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(71) Applicant: **PADLOCK THERAPEUTICS, INC.** [US/US]; Route 206 & Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors: **BEAUMONT, Edward Jean**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **DEVRAJ, Rajesh**; 301 Palomino Hill Court, Chesterfield, Missouri 63005 (US). **KERRY, Philip Stephen**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **KUMARAVEL, Gnanasambandam**; 21 Appletree Lane, Lexington, Massachusetts 02420 (US). **LOKE, Pui Leng**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **MENICONI, Mirco**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **PALFREY, Jordan John**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **NORTH, Carl**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **LECCI, Cristina**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB). **TYE, Heather**; 114 Innovation Drive, Milton Park; Abingdon, Oxfordshire OX14 4RZ (GB).

(74) Agent: **REID, Andrea L.C.** et al.; One International Place, 40th Floor, 100 Oliver Street, Boston, Massachusetts 02110-2605 (US).

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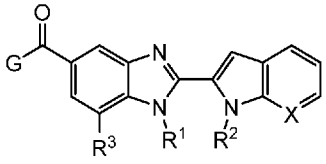
(54) Title: COVALENT INHIBITORS OF PAD4

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



(I)

COVALENT 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.

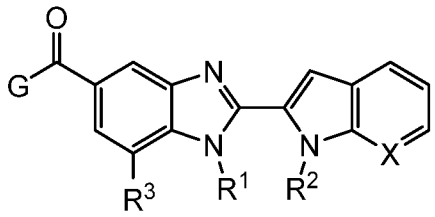
[0005] PAD4 inhibitors are also useful in the treatment of cancers (*Slack.J.L. et al, Cell. Mol. Life Sci., 68(4), (2011), 709-720*). Over-expression of PAD4 has been demonstrated in numerous cancers (*Chang X. et al, BMC Cancer, 9, (2009), 40*). An anti-proliferative role has been suggested for PAD4 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

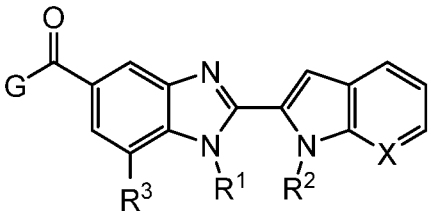
or a pharmaceutically acceptable salt thereof, wherein each of G, R^1, R^2, R^3 and X is as defined and described herein.

[0008] 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

[0009] 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**:



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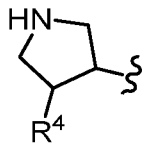
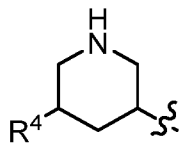
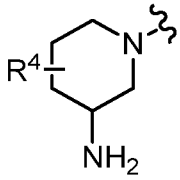
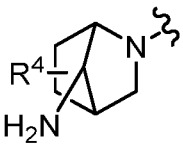
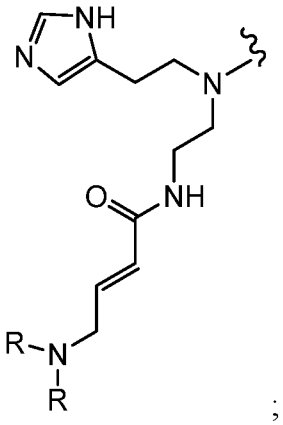
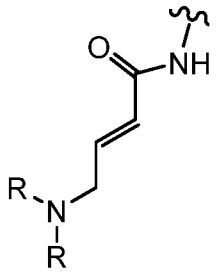
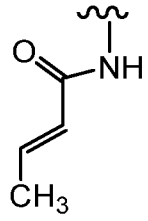
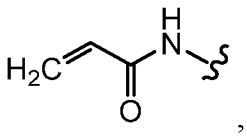
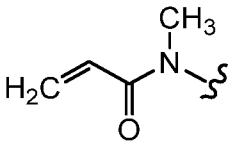
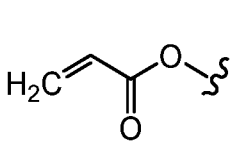
or a pharmaceutically acceptable salt thereof, wherein:

G is  ,  ,  ,  , or  ;

each R^4 is independently selected from  ,  ,  ,  , or  ;

R^1 is hydrogen or C_{1-6} aliphatic;

R^2 is hydrogen or C_{1-10} aliphatic;

X is selected from N or CH;

R^3 is –R, or –OR; and

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

2. *Definitions*

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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.

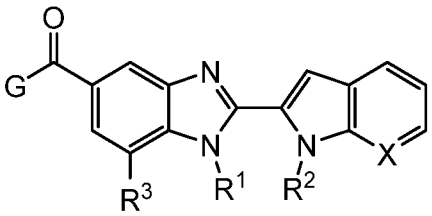
[0014] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and 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.

[0015] 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

[0016] According to one aspect, the present invention provides a compound of formula **I**:



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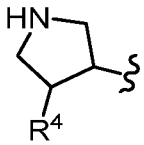
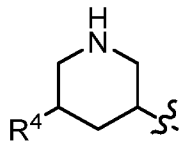
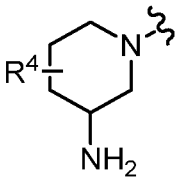
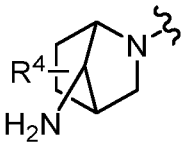
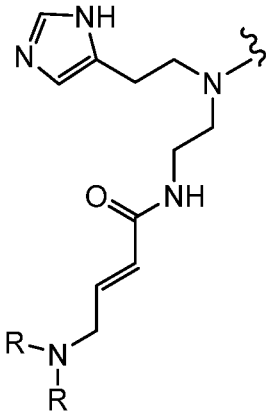
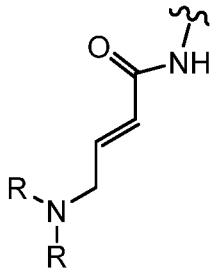
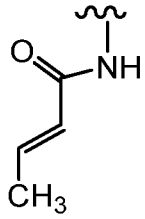
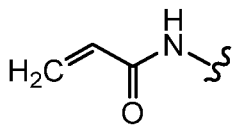
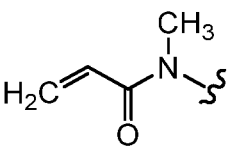
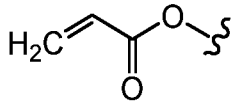
or a pharmaceutically acceptable salt thereof, wherein:

G is  ,  ,  ,  , or  ;

each R^4 is independently selected from  ,  ,  ,  , or  ;

R^1 is hydrogen or C_{1-6} aliphatic;

R^2 is hydrogen or C_{1-10} aliphatic;

X is selected from N or CH;

R^3 is –R, or –OR; and

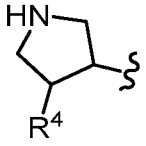
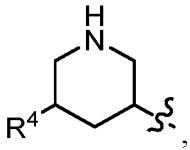
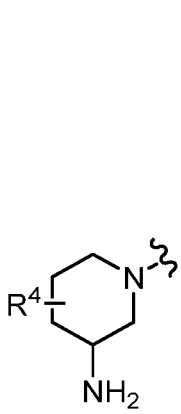
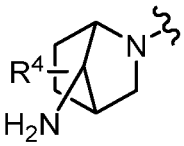
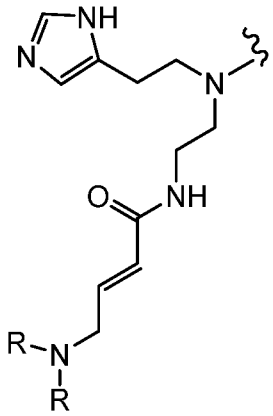
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

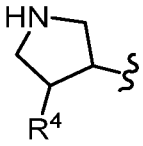
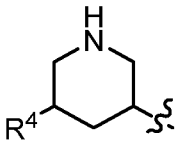
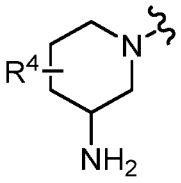
[0017] As defined above and described herein, R^1 is hydrogen, or C_{1-6} aliphatic. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_{1-6} aliphatic. In some embodiments, R^1 is methyl.

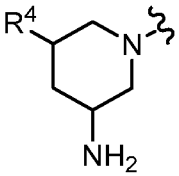
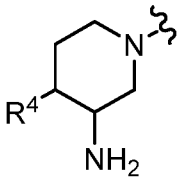
[0018] As defined above and described herein, R^2 is hydrogen or C_{1-10} aliphatic. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is C_{1-10} aliphatic. In some embodiments, R^2 is $–CH_2–$cyclopropyl.

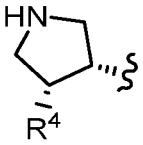
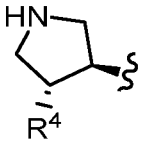
[0019] In some embodiments, R^3 is –R or –OR. In some embodiments, R^3 is –R. In some embodiments, R^3 is –OR. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is $-OCH_3$.

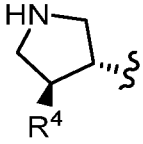
[0020] As defined above and described herein, X is selected from N or CH. In some embodiments, X is N. In some embodiments, X is CH.

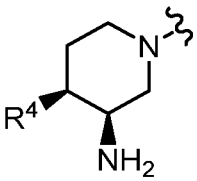
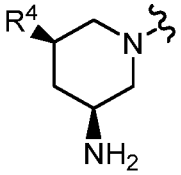
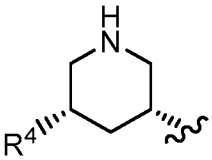
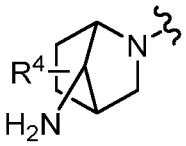
[0021] As defined above and described herein, G is  ,  ,  ,  , or  . In some embodiments, G is

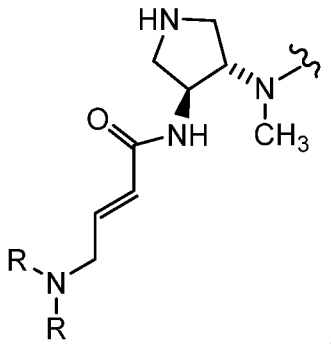

. In some embodiments, G is  . In other embodiments, G is  .

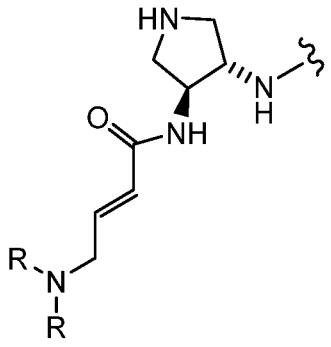
[0022] In some embodiments, G is  or  .

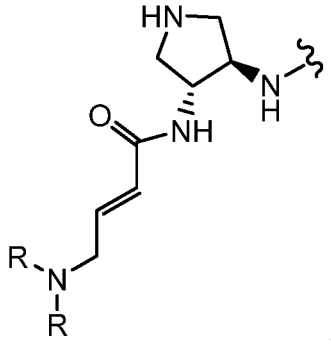
[0023] In some embodiments, G is  . In other embodiments, G is  .

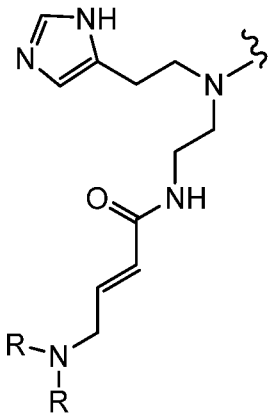
In certain embodiments, G is  .

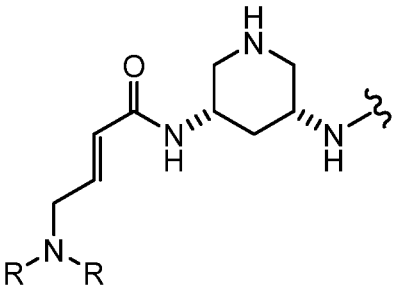
[0024] In some embodiments, G is  . In other embodiments, G is  . In certain embodiments, G is  . In some embodiments. G is  .

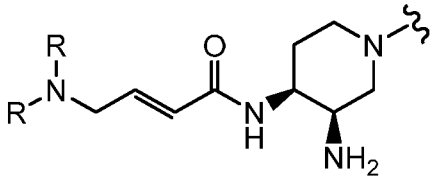
[0025] In some embodiments, G is  .

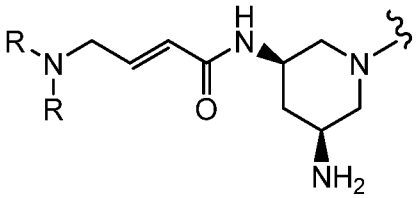
[0026] In some embodiments, G is  .

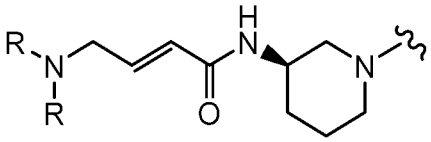
[0027] In some embodiments, G is  .

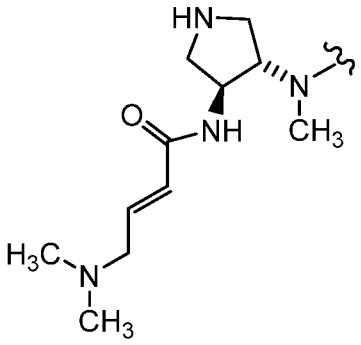
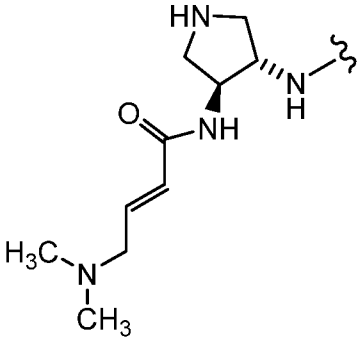
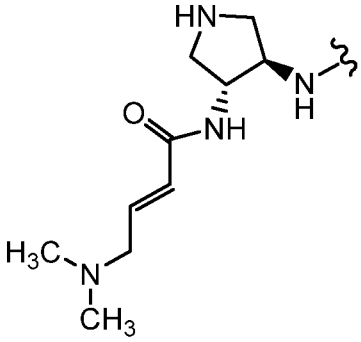
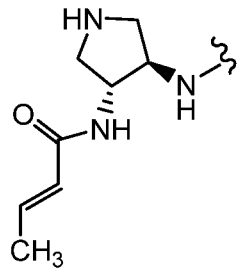
[0028] In some embodiments, G is  .

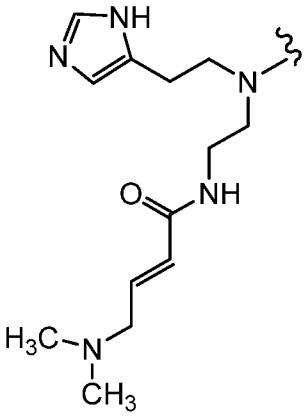
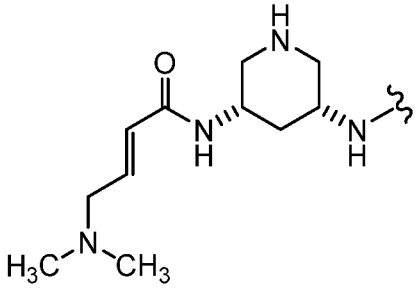
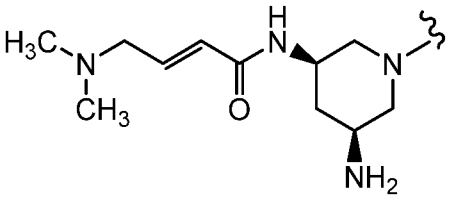
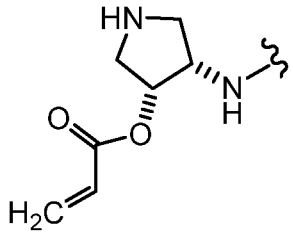
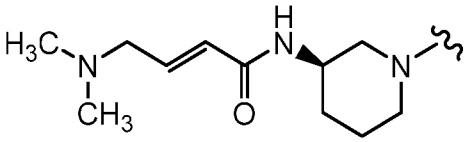
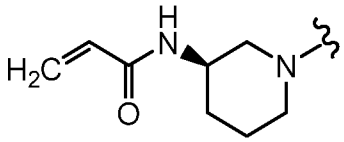
[0029] In some embodiments, G is  .

[0030] In some embodiments, G is  .

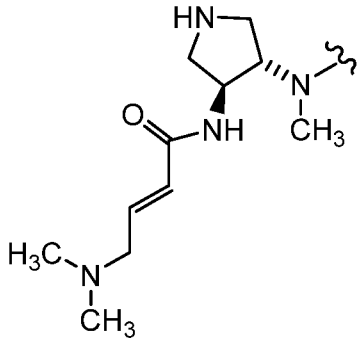
[0031] In some embodiments, G is  .

[0032] In some embodiments, G is  .

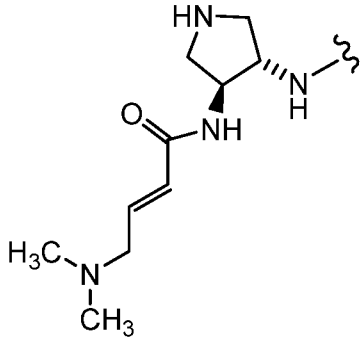
[0033] In some embodiments, G is selected from  ,  ,  ,  .

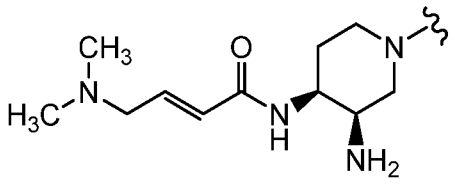
, or .

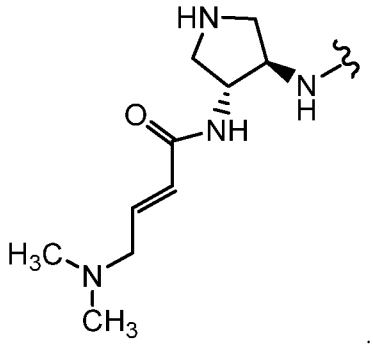


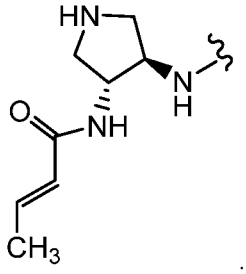
[0034] In some embodiments, G is .

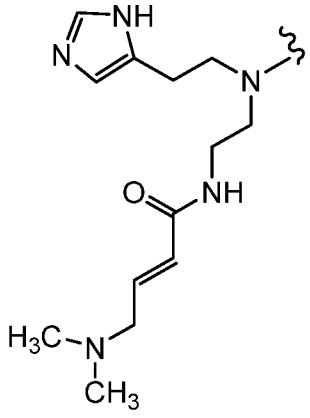


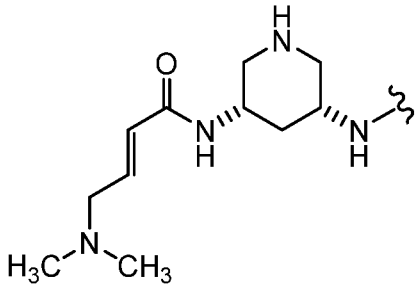
[0035] In some embodiments, G is .

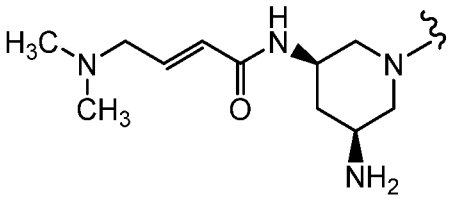
[0036] In some embodiments, G is  .

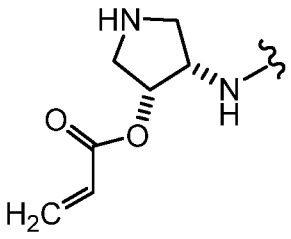
[0037] In some embodiments, G is  .

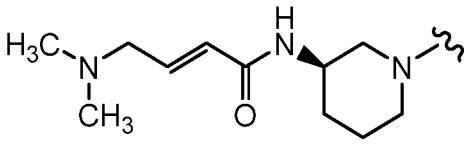
[0038] In some embodiments, G is  .

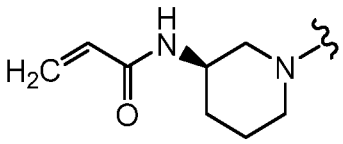
[0039] In some embodiments, G is  .

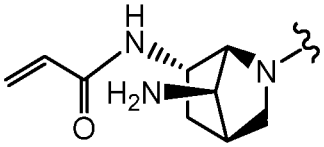
[0040] In some embodiments, G is  .

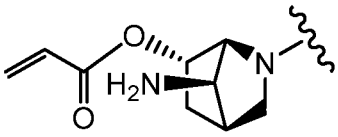
[0041] In some embodiments, G is  .

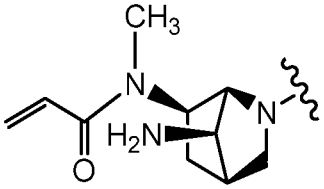
[0042] In some embodiments, G is  .

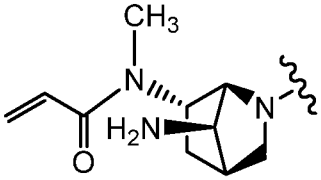
[0043] In some embodiments, G is  .

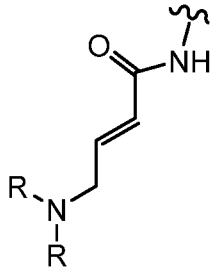
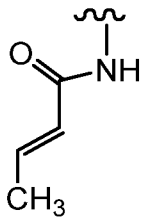
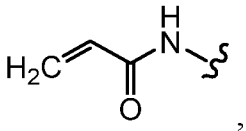
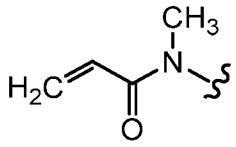
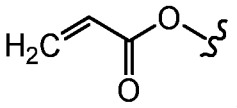
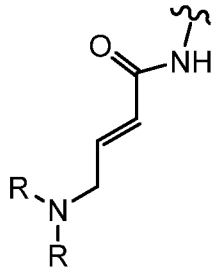
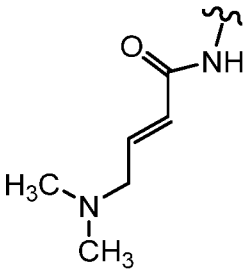
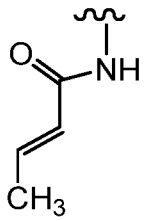
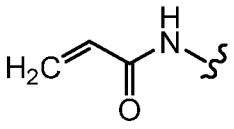
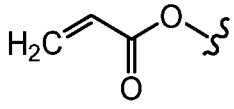
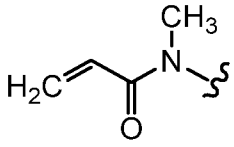
[0044] In some embodiments, G is  .

