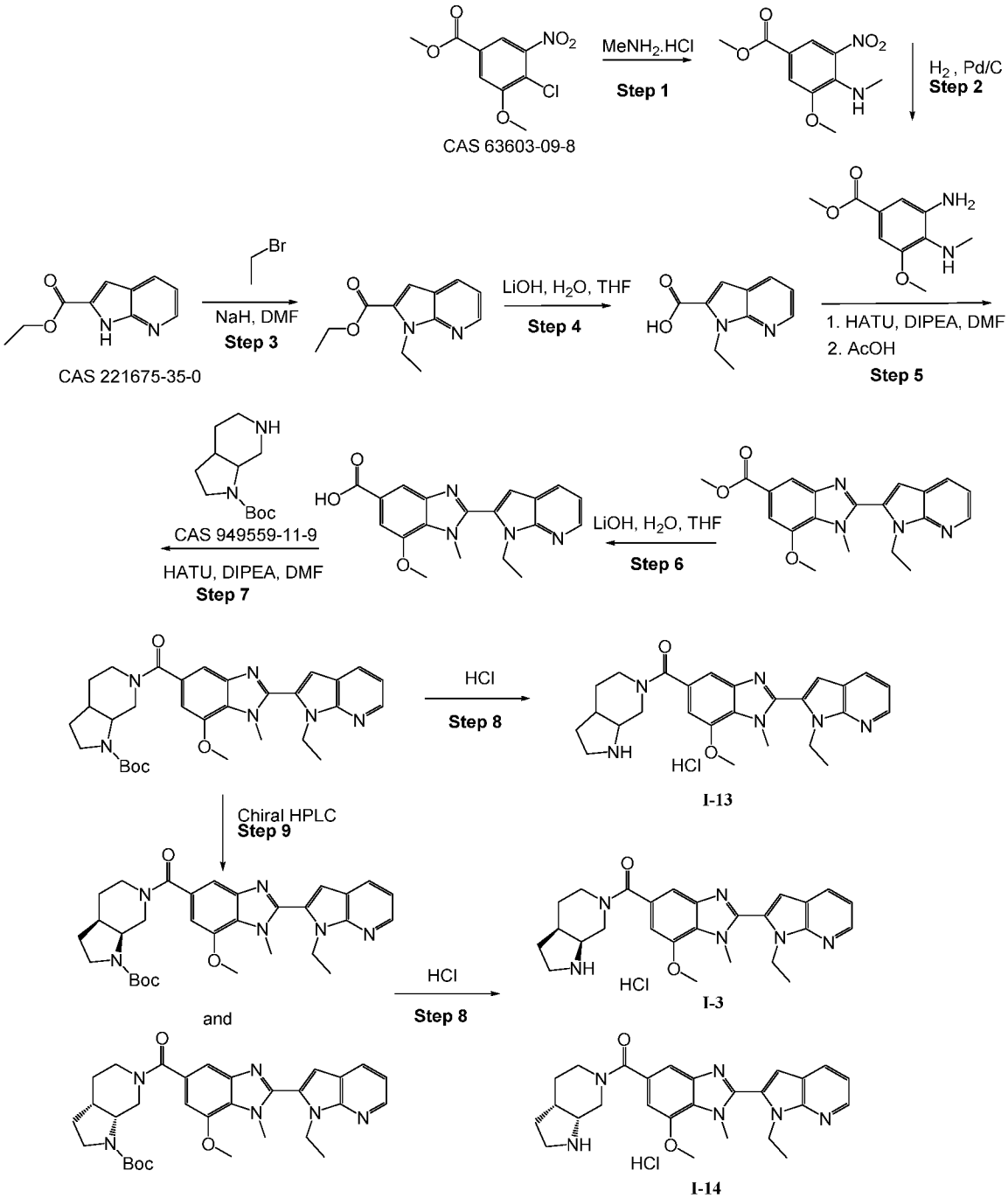
[00101] Method L:

Chiral purity analysis method
Column: Amy-C 4.6mm x 250mm, 5um
Flow Rate: 21 ml/min
Injection Vol: 1.0 µL

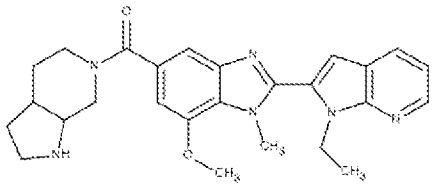
Temp.: Ambient
UV Detection: 254 nm
Isocratic Conditions 4:6 heptane:ethanol (0.1% v/v ammonia)

[00102] Certain compounds of the present invention were prepared according to Scheme 1, below.

Scheme 1



[00103] Synthesis of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AR0076-002 (EOAI3428370), I-13.



I-13

[00104] Methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate EV-AR0065-002 – step 1

[00105] To a stirred solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (CAS 63603-09-8, 2.0 g, 8.14 mmol) in DMF (10 ml) was added K_2CO_3 (99%, 1.37 g, 9.81 mmol). To this solution was added methanamine hydrochloride (1:1) (0.62 g, 9.18 mmol) and the mixture was stirred in a sealed tube under nitrogen at 80°C for 16h. The reaction crude was concentrated *in vacuo* and partitioned between DCM (100ml) and water (10ml). The organic layer was washed further with water (2 x 10ml) and saturated aqueous sodium chloride (10ml). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange powder which was purified by flash column chromatography (15-40% EtOAc/heptane) to obtain 1.49 g (76%) of methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate EV-AR0065-002 as an orange powder. LCMS (method D): retention time 1.13min, M/z = 241 (M + 1).

[00106] Methyl 3-amino-5-methoxy-4-(methylamino)benzoate EV-AR0068-002 – step 2

[00107] To a stirred solution of methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate **(EV-AR0065-002**, 1.49 g, 6.20 mmol) in ethanol (100ml) under nitrogen was added 10% Pd/C (0.18 g, 0.17 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Kieselguhr and the filter was washed through with methanol (150ml). The filtrate was concentrated *in vacuo* to afford 1.21 g (89%) of methyl 3-amino-5-methoxy-4-(methylamino)benzoate EV-AR0068-002 as a pale purple powder. LCMS (method D): retention time 0.63min, M/z = 211 (M + 1).

[00108] Ethyl 1-ethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylate EV-AQ1957-001 – step 3

[00109] Sodium hydride (60%, 59 mg, 1.47 mmol) was added portion wise to a stirred suspension of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 221675-35-0, 200 mg, 1.05 mmol) in DMF (5 ml) at room temperature. The mixture was stirred for 20 minutes then ethyl iodide (197 mg, 1.26 mmol) was added. The reaction mixture was stirred for 20h. The

mixture was partitioned between EtOAc (20ml) and water (20ml). The aqueous layer was extracted further with EtOAc (1 x 20ml), the combined organics were washed with water (20ml) and evaporated to dryness. The crude product was purified by flash column chromatography (0-50% EtOAc/heptane) to obtain 135 mg (57.1%) of ethyl 1-ethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylate EV-AQ1957-001 as a colourless oil. LCMS (method D): retention time 1.18min, M/z = 219 (M + 1).

[00110] 1-Ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AQ1960-001 – **step 4**

[00111] To a stirred solution of ethyl 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (EV-AQ1957-001, 135 mg, 0.62 mmol) in THF (2 ml) was added lithium hydroxide (74 mg, 3.09 mmol) in water (2 ml). The mixture was stirred at 50°C for 2.5h. The mixture was acidified with 1M HCl (3 ml) and extracted with DCM (2 x 5 ml). The combined organics were washed with water and evaporated to dryness to give 120 mg (99 %) of 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AQ1960-001 as a white solid. LCMS (method D): retention time 0.92min, M/z = 191 (M + 1).

[00112] Methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AR0070-003 – **step 5**

[00113] To a stirred solution of 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (EV-AQ1960-001, 120 mg, 0.63 mmol) in DMF (2ml) was added DIPEA (116 µl, 0.70 mmol) followed by HATU (236 mg, 0.62 mmol) and the resulting mixture was stirred at room temperature for 15 minutes. Methyl 3-amino-5-methoxy-4-(methylamino)benzoate (EV-AR0068-002**,** 148 mg, 0.70 mmol) was added and the resulting mixture was stirred at room temperature for 6h. The reaction mixture was concentrated *in vacuo*, dissolved in acetic acid (3ml) and stirred at 70°C for 16h. The solvent was removed *in vacuo* and the remaining material was purified by flash column chromatography (25-40% EtOAc/heptane) to obtain 150 mg (63%) of methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AR0070-003 as a white powder. LCMS (method D): retention time 1.18min, M/z = 365 (M + 1).

[00114] 2-{1-Ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid EV-AR0072-002 – step 6

[00115] To a stirred solution of methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate (EV-AR0070-003, 150 mg, 0.41 mmol) in THF (3ml) was added a solution of lithium hydroxide (30 mg, 1.25 mmol) in water (3ml) and the mixture was stirred at room temperature for 16h. The reaction mixture was concentrated *in vacuo,* taken up in water (5ml) and acidified with 5N HCl (0.5ml) whilst

stirring. The resulting suspension was stirred for 10 minutes then the precipitate was collected by vacuum filtration and dried to obtain 130 mg (89%) of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid EV-AR0072-002 as a white powder. LCMS (method D): retention time 1.03min, M/z = 351 (M + 1).

[00116] Tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0074-002 – step 7

[00117] To a stirred solution of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (EV-AR0072-002**,** 130 mg, 0.37 mmol) in 2:1 DMSO/MeCN (4.5ml) were added DIPEA (65 µl, 0.39 mmol) and HATU (148 mg, 0.39 mmol). The resulting mixture was stirred at room temperature for 15 minutes then tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (CAS 949559-11-9, 88 mg, 0.39 mmol) was added and the mixture was stirred at room temperature for 4h. The reaction mixture was diluted with 3:2 MeCN/water (1.5ml) and purified by preparative HPLC (basic method) to obtain 142 mg (81%) of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0074-002 as a white powder. LCMS (method A): retention time 3.41min, M/z = 559 (M + 1).

[00118] 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AR0076-002 (EOAI3428370), I-13 – step 8

[00119] To a stirred solution of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (EV-AR0074-002, 20 mg, 0.04 mmol) in methanol (1ml) was added 4M HCl in 1,4-dioxane (0.5 ml) and the resulting solution was stirred at room temperature for 4h. The reaction mixture was concentrated *in vacuo* and the residue was freeze-dried from water (4ml) to obtain 13.4 mg (75%) of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole hydrochloride EV-AR0076-002, **I-13**, as a yellow solid. LCMS (method A): retention time 1.80min, M/z = 459 (M + 1).

[00120] Chiral HPLC to obtain tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-001, and tert-butyl

(3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-002, – step 9

[00121] 107mg of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0074-002 were dissolved in ethanol and then purified by chiral HPLC (method E) to obtain 46.6 mg (43.6%) of tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-001 (absolute stereochemistry arbitrarily assigned) and 36.8 mg (33.4%) of tert-butyl (3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-002 (absolute stereochemistry arbitrarily assigned).

EV-AR0090-001, Chiral purity (UV, 254nm): 100%, retention time: 6.30min (method F)

EV-AR0090-002, Chiral purity (UV, 254nm): 97%, retention time: 9.96min (method F)

[00122] 5-[(3aS,7aS)-Octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AR0091-002 (EOAI3432499, absolute stereochemistry arbitrarily assigned) I-3 – step 8

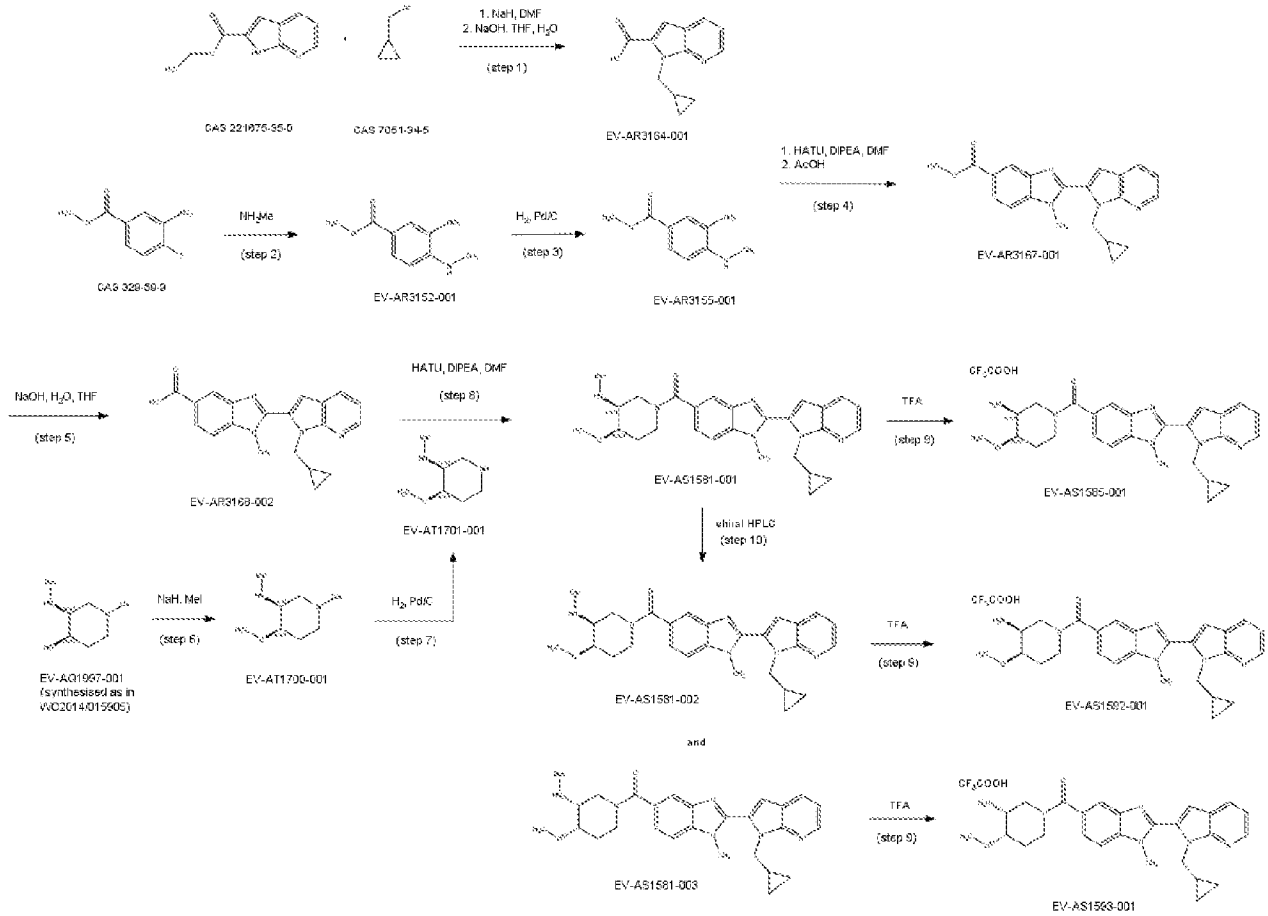
[00123] Tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (EV-AR0090-001**,** 46 mg, 0.08 mmol) was treated as in step 8, Scheme 1 to obtain 40 mg (97%) of 5-[(3aS,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole hydrochloride EV-AR0091-002, **I-3**, as an orange powder. LCMS (method A): retention time 1.83min, M/z = 459 (M + 1).

[00124] 5-[(3aR,7aR)-Octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AR0092-002 (EOAI3432500, absolute stereochemistry arbitrarily assigned) I-14 – step 8

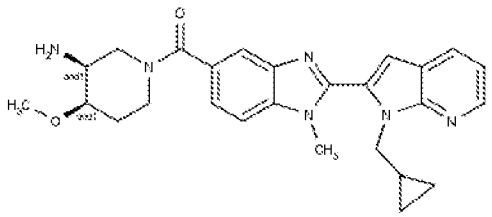
[00125] Tert-butyl (3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate

(EV-AR0090-002, 36.8 mg, 0.07 mmol) was treated as in step 8, Scheme 1 to obtain 31 mg (92.7%) of 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AR0092-002, **I-14**, as an orange powder. LCMS (method A): retention time 1.82min, M/z = 459 (M + 1).

Scheme 2



[00126] Synthesis of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine EV-AS1585-001 (EOAI3436357), I-62



I-62

[00127] 1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AR3164-001 – step 1

[00128] To a stirred solution of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 221675-35-0, 4.40 g, 23.1 mmol) in DMF (50 ml) was added sodium hydride (60%, 1.05 g, 26.3 mmol). The mixture was stirred under nitrogen at room temperature for 45 minutes and (bromomethyl)cyclopropane (CAS 7051-34-5, 2.70 ml, 27.8 mmol) was added. The mixture was stirred at room temperature for 2.5h and the solvent was removed in vacuo. The residue was suspended in THF (40 ml) and 5M aqueous sodium hydroxide (22 ml, 110 mmol) was added. The mixture was stirred at 50°C for 3.5h. Additional THF (20 ml) and 5M aqueous sodium hydroxide (22 ml, 110 mmol) were added and the reaction was stirred at 50°C for 16h. The reaction crude was concentrated in vacuo and water (10 ml) and 5M aqueous hydrochloric acid (100 ml) were added. The solid was filtered off, washed with water (2 x 100 ml) and dried in a vac oven to obtain 3.46 g (69.2%) of 1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AR3164-001** as a white powder. LCMS (method D): retention time 1.03min, M/z = 217 (M + 1).

[00129] Methyl 4-(methylamino)-3-nitrobenzoate EV-AR3152-001 – step 2

[00130] To a stirred solution of methyl 4-fluoro-3-nitrobenzoate (CAS 329-59-9, 5.00 g, 25.1 mmol) in DMF (50 ml) was added methanamine hydrochloride (1:1) (2.00 g, 29.6 mmol) and potassium carbonate (4.50 g, 32.6 mmol). The mixture was stirred at room temperature under nitrogen for 18h. The reaction crude was concentrated in vacuo and the residue was partitioned between in EtOAc (350 ml) and 1N aqueous hydrochloric acid (250 ml). The organic layer was washed further with 1N aqueous hydrochloric acid (150 ml) and saturated aqueous sodium chloride (100 ml). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to obtain 5.30 g (quantitative) of methyl 4-(methylamino)-3-nitrobenzoate **EV-AR3152-001** as a yellow powder. LCMS (method D): retention time 1.07min, M/z = 211 (M + 1).

[00131] Methyl 3-amino-4-(methylamino)benzoate EV-AR3155-001 – step 3

[00132] To a stirred solution of methyl 4-(methylamino)-3-nitrobenzoate (**EV-AR3152-001**, 5.30 g, 25.2 mmol) in ethanol (100 ml) under nitrogen was added 10% Pd/C (1.30 g, 0.05 mmol). The reaction was then placed under a hydrogen atmosphere and stirred at room temperature for 4h. The reaction mixture was diluted with methanol (100 ml) and Kieselguhr was added. The mixture was stirred at room temperature for 10 minutes and filtered under vacuum. The filter was washed with methanol (3 x 50 ml) and the filtrate was concentrated in vacuo to obtain 4.39g (96.6%) of methyl 3-amino-4-(methylamino)benzoate **EV-AR3155-001** as a brown powder. LCMS (method D): retention time 0.75min, M/z = 181 (M + 1).

[00133] Methyl 2-[1- (cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-

1H-1,3-benzodiazole- 5-carboxylate EV-AR3167-001 – step 4

[00134] To a solution of 1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AR3164-001**, 2.20 g, 10.2 mmol) in dry DMF (40 ml) was added HATU (4.95 g, 12.8 mmol) and DIPEA (2.25 ml, 12.8 mmol). The mixture was stirred at room temperature for 1h then methyl 3-amino-4-(methylamino)benzoate (**EV-AR3155-001**, 2.02 g, 11.2 mmol) was added. The mixture was stirred at room temperature for 16h. The solvent was removed in vacuo and the residue was dissolved in acetic acid and stirred at 80°C for 2h, then 85°C for 30 minutes then 90°C for 1h. The solvent was removed in vacuo and the crude material was purified by flash column chromatography (12-100% EtOAc/heptane) to obtain 3.08 g (83.2%) of methyl 2-[1- (cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole- 5-carboxylate **EV-AR3167-001** as a pink powder. LCMS (method D): retention time 1.20min, M/z = 361 (M + 1).

[00135] 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid EV-AR3168-002 – step 5

[00136] To a suspension of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AR3167-001**, 3.08 g, 8.46 mmol) in methanol (60 ml) was added 2M aqueous sodium hydroxide (30 ml, 60.0 mmol). The mixture was then stirred at 50°C for 2h. The reaction was allowed to cool to room temperature and the solvent was removed in vacuo. Water (50 ml) was added followed by 2M aqueous HCl until pH 3 was achieved. The mixture was stirred for 15 minutes and filtered through a sinter. The solid was washed with water (2 x 50 ml) and air-dried for 64h to afford 1.81g (61.2%) of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR3168-001** as a beige solid. LCMS (method D): retention time 1.05min, M/z = 347 (M + 1). The filtrate was further acidified by addition of 2M aqueous HCl until a precipitate started to form. The mixture was allowed to stand for 1h and filtered through a sinter. The solid was washed with water (2 x 20 ml) and air-dried under vacuum for 3h to obtain 460 mg of (15.7%) 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR3168-002** as an off white powder LCMS (method D): retention time 1.06min, M/z = 347 (M + 1).

[00137] Benzyl (3S,4R)-3-{[(tert-butoxy)carbonyl]amino}-4-methoxypiperidine-1-carboxylate EV-AT1700-001 – step 6

[00138] To a stirred solution of benzyl (3S,4R)-3-{[(tert-butoxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate (**EV-AQ1997-001**, synthesised as in WO2014/015905, 450 mg, 1.28 mmol) in anhydrous THF (10 ml) at 0°C under nitrogen was added sodium hydride

(60%, 62 mg, 1.54 mmol). The mixture was stirred at 0°C for 30 minutes then iodomethane (83.94 µl, 1.35 mmol) was added and the mixture was stirred at room temperature for 16h. Saturated aqueous ammonium chloride (2 ml) was added and the mixture was stirred for 10 minutes. The mixture was concentrated in vacuo and partitioned between water (50 ml) and DCM (50 ml). The aqueous layer was extracted further with DCM (2 x 50 ml) and the combined organics were concentrated in vacuo. The crude product was purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 248 mg (52.9%) of benzyl (3S,4R)-3-{[(tert-butoxy)carbonyl]amino}-4-methoxypiperidine-1-carboxylate **EV-AT1700-001** as a colourless oil. LCMS (method D): retention time 1.29min, M/z = 387 (M + 23).

[00139] Tert-butyl N-[(3S,4R)-4-methoxypiperidin-3-yl]carbamate EV-AT1701-001 – step 7

[00140] To a stirred solution of benzyl (3S,4R)-3-{[(tert-butoxy)carbonyl]amino}-4-methoxypiperidine-1-carboxylate (**EV-AT1700-001**, 235 mg, 0.64 mmol) in ethanol (10 ml) under nitrogen was added 10% Pd/C (34 mg, 0.03 mmol). The reaction was placed under a hydrogen atmosphere and stirred at room temperature for 16h. The reaction mixture was filtered through Kieselguhr and the filter was washed through with ethanol (20 ml). The filtrate was concentrated in vacuo to obtain 135 mg (68.0%) of tert-butyl N-[(3S,4R)-4-methoxypiperidin-3-yl]carbamate **EV-AT1701-001** as a colourless oil. LCMS (method D): retention time 0.79min, M/z = 231 (M + 1).

[00141] Tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate EV-AS-1581-001 – step 8

[00142] To a stirred solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AR3168-002**, 150 mg, 0.43 mmol) in DMF (5 ml) was added HATU (197.6 mg, 0.52 mmol) followed by DIPEA (0.15 ml, 0.87 mmol). The mixture was stirred for 1h then tert-butyl N-[(3S,4R)-4-methoxypiperidin-3-yl]carbamate (**EV-AT1701-001**, 99.7 mg, 0.43 mmol) was added. The reaction was stirred at room temperature for 16h. The solvent was removed in vacuo and the residue was partitioned between DCM (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml). The aqueous layer was extracted with DCM (20 ml) and the combined organics were washed with water (20 ml) and saturated aqueous sodium chloride (20 ml). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil which was purified by preparative HPLC (basic method) to obtain 205 mg (82.9%) of tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-

benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate **EV-AS1581-001** as a white crystalline solid. LCMS (method A): retention time 3.36min, M/z = 559 (M + 1).

[00143] 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine EV-AS1585-001 (EOAI3436357) I-62 – step 9

[00144] To a stirred solution of tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate (**EV-AS1581-001**, 30 mg, 0.05 mmol) in DCM (2 ml) was added trifluoroacetic acid (1 ml, 13.0 mmol). The mixture was stirred at room temperature for 3h. The solvent was removed under a stream of nitrogen and the residue was freeze-dried from acetonitrile:water (1:1, 4 ml) to obtain 9.6 mg (96.3%) of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine trifluoroacetic acid **EV-AS1585-001**, **I-62**, as a white powder. LCMS (method A): retention time 1.86min, M/z = 459 (M + 1).

[00145] Chiral HPLC to obtain tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate EV-AS1581-002 and tert-butyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3- yl]carbamate EV-AS1581-003 – step 10

[00146] 90.4mg of tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate **EV-AS1581-001** were dissolved in methanol and then purified by chiral HPLC (method K) to obtain 36.2 mg of tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate **EV-AS1581-002** (absolute stereochemistry arbitrarily assigned) and 34.4 mg of tert-butyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate **EV-AS1581-003** (absolute stereochemistry arbitrarily assigned).

[00147] EV-AS1581-002 Chiral purity (UV, 254nm): 100%, retention time: 7.58min (method L)

[00148] EV-AS1581-003 Chiral purity (UV, 254nm): 100%, retention time: 10.07min (method L)

[00149] (3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine EV-AS1592-001 (EOAI3438020, absolute stereochemistry arbitrarily assigned) I-64 – step 9

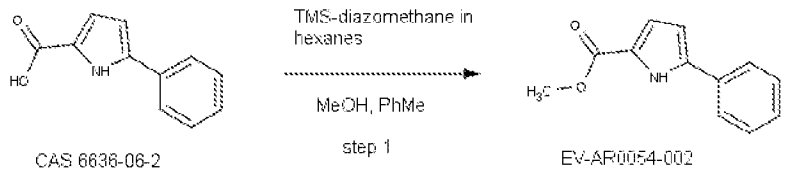
[00150] Tert-butyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-yl]carbamate (**EV-AS1581-002,** 36.2 mg, 0.07 mmol) was treated as in step 9, Scheme 1 to obtain 37.1 mg (64.6%) of (3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine trifluoroacetic acid **EV-AS1592-001**, **I-64**, as a white powder. LCMS (method A): retention time 1.86min, M/z = 459 (M + 1).

[00151] (3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine EV-AS1593-001 (EOAI3437979, absolute stereochemistry arbitrarily assigned) I-65 – step 9

[00152] Tert-butyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)- 1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3- yl]carbamate (**EV-AS1581-003**, 34.4 mg, 0.06 mmol) was treated as in step 9, Scheme 1 to obtain 33.6 mg (94.3%) of (3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-methoxypiperidin-3-amine trifluoroacetic acid **EV-AS1593-001**, **I-65**, as a white powder. LCMS (method A): retention time 1.86min, M/z = 459 (M + 1).

[00153] 5-[(3aR,7aR)-Octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-5-phenyl-1H-pyrrol-2-yl]-1-methyl-1H-1,3-benzodiazole EV-AS5709-003 (EOAI3434977) I-116 and 5-[(3aS,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-5-phenyl-1H-pyrrol-2-yl]-1-methyl-1H-1,3-benzodiazole **EV-AS5710-003 (EOAI3434978) I-117** were synthesised according to the procedures described in Scheme 2 via synthesis of methyl 5-phenyl-1H-pyrrole-2-carboxylate **EV-AR0054-002** described in Scheme 2.1:

[00154] Scheme 2.1

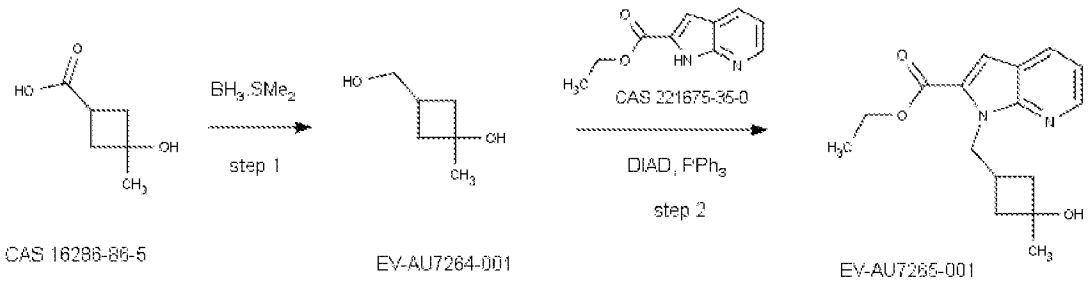


[00155] To a stirred solution of 5-phenyl-1H-pyrrole-2-carboxylic acid (CAS 6636-06-2,

500 mg, 2.67 mmol) in toluene (10 ml) and methanol (3 ml) was added 2M (diazomethyl)(trimethyl)silane in hexane (2 ml) and the mixture was stirred under nitrogen at room temperature for 30 minutes. To the reaction mixture was added acetic acid (1 ml) and the mixture was concentrated in vacuo to afford 530 mg (99%) of methyl 5-phenyl-1H-pyrrole-2-carboxylate **(EV-AR0054-002)** as a pale yellow powder. LCMS (method D): retention time 1.14min, M/z = 202 (M + 1).

[00156] 3-[(2-{5-[(3R)-3-Aminopiperidine-1-carbonyl]-1-methyl-1H-1,3-benzodiazol-2-yl}-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl]-1-methylcyclobutan-1-ol EV-AU7275-001 (EOAI3455096) I-110 was synthesised according to the procedures described in Scheme 1 via synthesis of ethyl 1-[(3-hydroxy-3-methylcyclobutyl)methyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU7265-001** described in Scheme 2.2:

[00157] Scheme 2.2



[00158] 3-(Hydroxymethyl)-1-methylcyclobutan-1-ol EV-AU7264-001 – step 1

[00159] To a stirred solution of 3-hydroxy-3-methylcyclobutanecarboxylic acid (CAS 16286-86-5, 950 mg, 7.30 mmol) in THF (30 ml) was added $BH_3.Me_2S$ (4.96 ml, 9.93 mmol) drop-wise at -78°C. The reaction was allowed to warm up to room temperature and stirred for 16h. The reaction was quenched with anhydrous MeOH (20 ml). The resulting mixture was reduced to dryness to obtain 200 mg (23.2%) of 3-(hydroxymethyl)-1-methylcyclobutan-1-ol **EV-AU7264-001** as a colourless oil.

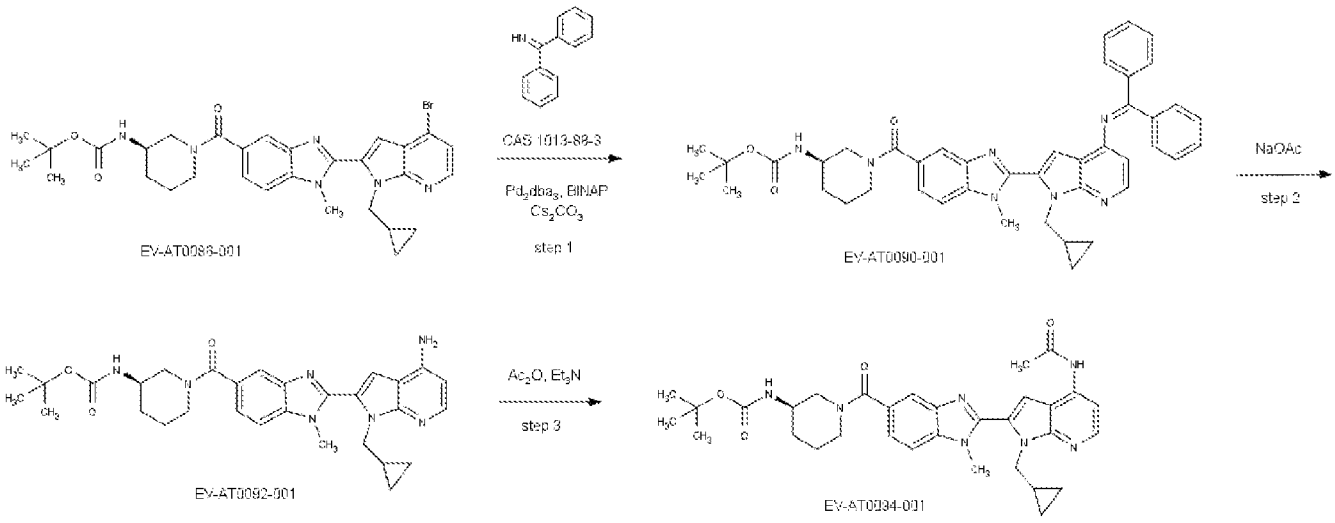
[00160] 1-[(3-Hydroxy-3-methylcyclobutyl)methyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AU7265-001 – step 2

[00161] To a stirred solution of DIAD (1.10 ml, 5.26 mmol) in dry THF (10 ml) under an atmosphere of nitrogen was added a solution of triphenylphosphine (1.39 g, 5.26 mmol) in THF (10 ml) at -20 °C. The reaction mixture was stirred for 30 minutes then a solution of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 221675-35-0, 500 mg, 2.63 mmol) in THF (10 ml) was added. Stirring at -20 °C was continued for a further 30 min. After this

period a solution of 3-(hydroxymethyl)-1-methylcyclobutan-1-ol (**EV-AU7264-001**, 458 mg, 3.94 mmol in THF (5 ml) was added drop-wise at -20 °C, the reaction mixture was allowed to warm to room temperature and stirred for 16h. The mixture was concentrated in vacuo and the residue purified by flash column chromatography (5-80% EtOAc/heptane) to obtain 200 mg (23.2%) of ethyl 1-[(3-hydroxy-3-methylcyclobutyl)methyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU7265-001** as a pale yellow oil. LCMS (method D): retention time 1.10min, M/z = 289 (M + 1).

[00162] N-(2-{5-[(3R)-3-Aminopiperidine-1-carbonyl]-1-methyl-1H-1,3-benzodiazol-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)acetamide EV-AT0096-001 (EOAI3447170) I-69 was obtained from Boc-deprotection of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-acetamido-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AT0094-001** obtained according to Scheme 2.3 starting from tert-butyl N-[(3R)-1-{2-[4-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AT0086-001** which was synthesised according to the procedures described in Scheme 2:

[00163] Scheme 2.3



[00164] Tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-[(diphenylmethylidene)amino]-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamateEV-AT0090-001 – step 1

[00165] A mixture of tert-butyl N-[(3R)-1-{2-[4-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AT0086-001**, 150 mg, 0.24 mmol), 1,1-diphenylmethanimine (53.2 mg, 0.29 mmol), Pd_2dba_3 (5.6 mg, 0.006 mmol), BINAP (11.4 mg, 0.018 mmol) and Cs_2CO_3 (111.5 mg, 0.34 mmol) in toluene (4.0 ml) in a sealed tube was stirred at 100°C for 5h. The reaction was cooled to room temperature and filtered through Kieselguhr washing with EtOAc. The filtrate was evaporated to dryness, the remaining residue was dissolved in DMSO and purified by preparative HPLC (basic method) to obtain 128 mg (73.2%) of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-[(diphenylmethylidene)amino]-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AT0090-001** as a yellow solid. LCMS (method D): retention time 1.38min, M/z = 708 (M + 1).

[00166] Tert-butyl N-[(3R)-1-{2-[4-amino-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AT0092-001 – step 2

[00167] Hydroxylamine hydrochloride (1:1) (58.3 mg, 0.839 mmol) and NaOAc (90 mg, 1.09 mmol) were added to a suspension of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-[(diphenylmethylidene)amino]-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AT0090-001**, 120 mg, 0.168 mmol) in MeOH (8 ml). The resulting mixture was stirred at room temperature for 16h. The solvent was removed in vacuo, the remaining residue was dissolved in DMSO and purified by preparative HPLC (basic method) to obtain

[00168] 86 mg (94.3%) of tert-butyl N-[(3R)-1-{2-[4-amino-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AT0092-001** as a white solid. LCMS (method D): retention time 0.95min, M/z = 544 (M + 1).

[00169] Tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-acetamido-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AT0094-001 – step 3

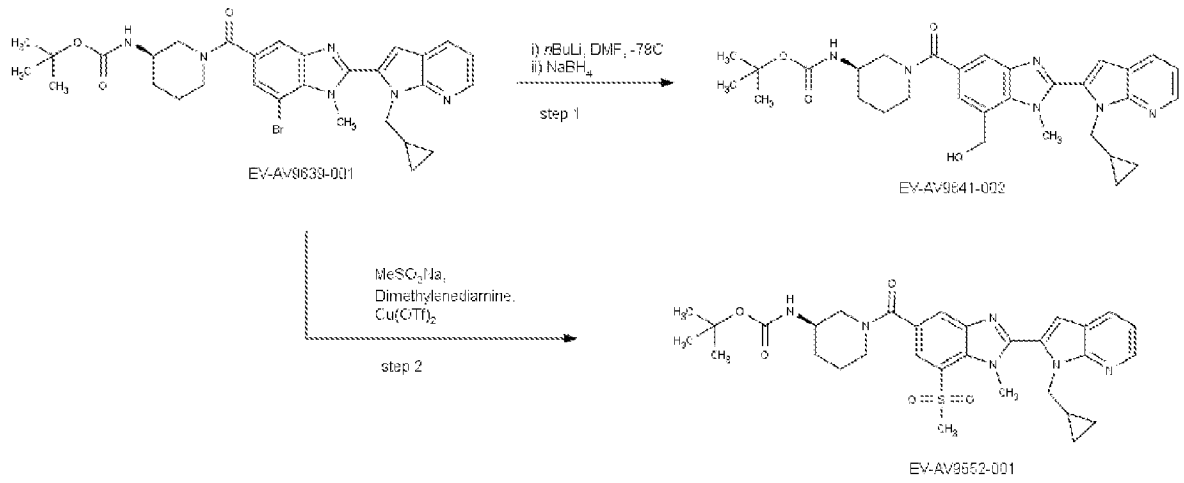
[00170] To a solution of tert-butyl N-[(3R)-1-{2-[4-amino-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AT0092-001**, 80 mg, 0.15 mmol) in DCM (4 ml) was added acetic anhydride (18 mg, 0.18 mmol) and triethylamine (30 mg, 0.29 mmol) at room temperature

and the reaction was stirred at room temperature for 16h then at 50°C for 24h. The solvent was removed in vacuo, the remaining residue was dissolved in DMSO and purified by preparative HPLC (basic method) to obtain 82 mg (95.1%) of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-4-acetamido-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AT0094-001** as a white foam. LCMS (method D): retention time 1.09min, M/z = 586 (M + 1).

[00171] {5-[(3R)-3-aminopiperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-7-yl}methanol EV-AV9647-001 (EOAI3455579) I-128 was synthesised according to the procedures described in Scheme 2 via synthesis of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(hydroxymethyl)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV9641-002** described in Scheme 2.4**.**

[00172] (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methanesulfonyl-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine EV-AV9654-001 (EOAI3455786) I-131 was synthesised according to the procedures described in Scheme 2 via synthesis of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methanesulfonyl-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV9652-001** described in Scheme 2.4**:**

[00173] Scheme 2.4



[00174] Tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(hydroxymethyl)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AV9641-002 – step 1

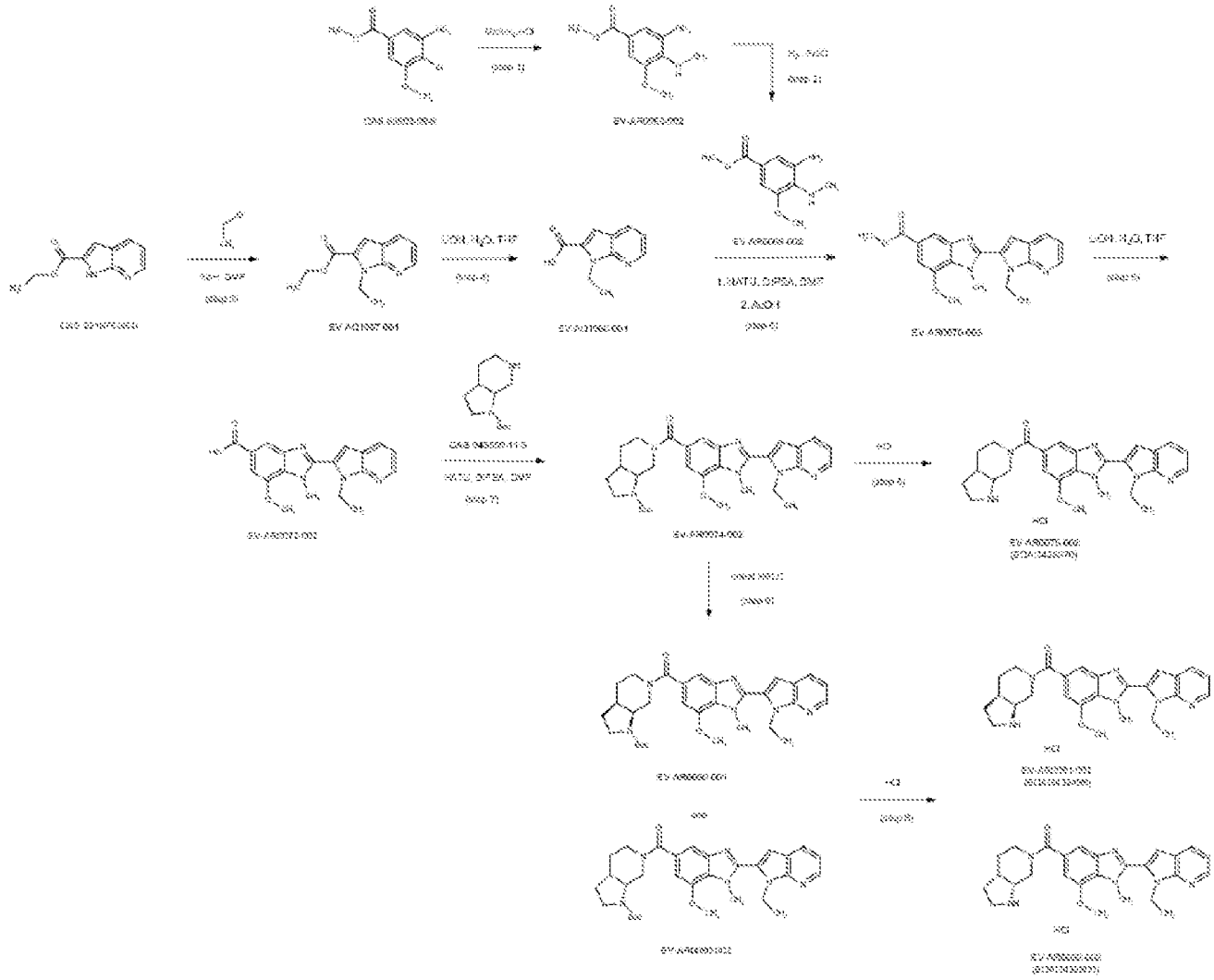
[00175] To a stirred solution of tert-butyl N-[(3R)-1-{7-bromo-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-

yl]carbamate (**EV-AV9639-001**, 50 mg, 0.08 mmol) in anhydrous THF (5.0 ml) at -78°C was added drop-wise n-butyllithium (1.6M in hexane, 0.11 ml, 0.17 mmol). The reaction was stirred at -78°C for 10 minutes and anhydrous DMF (0.01 ml, 0.16 mmol) was added in one portion. The reaction mixture was stirred for 10 minutes at -78°C and allowed to warm to room temperature over 1h. The reaction mixture was then cooled to 0°C and saturated aqueous ammonium chloride solution (1 ml) was added. The biphasic mixture was stirred for 30 minutes and the layers were then separated. The aqueous phase was re-extracted with EtOAc (2 x 3 ml) and the combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was dissolved in methanol (5 ml) at 0°C and sodium borohydride (6 mg, 0.16 mmol) was added. The reaction was stirred for 16h at room temperature and quenched by the addition of water (2 ml) and concentrated *in vacuo*. The residue was partitioned between EtOAc (5 ml) and water (2 ml), the aqueous layer was extracted further with EtOAc (2 x 2 ml) and the combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude was purified by preparative HPLC (basic method) to obtain 20 mg (43%) of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(hydroxymethyl)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV9641-002** as an off-white powder. LCMS (method D): retention time 1.10min, M/z = 559 (M + 1).

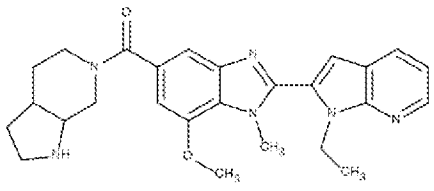
[00176] Tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methanesulfonyl-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AV9652-001 – step 2

[00177] To a pressure tube was added copper(II) triflate (45 mg, 0.12 mmol), sodium methanesulfinate (25 mg, 0.25 mmol) and N,N'-dimethylethane-1,2-diamine (0.03 ml, 0.26 mmol) and DMSO (2.0 ml) under an atmosphere of nitrogen. The deep blue reaction was stirred at room temperature for 5 minutes and tert-butyl N-[(3R)-1-{7-bromo-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AV9639-001**, 75 mg, 0.12 mmol) was added. The vessel was sealed and heated at 120°C for 2h. The cooled reaction was diluted with water (15 ml) and extracted with EtOAc (2 x 10 ml). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (acidic method) to obtain 20 mg (27%) of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methanesulfonyl-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV9652-001** as an off-white powder. LCMS (method D): 1.18min, M/z = 607 (M + 1).

[00178] Scheme 3



[00179] Synthesis of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AR0076-002 (EOAI3428370) I-13



I-13

[00180] Methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate EV-AR0065-002 – step 1

[00181] To a stirred solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (CAS 63603-

09-8, 2.00 g, 8.14 mmol) in DMF (10 ml) was added K_2CO_3 (99%, 1.37 g, 9.81 mmol). To this solution was added methanamine hydrochloride (1:1) (0.62 g, 9.18 mmol) and the mixture was stirred in a sealed tube under nitrogen at 80°C for 16h. The reaction crude was concentrated *in vacuo* and partitioned between DCM (100ml) and water (10ml). The organic layer was washed further with water (2 x 10ml) and saturated aqueous sodium chloride (10ml). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange powder which was purified by flash column chromatography (15-40% EtOAc/heptane) to obtain 1.49 g (76%) of methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate **EV-AR0065-002** as an orange powder. LCMS (method D): retention time 1.13min, M/z = 241 (M + 1).

[00182] Methyl 3-amino-5-methoxy-4-(methylamino)benzoate EV-AR0068-002 – step 2

[00183] To a stirred solution of methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate (**EV-AR0065-002**, 1.49 g, 6.20 mmol) in ethanol (100ml) under nitrogen was added 10% Pd/C (0.18 g, 0.17 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Kieselguhr and the filter was washed through with methanol (150ml). The filtrate was concentrated *in vacuo* to afford 1.21 g (89%) of methyl 3-amino-5-methoxy-4-(methylamino)benzoate **EV-AR0068-002** as a pale purple powder. LCMS (method D): retention time 0.63min, M/z = 211 (M + 1).

[00184] Ethyl 1-ethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylate EV-AQ1957-001 – step 3

[00185] Sodium hydride (60%, 59 mg, 1.47 mmol) was added portion wise to a stirred suspension of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 221675-35-0, 200 mg, 1.05 mmol) in DMF (5 ml) at room temperature. The mixture was stirred for 20 minutes then ethyl iodide (197 mg, 1.26 mmol) was added. The reaction mixture was stirred for 20h. The mixture was partitioned between EtOAc (20ml) and water (20ml). The aqueous layer was extracted further with EtOAc (1 x 20ml), the combined organics were washed with water (20ml) and evaporated to dryness. The crude product was purified by flash column chromatography (0-50% EtOAc/heptane) to obtain 135 mg (57.1%) of ethyl 1-ethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylate **EV-AQ1957-001** as a colourless oil. LCMS (method D): retention time 1.18min, M/z = 219 (M + 1).

[00186] 1-Ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AQ1960-001 – step 4

[00187] To a stirred solution of ethyl 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AQ1957-001**, 135 mg, 0.62 mmol) in THF (2 ml) was added lithium hydroxide (74 mg, 3.09 mmol) in water (2 ml). The mixture was stirred at 50°C for 2.5h, acidified with 1M HCl (3 ml) and extracted with DCM (2 x 5 ml). The combined organics were washed with water and evaporated to dryness to give 120 mg (99 %) of 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AQ1960-001** as a white solid. LCMS (method D): retention time 0.92min, M/z = 191 (M + 1).

[00188] Methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AR0070-003 – step 5

[00189] To a stirred solution of 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AQ1960-001**, 120 mg, 0.63 mmol) in DMF (2ml) was added DIPEA (116 µl, 0.70 mmol) followed by HATU (236 mg, 0.62 mmol) and the resulting mixture was stirred at room temperature for 15 minutes. Methyl 3-amino-5-methoxy-4-(methylamino)benzoate (**EV-AR0068-002,** 148 mg, 0.70 mmol) was added and the resulting mixture was stirred at room temperature for 6h. The reaction mixture was concentrated in vacuo, dissolved in acetic acid (3ml) and stirred at 70°C for 16h. The solvent was removed in vacuo and the remaining material was purified by flash column chromatography (25-40% EtOAc/heptane) to obtain 150 mg (63%) of methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AR0070-003** as a white powder. LCMS (method D): retention time 1.18min, M/z = 365 (M + 1).

[00190] 2-{1-Ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid EV-AR0072-002 – step 6

[00191] To a stirred solution of methyl 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AR0070-003**, 150 mg, 0.41 mmol) in THF (3ml) was added a solution of lithium hydroxide (30 mg, 1.25 mmol) in water (3ml) and the mixture was stirred at room temperature for 16h. The reaction mixture was concentrated in vacuo, taken up in water (5ml) and acidified with 5N HCl (0.5ml) whilst stirring. The resulting suspension was stirred for 10 minutes then the precipitate was collected by vacuum filtration and dried to obtain 130 mg (89%) of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR0072-002** as a white powder. LCMS (method D): retention time 1.03min, M/z = 351 (M + 1).

[00192] Tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0074-002 – step 7

[00193] To a stirred solution of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AR0072-002,** 130 mg, 0.37 mmol) in 2:1 DMSO/MeCN (4.5ml) were added DIPEA (65 µl, 0.39 mmol) and HATU (148 mg, 0.39 mmol). The resulting mixture was stirred at room temperature for 15 minutes then tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (CAS 949559-11-9, 88 mg, 0.39 mmol) was added and the mixture was stirred at room temperature for 4h. The reaction mixture was diluted with 3:2 MeCN/water (1.5ml) and purified by preparative HPLC (basic method) to obtain 142 mg (81%) of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AR0074-002** as a white powder. LCMS (method A): retention time 3.41min, M/z = 559 (M + 1).

[00194] 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AR0076-002 (EOAI3428370) I-13 – step 8

[00195] To a stirred solution of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (**EV-AR0074-002**, 20 mg, 0.04 mmol) in methanol (1ml) was added 4M HCl in 1,4-dioxane (0.5 ml) and the resulting solution was stirred at room temperature for 4h. The reaction mixture was concentrated in vacuo and the residue was freeze-dried from water (4ml) to obtain 13.4 mg (75%) of 2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole hydrochloride **EV-AR0076-002**, **I-13**, as a yellow solid. LCMS (method A): retention time 1.80min, M/z = 459 (M + 1).

[00196] Chiral HPLC to obtain tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-001 and tert-butyl (3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AR0090-002 – step 9

[00197] 107mg of tert-butyl 6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AR0074-002** were dissolved in ethanol and then purified by chiral HPLC (method E) to obtain 46.6 mg (43.6%) of tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]-pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AR0090-001** (absolute stereochemistry arbitrarily assigned) and 36.8 mg (33.4%) of tert-butyl (3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]-pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AR0090-002** (absolute stereochemistry arbitrarily assigned).

[00198] **EV-AR0090-001** Chiral purity (UV, 254nm): 100%, retention time: 6.30min (method F)

[00199] **EV-AR0090-002** Chiral purity (UV, 254nm): 97%, retention time: 9.96min (method F)

[00200] **5-[(3aS,7aS)-Octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AR0091-002 (EOAI3432499, absolute stereochemistry arbitrarily assigned) I-3 – step 8**

[00201] Tert-butyl (3aR,7aS)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (**EV-AR0090-001,** 46 mg, 0.08 mmol) was treated as in step 8, Scheme 2 to obtain 40 mg (97%) of 5-[(3aS,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole hydrochloride **EV-AR0091-002**, **I-3**, as an orange powder. LCMS (method A): retention time 1.83min, M/z = 459 (M + 1).

[00202] **5-[(3aR,7aR)-Octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AR0092-002 (EOAI3432500, absolute stereochemistry arbitrarily assigned) I-14 – step 8**

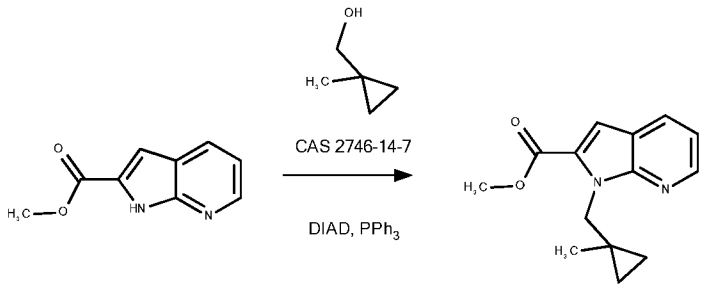
[00203] Tert-butyl (3aS,7aR)-6-(2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (**EV-AR0090-002**, 36.8 mg, 0.07 mmol) was treated as in step 8, Scheme 2 to obtain 31 mg (92.7%) of 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-{1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3

-benzodiazole **EV-AR0092-002**, **I-14**, as an orange powder. LCMS (method A): retention time 1.82min, M/z = 459 (M + 1).

Special cases for Scheme 3

[00204] (3S,5S)-5-Fluoro-1-(7-methoxy-1-methyl-2-{1-[(1-methylcyclopropyl)methyl]-1H-pyrrolo[2,3-b]pyridin-2-yl}-1H-1,3-benzodiazole-5-carbonyl)piperidin-3-amine **EV-AV3056-001 (EOAI3454078) I-93** was synthesised according to the procedures described in Scheme 2 via synthesis of ethyl 1-[(1-methylcyclopropyl)methyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3682-002** described in Scheme 3.1:

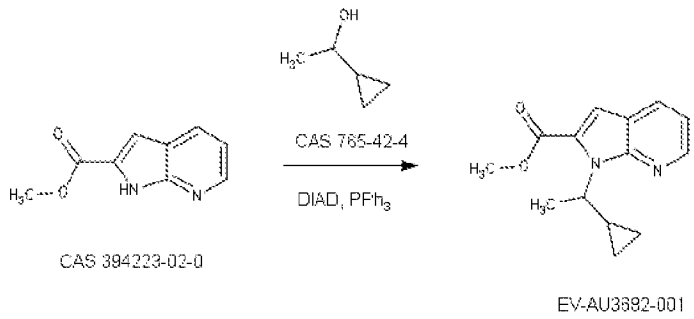
[00205] Scheme 3.1



[00206] To a solution of DIAD (0.44 ml, 2.10 mmol) in dry THF (5 ml) under nitrogen at -20°C was added a solution of triphenylphosphine (557 mg, 2.10 mmol) in THF (5 ml) and the reaction mixture was stirred for 30 minutes. To the reaction mixture was added a solution of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 394223-02-0, 200 mg, 1.05 mmol) in THF (7.5 ml) at -20°C and the reaction mixture was stirred at -20°C for a further 30 minutes. (1-Methylcyclopropyl)methanol (CAS 2746-14-7, 0.15 ml, 1.58 mmol) was added dropwise at -20 °C and the reaction mixture was allowed to warm to room temperature and stirred for 1 h 15min. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (0-100% EtOAc) to obtain 240 mg (87%) of ethyl 1-[(1-methylcyclopropyl)methyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3682-002** as a yellow gum. LCMS (method D): retention time 1.35min, M/z = 259 (M + 1).

[00207] (3R)-1-(2-{1-[(1R)-1-cyclopropylethyl]-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)piperidin-3-amine EV-AV3097-001 (EOAI3454812) I-101 and **(3R)-1-(2-{1-[(1S)-1-cyclopropylethyl]-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl)piperidin-3-amine EV-AV3098-001 (EOAI3454813) I-102** were synthesised according to the procedures described in Scheme 2 via synthesis of ethyl 1-(1-cyclopropylethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3682-001** described in Scheme 3.2:

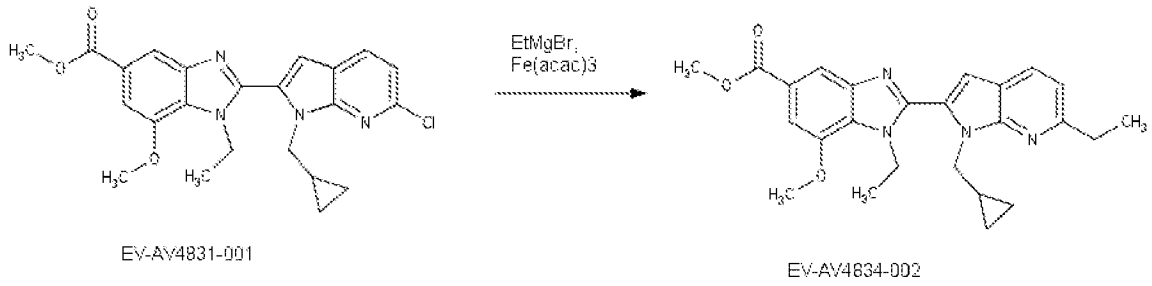
[00208] Scheme 3.2



[00209] To a solution of DIAD (0.44 ml, 2.1 mmol) in dry THF (5 ml) under nitrogen at -20 °C was added a solution of triphenylphosphine (557.18 mg, 2.1 mmol) in THF (5 ml) and the reaction mixture was stirred for 30 minutes. To the reaction mixture was added a solution of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (CAS 394223-02-0, 200 mg, 1.05 mmol) in THF (7.5 ml) at -20°C and the reaction mixture was stirred at -20 °C for a further 30 minutes. 1-Cyclopropylethan-1-ol (CAS 765-42-4, 0.15 mL, 1.58 mmol) was added dropwise at -20 °C and the reaction mixture was allowed to warm to room temperature and stirred for 1h 15 minutes. The reaction mixture was concentrated in vacuo and purified by purified using by flash column chromatography (0-100% EtOAc) to obtain 205 mg (75%) of ethyl 1-(1-cyclopropylethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3682-001** as a yellow gum. LCMS (method D): retention time 1.35min, M/z = 259 (M + 1).

[00210] (3R)-1-{2-[1-(cyclopropylmethyl)-6-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine EV-AV4845-001 (EOAI3454972) I-105 was synthesised according to the procedures described in Scheme 2 via synthesis of methyl 2-[1-(cyclopropyl methyl)-6-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3- benzodiazole-5- carboxylate **EV-AV4834-002** described in Scheme 3.3:

[00211] Scheme 3.3

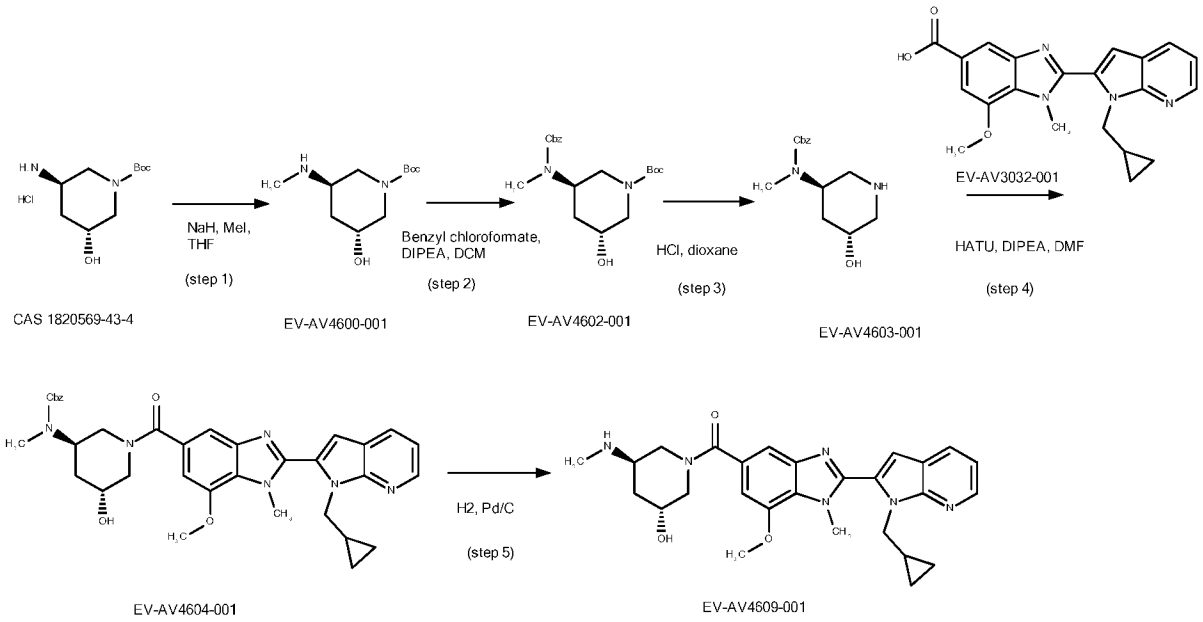


EV-AV4831-001 EV-AV4834-002

[00212] To a solution of methyl 2-[6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AV4831-001** (synthesised according to Scheme 2, 150 mg, 0.31 mmol) in anhydrous THF (5 ml) was added $Fe(acac)_3$ (6 mg, 0.02 mmol) and NMP (150 µl). A solution of ethylmagnesium bromide (0.9M in THF, 411 µl, 0.37 mmol) was added drop-wise over 1 minute and the reaction mixture stirred at room temperature for 3h. Further $Fe(acac)_3$ (6 mg, 0.02 mmol) and ethylmagnesium bromide (0.9M in THF, 411 µl, 0.37 mmol) were added and the reaction mixture was stirred for 16h at room temperature. The reaction mixture was quenched by the addition of 1M HCl (~1 ml) and extracted with DCM (3 x 15 ml). The combined organics were washed with brine (20 ml), dried over magnesium sulphate and concentrated in vacuo. The crude residue was purified by preparative HPLC (acidic method) to obtain 81 mg (55%) of methyl 2-[1-(cyclopropyl methyl)-6-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3- benzodiazole-5- carboxylate **EV-AV4834-002** as a colourless glass. LCMS (method A): retention time 4.59min, M/z = 433 (M + 1).

[00213] 1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methylamino)piperidin-3-ol EV-AV4609-001 (EOAI3451154) I-77 was synthesised according to Scheme 3.4:

[00214] Scheme 3.4



[00215] Rel-tert-butyl (3R,5R)-3-hydroxy-5-(methylamino)piperidine-1-carboxylate EV-AV4600-001 – step 1 Note: starting material and products are all trans-racemate.

[00216] To a solution of rel-tert-butyl (3R,5R)-3-amino-5-hydroxypiperidine-1-carboxylate hydrochloride (100 mg, 0.40 mmol) in anhydrous THF (5 ml) at 0 °C, was added sodium hydride (60%, 35 mg, 0.87 mmol) and the mixture was stirred at 0 °C for 30 minutes. To the reaction mixture was added methyl iodide (26 µl, 0.41 mmol) and the mixture was allowed to warm to room temperature and left stirring for 16h. The reaction mixture was partitioned between ethyl acetate (20 ml) and water (20 ml). The aqueous extract was washed with further ethyl acetate (2 x 15 ml), the combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuo to obtain 91 mg (quant) of rel-tert-butyl (3R,5R)-3-hydroxy-5-(methylamino)piperidine-1-carboxylate **EV-AV4600-001** as a yellow oil. LCMS (method D): retention time 0.23min, M/z = 231 (M + 1).

[00217] Rel-tert-butyl (3R,5R)-3-{[(benzyloxy)carbonyl](methyl)amino}-5-hydroxypiperidine-1-carboxylate EV-AV4602-001 – step 2 Note: starting materials and products are trans-racemate

[00218] To a stirred solution of rel-tert-butyl (3R,5R)-3-hydroxy-5-(methylamino)piperidine-1-carboxylate **EV-AV4600-001** (91 mg, 0.40 mmol) in DCM (2 ml) was added DIPEA (103 µl, 0.59 mmol) followed by benzyl chloroformate (56 µl, 0.40 mmol). The reaction mixture was stirred for 1.5h, diluted with DCM (20 ml) and washed with water (15 ml). The organic extract was dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (0-

100% EtOAc/heptane) to obtain 58 mg (18%) of rel-tert-butyl (3R,5R)-3-{[(benzyloxy)carbonyl](methyl)amino}-5-hydroxypiperidine-1-carboxylate **EV-AV4602-001** as a transparent oil. LCMS (method D): retention time 1.12min, M/z = 387 (M + Na).

[00219] Rel-benzyl N-[(3R,5R)-5-hydroxypiperidin-3-yl]-N-methylcarbamate hydrochloride EV-AV4603-001 – step 3 Note: starting materials and products are trans-racemate

[00220] To a solution of rel-tert-butyl (3R,5R)-3-{[(benzyloxy)carbonyl](methyl)amino}-5-hydroxypiperidine-1-carboxylate **EV-AV4602-001** (58 mg, 0.16 mmol) in dioxane (1 ml) under nitrogen was added 4M HCl in dioxane (0.16 ml, 0.64 mmol). The mixture was left standing at room temperature for 16h. To the reaction mixture was added methanol (0.5 ml) and 4M HCl in dioxane (0.16 ml, 0.64 mmol) and the mixture was left standing at room temperature for 4h. The reaction mixture was then concentrated in *vacuo* to obtain 59 mg (43%) of rel-benzyl N-[(3R,5R)-5-hydroxypiperidin-3-yl]-N-methylcarbamate hydrochloride **EV-AV4603-001** as an off-white solid. LCMS (method D): retention time 0.76min, M/z = 265 (M + 1).

[00221] Benzyl N-[(3R,5R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-hydroxypiperidin-3-yl]-N-methylcarbamate EV-AV4604-001 – step 4

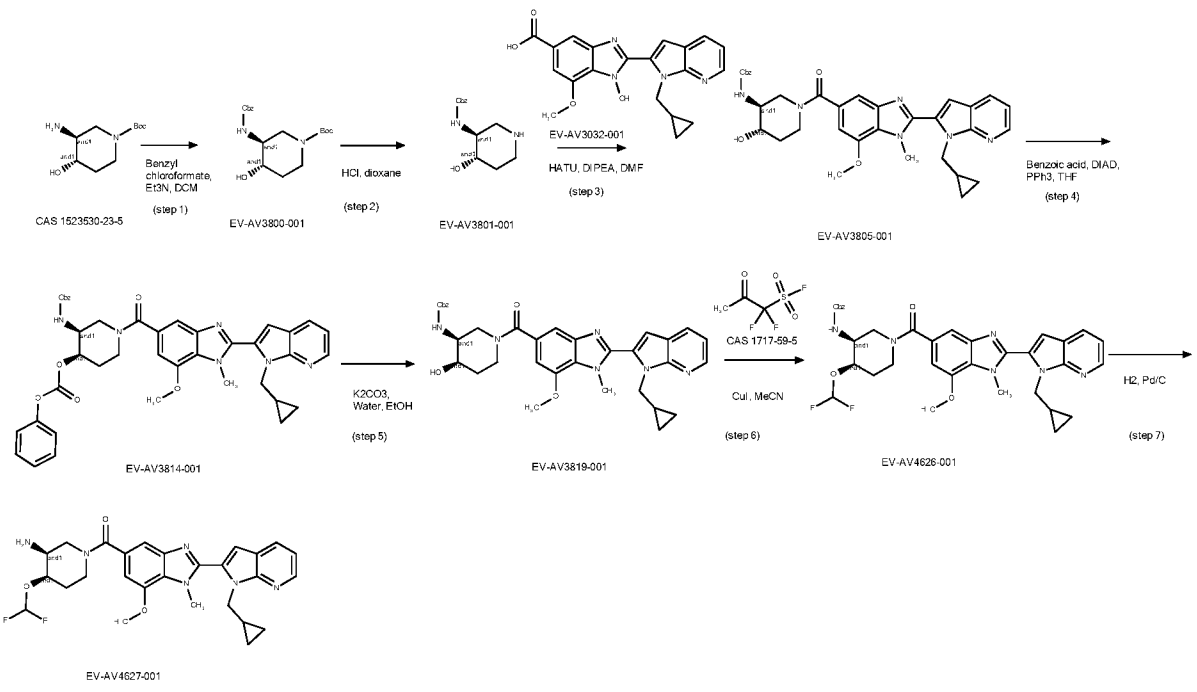
[00222] To a solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AU3032-001** (synthesised according to Scheme 2, 60 mg, 0.16 mmol) in DMF (3 ml) was added DIPEA (31 µl, 0.18 mmol), HATU (67 mg, 0.18 mmol) and rel-benzyl N-[(3R,5R)-5-hydroxypiperidin-3-yl]-N-methylcarbamate hydrochloride **EV-AV4603-001** (48 mg, 0.16 mmol) and the reaction mixture was stirred at room temperature for 1h. The mixture was then partitioned between EtOAc (40 ml) and water (40 ml) and the organic extract was dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by preparative HPLC (basic method) to obtain 22 mg (22%) of benzyl N-[(3R,5R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-hydroxypiperidin-3-yl]-N-methylcarbamate **EV-AV4604-001** as an off-white solid. LCMS (method D): retention time 1.17min, M/z = 623 (M + 1).

[00223] Rel-(3R,5R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methylamino)piperidin-3-ol hydrochloride EV-AV4609-001, I-77 – step 5 Note: starting materials and products are trans racemate

[00224] To a stirred solution of rel-benzyl N-[(3R,5R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-hydroxypiperidin-3-yl]-N-methylcarbamate **EV-AV4604-001** (22 mg, 0.04 mmol) in ethanol (1 ml) under nitrogen was added 10% Pd/C (2.3 mg, 0.001 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through a glass fibre sinter and the filtrate was then treated with 1.25M HCl in ethanol (0.2 ml). The mixture was left standing at room temperature for 30 minutes, concentrated in vacuo and freeze dried to obtain 10.2 mg (52%) of rel-(3R,5R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methylamino)piperidin-3-ol hydrochloride **EV-AV4609-001**, **I-77**, as an off-white powder. LCMS (method A): retention time 1.93min, M/z = 489 (M + 1).

[00225] **1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-amine EV-AV4627-001 (EOAI3452884) I-86** was synthesised according to Scheme 3.5:

[00226] **Scheme 3.5**



[00227] **Rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate EV-AV3800-001 – step 1** (trans racemate)

[00228] To a solution of rac-tert-butyl (3R,4R)-3-amino-4-hydroxypiperidine-1-carboxylate (CAS 1523530-23-5, 750 mg, 3.47 mmol) in DCM (10 ml) at 0 °C was added

triethylamine (1.45 ml, 10.4 mmol) and benzyl chloroformate (0.59 ml, 4.16 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and then allowed to warm to room temperature and stirred for a further 4h. The reaction mixture was then quenched with water (10 ml) and extracted with DCM (3 x 10 ml). The combined organic fractions were dried with sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified was purified by flash column chromatography (20-80% EtOAc/heptane) to obtain 615 mg (52%) of rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate **EV-AV3800-001** as a white solid (trans-racemate). LCMS (method D): retention time 1.08min, M/z = 373 (M + Na).

[00229] rac-Benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate EV-AV3801-001 – step 2 (trans racemate)

[00230] Rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate **EV-AV3800-001** (610 mg, 1.74 mmol) was dissolved in dioxane (4M in dioxane, 8.7 ml) and left to stir at room temperature for 1h. The reaction mixture was concentrated in vacuo to obtain 408 mg (82%) of rac-benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate **EV-AV3801-001** as a white solid. LCMS (method D): retention time 0.48min, M/z = 251 (M + 1).

[00231] rac-Benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate EV-AV3805-001 – step 3 (trans racemate)

[00232] To a solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AV3032-001** (535 mg, 1.42 mmol) in DMF (5 ml) were added HATU (595 mg, 1.57 mmol) and DIPEA (0.59 ml, 3.56 mmol) and the reaction was left to stir at room temperature for 30 minutes. rac-Benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate **EV-AV3801-001** (synthesised according to Scheme 2, 408 mg, 1.42 mmol) was then added and the reaction was left to stir at room temperature for a further 2h. The reaction mixture was then diluted with EtOAc (10 ml), washed with water (3 x 10 ml) and saturated aqueous sodium chloride (10 ml). The organic fraction was then dried (sodium sulfate), filtered and concentrated in vacuo to obtain 775 mg (79%) of rac-benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate **EV-AV3805-001** as an orange solid. LCMS (method D): retention time 1.12min, M/z = 609 (M + 1).

[00233] rac-(3R,4S)-3-{[(Benzyloxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl benzoate EV-AV3814-001 – step 4 (cis racemate)

[00234] To a solution of triphenylphosphine (411 mg, 1.55 mmol) in THF (1 mol) at 0°C was added DIAD (325 µl, 1.55 mmol). The reaction mixture was allowed to stir for 5 minutes and rac-benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate **EV-AV3805-001** (675 mg, 1.11 mmol) and benzoic acid (190 mg, 1.55 mmol) were added. The reaction mixture was stirred at room temperature for 3h and then diluted with EtOAc (15 ml). The mixture was washed with water (10 ml) and saturated aqueous sodium chloride (10 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (50-100% EtOAc/heptane) to obtain 743 mg (49%) of rac-(3R,4S)-3-{[(benzyloxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl benzoate **EV-AV3814-001**. LCMS (method D): retention time 1.36min, M/z = 713 (M + 1).

[00235] rac-Benzyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate EV-AV3819-001 – step 5 (cis racemate)

[00236] To a solution of rac-(3R,4S)-3-{[(benzyloxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl benzoate **EV-AV3814-001** (0.74 g, 0.54 mmol) in ethanol (10 ml) and water (5 ml) was added K_2CO_3 (0.11 g, 0.81 mmol) and the solution was stirred at room temperature for 3h. The reaction mixture was then concentrated in vacuo, the crude residue was dissolved in DCM (10 ml) and washed with water (10 ml). The organic layer was then washed with saturated aqueous sodium chloride (10 ml), dried over sodium sulfate, filtered and concentrated in vacuo. The crude was purified by flash column chromatography (0-20% methanol/EtOAc) to obtain 214mg (64%) of rac-benzyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate **EV-AV3819-001** as a white solid. LCMS (method D): retention time 1.14min, M/z = 609 (M + 1).

[00237] rac-benzyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-yl]carbamate EV-AV4626-001 – step 6 (cis racemate)

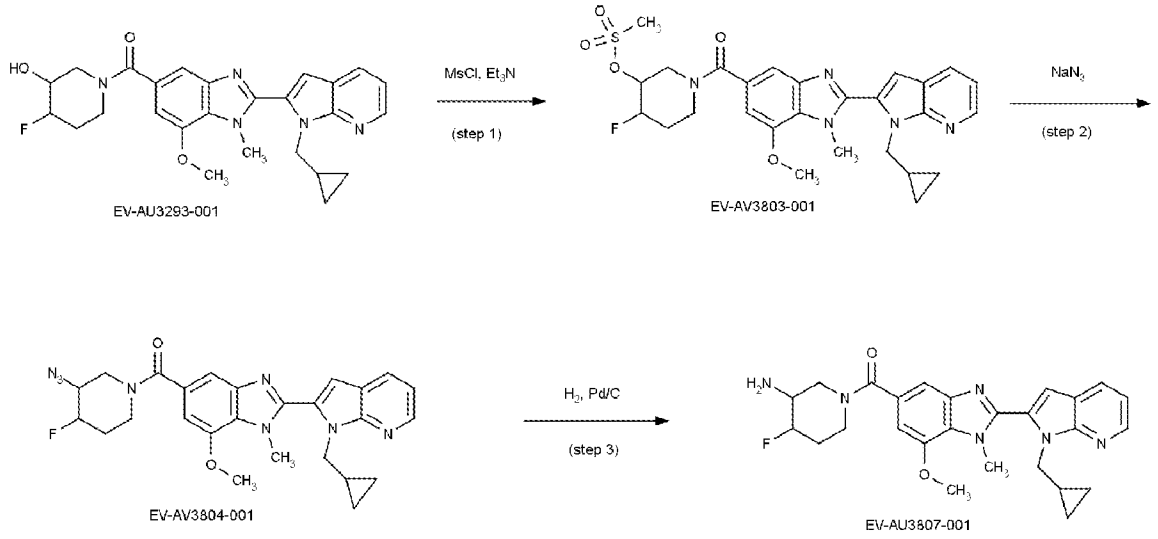
[00238] To a stirred suspension of rac-benzyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate (**EV-AV3819-001**, 214 mg, 0.35 mmol) and copper(I) iodide (13.4 mg, 0.070 mmol) in acetonitrile (2 ml) in a pressure tube was added 2,2-difluoro-2-(fluorosulfonyl)acetic acid (125 mg, 0.70 mmol). The vessel was sealed and reaction mixture was stirred at 80°C for 2h. To the cooled reaction mixture was added 2,2-difluoro-2-(fluorosulfonyl)acetic acid (125 mg, 0.70 mmol), the vessel was sealed and reaction mixture was stirred at 80°C for a further 2h. The reaction mixture was again cooled and 2,2-difluoro-2-(fluorosulfonyl)acetic acid (125 mg, 0.70 mmol) was added, the vessel was sealed and reaction mixture was stirred at 80°C for a further 2h. The reaction mixture was then concentrated in vacuo and the residue was purified by flash column chromatography (20-100% EtOAc/heptane) followed by preparative HPLC (basic method) to obtain 33 mg (14%) of rac-benzyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-yl]carbamate **EV-AV4626-001** as a white solid. LCMS (method D): retention time 1.27min, M/z = 659 (M + 1).

[00239] rac-(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-amine EV-AV4627-001 (EOAI3452884) I-86 – step 7 (cis racemate)

[00240] To a stirred solution of rac-benzyl N-[(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-yl]carbamate (**EV-AV4626-001,** 33 mg, 0.05 mmol) in ethanol (2 ml) under nitrogen was added 10% Pd/C (3.2 mg, 0.002 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 5h. The reaction mixture was filtered through a glass fibre sinter and the filtrate was then treated with 1.25M HCl in ethanol (0.3 ml). The mixture was left standing at room temperature for 30 minutes, concentrated in vacuo and freeze dried to obtain 28.2 mg (98%) of rac-(3R,4S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(difluoromethoxy)piperidin-3-amine **EV-AV4627-001** (**I-86**) as an off-white powder. LCMS (method A): retention time 2.20min, M/z = 524 (M + 1).

[00241] 1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-amine EV-AV3807-001 (**EOAI3451007**) **I-75** was synthesised according to the procedures described in Scheme 3.6:

[00242] Scheme 4.6



[00243] 1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-yl methanesulfonate EV-AV3803-001 – step 1

[00244] To a stirred solution of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-ol (**EV-AU3293-001,** synthesised according to Scheme 2, 570 mg, 1.19 mmol) in DCM (10 ml) at 0°C was added triethylamine (0.25 ml, 1.79 mmol) and mesyl chloride (0.11 ml, 1.43 mmol). The reaction was stirred at room temperature for 2h. Water (5ml) was added to the mixture and the organic layer was collected, dried over sodium sulfate and concentrated in vacuo to obtain 663 mg (quantitative) of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-yl methanesulfonate **EV-AV-3803-001**. LCMS (method D): retention time 1.14min, M/z = 556 (M + 1).

[00245] 5-(3-Azido-4-fluoropiperidine-1-carbonyl)-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AV3804-001 – step 2

[00246] To a stirred solution of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-yl methanesulfonate (**EV-AV-3803-001,** 610 mg, 1.10 mmol) in DMSO (10 ml) was added sodium azide (285 mg, 4.39 mmol). The reaction was stirred at 120°C for 14h. The reaction was allowed to cool to room temperature then diluted with EtOAc (20 ml), washed with water (3 x 20 ml) and then saturated aqueous sodium chloride (20 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified

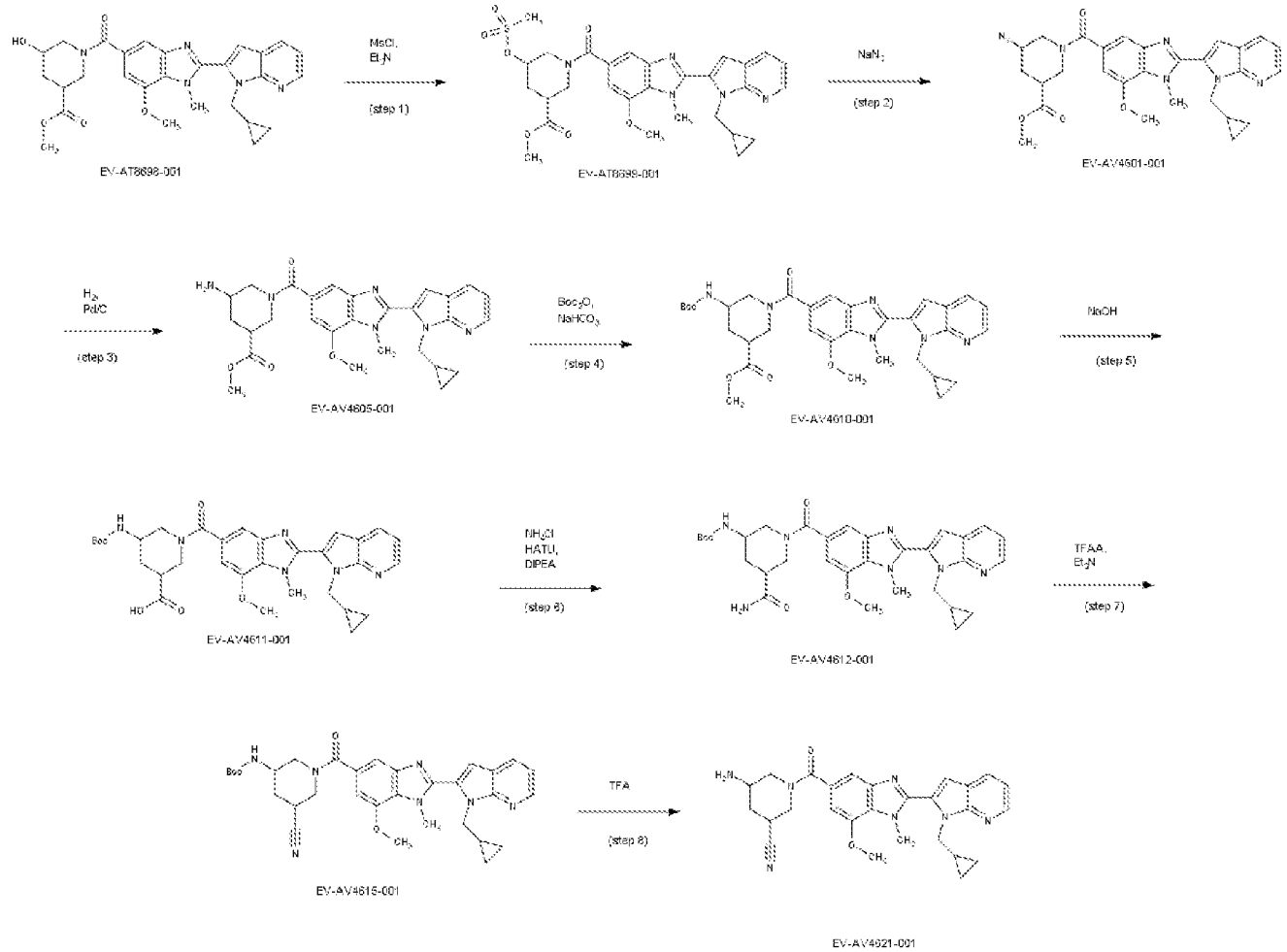
by flash column chromatography (50–100% EtOAc/heptane) to obtain 191 mg (34.6%) of 5-(3-azido-4-fluoropiperidine-1-carbonyl)-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole **EV-AU3804-001** as an orange solid. LCMS (method D): retention time 1.19min, M/z = 503 (M + 1).

[00247] 1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-amine EV-AV3807-001 (EOAI3451007) I-75 – step 3

[00248] To a stirred solution of 5-(3-azido-4-fluoropiperidine-1-carbonyl)-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole (**EV-AU3804-001,** 191mg, 0.38 mmol) in EtOAc (5 ml) under nitrogen was added 10% Pd/C (81 mg, 0.04 mmol). The mixture was placed under a hydrogen atmosphere and stirred at room temperature for 12h. The mixture was filtered through a glass fibre filter and the filter washed with methanol. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (basic method) to obtain 80 mg (44.2%) of 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-fluoropiperidin-3-amine **EV-AV3807-001** (**I-75**) as a white solid. LCMS (method A): retention time 2.01min, M/z = 477 (M + 1).

[00249] 5-Amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carbonitrile EV-AV4621-001 (EOAI3452077) I-82 was synthesised according to the procedures described in Scheme 3.7 via methyl 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-hydroxypiperidine-3-carboxylate **EV-AT8698-001**. This was prepared according to the procedure described in Scheme 3, step 7 using methyl 5-hydroxypiperidine-3-carboxylate. Methyl 5-hydroxypiperidine-3-carboxylate was prepared from 1-benzyl 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (CAS 1095010-45-9) according to the procedure described in Scheme 3, step 7.