[0045] In some embodiments, G is  .

[0046] In some embodiments, G is  .

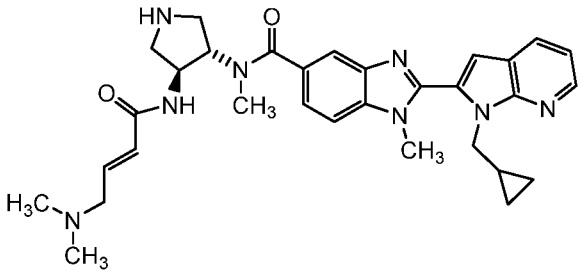
[0047] In some embodiments, G is  .

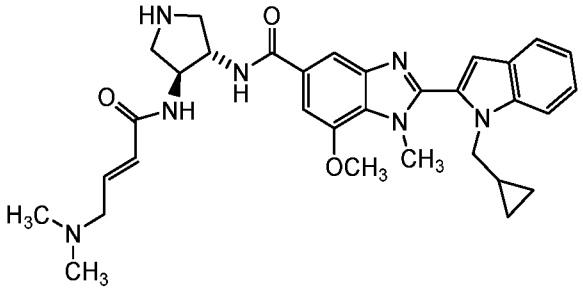
[0048] In some embodiments, G is  .

[0049] As defined above and described herein, each R^4 is independently selected from  ,  ,  ,  , or  . 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,  . In some embodiments, R^4 is  .

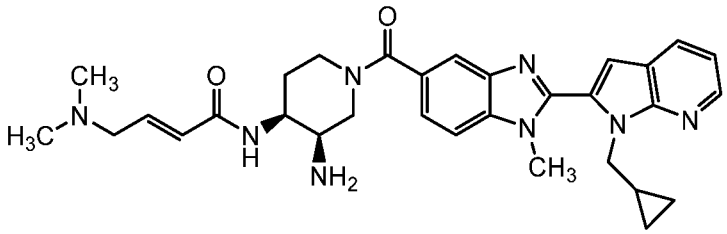
[0050] In some embodiments, the compound of formula **I** is selected from those depicted below in Table 1.

Table 1. Exemplary Compounds of Formula I

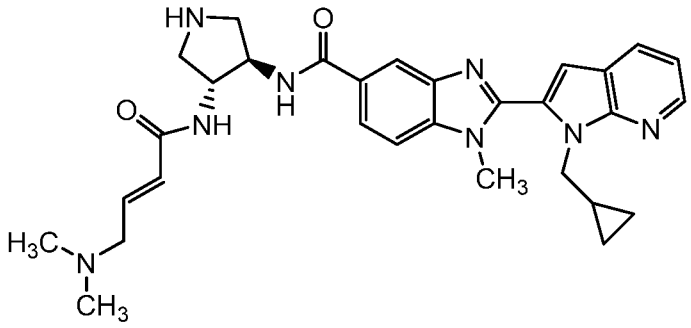




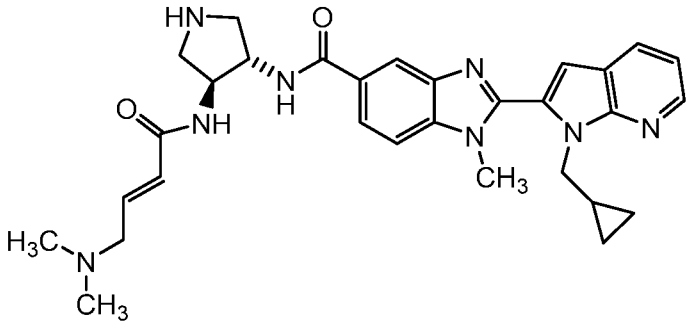
I-1 I-2



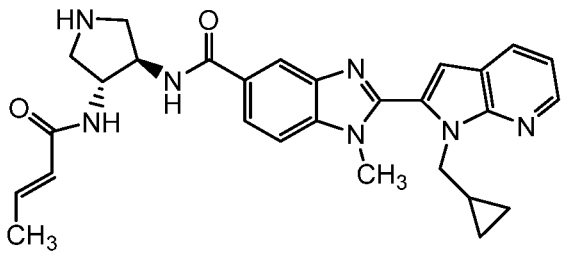
I-3



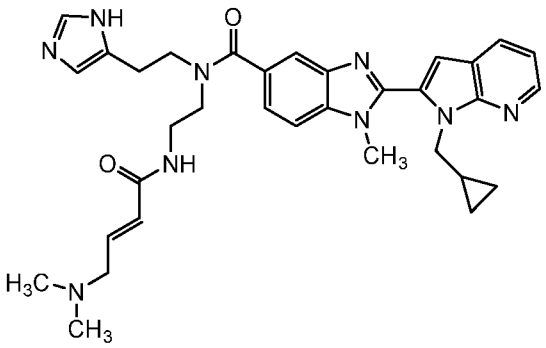
I-4



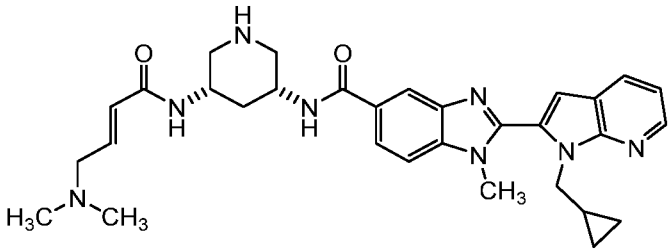
I-5



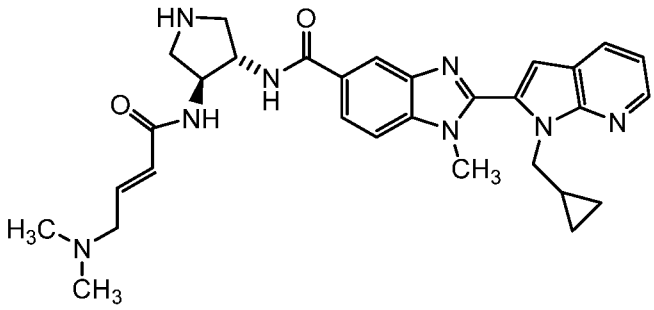
I-7



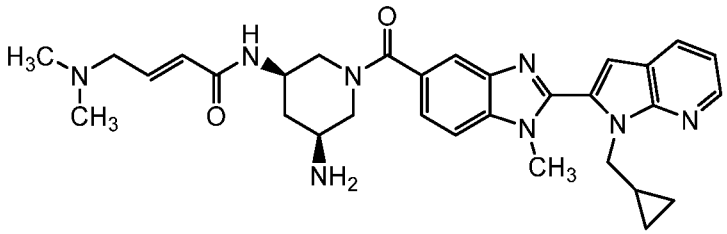
I-6



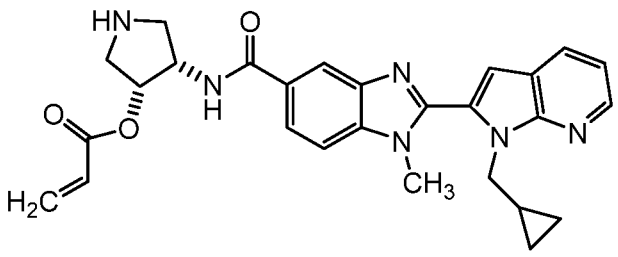
I-8



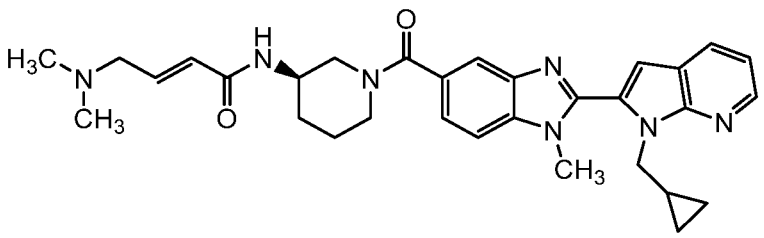
I-9



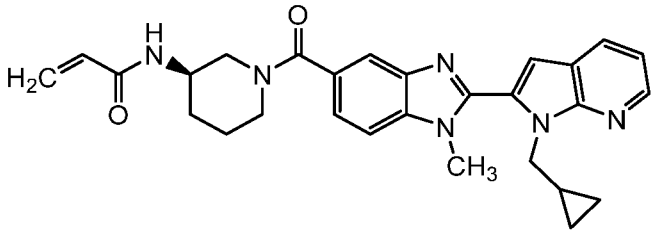
I-10



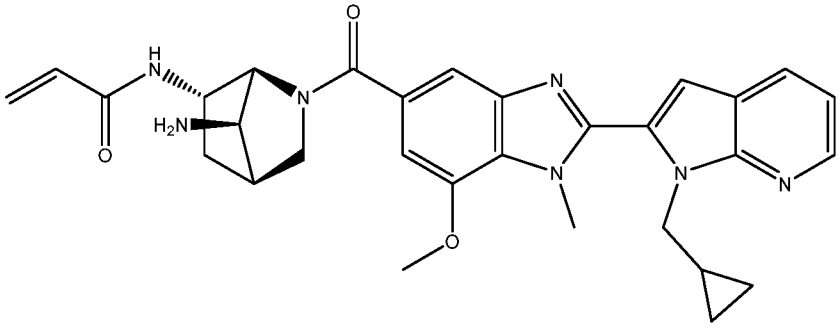
I-11



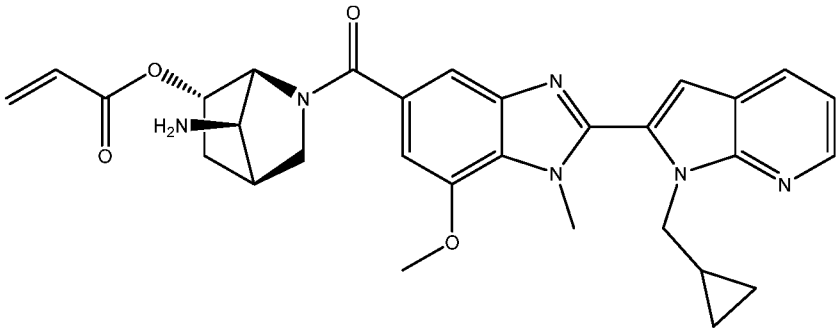
I-12



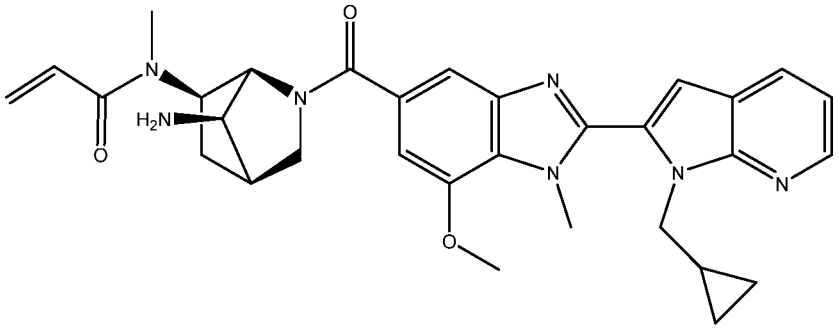
I-13



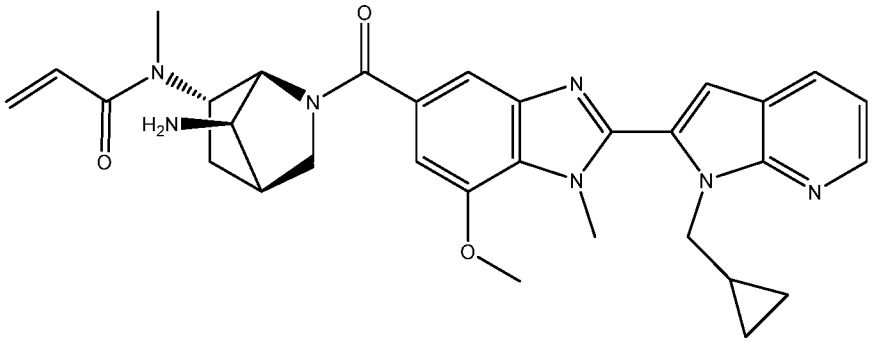
I-14



I-15



I-16

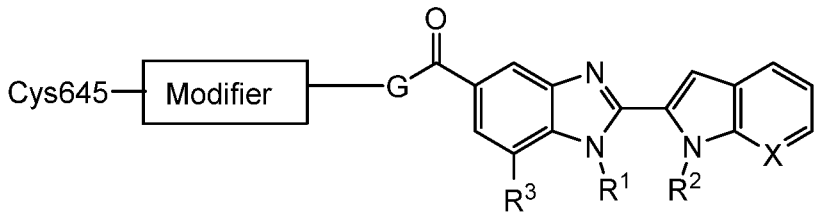


I-17

[0051] 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.

[0052] In certain embodiments, the present invention provides a conjugate comprising PAD4 having a cysteine residue, Cys645, wherein the Cys645 is covalently, and irreversibly, bonded to an inhibitor described above and herein, such that inhibition of the PAD4 is maintained.

[0053] In certain embodiments, the present invention provides a conjugate of formula **X**:



X

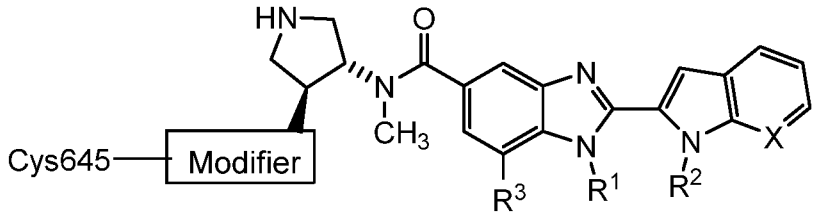
wherein:

Cys645 is cysteine 645 of PAD4;

Modifier is a bivalent group resulting from covalent bonding of a Warhead Group with the Cys645 of the PAD4; and

Warhead Group is a functional group on G capable of covalently binding to the Cys645 of the PAD4.

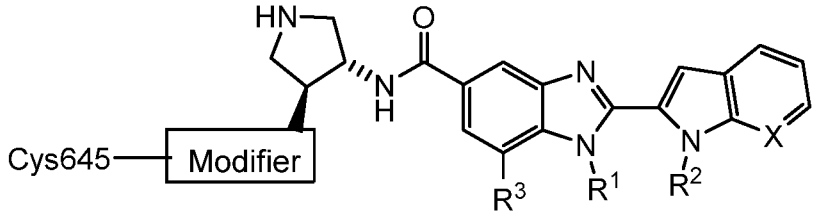
[0054] In some embodiments, the present invention provides a conjugate of formula **X-a**:



X-a

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

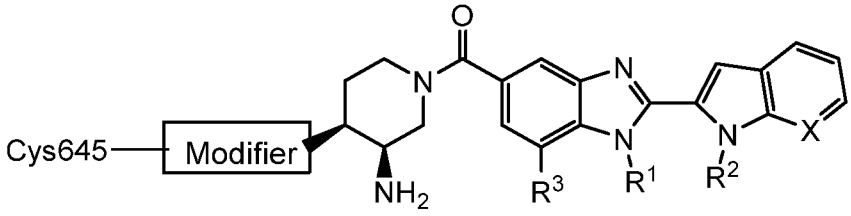
[0055] In some embodiments, the present invention provides a conjugate of formula **X-b**:



X-b

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

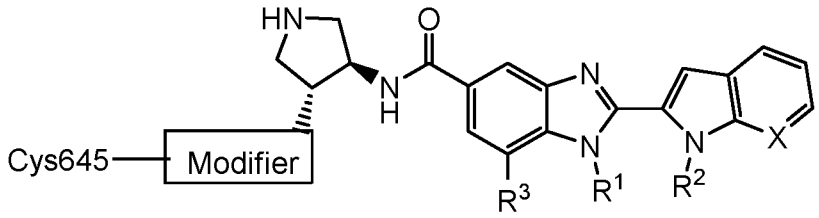
[0056] In some embodiments, the present invention provides a conjugate of formula **X-c**:



X-c

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

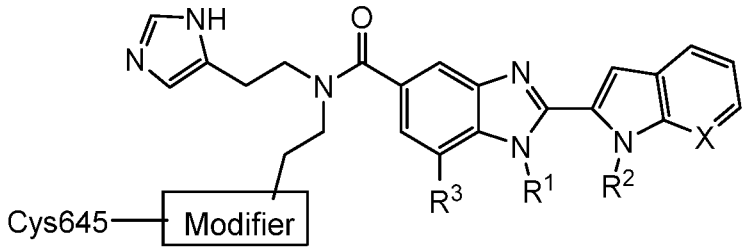
[0057] In some embodiments, the present invention provides a conjugate of formula **X-d**:



X-d

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

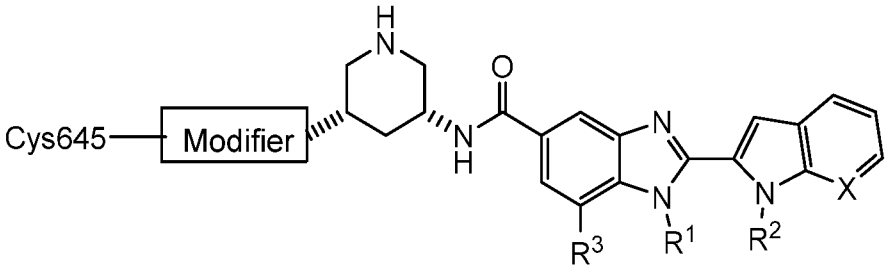
[0058] In some embodiments, the present invention provides a conjugate of formula **X-e**:



X-e

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

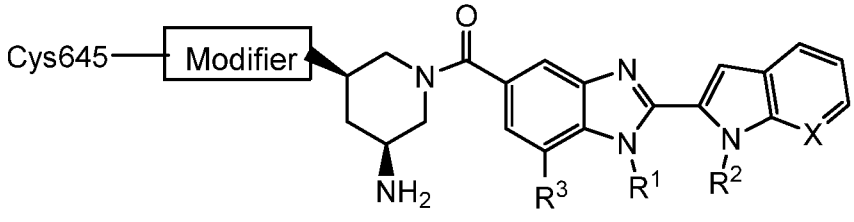
[0059] In some embodiments, the present invention provides a conjugate of formula **X-f**:



X-f

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

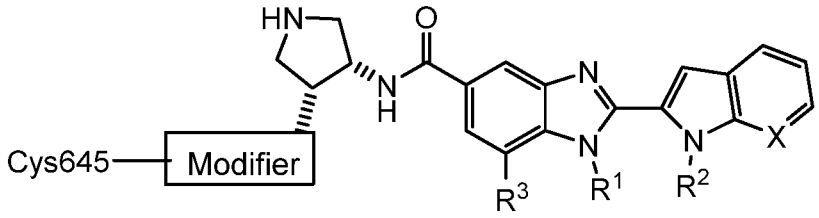
[0060] In some embodiments, the present invention provides a conjugate of formula **X-g**:



X-g

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

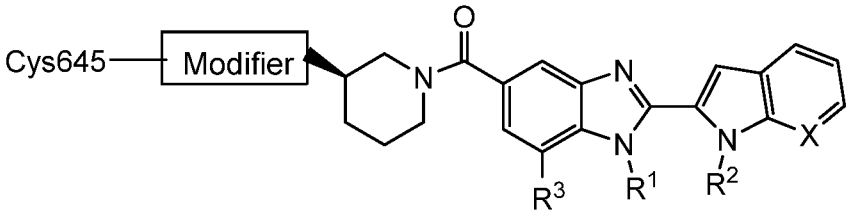
[0061] In some embodiments, the present invention provides a conjugate of formula **X-h**:



X-h

wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

[0062] In some embodiments, the present invention provides a conjugate of formula **X-i**:

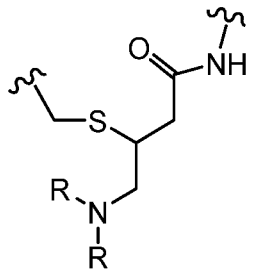


X-i

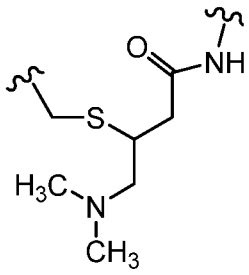
wherein each of Cys645, Modifier, R^1, R^2, R^3, and X is as defined above and described herein.

[0063] A Modifier of the present invention is a bivalent group resulting from covalent bonding of a Warhead Group with the Cys645 of PAD4. It will be understood that the exemplary modifiers below are shown as conjugated to the sulfhydryl of Cys645 of PAD4.

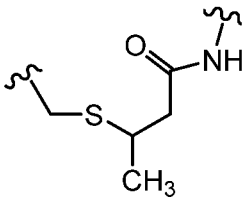
Table X. Modifiers Conjugated to Cys645



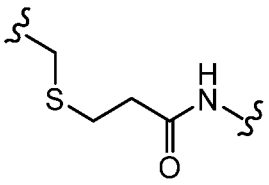
a



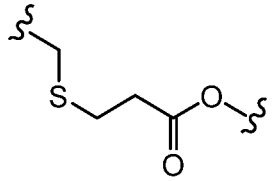
b



c



d



e

4. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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

[0095] Compounds and compositions described herein are generally useful for the inhibition of PAD4.

[0096] 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.

[0097] 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.

[0098] Provided compounds are inhibitors of PAD4 and 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.

[0099] 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.

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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

[00104] All features of each of the aspects of the invention apply to all other aspects mutatis mutandis.

[00105] 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

[00106] 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.

[00107] **List of common abbreviations used in the experimental section.**

AcOH: acetic acid

$(Boc)_2O$: di-tert-butyl dicarbonate

Chiral HPLC: chiral high performance liquid chromatography

DCM: dichloromethane

Dess Martin Periodinane: 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one

DIAD: diisopropyl azodicarboxylate

DIPEA: *N,N*-diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

DMSO: dimethyl sulfoxide

EtOAc: ethyl acetate

EtOH: ethanol

HATU: *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide

H-Cube: continuous flow hydrogenation reactor

HPLC: high performance liquid chromatography

HCl: hydrochloric acid

Kieselguhr: diatomaceous earth

LCMS: Liquid chromatography–mass spectrometry

M: molar

Me: methyl

MeCN: acetonitrile

MeI: methyl iodide

min: minutes

mL: millilitres

MeOH: methanol

MsCl: methanesulfonyl chloride

NaHMDS: sodium bis(trimethylsilyl)amide

NMR: Nuclear Magnetic Resonance

°C: degrees Celsius

Pd/C: palladium on carbon

$Pd(OH)_2/C$: palladium hydroxide on carbon

prep HPLC: preparative high performance liquid chromatography

STAB: sodium triacetoxyborohydride

TBAF: tetrabutylammonium fluoride

TBDMSCl: tert-Butyldimethylsilyl chloride

TBTU: *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

TEA: triethylamine

TFA: trifluoracetic acid

THF: tetrahydrofuran

T_{ret}: retention time

[00108] Preparative HPLC methods

[00109] Basic HPLC preparative method

Column: XBridgeTM Prep. C18 10 um OBDTM, 30 x 100 mm

Mobile Phase: 5 - 95 % Acetonitrile (0. 2 % ammonium hydroxide) in Water (0. 2 % ammonium hydroxide) over 14 minutes

Flow Rate: 40 mL/min

UV Detection: 215 and 254 nm

[00110] Acidic HPLC preparative method

Column: SunfireTM Prep. C18 10 um OBDTM, 30 x 100 mm

Mobile Phase: 5 - 95 % Acetonitrile (0. 1 % formic acid) in Water (0. 1 % formic acid) over 14 minutes

Flow Rate: 40 mL/min

UV Detection: 215 and 254 nm

[00111] Analytical LCMS methods:

[00112] Method A

MET/u-HPLC (MSQ1 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

[00113] Method B

MET/CR/1600 (MS10 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

[00114] 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

[00115] 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

[00116] 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

[00117] 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

[00118] Analytical and preparative chiral HPLC methods:

[00119] Method E:

Chiral HPLC preparative method

Column: Lux C1 (21.2mm x 250mm, 5µm)

Flow rate: 50 mL/min

Mobile Phase: 40:60 MeOH:CO2 (0.1% v/v NH3)

Injection Vol: 500 µL (2.5 mg)

Temp.: 40°C

Detection: 220 nm

[00120] **Method F:**

Chiral purity analysis method

Column: Lux C1 (4.6mm x 250mm, 5um)

Flow Rate: 4 mL/min

Injection Vol: 1.0 µL

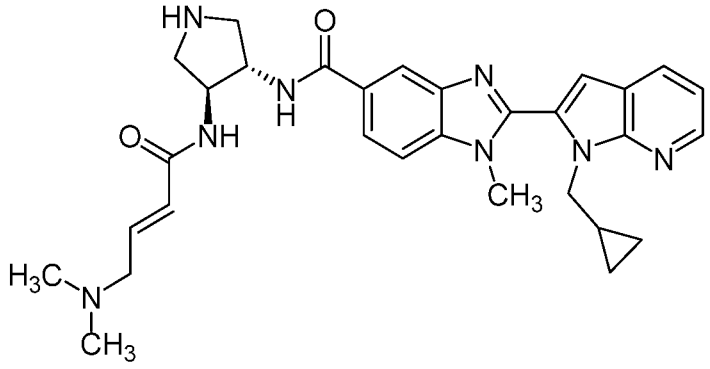
Temp.: 40 C

UV Detection: 210-400 nm

Isocratic Conditions 40:60 MeOH:CO2 (0.1% v/v NH_3)

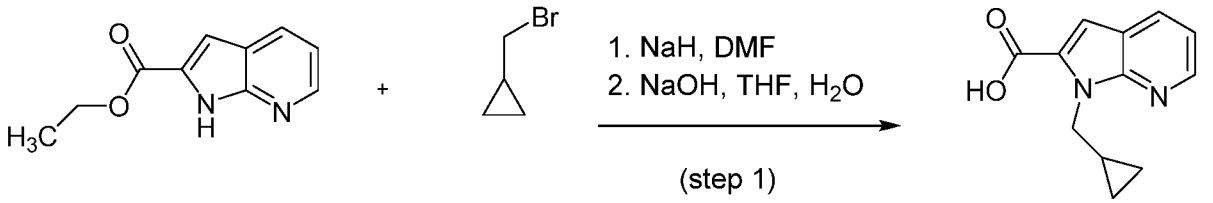
[00121] Certain compounds of the present invention were prepared according to Scheme 1, steps 1 to 9, below.

[00122] **Example 1. Synthesis of trans-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide EV-AE3989-001 (EOAI3442248, I-9)**



I-9

[00123] **Scheme 1 Step 1**

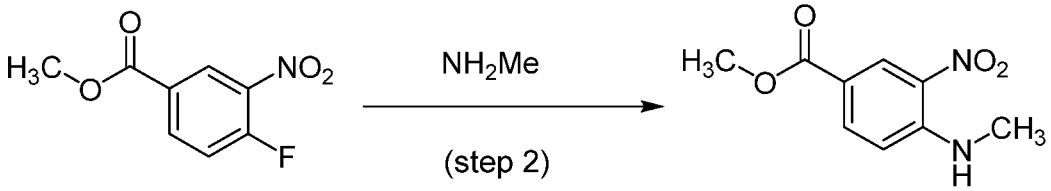


CAS 221675-35-0 CAS 7051-34-5 EV-AR3164-001

[00124] 1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid EV-AR3164-001 – step 1

[00125] 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 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).

[00126] Scheme 1 Step 2



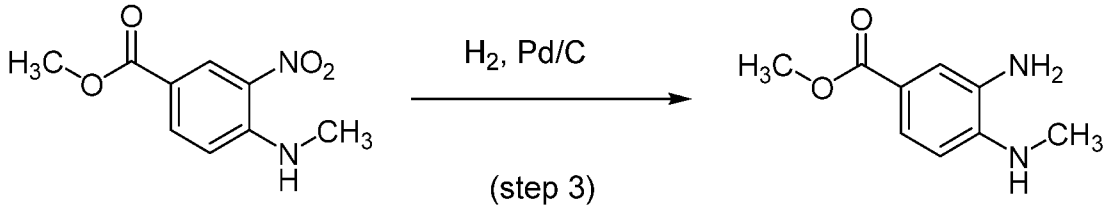
CAS 329-59-9 EV-AR3152-001

[00127] Methyl 4-(methylamino)-3-nitrobenzoate EV-AR3152-001 – step 2

[00128] 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).

[00129] Scheme 1 Step 3

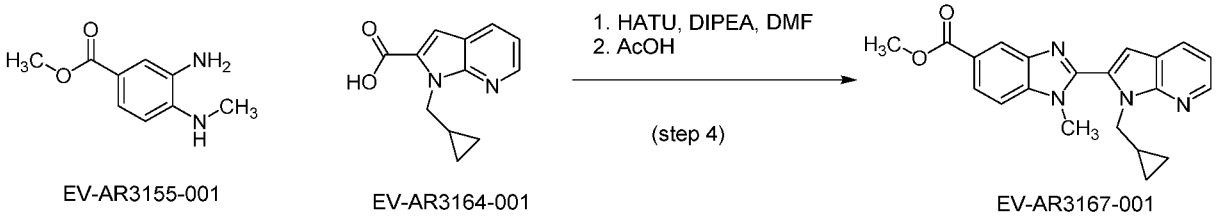


EV-AR3152-001 EV-AR3155-001

[00130] Methyl 3-amino-4-(methylamino)benzoate EV-AR3155-001 – step 3

[00131] 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).

[00132] Scheme 1 Step 4

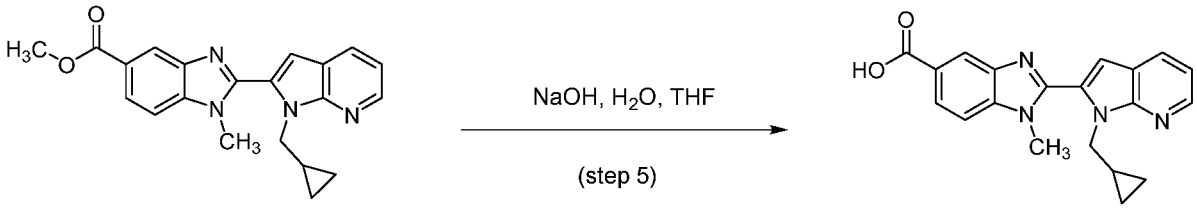


EV-AR3155-001 EV-AR3164-001 EV-AR3167-001

[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 (40 ml) 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] Scheme 1 Step 5



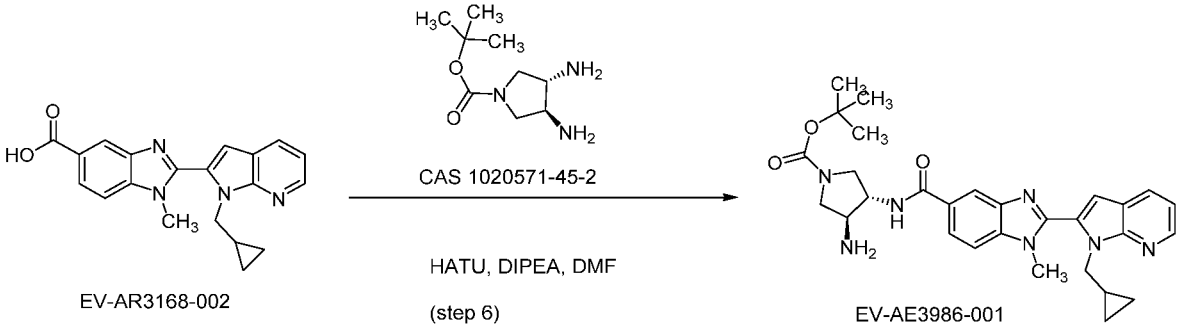
EV-AR3167-001 EV-AR3168-002

[00136] 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

[00137] 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).

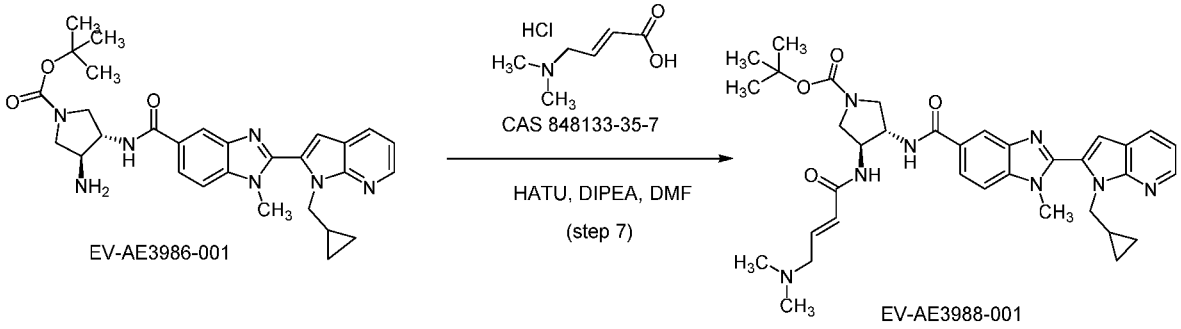
[00138] Scheme 1 Step 6



[00139] Trans-rac-tert-butyl (3R,4R)-3-amino-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate– EV-AE3986-001 - step 6

[00140] A solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AQ1914-001**, 100 mg, 0.29 mmol) and HATU (121 mg, 0.32 mmol) in dry DMF (2ml) was treated with DIPEA (55 µL, 0.32 mmol) at room temperature. The mixture was stirred for 1h then trans-rac-tert-butyl (3R,4R)-3,4-diaminopyrrolidine-1-carboxylate (CAS 1020571-45-2, 58mg, 0.29 mmol) was added and the reaction mixture stirred at room temperature for 1h. The reaction mixture was diluted with EtOAc (10 ml), washed with water (5 ml) then saturated aqueous sodium chloride (3 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography (1-9% MeOH/DCM) to obtain 40 mg (25%) of trans-rac-tert-butyl (3R,4R)-3-amino-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AE3986-001** as a colourless crystalline solid. LCMS (method D): retention time 0.98min, M/z = 530 (M + 1).

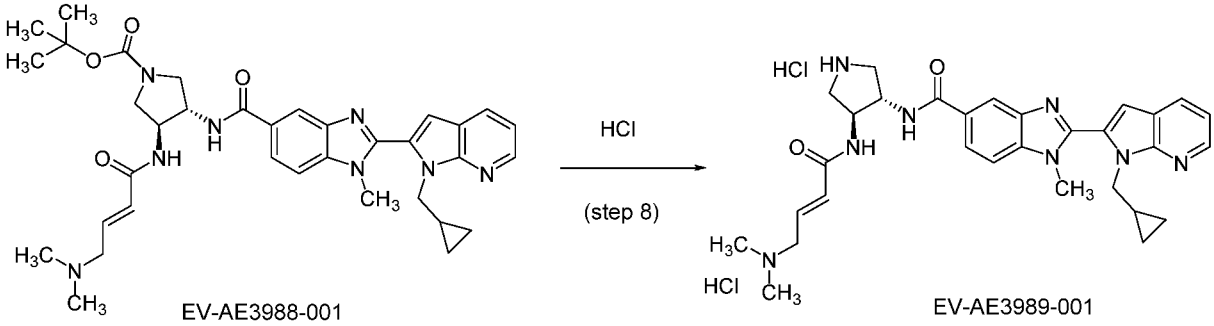
[00141] Scheme 1 Step 7



[00142] Trans-rac-formic acid; tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate – EV-AE3988-001 - step 7

[00143] A solution of trans-rac-tert-butyl (3R,4R)-3-amino-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AE3986-001**, 40 mg, 0.08 mmol), (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (15 mg, 0.091 mmol) and HATU (34 mg, 0.091 mmol) in dry DMF (1ml) was treated with DIPEA (29 µl, 0.16 mmol) at room temperature and the mixture was stirred for 20 minutes. The reaction mixture was diluted with EtOAc (10 ml) and washed with water (5 ml). The aqueous layer was re-extracted with EtOAc (5 ml). The EtOAc layers were combined, washed with saturated aqueous sodium chloride (5 ml), dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep HPLC (acidic method) to obtain 18 mg (34.7%) of trans-rac-formic acid; tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate **EV-AE3988-001** as a colourless crystalline solid. LCMS (method D): retention time 1.00min, M/z = 641 (M + 1).

[00144] Scheme 1 Step 8



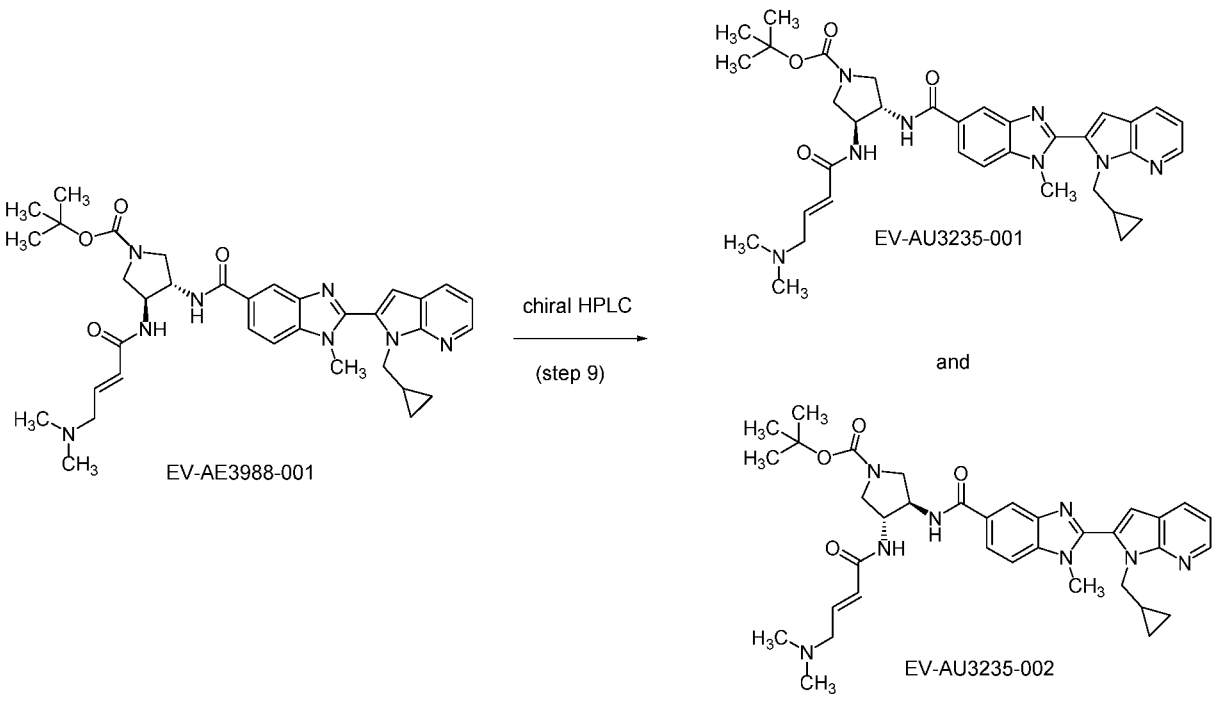
I-9

[00145] Trans-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride – EV-AE3989-001 - step 8

[00146] To trans-rac-formic acid; tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate (**EV-AE3988-001**, 17 mg, 0.03 mmol) was added 2M HCl in ether (0.13 ml, 0.25 mmol) and the mixture was left standing at room temperature for 1h. Another portion of 2M HCl in ether (0.13 ml) was added and swirled around the reaction vial, then allowed to stand for 30 mins. The reaction mixture was concentrated to dryness and dried in vacuo to obtain 15 mg (97%) of trans-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride **EV-AE3989-001** as an off-white crystalline solid. LCMS (method C): retention time 2.80min, M/z = 541 (M + 1).

[00147] Example 2. Chiral HPLC to obtain trans-tert-butyl (3S,4S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate and trans-tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate - EV-AU3235-001 and EV-AU3235-002 – step 9

[00148] Scheme 1 Step 9



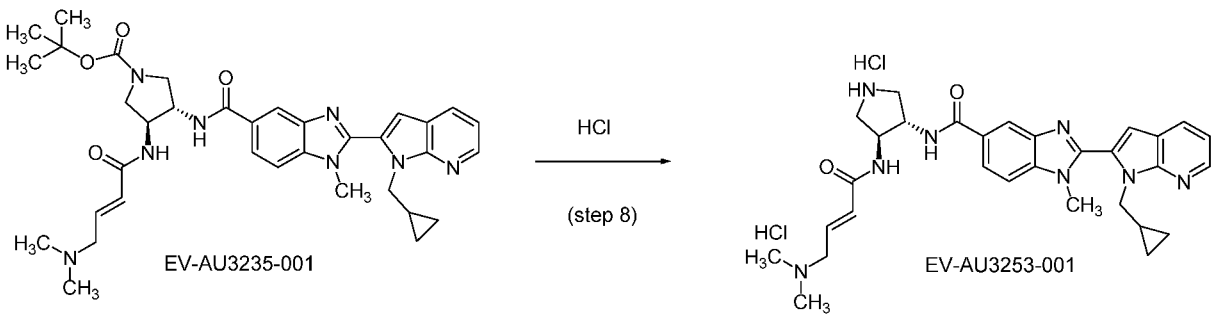
[00149] 115mg of trans-rac-tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate was purified by chiral HPLC (method E) to obtain 35 mg of trans-tert-butyl (3S,4S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate **EV-AU3235-001** (absolute stereochemistry arbitrarily assigned) and 39 mg of trans-tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate **EV-AU3235-002** (absolute stereochemistry arbitrarily assigned).

EV-AU3235-001 Chiral purity (UV, 254nm): 100%, retention time: 1.89min (method F)

EV-AU3235-002 Chiral purity (UV, 254nm): 99%, retention time: 2.27min (method F)

[00150] Example 3. Synthesis of 2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3S,4S)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide trihydrochloride– I-5, EV-AU3253-001 – Step 8

[00151] Scheme 1 Step 8

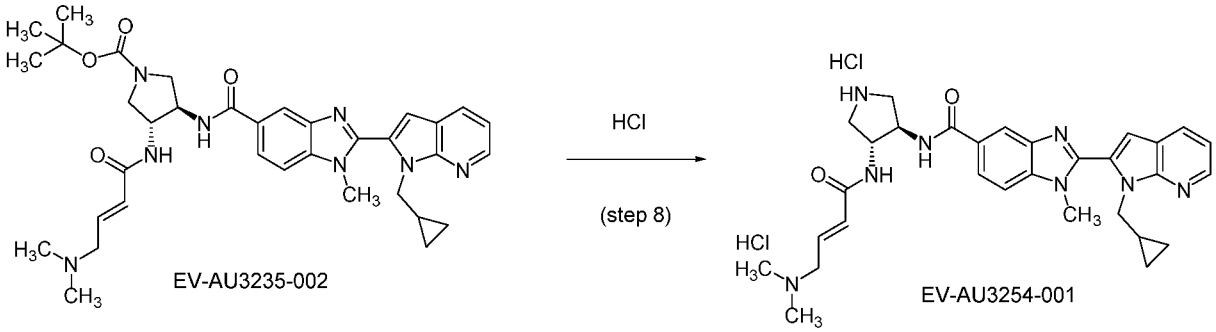


I-5

[00152] Tert-butyl (3S,4S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate (**EV-AU3253-001**, 35 mg, 0.054 mmol) was treated as in step 8, Scheme 1 to obtain 35 mg (99%) of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3S,4S)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide **I-5**, **EV-AU3253-001**, as a white powder. LCMS (method A): retention time 1.43min, M/z = 541 (M + 1).