[00250] Scheme 3.7



[00251] Methyl 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methanesulfonyloxy)piperidine-3-carboxylate EV-AT8699-001 – step 1

[00252] To a stirred solution of methyl 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-hydroxypiperidine-3-carboxylate (**EV-AT8698-001**, 275 mg, 0.53 mmol) in DCM (8 ml) at 0°C was added triethylamine (0.11 ml, 0.80 mmol) and mesyl chloride (49 µl, 0.64 mmol). The mixture was stirred with ice cooling for 2h. Further mesyl chloride (25 µl, 0.32 mmol) was added and the reaction was stirred at room temperature for 16h. Water (5 ml) was added to the mixture and the organic layer was collected, dried over sodium sulfate and concentrated in vacuo to obtain 316 mg (quantitative) of methyl 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methanesulfonyloxy)piperidine-3-carboxylate **EV-AT8699-001** as a yellow oil. LCMS (method D): retention time 1.12min, M/z = 596 (M + 1).

[00253] Methyl 5-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate EV-AV4601-001 – step 2

[00254] To a stirred solution of methyl 1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-(methanesulfonyloxy)piperidine-3-carboxylate (**EV-AT8699-001**, 316 mg, 0.53 mmol) in DMSO (2 ml) was added sodium azide (86 mg, 1.33 mmol). The resulting mixture was stirred at 90°C for 16h. The reaction was allowed to cool to room temperature and partitioned between EtOAc (40 ml) and water (30 ml). The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography (50-100% EtOAc/heptane) to obtain 141 mg (43.1%) of methyl 5-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate **EV-AV4601-001** as an off white solid. LCMS (method D): retention time 1.19min, M/z = 543 (M + 1).

[00255] Methyl 5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate EV-AV4605-001 – step 3

[00256] To a stirred solution of methyl 5-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate (**EV-AV4601-001**, 131 mg, 0.24 mmol) in ethanol under nitrogen was added 10% Pd/C (0.15 g, 0.01 mmol). The reaction mixture was placed under a hydrogen atmosphere and stirred at room temperature for 16h. The reaction was filtered through a glass fibre filter and the filtrate concentrated in vacuo to obtain 98mg (46.0%) of methyl 5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate **EV-AV4605-001** as a yellow oil. LCMS (method D): retention time 0.92min, M/z = 517 (M + 1).

[00257] Methyl 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate EV-AV4610-001 – step 4

[00258] To a stirred solution of methyl 5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate (**EV-AV4605-001**, 77 mg, 0.15 mmol) in dioxane (1 ml) was added saturated aqueous sodium hydrogen carbonate (1 ml) and boc anhydride (39 mg, 0.18 mmol). The resulting mixture was stirred at room temperature for 1h. The mixture was

partitioned between EtOAc (20 ml) and water (20 ml). The aqueous layer was extracted with EtOAc (15 ml) and the combined organics were dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 62 mg (63.2%) of methyl 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate **EV-AV4610-001** as an off white powder. LCMS (method D): retention time 1.20min, M/z = 617 (M + 1).

[00259] 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylic acid EV-AV4611-001 – step 5

[00260] To a stirred solution of methyl 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylate (**EV-AV4610-001**, 62 mg, 0.10 mmol) in methanol (1 ml) was added 1M aqueous sodium hydroxide (0.5 ml). The resulting mixture was stirred at room temperature for 16h. The mixture was concentrated in vacuo to remove the methanol. The resulting aqueous solution was acidified using 1M aqueous hydrochloric acid to pH ~4-5 until a precipitate was formed. The solid was filtered off and dried under vacuum to obtain 58mg (89.4%) of 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylic acid **EV-AV4611-001** as an off white powder. LCMS (method D): retention time 1.13min, M/z = 603 (M + 1).

[00261] Tert-butyl N-(5-carbamoyl-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate EV-AV4612-001 – step 6

[00262] To a stirred solution of 5-{[(tert-butoxy)carbonyl]amino}-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carboxylic acid (**EV-AV4611-001,** 58mg, 0.96 mmol) in DMF (1 ml) was added DIPEA (34 µl, 0.19 mmol), HATU (46 mg, 0.12 mmol) and ammonium chloride (10 mg, 0.19 mmol). The resulting mixture was stirred at room temperature for 1h. The mixture was partitioned between EtOAc (40 ml) and water (40 ml). The aqueous layer was further extracted with EtOAc (40 ml) and the combined organics were dried over sodium sulfate and concentrated in vacuo to obtain 65 mg (97.7%) of tert-butyl N-(5-carbamoyl-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-

methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate **EV-AV4612-001** as a yellow oil. LCMS (method D): retention time 1.09min, M/z = 602 (M + 1).

[00263] Tert-butyl N-(5-cyano-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate EV-AV4615-004 – step 7

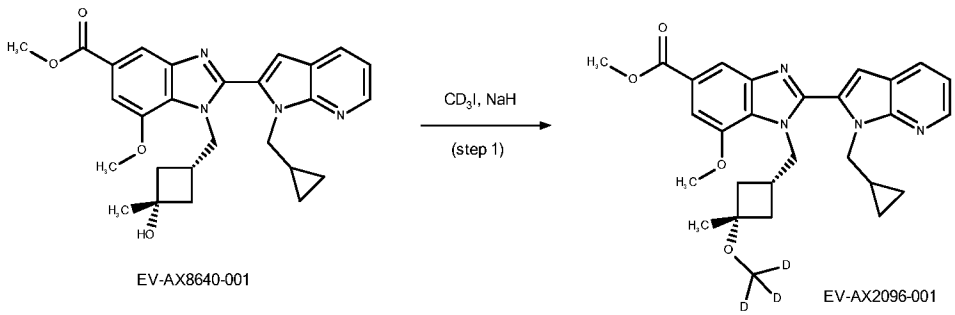
[00264] To a stirred solution of tert-butyl N-(5-carbamoyl-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate (**EV-AV4612-001**, 65 mg, 0.10 mmol) in anhydrous dioxane (1 ml) was added triethylamine (44.3 µl, 0.32 mmol) and trifluoroacetic anhydride (30 µl, 0.22 mmol). The reaction was stirred at room temperature for 5h. The mixture was re-treated with triethylamine (44.3 µl, 0.32 mmol) and trifluoroacetic anhydride (30 µl, 0.22 mmol) and stirred at room temperature for 16h. The mixture was re-treated with triethylamine (44.3 µl, 0.32 mmol) and trifluoroacetic anhydride (30 µl, 0.22 mmol) and stirred at room temperature for 2h. The mixture was re-treated with (44.3 µl, 0.32 mmol) and trifluoroacetic anhydride (30 µl, 0.22 mmol) and stirred for 2h. The mixture was re-treated with triethylamine (44.3 µl, 0.32 mmol) and trifluoroacetic anhydride (30 µl, 0.22 mmol) and stirred at room temperature for 2h. The mixture was partitioned between EtOAc (20 ml) and saturated aqueous ammonium chloride (20 ml). The aqueous layer was extracted with EtOAc (20 ml) and the combined organics were dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 2 batches of product which were separately purified by preparative HPLC (basic method) to obtain 9 mg (14.3%) of tert-butyl N-[(3R,5S)-5-cyano-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV4615-003** as an off white powder. Arbitrarily assigned as racemic cis-diastereomer. LCMS (method D): retention time 1.21min, M/z = 584 (M + 1). 11mg (17.5%) of tert-butyl N-[(3R,5S)-5-cyano-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV4615-004** were also obtained as an off white powder. Arbitrarily assigned as a racemic trans-diastereomer. LCMS (method D): retention time 1.19min, M/z = 584 (M + 1).

[00265] 5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carbonitrile EV-AV4621-001 (EOAI3452077) I-82 – step 8

[00266] A solution of tert-butyl N-(5-cyano-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate (**EV-AV4615-004**, 11 mg, 0.02 mmol) in 10% trifluoroacetic acid in DCM (1 ml) was left standing at room temperature for 1h. The reaction was concentrated in vacuo and the residue was freeze-dried from 1:1 aceronitrile:water (4 ml) to obtain 11.6 mg (quantitative) of 5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3-carbonitrile trifluoroacetic acid **EV-AV4621-001** (**I-82**)as a white powder. LCMS (method A): retention time 2.08min, M/z = 484 (M + 1).

[00267] **(1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-{[3-($^2H_3$)methoxy-3-methylcyclobutyl]methyl}-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AY5000-002 (EOAI3462946) I-238** was obtained according to the procedures described in Scheme 3 via deuteromethylation of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-{[(1r,3s)-3-hydroxy-3-ethylcyclobutyl]methyl}-1H-1,3-benzodiazole-5-carboxylate **EV-AX8640-001** as described in Scheme 3.8:

[00268] **Scheme 3.8**



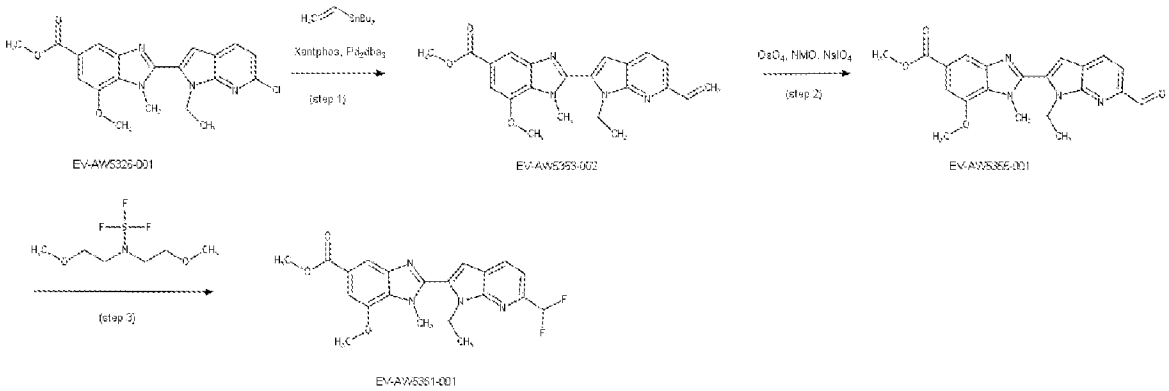
[00269] **Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-{[(1r,3s)-3-($^2H_3$)methoxy-3-methylcyclobutyl]methyl}-1H-1,3-benzodiazole-5-carboxylate EV-AX2096-001 – step 1**

[00270] To a stirred solution of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-{[(1r,3s)-3-hydroxy-3-methylcyclobutyl]methyl}-1H-1,3-benzodiazole-5-carboxylate (**EV-AX8640-001**, 85%, 250 mg, 0.45 mmol) in DMF (2.0 ml) was added sodium hydride (60%, 36 mg, 0.90 mmol). The resulting mixture was stirred at room temperature for 10 minutes and iodo($^2H_3$)methane (CAS 865-50-9, 84 µl, 1.34 mmol) was added. The reaction mixture was stirred at room temperature for 4.5h and concentrated *in*

vacuo. The residue was partitioned between EtOAc (20 ml) and water (15 ml). The aqueous layer was re-extracted with EtOAc (2 x 10 ml) and the combined organics were washed with water (10 ml), saturated aqueous sodium chloride (10 ml), dried over sodium sulfate and concentrated *in vacuo*. The resulting material was purified by flash column chromatography (0 - 50% EtOAc/heptane) to obtain 184 mg (75%) of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-{[(1r,3s)-3-(2H-3-)methoxy-3-methylcyclobutyl]methyl}-1H-1,3-benzodiazole-5-carboxylate **EV-AX2096-001** as a pale yellow solid. LCMS (method D): retention time 1.43min, M/z = 492 (M + 1).

[00271] (1R,4R,7R)-2-{2-[6-(Difluoromethyl)-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AW5368-001 (EOAI3460286) I-189 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 2-[6-(difluoromethyl)-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AW5361-001** described in Scheme 3.9:

[00272] Scheme 3.9



[00273]

Methyl 2-{6-ethenyl-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AW5353-002 – step 1

[00274] To a solution of methyl 2-{6-chloro-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AW5326-001**, 500 mg, 1.25 mmol) in dioxane (10 ml) was added tributyl(ethenyl)stannane (477 mg, 1.50 mmol). The reaction mixture was purged with nitrogen for 15 min then Xantphos (54 mg, 0.04 mmol) and Pd_2dba_3 (29 mg, 0.03 mmol) were added. The resulting mixture was stirred at 110°C for 16h. The reaction was concentrated *in vacuo* and the crude residue was purified by flash column

chromatography (0-50% EtOAc/heptane) to obtain 340mg (66%) of methyl 2-{6-ethenyl-1-ethyl-1H-pyrrolo[2,3-b]pyridine -2-yl}-7-methoxy

[00275] -1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AW5353-002** as a white solid. LCMS (method D): retention time 1.34min, M/z = 391 (M + 1).

[00276] Methyl 2-{1-ethyl-6-formyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AW5355-001 – step 2

[00277] To a solution of methyl 2-{6-ethenyl-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AW5353-002**, 89%, 470 mg, 1.07 mmol) in THF : water (2:1, 9 ml) were added t-butanol (0.10 ml), 4-methylmorpholine 4-oxide (188 mg, 1.61 mmol) and OsO_4 (0.10 ml in water, 0.02 mmol). The reaction was stirred at room temperature for 5h, $NaIO_4$ (687 mg, 3.20 mmol) was added and stirring at room temperature was continued for 16h. The reaction mixture was filtered through a pad of celite and washed with EtOAc. The filtrate was diluted with water (20 ml) and extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (0-40% EtOAc/heptane) to obtain 270mg (62%) of methyl 2-{1-ethyl-6-formyl-1H-pyrrolo [2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AW5355-001** as a yellow solid. LCMS (method D): retention time 1.24min, M/z = 393 (M + 1).

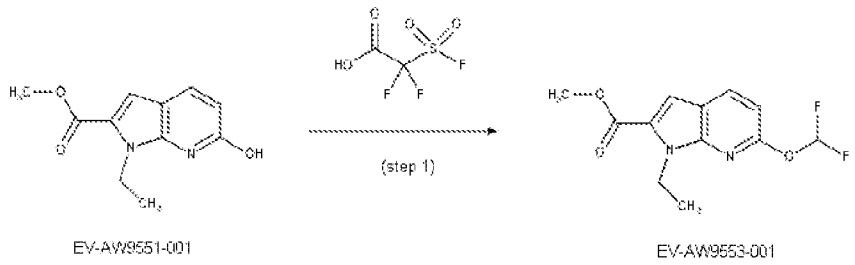
[00278] Methyl 2-[6-(difluoromethyl)-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AW5361-001 – step 3

[00279] To a solution of methyl 2-{1-ethyl-6-formyl-1H-pyrrolo[2,3-b]pyridin-2-yl}-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate (200 mg, 0.50 mmol) in DCM (10 ml) was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-lambda~4~-sulfanyl)ethanamine (CAS, 202289-38-1, 0.45 ml, 1.24 mmol) at room temperature. The reaction mixture was stirred at 45°C for 16h, cooled down to room temperature and poured onto ice/water. The aqueous layer was neutralised with saturated sodium bicarbonate and extracted with DCM (3 x 20 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (0-40% EtOAc/heptane) to obtain 105mg

(49%) of methyl 2-[6-(difluoromethyl)-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AW5361-001** as a white solid. LCMS (method D): retention time 1.33min, M/z = 415 (M + 1).

[00280] (1R,4R,7R)-2-{2-[6-(difluoromethoxy)-1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AW9564-001 (EOAI3460927) I-200 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 6-(difluoromethoxy)-1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AW9553-001** described in Scheme 3.10:

[00281] Scheme 3.10

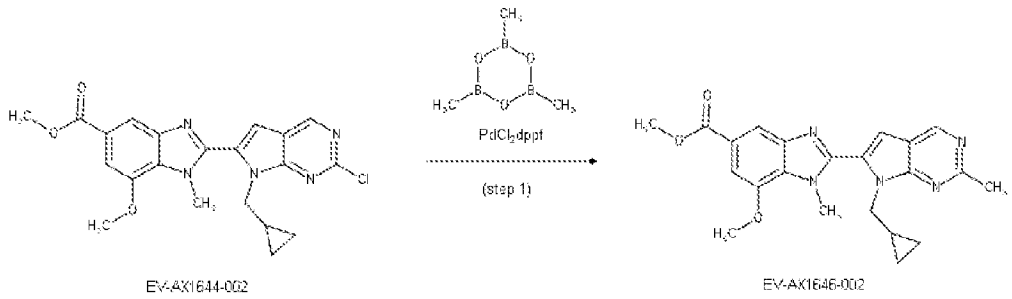


EV-AW9551-001 EV-AW9553-001

[00282] 2,2-Difluoro-2-(fluorosulfonyl)acetic acid (CAS 1717-59-5, 912 mg, 5.12 mmol) was added to a stirred suspension of benzyl N-[(3S,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate (**EV-AW9553-001** synthesised according to Scheme 3.18, 451 mg, 2.05 mmol) and sodium sulfate (291 mg, 2.05 mmol) in acetonitrile (10 ml). The resulting mixture was stirred at room temperature for 16h. The reaction crude was concentrated *in vacuo* and the residue was purified by flash column chromatography (0-60% EtOAc/heptane) to obtain 327 mg (59%) of methyl 6-(difluoromethoxy)-1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AW9553-001** as an off-white solid. LCMS (method D): retention time 1.30min, M/z = 271 (M + 1).

[00283] (1R,4R,7R)-2-{2-[7-(Cyclopropylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AX1665-002 (EOAI3460929) I-202 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 2-[7-(cyclopropylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AX1646-002** described in Scheme 3.11:

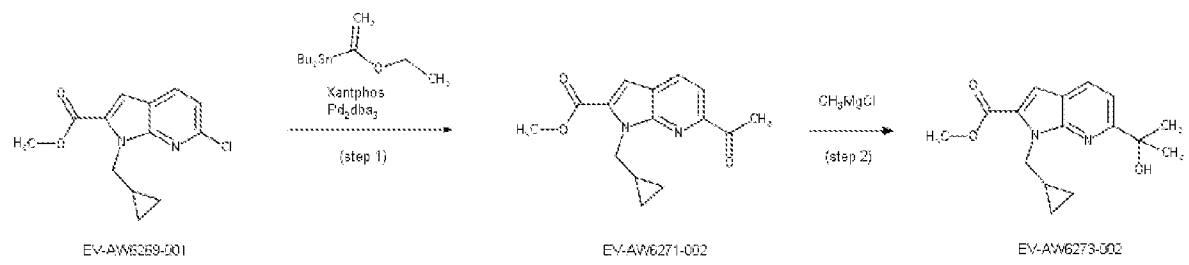
[00284] Scheme 3.11



[00285] To a solution of methyl 2-[2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1- methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AX1644-002**, 134 mg, 0.31 mmol) in DME (5 ml) were added potassium carbonate (87 mg, 0.63 mmol), $PdCl_2dppf$ (26 mg, 0.03 mmol) and trimethylboroxin (3.5M in THF, 0.36 ml, 1.26 mmol). The reaction mixture was stirred at 100°C for 15h. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (0-100% EtOAc/heptane then 0-40% methanol/EtOAc) to obtain 94 mg (70%) of methyl 2-[7-(cyclopropylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl- 1H-1,3-benzodiazole-5-carboxylate **EV-AX1646-002** as an off-white solid. LCMS (method D): retention time 1.05min, M/z = 406 (M + 1).

[00286] 2-(2-{5-[(1R,4R,7R)-7-Amino-2-azabicyclo[2.2.1]heptane-2-carbonyl]-7-methoxy-1-methyl-1H-1,3-benzodiazol-2-yl}-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)propan-2-ol EV-AW6283-001 (EOAI3461372) I-210 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AW6273-002** described in Scheme 3.12:

[00287] Scheme 3.12



[00288] Methyl 6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AW6271-002 – step 1

[00289] To a solution of methyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AW6269-001**, 90%, 1.16 g, 3.93 mmol) in anhydrous dioxane (3 ml) were added tributyl(1-ethoxyethenyl)stannane (1.59 ml, 4.71 mmol), Xantphos (0.17 g, 0.29 mmol) and Pd_2dba_3 (0.09 g, 0.10 mmol). The reaction mixture was stirred at 90°C for 17h. The solvent was removed *in vacuo* and 1M HCl (50 ml) and DCM (50 ml) were added to the residue. The biphasic mixture was stirred for 20 minutes then the organic layer was separated and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (0-10% EtOAc/heptane) to obtain 0.512 g (47%) of methyl 6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AW6271-002** as an off-white solid. LCMS (method D): retention time 1.40min, M/z = 273 (M + 1).

[00290] Methyl 1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate

EV-AW6273-002 – step 2

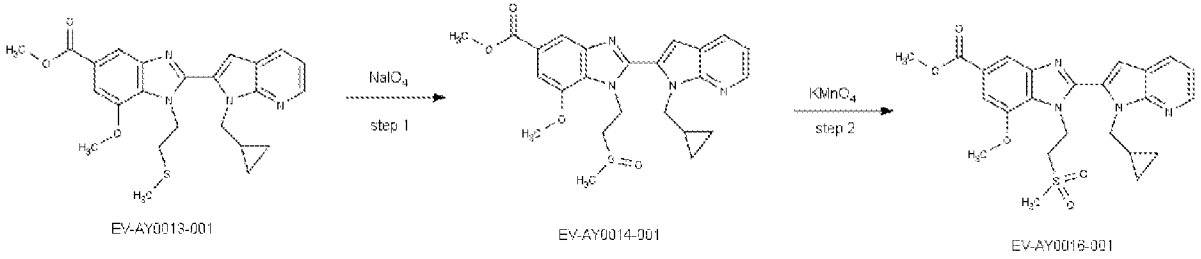
[00291] Methylmagnesium chloride (3M in THF, 642 µl) was added drop-wise to a stirred solution of methyl 6-acetyl-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AW6271-002,** 510 mg, 1.84 mmol) in anhydrous THF (5 ml) at -78°C. The reaction was stirred at -78°C for 2.5h. Further methylmagnesium chloride (3M in THF, 61 µl) was added at -78°C and stirring was continued for 30 minutes. The reaction was quenched with water (20 ml) and THF was removed *in vacuo*. 1M HCl was added to the aqueous layer until pH 3. The aqueous layer was extracted with EtOAc (2 x 30 ml). The combined extracts dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (0-35% EtOAc/heptane) to obtain 410 mg (76%) of methyl 1-(cyclopropylmethyl)-6-(2-hydroxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AW6273-002** as an off-white solid. LCMS (method D): retention time 1.23min, M/z = 289 (M + 1).

[00292] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfonylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AY0021-001 (EOAI3461556) I-214 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfonylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AY0016-001** described in Scheme 3.13.

[00293] (1R,4R,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfinylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}-2-

azabicyclo[2.2.1]heptan-7-amine EV-AY0020-001 (EOAI3461555) I-213 was synthesised according to the procedures described in Scheme 3 via synthesis of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfinylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AY0014-001** described in Scheme 3.13.

[00294] Scheme 3.13



[00295] Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfinylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate EV-AY0014-001 – step 1

[00296] To a stirred solution of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-[2-(methylsulfanyl)ethyl]-1H-1,3-benzodiazole-5-carboxylate (**EV-AY0013-001**, 260 mg, 0.52 mmol) in methanol (8 ml) and water (2 ml) was added $NaIO_4$ (122 mg, 0.57 mmol). The reaction was stirred at room temperature for 18h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (20 ml) and water (50 ml). The aqueous layer was extracted further with EtOAc (2 x 20 ml). The combined organics were washed with saturated aqueous sodium chloride (20 ml), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (0-50% EtOAc/heptane then 1-10% Methanol/DCM) to obtain 220 mg (91%) of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfinylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AY0014-001** as a red foam. LCMS (method D): retention time 1.08min, M/z = 467 (M + 1).

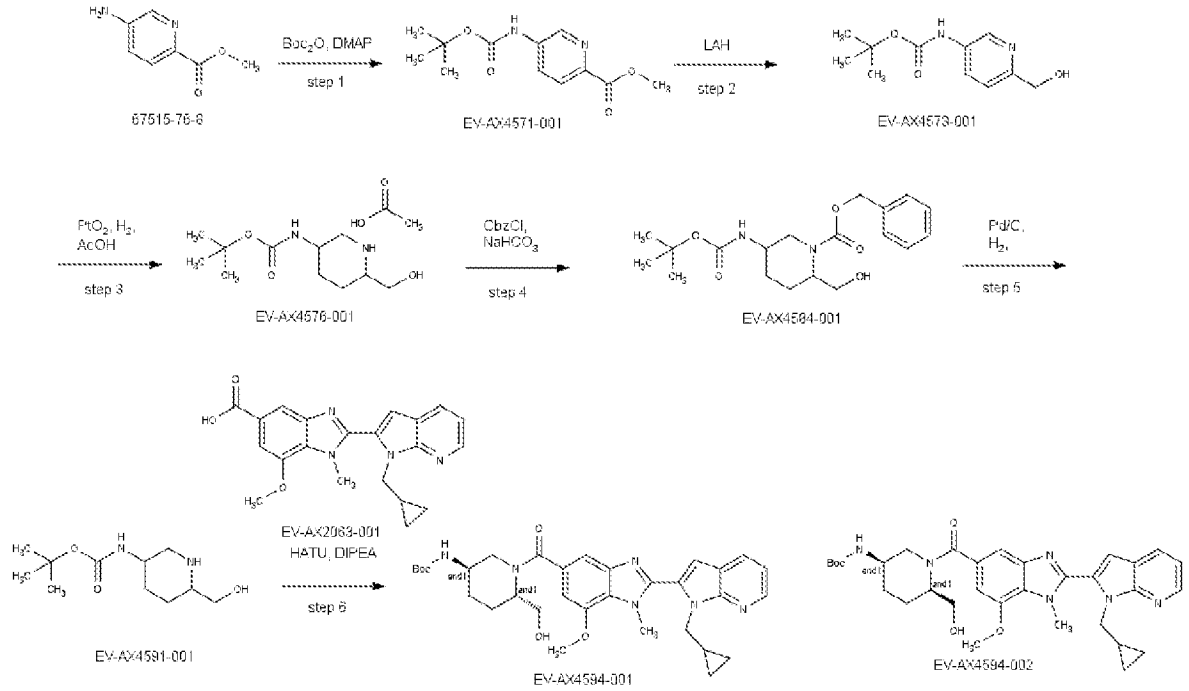
[00297] Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfonylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate EV-AY0016-001 – step 2

[00298] To a stirred solution of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfinylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate (**EV-AY0014-001**, 135 mg, 0.29 mmol) in Methanol (40 ml) was added $KMnO_4$ (50 mg, 0.32 mmol). The reaction was stirred at room temperature for 15 minutes. The reaction was quenched by the addition of saturated aqueous sodium bisulfate (20 ml). The

mixture was filtered through Kieselguhr and the filtrate was concentrated *in vacuo*. The residue was diluted in EtOAc (20 ml) and water (50 ml) and the aqueous layer was extracted with EtOAc (2 x 20 ml). The combined organics were washed with saturated aqueous sodium chloride (20 ml), dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain 115 mg (81%) of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2-methanesulfonylethyl)-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AY0016-001** as a brown solid. LCMS (method D): retention time 1.15min, M/z = 483 (M + 1).

[00299] Rac-[(2R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4303-001 (EOAI3462115) I-220 and **rac-[(2R,5R)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4304-001 (EOAI3462116) I-221** were obtained from the Boc-deprotection of rac-tert-butyl N-[(3R,6S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-001** and rac-tert-butyl N-[(3R,6R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-002** respectively following the procedures described in Schemes 3 and 3.14:

[00300] Scheme 3.14



[00301] Methyl 5-{[(tert-butoxy)carbonyl]amino}pyridine-2-carboxylate EV-AX4571-001 – step 1

[00302] To a stirred solution of methyl 5-aminopyridine-2-carboxylate (CAS 67515-76-8, 1.8 g, 11.83 mmol) in DCM (40 ml) under an atmosphere of nitrogen was added di-tert-butyl dicarbonate (2.84 g, 13.01 mmol) and N,N-dimethylpyridin-4-amine (0.14 g, 1.18 mmol) and the reaction was stirred at room temperature for 5h. The reaction mixture was filtered (rinsing the filter with DCM), the filtrate was diluted with DCM (100 ml) and washed with water (2 x 100 ml). The organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo* to obtain 2.73 g (60%) of methyl 5-{[(tert-butoxy)carbonyl]amino}pyridine-2-carboxylate **EV-AX4571-001** as an off-white solid. LCMS (method D): retention time 1.01min, M/z = 253 (M + 1).

[00303] Tert-butyl N-[6-(hydroxymethyl)pyridin-3-yl]carbamate EV-AX4573-001 – step 2

[00304] To a stirred solution of methyl 5-{[(tert-butoxy)carbonyl]amino}pyridine-2-carboxylate (**EV-AX4571-001,** 2.73 g, 10.82 mmol) in THF (60 ml) at 0 °C under an atmosphere of nitrogen was added 4M lithium tetrahydridoaluminate(1-) in diethyl ether (4.1 ml) drop-wise, the reaction was allowed to warm to room temperature and stirred for a further 12h. The reaction was quenched by addition of THF:water (9:1, 15 ml), followed by 10% sodium hydroxide (10 ml) and then water (10 ml). The reaction mixture was then filtered through a pad of Kieselguhr, rinsing with THF (3 x 50 ml). The filtrate was concentrated *in vacuo* and the crude was purified by flash column chromatography (50-100% EtOAc/heptane then 0-10% Methanol/EtOAc) to obtain 1.50 g (60%) of tert-butyl N-[6-(hydroxymethyl)pyridin-3-yl]carbamate **EV-AX4573-001** as an off-white solid. LCMS (method D): retention time 0.70min, M/z = 224 (M + 1).

[00305] Acetic acid tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate EV-AX4576-001 – step 3

[00306] To a pressure vessel was added a solution of tert-butyl N-[6-(hydroxymethyl)pyridin-3-yl]carbamate (**EV-AX4573-001**, 1.50 g, 6.69 mmol) in ethanol (25 ml) and Acetic acid (1.5 ml). PtO_2 (266 mg, 1.17 mmol) was added and the pressure vessel was purged with nitrogen before the reaction was sealed and stirred under a hydrogen atmosphere (55psi, 3.75 atm) at 65°C for 16h. The reaction mixture was filtered through a pad of Kieselguhr and concentrated *in vacuo* to obtain 2.40 g (99%) of acetic acid tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4576-001** as an orange oil. No LCMS data.

[00307] Benzyl 5-{[(tert-butoxy)carbonyl]amino}-2-(hydroxymethyl)piperidine-1-carboxylate EV-AX4584-001 – step 4

[00308] To a stirred solution of acetic acid tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate (**EV-AX4576-001**, 70%, 2.00 g, 4.82 mmol) in THF (40 ml) and water (12 ml) at 0°C was added sodium bicarbonate (1.22 g, 14.47 mmol) and benzyl carbonochloridate (0.62 ml, 4.34 mmol). The reaction mixture was stirred at 0°C for 15 minutes, the solution was allowed to warm to room temperature and stirring was continued for 4h. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc (3 x 5 ml).The combined organics were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (40-100% EtOAc/heptane) to obtain 1.40 g (80%) of benzyl 5-{[(tert-butoxy)carbonyl]amino}-2-(hydroxymethyl)piperidine-1-carboxylate **EV-AX4584-001** as a white solid. LCMS (method D): retention time 1.12min, M/z = 387 (M + 23).

[00309] Tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate EV-AX4591-001 – step 5

[00310] To solution of benzyl 5-{[(tert-butoxy)carbonyl]amino}-2-(hydroxymethyl)piperidine-1-carboxylate (**EV-AX4584-001**, 1.40 g, 3.84 mmol) in ethanol (20 ml) was added palladium on carbon (5%, 0.82 g, 0.38 mmol) and the reaction mixture was stirred for 14h at room temperature under a hydrogen atmosphere. The mixture was filtered through a pad of Kieselguhr (washing with Methanol) and the filtrate was concentrated *in vacuo* to obtain 0.82 g (93%) of tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4591-001** as a colourless oil. LCMS (method D): retention time 1.20min, M/z = 231 (M + 1).

[00311] Rac-tert-butyl N-[(3R,6S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate EV-AX4594-001 and rac-tert-butyl N-[(3R,6R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate EV-AX4594-002 – step 6

[00312] To a stirred solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AX2063-001**, 200 mg, 0.53 mmol) in DMF (5 ml) were added DIPEA (463 µl, 2.66 mmol), HATU (222 mg, 0.58 mmol) and tert-butyl N-[6-(hydroxymethyl)piperidin-3-yl]carbamate (**EV-AX4591-001**, 122 mg, 0.53 mmol) at room temperature. The reaction mixture was stirred for 1h and

concentrated *in vacuo*. The crude was purified by preparative HPLC (acidic) to obtain 2 products:

[00313] 70 mg (22%) of rac-tert-butyl N-[(3R,6S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-001** as an off-white solid. LCMS (method D): retention time 1.18min, M/z = 589 (M + 1).

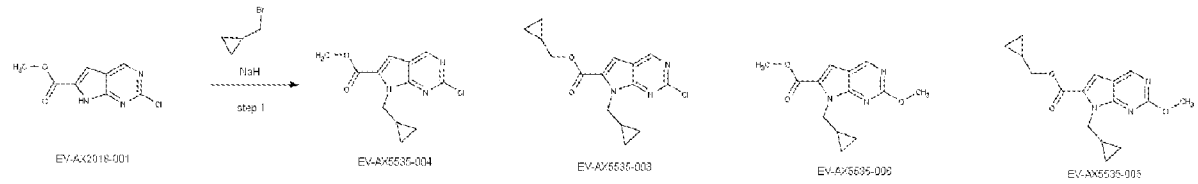
[00314] 220 mg (70 %) of rac-tert-butyl N-[(3R,6R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-002** as an off-white solid. LCMS (method D): retention time 1.19min, M/z = 589 (M + 1).

[00315] [(2S,5R)-5-Amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4308-001 (EOAI3462646) I-226 and **[(2R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4309-001 (EOAI3462647) I-227** were both obtained from chiral resolution of rac-tert-butyl N-[(3R,6S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-001** followed by Boc-deprotection as described in Scheme 3. The absolute configuration of both products was arbitrarily assigned.

[00316] [(2R,5R)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4310-001 (EOAI3462648) I-228 and **[(2S,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-2-yl]methanol EV-AY4311-001 (EOAI3462649) I-229** were both obtained from chiral resolution of rac-tert-butyl N-[(3R,6R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(hydroxymethyl)piperidin-3-yl]carbamate **EV-AX4594-002** followed by Boc-deprotection as described in Scheme 3. The absolute configuration of both products was arbitrarily assigned.

[00317] (1R,4R,7R)-2-{2-[7-(cyclopropylmethyl)-2-methoxy-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AX5554-001 (EOAI3468827) I-239 was synthesised according to procedures described in Scheme 3 via synthesis of methyl 7-(cyclopropylmethyl)-2-methoxy-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AX5535-006** described in Scheme 3.15:

[00318] Scheme 3.15



[00319] Methyl 7-(cyclopropylmethyl)-2-methoxy-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate EV-AX5535-006 – step 1

[00320] To s stirred solution of methyl 2-chloro-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (**EV-AX2018-001**, 1.00 g, 4.68 mmol) in anhydrous DMF (20 ml) at 0 °C was added sodium hydride (60%, 0.28 g, 7.02 mmol) portion-wise over 1 minute. (Bromomethyl)cyclopropane (680 µl, 7.01 mmol) was added at 0°C after 30 minutes. The reaction was allowed to warm to room temperature and stirred for 60h. The reaction mixture was concentrated *in vacuo* and the resulting residue partitioned between EtOAc (50 ml) and water (30 ml). The layers were separated and the organic phase washed with 0.5M HCl (30 ml) and saturated aqueous sodium chloride (30ml). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (5-40% EtOAc/heptane) to obtain 4 products:

[00321] 113 mg (8%) of cyclopropylmethyl 2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AX5535-003** as an off-white powder. LCMS (method D): retention time 1.38min, M/z = 306/308 (M + 1).

[00322] 256 mg (20%) of methyl 2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AX5535-004** as an off-white crystalline solid. LCMS (method D): 1.24min, M/z = 266/268 (M + 1).

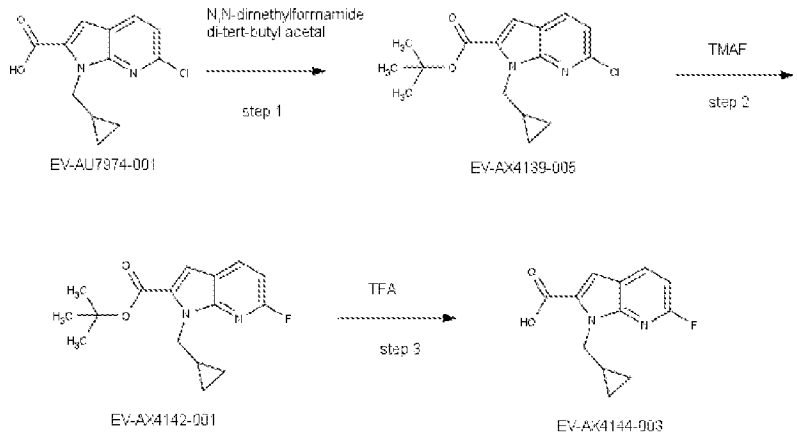
[00323] 93 mg (6%) of cyclopropylmethyl 7-(cyclopropylmethyl)-2-methoxy-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AX5535-005** as a yellow gum. LCMS (method D): retention time 1.32min, M/z = 302 (M + 1).

[00324] 197 mg (16%) of methyl 7-(cyclopropylmethyl)-2-methoxy-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AX5535-006** as a yellow crystalline solid. LCMS (method D): retention time 1.20min, M/z = 262 (M + 1).

[00325] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AX4151-006 (EOAI3476815) I-269 was synthesised following the procedures

described in Scheme 3 via synthesis of 1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AX4144-003** described in Scheme 3.16:

[00326] Scheme 3.16



[00327] Tert-butyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AX4139-001 – step 1

[00328] A stirred suspension of 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AU7974-001**, 500 mg, 1.99 mmol) in toluene (30 ml) was heated to 85°C before N,N-dimethylformamide di-tert-butyl acetal (2.0 ml, 8.34 mmol) was added drop-wise. The reaction was stirred at 85°C for 2h and further N,N-dimethylformamide di-tert-butyl acetal (2.0 ml, 8.34 mmol) was added. Stirring was continued at 85°C for 18h then at 100°C for 3h. After cooling, the reaction mixture was diluted with EtOAc (200 ml), washed with saturated aqueous sodium chloride (50 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (0-10% EtOAc/heptane) to obtain 366 mg (60%) of tert-butyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AX4139-005** as a colourless oil. LCMS (method D): retention time 1.66min, M/z = 307/309 (M + 1)

[00329] Tert-butyl 1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AX4142-001 – step 2

[00330] To a stirred solution of tert-butyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AX4139-005**, 366 mg, 1.19 mmol) in DMF (5 ml) was added tetramethylammonium fluoride (CAS 373-68-2, 250 mg, 2.68 mmol) and the mixture was stirred at 80°C for 18h. After cooling, the reaction mixture was partitioned among DCM (200 ml), water (100 ml) and saturated aqueous sodium chloride (100 ml). The organic layer was separated, further washed with saturated aqueous sodium chloride (50 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by

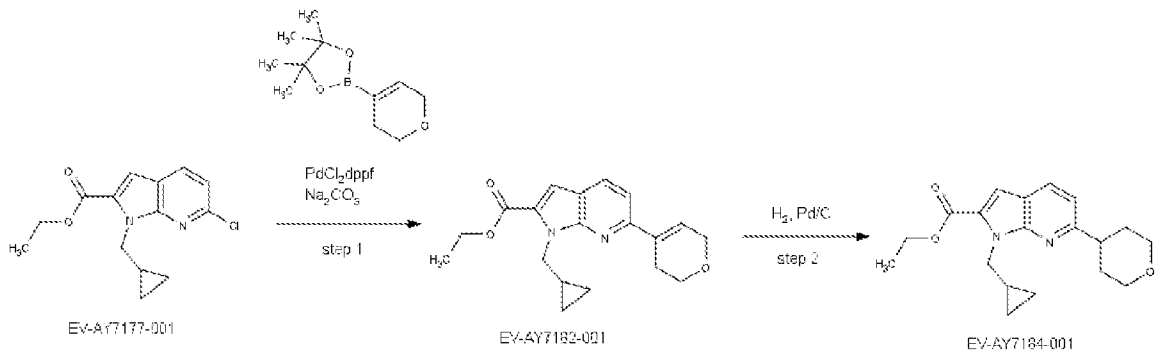
flash column chromatography (0-10% EtOAc/heptane) to obtain 112 mg (32%) of tert-butyl 1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AX4142-001** as a colourless oil. LCMS (method D): retention time 1.61 min, M/z = 291 (M + 1).

[00331] 1-(Cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AX4144-003 – step 3

[00332] A solution of tert-butyl 1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AX4142-001**, 100 mg, 0.34 mmol) in TFA (2.0 ml, 26.2 mmol) was stirred at room temperature for 3h. After concentration *in vacuo* the residue was taken up in DCM and concentrated to give 80 mg (89%) of 1-(cyclopropylmethyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AX4144-003** as a yellow solid. LCMS (method D): retention time 1.15min, M/z = 235 (M + 1).

[00333] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-6-(oxan-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AY7194-001 (EOAI3477013) I-275 was synthesised according to the procedures described in Scheme 3 via synthesis of ethyl 1-(cyclopropylmethyl)-6-(oxan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AY7184-001** described in Scheme 3.17:

[00334] Scheme 3.17



[00335] Ethyl 1-(cyclopropylmethyl)-6-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AY7182-001 – step 1

[00336] Ethyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AY7177-001,** 90%, 950 mg, 3.07 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS 287944-16-5, 709 mg, 3.37 mmol) were dissolved in THF: toluene (4:1, 10 ml) and 2M sodium carbonate (3.07 ml) was added. The reaction mixture was purged with nitrogen for 5 minutes and Pd(dppf)Cl_2 (449 mg, 0.61 mmol) was added. The reaction mixture was stirred at 100°C for 4h, cooled down to room temperature

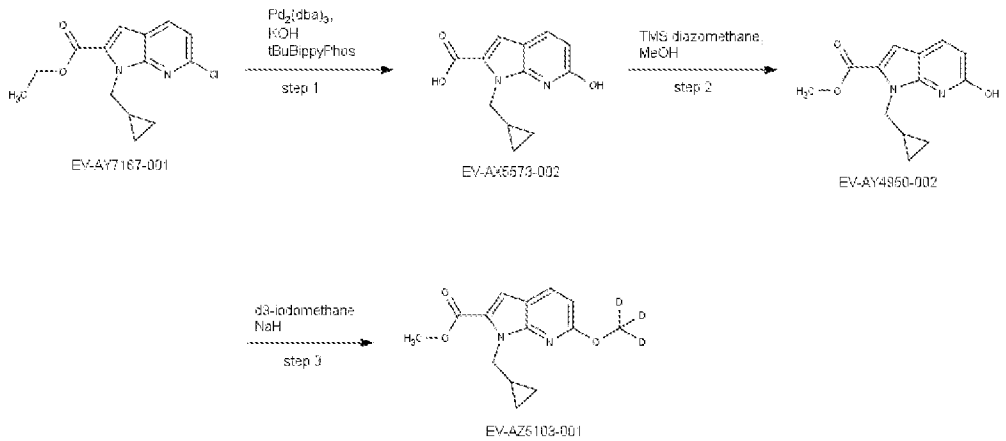
and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (20 ml) and washed with water (2 x 10 ml) and saturated aqueous sodium chloride (10 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by flash column chromatography (0-50% EtOAc/heptane) to obtain 587 mg (56%) of ethyl 1-(cyclopropylmethyl)-6-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AY7182-001** as an orange oil. LCMS (method D): 1.52min, M/z = 327 (M + 1).