[00153] Example 4. Synthesis of 2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide trihydrochloride– I-4, EV-AU3254-001 – Step 8

[00154] Scheme 1 Step 8



I-4

[00155] Tert-butyl (3R,4R)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidine-1-carboxylate (**EV-AU3254-001**, 39 mg, 0.06 mmol) was treated as in step 8, Scheme 1 to obtain 39 mg (98%) of

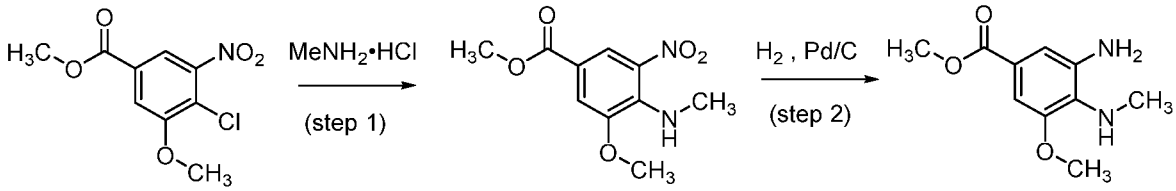
2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide trihydrochloride **I-4**, **EV-AU3254-001,** as an off-white powder. LCMS (method A): retention time 1.44min, M/z =541 (M + 1).

[00156] Special cases for Scheme 1 (Schemes 1.1 – 1.9)

[00157] Example 5. Synthesis of Rac-2-[1-(cyclopropylmethyl)-1H-indol-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxamide, I-2

[00158] Rac-2-[1-(cyclopropylmethyl)-1H-indol-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carboxamide **EV-AU9306-001 (EOAI3449033, I-2)** was synthesised according to the procedures described in Scheme 1 via synthesis of methyl 3-amino-5-methoxy-4-(methylamino)benzoate **EV-AR0068-002** as described in Scheme 1.1:

Scheme 1.1



CAS 63603-09-8 EV-AR0065-002 EV-AR0068-002

[00159] Methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate EV-AR0065-002 – step 1

[00160] 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 (100 ml) and water (10 ml). 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).

[00161] Methyl 3-amino-5-methoxy-4-(methylamino)benzoate EV-AR0068-002 – step 2

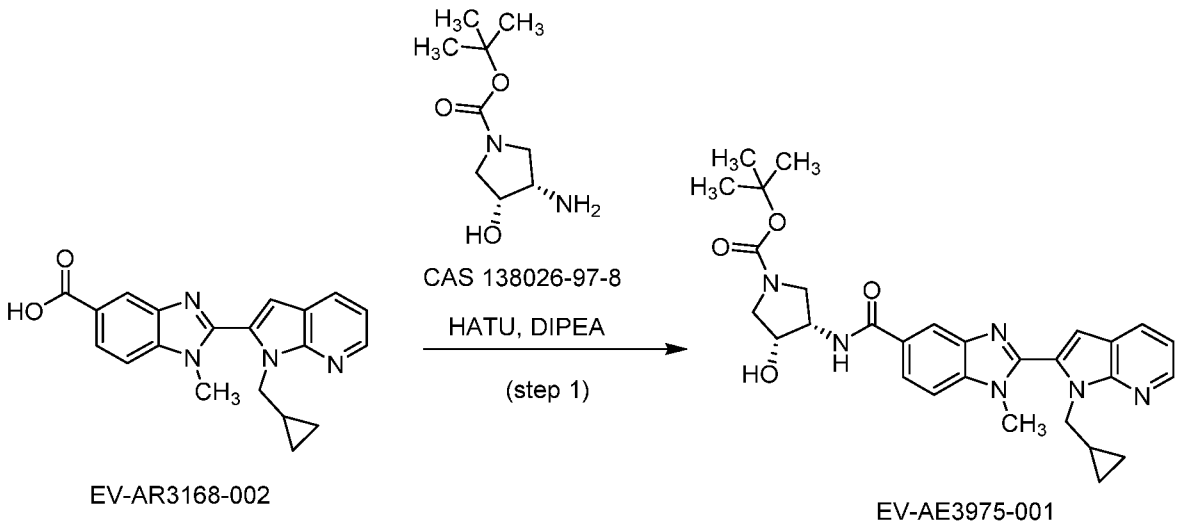
[00162] To a stirred solution of methyl 3-methoxy-4-(methylamino)-5-nitrobenzoate (**EV-AR0065-002**, 1.49 g, 6.20 mmol) in ethanol (100ml) under nitrogen was added 10% Pd/C (0.18 g, 0.17 mmol) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 16h. The reaction 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).

[00163] Example 6. Synthesis of Rac-(3R,4S)-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidin-3-yl prop-2-enoate, I-11

[00164] Rac-(3R,4S)-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidin-3-yl prop-2-enoate **EV-AE3981-002** (**EOAI3441779**, **I-11**) was synthesised according to the procedures described in Scheme 1.2, steps 1 to 3, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR3168-002** synthesised as described in Scheme 1:

[00165] Cis-rac-tert-butyl (3R,4S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-hydroxypyrrolidine-1-carboxylate EV-AE3975-001 – step 1

[00166] Scheme 1.2 Step 1



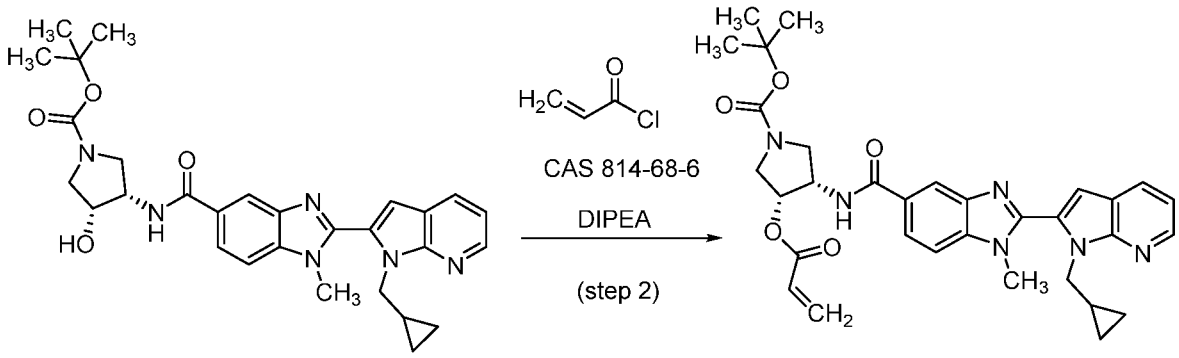
EV-AR3168-002

EV-AE3975-001

[00167] 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**, 100 mg, 0.29 mmol) and HATU (131 mg, 0.35 mmol) in DMF (3 ml) was added DIPEA (60 µl, 0.35 mmol). The resulting mixture was stirred at room temperature for 1h then cis-rac-tert-butyl(3S,4R)-3-amino-4-hydroxypyrrolidine-1-carboxylate (CAS 138026-97-8, 70 mg, 0.35 mmol) was added and the reaction was continued for 2h. The reaction was diluted with EtOAc (5 ml) and washed with water (5 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (0-5% MeOH/DCM) to afford 135 mg (84%) of cis-rac-tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-hydroxypyrrolidine-1-carboxylate **EV-AE3975-001** as a tan powder. LCMS (method D): retention time 1.14min, M/z = 531 (M + 1).

[00168] Cis-rac-tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-(prop-2-enoyloxy)pyrrolidine-1-carboxylate EV-AE3979-001 – step 2

[00169] Scheme 1.2 Step 2

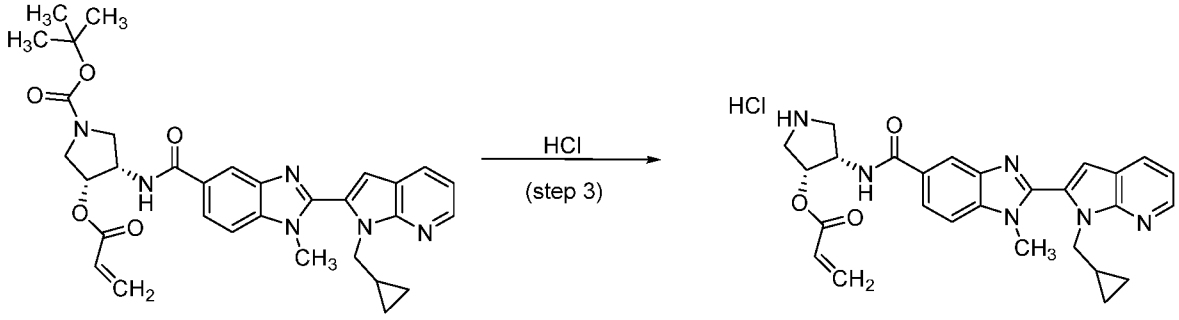


EV-AE3975-001 EV-AE3979-001

[00170] To a stirred solution of cis-rac-tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-hydroxypyrrolidine-1-carboxylate (**EV-AE3975-001**, 50 mg, 0.094 mmol) in DCM (1 ml) was added prop-2-enoyl chloride (CAS 814-68-6, 0.011 ml, 0.14 mmol) and DIPEA (0.025 ml, 0.14 mmol). The mixture was stirred at room temperature for 1h. The reaction mixture was diluted with DCM (5 ml) and washed with water (2 ml) and brine (2 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (0-3% MeOH/DCM) to obtain 32 mg (58%) of cis-rac-tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-(prop-2-enoyloxy)pyrrolidine-1-carboxylate **EV-AE3979-001** as a colourless oil. LCMS (method D): retention time 1.31 min, M/z = 585 (M + 1).

[00171] Cis-rac-(3R,4S)-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidin-3-yl prop-2-enoate hydrochloride EV-AE3981-002 – step 3

[00172] Scheme 1.2 Step 3



EV-AE3979-001 EV-AE3981-002

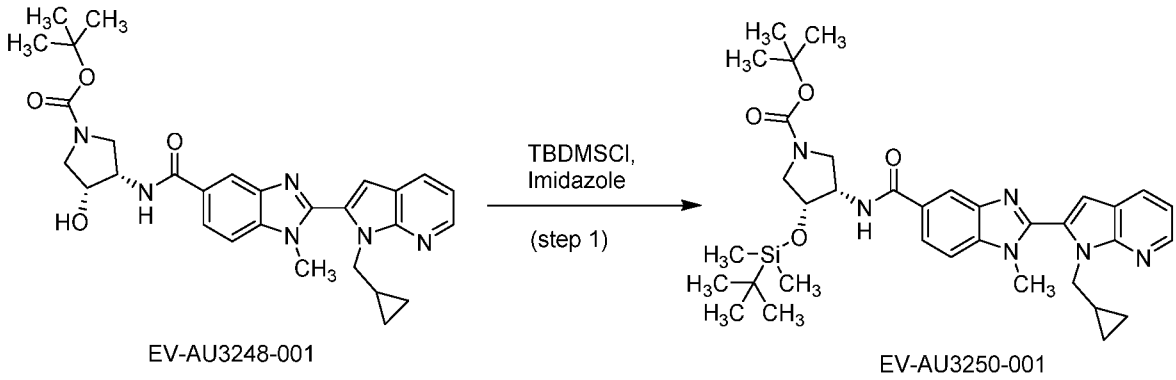
[00173] 2M HCl in ether (0.23 ml, 0.57 mmol) was added to cis-rac-tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-(prop-2-enoyloxy)pyrrolidine1carboxylate (**EV-AE3979-001**, 30 mg, 0.057 mmol) and the resulting mixture was allowed to stand at room temperature for 2h. The solvent was removed in vacuo and the solid azeotroped with DCM (1 ml). The solvent was removed in vacuo and the solid was dried to obtain 25 mg (83%) of cis-rac-(3R,4S)-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidin-3-yl prop-2-enoate hydrochloride **EV-AE3981-002** as an off white powder. LCMS (method A): retention time 1.96min, M/z = 485 (M + 1).

[00174] Example 7. Synthesis of Cis-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-N,1-dimethyl-1H-1,3-benzodiazole-5-carboxamide, I-1

[00175] Cis-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-N,1-dimethyl-1H-1,3-benzodiazole-5-carboxamide **EV-AU3282-001** (**EOAI3449646**, **I-1**) was synthesised according to the procedures described in Scheme 1.3, steps 1 to 8, from tert-butyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-hydroxypyrrolidine-1-carboxylate **EV-AU3248-001** synthesised as described in Scheme 1.2:

[00176] Cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3250-001 – step 1

[00177] Scheme 1.3 Step 1

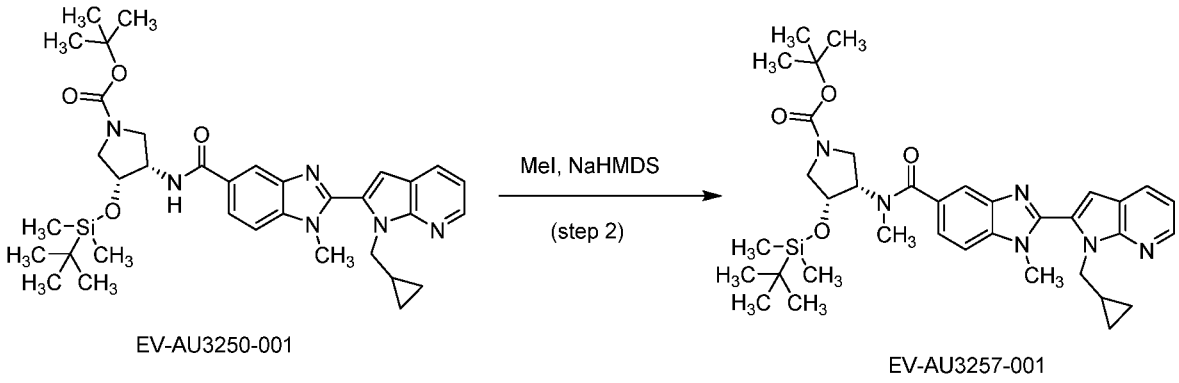


EV-AU3248-001 EV-AU3250-001

[00178] To a stirred solution of cis-rac-tert-butyl (3R,4S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-4-hydroxypyrrolidine-1-carboxylate (**EV-AU3248-001**, 820 mg, 1.55 mmol) in DMF (7.5 ml) was added imidazole (158 mg, 2.32 mmol) and TBDMSCl (280 mg, 1.85 mmol). The reaction was stirred at room temperature for 16h. The reaction was diluted with water (20 ml) and extracted with EtOAc (3 x 10 ml). The combined organics were washed with water (2 x 20 ml), dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (50-100% EtOAc/heptanes) to obtain 638 mg (61%) of cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3250-001** as a colourless powder. LCMS (method D): retention time 1.55min, M/z = 645 (M + 1).

[00179] Cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3257-001 – step 2

[00180] Scheme 1.3 Step 2



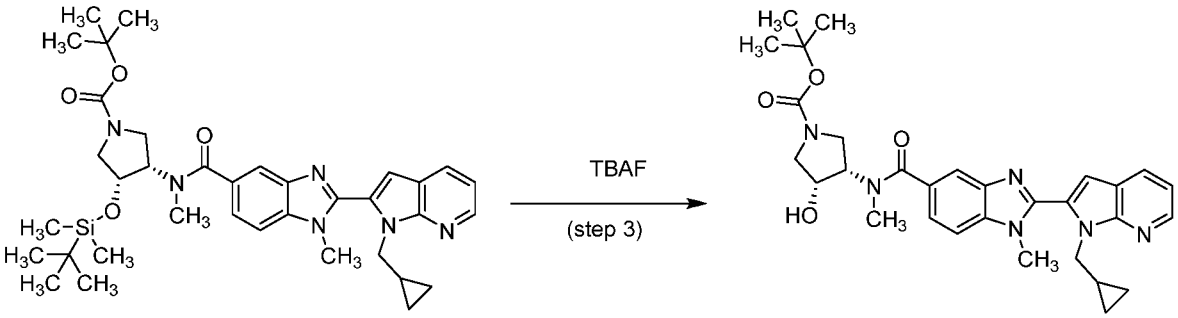
EV-AU3250-001 EV-AU3257-001

[00181] To a stirred solution of cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3250-001,** 630 mg, 0.98 mmol) in THF (12 ml) at -78°C was added 2M NaHMDS in THF (1.47 ml) and the reaction was left to stir for 10 minutes. Iodomethane (0.36 ml, 5.86 mmol) was then added and the reaction was allowed to warm to room temperature while stirring for 3h. The reaction mixture was diluted with diethyl ether (20 ml), washed with aq saturated sodium bicarbonate (10 ml) and then saturated aqueous sodium chloride (10 ml). The organic extract was then dried with sodium

sulfate, filtered and concentrated under vacuum. The crude material was purified by flash column chromatography (40-100% EtOAc/heptanes) to obtain 470 mg (67%) of cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3257-001** as a colourless powder. LCMS (method D): retention time 1.60min, M/z = 659 (M + 1).

[00182] Cis-rac-tert-butyl (3R,4S)-3-hydroxy-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3260-001 – step 3

[00183] Scheme 1.3 Step 3

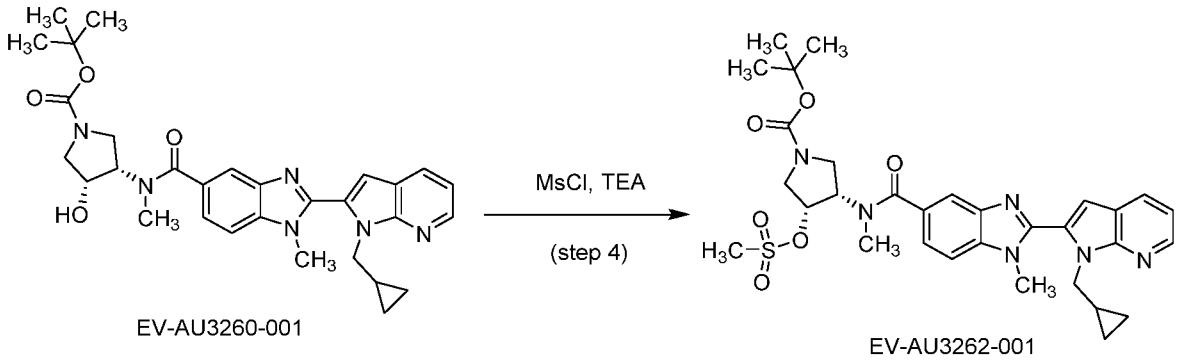


EV-AU3257-001 EV-AU3260-001

[00184] To a stirred solution of cis-rac-tert-butyl (3R,4S)-3-[(tert-butyldimethylsilyl)oxy]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3257-001**, 420 mg, 0.64 mmol) in THF (7 ml) at 0°C was added 1M TBAF in THF (1.27 ml). The reaction was allowed to warm to room temperature and stirred for 1h. The reaction mixture was diluted with EtOAc (10 ml), washed with water (3 x 10 ml) and saturated aqueous sodium chloride (10 ml). The organic extract was dried over sodium sulphate, filtered and concentrated under vacuo. The crude material was purified by flash column chromatography (0-10% MeOH/EtOAc) to obtain 379 mg (98%) of cis-rac-tert-butyl (3R,4S)-3-hydroxy-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3260-001** as a colourless powder. LCMS (method D): retention time 1.18min, M/z = 545 (M + 1).

[00185] Cis-rac-tert-butyl (3R,4S)-3-(methanesulfonyloxy)-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3262-001 – step 4

[00186] Scheme 1.3 Step 4



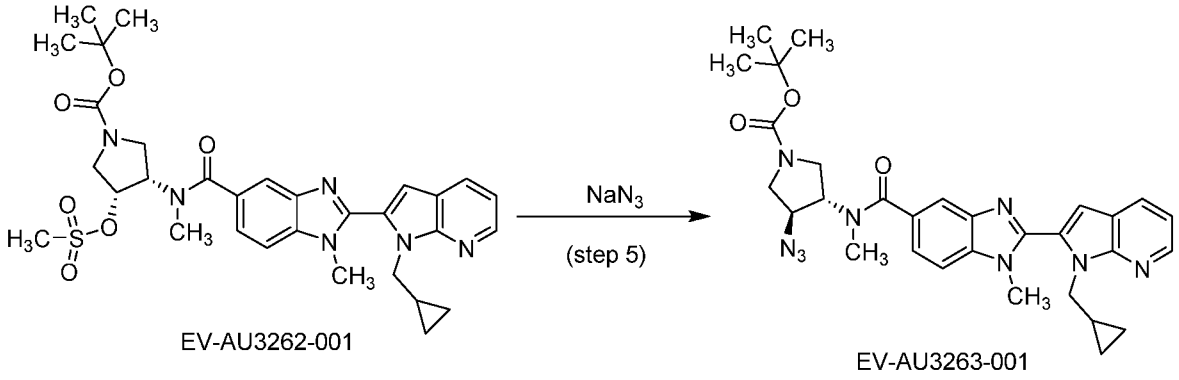
EV-AU3260-001

EV-AU3262-001

[00187] To a stirred solution of rac-tert-butyl (3R,4S)-3-hydroxy-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3260-001,** 379 mg, 0.7 mmol) in DCM (10 ml) at 0°C was added Et_3N (145 µl, 1.04 mmol) and MsCl (65 µl, 0.84 mmol). The reaction was allowed to reach room temperature while stirring for 2h. The reaction mixture was washed with water (5 ml) and the organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to obtain 410 mg (95%) of cis-rac-tert-butyl (3R,4S)-3-(methanesulfonyloxy)-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3262-001** as a colourless powder. LCMS (method D): retention time 1.24min, M/z = 623 (M + 1).

[00188] Trans-rac-tert-butyl (3R,4R)-3-azido-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3263-001 – step 5

[00189] Scheme 1.3 Step 5

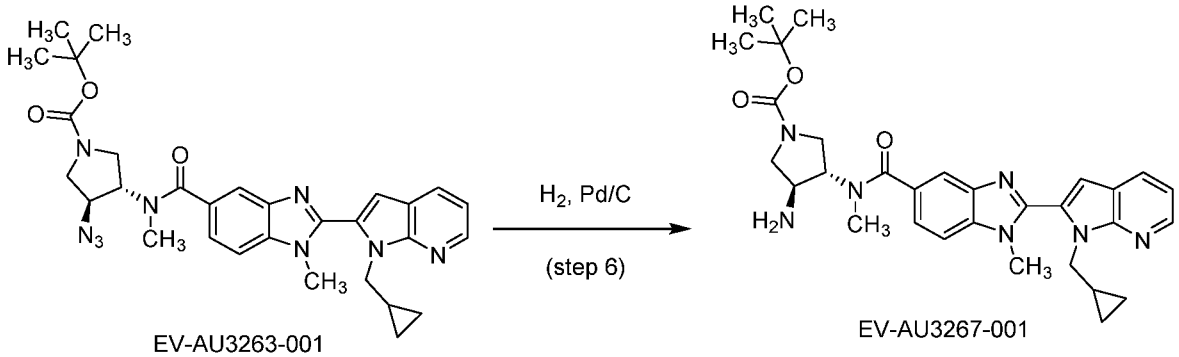


EV-AU3262-001 EV-AU3263-001

[00190] To a stirred solution of cis-rac-tert-butyl (3R,4S)-3-(methanesulfonyloxy)-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3262-001**, 410 mg, 0.66 mmol) in DMSO (2 ml) was added sodium azide (128 mg, 1.98 mmol) and the reaction was stirred at 90°C for 14h. The reaction was then cooled to room temperature and diluted with EtOAc (10 ml). The solution was washed with water (3 x 10 ml), saturated aqueous sodium chloride (2 x 10 ml) and the organic extract was dried over sodium sulphate, filtered and concentrated in vacuo. The crude was purified by flash column chromatography (eluting with 50-100% EtOAc/heptanes) to obtain 272 mg (72%) of trans-rac-tert-butyl (3R,4R)-3-azido-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3263-001** as a colourless powder. LCMS (method D): retention time 1.32min, M/z = 570 (M + 1).