[00337] Ethyl 1-(cyclopropylmethyl)-6-(oxan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AY7184-001 – step 2

[00338] To stirred solution of ethyl 1-(cyclopropylmethyl)-6-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AY7182-001**, 587 mg, 1.71 mmol) in EtOAc:Ethanol (1:1, 30 ml) was added Pd/C (10%, 91 mg, 0.09 mmol). The reaction was placed under a hydrogen atmosphere and stirred at room temperature for 18h. The reaction was filtered through a pad of Kieselguhr and washed through with methanol (30 ml). The filtrate was concentrated *in vacuo* to obtain 516 mg (83%) of ethyl 1-(cyclopropylmethyl)-6-(oxan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AY7184-001** as an off-white powder. LCMS (method D): retention time 1.51min, M/z = 329 (M + 1).

[00339] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-6-($^2H_3$)methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AZ5120-001 (EOAI3478073) I-285 was synthesised following the procedures described in Scheme 3 via synthesis of methyl 1-(cyclopropylmethyl)-6-($^2H_3$)methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ5103-001** described in Scheme 3.18:

[00340] Scheme 3.18



[00341] 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AX5573-002 – step 1

[00342] Ethyl 6-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AY7167-001**, 90%, 1.45 g, 4.68 mmol), $Pd_2(dba)_3$ (214 mg, 0.23 mmol), ^{t}Bu-BippyPhos (237 mg, 0.47 mmol) and potassium hydroxide (788 mg, 14.0 mmol) were combined in dioxane (7 ml) and water (7 ml) in a pressure tube. The reaction mixture was purged with nitrogen for 5 minutes then the vessel was sealed and heated at 70°C for 1.5h. The reaction mixture was cooled down to room temperature and filtered through a glass fibre filter paper. The filtrate was partitioned between water (10 ml) and EtOAc (30 ml). The aqueous layer was acidified to pH 5 with 2M HCl and the resulting precipitate was filtered and dried to obtain 0.80 g (62%) of 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AX5573-002** as an off-white powder. LCMS (method D): retention time 0.95min, M/z = 233 (M + 1).

[00343] Methyl 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AY4950-002 – step 2

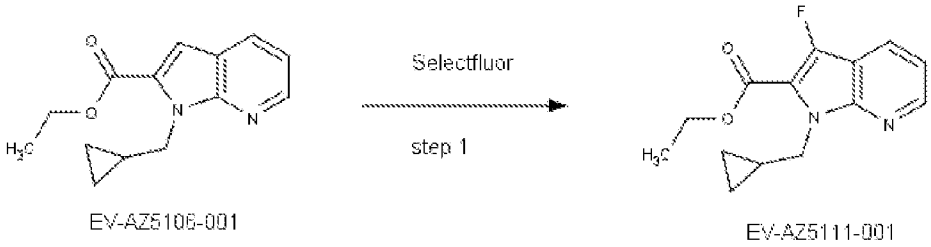
[00344] To a stirred suspension of 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AX5573-002**, 73%, 550 mg, 1.73 mmol) in anhydrous toluene (6 ml) and anhydrous methanol (2 ml, 49.44 mmol) under an atmosphere of nitrogen was added 2M (diazomethyl)(trimethyl)silane (1.73 ml in diethylether). The resulting mixture was stirred at room temperature for 1.5h. Acetic acid (~0.7 ml) was added until the bright yellow colour disappeared. The reaction mixture was concentrated *in vacuo* and triturated with DCM (5 ml). The solid was filtered off and dried to afford 131 mg (28%) of 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid **EV-AY4950-001** as a pale beige solid. LCMS (method D): retention time 1.13min, M/z = 247 (M + 1).

[00345] Methyl 1-(cyclopropylmethyl)-6-($^2H_3$)methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AZ5013-001 – step 3

[00346] To a stirred solution of 1-(cyclopropylmethyl)-6-hydroxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AY4950-001,** 100 mg, 0.40 mmol) in DMF (30ml) was added sodium hydride (60%, 32 mg, 0.80 mmol). The reaction was stirred at room temperature for 10 minutes then iodo($^2H_3$)methane (74 µl, 1.19 mmol) was added. The reaction mixture was stirred at room temperature for 17h, diluted with EtOAc (20 ml), washed with water (2 x 20 ml) and saturated aqueous sodium chloride (10 ml). The organic phase was dried and concentrated *in vacuo* to obtain methyl 1-(cyclopropylmethyl)-6-($^2H_3$)methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ5013-001** (85 mg, 75%) as a yellow powder. LCMS (method D): retention time 1.36min, M/z = 264 (M + 1).

[00347] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-3-fluoro-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AZ5131-001 (EOAI3478196) I-292 was synthesised according to the procedures described in Scheme 3 via synthesis of ethyl 1-(cyclopropylmethyl)-3-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ5111-001** described in Scheme 3.19:

[00348] Scheme 3.19

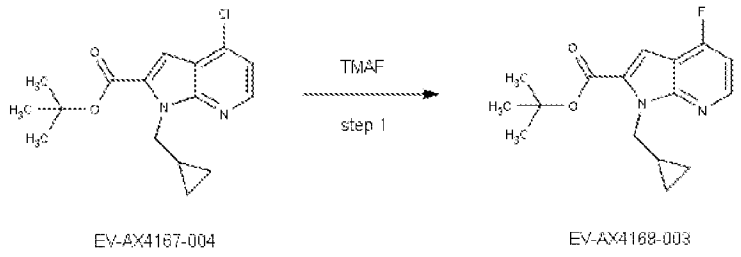


[00349] Ethyl 1-(cyclopropylmethyl)-3-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AZ5111-001 – step 1

[00350] To a stirred solution of ethyl 1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AZ5106-001**, 1.00 g, 4.09 mmol) in DMF (20 ml) was added Selectfluor® (CAS 140681-55-6, 1.45 g, 4.09 mmol). The resulting mixture was stirred at room temperature for 60h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (20 ml) and washed with water (3 x 20 ml). The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by flash column chromatography (0-50% DCM/heptane) to obtain 245 mg (22%) of ethyl 1-(cyclopropylmethyl)-3-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ5111-001** as a yellow oil. LCMS (method D): retention time 1.33min, M/z = 263 (M + 1).

[00351] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AY4588-001 (EOAI3478689) I-294 was synthesised following procedures described in Scheme 3 via synthesis of tert-butyl 1-(cyclopropylmethyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AX4168-003** described in Scheme 3.16 and 3.20:

[00352] Scheme 3.20

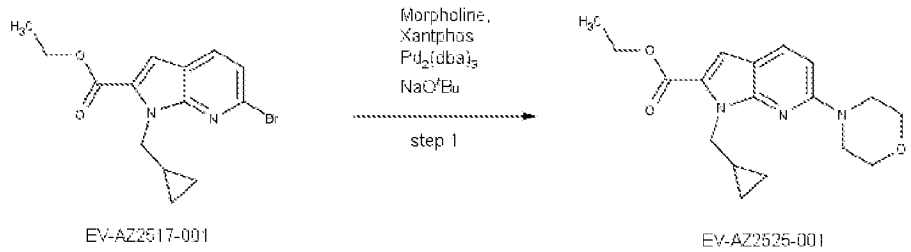


[00353] Tert-butyl 1-(cyclopropylmethyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AX4168-003 – step 1

[00354] To a stirred solution of tert-butyl 4-chloro-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AX4167-001**, 820 mg, 2.67 mmol) in anhydrous DMF (10 ml) was added tetramethylammonium fluoride (500 mg, 5.36 mmol) and the mixture was stirred at 80°C for 18h. The reaction mixture was partitioned between DCM (200 ml) and saturated aqueous sodium bicarbonate (200 ml). The aqueous layer was washed with DCM (2 x 100 ml) and the combined organics were washed with saturated aqueous sodium chloride (100 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (0-10% EtOAc/heptane) to obtain 401 mg (52%) of tert-butyl 1-(cyclopropylmethyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AX4168-003** as a colourless oil. LCMS (method D): retention time 1.48min, M/z = 291 (M + 1).

[00355] (1R,4R,7R)-2-{2-[1-(cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine EV-AX5592-001 (EOAI3478190) I-287 was synthesised according to the procedures described in Scheme 3 via synthesis of ethyl 1-(cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ2525-001** described in Scheme 3.21:

[00356] Scheme 3.21

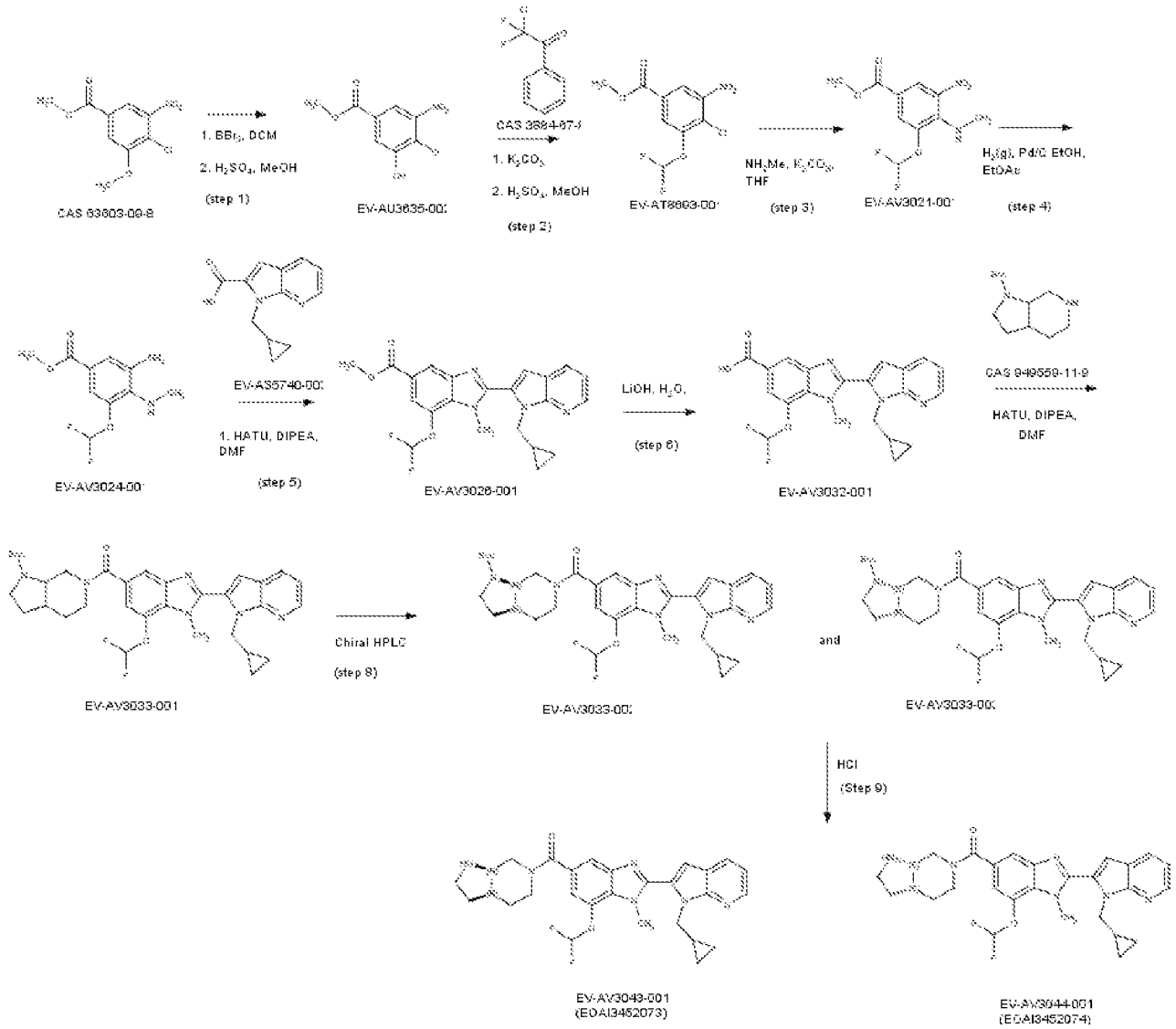


[00357] Ethyl 1-(cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AZ2525-001 – step 1

[00358] Morpholine (74 µl, 0.86 mmol), $Pd_2(dba)_3$ (33 mg, 0.04 mmol), Xantphos (41 mg, 0.07 mmol) and sodium tert butoxide (103 mg, 1.07 mmol) were added to a pressure tube containing a nitrogen-purged solution of ethyl 6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AZ2517-001**, 231 mg, 0.71 mmol) in toluene (6

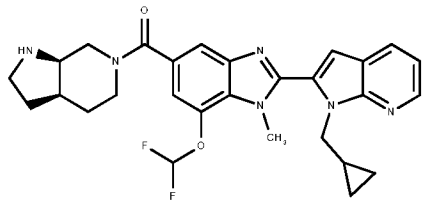
ml). The pressure tube was sealed under a nitrogen environment. The reaction mixture was heated at 110°C for 2h, cooled down to room temperature, diluted with water (10 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with saturated aqueous sodium chloride (10 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (0-20% EtOAc/heptane) to obtain 60 mg (25%) of ethyl 1-(cyclopropylmethyl)-6-(morpholin-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AZ2525-001** as a yellow solid. LCMS (method D): retention time 1.35min, M/z = 330 (M + 1).

[00359] Scheme 4



[00360] Synthesis of 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-

1H-1,3-benzodiazole hydrochloride EV-AV3043-001 (EOAI3452073, absolute stereochemistry arbitrarily assigned) I-24



I-24

[00361] Methyl 4-chloro-3-hydroxy-5-nitrobenzoate EV-AU3635-002 - step 1

[00362] Please note: reaction carried out in duplicate under identical set of conditions. The crudes from each reaction were combined after methanol quench as described below.

[00363] To a stirred solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (CAS 63603-09-8, 5.00 g, 20.4 mmol) in anhydrous DCM (20 ml) at 0 °C under nitrogen was added BBr_3 (1M in DCM, 40.71 ml, 2.81 mmol) drop wise over 20 minutes. The reaction mixtures were stirred at 0°C for 30 minutes and then allowed to warm to room temperature and stirred for 15h. The reaction mixtures were cooled to 0°C, quenched carefully with methanol, combined and concentrated in vacuo. The residue was dissolved in methanol (300 ml), concentrated sulfuric acid (10 drops) was added and the reaction mixture stirred at 75 °C for 5h. The cooled mixture was concentrated in vacuo and to the residue was added water (50 ml) and saturated $NaHCO_3$ (50 mL) carefully to achieve a basic pH. The suspension was sonicated for 15 minutes and stirred for a further 30 minutes before the resultant solid was collected and dried under vacuum filtration. The solid was washed with water (25 ml) and dried to afford 8.14 g (82.9%) of methyl 4-chloro-3-hydroxy-5-nitrobenzoate **EV-AU3635-002** as a light brown powder. LCMS (method D): retention time 1.11min, M/z = 230 (M + 1).

[00364] Methyl 4-chloro-3-(difluoromethoxy)-5-nitrobenzoate EV-AT8693-001 – step 2

[00365] Please note: reaction carried out in triplicate under identical set of conditions. The crudes from each reaction were combined for work-up as described below.

[00366] To a solution of methyl 4-chloro-3-hydroxy-5-nitrobenzoate (**EV-AU3635-002,** 333 mg, 4.32 mmol) and potassium carbonate (7.17 g, 155.4 mmol) in acetonitrile: water (1:1, 20 ml) in a pressure tube was added 2-chloro-2,2-difluoro-1-phenylethanone (1.06 ml, 21.6 mmol). The vessel was sealed and heated at 80 °C for 16h. The cooled reaction mixtures were combined and partitioned between EtOAc (200 ml) and 2M HCl (aq). The aqueous fraction (at ~pH5) was back-extracted with more EtOAc (2x 100 ml). The combined organics

were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in methanol (150 ml), concentrated sulfuric acid (3 drops) was added and the reaction stirred at 75 °C for 40h. The cooled mixture was concentrated in vacuo and to the residue was added saturated $NaHCO_3$ carefully to achieve a basic pH. The aqueous layer was extracted with EtOAc (3x 100 ml) and the combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (0-20% EtOAc/heptane) to obtain 775 mg (60%) of methyl 4-chloro-3-(difluoromethoxy)-5-nitrobenzoate **EV-AT8693-001** as a yellow solid. LCMS (method D): retention time 1.20min, no mass ion observed.

[00367] Methyl 3-(difluoromethoxy)-4-(methylamino)-5-nitrobenzoate EV-AV3021-001 – step 3

[00368] To a stirred solution of methyl 4-chloro-3-(difluoromethoxy)-5-nitrobenzoate (**EV-AT8693-001,** 400 mg, 1.34 mmol) in THF (10 ml) was added K_2CO_3 (1.29 g, 9.35 mmol) and methanamine (2.0M in THF, 1 ml, 2.00 mmol). The reaction mixture was stirred at room temperature for 24h, concentrated in vacuo and partitioned between EtOAc (30 ml) and 1M HCl (15 ml). The organic fraction was washed with more 1M HCl (15 ml), saturated aqueous sodium chloride (10 ml), dried over sodium sulfate, filtered and concentrated in vacuo to obtain methyl 3-(difluoromethoxy)-4-(methylamino)-5-nitrobenzoate **EV-AV3021-001** (370 mg, 88%) as an orange powder. LCMS (method D): retention time 1.17min, M/z = 277 (M + 1).

[00369] Methyl 3-amino-5-(difluoromethoxy)-4-(methylamino)benzoate EV-AV3024-001 – step 4

[00370] To a stirred solution methyl 3-(difluoromethoxy)-4-(methylamino)-5-nitrobenzoate (**EV-AV3021-001**, 370 mg, 1.18 mmol) in EtOAc: EtOH (1:1 20 ml) under nitrogen was added 10% Pd/C (62.7 mg, 0.06 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Kieselguhr and the filter cake was washed through with EtOAc. The filtrate was concentrated in vacuo to obtain 296 mg (93%) of methyl 3-amino-5-(difluoromethoxy)-4-(methylamino)benzoate **EV-AV3024-001** as a pale brown powder. LCMS (method D): retention time 0.97min, M/z = 247 (M + 1).

[00371] Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylate EV-AV3026-001 – step 5

[00372] To a stirred solution of 1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AS5740-003** synthesised according to Scheme 1, step 1, 139 mg, 0.55 mmol) in DMF (5 ml) was added DIPEA (0.08 ml, 0.47 mmol) followed by HATU (177 mg, 0.47 mmol) at 0°C. The resulting mixture was stirred at 0°C for 10 minutes, methyl 3-amino-5-(difluoromethoxy)-4-(methylamino)benzoate (**EV-AV3024-001,** 150 mg, 0.55 mmol) was added and the reaction mixture was stirred at room temperature for 16h. The reaction mixture was then stirred at 50°C for 22h and then concentrated in vacuo. The crude residue was dissolved in acetic acid (3ml) and heated in a sealed tube at 80°C for 2h. The solvent was removed in vacuo and the remaining material was purified by flash column chromatography (0-70% EtOAc/heptane) to obtain 131 mg (48%) of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylate **EV-AV3026-001** as a pale brown powder white powder. LCMS (method D): retention time 1.29min, M/z = 427 (M + 1).

[00373] 2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid EV-AV3032-001 – step 6

[00374] To a stirred solution of methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylate (**EV-AV3026-001**, 131 mg, 0.26 mmol) in THF: MeOH (4 ml: 1 ml) was added 2M lithium hydroxide (528 µl, 1.06 mmol) and the reaction mixture was stirred at 40°C for 16h. The reaction mixture was concentrated in vacuo, suspended in water (2 ml) and acidified to pH 2 using 2M HCl. The resulting suspension was stirred for 10 minutes and the resultant precipitate was collected by vacuum filtration and dried to obtain 108 mg (97%) of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AV3032-001** as an orange powder. LCMS (method D): retention time 1.15min, M/z = 413 (M + 1).

[00375] Tert-butyl 6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AV3033-001 – step 7

[00376] To a solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AV3032-001,** 108 mg, 0.26 mmol) in DMSO (2 ml), at 0°C was added HATU (117.1 mg, 0.31 mmol) and DIPEA (87.87 µl, 0.51 mmol). The reaction mixture was stirred for 10 minutes, tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (CAS 949559-11-9, 61 mg, 0.27 mmol)

was added and the reaction mixture was stirred at room temperature for 16h. The reaction mixture was diluted with water (1 ml) and purified by preparative HPLC (basic method) to obtain 125 mg (79%) of tert-butyl 6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AV3033-001** as a white powder. LCMS (method A): retention time 3.96min, M/z = 621 (M + 1).

[00377] Chiral HPLC to obtain tert-butyl (3aS,7aR)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AV3033-002 and tert-butyl (3aR,7aS)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate EV-AV3033-003 – step 8

[00378] 125mg of tert-butyl 6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AV3033-001** was dissolved in methanol and then purified by chiral HPLC (method G) to obtain 47.6 mg (27%) of tert-butyl (3aS,7aR)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AV3033-002** and 50.1 mg (29%) of tert-butyl (3aS,7aS)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate **EV-AV3033-003** both as colourless gums (absolute stereochemistry arbitrarily assigned).

[00379] **EV-AV3033-002** Chiral purity (UV, 254nm): 100%, retention time: 5.46min (method I)

[00380] **EV-AV3033-003** Chiral purity (UV, 254nm): 100%, retention time: 7.87min (method I)

[00381] 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole hydrochloride EV-AV3043-001 (EOAI3452073, absolute stereochemistry arbitrarily assigned) I-24 – step 9

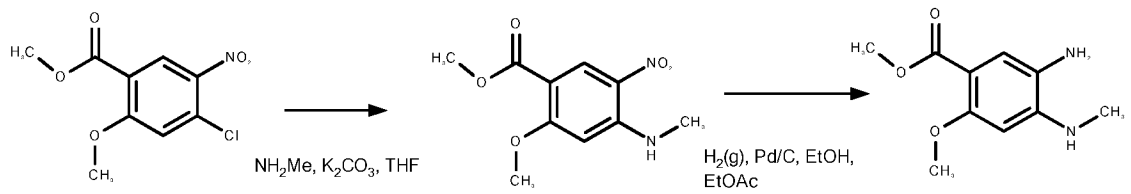
[00382] Tert-butyl (3aS,7aR)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (**EV-AV3033-002,** 47.6 mg, 0.07 mmol) was dissolved in 1.25M HCl in EtOH (1 ml) and stirred at 40 °C for 6h. The reaction mixture was

concentrated under vacuum, dissolved in water (2 ml) and freeze dried to obtain 29 mg (71%) of 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole hydrochloride **EV-AV3043-001 (I-24)** as a yellow powder. LCMS (method A): retention time 2.23min, M/z = 521 (M + 1).

[00383] 5-[(3aR,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole hydrochloride EV-AV3044-001 (EOAI3452074, absolute stereochemistry arbitrarily assigned) I-25 – step 9

[00384] Tert-butyl (3aS,7aS)-6-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (**EV-AV3033-003,** 50.1 mg, 0.08 mmol) was dissolved in 1.25M HCl in EtOH (1 ml) and stirred at 40°C for 6h. The reaction mixture was concentrated under vacuum, dissolved in water (2 ml) and freeze dried to obtain 37 mg (87%) of 5-[(3aR,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole hydrochloride **EV-AV3044-001 (I-25)** as a yellow powder. LCMS (method A): retention time 2.26min, M/z = 521 (M + 1).

[00385] Scheme 5



CAS 109069-75-2 EV-AS3796-002 EV-AS3799-001

[00386] Methyl 2-methoxy-4-(methylamino)-5-nitrobenzoate EV-AS3796-002 – step 1

[00387] To a solution of methyl 4-chloro-2-methoxy-5-nitrobenzoate (CAS 109069-75-2, 1.50 g, 6.11 mmol) in DMF (15 ml) at 0 °C was added methylamine (2.0M in THF, 3.66 ml, 7.33 mmol), the resulting reaction mixture was allowed to warm to room temperature and stirred for 20h. Potassium carbonate (1.01 g, 7.33 mmol) was added and the reaction mixture stirred at room temperature for 1h before more methylamine (2.0M in THF, 3.66 ml, 7.33 mmol) was added. The reaction was stirred at room temperature for a further 5h. The reaction

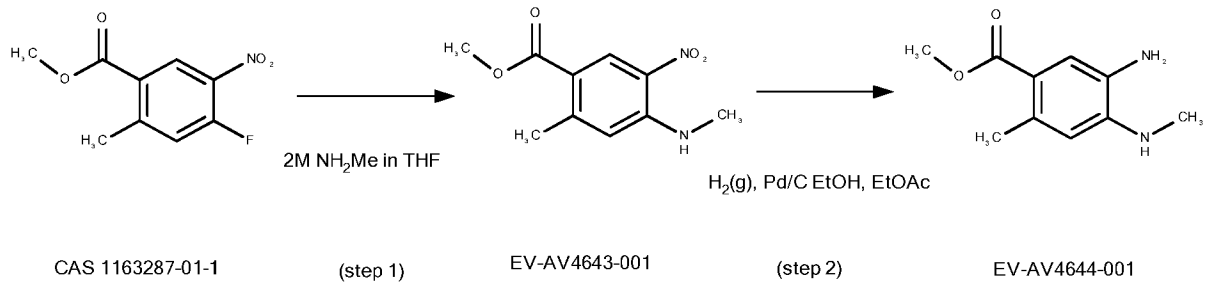
mixture was concentrated in vacuo and the crude residue was purified using by flash column chromatography (0-100% EtOAc/heptane followed by 50% EtOAc/methanol) to obtain 905 mg (56%) of methyl 2-methoxy-4-(methylamino)-5-nitrobenzoate **EV-AS3796-002** as a yellow powder. LCMS (method D): retention time 1.04min, M/z = 241 (M + 1).

[00388] Methyl 5-amino-2-methoxy-4-(methylamino)benzoate EV-AS3799-003 – step 2

[00389] To a stirred solution of methyl 2-methoxy-4-(methylamino)-5-nitrobenzoate (**EV-AS3796-002,** 905 mg, 3.77 mmol) in ethanol: EtOAc (1:2, 60ml) under nitrogen was added Pd/C (10%, 200 mg, 0.19 mmol) and the reaction mixture was stirred under an atmosphere of hydrogen for 5.5h. The reaction mixture was filtered through Kieselguhr and the filter cake was washed through with EtOAc, ethanol and DCM. The filtrate was concentrated in vacuo and the residue was dissolved in DCM: ethanol (6:1, 70 ml). Pd/C (10%, 200 mg, 0.19 mmol) was added under nitrogen and the reaction mixture was stirred under an atmosphere of hydrogen for 6.5h. The reaction mixture was filtered through Kieselguhr and the filter cake was washed through with ethanol and DCM. The filtrate was concentrated in vacuo and the residue was dissolved in DCM: ethanol (1:1, 120 mL). Pd/C (10%, 200 mg, 0.19 mmol) was added under nitrogen and the reaction mixture was stirred under an atmosphere of hydrogen for 22h. The reaction mixture was filtered through Kieselguhr and the filter cake was washed through with ethanol and DCM. The filtrate was concentrated in vacuo to obtain 656 mg (76%) of methyl 5-amino-2-methoxy-4-(methylamino)benzoate **EV-AS3799-003** as a dark brown powder. LCMS (method A): retention time 0.90min, M/z = 211 (M + 1).

[00390] **EV-AS3799-003** was used to synthesise (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-6-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride **EV-AV3612-001 (EOAI3447040) I-68** according to the procedures described in Scheme 1.

[00391] Scheme 6



[00392] Methyl 2-methyl-4-(methylamino)-5-nitrobenzoate EV-AV4643-001 - step 1

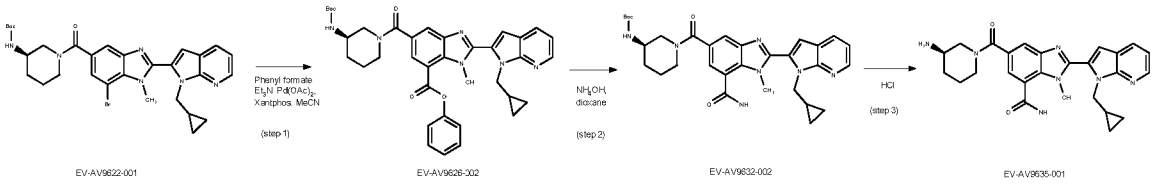
[00393] To a stirred solution of methyl 4-fluoro-2-methyl-5-nitrobenzoate (CAS 1163287-01-1, 1.00 g, 4.69 mmol) in THF (12 ml) was added methylamine (2.0M in THF, 5.4 ml, 10.8 mmol) and the reaction mixture was stirred at room temperature for 10 minutes. The reaction mixture was partitioned between ethyl acetate (250 ml) and saturated aqueous $NaHCO_3$ (100 ml). The organic extract was washed with water (100 ml), dried over sodium sulfate, filtered and concentrated in vacuo to obtain 1.07 g (quantitative) of methyl 2-methyl-4-(methylamino)-5-nitrobenzoate **EV-AV4643-001** as a yellow powder. LCMS (method D): retention time 1.14min, M/z = 225 (M + 1).

[00394] **Methyl 5-amino-2-methyl-4-(methylamino)benzoate EV-AV4644-001 – step 2**

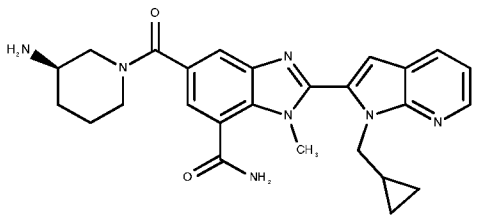
[00395] To a stirred solution of methyl 2-methyl-4-(methylamino)-5-nitrobenzoate (**EV-AV4643-001,** 1.07 g, 4.77 mmol) in ethanol (100 ml) under ntirogen was added 10% Pd/C (102 mg, 0.048 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through glass fibre sinter and the filtrate was concentrated in vacuo to obtain 1.02 g (98%) of methyl 5-amino-2-methyl-4-(methylamino)benzoate **EV-AV4644-001** as a light brown crystalline solid. LCMS (method D): retention time 0.77min, M/z = 195 (M + 1).

[00396] Methyl 5-amino-2-methyl-4-(methylamino)benzoate **EV-AV4644-001** was used to synthesise (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1,6-dimethyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride **EV-AV4649-001 (EOAI3454825) I-103** according to the procedures described in Scheme 2.

[00397] **Scheme 6**



[00398] **Synthesis of 5-[(3R)-3-aminopiperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3- b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-7-carboxamide hydrochloride EV-AV9635-001 (EOAI3455108) I-112**



I-112

[00399] Phenyl 5-[(3R)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo [2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-7-carboxylate EV-AV9626-002 – step 1

[00400] A solution of $Pd(OAc)_2$ (6 mg, 0.03 mmol) and Xantphos (30 mg, 0.05 mmol) in acetonitrile (20 ml) in a pressure tube was de-gassed for 5 minutes and tert-butyl N-[(3R)-1-{7-bromo-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AV9622-001,** synthesised according to Scheme 1, 520 mg, 0.86 mmol), phenyl formate (0.19 ml, 1.71 mmol) and triethylamine (0.24 ml, 1.71 mmol) were added. The reaction vessel was sealed and heated to 80°C for 4h. The cooled reaction mixture was diluted with EtOAc and washed with water. The organic fraction was dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (0-100% EtOAc) to obtain 220 mg (39%) of phenyl 5-[(3R)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)- 1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-7-carboxylate **EV-AV9626-002** as a beige solid. LCMS (method D): retention time 1.35min, M/z = 649 (M + 1).

[00401] Tert-butyl N-[(3R)-1-{7-carbamoyl-2-[1-(cyclopropylmethyl)-1H-pyrrolo [2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AV9632-002 – step 2

[00402] To a solution of phenyl 5-[(3R)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H- pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-7-carboxylate (**EV-AV9626-002,** 110 mg, 0.17 mmol) in dioxane (5 ml) in a pressure tube was added ammonium hydroxide (35% w/w, 0.1 ml, 2.54 mmol). The vessel was sealed and heated at 50°C 2.5h. More ammonium hydroxide (35% w/w, 0.5 ml) was added and the vessel was sealed and heated at 50°C for 17h. More ammonium hydroxide (35% w/w, 0.5 ml) was added and the vessel was sealed and heated at 50°C for a further 23h. The reaction mixture was concentrated in vacuo, re-dissolved in DCM and washed with 5% NaOH (aq). The organic fraction was passed through a phase separator cartridge and concentrated in vacuo. The crude residue was purified by preparative HPLC (basic method) to obtain 75 mg (77%) of tert-butyl N-[(3R)-1-{7-carbamoyl-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl- 1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AV9632-002** an off-white powder. LCMS (method D): retention time 1.08min, M/z = 572 (M + 1).

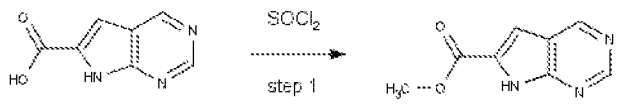
[00403] 5-[(3R)-3-aminopiperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]- 1-methyl-1H-1,3-benzodiazole-7-carboxamide hydrochloride EV-AV9635-001 (I-112) – step 3

[00404] To tert-butyl N-[(3R)-1-{7-carbamoyl-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3- benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AV9632-002,** 75 mg, 0.13 mmol) was added 1.25 M HCl in ethanol (3 ml) and the reaction mixture was stirred at 40°C for 1.5h. The reaction mixture was concentrated in vacuo and the residue was freeze-dried from water (3 mL) to obtain 57.6 mg (84%) of 5-[(3R)-3-aminopiperidine-1-carbonyl]-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]- 1-methyl-1H-1,3-benzodiazole-7-carboxamide hydrochloride **EV-AV9635-001 (I-112)** as an off-white powder. LCMS (method A): retention time 1.53min, M/z = 472 (M + 1).

[00405] Special cases

[00406] 2-[7-(Cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AQ4191-002 (EOAI3434971) I-9 was synthesised according to the procedures described in Scheme 1, **2-[7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-5-{octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl}-1H-1,3-benzodiazole EV-AS1566-001 (EOAI3435740) I-15, 5-[(3aR,7aR)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AS1590-001 (EOAI3437977) I-12** and **5-[(3aS,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridine-6-carbonyl]-2-[7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole EV-AS1591-001 (EOAI3437978) I-4** were synthesised according to the procedures described in Scheme 2 via synthesis of methyl 7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AQ1970-001** described in Scheme 7:

[00407] Scheme 7

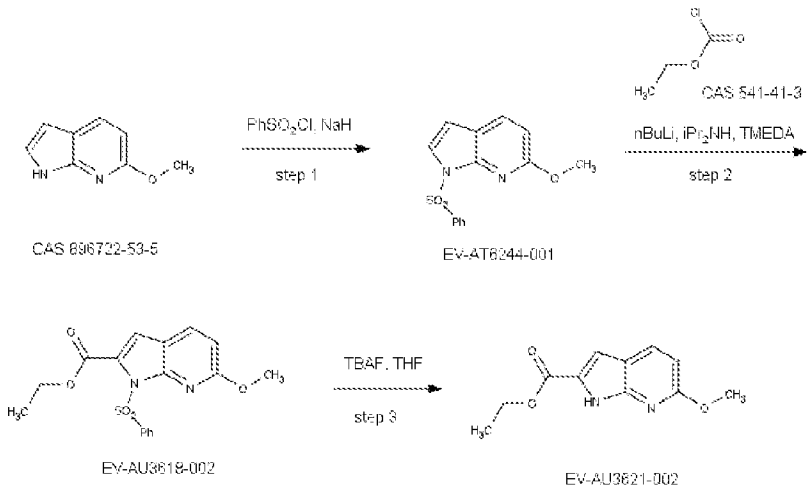


[00408] To a stirred suspension of 7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (CAS 1016241-64-7, 0.50 g, 3.06 mmol) in methanol (10ml) at 0°C was added thionyl dichloride (0.56 ml, 7.66 mmol) dropwise under an atmosphere of nitrogen. The resulting mixture was

allowed to warm to room temperature and then heated up to reflux for 24h. Additional methanol (15ml) was added to aid dissolution, the mixture was cooled to 0°C and further thionyl dichloride (0.56 ml, 7.66 mmol) was added dropwise under an atmosphere of nitrogen. The mixture was heated again to reflux for 3h and evaporated to dryness to obtain 0.66 g (quantitative) of methyl 7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate **EV-AQ1970-001** as a pink powder. LCMS (method J): retention time 1.02min, M/z = 178 (M + 1).

[00409] (3R)-1-{2-[1-(Cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine EV-AU3631-001 (EOAI3447868) I-70 was synthesised according to the procedures described in Scheme 1, (3R)-1-{2-[1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-(2,2-difluoroethyl)-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine **EV-AV3086-001 (EOAI3454400) I-94** and (3R)-1-{2-[1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine **EV-AV4830-003 (EOAI3454405) I-33** were synthesised according to the procedures described in Scheme 2, (3R)-1-{2-[1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine **EV-AV3852-001 (EOAI3454816) I-104** and (3R,5R)-1-{2-[1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-(difluoromethoxy)-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-fluoropiperidin-3-amine **EV-AV4849-001 (EOAI3455105) I-109** were synthesised according to the procedures described in Scheme 3 via synthesis of ethyl 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3621-002** described in Scheme 8:

[00410] Scheme 8



[00411] 1-(Benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine EV-AT6244-001 – step 1

[00412] To a stirred solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine (CAS 896722-53-5, 300 mg, 2.02 mmol) in THF (15 ml) at 0°C was added sodium hydride (60%, 121 mg, 3.04 mmol) portion-wise under an atmosphere of nitrogen. The resulting mixture was stirred at 0°C for 30 minutes before the addition of benzenesulfonyl chloride (0.31 ml, 2.44 mmol). The mixture was stirred at room temperature for 2h. The reaction mixture was poured onto water (20 ml) and extracted with EtOAc (3 x 10ml). The combined organic layers were washed with saturated aqueous sodium chloride (20ml), dried over sodium sulfate, filtered and concentrated in vacuo to afford 607 mg (97.7%) of 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine **EV-AT6244-001** as a beige solid. LCMS (method D): retention time 1.26 min, M/z = 289 (M + 1).

[00413] Ethyl 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AU3618-002 – step 2

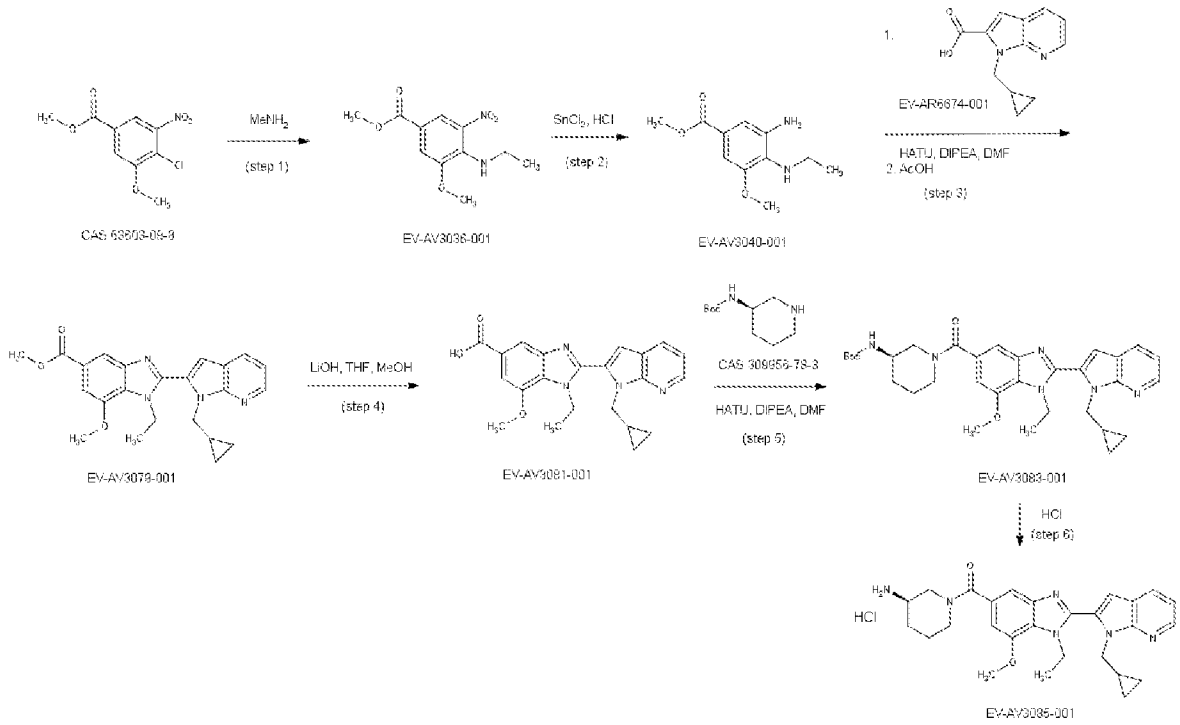
[00414] To a stirred solution of diisopropylamine (0.15 ml, 1.04 mmol) in anhydrous THF (5 ml) at -78°C was added n-butyllithium (2.5M in hexanes, 0.37 ml, 0.94 mmol) drop-wise over 10 minutes under an atmosphere of nitrogen. The resulting mixture was stirred for 30 minutes, warmed to room temperature and stirred for 1h. The mixture was then diluted with anhydrous THF (5 ml) and cooled to -30°C. A solution of 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine (**EV-AT6244-001**, 200 mg, 0.69 mmol) and TMEDA (0.16 ml, 1.04 mmol) in anhydrous THF (10ml) was added via cannula over 20 minutes. The resulting mixture was stirred between -30°C and -20°C for 2.5h. Ethyl chloroformate (CAS 541-41-3, 0.20 ml, 2.08 mmol) was added drop-wise over 10 minutes, the mixture was stirred at -30°C for 2h before warming to room temperature over 16h. The reaction mixture was cooled to 0°C and quenched with water (15ml). The aqueous layer was extracted with DCM (3 x 15ml), the combined layers were washed with water (3x 10 ml), dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 93 mg (36.5%) of ethyl 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3618-002** as an off-white solid. LCMS (method D): retention time 1.31 min, M/z = 361 (M + 1).