[00191] Trans-rac-tert-butyl (3R,4R)-3-amino-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3267-001 – step 6

[00192] Scheme 1.3 Step 6

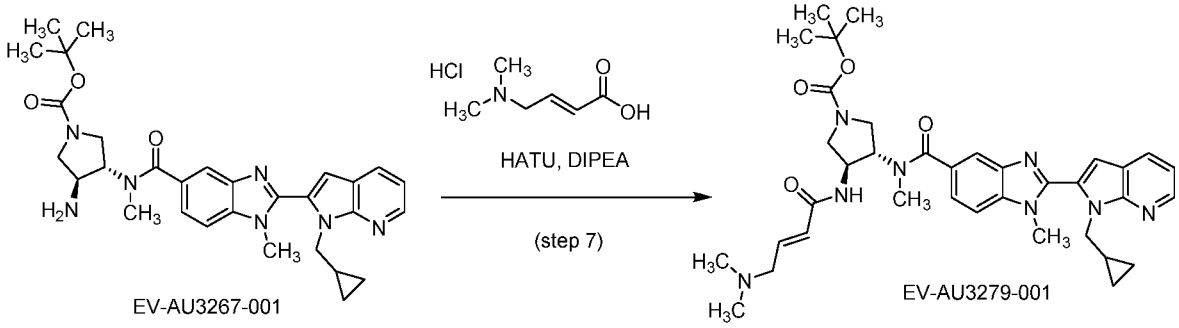


EV-AU3263-001 EV-AU3267-001

[00193] A solution of trans-rac-tert-butyl (3R,4R)-3-azido-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3263-001**, 272 mg, 0.48 mmol) in EtOAc (8 ml) was stirred under a hydrogen atmosphere at room temperature for 12h. The reaction mixture was filtered through a filter paper, the filter was washed with MeOH and the filtrate concentrated in vacuo to obtain 230 mg (80%) of trans-rac-tert-butyl (3R,4R)-3-amino-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3267-001** as an off white powder. LCMS (method D): retention time 1.07min, M/z = 544 (M + 1).

[00194] Trans-rac-tert-butyl (3R,4R)-3-[(2E)-4-(dimethylamino)but-2-enamido]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate EV-AU3279-001 – step 7

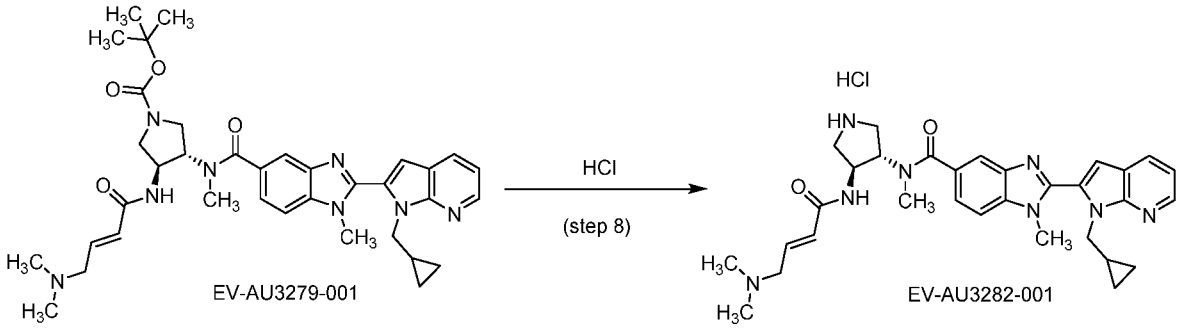
[00195] Scheme 1.3 Step 7



[00196] To a stirred solution of trans-rac-tert-butyl (3R,4R)-3-amino-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3267-001,** 70 mg, 0.13 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (26 mg, 0.15 mmol) in DMF (1 ml) was added HATU (59 mg, 0.15 mmol) and DIPEA (49 µl, 0.28 mmol) and the reaction was stirred at room temperature for 2h. The solvent was then removed under vacuum and the crude was purified by preparative HPLC (acidic method) to give 20 mg (24%) of trans-rac-tert-butyl (3R,4R)-3-[(2E)-4-(dimethylamino)but-2-enamido]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate **EV-AU3279-001** as an off white solid. LCMS (method D): retention time 1.14min, M/z = 655 (M + 1).

[00197] Trans-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-N,1-dimethyl-1H-1,3-benzodiazole-5-carboxamide hydrochloride, I-1 (EV-AU3282-001) – step 8

[00198] Scheme 1.3 Step 8



I-1

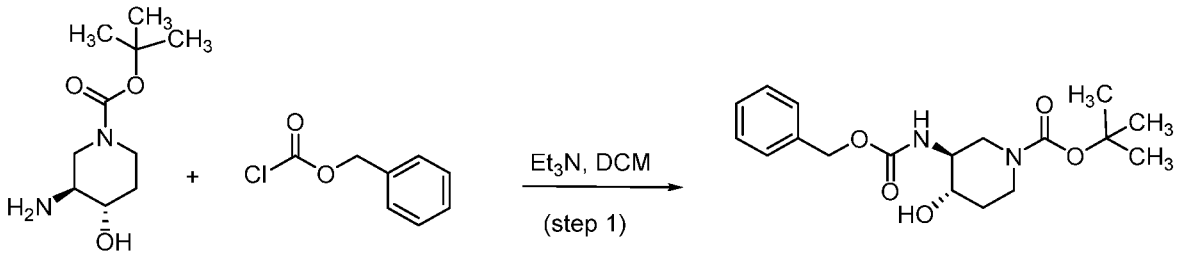
[00199] 2M HCl in diethyl ether (0.76 ml) was added to trans-rac-tert-butyl (3R,4R)-3-[(2E)-4-(dimethylamino)but-2-enamido]-4-{N-methyl2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}pyrrolidine-1-carboxylate (**EV-AU3279-001**, 20 mg, 0.03 mmol) and the resulting mixture was stirred at room temperature for 2h. The reaction mixture was concentrated in vacuo to obtain 17 mg (78%) of rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,4R)-4-[(2E)-4-(dimethylamino)but-2-enamido]pyrrolidin-3-yl]-N,1-dimethyl-1H-1,3-benzodiazole-5-carboxamide hydrochloride **I-1** (**EV-AU3282-001**) as an off white solid. LCMS (method A): retention time 1.43min, M/z = 555 (M + 1).

[00200] Example 8. Synthesis of Cis-rac-(2E)-N-[(3R,4S)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl]-4-(dimethylamino)but-2-enamide, I-3

[00201] Cis-rac-(2E)-N-[(3R,4S)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl]-4-(dimethylamino)but-2-enamide **EV-AU3261-001 (EOAI3449030, I-3)** was synthesised according to the procedures described in Scheme 1.4, steps 1 to 10, using intermediate methyl 2-[1- (cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole- 5-carboxylate **EV-AR6658-001** synthesised as described in Scheme 1:

[00202] Trans-rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate EV-AU3233-001 – Step 1

[00203] Scheme 1.4 Step 1

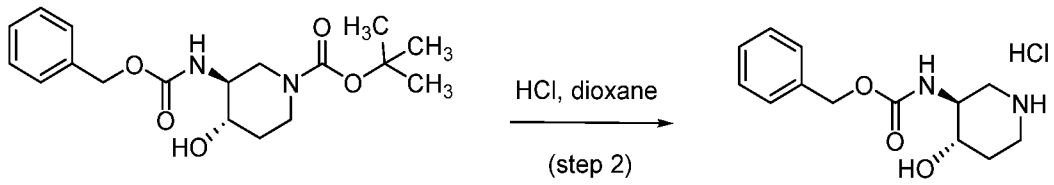


EV-AU3233-001

[00204] To a solution of trans-rac-tert-butyl (3R,4R)-3-amino-4-hydroxypiperidine-1-carboxylate (250 mg, 1.16 mmol) in DCM (5 ml) at 0°C was added triethylamine (484 µl, 3.47 mmol) and benzyl chloroformate (198 µl, 1.39 mmol). The reaction mixture was left to stir at 0°C for 15 minutes. The solution was allowed to warm to room temperature and stirred for a further 12h. The reaction was 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 under vacuum. The crude product was purified by column chromatography (20-80% EtOAc/heptanes) to obtain 0.21 g (52%) of trans-rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate **EV-AU3233-001** as a colourless viscous oil. LCMS (method D): retention time 1.12min, M/z = 373 (M + Na).

[00205] Trans-rac-benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate hydrochloride EV-AU3238-001 – Step 2

[00206] Scheme 1.4 Step 2

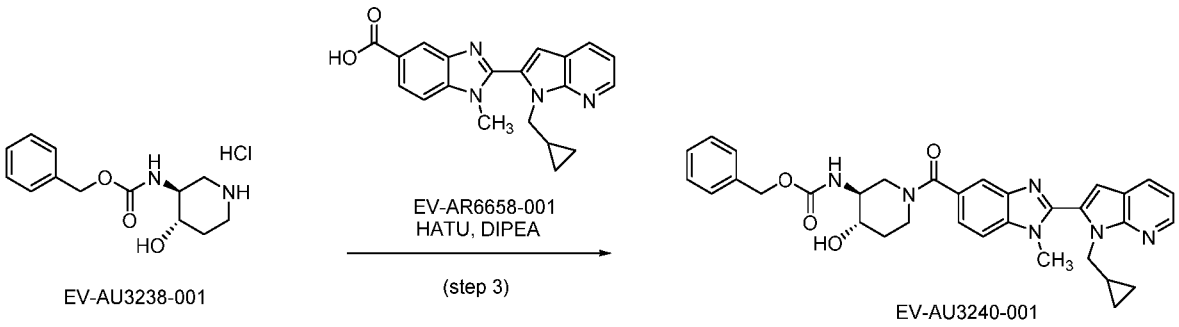


EV-AU3233-001 EV-AU3238-001

[00207] Trans-rac-tert-butyl (3R,4R)-3-{[(benzyloxy)carbonyl]amino}-4-hydroxypiperidine-1-carboxylate (**EV-AU3233-001** and **EV-AU3236-001** combined, 390 mg, 1.11 mmol) was dissolved in 4M HCl in dioxane (5.56 ml) and stirred at room temperature for 1h. The solvent was removed under vacuum to obtain 0.27 g (86%) of trans-rac-benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate hydrochloride **EV-AU3238-001** as a white solid. LCMS (method D): retention time 0.64min, M/z = 251 (M + 1).

[00208] Trans-rac-benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate EV-AU3240-001 – Step 3

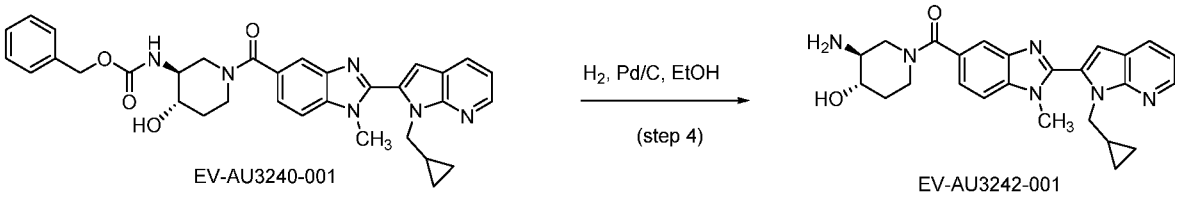
[00209] Scheme 1.4 Step 3



[00210] To a solution of methyl 2-[1- (cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole- 5-carboxylate (**EV-AR6658-001**, 330 mg, 0.95 mmol) in DMF (5 ml) was added DIPEA (0.55 ml, 3.33 mmol) and HATU (435 mg, 1.14 mmol) and the reaction was stirred under nitrogen at room temperature for 1h. Benzyl N-[(3R,4R)-4-hydroxypiperidin-3-yl]carbamate hydrochloride (273 mg, 0.95 mmol) was added and the reaction was stirred for a further 2h at room temperature. The reaction was quenched with water (5 ml) and extracted with ethyl acetate (5 ml x 3). The combined organic extracts were washed with water (5 ml) and saturated aqueous sodium chloride (2 x 5 ml), dried with sodium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography (50-100% EtOAc/heptanes, followed by 0-20% MeOH/EtOAc) to obtain 0.48 g (70%) of trans-rac-benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate **EV-AU3240-001** as a colourless viscous oil. LCMS (method D): retention time 1.11min, M/z = 579 (M + 1).

[00211] Trans-rac-(3R,4R)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-ol EV-AU3242-001 – Step 4

[00212] Scheme 1.4 Step 4

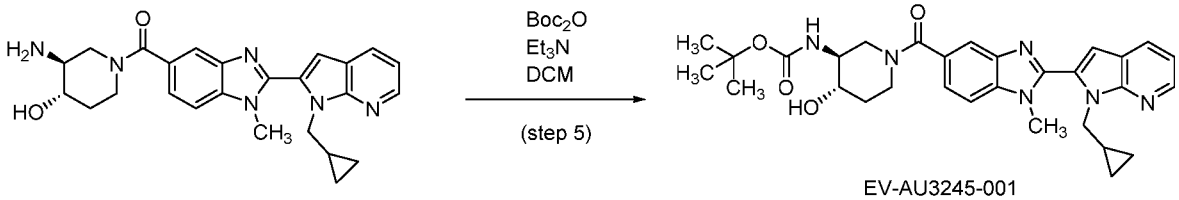


EV-AU3240-001 EV-AU3242-001

[00213] A solution of trans-rac-benzyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate (**EV-AU3240-001**, 480 mg, 0.83 mmol) in ethanol (10 ml) was stirred at room temperature for 12h under a hydrogen atmosphere in the presence of Pd/C (5%, 176.55 mg, 0.08 mmol). The reaction was filtered through a Kieselguhr pad, the filter was washed with MeOH and concentrated under vacuum to obtain 0.38 g (90%) of trans-rac-(3R,4R)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-ol **EV-AU3242-001** as a white solid. LCMS (method D): retention time 0.90min, M/z = 445 (M + 1).

[00214] Trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate EV-AU3245-001 – Step 5

[00215] Scheme 1.4 Step 5



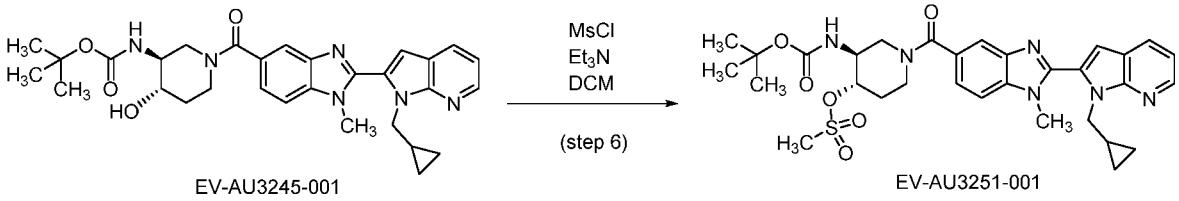
EV-AU3242-001 EV-AU3245-001

[00216] To a solution of trans-rac-(3R,4R)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-ol (**EV-AU3242-001**, 87%, 380 mg, 0.74 mmol) in DCM (5 ml) was added triethylamine (114 µl, 0.82 mmol) and di-tert-butyl dicarbonate (178 mg, 0.82 mmol) and the reaction was stirred at room temperature for 1h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with DCM (10 ml). The aqueous layer was washed with DCM (10 ml) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum to obtain 0.27 g (63%) of trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-

carbonyl}-4-hydroxypiperidin-3-yl]carbamate **EV-AU3245-001** as a white solid. LCMS (method D): retention time 1.09 min, M/z = 545 (M + 1).

[00217] Trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(methanesulfonyloxy)piperidin-3-yl]carbamate EV-AU3251-001 – Step 6

[00218] Scheme 1.4 Step 6

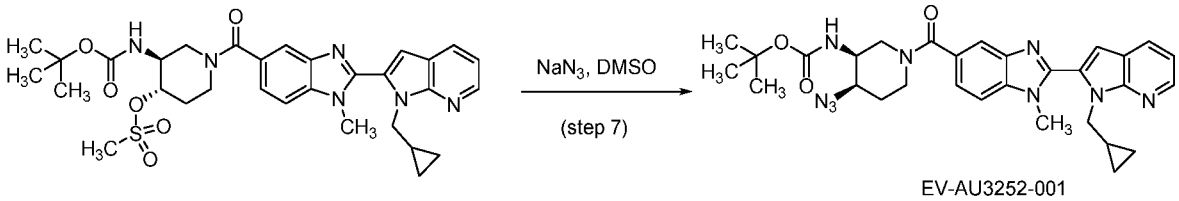


EV-AU3245-001 EV-AU3251-001

[00219] To a solution of trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-hydroxypiperidin-3-yl]carbamate (**EV-AU3245-001**, 269 mg, 0.49 mmol) in DCM (8 ml) at 0°C was added triethylamine (103 µl, 0.74 mmol) and mesyl chloride (46 µl, 0.59 mmol). The reaction was stirred and allowed to reach room temperature over 2h. The reaction mixture was washed with water (5 ml) and the organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to obtain 0.31 g (81%) of trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(methanesulfonyloxy)piperidin-3-yl]carbamate **EV-AU3251-001** as a colourless viscous oil. LCMS (method D): retention time 1.18min, M/z = 623 (M + 1).

[00220] Cis-rac-tert-butyl N-[(3R,4S)-4-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AU3252-001 – Step 7

[00221] Scheme 1.4 Step 7

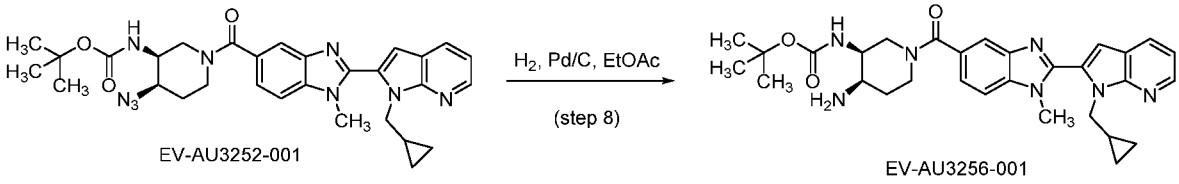


EV-AU3251-001 EV-AU3252-001

[00222] To a solution of trans-rac-tert-butyl N-[(3R,4R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-4-(methanesulfonyloxy)piperidin-3-yl]carbamate (**EV-AU3251-001**, 313 mg, 0.5 mmol) in DMSO (1.5 ml) was added sodium azide (98 mg, 1.51 mmol) and the reaction was left to stir at 90°C for 14h. The reaction was cooled to room temperature and diluted with EtOAc (10 ml). The organic layer was washed with water (3 x 10 ml) and saturated aqueous sodium chloride (2 x 10 ml). The organic extract was dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography (50-100% EtOAc/heptanes) to obtain 0.12 g (43%) of cis-rac-tert-butyl N-[(3R,4S)-4-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AU3252-001** as a white solid. LCMS (method D): retention time 1.25min, M/z = 570 (M + 1).

[00223] Cis-rac-tert-butyl N-[(3R,4S)-4-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AU3256-001 – Step 8

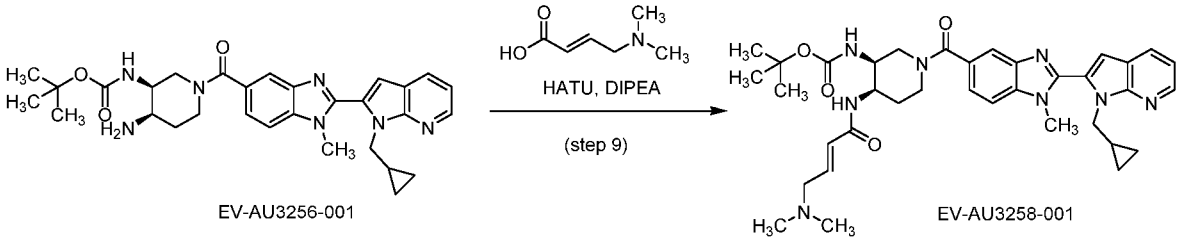
[00224] Scheme 1.4 Step 8



[00225] A solution of cis-rac-tert-butyl N-[(3R,4S)-4-azido-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AU3252-001**, 125 mg, 0.22 mmol) in EtOAc (4 ml) was treated with Pd/C (5% w/w, 47 mg, 0.02 mmol) and stirred under one atmosphere of hydrogen for 12h. The crude mixture was filtered through glass fibre filter paper, the filter was washed with MeOH and the filtrate concentrated to obtain 0.10 g (85%) of cis-rac-tert-butyl N-[(3R,4S)-4-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AU3256-001** as an off white solid. LCMS (method D): retention time 0.98min, M/z = 544 (M + 1).