[00415] Note: the reaction was repeated to obtain an additional batch of ethyl 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (165 mg, 29.6%, **EV-AU3619-002**) which was combined with **EV-AU3618-002** to carry out step 3.

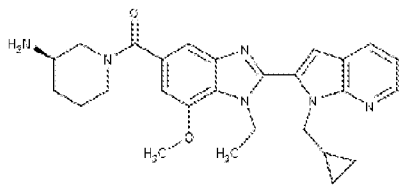
[00416] Ethyl 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate EV-AU3621-002 – step 3

[00417] To a stirred solution of ethyl 1-(benzenesulfonyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**EV-AU3618-002** and **EV-AU3619-002**, 84%, 258 mg, 0.60 mmol) in THF (10 ml) was added TBAF (1M in THF, 0.78 ml, 0.78 mmol) and the mixture was stirred at 70°C for 30 minutes. The reaction mixture was concentrated to around 1/4 volume and purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 95 mg (71.7%) of ethyl 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **EV-AU3621-002** as an off-white powder. LCMS (method D): retention time 1.14 min, M/z = 221 (M + 1).

[00418] Scheme 9



[00419] Synthesis of 1 (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine EV-AV3085-001 (EOAI3449644) I-119



I-119

[00420] Methyl 4-(ethylamino)-3-methoxy-5-nitrobenzoate EV- AV3036-001 – step 1

[00421] Ethylamine (2M in THF, 18.3 ml) and potassium carbonate (21.1 g, 152.7 mmol) were added to a stirred solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (CAS 63603-09-8, 7.50 g, 30.5 mmol) in THF (100 ml). The reaction mixture was stirred at 50°C for 16h then at 60°C for 7h. Further potassium carbonate (21.1 g, 152.7 mmol) and ethylamine (2M in THF, 7.63 ml) were added and the stirring was continued at room temperature for 60h. The volatiles were removed *in vacuo* and the resulting residue was diluted with EtOAc (150 ml), washed with water (2 x 50 ml) and saturated aqueous sodium chloride (50 ml). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 6.88g (85%) of methyl 4-(ethylamino)-3-methoxy-5-nitrobenzoate **EV-AV3036-001** as an orange powder. LCMS (method D): retention time 1.21min, M/z = 255 (M + 1).

[00422] **Methyl 3-amino-4-(ethylamino)-5-methoxybenzoate EV-AV3040-001 – step 2**

[00423] $SnCl_2$ (19.7 g, 103.9 mmol) and 2M HCl (52 ml) were added to a stirred suspension of methyl 4-(ethylamino)-3-methoxy-5-nitrobenzoate (**EV-AV3036-001**, 6.88 g, 26.0 mmol) in ethanol (150 ml). The reaction mixture was stirred with reflux for 1h and the volatiles were removed *in vacuo*. The resulting residue was basified with 5M aqueous sodium hydroxide (50 ml) then diluted with EtOAc (150 ml) and stirred for 15 minutes. The mixture was then filtered through Kieselguhr and the filter was washed with EtOAc. The organic phase of the filtrate was separated and washed with saturated aqueous sodium chloride (50 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to obtain 4.20 g (71%) of methyl 3-amino-4-(ethylamino)-5-methoxybenzoate **EV-AV3040-001** as a brown powder. LCMS (method D): retention time 0.70min, M/z = 225 (M + 1).

[00424] **Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylate EV-AV3079-001 – step 3**

[00425] To a solution of 1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**EV-AR6674-001**, synthesised according to Scheme 1, step 1, 300 mg, 1.36 mmol) in DMF (5 ml) at 0°C were added HATU (620 mg, 1.63 mmol) and DIPEA (0.47 ml, 2.72 mmol). The mixture was stirred at 0°C for 10 minutes then 3-amino-4-(ethylamino)-5-methoxybenzoate (**EV-AV3040-001**, 311 mg, 1.36 mmol). was added. The mixture was heated to 50°C and stirred for 3h. The solvent was removed *in vacuo*, the residue was dissolved in acetic acid (3 ml) and heated in a sealed tube at 80°C for 2h. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 488mg (76%) of methyl

2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylate **EV-AV3079-001** as a yellow powder. LCMS (method D): retention time 1.31min, M/z = 405 (M + 1).

[00426] 2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylic acid EV-AV3081-001 – step 4

[00427] Methyl 2-[1-(cyclopropylmethyl)-1H-pyrrolo [2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylate (**EV-AV3079-001**, 488 mg, 1.04 mmol) was dissolved in THF/Methanol (4 ml/ 1 ml) and 2M aqueous lithium hydroxide (5.19 ml) was added. The mixture was stirred at 40°C for 16h and the solvent was removed *in vacuo*. The resulting residue was dissolved in water (2 ml) and acidified to pH 2 using 2M HCl. The mixture was stirred at room temperature for 10 minutes, the precipitate formed was filtered under vacuum and dried to give 350 mg (80%) of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylic acid **EV-AV3081-001** as a white powder. LCMS (method D): retention time 1.14min, M/z = 391 (M + 1).

[00428] Tert-butyl N-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate EV-AV3083-001 – step 5

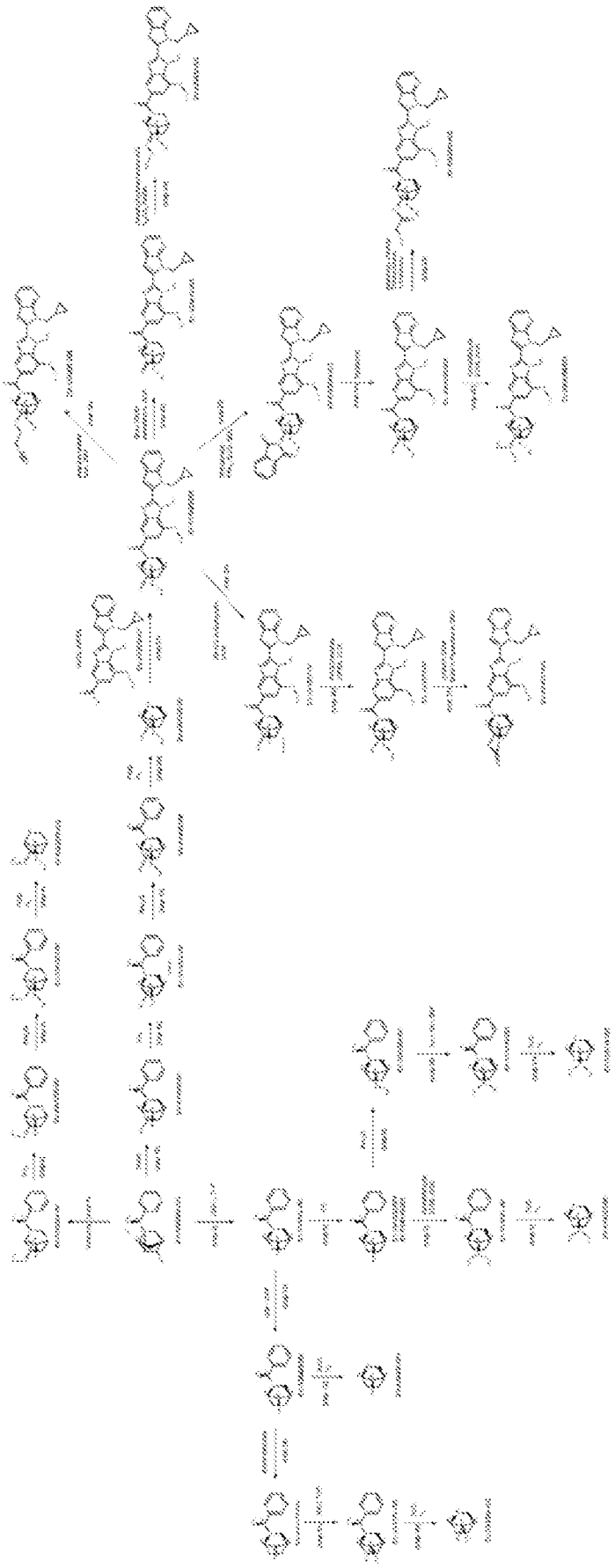
[00429] HATU (217 mg, 0.57 mmol) and DIPEA (163 µl, 0.95 mmol) were added to a stirred solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AV3081-001**, 200 mg, 0.48 mmol) in DMSO (2 ml) at 0°C. The reaction mixture was stirred at 0°C for 10 minutes then tert-butyl tert-butyl N-[(3R)-piperidin-3-yl]carbamate (CAS 309956-78-3, 100 mg, 0.50 mmol) was added. The mixture was allowed to warm up to room temperature and stirred for 20 minutes. The crude was purified by preparative HPLC (basic method) to obtain 211 mg (74%) of tert-butyl N-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo [2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate **EV-AV3083-001** as a white powder. LCMS (method D): retention time 1.25min, M/z = 573 (M + 1).

[00430] (3R)-1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine EV-AV3085-001 (EOAI3449644) – step 6

[00431] Tert-butyl N-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo [2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carb amate (**EV-AV3083-001**, 210 mg, 0.35 mmol) was dissolved in DCM (2 ml) and 2M HCl in diethyl ether (2 ml) was added. The reaction mixture was stirred at room temperature for 2h and the solvent was removed *in vacuo*. The residue was re-dissolved in water/acetonitrile (2 ml/0.5 ml), concentrated *in vacuo* and further dried to give 147 mg (81%) of (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-ethyl-7-methoxy-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloric acid **EV-AV3085-001** as a yellow powder. LCMS (method A): retention time 2.19min, M/z = 473 (M + 1).

[00432] **(1S,4R,6S,7R)-7-Amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-ol EV-AW5575-001 (EOAI3459241) I-162** was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW5569-001** described in Scheme 10:

[00433] **Scheme 10**



[00434] (1S,4R,6S,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-methoxy-2-azabicyclo[2.2.1]heptan-7-amine EV-AW5584-001 (EOAI3459405) I-167 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1S,4R,6S,7R)-6-methoxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW5577-001** described in Scheme 10.

[00435] (1R,4R,6S,7R)-7-bromo-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane EV-AW5568-001 – step 1 (Scheme 10)

[00436] (4R,6R)-3-bromo-1-[(1S)-1-phenylethyl]-1-azatricyclo[2.2.1.0]heptan-1-ium bromide (**EV-AW8588-001**, 1.00 g, 3.58 mmol) was dissolved in Methanol: acetonitrile (1:1, 40 ml) and the resulting suspension was heated to 65°C for 12h. The reaction was concentrated *in vacuo* and purified by flash column chromatography (0-30% EtOAc/heptane) to afford 0.85 g (98%) of (1R,4R,6S,7R)-7-bromo-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane **EV-AW5568-001** as an orange oil. LCMS (method D): retention time 0.73min, M/z = 312 (M + 1).

[00437] (1S,4R,6S,7R)-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine EV-AW5570-001 – step 2 (Scheme 10)

[00438] To (1R,4R,6S,7R)-7-bromo-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (**EV-AW5568-001**, 0.84 g, 2.71 mmol) was added 7M ammonia in methanol (7.74 ml). The solution was stirred for 2h at 80°C. The reaction mixture was concentrated *in vacuo* to afford 0.82 g (98%) of (1S,4R,6S,7R)-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine **EV-AW5570-001** as an orange solid. LCMS (method D): retention time 0.27min, M/z = 247 (M + 1).

[00439] Tert-butyl N-[(1S,4R,6S,7R)-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW5572-001 – step 3 (Scheme 10)

[00440] The title compound was synthesised from (1S,4R,6S,7R)-6-methoxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine (**EV-AW5570-001**) according to the procedure described in Scheme 10 step 19. LCMS (method D): retention time 0.86min, M/z = 347 (M + 1).

[00441] Tert-butyl N-[(1S,4R,6S,7R)-6-methoxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW5577-001 – step 4 (Scheme 10)

[00442] The title compound was synthesised from tert-butyl N-[(1S,4R,6S,7R)-6-methoxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW5572-001**) according to the procedure described in Scheme 10 step 20. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.78 – 5.48

(m, 1H), 3.94 (d, *J* = 7.6 Hz, 1H), 3.49 (d, *J* = 6.1 Hz, 1H), 3.34 (s, 3H), 3.22 (s, 1H), 2.99 (d, *J* = 9.2 Hz, 1H), 2.47 (d, *J* = 9.5 Hz, 1H), 2.41 (s, 1H), 1.90 (dd, *J* = 13.5, 7.1 Hz, 1H), 1.75 – 1.63 (m, 2H), 1.44 (s, 9H). No LCMS data.

[00443] (1R,4R,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-N-methyl-2-azabicyclo[2.2.1]heptan-7-amine EV-AY4518-001 (EOAI3462944) I-237 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1R,4R,7R)-2-azabicyclo[2.2.1]heptan-7-yl]-N-methylcarbamate **EV-AY4514-001** described in Scheme 10.

[00444] (1R,4R,7R)-7-bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane EV-AX4162-002 – step 5 (Scheme 10)

[00445] To a solution of (4R,6R)-3-bromo-1-[(1S)-1-phenylethyl]-1-azatricyclo[2.2.1.0]heptan-1-ium bromide (**EV-AW8588-001**, 3.10 g, 8.63 mmol) in anhydrous THF (60 ml) was added 4M lithium aluminium hydride in diethyl ether (2.5 ml, 10 mmol) at -10 to -15°C. The mixture was stirred at -10 to -15°C for 2h and quenched with saturated aqueous sodium bicarbonate (60 ml). The mixture was added to water (200 ml) and extracted with ethyl acetate (4 x 100 ml). The combined extracts were washed with saturated aqueous sodium chloride (100 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 2.11 g (87%) of (1R,4R,7R)-7-bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane **EV-AX4162-002** as a brown oil. LCMS (method D): retention time 0.81min, M/z = 279.95/281.85 (M + 1).

[00446] (1R,4R,7R)-2-[(1S)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine EV-AW5552-001 – step 6 (Scheme 10)

[00447] The title compound was synthesised from (1R,4R,7R)-7-bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (**EV-AX4162-002**) according to the procedure described in Scheme 10 step 2. LCMS (method D): retention time 0.20min, M/z = 217 (M + 1).

[00448] Tert-butyl N-[(1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW5553-001 – step 9 (Scheme 10)

[00449] The title compound was synthesised from (1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine (**EV-AW5552-001**) according to the procedure described in Scheme 10 step 19. LCMS (method D): retention time 0.83min, M/z = 317 (M + 1).

[00450] Tert-butyl N-methyl-N-[(1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-

azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AY4510-001 – step 10 (Scheme 10)

[00451] To a stirred solution of tert-butyl N-[(1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW5553-001**, 100 mg, 0.32 mmol) in DMF (2 ml) under an atmosphere of nitrogen was added sodium hydride (60%, 15 mg, 0.38 mmol) followed by iodomethane (39 µL, 0.63 mmol). The reaction mixture was stirred at room temperature for 16h, diluted with water (30 ml) and extracted with EtOAc (2 x 30 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 110 mg (quantitative) of tert-butyl N-methyl-N-[(1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY4510-001** as a colourless viscous oil. LCMS (method D): retention time 1.06min, M/z = 331 (M + 1).

[00452] Tert-butyl N-[(1R,4R,7R)-2-azabicyclo[2.2.1]heptan-7-yl]-N-methylcarbamate EV-AY4514-001 – step 11 (Scheme 10)

[00453] The title compound was synthesised from tert-butyl N-methyl-N-[(1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AY4510-001**) according to the procedure described in Scheme 10 step 20. ^{1}H NMR (500 MHz, Methanol-d_4) δ 4.56 (s, 1H), 4.33 (s, 1H), 3.61 (s, 1H), 3.22 (d, J = 10.9 Hz, 1H), 2.98 (d, J = 11.1 Hz, 1H), 2.92 – 2.87 (m, 3H), 2.82 (s, 1H), 1.98 – 1.83 (m, 2H), 1.81 – 1.72 (m, 1H), 1.63 – 1.56 (m, 1H), 1.48 (s, 9H). No LCMS data.

[00454] (1R,4R,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-N,N-dimethyl-2-azabicyclo[2.2.1]heptan-7-amine EV-AY4524-001 (EOAI3468840) I-243 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1R,4R,7R)-2-azabicyclo[2.2.1]heptan-7-yl]-N-methylcarbamate **EV-AY4523-001** described in Scheme 10:

[00455] (1R,4R,7R)-N,N-dimethyl-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine EV-AY4521-001 – step 7 (Scheme 10)

[00456] To a stirred solution of (1R,4R,7R)-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine dihydrochloride (**EV-AY4519-001**, 210 mg, 0.73 mmol) (synthesised in Scheme 10, step 6) in DCM (10 ml) under an atmosphere of nitrogen was added an aqueous solution of formaldehyde (37%, 0.27 ml, 3.63 mmol) followed by STAB (923 mg, 4.36 mmol). The reaction mixture was stirred at room temperature for 16h, diluted with water (30 ml) and extracted with EtOAc (2 x 30 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 189 mg (quantitative) of (1R,4R,7R)-N,N-dimethyl-2-[(1S)-1-phenylethyl]-2-

azabicyclo[2.2.1]heptan-7-amine (EV-AY4521-001) as a colourless viscous oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 – 7.12 (m, 6H), 3.57 (s, 1H), 3.01 (s, 1H), 2.84 (s, 1H), 2.31 – 2.12 (m, 3H), 2.07 – 1.95 (m, 6H), 1.67 (s, 2H), 1.36 (s, 1H), 1.23 – 1.12 (m, 3H). No LCMS data.

[00457] Tert-butyl N-[(1R,4R,7R)-2-azabicyclo[2.2.1]heptan-7-yl]-N-methylcarbamate EV-AY4523-001 – step 8 (Scheme 10)

[00458] The title compound was synthesised from (1R,4R,7R)-N,N-dimethyl-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-amine (**EV-AY4521-001**) according to the procedure described in Scheme 10 step 20. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.41 (s, 1H), 2.12 (dt, J = 9.8, 3.0 Hz, 1H), 1.79 (d, J = 9.8 Hz, 1H), 1.49 (s, 1H), 1.47 – 1.37 (m, 7H), 1.10 – 0.99 (m, 2H), 0.71 – 0.61 (m, 1H), 0.58 – 0.48 (m, 1H). No LCMS data.

[00459] 3-{[(1S,4R,6S,7R)-7-Amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-yl]oxy}propanenitrile EV-AY4932-001 (EOAI3472707) I-256 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1S,4R,6S,7R)-6-(2-cyanoethoxy)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY4931-001** described in Scheme 10. The final deprotection was performed according to the procedures described in Scheme 1.

[00460] Tert-butyl N-[(1S,4R,6S,7R)-6-(2-cyanoethoxy)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AY4931-001 – step 22 (Scheme 10)

[00461] To a stirred solution of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AY5029-001**, 120 mg, 0.18 mmol) in DMF (3 ml) at 0°C was added sodium hydride (60%, 7.8 mg, 0.20 mmol). The reaction was stirred for 5 minutes then prop-2-enenitrile (12 µl, 0.18 mmol) was added. The reaction was stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (10 ml) and water (10 ml). The aqueous layer was extracted with EtOAc (2 x 5 ml) and the combined organics were washed with water (5 ml), dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by preparative HPLC (acidic method) to obtain 80 mg (67%) of tert-butyl N-[(1S,4R,6S,7R)-6-(2-cyanoethoxy)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY4931-001** as a

colourless oil. LCMS (method D): retention time 1.28min, M/z = 640 (M + 1).

[00462] 2-{[(1S,4R,6S,7R)-7-Amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-yl]oxy}acetonitrile EV-AY4925-001 (EOAI3470051) I-246 was synthesised according to the procedure described in Scheme 10 step 22 using bromoacetonitrile. The final deprotection was performed according to the procedures described in Scheme 1. LCMS (method A): retention time 2.05min, M/z = 526 (M + 1).

[00463] 1S,4R,6E,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(methoxyimino)-2-azabicyclo[2.2.1]heptan-7-amine EV-AZ4422-001 (EOAI3482317) I-307 was synthesised according to the N-Boc deprotection procedure described in Scheme 3 via synthesis of N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(methoxyimino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4420-002** described in Scheme 10:

[00464] Tert-butyl N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-oxo-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AZ4415-001 – step 23 (Scheme 10)

[00465] To a solution of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AY5029-001**, 490 mg, 0.84 mmol) in DCM (10 ml) at 0°C was added Dess-Martin periodinane (710 mg, 1.67 mmol) and the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 24h, quenched with saturated aqueous sodium thiosulfate (10 ml) and extracted with DCM (3 x 20 ml). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The remaining residue was purified by preparative HPLC (acidic method) to afford 471 mg (89%) of tert-butyl N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-oxo-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4415-001** as a white solid. LCMS (method D): retention time 1.25min, M/z = 585 (M + 1).

[00466] N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(methoxyimino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AZ4420-002 – step 24 (Scheme 10)

[00467] To a suspension of tert-butyl N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-

pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-oxo-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AZ4415-001**, 50 mg, 0.08 mmol) in methanol (1 ml) was added O-methylhydroxylamine HCl (6.7 mg, 0.08 mmol) and sodium bicarbonate (6.6 mg, 0.08 mmol). The reaction was heated at 65°C for 15h before cooling to room temperature. Further O-methylhydroxylamine HCl (6.7 mg, 0.08 mmol) and sodium bicarbonate (6.6 mg, 0.08 mmol) were added after 2h and the reaction was continued at 65°C for an additional 6h. The temperature was reduced to 60°C and the reaction was stirred for 16h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The resulting yellow oil was purified by preparative HPLC (acidic method) to afford 12 mg (26%) of N-[(1S,4R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(methoxyimino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4420-002** as a white solid. LCMS (method D): retention time 1.30 min, M/z = 614 (M + 1).

[00468] (1R,4R,6S,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptane-6,7-diamine EV-AY5019-001, (**EOAI3469927**) **I-245** was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1R,4R,6S,7R)-6-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8585-005** described in Scheme 10.

[00469] Tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW8584-001-step 25 (Scheme 10)

[00470] DIAD (107 µl, 0.51 mmol) was added to a stirred solution of triphenylphosphane (134 mg, 0.51 mmol) in anhydrous THF (5 ml) under an atmosphere of nitrogen at 0°C. The reaction was stirred at 0°C for 5 minutes then a solution of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AY5029-001**, 200 mg, 0.34 mmol) in anhydrous THF (5 ml) was added followed by 1H-isoindole-1,3(2H)-dione (41 µl, 0.34 mmol). The reaction mixture was stirred at room temperature for 18h, concentrated *in vacuo* and purified by flash column chromatography (0-100% EtOAc/heptane) to obtain 138 mg (48%) of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-

benzodiazole-5-carbonyl}-6-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8584-001** as a white foam. LCMS (method D): retention time 1.28min, M/z = 716 (M + 1).

[00471] Tert-butyl N-[(1R,4R,6S,7R)-6-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW8585-005 – step 26 (Scheme 10)

[00472] To a solution of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW8584-001**, 134 mg, 0.19 mmol) in DCM (3 ml) was added hydrazine hydrate (1:1) (27 µl, 0.56 mmol). The reaction mixture was stirred at room temperature for 45 minutes and at 50°C for 18h, filtered and the filtrate was concentrated *in vacuo*. EtOAc (10 ml) was added to the residue and the mixture was stirred for 5 minutes then filtered. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (20-100% EtOAc/heptane) to obtain 75 mg (63%) of tert-butyl N-[(1R,4R,6S,7R)-6-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8585-005** as a white foam. LCMS (method D): retention time 1.05min, M/z = 586 (M + 1).

[00473] (1S,4R,6S,7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-N6,N6-dimethyl-2-azabicyclo[2.2.1]heptane-6,7-diamine EV-AW8596-002 (EOAI3476814) I-268 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(dimethylamino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8594-001** as described in Scheme 10.

[00474] Tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(dimethylamino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW8594-001 – step 27 (Scheme 10)

[00475] To a stirred mixture of tert-butyl N-[(1R,4R,6S,7R)-6-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW8585-005**, 80 mg, 0.12 mmol) in DCM (1 ml) at room temperature was added 3M formaldehyde solution (37% in WATER, 10 µl). The reaction mixture was stirred for 15 minutes then sodium

tris(acetato-kappaO)(hydrido)borate(1-) (37 mg, 0.18 mmol) was added. The reaction was continued for 17h. Additional sodium tris(acetato-kappaO)(hydrido)borate(1-) (37 mg, 0.18 mmol) was added and the reaction continued for 2h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (acidic method) to afford 20 mg (28%) of tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(dimethylamino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8594-001** as a white solid. LCMS (method D): retention time 1.16min, M/z = 614 (M + 1).

[00476] N-[(1S,4R,6S,7R)-7-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-yl]propanamide EV-AW8592-002 (EOAI3476589) I-264 was synthesised according to the procedures described in Scheme 3 via synthesis of tert-butyl N-[(1R,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-propanamido-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8590-002** as described in Scheme 10.

[00477] Tert-butyl N-[(1R,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-propanamido-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW8590-002 – step 28 (Scheme 10)

[00478] To a stirred solution of tert-butyl N-[(1R,4R,6S,7R)-6-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW8585-005**, 62 mg, 0.10 mmol) in dioxane (3 ml) was added triethylamine (16 µl, 0.12 mmol) followed by propanoyl chloride (10 µl, 0.12 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (acidic method) to afford 34 mg (50 %) of tert-butyl N-[(1R,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-propanamido-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8590-002** as a white solid. LCMS (method D): 1.19min, M/z = 642 (M + 1).

[00479] (1S,2R,8R)-10-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-oxa-3,10-diazatricyclo[4.4.0.0^{2,8}]decan-4-one EV-AX4517-002 (EOAI3460130) I-187 was synthesised according to the procedures described in Scheme 10:

[00480] (1S,4R,6S,7R)-7-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-ol EV-AX4510-001 – step 29 (Scheme 10)

[00481] The title compound was synthesised from tert-butyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY5029-001** according to the procedures described in Scheme 9 step 6. LCMS (method D): retention time 0.92min, M/z = 487.15 (M + 1).

[00482] 9H-Fluoren-9-ylmethyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AX4513-001 – step 30 (Scheme 10)

[00483] To a solution of (1S,4R,6S,7R)-7-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-ol (**EV-AX4510-001**, 112 mg, 0.21 mmol) in DCM (2 ml) were added DIPEA (0.11 ml, 0.64 mmol) and FMOC chloride (83 mg, 0.32 mmol) at 0°C. The resulting mixture was stirred at 0°C for 2h, saturated aqueous sodium bicarbonate (1 ml) was added and the aqueous layer was extracted with DCM (2 x 1 ml). The combined organic fractions were dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude was purified by preparative HPLC (acidic method) to obtain 47 mg (31%) of 9H-fluoren-9-ylmethyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AX4513-001** as a white solid. LCMS (method D): retention time 1.33min, M/z = 409.4 (M + 1).

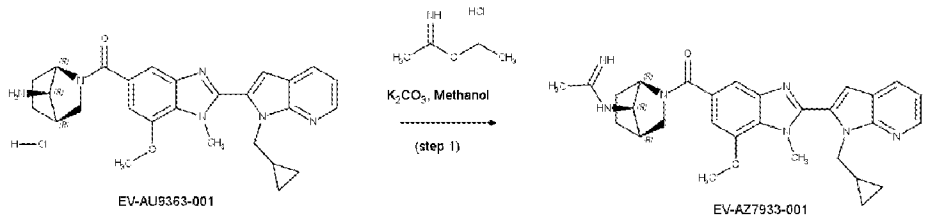
[00484] (1S,2R,8R)-10-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-oxa-3,10-diazatricyclo[4.4.0.0^{2,8}]decan-4-one EV-AX4517-002 – step 31 (Scheme 10)

[00485] To a solution of 9H-fluoren-9-ylmethyl N-[(1S,4R,6S,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AX4513-001**, 46 mg, 0.06 mmol) in DCM (1 ml) was added N-ethyl-N-(trifluoro-lambda~4~-sulfanyl)ethanamine (34 µl, 0.26 mmol) at -78^{O}C under atmosphere of nitrogen and the reaction was stirred at -78 ^{O}C for 1h. The reaction was warmed up to room

temperature and stirred for a further 12h. Saturated aqueous sodium bicarbonate (5 ml) was added and the aqueous layer was extracted with DCM (2 x 5 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was dissolved in 20% piperidine in DMF (2 ml) and the solution stirred at room temperature under an atmosphere of nitrogen for 2h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (basic method) to obtain 16 mg (55%) of (1S,2R,8R)-10-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-oxa-3,10-diazatricyclo[4.4.0.0^{2,8}]decan-4-one **EV-AX4517-002** as a white solid. LCMS (method A): retention time 2.90min, M/z = 513.2 (M + 1).

[00486] N-[(7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]ethanimidamide EV-AZ7933-001 (EOAI3669061) I-340 was synthesised according to the procedures described in Scheme 10.1:

[00487] Scheme 10.1



[00488] N-[(7R)-2-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]ethanimidamide EV-AZ7933-001 – step 1

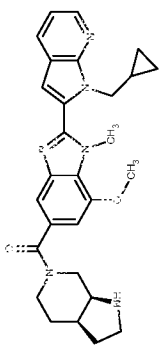
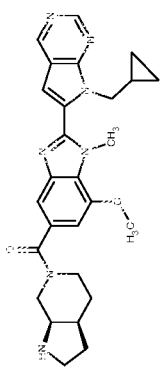
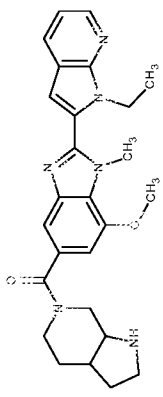
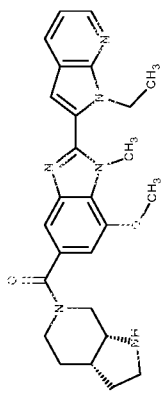
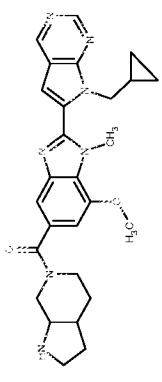
[00489] To a stirred solution of (7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-amine hydrochloride (**EV-AU9363-001** synthesised according to the procedures described in Scheme 3, 140 mg, 0.28 mmol) in Methanol (5 ml), was added potassium carbonate (153 mg, 1.10 mmol) and the reaction mixture was stirred at room temperature for 24h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep HPLC (basic method initially followed by re-purification with acidic method) to obtain 27 mg (18%) of N-[(7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-7-yl]ethanimidamide formate salt **EV-AZ7933-001** as a white

powder. LCMS (method A): retention time 2.05min, M/z = 512.3 (M + 1).

[00490] The following compounds were synthesised according to procedures described above:

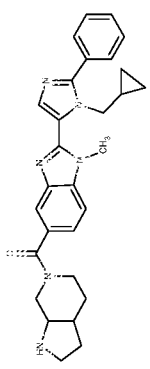
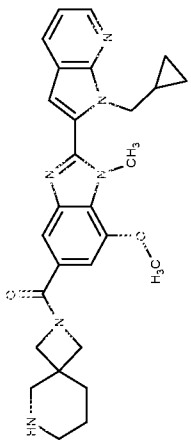
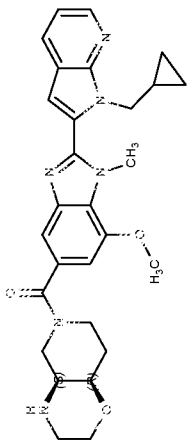
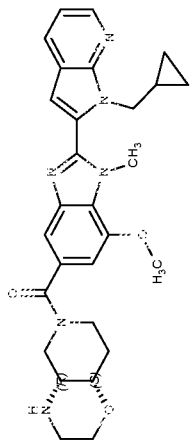
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-1	428.529	1.64min	429	A	TFA	1
	I-2	453.579	2.19min	454	A	HCl	1
	I-3	458.555	1.83 min	459	A	HCl	1
	I-4	485.581	1.53min	486	A	TFA	1
	I-5	428.529	1.65min	429	A	N/A	N/A

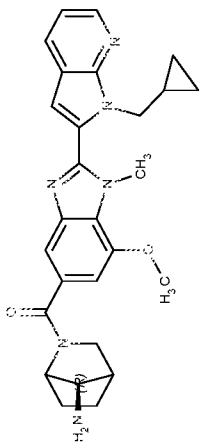
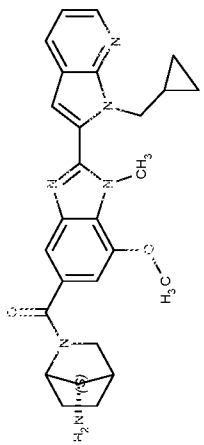
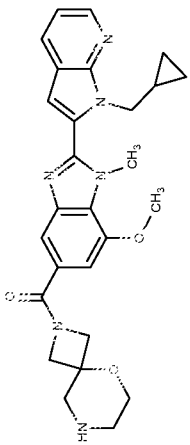
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-6	454.567	1.83min	455	A	N/A	N/A
	I-7	453.579	2.17min	454	A	HCl	1
	I-8	484.593	2.02min	485	A	HCl	1
	I-9	455.555	1.33min	456	A	N/A	N/A
	I-10	454.567	2.64min	455	B	HCl	1

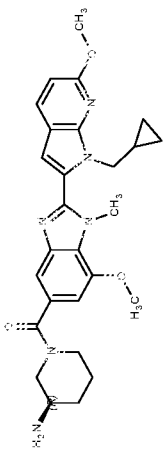
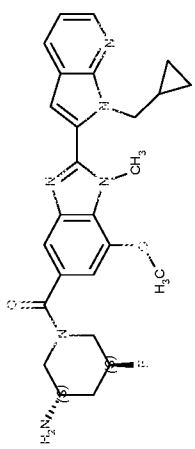
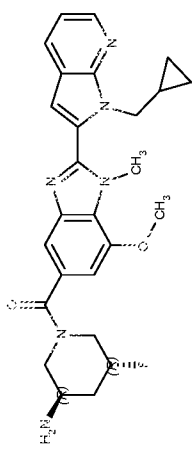
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-11**	484.593	2.01 min	485	A	HCl	1
	**I-12**	485.581	1.52min	486	A	TFA	1
	**I-13**	458.555	1.80min	459	A	HCl	1
	**I-14**	458.555	1.82 min	459	A	HCl	1
	**I-15**	485.581	1.52min	486	A	N/A	N/A

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-16	428.529	1.64 min	429	A	TFA	1
	I-17	484.593	2.03 min	485	A	HCl	1
	I-18	454.567	2.71min	455	B	HCl	1
	I-19	512.527	2.12min	513	A	HCl	1
	I-20	512.527	2.11min	513	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-21	512.527	2.11min	513	A	HCl	1
	I-22	498.619	2.26 min	499	A	HCl	1
	I-23	498.619	2.26 min	499	A	HCl	1
	I-24	520.574	2.23min	521	A	HCl	1
	I-25	520.574	2.26min	521	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-26**		1.42 min	481	A	HCl	1
	**I-27**		2.09 min	485	A		
	**I-28**		2.11 min	501	A		
	**I-29**		2.11 min	501	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-30**		1.97 min	471	A	HCl	1
	**I-31**		1.96 min	471	A	HCl	1
	**I-32**		2.07 min	487	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-33**		2.41 min	489	A		
	**I-34**		2.08 min	477	A	HCl	1
	**I-35**		2.04 min	477	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-36		3.02 min	473	C	HCl	1
	I-37		1.70 min	427	A	HCl	1
	I-38		1.68 min	427	A	HCl	1
	I-39		1.77 min	455	A	HCl	1
	I-40		1.76 min	441	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-41		1.87 min	469	A		
	I-42		2.72 min	455	C		
	I-43		1.87 min	455	A	TFA	1
	I-44		1.88 min	455	A	TFA	1
	I-45		2.00 min	483	A	TFA	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-46		1.93 min	469	A	TFA	1
	I-47		1.81 min	455	A	TFA	1
	I-48		1.94 min	483	A	TFA	1
	I-49		1.82 min	447	A	TFA	1
	I-50		1.83 min	455	A	TFA	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-51		1.94 min	465	A		
	I-52		1.84 min	455	A	HCl	1
	I-53		2.76 min	469	C	TFA	1
	I-54		3.05 min	447	C	TFA	1
	I-55		3.08 min	447	C	TFA	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-56		2.03 min	477	A	HCl	1
	I-57		2.03 min	477	A		
	I-58		2.04 min	477	A		
	I-59		2.35 min	527	A	HCl	1
	I-60		1.85 min	455	A	HCl	1

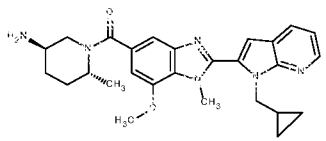
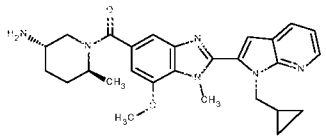
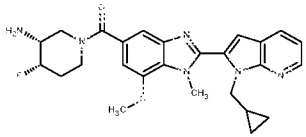
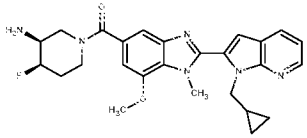
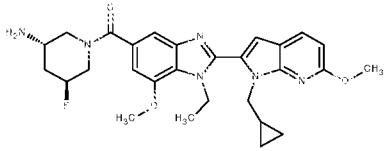
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-61		1.85 min	455	A	HCl	1
	I-62		1.86 min	459	A	TFA	1
	I-63		1.97 min	455	A		
	I-64		1.86 min	459	A	TFA	1
	I-65		1.86 min	459	A	HCl	1

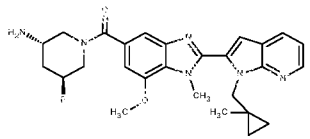
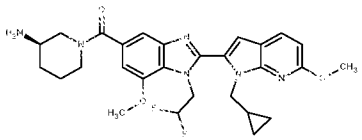
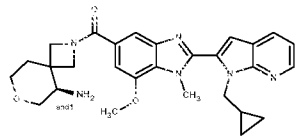
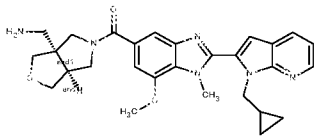
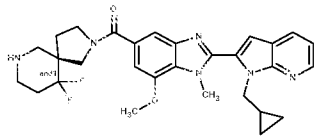
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-66		1.84 min	447	A	HCl	1
	I-67		1.77 min	447	A	HCl	1
	I-68		1.80 min	459	A	HCl	1
	I-69		1.56 min	486	A	HCl	1
	I-70		2.27 min	459	A	HCl	1

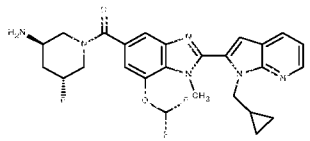
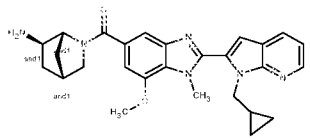
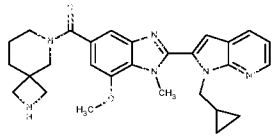
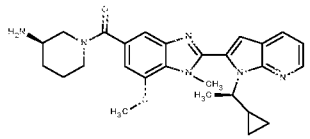
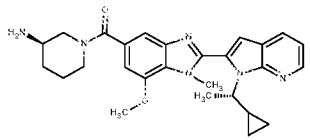
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-71		2.22 min	491	A	HCl	1
	I-72		2.23 min	527	A	HCl	1
	I-73		2.25 min	513	A	HCl	!
	I-74		2.11 min	515	A		
	I-75		2.02 min	477	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-76		1.94 min	457	A	HCl	1
	I-77		1.93 min	489	A	HCl	1
	I-80		1.91 min	475	A		
	I-81		2.02 min	471	A	HCl	1
	I-82		2.08 min	484	A	TFA	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-83		2.11 min	501	A	HCl	1
	I-84		2.07 min	515	A	HCO_2H	1
	I-85		2.05 min	471	A	TFA	1
	I-86		2.20 min	525	A	HCl	1
	I-87		3.03 min	473	C	HCl	1

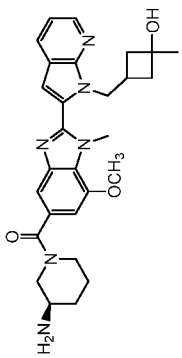
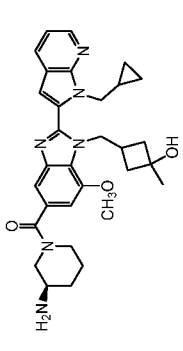
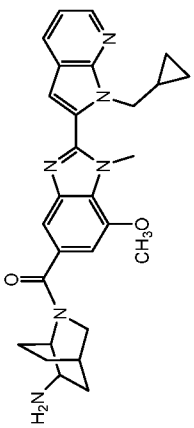
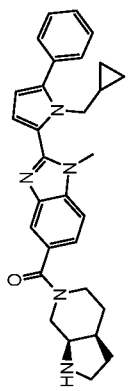
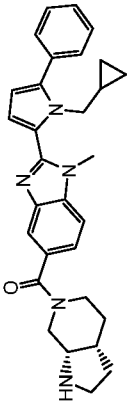
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-88**		3.04 min	473	C	HCl	1
	**I-89**		3.04 min	473	C	HCl	1
	**I-90**		2.99 min	477	C		
	**I-91**		3.01 min	477	C		
	**I-92**		2.64 min	521	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-93**		2.20 min	491	A	HCl	1
	**I-94**		2.63 min	539	A	HCl	1
	**I-95**		2.06 min	501	A		
	**I-96**		2.01 min	501	A		
	**I-97**		2.22 min	535	A	HCl	1

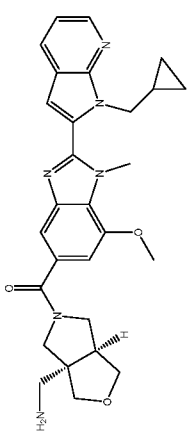
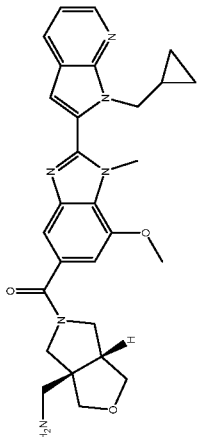
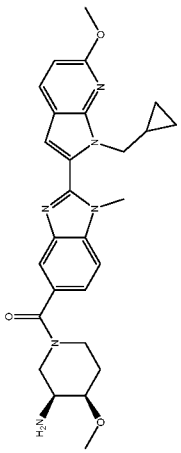
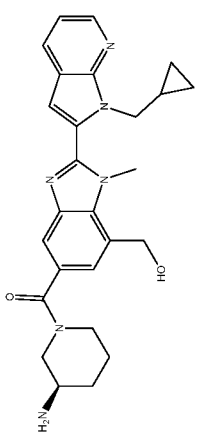
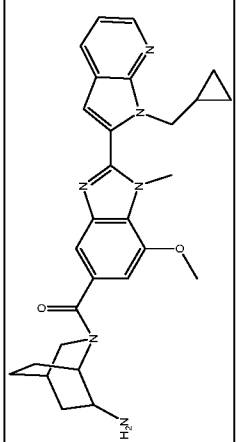
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-98**		2.26 min	513	A	HCl	1
	**I-99**		2.07 min	471	A		
	**I-100**		2.12 min	485	A		
	**I-101**		2.25 min	473	A	HCl	1
	**I-102**		2.26 min	473	A	HCl	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-103		1.86 min	443	A	HCl	1
	I-104		2.66 min	525	A	HCl	1
	I-105		2.62 min	501	A	HCl	1
	I-106		2.59 min	503	A	HCl	1
	I-107		2.21 min	535	A		