[00226] Cis-rac-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-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]carbamate EV-AU3258-001 – Step 9

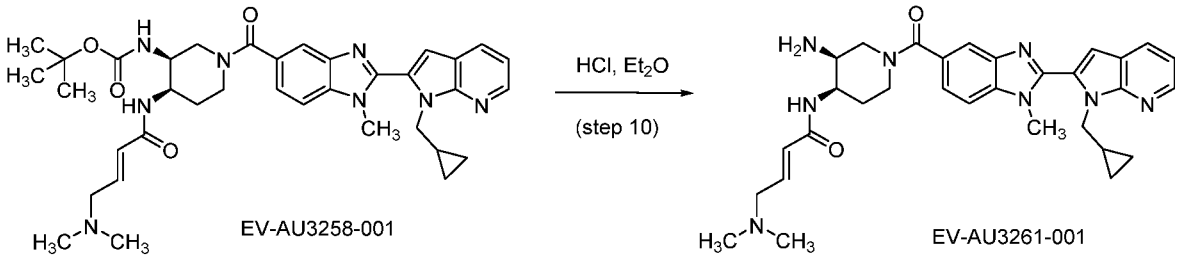
[00227] Scheme 1.4 Step 9



[00228] To a solution of (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (18 mg, 0.11 mmol) and cis-rac-tert-butyl N-[(3R,4S)-4-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AU3256-001**, 50 mg, 0.09 mmol) in DMF (1 ml) were added HATU (42 mg, 0.11 mmol) and DIPEA (35 µl, 0.2 mmol) and the reaction was stirred at room temperature for 2h. The solvent was removed under vacuum and the crude purified by preparative HPLC (acidic method) to obtain 25 mg (37%) of cis-rac-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-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]carbamate **EV-AU3258-001** as an off white solid. LCMS (method D): retention time 2.12min, M/z = 655 (M + 1).

[00229] Cis-rac-(2E)-N-[(3R,4S)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl]-4-(dimethylamino)but-2-enamide, I-3 (EV-AU3261-001) – Step 10

[00230] Scheme 1.4 Step 10



I-3

[00231] Cis-rac-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-[(2E)-4-(dimethylamino)but-2-

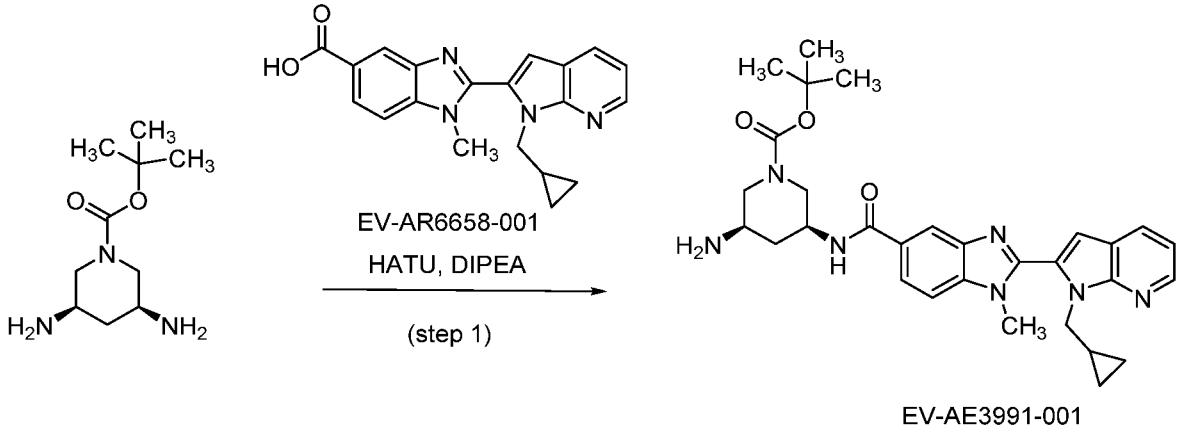
enamido]piperidin-3-yl]carbamate (**EV-AU3258-001**, 25 mg, 0.04 mmol) was dissolved in 2M HCl in diethyl ether (1.93 ml) and left to stir at room temperature for 2h. The solvent was removed under vacuum to obtain 18 mg (75%) of cis-rac-(2E)-N-[(3R,4S)-3-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-4-yl]-4-(dimethylamino)but-2-enamide **I-3 (EV-AU3261-001)** as an off white solid. LCMS (method A): retention time 1.48min, M/z = 555 (M + 1).

[00232] Example 9. Synthesis of Cis-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,5S)-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide, I-8

[00233] Cis-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,5S)-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide **EV-AE3994-001 (EOAI3447033, I-8)** was synthesised according to the procedures described in Scheme 1.5, steps 1 to 3, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR6658-001** synthesised as described in Scheme 1:

[00234] Cis-rac-tert-butyl (3R,5S)-3-amino-5-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}piperidine-1-carboxylate EV-AE3991-001 – Step 1

[00235] Scheme 1.5 Step 1

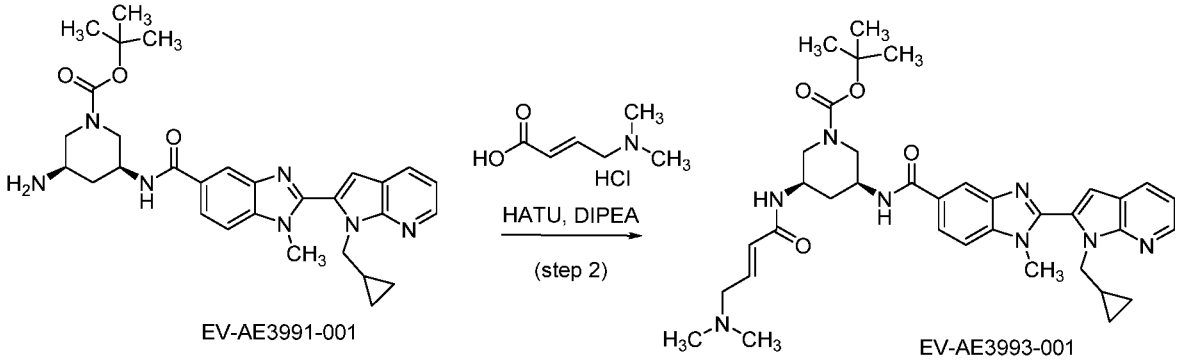


[00236] To a solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AR6658-001**, prepared as in Scheme 1, 100 mg, 0.14 mmol) in DMF (1 ml) was added DIPEA (167 µl, 1.01mmol) and HATU (132

mg, 0.35mmol) and the reaction was left to stir under nitrogen at room temperature for 20 minutes. Cis-rac-tert-butyl (3R,5S)-3,5-diaminopiperidine-1-carboxylate (**EV-AU3202-001** prepared as described in *J. Org. Chem., 2013, 78(23), p 12236-12242)*, 155 mg, 0.72 mmol) in DMF (1 ml) was added and the reaction was stirred for a further 2h at room temperature. The reaction was quenched with water (5 ml) and extracted with ethyl acetate (5 ml x 3). The combined organic extracts were washed with saturated aqueous sodium chloride (5 ml), dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by preparative HPLC (acidic method) to obtain 22 mg (14%) of cis-rac-tert-butyl (3R,5S)-3-amino-5-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}piperidine-1-carboxylate **EV-AE3991-001** as a white solid. LCMS (method D): retention time 1.00min, M/z = 544 (M + 1).

[00237] Cis-rac-tert-butyl (3R,5S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidine-1-carboxylate EV-AE3993-001 – Step 2

[00238] Scheme 1.5 Step 2

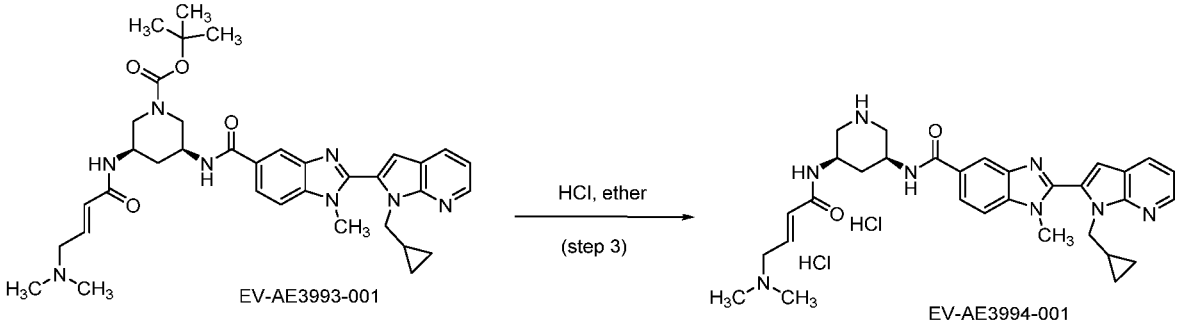


[00239] A solution of cis-rac-tert-butyl (3R,5S)-3-amino-5-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}piperidine-1-carboxylate (**EV-AE3991-001**, 22 mg, 0.04 mmol), (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (8 mg, 0.049 mmol) and HATU (18 mg, 0.049 mmol) in dry DMF (0.5ml) was treated with DIPEA (16 µl, 0.089 mmol) at room temperature. The mixture was stirred for 20 minutes at room temperature. The reaction mixture was diluted with EtOAc (5 ml) and washed with water (2 ml). The aqueous layer was re-extracted with EtOAc (5 ml). The EtOAc layers were combined, washed with saturated aqueous sodium chloride (5 ml), dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC (acidic method) to obtain 6 mg (22%) of cis-rac-tert-butyl (3R,5S)-3-{2-

[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidine-1-carboxylate **EV-AE3993-001** as a colourless crystalline solid. LCMS (method D): retention time 1.03min, M/z = 655 (M + 1).

[00240] Cis-rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,5S)-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride, I-8 (EV-AE3994-001) – Step 3

[00241] Scheme 1.5 Step 3



[00242] To cis-rac-tert-butyl (3R,5S)-3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-amido}-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidine-1-carboxylate (**EV-AE3993-001**, 6 mg, 0.009 mmol) was added 2M HCl in ether (0.05 ml, 0.092 mmol). The suspension mixture was allowed to stand at room temperature for 1h. Another portion of 2M HCl in ether (0.05 ml) was added, the reaction mixture was stirred briefly then allowed to stand for 30 mins. The reaction mixture was concentrated to dryness to obtain 5 mg (92%) of rac-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[(3R,5S)-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride **I-8** (**EV-AE3994-001**) as a white powder. LCMS (method C): retention time 2.90min, M/z = 555 (M + 1).

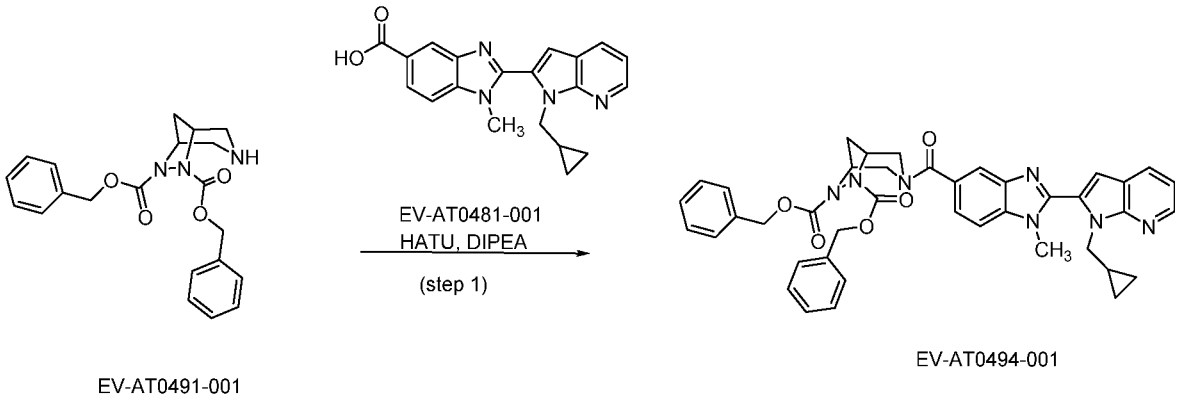
[00243] Example 10. Synthesis of Cis-rac-(2E)-N-[(3R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide, I-10

[00244] Cis-rac-(2E)-N-[(3R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide **EV-AU3215-001** (**EOAI3442261, I-10**) was synthesised

according to the procedures described in Scheme 1.6, steps 1 to 5, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (synthesised as described in Scheme 1).

[00245] 6,7-dibenzyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate EV-AT0494-001 – Step 1

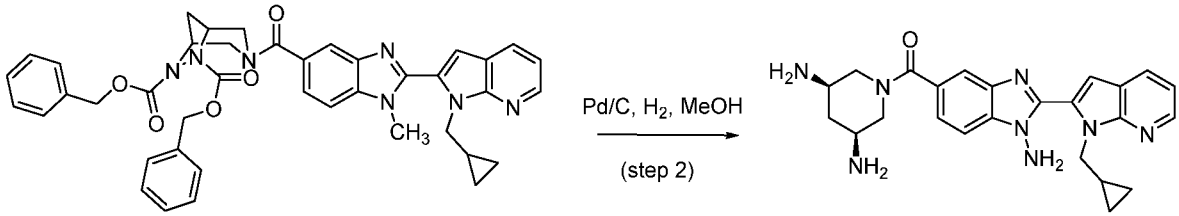
[00246] Scheme 1.6 Step 1



[00247] To a solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AT0481-001**, 410 mg, 1.18 mmol) in DMF (8 ml) was added DIPEA (235 µl, 1.42 mmol) and HATU (540 mg, 1.42 mmol) and the reaction was stirred under nitrogen at room temperature for 1h. 6,7-Dibenzyl 3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (**EV-AT0491-001** prepared as described in *J. Org. Chem., 2013, 78(23), p 12236-12242*, 497 mg, 1.3 mmol) in DMF (2 ml) was added and the reaction was stirred for a further 2h. The mixture was quenched with saturated aqueous ammonium chloride (5 ml) and extracted with ethyl acetate (5 ml x 3). The combined organic extracts were washed with water (5 ml), saturated aqueous sodium chloride (5 ml), dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified via column chromatography (80:100 EtOAc/heptanes, then 0:5% MeOH/EtOAc) to obtain 0.82 g (96%) of 6,7-dibenzyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate **EV-AT0494-001** as an orange solid. LCMS (method D): retention time 1.28min, M/z = 710 (M + 1).

[00248] Cis-rac-(3R,5S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3,5-diamine EV-AT0497-001 – Step 2

[00249] Scheme 1.6 Step 2

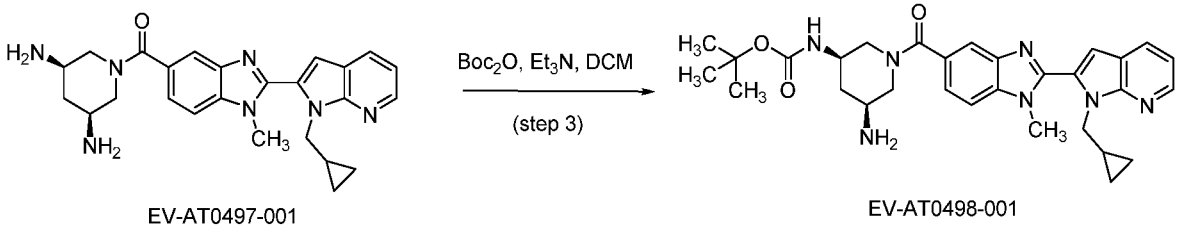


EV-AT0494-001 EV-AT0497-001

[00250] A 0.05M solution of 6,7-dibenzyl 3-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate (**EV-AT0494-001**, 22 ml) in EtOH was subjected to H-Cube conditions (1ml/min, 1 bar, 80 °C, full hydrogen mode) over a Pd/C (10%) catalyst cartridge. The solvent was removed under vacuum to obtain 0.41 g (82%) of cis-rac-(3R,5S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3,5-diamine **EV-AT0497-001** as an orange oil. LCMS (method D): retention time 0.76min, M/z = 444 (M + 1).

[00251] Formic acid; cis-tert-butyl N-(5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate EV-AT0498-001 – Step 3

[00252] Scheme 1.6 Step 3



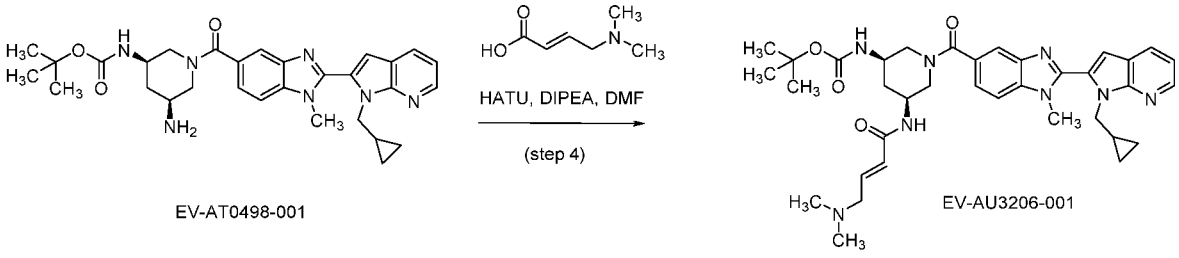
EV-AT0497-001 EV-AT0498-001

[00253] To a solution of cis-rac-(3R,5S)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidine-3,5-diamine (**EV-AT0497-001**, 415 mg, 0.94 mmol) in DCM (7.5 ml) was added triethylamine (144 µl, 1.03 mmol) and di-tert-butyl dicarbonate (184 mg, 0.84 mmol) and the reaction was stirred at

room temperature for 1h. The reaction was quenched with saturated aqueous sodium bicarbonate (10 ml) and extracted with DCM (10 ml). The aqueous layer was washed with DCM (10 ml), the combined organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by reverse phase column chromatography (10-90% MeCN in water, with both solvents containing 0.1% formic acid) to obtain 0.17 g (30%) of formic acid; cis-tert-butyl N-(5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate **EV-AT0498-001** as an off-white solid. LCMS (method A): retention time 2.17min, M/z = 544 (M + 1).

[00254] Cis-tert-butyl N-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-5-[(2E)-4-(dimethylamino)but-2-enamido]piperidin-3-yl)carbamate EV-AU3206-001 – Step 4

[00255] Scheme 1.6 Step 4

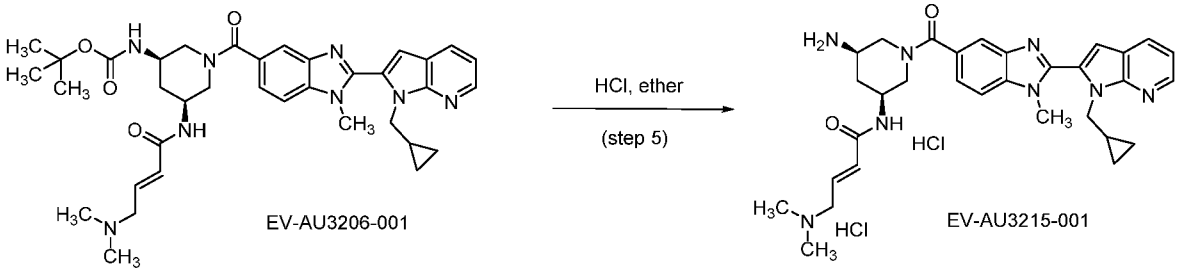


EV-AT0498-001 EV-AU3206-001

[00256] To a solution of (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (20 mg, 0.12 mmol) in DMF (0.5 ml) was added HATU (55 mg, 0.14 mmol) and DIPEA (60 µl, 0.36 mmol) and the solution was stirred at room temperature for 1h. Formic acid; cis-tert-butyl N-(5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate (**EV-AT0498-001,** 52.52 mg, 0.1 mmol) in DMF (0.5 ml) was added and the reaction was stirred for a further 3h. The solvent was removed under vacuum and the crude was purified by preparative HPLC (acidic method) to obtain 14 mg (18%) of formic acid; cis-tert-butyl N-(5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate **EV-AU3206-001** as a white solid. LCMS (method A): retention time 2.24min, M/z = 655 (M + 1).

[00257] Cis-rac-(2E)-N-[(3R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide, I-10 (EV-AU3215-001) – Step 5

[00258] Scheme 1.6 Step 5



I-10

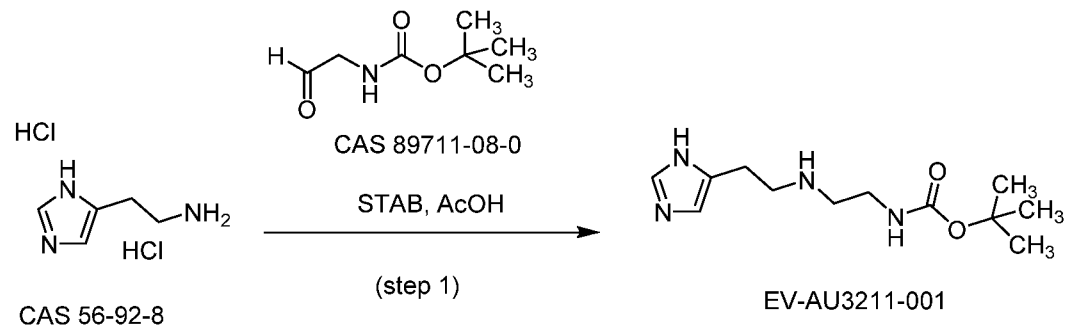
[00259] Formic acid; cis-tert-butyl N-(5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl)carbamate (**EV-AU3206-001**, 14 mg, 0.02 mmol) was dissolved in 2M HCl in diethyl ether (1.08 ml) and stirred at room temperature for 2h. The reaction mixture was concentrated under vacuum to obtain 19 mg (91%) of cis-rac-(2E)-N-[(3R,5S)-5-amino-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide **I-10**, (**EV-AU3215-001**) as an off white solid. LCMS (method A): retention time 1.33min, M/z = 555 (M + 1).