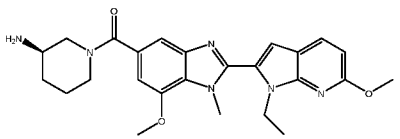
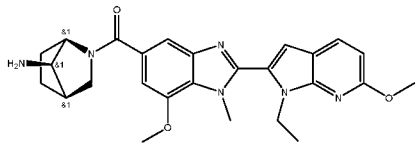
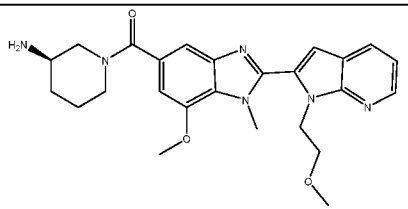
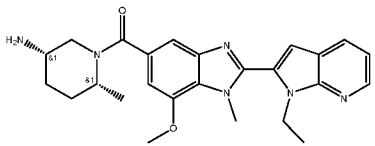
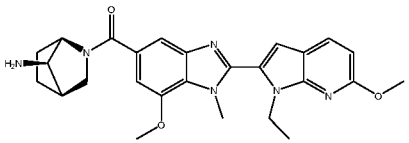
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-108		2.22 min	535	A		
	I-109		2.68 min	543	A	HCl	1
	I-110		3.18 min	473	H	HCl	1
	I-111		2.33 min	487	A	HCl	1
	I-112		1.53 min	472	A	HCl	1

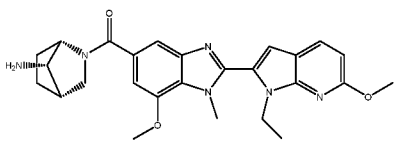
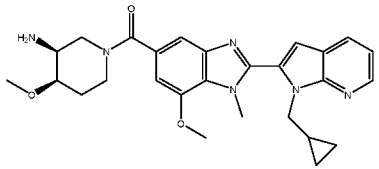
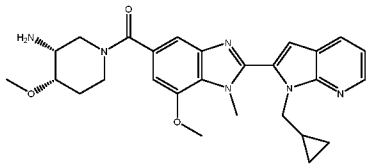
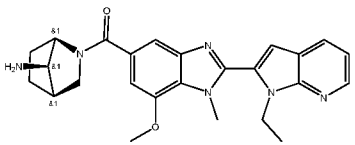
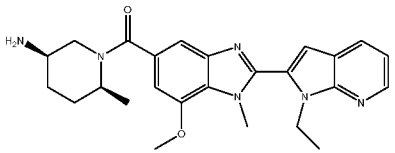
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-113**	502.608	1.85min	503	A	HCl	1
	**I-114**	542.6718	1.92min	543	A	HCl	1
	**I-115**	484.5927	2.08 min	485.2	A		
	**I-116**	479.62	2.20min	480	A		
	**I-117**	479.62	2.21min	480	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-119	472.582	2.19min	473	A	Hydrochloric acid	1
	I-121	488.5814	2.10min	489	A	Hydrochloric acid	1
	I-122	486.5655	2.04min	487	A	Hydrochloric acid	1
	I-123	506.5718	2.53min	507	A		
	I-124	524.5623	2.30min	525	A	Hydrochloric acid	1

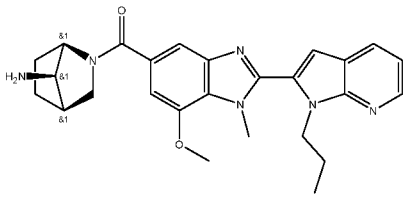
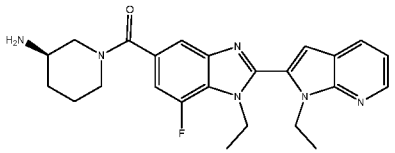
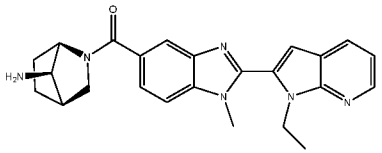
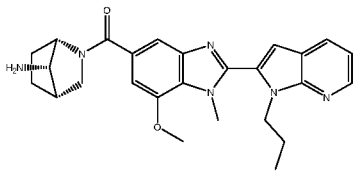
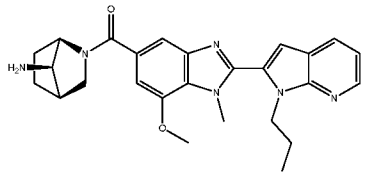
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-125**	500.5921	2.01 min	501	A		
	**I-126**	500.5921	1.98 min	501	A		
	**I-127**	488.5814	2.38 min	489	A	Hydrochloric acid	1
	**I-128**	458.5554	1.66 min	459	A	Hydrochloric acid	1
	**I-129**	484.5927	2.06 min	485	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-130	488.5814	3.39min	489	H		
	I-131	506.62	1.96min	507	A	Hydrochloric acid	1
	I-132	483.5649	2.13min	484	A	Hydrochloric acid	1
	I-133	524.5623	2.24min	525	A	Hydrochloric acid	1
	I-134	524.5623	2.23min	525	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-135**	462.5441	2.32min	463	A		
	**I-136**	474.5548	2.26min	475	A	Hydrochloric acid	1
	**I-137**	462.5441	1.78min	463	A	Hydrochloric acid	1
	**I-138**	446.5447	1.93min	447	A	Hydrochloric acid	1
	**I-139**	474.5548	2.24 min	475	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-140**	474.5548	2.24 min	475	A	Hydrochloric acid	1
	**I-141**	488.5814	2.11 min	489	A	Hydrochloric acid	1
	**I-142**	488.5814	2.12 min	489	A	Hydrochloric acid	1
	**I-143**	444.5288	1.82min	445	A	Hydrochloric acid	1
	**I-144**	446.5447	1.94 min	447	A	Hydrochloric acid	1

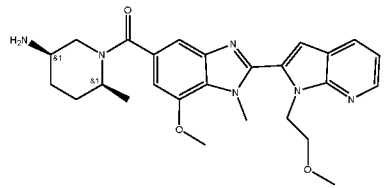
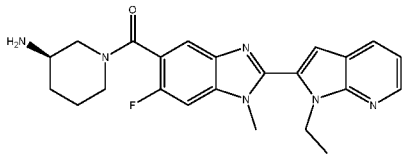
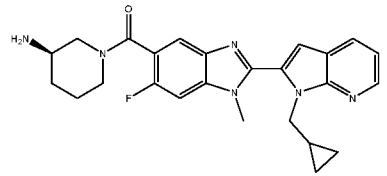
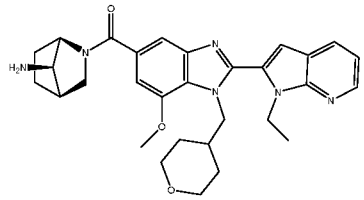
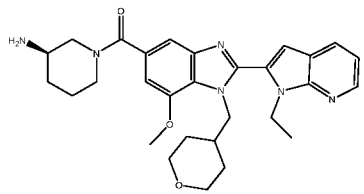
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-145	446.5447	1.95 min	447	A	Hydrochloric acid	1
	I-146	450.5086	2.70 min	451	H	Hydrochloric acid	1
	I-147	462.5193	1.81 min	463	A	Hydrochloric acid	1
	I-148	460.5713	2.05 min	461	A	Hydrochloric acid	1
	I-149	446.5447	1.96 min	447	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-150**	458.5554	1.93 min	459	A	Hydrochloric acid	1
	**I-151**	434.5092	1.97min	435	A	Hydrochloric acid	1
	**I-152**	414.5028	1.58 min	415	A	Hydrochloric acid	1
	**I-153**	458.5554	1.91min	459	A	Hydrochloric acid	1
	**I-154**	458.5554	1.92min	459	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-155	528.6452	1.72min	529	A	Hydrochloric acid	1
	I-156	462.5193	1.78min	463	A	Hydrochloric acid	1
	I-157	462.5193	1.79min	463	A	Hydrochloric acid	1
	I-158	444.5288	1.80min	445	A	Hydrochloric acid	1
	I-159	444.5288	1.80min	445	A	Hydrochloric acid	1

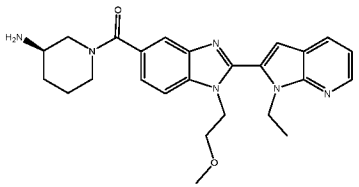
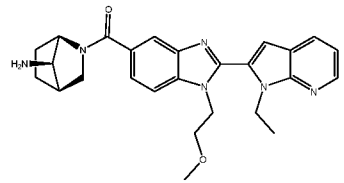
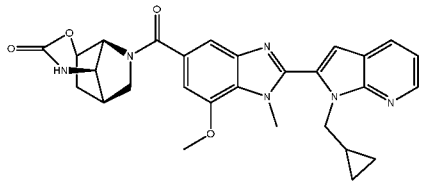
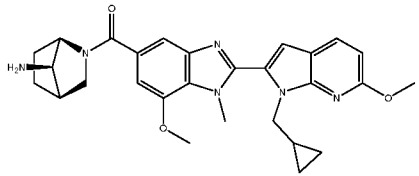
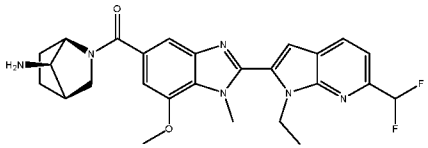
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-160	458.5554	1.89min	459	A	Hydrochloric acid	1
	I-161	446.5447	1.94min	447	A	Hydrochloric acid	1
	I-162	486.5655	1.96min	487	A	Hydrochloric acid	1
	I-163	530.6611	2.14min	531	A	Hydrochloric acid	1
	I-164	420.4826	1.72min	421	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-165	432.4933	1.78min	433	A	Hydrochloric acid	1
	I-166	446.5199	2.05 min	447	A	Hydrochloric acid	1
	I-167	500.5921	2.07 min	501	A	Hydrochloric acid	1
	I-168	542.6718	2.09 min	543	A	Hydrochloric acid	1
	I-169	474.5548	1.75 min	475	A	Hydrochloric acid	1

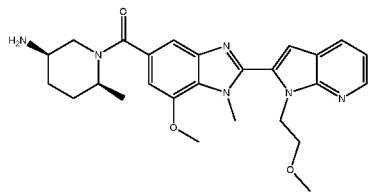
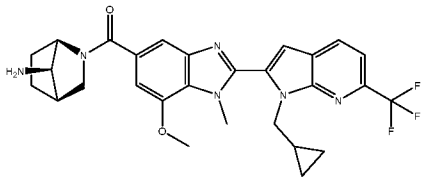
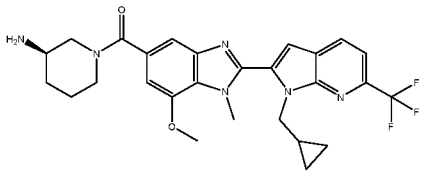
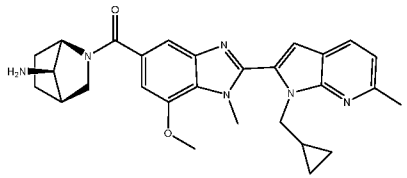
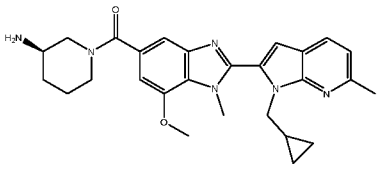
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-170**	476.5707	1.87 min	477	A	Hydrochloric acid	1
	**I-171**	420.4826	1.70 min	421	A		
	**I-172**	446.5199	1.92 min	447	A	Hydrochloric acid	1
	**I-173**	528.6452	1.85 min	529	A	Hydrochloric acid	1
	**I-174**	516.6345	1.90 min	517	A	Hydrochloric acid	1

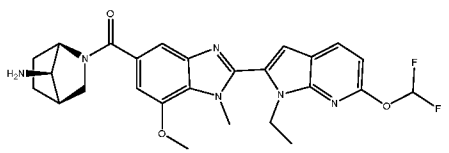
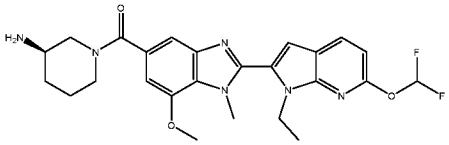
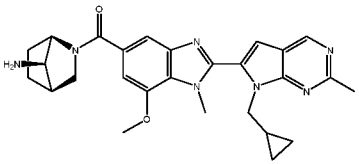
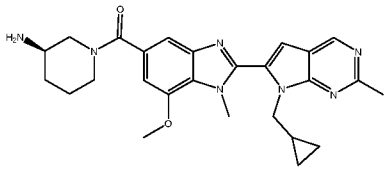
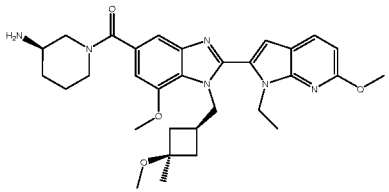
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-175	488.5814	1.83 min	489	A	Hydrochloric acid	1
	I-176	476.5707	1.87 min	477	A	Hydrochloric acid	1
	I-177	502.608	2.08 min	503	A	Hydrochloric acid	1
	I-178	514.6187	2.05 min	515	A	Hydrochloric acid	1
	I-179	534.6002	2.18 min	535	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-180	522.5895	2.20 min	523	A	Hydrochloric acid	1
	I-181	568.7091	2.27 min	569	A	Hydrochloric acid	1
	I-182	556.6984	2.25 min	557	A	Hydrochloric acid	1
	I-183	512.5268	2.42 min	513	A	Hydrochloric acid	1
	I-184	500.5161	2.51 min	501	A	Hydrochloric acid	1

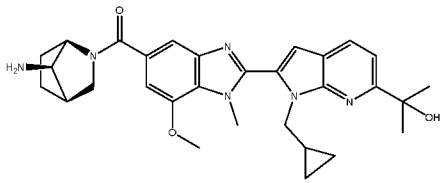
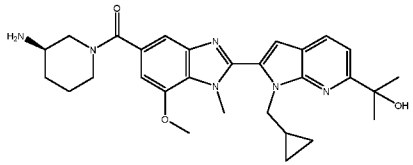
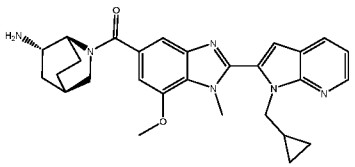
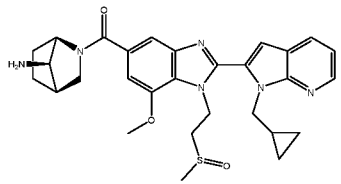
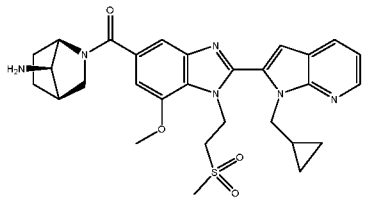
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-185**	446.5447	1.71 min	447	A	Hydrochloric acid	1
	**I-186**	458.5554	1.66 min	459	A	Hydrochloric acid	1
	**I-187**	512.5597	2.90 min	513	A		
	**I-188**	500.5921	2.37 min	501	A	Hydrochloric acid	1
	**I-189**	494.5363	2.26 min	495	A		

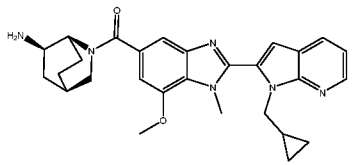
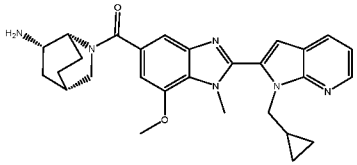
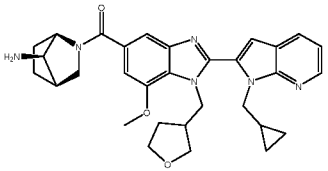
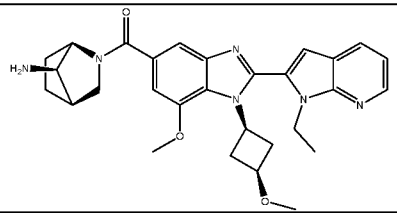
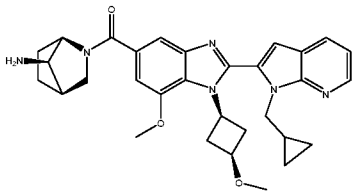
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-190	476.5707	1.86 min	477	A	Hydrochloric acid	1
	I-191	458.5306	1.98 mln	459	A	Hydrochloric acid	1
	I-192	474.5548	1.88 min	475	A	Hydrochloric acid	1
	I-193	462.5441	1.91 min	463	A	Hydrochloric acid	1
	I-194	458.5306	1.86 min	459	A	Hydrochloric acid	1

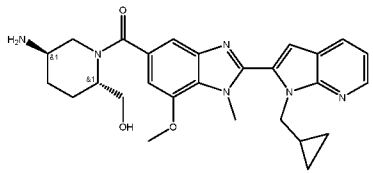
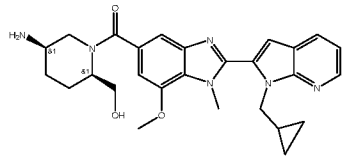
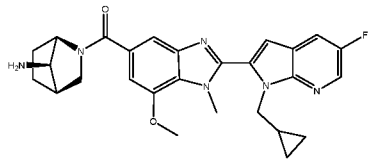
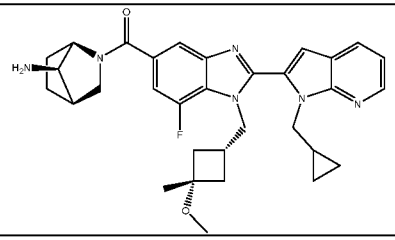
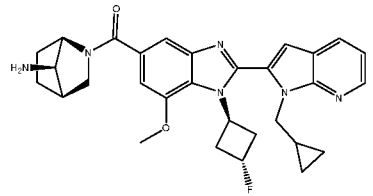
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-195**	476.5707	1.88 min	477	A	Hydrochloric acid	1
	**I-196**	538.5641	2.65 min	539.2	A	Hydrochloric acid	1
	**I-197**	526.5534	2.69 min	527.2	A	Hydrochloric acid	1
	**I-198**	484.5927	2.14 min	485.1	A	Hydrochloric acid	1
	**I-199**	472.582	2.19 min	473.2	A	Hydrochloric acid	1

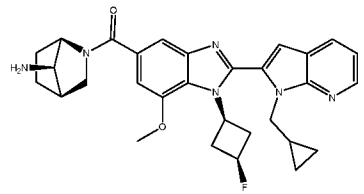
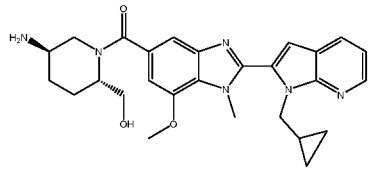
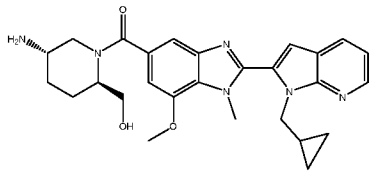
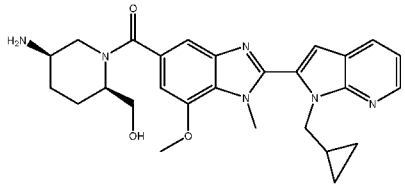
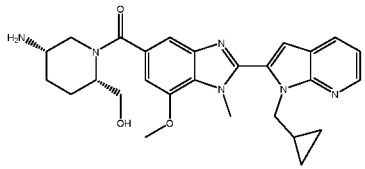
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-200**	510.5357	2.46 min	511.2	A	Hydrochloric acid	1
	**I-201**	498.525	2.52 min	499.2	A	Hydrochloric acid	1
	**I-202**	485.5807	1.37 min	486.1	A	Hydrochloric acid	1
	**I-203**	473.57	1.38 min	474.2	A	Hydrochloric acid	1
	**I-204**	560.6871	2.56 min	561.3	A	Hydrochloric acid	1

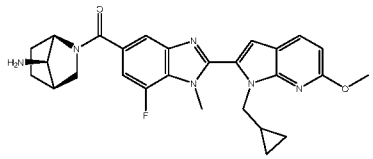
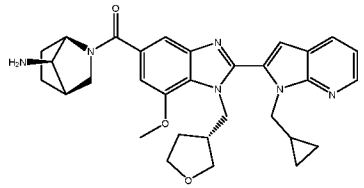
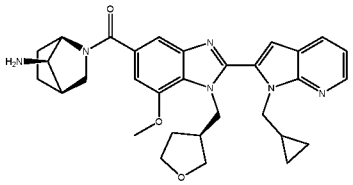
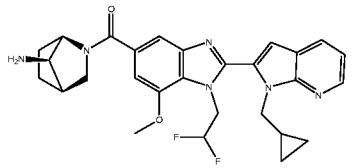
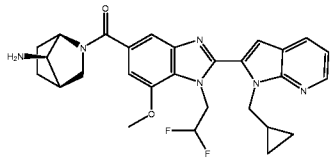
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-205	578.6776	2.58 min	579.2	A	Hydrochloric acid	1
	I-206	572.6978	2.52 min	573.2	A	Hydrochloric acid	1
	I-207	514.6187	1.92 min	515.2	A	Hydrochloric acid	1
	I-208	544.5438	2.70 min	545.2	A	Hydrochloric acid	1
	I-209	574.6889	2.35 min	575.2	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-210**	528.6452	2.17 min	529.2	A	Hydrochloric acid	1
	**I-211**	516.6345	2.22 min	517.2	A	Hydrochloric acid	1
	**I-212**	484.5927	2.08 min	485.2	A		
	**I-213**	546.684	2.18 min	547.4	H	Formic acid	1
	**I-214**	562.683	1.73min	563.2	A	Hydrochloric acid	1

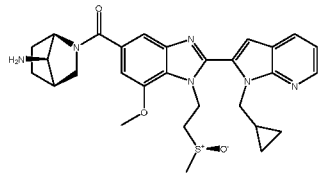
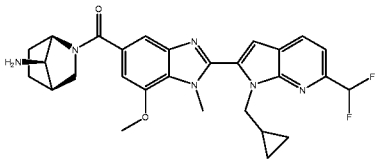
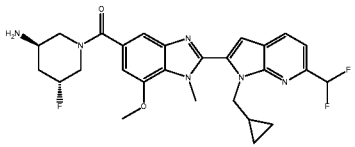
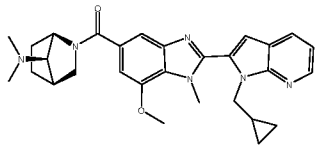
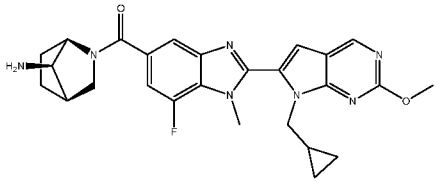
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-215**	484.5927	2.10 min	485.2	A		
	**I-216**	484.5927	2.13 min	485.2	A		
	**I-217**	540.6559	3.69 min	541.3	B	Hydrochloric acid	1
	**I-218**	514.6187	2.79 min	515.4	H	Hydrochloric acid	1
	**I-219**	540.6559	2.18 min	541.4	A	Hydrochloric acid	1

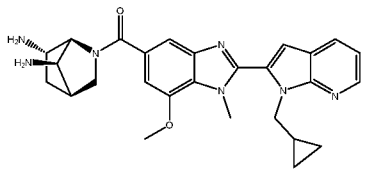
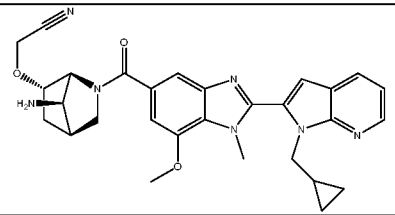
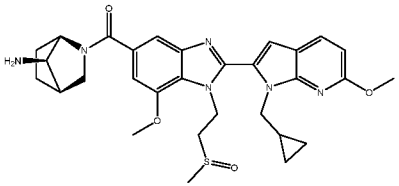
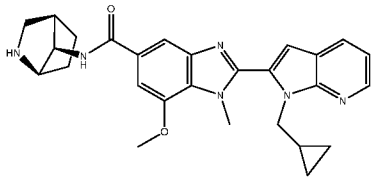
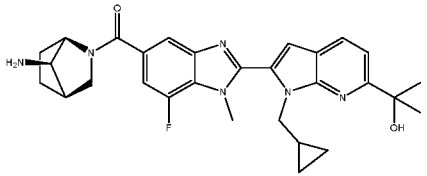
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-220**	488.5814	3.81 min	489.1	C		
	**I-221**	488.5814	1.92 min	489.4	A	Hydrochloric acid	1
	**I-222**	488.5566	2.22 min	489.3	A	Hydrochloric acid	1
	**I-223**	556.6736	2.30 min	557.5	A		
	**I-224**	528.6204	2.20 min	529.3	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-225**	528.6204	2.21 min	529.3	A	Hydrochloric acid	1
	**I-226**	488.5814	1.86 min	489.3	A	Hydrochloric acid	1
	**I-227**	488.5814	1.85 min	489.3	A	Hydrochloric acid	1
	**I-228**	488.5814	1.91 min	489.3	A	Hydrochloric acid	1
	**I-229**	488.5814	1.90 min	489.3	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-230**	488.5566	2.46 min	489.3	A	Hydrochloric acid	1
	**I-231**	540.6559	1.99 min	541.3	A	Hydrochloric acid	1
	**I-232**	540.6559	1.98 min	541.3	A	Hydrochloric acid	1
	**I-233**	520.5736	2.18 min	521.3	A	Hydrochloric acid	1
	**I-234**	494.5363	1.97 min	495.3	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-235	530.684	2.28 min	531.3	A	Formic acid	0.5
	I-236	554.6825	2.16 min	555.3	A	Hydrochloric acid	1
	I-237	484.5927	2.06 min	485.3	A	Hydrochloric acid	1
	I-238	571.7276	2.26 min	572.4	H		
	I-239	501.5801	1.87 min	502.3	A	Hydrochloric acid	1

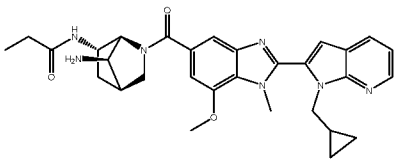
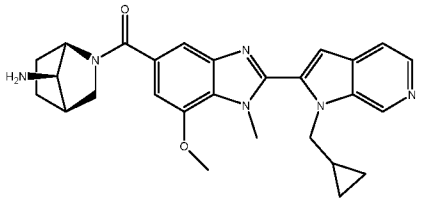
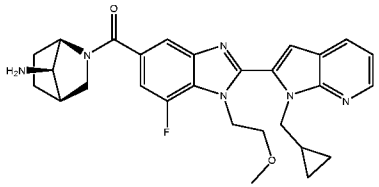
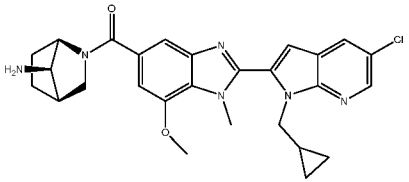
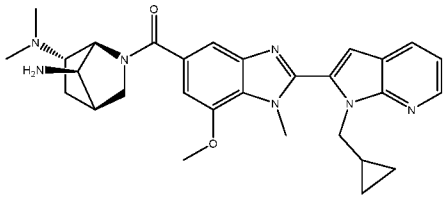
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-240**	546.684	2.20 min	547.4	A	Formic acid	0.5
	**I-241**	520.5736	2.39 min	521.3	A	Hydrochloric acid	1
	**I-242**	526.5534	2.48 min	527.2	A	Hydrochloric acid	1
	**I-243**	498.6193	3.58 min	499.4	H	Hydrochloric acid	1
	**I-244**	489.5446	1.85 min	490.3	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-245**	485.5807	2.02 min	486.3	A		
	**I-246**	525.6015	2.05 min	526.3	A	Trifluoroacetic acid	1
	**I-247**	576.71	1.96 min	577.3	A	Hydrochloric acid	1
	**I-248**	470.5661	2.14 min	471.3	A		
	**I-249**	516.6097	2.19 min	517.3	A		

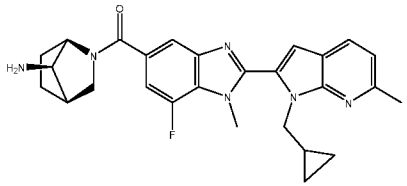
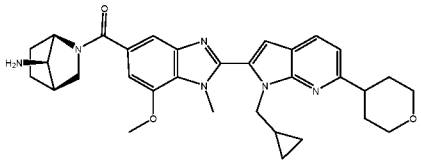
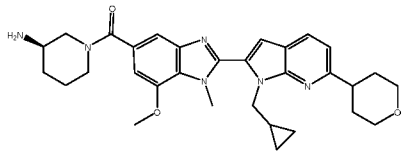
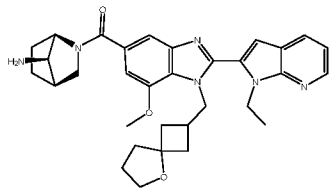
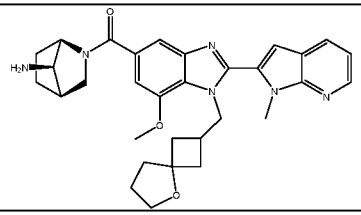
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-250	546.684	1.55 min	547.2	A	Formic acid	0.5
	I-251	540.6559	2.00 min	541.3	A	Hydrochloric acid	1
	I-252	440.5401	1.79 min	441.3	A	Hydrochloric acid	1
	I-253	554.6825	2.19 min	555.3	A	Hydrochloric acid	1
	I-254	526.6294	2.79 min	527.4	H	Hydrochloric acid	1

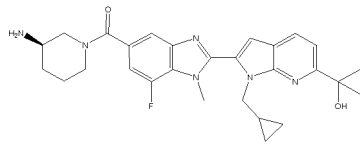
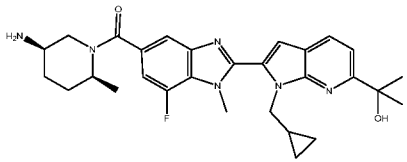
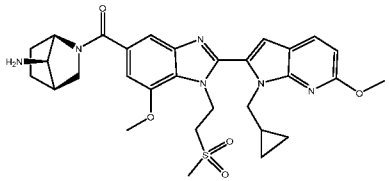
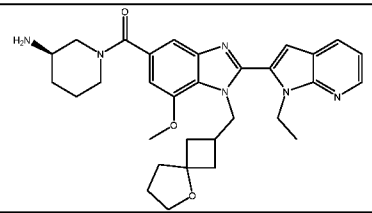
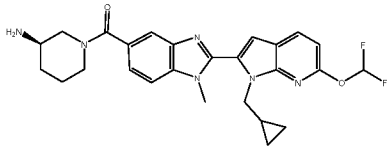
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-255	476.521	2.14 min	477.3	A	Hydrochloric acid	1
	I-256	539.6281	3.29 min	540.2	C		
	I-257	526.6294	2.79 min	527.4	H	Hydrochloric acid	1
	I-258	580.7198	2.18 min	581.3	A	Hydrochloric acid	1

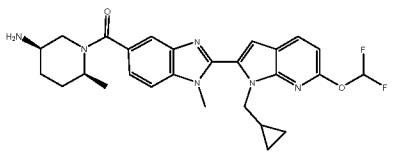
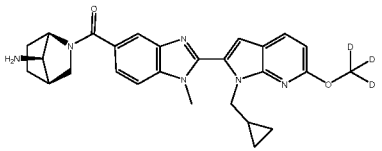
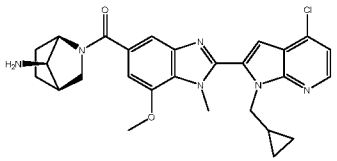
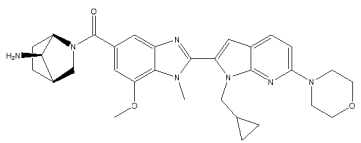
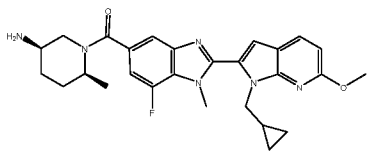
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-259	545.6903	2.00 min	546.4	A	Hydrochloric acid	1
	I-260	505.011	2.04 min	505.3	A	Hydrochloric acid	1
	I-261	506.547	2.34 min	507.3	A	Hydrochloric acid	1
	I-262	576.71	1.90 min	577.3	A		
	I-263	576.71	1.90 min	577.3	A		

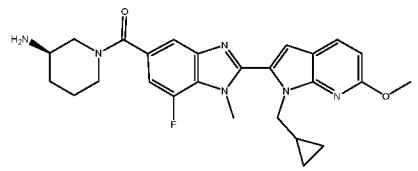
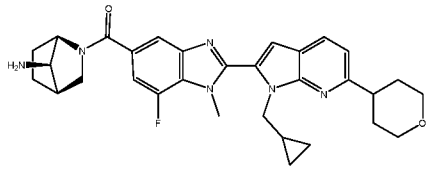
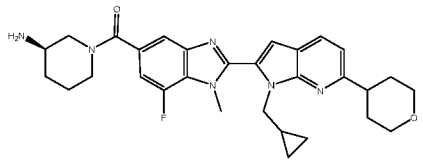
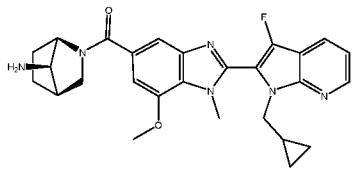
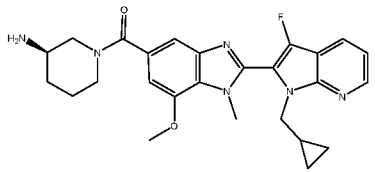
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-264**	541.644	1.97 min	542.3	A	Hydrochloric acid	1
	**I-265**	470.5661	1.10 min	471.4	A		
	**I-266**	502.5831	2.00 min	503.4	A		
	**I-267**	505.011	2.36 min	505.3	A	Hydrochloric acid	1
	**I-268**	513.6339	1.99 min	514.3	A	Hydrochloric acid	2

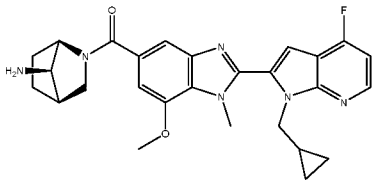
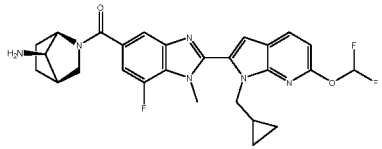
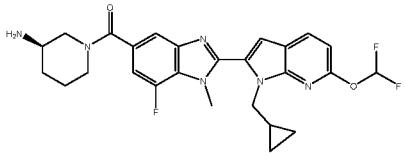
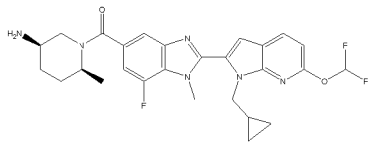
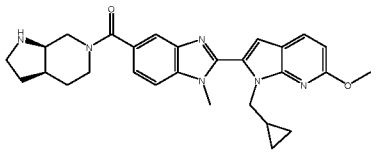
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-269	488.5566	3.26 min	489.4	H	Hydrochloric acid	1
	I-270	568.7091	2.19 min	569.5	A	Hydrochloric acid	1
	I-271	557.701	2.12 min	558.4	H		
	I-272	528.6204	2.86 min	529.4	H	Hydrochloric acid	1
	I-273	528.6204	2.86 min	529.5	H	Hydrochloric acid	1

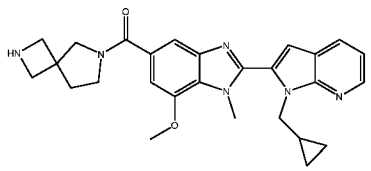
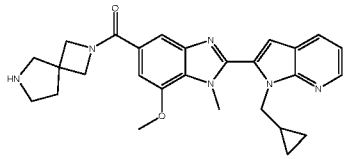
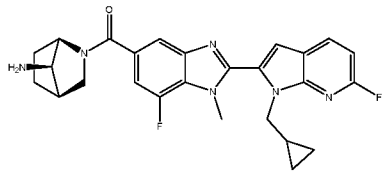
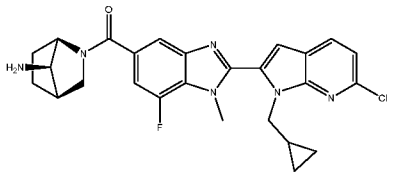
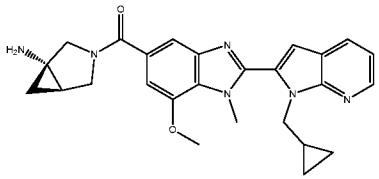
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-274**	472.5572	2.12 min	473.3	A	Hydrochloric acid	1
	**I-275**	554.6825	3.41 min	555.4	H	Hydrochloric acid	1
	**I-276**	542.6718	3.66 min	543.5	H	Hydrochloric acid	1
	**I-277**	554.6825	2.03 min	555.4	A	Hydrochloric acid	1
	**I-278**	540.6559	1.93 min	541.4	A	Hydrochloric acid	1

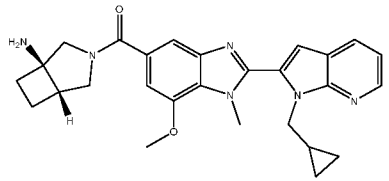
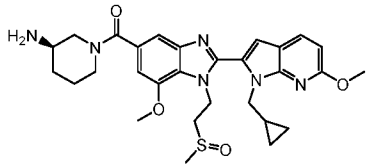
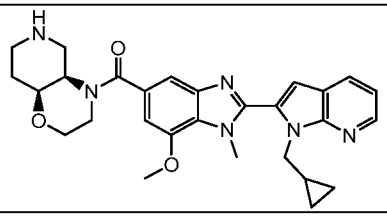
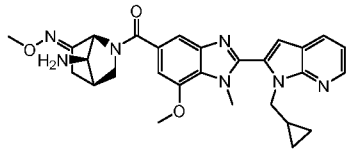
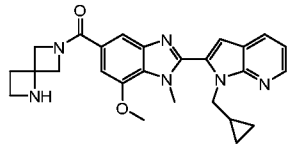
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-279**	504.599	3.28 min	505.4	H	Hydrochloric acid	1
	**I-280**	518.6256	3.41 min	519.4	H	Hydrochloric acid	1
	**I-281**	592.709	3.03 min	593.4	H	Hydrochloric acid	1
	**I-282**	542.6718	2.05 min	543.4	A		
	**I-283**	494.5363	2.39 min	595.4	A	Hydrochloric acid	1

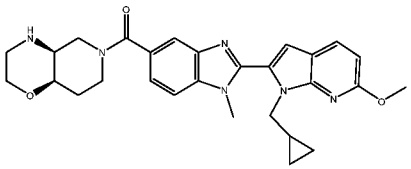
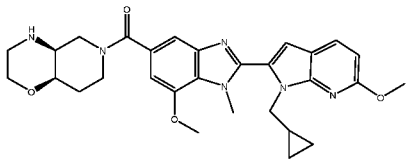
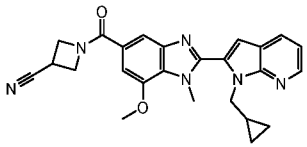
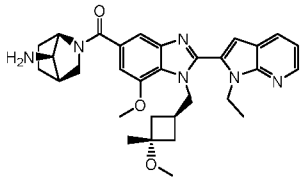
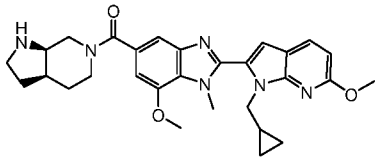
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-284**	508.5629	2.46 min	509.4	A	Hydrochloric acid	1
	**I-285**	473.5846	3.28 min	474.4	H	Hydrochloric acid	1
	**I-286**	505.011	3.42 min	505.4	H	Hydrochloric acid	1
	**I-287**	555.6706	2.22 min	556.3	A	Hydrochloric acid	1
	**I-288**	490.5724	2.52 min	491.4	A	Hydrochloric acid	1

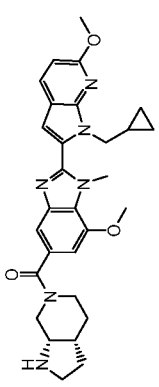
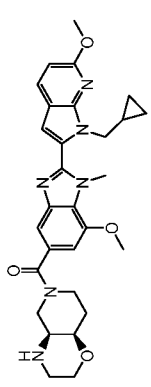
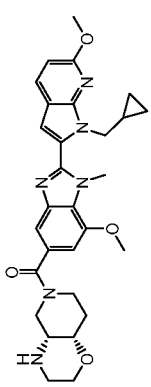
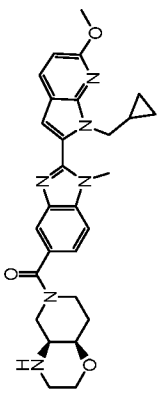
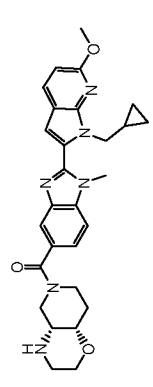
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-289**	476.5459	2.43 min	477.3	A	Hydrochloric acid	1
	**I-290**	542.647	2.33 min	543.3	A	Hydrochloric acid	1
	**I-291**	530.6363	2.35 min	531.3	A	Hydrochloric acid	1
	**I-292**	488.5566	2.12 min	489.3	A	Hydrochloric acid	1
	**I-293**	476.5459	2.18 min	477.4	A	Hydrochloric acid	1

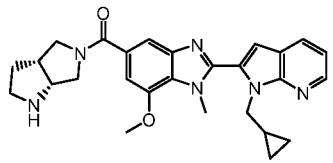
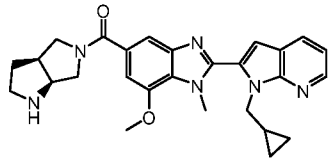
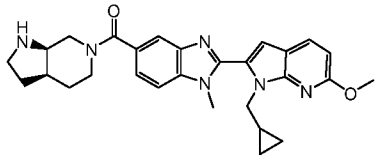
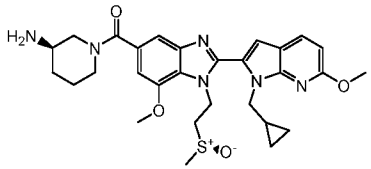
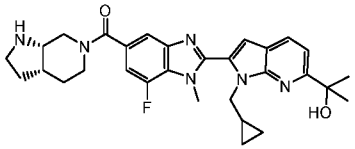
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-294**	488.5566	2.10 min	489.3	A	Hydrochloric acid	1
	**I-295**	524.5375	3.63 min	525.3	H	Hydrochloric acid	1
	**I-296**	512.5268	2.49 min	513.3	A	Hydrochloric acid	1
	**I-297**	526.5534	2.61 min	527.3	A	Hydrochloric acid	1
	**I-298**	484.5927	2.27 min	485.4	A		

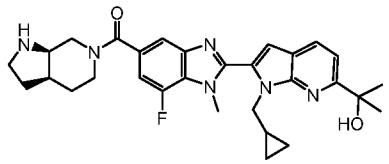
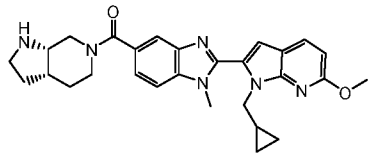
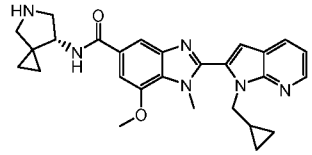
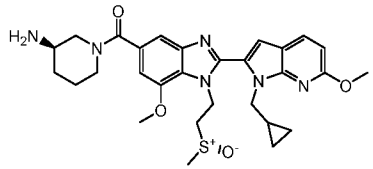
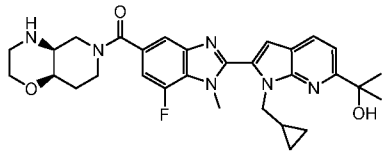
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-299**	470.5661	1.90 min	471.4	A		
	**I-300**	470.5661	1.98 min	471.4	A	Trifluoroacetic acid	1
	**I-301**	476.521	2.15 min	477.4	A	Hydrochloric acid	1
	**I-302**	492.976	2.31 min	493.3	A	Hydrochloric acid	1
	**I-303**	456.5395	1.94 min	457.4	A	Hydrochloric acid	1

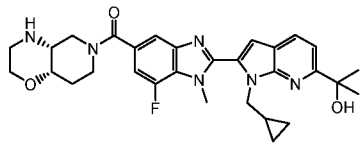
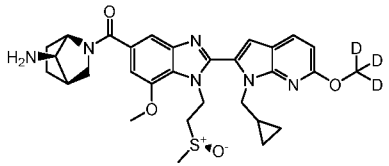
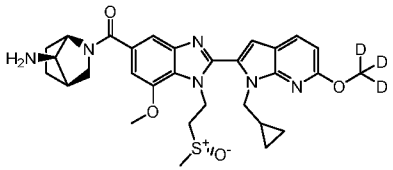
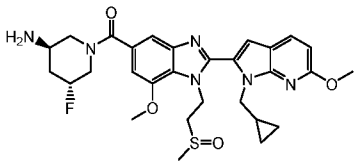
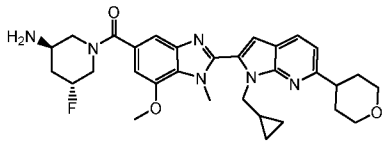
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-304**	470.5661	2.00 min	471.3	A		
	**I-305**	564.699	2.77 min	565.4	H		
	**I-306**	500.5921	2.06 min	501.3	A	Hydrochloric acid	1
	**I-307**	513.5908	2.08 min	514.3	A	Hydrochloric acid	1
	**I-308**	456.5395	1.96 min	457.3	A		

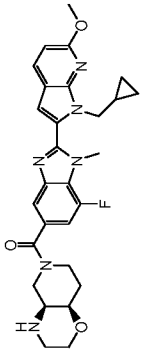
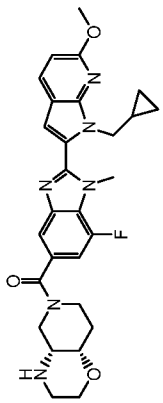
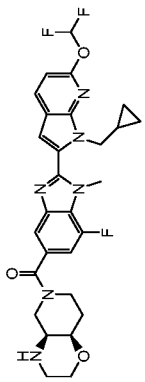
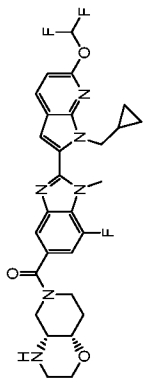
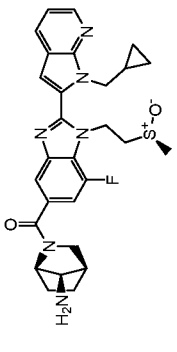
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-309**	500.5921	2.27 min	501.4	A		
	**I-310**	530.6181	2.47 min	531.4	A		
	**I-311**	440.4971	3.20 min	441.3	H		
	**I-312**	542.6718	2.03 min	543.4	A	Hydrochloric acid	1
	**I-313**	514.6187	2.41 min	515.3	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-314**	514.6187	2.42 min	515.3	A		
	**I-315**	530.6181	2.43 min	531.4	A		
	**I-316**	530.6181	2.47 min	531.3	A		
	**I-317**	500.5921	2.27 min	501.3	A		
	**I-318**	500.5921	2.27 min	501.3	A		

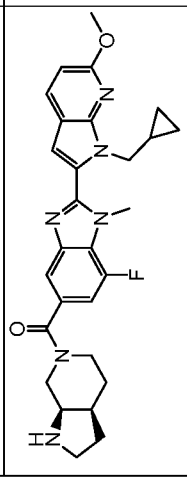
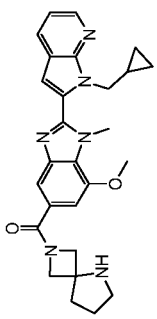
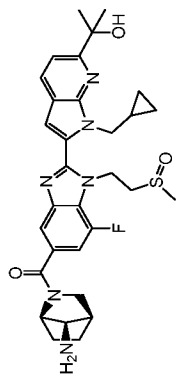
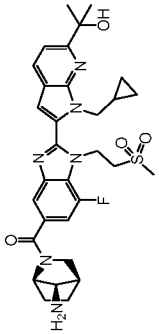
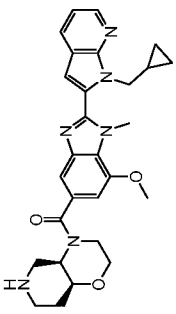
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-319**	470.5661	1.93 min	471.3	A	Hydrochloric acid	1
	**I-320**	470.5661	1.94 min	471.3	A		
	**I-321**	484.5927	2.26 min	485.3	A	Hydrochloric acid	1
	**I-322**	564.699	1.93 min	565.3	A		
	**I-323**	530.6363	2.10 min	531.3	A	Hydrochloric acid	1

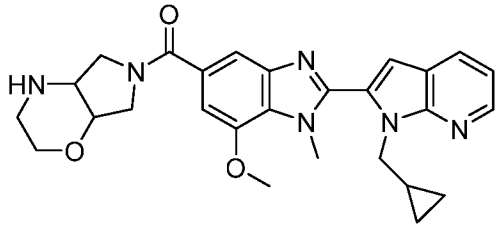
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-324**	530.6363	2.11 min	531.3	A	Hydrochloric acid	1
	**I-325**	484.5927	2.24 min	485.3	A	Hydrochloric acid	1
	**I-326**	470.5661	2.12 min	471.3	A		
	**I-327**	564.699	1.93 min	565.3	A		
	**I-328**	546.6357	3.54 min	547.3	C		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-329**	546.6357	3.56 min	547.3	C		
	**I-330**	579.728	2.70 min	580.4	H		
	**I-331**	579.728	2.70 min	580.4	H		
	**I-332**	582.689	1.93 min	583.2	A	Trifluoroacetic acid	1
	**I-333**	560.6623	2.34 min	561.3	A	Hydrochloric acid	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-334**	518.5825	2.44 min	519.3	A		
	**I-335**	518.5825	2.44 min	519.3	A		
	**I-336**	554.5635	2.53 min	555.2	A		
	**I-337**	554.5635	2.53 min	555.2	A		
	**I-338**	534.648	1.48 min	535.2	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-339	534.648	1.49 min	535.2	A		
	I-340	511.618	2.05 min	512.3	A	Formic acid	1
	I-341	500.5921	2.03 min	501.3	A		
	I-342	598.689	2.12 min	599.3	A	Trifluoroacetic acid	1
	I-343	568.663	2.12 min	569.3	A		

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-344**	502.5831	2.40 min	503.3	A		
	**I-345**	470.5661	2.01 min	471.3	A		
	**I-346**	592.727	1.69 min	593.4	A		
	**I-347**	608.727	1.86 min	609.3	A		
	**I-348**	500.5921	2.01 min	501.3	A		



I-349

[00491] (2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)((cis)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone. I-349 Note: Starting material was the cis-racemate.

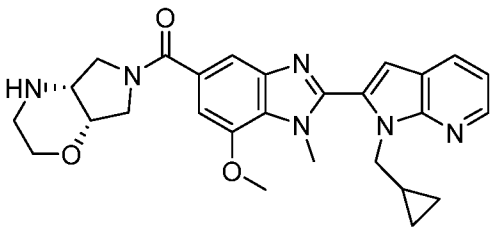
[00492] Prepared in a similar manner to Scheme 1. Mol wt = 486.57; LC/MS Ret. Time = 1.19 min.

(Column: Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1 % trifluoroacetic acid; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm)). M/Z (+) = 487.12; Salt = freebase.

[00493] Chiral HPLC to obtain **(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)((4aR,7aS)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone** and **(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone.** Note: Starting material was the cis-racemate. Absolute stereochemistry arbitrarily assigned.

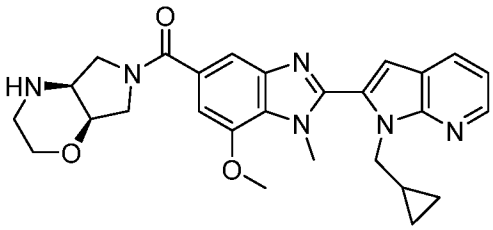
[00494] Prepared in a similar manner to Scheme 1. (2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)((cis)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone was dissolved in ethanol and then purified by chiral HPLC (Chiralcel OD 21 x 250mm 10u, wavelength: 254, Flow Rate: 15 ml/min, Solvent A: 100% Heptane, Solvent B: 100% Ethanol, Isocratic Collection by UV, %B: 35) to obtain 25.7 mg (50.4 %) of (2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)((4aR,7aS)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone as Isomer A and 25.4 mg (97.0 %) of (2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-

benzo[d]imidazol-5-yl)((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)methanone as Isomer (absolute stereochemistry arbitrarily assigned).



I-350

[00495] **Isomer A I-350** Chiral purity (UV, 254nm): 100%, retention time: 17.36 min (Chiralcel OD 21 x 250mm 10u, wavelength: 254, Flow Rate: 15 ml/min, Solvent A: 100% Heptane, Solvent B: 100% Ethanol, Isocratic Collection by UV, %B: 35). Salt = freebase.



I-351

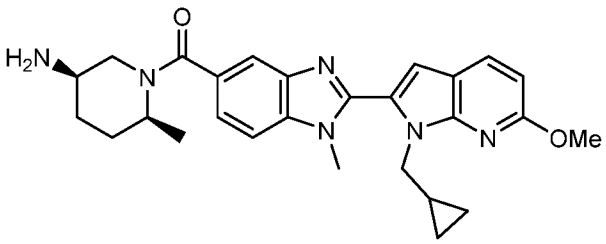
[00496] **Isomer B I-351** Chiral purity (UV, 254nm): 100%, retention time: 27.17 min (Chiralcel OD 21 x 250mm 10u, wavelength: 254, Flow Rate: 15 ml/min, Solvent A: 100% Heptane, Solvent B: 100% Ethanol, Isocratic Collection by UV, %B: 35). Salt = freebase.

[00497] **LC-MS Condition for Schemes 9 and 10:**

Column:	Waters Acquity SDS
Mobile Phase:	Solvent A: water Solvent B: Acetonitrile
Gradient Range:	Linear gradient of 2% to 98% solvent B over 1 minutes ("min"), with 0.5 minute ("min") hold at 98% B.
Gradient Time:	1 min
Analysis Time:	1.7 min

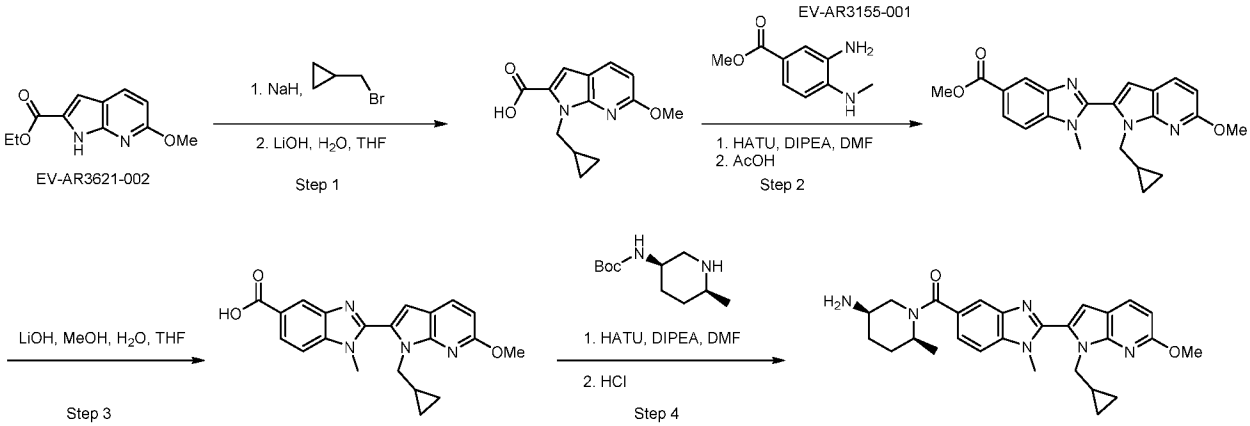
Detector: Ultraviolet ("UV") visualization at 254 nanometers ("nm")

[00498] Tert-butyl ((3R,6S)-1-(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-6-methylpiperidin-3-yl)carbamate. I-352 Prepared using Scheme 11.



I-352

[00499] Scheme 11



[00500] Methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-indole-5-carboxylate - Step 2

[00501] 1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (5 g, 20.30 mmol) (prepared from EV-AR3621-002 following Scheme 2) was combined with 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU, 7.72 g, 20.30 mmol) and N,N-Diisopropylethylamine (DIPEA, 3.90 mL, 22.33 mmol) in dimethylformamide (DMF, 80 mL). The reaction was stirred for 15 minutes and then methyl 3-amino-4-(methylamino)benzoate EV-AR3155-001 (4.02 g, 22.33 mmol) was added to the reaction. The reaction was stirred at room temperature for 2 hours. Upon completion of the reaction the solvent was removed in vacuo. To the residue was added acetic acid (AcOH, 120 mL) and the vessel was warmed to 70 °C and stirred for 3 hours. The solvent was removed and the reaction was purified using automated

chromatography, the product came off the column at 40% ethyl acetate in hexane, yielding methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate (6.9 g, 17.67 mmol, 87 % yield). LCMS: retention time 0.95 min, M/z = 391.0 (M + 1).

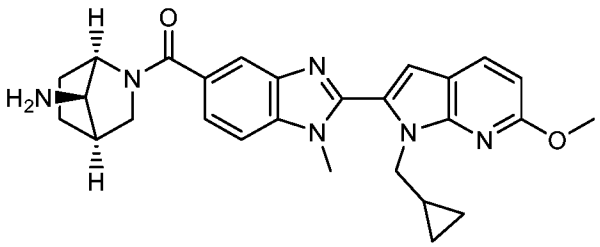
[00502] 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid – Step 3

[00503] To a solution of methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate (500 mg, 1.281 mmol) in THF (7 mL) and methanol (3.50 mL) was added water (3.50 mL) and a solution of lithium hydroxide monohydrate in water (3 M, 1.281 mL, 3.84 mmol). After 30 minutes, the starting material crushed out of the solution, additional THF (9 mL) was added and the reaction was stirred overnight. The reaction was concentrated in vacuo and then neutralized with hydrochloric acid (1 M in water, 3.84 mL, 3.84 mmol). Water was added to the suspension and after sonication the suspension was filtered and the solid air dried to provide the product 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (470 mg, 1.249 mmol, 98 % yield). LCMS: retention time 0.85 min, M/z = 376.8 (M + 1).

[00504] Tert-butyl ((3R,6S)-1-(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-6-methylpiperidin-3-yl)carbamate, I-352 – Step 4

[00505] 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (30 mg, 0.080 mmol), tert-butyl ((3R,6S)-6-methylpiperidin-3-yl)carbamate (25.6 mg, 0.120 mmol), HATU (36.4 mg, 0.096 mmol) and DIPEA (0.042 mL, 0.239 mmol) were combined in DMF (1 mL) and the reaction stirred for 30 minutes. Upon the completion of amide formation (as measured by LCMS), HCl (4 M in dioxane, 1 mL, 4 mmol) was added to the reaction. The reaction was warmed to 50 °C and stirred for 3 hours. The reaction was cooled to room temperature, filtered and then purified using preparative HPLC to provide ((2S,5R)-5-amino-2-methylpiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, **I-352**, (22.6 mg, 0.047 mmol, 59.4 % yield, 99% purity) LCMS: retention time 0.73 min, M/z = 472.9 (M + 1).

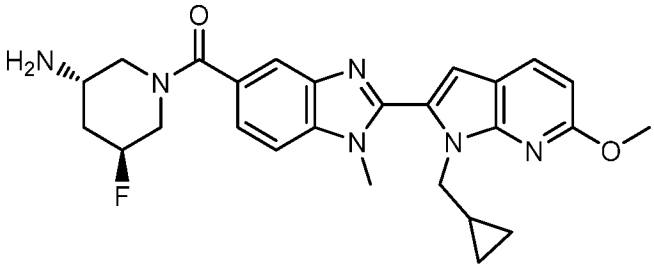
[00506] 1H NMR (500 MHz, DMSO-d6) Shift 8.04 - 8.00 (m, 1H), 7.78 - 7.72 (m, 2H), 7.40 - 7.33 (m, 1H), 7.11 - 7.02 (m, 2H), 6.72 - 6.63 (m, 1H), 4.54 - 4.42 (m, 2H), 4.01 - 3.96 (m, 3H), 3.96 - 3.91 (m, 3H), 3.03 - 2.91 (m, 1H), 1.95 - 1.82 (m, 1H), 1.79 - 1.68 (m, 2H), 1.66 - 1.51 (m, 1H), 1.26 - 1.13 (m, 4H), 0.36 - 0.29 (m, 2H), 0.25 - 0.19 (m, 2H)



I-353

[00507] ((1R,4R,7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, I-353

[00508] Following the procedure in Scheme 11 afforded **I-353** (95 % yield, 97% purity). LCMS: retention time 0.71 min, M/z = 470.9 (M + 1). (several signals appear hidden under water peak) ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (br d, *J*=8.25 Hz, 2H), 7.81 (s, 1H), 7.67-7.78 (m, 1H), 7.42-7.55 (m, 1H), 7.12-7.33 (m, 1H), 7.07 (br s, 2H), 6.68 (d, *J*=8.41 Hz, 1H), 4.41-4.59 (m, 2H), 3.97 (br s, 3H), 3.94 (s, 3H), 3.08-3.28 (m, 1H), 2.66 (br s, 1H), 1.79-2.04 (m, 3H), 1.55-1.72 (m, 1H), 1.09-1.28 (m, 1H), 0.31 (br d, *J*=7.83 Hz, 2H), 0.22 (br s, 2H).



I-354

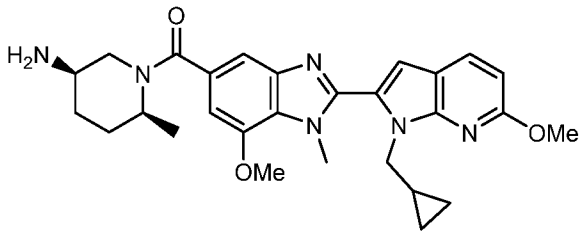
[00509] ((3S,5S)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-1-methyl-1H-benzo[d]imidazol-5-yl)methanone

[00510] Following the procedure in Scheme 11 afforded **I-354** (90 % yield, 96% purity). LCMS: retention time 0.72 min, M/z = 476.9 (M + 1).

1H NMR (500 MHz, DMSO-d6) Shift 8.03 - 7.96 (m, 1H), 7.80 - 7.70 (m, 2H), 7.44 - 7.36 (m, 1H), 7.06 - 7.02 (m, 1H), 6.71 - 6.60 (m, 1H), 4.56 - 4.36 (m, 2H), 4.01 - 3.94 (m, 3H),

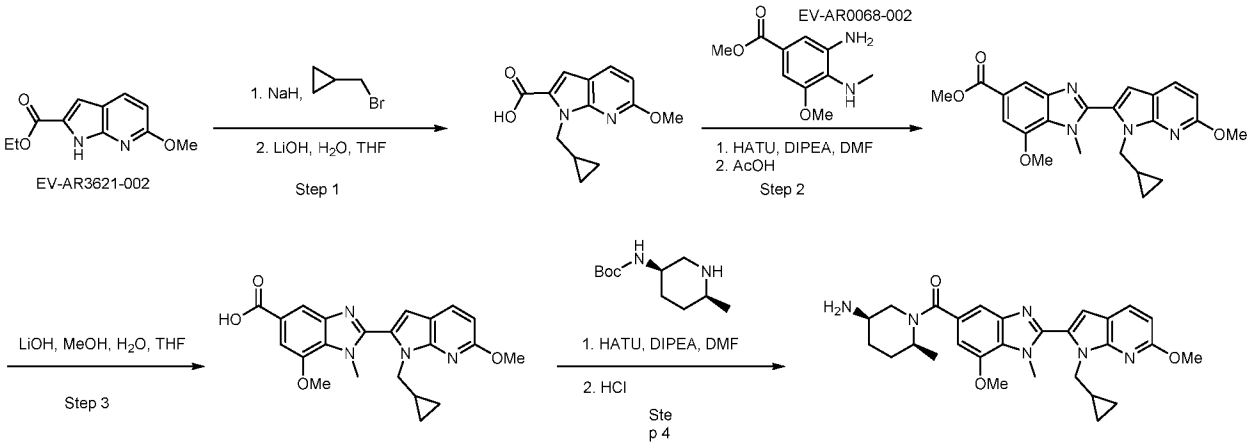
3.94 - 3.89 (m, 3H), 3.48 - 3.33 (m, 1H), 3.07 - 2.87 (m, 1H), 2.42 - 2.28 (m, 1H), 1.93 - 1.72 (m, 1H), 1.21 - 1.04 (m, 1H), 0.35 - 0.24 (m, 2H), 0.22 - 0.08 (m, 2H)

[00511] ((2S,5R)-5-amino-2-methylpiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone. I 355 Prepared according to Scheme 12.



I-355

[00512] Scheme 12



[00513] Methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylate – Step 2

[00514] 1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (5 g, 20.30 mmol), HATU (7.72 g, 20.30 mmol) and DIPEA (10.64 ml, 60.9 mmol) were added to DMF (80 ml). The reaction was stirred for 15 minutes at room temperature at which point methyl 3-amino-5-methoxy-4-(methylamino)benzoate HCl salt (5.51 g, 22.33 mmol) was added and the reaction was stirred overnight. The solvent was removed under vacumn and AcOH (120 mL) was added to the residue. The reaction was stirred at 70 °C for 4 hours and then the AcOH was removed in vacuo and the crude product was absorbed onto celite and purified using automated chromatography to provide methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-

carboxylate (6.5 g, 15.46 mmol, 76 % yield). LCMS: retention time 0.98 min, M/z = 421.0 (M + 1).

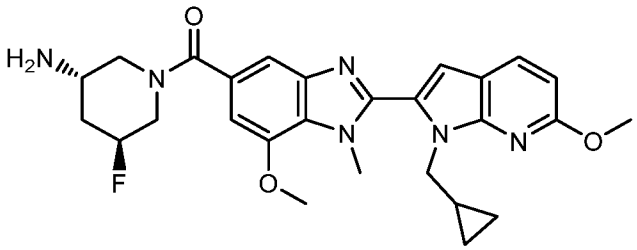
[00515] 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid – Step 3

[00516] Methyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylate (500 mg, 1.189 mmol) was dissolved in THF (10 mL), MeOH (5.00 mL) and water (2.500 mL), and a solution of lithium hydroxide in water (3M, 1.189 mL, 3.57 mmol) was added to the reaction. Additional THF was added until the reaction was homogenous. The reaction was stirred at room temperature for two days. The reaction was concentrated under vacuum and HCl in water (1 M, 3.6 mL, 3.6 mmol) was added to adjust the pH to about 6. The resulting solid was collected via to provide the product 2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid (435 mg, 1.07 mmol, 90 % yield). LCMS: retention time 0.89 min, M/z = 406.8 (M + 1).

[00517] ((2S,5R)-5-amino-2-methylpiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, I-355 – Step 4

[00518] Follow the procedure Step 4 in Scheme 12 to make ((2S,5R)-5-amino-2-methylpiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, **I-355**, (68.7 % yield, 100% Purity). LCMS: retention time 0.76 min, M/z = 502.9 (M + 1).

[00519] 1H NMR (500 MHz, DMSO-d6) Shift 8.03 - 7.98 (m, 1H), 7.28 - 7.22 (m, 1H), 7.01 - 6.94 (m, 1H), 6.83 - 6.77 (m, 1H), 6.70 - 6.61 (m, 1H), 4.48 - 4.38 (m, 2H), 4.17 - 4.06 (m, 3H), 4.00 - 3.96 (m, 3H), 3.96 - 3.93 (m, 3H), 2.70 - 2.62 (m, 1H), 2.56 - 2.52 (m, 3H), 1.90 - 1.88 (m, 2H), 1.76 - 1.62 (m, 2H), 1.58 - 1.39 (m, 2H), 1.26 - 1.12 (m, 4H), 0.38 - 0.27 (m, 2H), 0.25 - 0.14 (m, 2H)



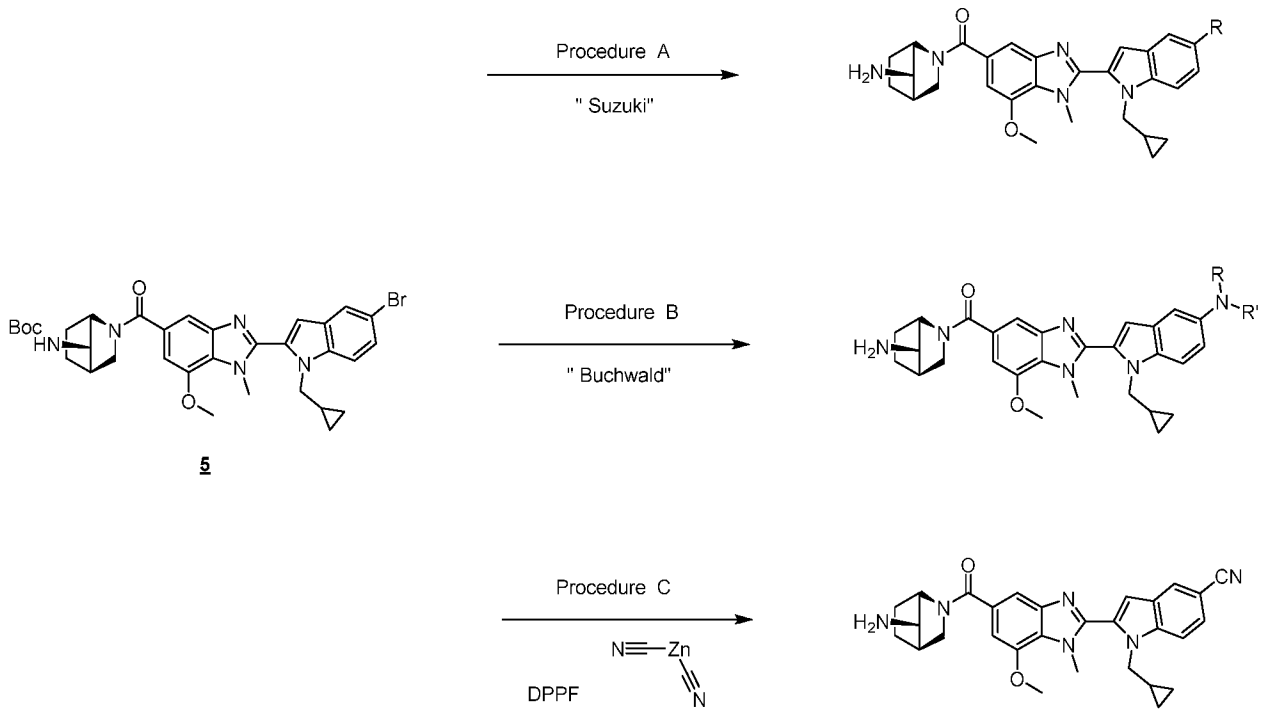
I-356

[00520] ((3S,5S)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone. I-356

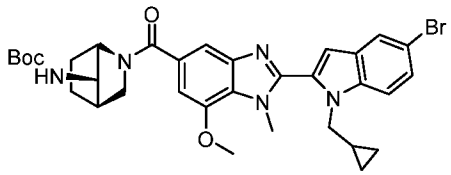
[00521] Following the procedure in Scheme 12 afforded ((3S,5S)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-pyrrolo[2,3-b]pyridin-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, **I-356**, (56.7 % yield, 99% Purity). LCMS: retention time 0.75 min, M/z = 506.9 (M + 1).

[00522] 1H NMR (500 MHz, DMSO-d6) Shift 8.06 - 7.96 (m, 1H), 7.36 - 7.25 (m, 1H), 7.01 - 6.93 (m, 1H), 6.87 - 6.79 (m, 1H), 6.70 - 6.61 (m, 1H), 4.44 - 4.37 (m, 2H), 4.14 - 4.08 (m, 3H), 4.01 - 3.95 (m, 3H), 3.95 - 3.92 (m, 3H), 3.54 - 3.43 (m, 1H), 3.31 - 3.21 (m, 1H), 3.06 - 2.96 (m, 1H), 2.23 - 2.10 (m, 1H), 1.94 - 1.84 (m, 2H), 1.65 - 1.43 (m, 1H), 1.21 - 1.06 (m, 1H), 0.37 - 0.24 (m, 2H), 0.23 - 0.11 (m, 2H)

[00523] Scheme 13

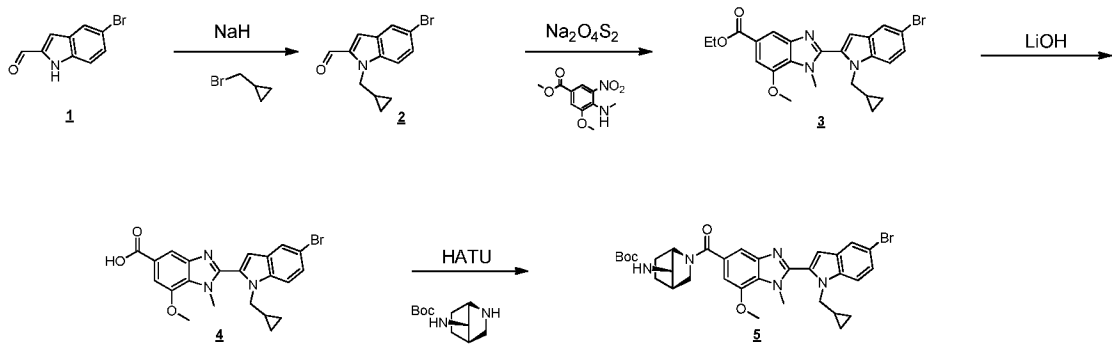


[00524] Tert-butyl ((1S,4R)-2-(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 5 Prepared using Scheme 13.1



5

[00525] Scheme 13.1



[00526] 5-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde: 2

[00527] A cold (0°C) solution of commercially available 5-bromo-1H-indole-2-carbaldehyde **1** (1 g, 4.46 mmol), in DMF was treated with NaH (0.196 g, 4.91 mmol) portion wise. The reaction was then stirred at 0°C for an additional 30 min. (bromomethyl)cyclopropane (0.723 g, 5.36 mmol) was then added, and the ice bath was removed. After 14 hrs, the reaction was quenched with H_2O (2 mL) then diluted with EtOAc and extracted with H_2O, brine, dried ($MgSO_4$) and concentrated to give an orange wax. The wax was then purified by Biotage (80g col, 0-60% EtOAc/hexanes, 12 CV) to give desired product, 800mg (64%), as a lt. yellow oil, LCMS (method A): retention time 2.18min, M/z = 280.10 (M + 2).

[00528] Methyl-2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylate: 3

[00529] A suspension of 5-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde **2** (2.2 g, 7.91 mmol), and methyl-3-methoxy-4-(methylamino)-5-nitrobenzoate (WO 2014/015905 A1, intermediate 23) (1.900 g, 7.91 mmol), in ethanol (30 mL) was treated with a solution of sodium hydrosulfite (4.13 g, 23.73 mmol) in H_2O (10 mL) in one portion. The reaction was then heated to reflux for 18 hrs. After which time the reaction was diluted with DCM (150

ml) dried, $MgSO_4$, and concentrated to give an orange solid. The solid was purified by Biotage (80g col, 0-30% EtOAc / hexanes, 12 CV) to give, 1g of recovered aldehyde, 1.4 g of recovered nitro compound. Along with 430 mg (12%) desired product, as a yellow solid, LCMS (method A): retention time 2.25min, M/z = 470.20 (M + 2).

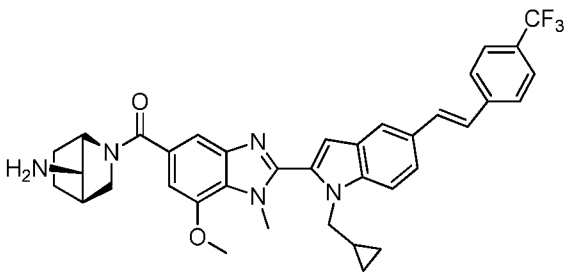
[00530] 2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid: 4

[00531] A room temperature solution of methyl 2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylate **3** (1.1 g, 2.349 mmol) in THF (15 mL) was treated with a solution of LiOH (0.225 g, 9.39 mmol) in H_2O (6 mL). The reaction was then heated to reflux for 1.5hrs. The suspension was cooled with Ice, then made acidic with 1N HCl (approx. 25 ml). The resulting red solid was filtered off, washed with H_2O, and dried (High Vac). The solid was then taken into EtOAc / DCM and dried again with $MgSO_4$, filtered, then concentrated to give a red solid. 940mg (88%), LCMS (method A): retention time 1.27min, M/z = 456.20 (M + 2).

[00532] tert-butyl((1S,4R)-2-(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate: 5

[00533] A room temperature solution of 2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid **4** (940 mg, 2.069 mmol), DIEA (0.542 mL, 3.10 mmol) in DCM (50 mL) was treated with HATU (865 mg, 2.276 mmol) in one portion. tert-Butyl (1R, 4R, 7R)-2-azabicyclo [2.2.1] heptan-7-ylcarbamate (483 mg, 2.276 mmol) was added and stirring was continued for 18 hrs. The reaction was diluted with DCM, and washed with H_2O, Sat. Bicarb, brine, dried ($MgSO_4$) and concentrated to give an orange oil. The oil was then purified by Biotage (80g col, 50--90% EtOAc/ Hexanes, 12 CV, then 90% EtOAc /Hexanes, 2 CV) to give desired product, as a lt. orange oil, 1.07 g (80%), LCMS (method A): retention time 1.09min, M/z = 649.50 (M + 1). M/z = 650.13 (M + 2).

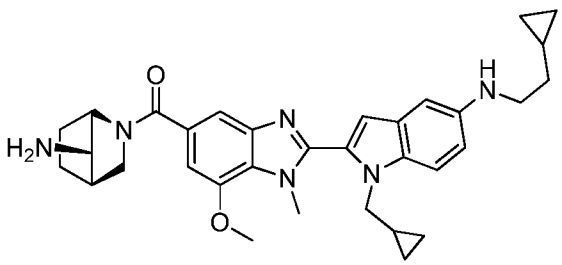
[00534] Procedure A



[00535] ((1S,4R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-((E)-4-(trifluoromethyl)styryl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, I-361:

[00536] A suspension of tert-butyl ((1S,4R)-2-(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **5** (50 mg, 0.077 mmol), (E)-(4-(trifluoromethyl)styryl)boronic acid (16.65 mg, 0.077 mmol), and an aqueous solution (0.5M) of potassium phosphate tribasic (0.925 mL, 0.463 mmol) in THF (5 mL) was added 2-dicyclohexylphosphino-2',6'-di-I-propoxy-1,1'biphenyl (21.58 mg, 0.046 mmol) and palladium(II) chloride (2.73 mg, 0.015 mmol) in one portion. The resulting reddish suspension was heated to 80 °C for 4hrs. The reaction was diluted with EtOAc washed with H_2O, brine, dried ($MgSO_4$) and concentrated to give a light orange wax. The wax was clean enough by LCMS (MW = 739) to carry on to the deprotection step. The wax was taken into DCM (2 mL) then treated with 4M HCl (0.5 mL, 2.000 mmol) (4M in Dioxane). After 1hr, the reaction was concentrated, taken into DCM and filtered, dried (MgSO4), concentrated, then purified, 32 mg in 2ml DMF. The crude material was purified via preparative LC/MS: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 50-90% B over 19 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. The yield of the product was 20.3 mg, (34% yield) and its estimated purity by LCMS analysis was 100%. LCMS (method B): retention time 2.42min, M/z = 640.14 (M + 1).

[00537] Procedure B



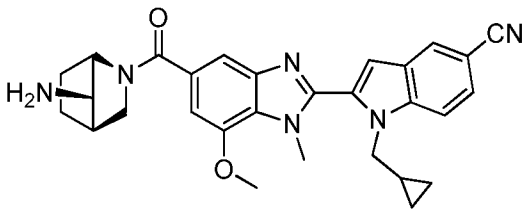
I-374

[00538] ((1S,4R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-((2-cyclopropylethyl)amino)-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-5-yl)methanone, I-374:

[00539] A suspension of **5** (50 mg, 0.077 mmol), 2-cyclopropylethanamine (6.56 mg, 0.077 mmol), X-PHOS (7.35 mg, 0.015 mmol), in toluene (15 mL) was degassed for 15 min with nitrogen. $Pd_2(dba)_3$ (7.06 mg, 7.71 μmol) and sodium tert-butoxide (14.82 mg, 0.154 mmol) were then added and the suspension was heated to 80 °C for 4 hrs. The reaction was cooled, diluted with EtOAc, then washed with H_2O, brine, dried ($MgSO_4$) and concentrated to give a tan wax. The wax was shown by LCMS to contain desired product by LCMS (MW = 652) which was then deprotected directly.

[00540] The material was taken into DCM (0.5mL) then treated with HCl (0.5 mL, 2 mmol, 4M in dioxane). After 1hr the reaction was concentrated, then evaporated from DCM (2x). The crude material was dissolved in MeOH (filtered) and evaporated to give a red solid: 37 mg. The crude material was purified via preparative LC/MS: Column: XBridge C18, 19 x 200 mm, 5-μm particle size; mobile phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; mobile phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 35-75% B over 20 minutes, then a 7-minute hold at 100% B; flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. The yield of the product was 10.9 mg, (16%) and its estimated purity by LCMS analysis was 98%. LCMS (method B): retention time 1.84min, M/z = 553.26 (M + 1).

[00541] Procedure C



I-370

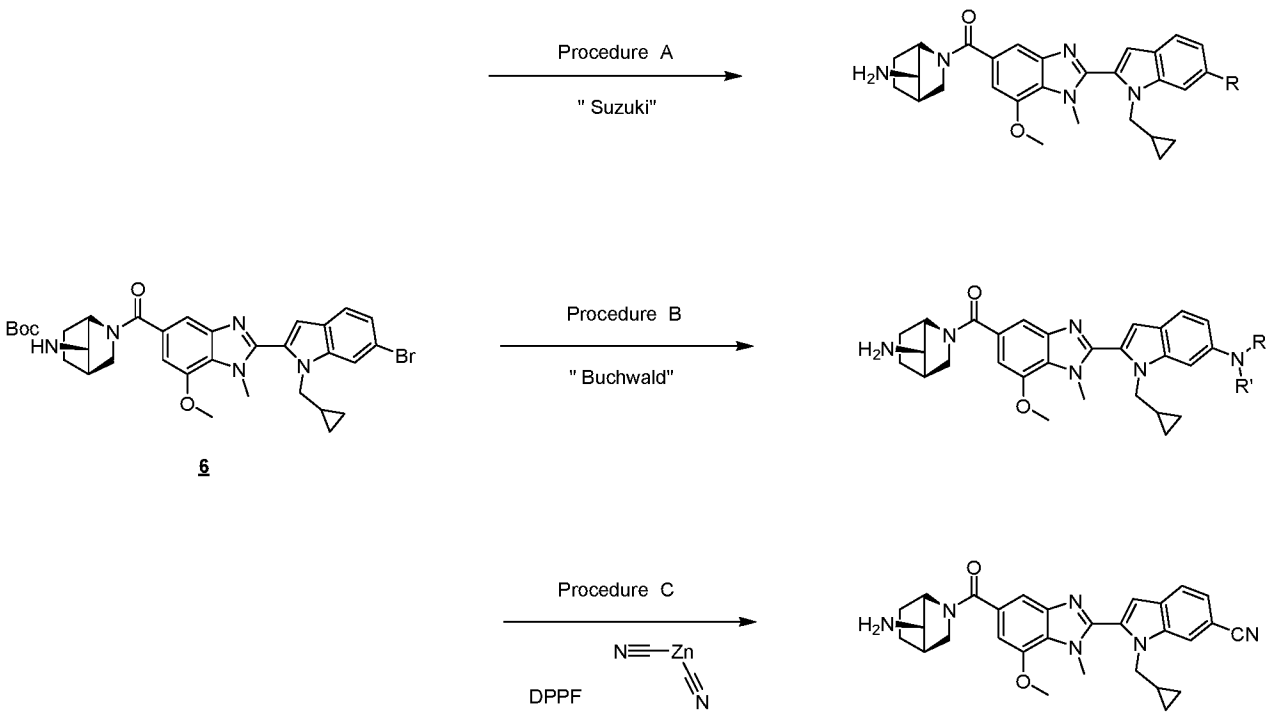
Step 1: tert-butyl ((1S,4R)-2-(2-(5-cyano-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate:

[00542] A suspension of tert-butyl ((1S,4R)-2-(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (100 mg, 0.154 mmol) **5**, zinc cyanide(18.10 mg, 0.154 mmol), Pd2dba3 (7.06 mg, 7.71 µmol) and DPPF (10.26 mg, 0.019 mmol) in DMF (4 mL) and water (0.4 mL) was heated to 120 °C for 18hrs. Additional zinc cyanide (18.10 mg, 0.154 mmol), Pd2dba3 (7.06 mg, 7.71 µmol) and DPPF (10.26 mg, 0.019 mmol) were added, and stirring at 120 °C was continued for 4 hrs. The reaction was cooled, diluted with EtOAc, washed with H_2O, sat. bicarb, dried ($MgSO_4$) and concentrated to give a black wax. The wax was purified by Biotage (40g col, 20-100% EtOAc/Hexanes, 12 CV then 100% EtOAc for 4 CV) to give desired product as a light yellow wax: 89 mg (97% yield), LCMS (method A): retention time min 2.11 min, M/z = 595.65 (M + 1).