[00260] Example 11. Synthesis of (2E)-N-[2-(1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]-4-(dimethylamino)but-2-enamide, I-7

[00261] (2E)-N-[2-(1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]-4-(dimethylamino)but-2-enamide **EV-AE3995-001** (**EOAI3447034**, **I-7**) was synthesised according to the procedures described in Scheme 1.7, steps 1 to 4, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR3168-002** synthesised as described in Scheme 1:

[00262] Tert-butyl N-(2-{[2-(1H-imidazol-5-yl)ethyl]amino}ethyl)carbamate EV-AU3211-001 – Step 1

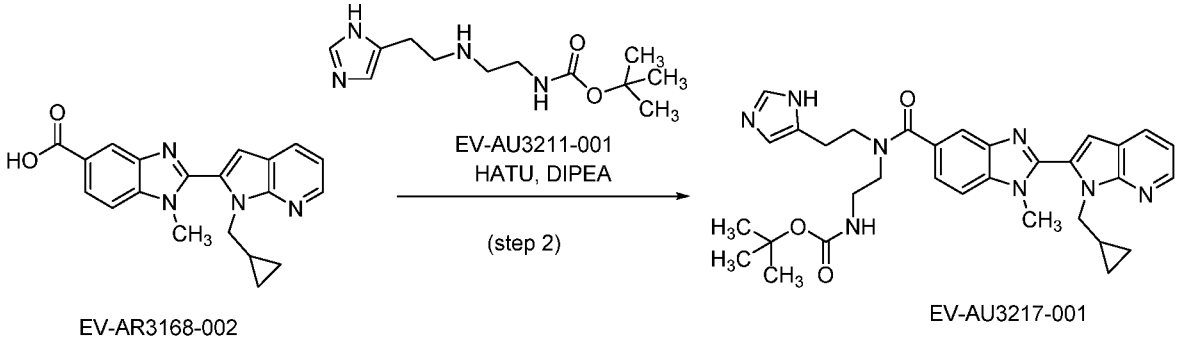
[00263] Scheme 1.7 Step 1



[00264] To a stirred solution of tert-butyl N-(2-oxoethyl)carbamate (CAS 89711-08-0, 649 mg, 4.07 mmol) and 2-(1H-imidazol-5-yl)ethan-1-amine dihydrochloride (CAS 56-92-8, 500 mg, 2.72 mmol) in MeOH (15 ml) was added acetic acid (0.16 ml, 2.72 mmol) followed by portion wise addition of sodium triacetoxyborohydride (2.0 g, 9.42 mmol). The reaction was stirred at room temperature for 16h. The solvent was removed in vacuo and the residue was purified by reverse phase flash column chromatography (10-100% in MeCN/water, both solvents containing 0.1% NH_3) to obtain 80 mg (9%) of tert-butyl N-(2-{[2-(1H-imidazol-5-yl)ethyl]amino}ethyl)carbamate **EV-AU3211-001** as a yellow oil. LCMS (method J): retention time 1.28min, M/z = 255 (M + 1).

[00265] Tert-butyl N-[2-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]carbamate EV-AU3217-001 – step 2

[00266] Scheme 1.7 Step 2

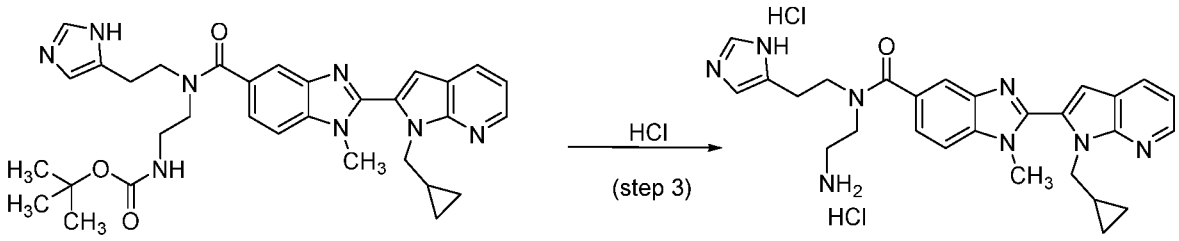


[00267] To a stirred solution of 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid (**EV-AR3168-002**, 109 mg, 0.31 mmol) in DMF (2 ml) was added HATU (132 mg, 0.35 mmol) and DIPEA (110 µl, 0.63 mmol) and the reaction was stirred at room temperature for 2h. The reaction mixture was submitted directly for preparative HPLC (basic method) to obtain 25 mg (14%) of tert-butyl N-[2-(1-{2-

[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]carbamate **EV-AU3217-001** as a colourless powder. LCMS (method D): retention time 0.99min, M/Z = 583 (M + 1).

[00268] N-(2-Aminoethyl)-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[2-(1H-imidazol-5-yl)ethyl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride EV-AE3992-001 – step 3

[00269] Scheme 1.7 Step 3

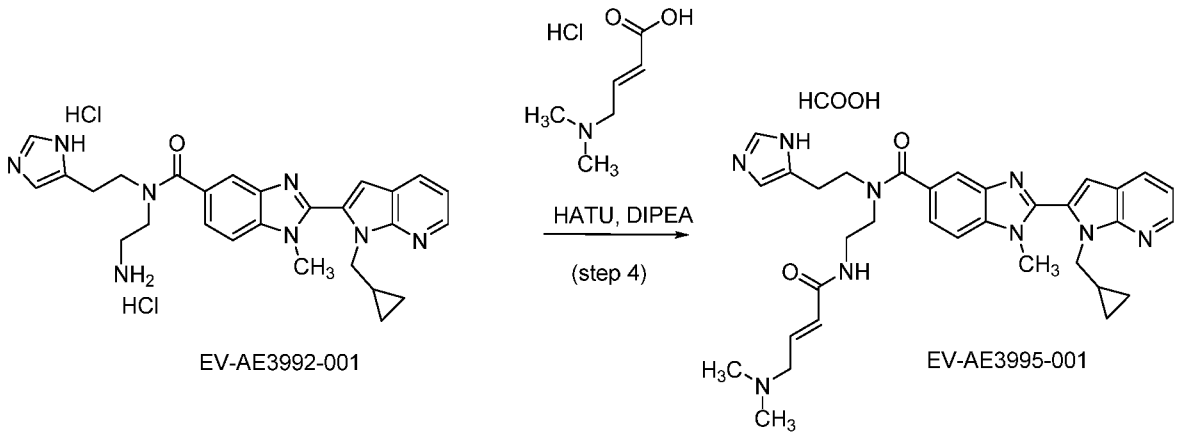


EV-AU3217-001 EV-AE3992-001

[00270] 2M HCl in ether (0.22 ml, 0.43 mmol) was added to tert-butyl N-[2-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]carbamate (**EV-AU3217-001**, 25 mg, 0.043 mmol) and the resulting mixture was stirred at room temperature for 2h. The solvent was removed in vacuo and the residue azeotroped with DCM (2 ml). The resulting solid was dried to afford 27 mg (quantitative) of N-(2-aminoethyl)-2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[2-(1H-imidazol-5-yl)ethyl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride **EV-AE3992-001** as a white powder. LCMS (method D): retention time 0.78min, M/z = 483 (M + 1).

[00271] (2E)-N-[2-(1-{2-[1-(Cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]-4-(dimethylamino)but-2-enamide formate, I-7 (EV-AE3995-001) – step 4

[00272] Scheme 1.7 Step 4



I-7

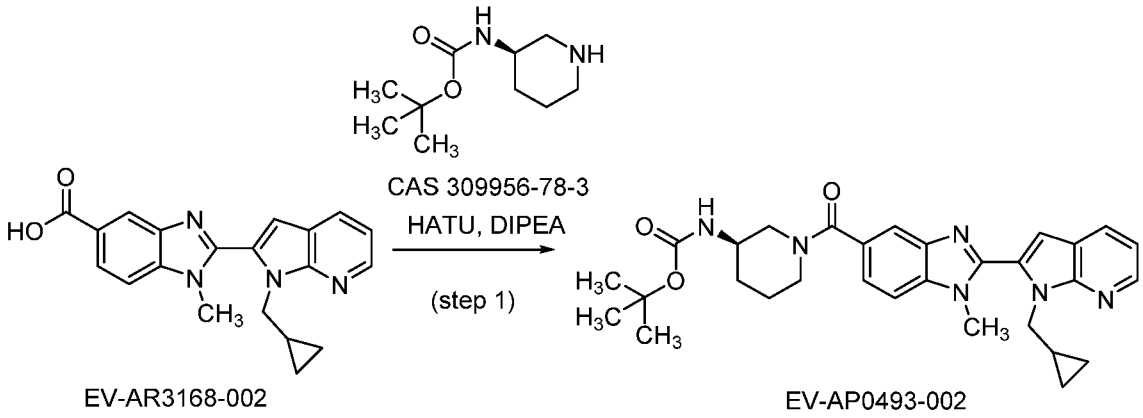
[00273] To a stirred solution of N-(2-aminoethyl) -2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-N-[2-(1H-imidazol-5-yl)ethyl]-1-methyl-1H-1,3-benzodiazole-5-carboxamide dihydrochloride (**EV-AE3992-001**, 27 mg, 0.049 mmol), HATU (22 mg, 0.058 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (10 mg, 0.058 mmol) in dry DMF (1 ml) was added DIPEA (30 µl, 0.17 mmol). The reaction was stirred at room temperature for 20 minutes. The solvent was removed in vacuo and the residue was submitted for preparative HPLC (acidic method) to afford 2.6 mg (8%) of (2E)-N-[2-(1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazol-5-yl}-N-[2-(1H-imidazol-5-yl)ethyl]formamido)ethyl]-4-(dimethylamino)but-2-enamide formate **EV-AE3995-001** as a colourless solid. LCMS (method C): retention time 2.72min, M/z = 594 (M + 1).

[00274] Example 12. Synthesis of (2E)-N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide, I-12

[00275] (2E)-N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide **EV-AQ1925-001** (**EOAI3426752**, **I-12**) was synthesised according to the procedures described in Scheme 1.8, steps 1 to 3, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carboxylic acid **EV-AR3168-002** synthesised as described in Scheme 1:

[00276] Tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate EV-AP0493-002 – Step 1

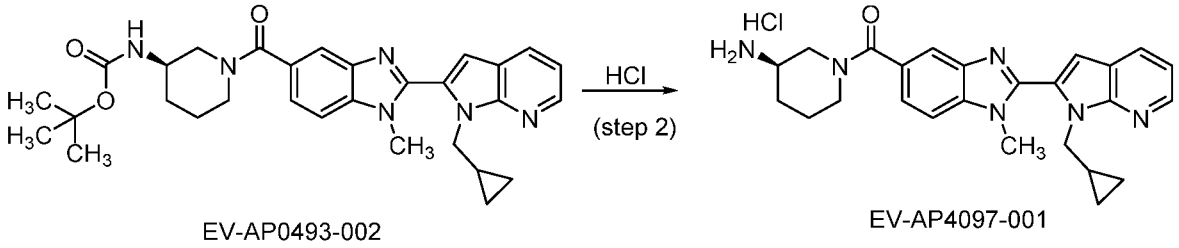
[00277] Scheme 1.8 Step 1



[00278] 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**, 300 mg, 0.87 mmol) and HATU (362 mg, 0.95 mmol) in dry DMF (9 ml) was added DIPEA (166 µl, 0.95 mmol). The reaction was stirred for 1h at room temperature and tert-butyl N-[(3R)-piperidin-3-yl]carbamate (CAS 309956-78-3, 208 mg, 1.04 mmol) was added. The reaction was stirred at room temperature for 16h and concentrated in vacuo. The residue was partitioned between DCM (30 ml) and saturated aqueous sodium bicarbonate (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), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (1-10% MeOH/DCM) to obtain 352 mg (76%) of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate **EV-AP0493-002** as a yellow crystalline solid. LCMS (method D): retention time 1.34min, M/z = 529 (M + 1).

[00279] (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride EV-AP4097-001 – Step 2

[00280] Scheme 1.8 Step 2

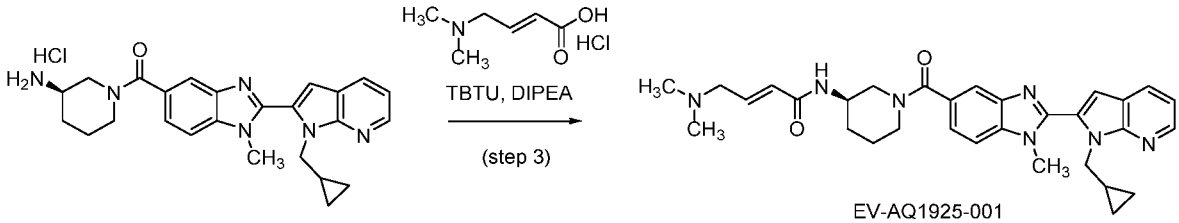


EV-AP0493-002 EV-AP4097-001

[00281] To a stirred solution of tert-butyl N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]carbamate (**EV-AP0493-002,** 352 mg, 0.66 mmol) in methanol (3 ml) was added 4M HCl in dioxane (7 ml). The reaction was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuo and the resulting solid was dried to obtain 299 mg (96%) of (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride **EV-AP4097-001** as a yellow powder. LCMS (method D): retention time 1.00min, M/z = 429 (M + 1).

[00282] (2E)-N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide, I-12 (EV-AQ1925-001) – Step 3

[00283] Scheme 1.8 Step 3



EV-AP4097-001 EV-AQ1925-001

I-12

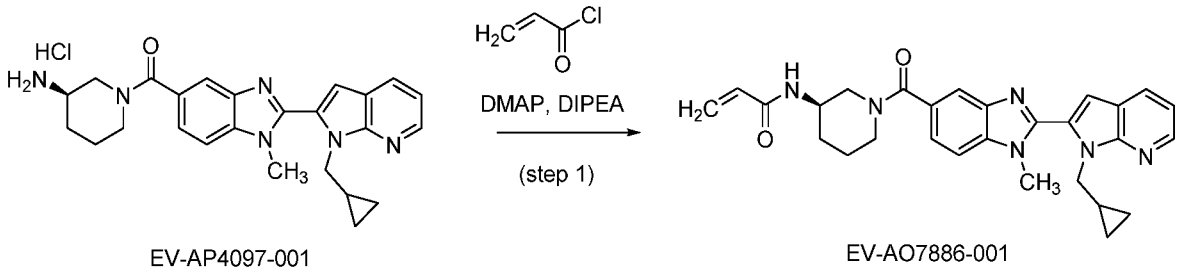
[00284] To a stirred solution of (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride (**EV-AP4097-001**, 50 mg, 0.11 mmol) in DMF (1 ml) was added (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (21 mg, 0.13 mmol), DIPEA (62 mg, 0.54 mmol) and TBTU (45 mg, 0.14 mmol). The mixture was stirred at room temperature for 2h. The reaction mixture was filtered and the filtrate was submitted for preparative HPLC (basic method) to afford 25 mg (43%) of (2E)-N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]-4-(dimethylamino)but-2-enamide **I-**

12 (EV-AQ1925-001) as a white solid. LCMS (method A): retention time 1.88min, M/z = 540 (M + 1).

[00285] Example 13. Synthesis of N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]prop-2-enamide, I-13

[00286] N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]prop-2-enamide **EV-AO7886-002 (EOAI3426521, I-13)** was synthesised according to the procedures described in Scheme 1.9 from 3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride **EV-AP4097-001** synthesised as described in Scheme 1.8:

[00287] Scheme 1.9



EV-AP4097-001

EV-AO7886-001

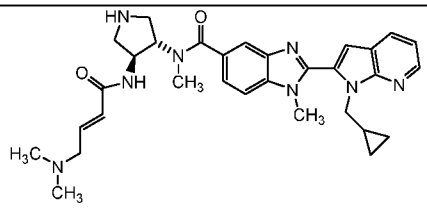
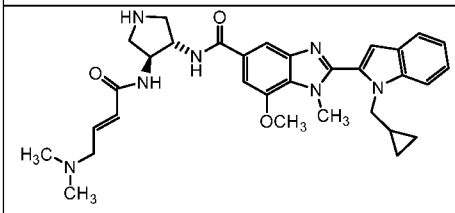
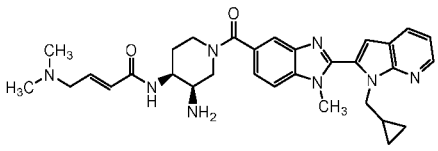
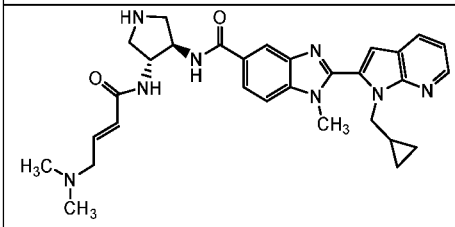
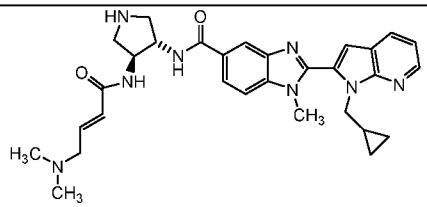
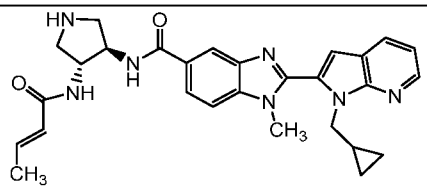
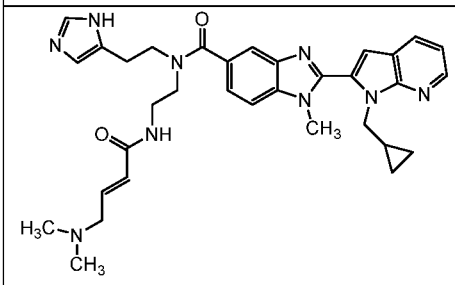
I-13

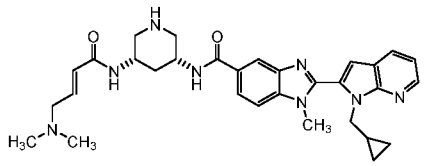
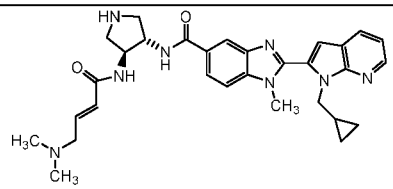
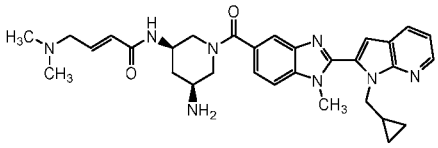
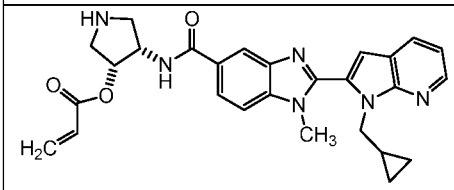
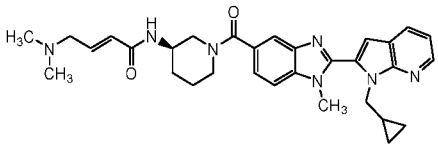
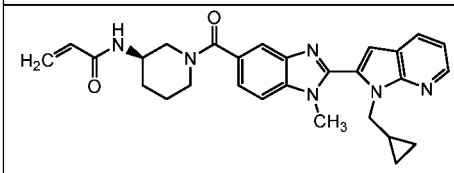
[00288] N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]prop-2-enamide, I-13 (EV-AO7886-002) – Step 1

[00289] To a stirred solution of DIPEA (178 µl, 1.02 mmol), DMAP (1.2 mg, 0.01 mmol) and (3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-amine hydrochloride (**EV-AP4097-001**, 50 mg, 0.11 mmol) in DCM (5 ml) at 0°C was added a solution of prop-2-enoyl chloride (26 µl, 0.32 mmol) in DCM (3 ml) dropwise. The reaction was stirred at 0°C for 1h. Water (1 ml) was added and the layers were separated using a hydrophobic filter. The organic phase was concentrated in vacuo and the crude material purified by preparative HPLC (acidic method) to afford 21 mg (41%) of N-[(3R)-1-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-1-methyl-1H-1,3-benzodiazole-5-carbonyl}piperidin-3-yl]prop-2-enamide **I-13 (EV-**

AO7886-002) as a colourless crystalline solid. LCMS (method A): retention time 2.61min, M/z = 483 (M + 1).

[00290] The following compounds were synthesised according to procedures described above:

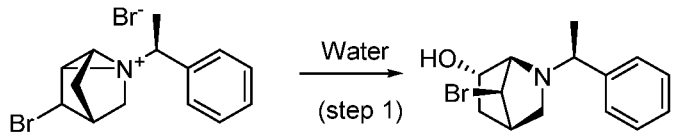
Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-1	554.686	1.43 min	555.3	A	HCl	2
	I-2	569.697	1.98 min	571.2	A	HCl	2
	I-3	554.686	1.48 min	555.3	A	HCl	2
	I-4	540.659	1.44 min	541.3	A	HCl	2
	I-5	540.659	1.43 min	541.3	A	HCl	2
	I-6	497.591	3.35 min	498.2	C	HCl	1
	I-7	593.722	2.72 min	594.3	C	HCO2H	1

Structure	#	Mol Wt	LCMS T_{ret}	M/z (+)	LCMS Method	Salt	Salt Stoichiometry
	I-8	554.686	2.90 min	555.2	C	HCl	2
	I-9	540.659	2.80 min	541.2	C	HCl	2
	I-10	554.686	1.33 min	555.2	A	HCl	2
	I-11	484.550	1.96 min	485.1	A	HCl	1
	I-12	539.671	1.88 min	540.3	A		
	I-13	482.577	2.61 min	483.3	A		

[00291] Example 14. Synthesis of N-[(1S,4R,6R,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]-N-methylprop-2-enamide, I-16 and 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]-N-methylprop-2-enamide, I-17

[00292] N-[(1S,4R,6R,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]-N-methylprop-2-enamide **I-16** (**EV-AZ4416-001**) (**EOAI3478697**) LCMS (method A): retention time 1.93 min, M/z = 554.4 (M+1) and 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]-N-methylprop-2-enamide **I-17** (**EV-AZ4417-001**) (**EOAI3478698**) LCMS (method A): retention time 2.10 min, M/z = 554.4 (M+1) were synthesised according to procedures described in Scheme 1.10, steps 1-10, from 2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole -5-carboxylic acid **EV-AV3032-001** which was synthesised according to the procedures described in Scheme 1.

[00293] Scheme 1.10 Step 1



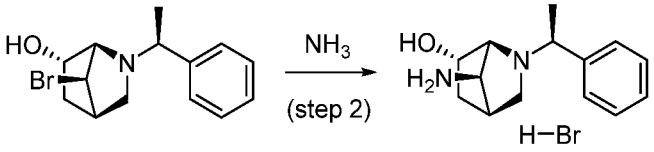
EV-AW8588-001 EV-AY4949-001

[00294] (1R,4R,6S,7R)-7-Bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol EV-AY4949-001 – step 1

[00295] A solution of (4R,6R)-3-bromo-1-[(1S)-1-phenylethyl]-1-azatricyclo[2.2.1.0]heptan-1-ium bromide (**EV-AW8588-001**, 8.70 g, 19.4 mmol) (synthesised as in *Adv. Synth. Catal.* **2005**, *347*, 1242 – 1246) in acetonitrile: water (1:1, 100 ml) was stirred at 65°C for 20h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (20-80% EtOAc/heptane) to afford 4.29 g (73%) of (1R,4R,6S,7R)-7-bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol **EV-AY4949-001** as an off-white solid. ^{1}H NMR (250 MHz, Chloroform-d) δ 7.38 - 7.14 (m, 5H), 4.10 (s, 2H), 3.58 (q, J = 6.1 Hz, 1H), 3.36 - 3.23 (m, 1H), 2.65 (dt, J = 9.0, 3.1 Hz,

1H), 2.58 - 2.46 (m, 1H), 2.28 - 1.91 (m, 4H), 1.32 (d, J = 6.4 Hz, 3H). No LCMS data.