Step 2: 2-(5-((1S,4R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-7-methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(cyclopropylmethyl)-1H-indole-5-carbonitrile, I-370:

[00543] A solution of tert-butyl ((1S,4R)-2-(2-(5-cyano-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (35 mg, 0.059 mmol) in DCM (1 mL) was treated with HCl (0.5 ml, 2 mmol, 4M in dioxane) dropwise. After 1hr the reaction was concentrated then sequentially dissolved in DCM and concentrated (2x). The crude material was dissolved in MeOH (filtered) and evaporated to give a red solid, 22 mg which was dissolved in 1.5 ml of DMF and purified via preparative LC/MS: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-55% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. The yield of the product was 14.4 mg (38% yield), and its estimated purity by LCMS analysis was 100%. LCMS (method B): retention time min 1.81 min, M/z = 495.07 (M + 1).

[00544] Scheme 14



Tert-butyl ((1S,4R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate 6:

[00545] The bromide was made as described in Scheme 13.1 starting from the commercially available 6-bromo-1H-indole-2-carbaldehyde to give an orange wax, LCMS (method A): retention time 1.29min, M/z = 650.30 (M + 2).

[00546] All 6 substituted -1H-indol-2yl compounds were made from **tert-butyl ((1S,4R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate 6** using the same procedures as described for the 5- substituted compounds (Scheme 13).

[00547] HPLC Methods for Schemes 13 and 14

Method A

(low pH Shimadzu 3min method)

Column: Waters Acquity UPLC BEH dC18, 2.1mmx50mm, 1.7µm column

Flow rate: 0.6 ml/min

Mobile Phase: A, TFA (aqueous) 0.05% and B, TFA (acetonitrile) 0.05%

Injection Vol: 3 µl

Temp.: 40 °C

Detection: 220 nm (nominal)

Gradient – 0-100% B

Method B

Column: Water Xbridge C18, 2.1mmx50mm, 1.7 µm column

Flow rate: 0.6 ml/min

Mobile Phase: acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature:

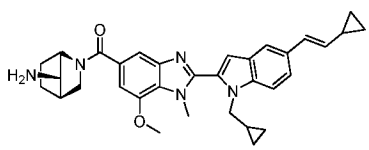
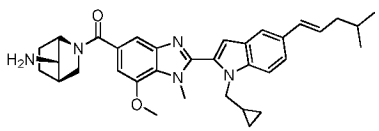
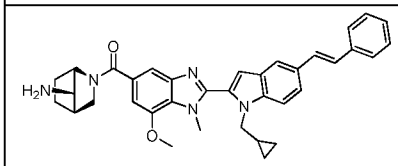
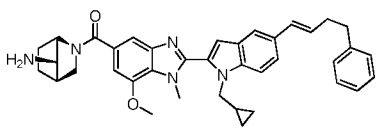
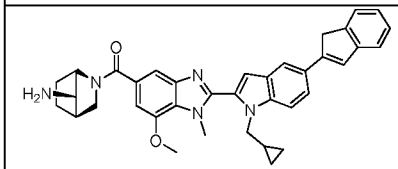
50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B

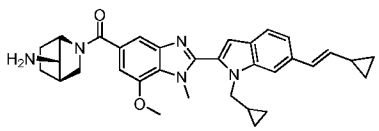
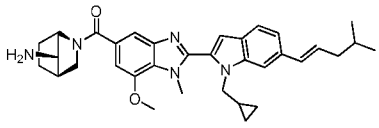
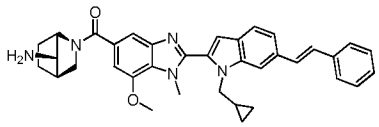
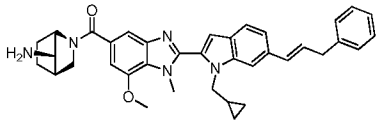
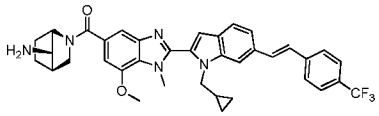
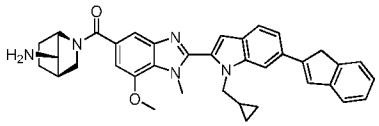
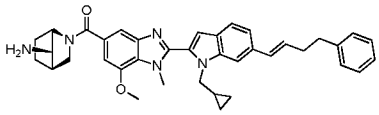
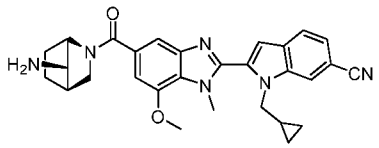
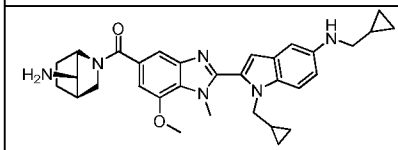
Injection Vol: 3 µl

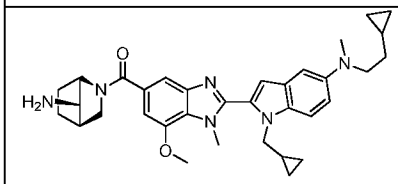
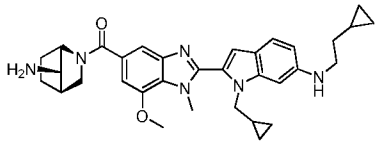
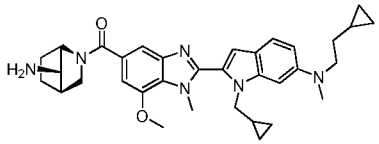
Temp.: 40 °C

Detection: 220 nm (nominal)

[00548] The following compounds were prepared using Method A, B, or C as described in Schemes 13 and 14:

Structure	#	Method	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-357**	A	535.679	2.11min	536.19	B		
	**I-358**	A	551.722	2.39min	552.15	B		
	**I-359**	A	571.71	2.16min	572.13	B		
	**I-360**	A	599.764	2.25min	600.40	A	TFA	1
	**I-362**	A	583.722	2.21min	584.12	B		

Structure	#	Method	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-363**	A	535.679	2.04min	536.24	B		
	**I-364**	A	551.722	2.35min	552.26	B		
	**I-365**	A	571.711	2.16min	572.25	B		
	**I-366**	A	585.738	2.57min	586.10	B		
	**I-367**	A	639.709	2.36min	640.24	B		
	**I-368**	A	583.722	2.19min	584.24	B		
	**I-369**	A	599.764	2.65min	600.12	B		
	**I-371**	C	494.588	0.91min	495.30	A	TFA	1
	**I-372**	B	538.683	1.19min	539.22	A	TFA	1

Structure	#	Method	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	**I-373**	B	566.736	2.20min	567.22	B		
	**I-375**	B	552.710	2.17min	553.12	B		
	**I-376**	B	556.736	1.31min	567.30	A		

Biological Assays

[00549] Compounds of the present invention were assayed as inhibitors of PAD4 using the assay protocol described below.

[00550] Compounds were solubilised in 100% DMSO to achieve 100 mM final compound concentration. Compound stock solutions were stored at RT. A series of dilutions were prepared in DMSO and mixed 8 times with 20 µL mixing volume. Final assay conditions were as follows:

Reaction volume: 20 µl

Assay buffer (as aforementioned): 100 mM Tris-HCl (pH 7.6), 2 mM DTT, 1 mM $CaCl_2$

Final concentrations:

-100 nM hPAD4 enzyme

-50 µM (8-fold sub-K_m) substrate peptide

-0.5% DMSO

Total incubation time: 65 mins at 37 °C

Stop solution: 40 µl 5% TCA in ACN

0.25 µL of compound solution was added to 10 µL of 200 nM PAD4 in assay buffer (100 mM Tris-HCl pH 7.6, 2 mM DTT). After 5 mins, 10 µL of 100 µM of substrate in buffer (100 mM Tris-HCl pH 7.6, 2 mM DTT, 2 mM CaCl2) was added and the reaction incubated for 60 mins at 37 ºC. The enzymatic reaction was quenched by addition of 40 µl of 5% TCA

in ACN (1.7% TCA final concentration) stop solution. Arginine containing substrate and citrulline containing product (+1 Da mass shift) were subjected to solid phase extraction on Agilent RapidFire (RF) 300 system and detected on a coupled, triple quadrupole Agilent 6460 QQQ mass spectrometry (MS) device under application of multiple reaction monitoring (MRM) for quantitation.

[00551] IC50 determinations against PAD isozymes

[00552] The IC50 for a given test compound was measured using a mass spec assay which detected the citrullinated product of BAEE after reaction with phenylglyoxal. Test compounds were dissolved in 100% DMSO and 0.125 uL were delivered to a 384 well REMP polypropylene plate prior to the addition of enzyme. The enzyme and the compound were pre-incubated for 30 mins at 37°C and the reaction was initiated by the addition of the BAEE substrate such that the final concentration in each assay well was equal to the Km value for BAEE at saturating calcium concentration (250 uM). The buffer used for the reaction contained 25 mM Hepes pH 7.5, 5 mM NaCl, 1 mM DTT, 0.01% Chaps, 0.2 mg/mL BSA and either 50 uM or 1 mM $CaCl_2$ which corresponds the one-fifth of the $K_{0.5}$ for Ca^{2+} or 20 x $K_{0.5}$ for Ca^{2+}, respectively, as measured at 10-fold Km of BAEE. A typical enzyme concentration used was 5 nM in the final reaction and the total reaction volume was 25 uL. The reaction was allowed to proceed for 1.5 hours at 37°C after the addition of BAEE before being quenched with 15 ul of 6.1 N TCA and 35 ul of 8.5 mM phenylglyoxal. The final concentration of phenyl glyoxal was 4 mM. The mixture was allowed to incubate for an additional 30 mins at 37°C with agitation to allow complete modification of the citrullinated product by phenyl glyoxal. The quenched reaction plate was centrifuged at 5000 x g for 3 minutes and an equal volume of methanol containing an internal standard (phenylglyoxal modified citrulline) was added to each well. The contents were transferred to a new 384-well REMP plate for rapidfire MS analysis.

[00553] Samples were loaded on to the RapidFire RF300 system (Agilent) wherein they were first sipped for 1000 ms and then directly loaded to a C18 separations cartridge using a mixture of acetonitrile containing 0.01% formic acid for 3000 ms desalting. The flow rate of the mobile phase was 1.5 ml/min. Once the samples were eluted from the cartridge, a mobile phase of acetonitrile containing 0.01% formic acid was used to move the samples into the mass spectrometer for 4000 ms at a flow rate of 1.25 ml/min. Sciex API4000 triple quadrupole mass spectrometer (Applied Biosystems) equipped with ESI was used to analyze the peptidyl citrulline and internal standard ions. MRM transition of product and internal standard were monitored at m/z 424.5 to 350.4 and m/z 293 to 247, respectively. The dwell

time for each transition was set at 200 ms, and the ESI voltage was used at 5500 V with a source temperature of 400°C. Extracted ion peaks for each transition were integrated using the rapidfire integrator software. Peak area was normalized against the internal standard.

[00554] For IC50 determinations, compounds were 3-fold serially diluted in DMSO and tested at 11 different concentrations. Peak area ratios were calculated by dividing peak area of analyte with peak area of internal standard. The peak area ratio from the DMSO control and the no enzyme background were used to calculate percent inhibition occurring at each concentration of inhibitor, and the IC50 was calculated using the following equation

$$Y = A + \frac{(B - A)}{1 + \left(\frac{C}{x}\right)^{D}}$$

where Y = % inhibition at each inhibitor concentration, A = minimal Y value, B = maximal Y value, C= logIC50, D = hill slope, and x = concentration of inhibitor.

[00555] **Table 2**, below, shows the activity of selected compounds of this invention in the PAD4 assays described above. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as "A" provided an $IC_{50} \leq 1$ μM; compounds having an activity designated as "B" provided an IC_{50} of 1.0 – 5.0 μM; compounds having an activity designated as "C" provided an IC_{50} of 5.0 – 10.0 μM; and compounds having an activity designated as "D" provided an IC_{50} of ≥ 10.0 μM. The term pIC_{50} = -log(IC_{50}). Compounds having an activity designated as "E" provided a $pIC_{50} \leq 4$; compounds having an activity designated as "F" provided a pIC_{50} of 4.0-5.0; compounds having an activity designated as "G" provided a pIC_{50} of 5.0-6.0; and compounds having an activity designated as "H" provided a pIC_{50} of ≥ 6. "NA" stands for "not assayed."

Table 2. PAD4 Activity

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-1	D	F	NA	NA
I-2	D	F	NA	NA
I-3	B	G	NA	NA
I-4	D	F	NA	NA
I-5	D	F	NA	NA
I-6	B	G	NA	NA
I-7	A	H	NA	NA
I-8	A	H	NA	NA

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-9	C	G	D	F
I-10	B	G	C	G
I-11	A	H	A	H
I-12	B	G	D	F
I-13	B	G	NA	NA
I-14	D	F	NA	NA
I-15	C	G	NA	NA
I-16	C	G	NA	NA
I-17	D	F	D	F
I-18	D	F	D	F
I-19	B	G	C	G
I-20	D	F	NA	NA
I-21	B	G	B	G
I-22	D	F	D	F
I-23	A	H	B	G
I-24	D	F	D	F
I-25	B	G	B	G
I-26	D	F	D	E
I-27	B	G	B	G
I-28	A	H	A	H
I-29	C	F	C	G
I-30	D	F	D	F
I-31	A	H	A	H
I-32	D	E	D	F
I-33	A	H	A	H
I-34	A	H	A	H
I-35	A	H	A	H
I-36	A	H	A	H
I-37	D	E	NA	NA
I-38	D	E	NA	NA
I-39	D	F	NA	NA
I-40	D	F	NA	NA
I-41	D	F	NA	NA
I-42	D	E	NA	NA
I-43	D	E	NA	NA
I-44	D	E	NA	NA
I-45	D	E	NA	NA
I-46	D	E	NA	NA
I-47	D	E	NA	NA
I-48	D	F	NA	NA
I-49	C	G	NA	NA
I-50	D	E	NA	NA
I-51	D	F	NA	NA
I-52	D	F	D	F
I-53	D	E	NA	NA
I-54	C	G	D	F

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-55	D	F	D	F
I-56	B	G	B	G
I-57	B	G	NA	NA
I-58	D	F	NA	NA
I-59	B	G	A	H
I-60	D	F	NA	NA
I-61	D	E	NA	NA
I-62	B	G	C	G
I-63	D	F	NA	NA
I-64	B	G	C	G
I-65	D	F	D	F
I-66	A	G	B	G
I-67	D	F	NA	NA
I-68	C	G	D	F
I-69	A	G	D	F
I-70	A	H	A	H
I-71	B	G	A	H
I-72	B	G	A	H
I-73	B	G	A	H
I-74	D	F	D	F
I-75	B	G	B	G
I-76	D	F	D	F
I-77	D	F	D	F
I-80	C	G	B	G
I-81	A	H	A	H
I-82	D	F	D	F
I-83	B	G	B	G
I-84	D	F	D	F
I-85	D	F	D	F
I-86	A	H	A	H
I-87	A	H	A	H
I-88	D	F	C	G
I-89	D	F	D	F
I-90	B	G	B	G
I-91	A	H	A	H
I-92	B	G	A	H
I-93	B	G	B	G
I-94	A	H	A	H
I-95	D	F	D	F
I-96	D	F	D	F
I-97	D	F	D	F
I-98	A	H	A	H
I-99	D	E	D	E
I-100	D	E	D	E
I-101	B	G	B	G
I-102	A	G	B	G

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-103	D	F	D	F
I-104	A	H	A	H
I-105	A	H	A	H
I-106	A	H	A	H
I-107	D	F	D	F
I-108	D	F	D	F
I-109	A	H	A	H
I-110	B	G	D	F
I-111	B	G	A	H
I-112	C	G	B	G
I-113	B	G	C	G
I-114	A	H	A	H
I-115	A	H	A	H
I-116	D	F	NA	NA
I-117	B	G	D	F
I-119	A	H	A	H
I-121	A	H	A	H
I-122	D	E/F	D	E
I-123	A	H	A	H
I-124	D	F	C	G
I-125	D	F	D	F
I-126	D	F	D	F
I-127	B	G	B	G
I-128	B	G	B	G
I-129	B	G	B	G
I-130	A	H	B	G
I-131	C	G	D	F
I-132	A	H	B	G
I-133	D	F	B	G
I-134	B	G	A	H
I-135	A	H	A	H
I-136	A	H	A	H
I-137	B	G	B	G
I-138	A	H	A	H
I-139	A	H	A	H
I-140	C	G	D	F
I-141	A	H	A	H
I-142	B	G	B	G
I-143	A	H	A	H
I-146	B	G	A	H
I-149	A	H	A	H
I-151	B	G	C	G
I-152	B	G	C	G
I-154	A	H	A	H
I-155	A	H	A	H
I-157	B	G	B	G

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-159	A	H	A	H
I-160	A	H	A	H
I-161	A	H	A	H
I-162	A	H	B	G
I-163	B	G	A	H
I-164	B	G	C	G
I-165	B	G	B	G
I-166	A	H	B	G
I-167	B	G	NA	NA
I-168	A	H	NA	NA
I-169	A	H	NA	NA
I-170	B	G	NA	NA
I-171	C	G	C	G
I-172	B	G	B	G
I-173	A	H	B	G
I-174	B	G	B	G
I-175	A	H	B	G
I-176	B	G	B	G
I-177	B	G	A	H
I-178	A	H	A	H
I-179	A	H	B	G
I-180	B	G	A	H
I-181	A	H	A	H
I-182	A	H	A	H
I-183	A	H	A	H
I-184	A	H	A	H
I-185	C	G	D	F
I-186	B	G	D	F
I-187	D	F	D	F
I-188	A	H	A	H
I-189	A	H	A	H
I-190	B	G	B	G
I-191	A	H	B	G
I-192	A	H	C	G
I-193	B	G	B	G
I-194	B	G	C	G
I-195	C	G	B	G
I-196	A	H	A	H
I-197	A	H	A	H
I-198	A	H	A	H
I-199	A	H	A	H
I-200	A	H	A	H
I-201	A	H	A	H
I-202	A	H	B	G
I-203	A	H	B	G
I-204	A	H	A	H

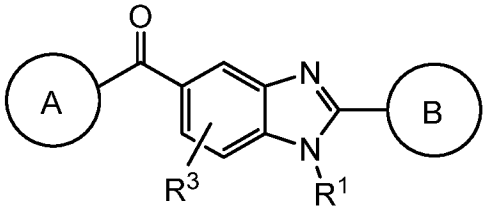
Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-205	A	H	A	H
I-206	A	H	A	H
I-207	C	G	B	G
I-208	A	H	A	H
I-209	A	H	A	H
I-210	A	H	A	H
I-211	A	H	A	H
I-212	D	F	D	F
I-213	A	H	A	H
I-214	A	H	B	G
I-215	D	E/F	D	E/F
I-216	D	F	D	F
I-217	A	H	A	H
I-218	B	G	B	G
I-219	A	H	B	G
I-220	D	E/F	D	E/F
I-221	D	F	B	G
I-222	A	H	A	H
I-223	A	H	A	H
I-224	A	H	A	H
I-225	A	H	A	H
I-226	D	E/F	D	E/F
I-227	D	F	D	E/F
I-228	C	G	B	G
I-229	D	F	C	G
I-230	A	H	A	H
I-231	A	H	A	H
I-232	A	H	A	H
I-233	A	H	A	H
I-234	A	H	B	G
I-235	A	H	A	H
I-236	A	H	A	H
I-237	D	F	D	F
I-238	A	H	A	H
I-352	A	H		
I-353	A	H		
I-354	A	H		
I-355	A	H		
I-356	A	H		
I-357	A	H		
I-358	A	H		
I-359	A	H		
I-360	A	H		
I-361	A	H		
I-362	A	H		
I-363	A	H		

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-364	A	H		
I-365	A	H		
I-366	A	H		
I-367	A	H		
I-368	A	H		
I-369	A	H		
I-371	A	H		
I-372	B	G/H		
I-373	B	G		
I-374	A	H		
I-375	A	H		
I-376	A	H		

CLAIMS

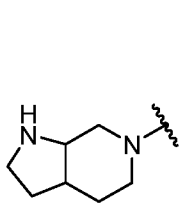
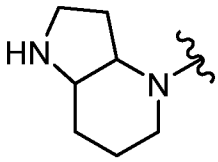
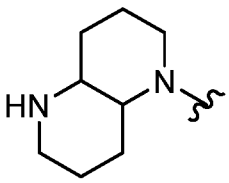
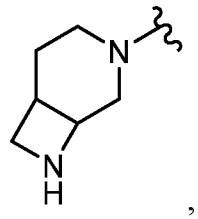
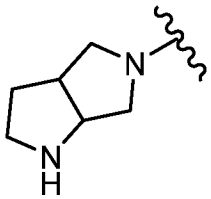
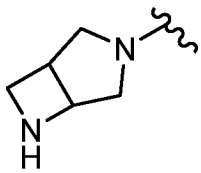
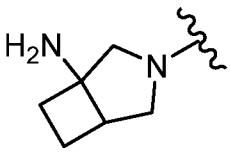
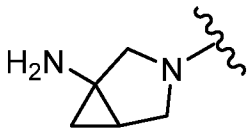
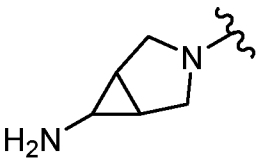
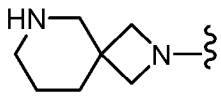
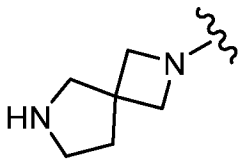
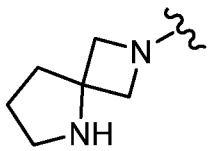
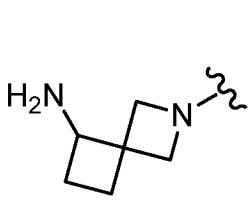
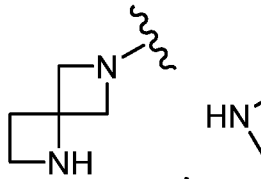
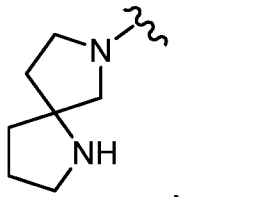
We claim:

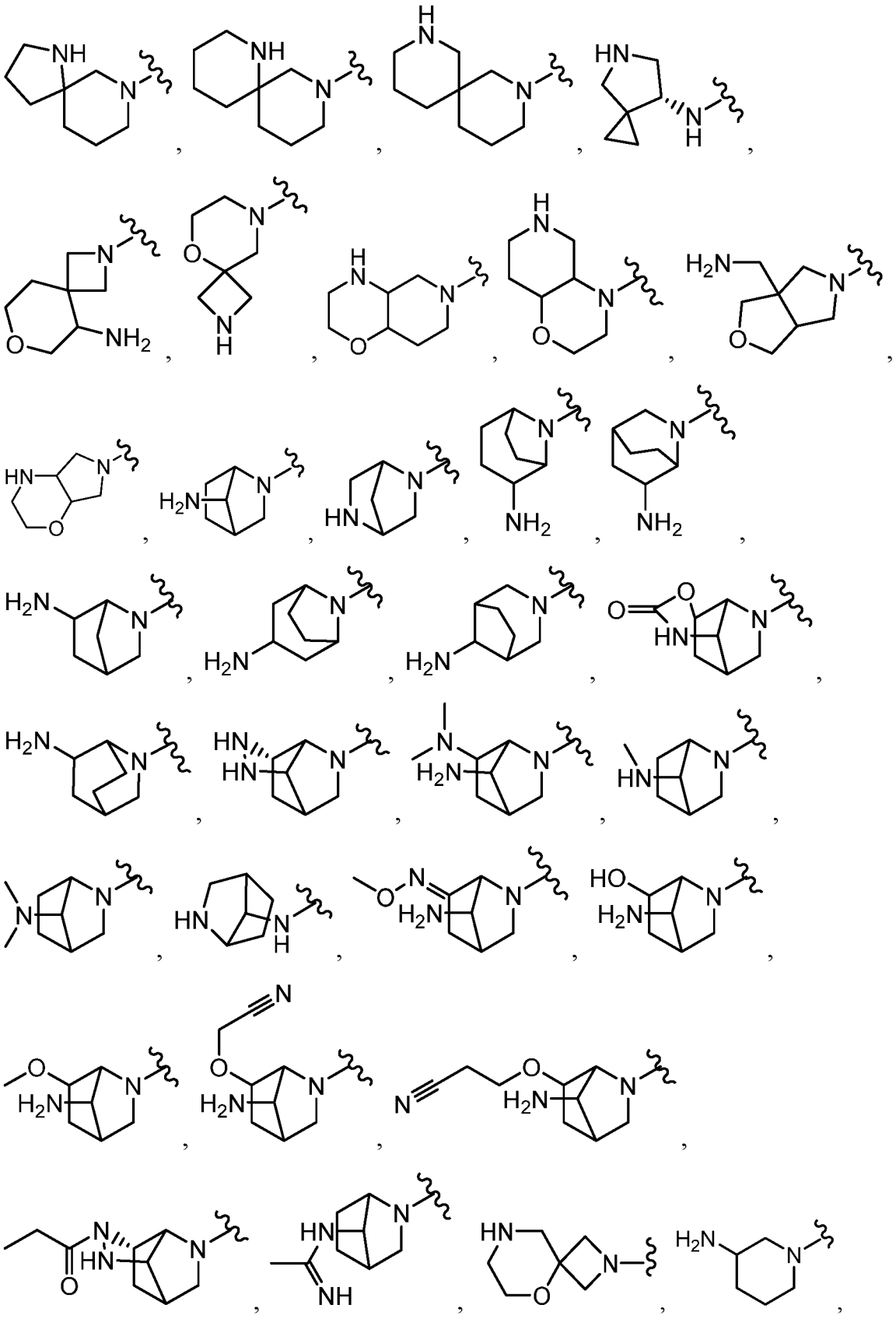
1. A compound of formula **I'**:

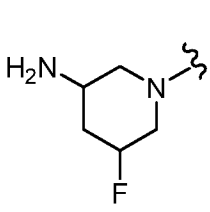


I'

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

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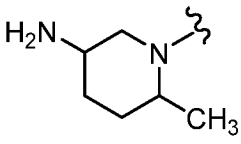
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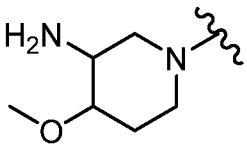
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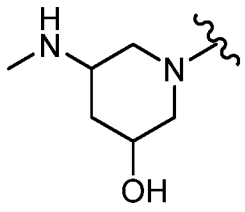
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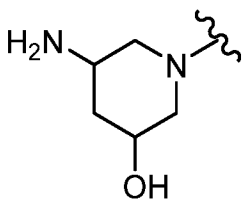
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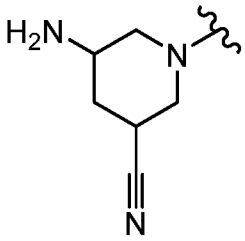
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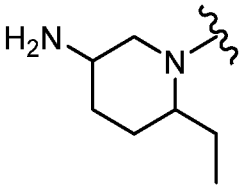
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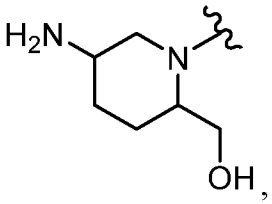
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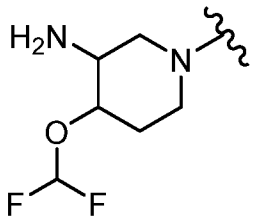
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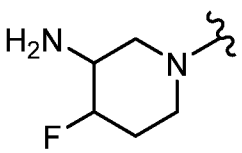
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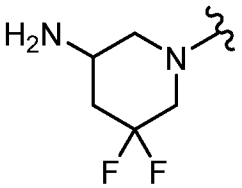
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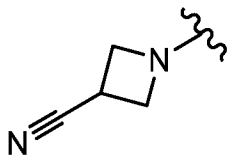
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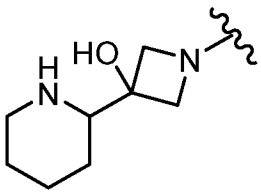
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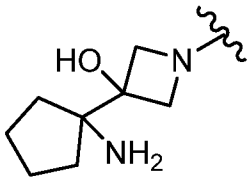
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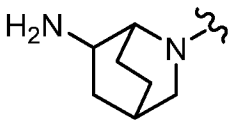
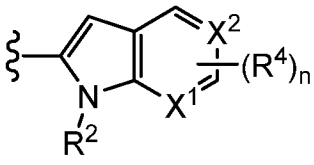

, wherein Ring A is optionally substituted with 1-4 groups selected from fluorine, -CN, -OR, or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms;

Ring B is

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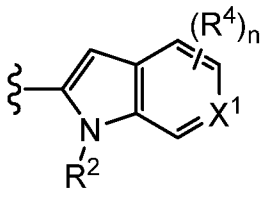
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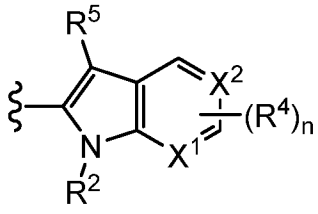
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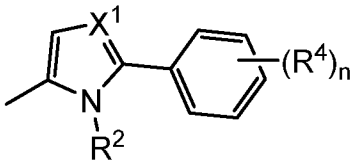
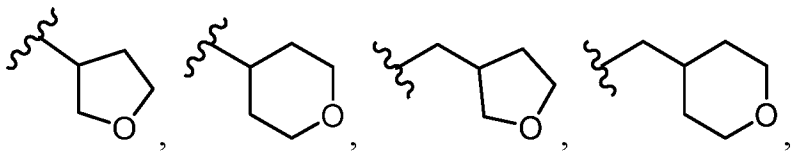
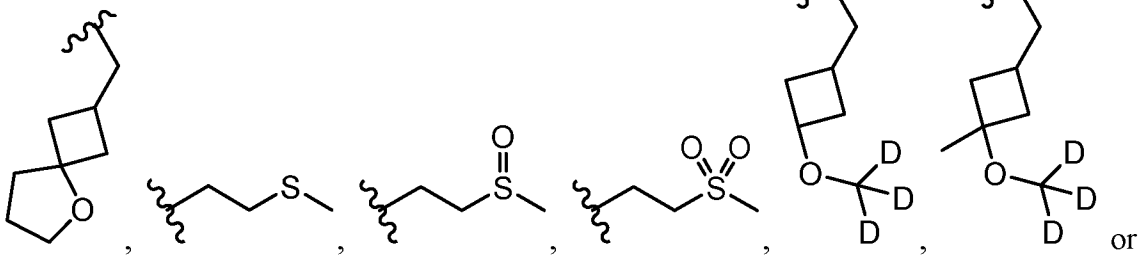
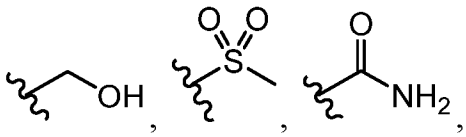

;

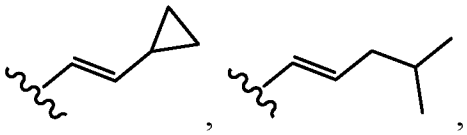
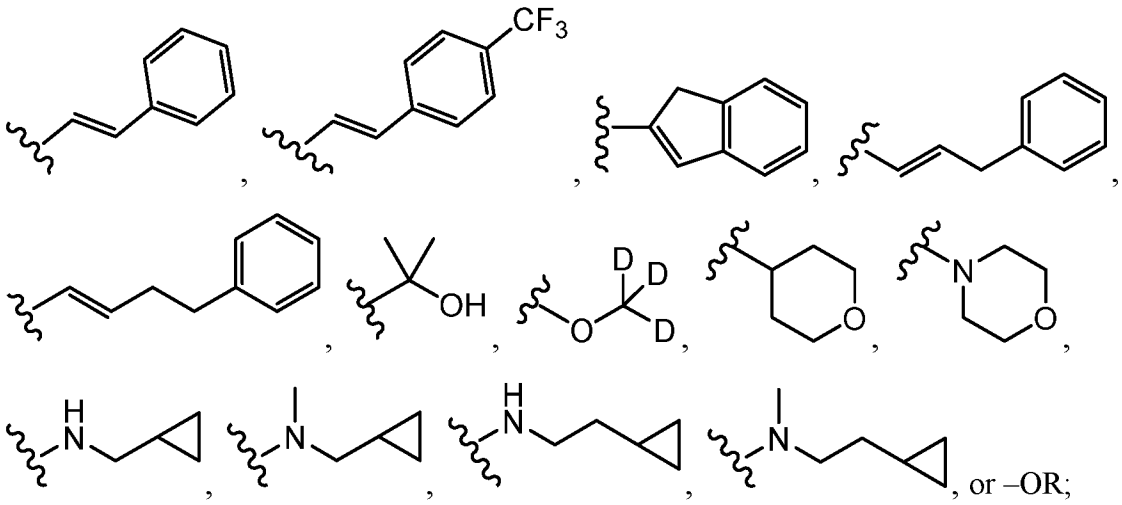
R^1 is hydrogen, –CN, -OR,  ,  , or

C_{1-6} aliphatic optionally substituted with 1-4 groups selected from fluorine, -CN, or -OR;

R^2 is hydrogen or C_{1-10} aliphatic optionally substituted with 1-5 groups selected from fluorine, –CN, or -OR;

each of X^1 and X^2 is independently selected from N or $C(R^4)$;

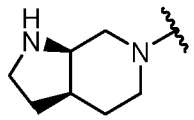
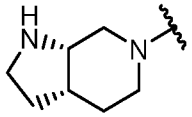
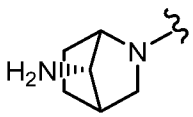
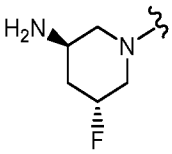
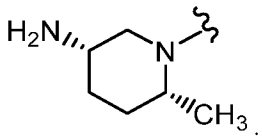
R^3 is halogen, -CN, –R,  , or –OR;

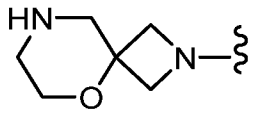
each R^4 is independently halogen, -CN, –R,  ,  , or –OR;

R^5 is hydrogen or halogen;

n is 0-4; and

each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

2. The compound according to claim 1, wherein Ring A is  ,  ,  ,  , or  .

3. The compound according to claim 1, wherein Ring A is  or  .

4. The compound according to any one of claims 1 through 3, wherein R^1 is methyl, ethyl, or propyl.

5. The compound according to any one of claims 1 through 4, wherein R^2 is C_{1-10} aliphatic, optionally substituted with 1-5 fluorine atoms.

6. The compound according to claim 5, wherein R^2 is methyl, ethyl, or -CH_2-cyclopropyl.

7. The compound according to claim 5, wherein R^2 is C_{1-10} aliphatic, substituted with 1-5 fluorine atoms.

8. The compound according to claim 7, wherein R^2 is $–CH_2CF_3$.

9. The compound according to any one of claims 1 through 8, wherein both of X^1 and X^2 are N.

10. The compound according to any one of claims 1 through 8, wherein X^1 is N, and X^2 is CH.

11. The compound according to any one of claims 1 through 8, wherein X^1 is CH, and X^2 is N.

12. The compound according to any one of claims 1 through 8, wherein both of X^1 and X^2 are CH.

13. The compound according to any one of claims 1 through 12, wherein R^4 is C_{1-6} aliphatic or –OR.

14. The compound according to claim 13, wherein R^4 is ethyl or $–OCH_3$.

15. A pharmaceutically acceptable composition comprising the compound according to any of claims 1 through 14, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

16. The composition according to claim 15, in combination with an additional therapeutic agent.

17. A method of inhibiting PAD4 in a subject or in a biological sample comprising the step of contacting the PAD4 with a compound according to any of claims 1 through 14.

18. A method of treating a PAD4-mediated disease, disorder, or condition in a subject in need thereof comprising the step of administering to said subject the composition according to claim 15.

19. The method according to claim 18, wherein said subject is a human subject.

20. The method according to claim 18, wherein the PAD4-mediated disease, disorder, or condition is selected from the group consisting of acid-induced lung injury, acne (PAPA), acute lymphocytic leukemia, acute, respiratory distress syndrome, Addison's disease, adrenal hyperplasia, adrenocortical insufficiency, ageing, AIDS, alcoholic hepatitis, alcoholic hepatitis, alcoholic liver disease, allergen induced asthma, allergic bronchopulmonary, aspergillosis, allergic conjunctivitis, alopecia, Alzheimer's disease, amyloidosis, amyotropic lateral sclerosis, and weight loss, angina pectoris, angioedema, anhidrotic ecodermal dysplasia-ID, ankylosing spondylitis, anterior segment, inflammation, antiphospholipid

syndrome, aphthous stomatitis, appendicitis, arthritis, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, autoimmune hepatitis, bee sting-induced inflammation, behcet's disease, Behcet's syndrome, Bells Palsey, berylliosis, Blau syndrome, bone pain, bronchiolitis, burns, bursitis, cancer, cardiac hypertrophy, carpal tunnel syndrome, catabolic disorders, cataracts, cerebral aneurysm, chemical irritant-induced inflammation, chorioretinitis, chronic heart failure, chronic lung disease of prematurity, chronic lymphocytic leukemia, chronic obstructive pulmonary disease, colitis, complex regional pain syndrome, connective tissue disease, corneal ulcer, crohn's disease, cryopyrin-associated periodic syndromes, cyrptococcosis, cystic fibrosis, deficiency of the interleukin-1–receptor antagonist (DIRA), dermatitis, dermatitis endotoxemia, dermatomyositis, diffuse intrinsic pontine glioma, endometriosis, endotoxemia, epicondylitis, erythroblastopenia, familial amyloidotic polyneuropathy, familial cold urticarial, familial mediterranean fever, fetal growth retardation, glaucoma, glomerular disease, glomerular nephritis, gout, gouty arthritis, graft-versus-host disease, gut diseases, head injury, headache, hearing loss, heart disease, hemolytic anemia, Henoch-Scholein purpura, hepatitis, hereditary periodic fever syndrome, herpes zoster and simplex, HIV-1, Hodgkin's disease, Huntington's disease, hyaline membrane disease, hyperammonemia, hypercalcemia, hypercholesterolemia, hyperimmunoglobulinemia D with recurrent fever (HIDS), hypoplastic and other anemias, hypoplastic anemia, idiopathic thrombocytopenic purpura, incontinentia pigmenti, infectious mononucleosis, inflammatory bowel disease, inflammatory lung disease, inflammatory neuropathy, inflammatory pain, insect bite-induced inflammation, iritis, irritant-induced inflammation, ischemia/reperfusion, juvenile rheumatoid arthritis, keratitis, kidney disease, kidney injury caused by parasitic infections, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, leptospiriosis, leukemia, Loeffler's syndrome, lung injury, lung injury, lupus, lupus, lupus nephritis, lymphoma, meningitis, mesothelioma, mixed connective tissue disease, Muckle-Wells syndrome (urticaria deafness amyloidosis), multiple sclerosis, muscle wasting, muscular dystrophy, myasthenia gravis, myocarditis, mycosis fungiodes, mycosis fungoides, myelodysplastic syndrome, myositis, nasal sinusitis, necrotizing enterocolitis, neonatal onset multisystem inflammatory disease (NOMID), nephrotic syndrome, neuritis, neuropathological diseases, non-allergen induced asthma, obesity, ocular allergy, optic neuritis, organ transplant, osterarthritis, otitis media, paget's disease, pain, pancreatitis, Parkinson's disease, pemphigus, pericarditis, periodic fever, periodontitis, peritoneal endometriosis, pertussis, pharyngitis and adenitis (PFAPA syndrome), plant irritant-induced inflammation, pneumonia, pneumonitis, pneumosysts

infection, poison ivy/ urushiol oil-induced inflammation, polyarteritis nodosa, polychondritis, polycystic kidney disease, polymyositis, psoriasis, psoriasis, psoriasis, psoriasis, psychosocial stress diseases, pulmonary disease, pulmonary hypertension, pulmonayr fibrosis, pyoderma gangrenosum, pyogenic sterile arthritis, renal disease, retinal disease, rheumatic carditis, rheumatic disease, rheumatoid arthritis, sarcoidosis, seborrhea, sepsis, severe pain, sickle cell, sickle cell anemia, silica-induced disease, Sjogren's syndrome, skin diseases, sleep apnea, solid tumors, spinal cord injury, Stevens-Johnson syndrome, stroke, subarachnoid hemorrhage, sunburn, temporal arteritis, tenosynovitis, thrombocytopenia, thyroiditis, tissue transplant, TNF receptor associated periodic syndrome (TRAPS), toxoplasmosis, transplant, traumatic brain injury, tuberculosis, type 1 diabetes, type 2 diabetes, ulcerative colitis, urticarial, uveitis, and Wegener's granulomatosis.

21. The method according to claim 18, wherein the PAD4-mediated disease, disorder, or condition is selected from rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosis, and psoriasis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/065857

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 19/02; A61K 31/00; A61P 35/00; C07D 401/14; C07D 471/04 (2017.01)

CPC - C07D 413/04; A61K 31/407; A61K 31/4184; C07D 401/14; C07D 519/00 (2017.02)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/015905 A1 (GLAXO GROUP LIMITED) 30 January 2014 (30.01.2014) entire document	1, 2
A	US 2014/0005183 A1 (PFIZER, INC) 02 January 2014 (02.01.2014) entire document	1, 2
A	PUBCHEM: Substance Record for SID 173022050. 10.03.2014. [retrieved on 24.03.2017]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/substance/173022050#section=Top>. entire document	1, 2
P, X	WO 2016/185279 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED) 24 November 2016 (24.11.2016) entire document	1, 2

☐ Further documents are listed in the continuation of Box C. ☐ 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
27 March 2017	17 APR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/065857

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1 and 2 have been analyzed subject to the restriction that claims read on a compound of formula I', or pharmaceutically acceptable salt thereof, wherein: Ring A is the first shown structure, which is unsubstituted; Ring B is the first shown structure; R1 is hydrogen; R3 is halogen; R2 is hydrogen; R4 is absent; X1 is N; X2 is N; n is 0.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/065857

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-4 are drawn to compounds of formula I'.

The first invention of Group I+ is restricted to a compound of formula I', or pharmaceutically acceptable salt thereof, wherein: Ring A is the first shown structure, which is unsubstituted; Ring B is the first shown structure; R1 is hydrogen; R3 is halogen; R2 is hydrogen; R4 is absent; X1 is N; X2 is N; n is 0. It is believed that claims 1 and 2 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula I', or pharmaceutically acceptable salt thereof, wherein: Ring A is the second shown structure, which is unsubstituted; Ring B is the second shown structure; R1 is hydrogen; R3 is halogen; R2 is hydrogen; R4 is absent; X1 is N; n is 0. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for Ring A; Ring B; R1; and R3.

The Groups I+ share the technical features of a compound having the core structure of formula I'. However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 173022050 to PubChem teaches a compound having the core structure of formula I' (Pg. 3, See shown structure).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.