[00296] Scheme 1.10 Step 2

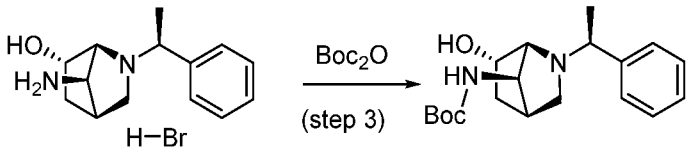


EV-AY4949-001 EV-AY4952-001

[00297] (1S,4R,6S,7R)-7-amino-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol hydrobromide EV-AY4952-001 – step 2

[00298] (1R,4R,6S,7R)-7-bromo-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol (**EV-AY4949-001**, 4.29 g, 14.2 mmol) was dissolved in 7N ammonia in methanol (15 ml) and the resulting mixture was heated at 65°C for 2h. The solvent was removed *in vacuo* to afford 4.62 g (quantitative) of (1S,4R,6S,7R)-7-amino-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol hydrobromide **EV-AY4952-001** as a yellow solid. LCMS (method D): retention time 0.20min, M/z = 233 (M + 1).

[00299] Scheme 1.10 Step 3

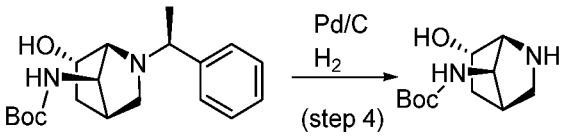


EV-AY4952-001 EV-AY4953-001

[00300] Tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AY4953-001 – step 3

[00301] Di-tert-butyl dicarbonate (3.41 g, 15.6 mmol) was added to a solution of (1R,4R,6S,7R)-7-amino-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-6-ol hydrobromide (**EV-AY4952-001**, 4.62 g, 14.2 mmol) and triethylamine (2.97 ml, 21.28 mmol) in DCM (50 ml). The resulting mixture was stirred at room temperature for 2.5h, washed with saturated aqueous sodium bicarbonate (35 ml), water (2 x 30 ml) and saturated aqueous sodium chloride (35 ml), dried over sodium sulfate and concentrated *in vacuo*. The resulting solid was triturated with DCM: diethyl ether (1:4, 20 ml), filtered and dried to obtain 3.24 g (65%) of tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY4953-001** as an off-white solid. LCMS (method D): retention time 1.02min, M/z = 333 (M + 1).

[00302] Scheme 1.10 Step 4

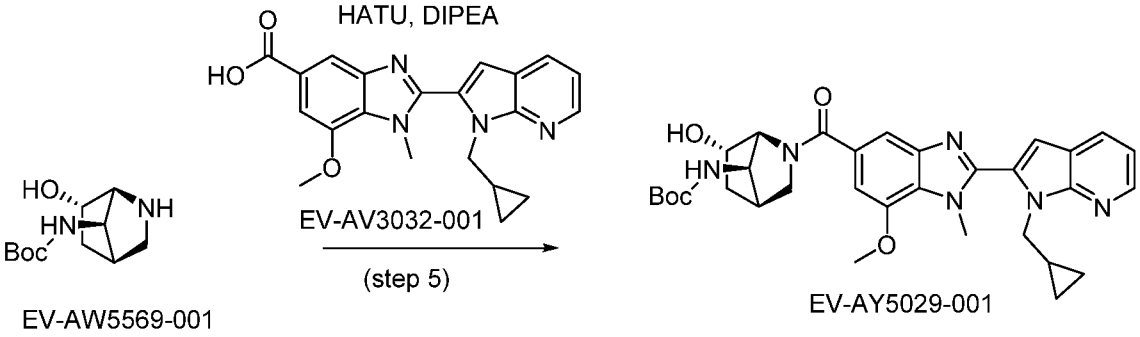


EV-AY4953-001 EV-AW5569-001

[00303] Tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW5569-001 – step 4

[00304] A solution of tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-[(1S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AY4953-001**, 350 mg, 1.05 mmol) in ethanol (10 ml) was purged with nitrogen. Pd/C (5%, 224 mg, 0.11 mmol) was added, the reaction mixture was purged with nitrogen and stirred under a hydrogen atmosphere for 12h. The reaction mixture was filtered through filter paper (washing with methanol). The filtrate was concentrated *in vacuo* to afford 170 mg (71%) of tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW5569-001** as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.84 (s, 1H), 3.99 (d, *J* = 40.5 Hz, 2H), 3.12 (s, 1H), 2.98 (d, *J* = 9.2 Hz, 1H), 2.53 – 2.41 (m, 2H), 1.98 (dd, *J* = 13.7, 6.9 Hz, 1H), 1.75 (d, *J* = 13.1 Hz, 1H), 1.44 (s, 9H). No LCMS data.

[00305] Scheme 1.10 Step 5



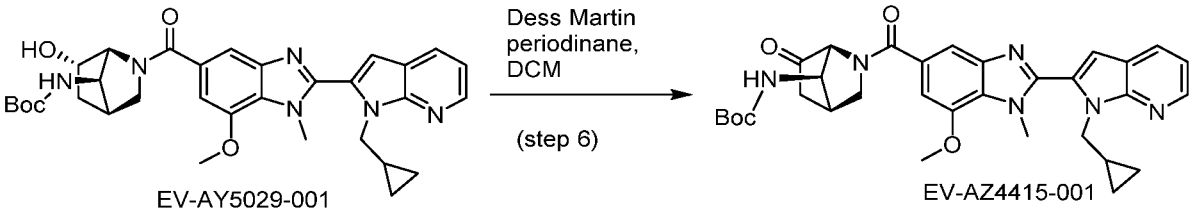
EV-AW5569-001 EV-AY5029-001

[00306] 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 – step 5

[00307] 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-AV3032-001**, 0.969 g, 2.58 mmol) in DMF (12 ml) was added HATU (1.08 g, 2.83 mmol) and DIPEA (1.12 ml, 6.44 mmol) followed by tert-butyl N-[(1S,4R,6S,7R)-6-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AW5569-001**, 98%, 0.60 g, 2.58 mmol). The resulting mixture was stirred

at room temperature for 30 minutes. The reaction was diluted with EtOAc (100 ml) and water (100 ml). The organic phase was collected and the aqueous phase was extracted with EtOAc (100 ml). The combined organics were washed with saturated aqueous sodium chloride (100 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50-100% EtOAc/heptane then 5% methanol/EtOAc) to afford 736 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-hydroxy-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AY5029-001** as an off-white solid. LCMS (method D) retention time 1.19min, M/z = 587 (M + 1).

[00308] Scheme 1.10 Step 6



[00309] 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 6

[00310] 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).

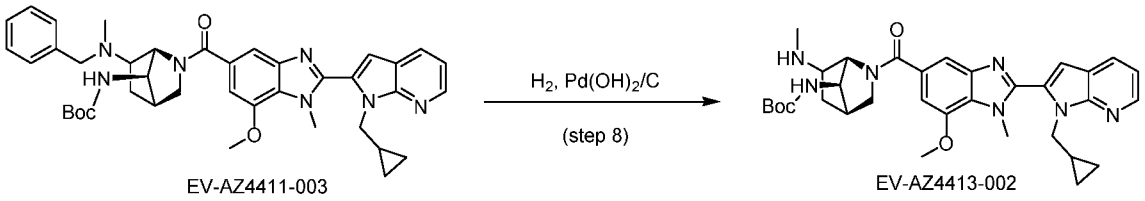
[00311] Scheme 1.10 Step 7

EV-AZ4415-001 EV-AZ4411-003

[00312] Tert-butyl N-[(1S,4R,7R)-6-[benzyl(methyl)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-AZ4411-003 – step 7

[00313] A solution 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**, 86%, 109 mg, 0.16 mmol) in DCE (1.5 ml) at room temperature was stirred with activated 3A molecular sieves. N-methyl-1-phenylmethanamine (41 µl, 0.32 mmol), sodium triacetoxyborohydride (STAB, 51 mg, 0.24 mmol) and acetic acid (10 µl, 0.17 mmol) were added and the reaction was stirred at room temperature for 72h. The reaction mixture was filtered and the molecular sieves were washed with DCM (20 ml). The DCM solution was washed with saturated aqueous sodium bicarbonate (15 ml) and the aqueous was re-extracted with DCM (3 x 15 ml). The combined organics were washed with saturated aqueous sodium chloride (15 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was dissolved in methanol (5 ml) and loaded on to a 2 g SCX-II cartridge. The cartridge was flushed through with methanol and 2.8 M ammonia in methanol. The relevant fractions were concentrated *in vacuo* to obtain 71 mg (52%) of tert-butyl N-[(1S,4R,7R)-6-[benzyl(methyl)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-AZ4411-003** as a colourless oil. LCMS (method H): retention time 4.43min and 4.83min, M/z = 690 (M + 1).

[00314] Scheme 1.10 Step 8



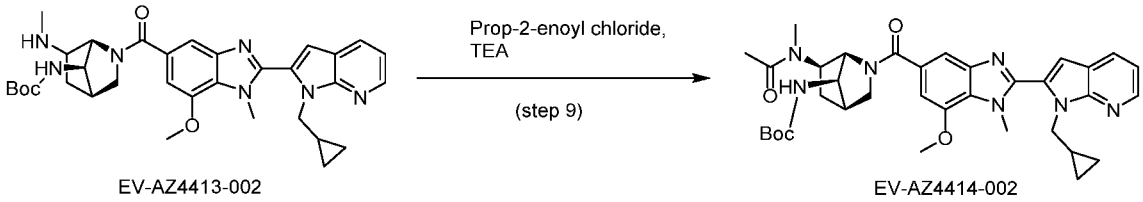
EV-AZ4411-003 EV-AZ4413-002

[00315] 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-(methylamino)-

2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AZ4413-002 – step 8

[00316] A solution of 0.05M tert-butyl N-[(1S,4R,6S,7R)-6-[benzyl(methyl)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-AZ4411-003**, 81%, 71 mg, 0.08 mmol) in methanol (2.1 ml) was subjected to H-Cube conditions (1 ml/min, 60 bar, 60°C, 2 passes) over a Pearlman's catalyst (20 % $Pd(OH)_2/C$) cartridge. The resulting solution was concentrated *in vacuo* to obtain 45 mg (60 %) 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-(methylamino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4413-002** as a yellow oil. LCMS (method D): retention time 1.08min, M/z = 600 (M + 1).

[00317] Scheme 1.10 Step 9



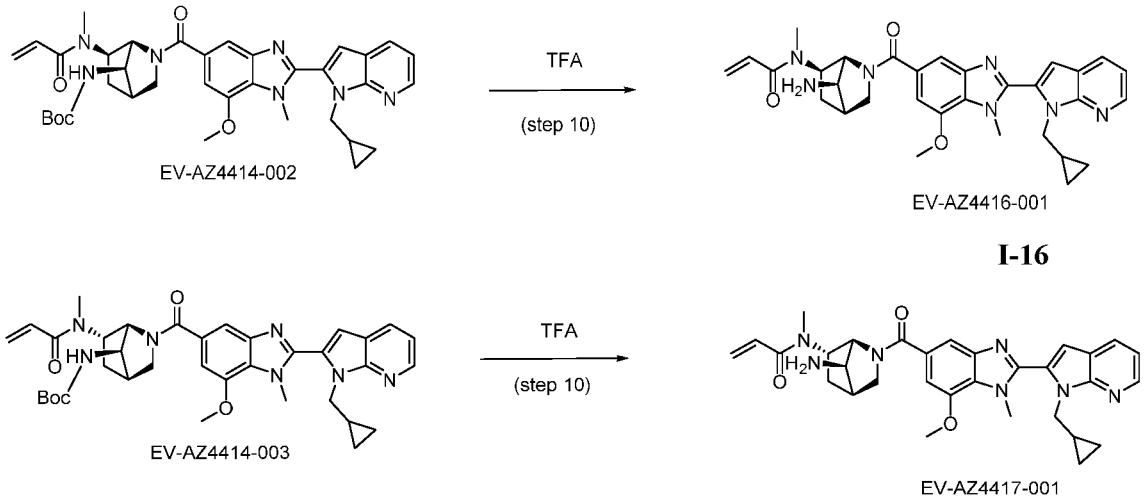
EV-AZ4413-002 EV-AZ4414-002

[00318] Tert-butyl N-[(1S,4R,6R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AZ4414-002 and 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-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AZ4414-003 - step 9

[00319] To a solution 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-(methylamino)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AZ4413-002**, 67%, 45 mg, 0.05 mmol) in dioxane (0.5 ml) was added triethylamine (14 µl, 0.1 mmol) followed by prop-2-enoyl chloride (9 µl, 0.11 mmol). The reaction mixture was stirred at room temperature for 50 minutes. Additional prop-2-enoyl chloride (5 ul) was added to the reaction and stirring was continued for an additional 1.5h. The resulting reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (acidic method) to obtain 14 mg (37%) of tert-butyl N-[(1S,4R,6R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4414-002** (chirality arbitrarily

assigned) as a white solid. LCMS (method A): retention time 3.19min, M/z = 654 (M + 1). 4.4 mg (12%) 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-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AZ4414-003** (chirality arbitrarily assigned) were also isolated as a white solid. LCMS (method A): retention time 3.29min, M/z = 654 (M + 1).

[00320] Scheme 1.10 Step 10



[00321] N-[(1S,4R,6R,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]-N-methylprop-2-enamide; trifluoroacetic acid I-16 (EV-AZ4416-001) (EOAI3478697) – step 10

[00322] To a stirred solution of tert-butyl N-[(1S,4R,6R,7R)-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-6-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AZ4414-002**, 14 mg, 0.02 mmol) in DCM (0.5 ml) was added TFA (20 µl, 0.26 mmol). The reaction was stirred at room temperature for 0.5h. Additional TFA (80 µl, 1.04 mmol) was added and the reaction was continued for 1h. The reaction mixture was concentrated *in vacuo*, re-dissolved in water and dried by lyophilization to afford 12 mg (78 %) of N-[(1S,4R,6R,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]-N-methylprop-2-enamide; trifluoroacetic acid **I-16 (EV-AZ4416-001) (EOAI3478697)** as a white solid. LCMS (method H): retention time 1.93min, M/z = 554 (M + 1).

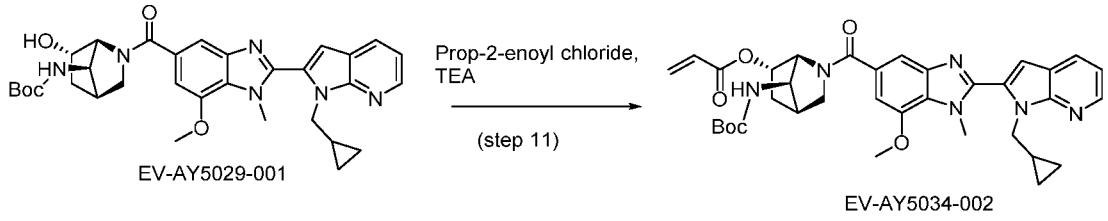
[00323] N-[(1S,4R,6S,7R)-7-amino-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-yl]-N-methylprop-2-enamide; trifluoroacetic acid I-17 (EV-AZ4417-001) (EOAI3478698) – step 10

[00324] 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-(N-methylprop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate (**EV-AZ4414-003**, 92%, 4.4 mg, 0.01 mmol) in DCM (0.4 ml) was added TFA (29 µl, 0.38 mmol). The reaction was stirred at room temperature for 2h. Additional TFA (20 µl, 0.26 mmol) was added and the reaction was continued for 30 minutes. The reaction mixture was concentrated *in vacuo*, re-dissolved in water and dried by lyophilization to afford 5 mg (quantitative) of 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]-N-methylprop-2-enamide; trifluoroacetic acid **I-17 (EV-AZ4417-001) (EOAI3478698)** as a sticky white solid. LCMS (method A): retention time 2.10min, M/z = 554 (M + 1).

[00325] Example 15. Synthesis 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-yl prop-2-enoate, I-15

[00326] (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 prop-2-enoate **I-15 (EV-AY5035-001) (EOAI3470264)** LCMS (method A): retention time 2.23 min, M/z = 541.3 (M+1) was synthesised according to the procedures described in Scheme 1 via synthesis of (1S,4R,6S,7R)-7-{[(tert-butoxy)carbonyl]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 prop-2-enoate **EV-AY5034-002** described in Scheme 1.10, step 11.

[00327] Scheme 1.10 Step 11



EV-AY5029-001

EV-AY5034-002

[00328] (1S,4R,6S,7R)-7-{[(Tert-butoxy)carbonyl]amino}-2-{2-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]-7-methoxy-1-methyl-1H-1,3-

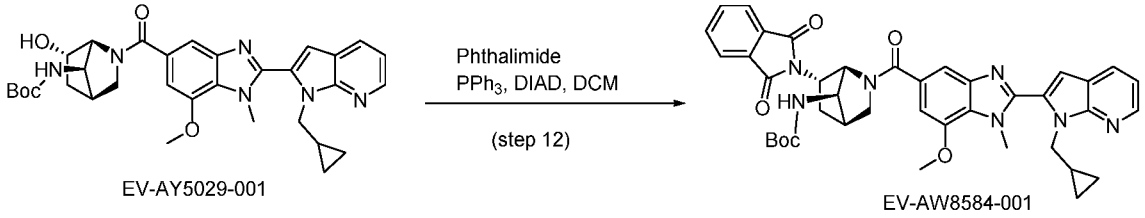
benzodiazole-5-carbonyl}-2-azabicyclo[2.2.1]heptan-6-yl prop-2-enoate (EV-AY5034-001) – step 11

[00329] To a cold solution (0°C) 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, 0.20 mmol) in DCM (2 ml) was added triethylamine (70 µl, 0.51 mmol) followed by prop-2-enoyl chloride (20 µl, 0.25 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1h. Triethylamine (70 µl, 0.51 mmol) was added followed by prop-2-enoyl chloride (40 µl, 0.50 mmol). The mixture was stirred at room temperature for 30 minutes. The reaction was quenched using saturated aqueous ammonium chloride (25 ml) and extracted using DCM (3 x 25 ml). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20-100% EtOAc/heptane) and by preparative HPLC (acidic method) to obtain 6 mg (18%) of (1S,4R,6S,7R)-7-{[(tert-butoxy)carbonyl]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 prop-2-enoate **EV-AY5034-002** as a white powder. LCMS (method D): retention time 1.25min, M/z = 641 (M + 1).

[00330] Example 16. Synthesis of 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]prop-2-enamide, I-14

[00331] 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]prop-2-enamide **I-14 (EV-AY4929-001) (EOAI3470263)** LCMS (method A): retention time 2.07 min, M/z = 540.3 (M+1) was synthesised according to procedures described in Scheme 1 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-(prop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8586-002** described in Scheme 1.10, steps 12-14.

[00332] Scheme 1.10 Step 12

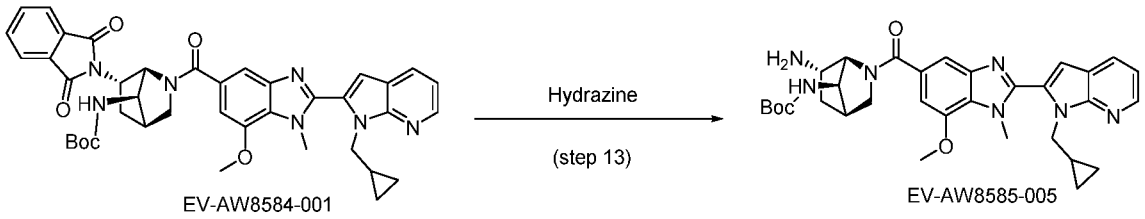


EV-AY5029-001 EV-AW8584-001

[00333] 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 12

[00334] 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).

[00335] Scheme 1.10 Step 13



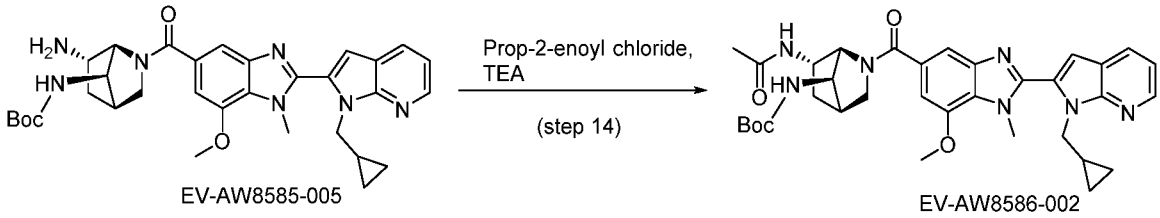
EV-AW8584-001 EV-AW8585-005

[00336] 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 13

[00337] 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).

[00338] Scheme 1.10 Step 14



[00339] 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-(prop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate EV-AW8586-002 – step 14

[00340] To a 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**, 92%, 75 mg, 0.12 mmol) in dioxane (2 ml) was added triethylamine (18 µl, 0.13 mmol) followed by prop-2-enoyl chloride (10 µl, 0.13 mmol). The reaction mixture was stirred at room temperature for 30 minutes, concentrated *in vacuo* and the resulting residue was purified by preparative HPLC (acidic method) to obtain 44 mg (59%) 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-(prop-2-enamido)-2-azabicyclo[2.2.1]heptan-7-yl]carbamate **EV-AW8586-002** as a white solid. LCMS (method A): retention time 3.13min, M/z = 640 (M + 1).

Biological Assays

[00341] Example 17. PAD4 RapidFire mass spectrometry (RFMS) activity assay

[00342] Compounds of the present invention were assayed as inhibitors of PAD4 using the assay protocol described below.

[00343] Compounds were solubilized 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 °C. 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.

[00344] **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} of 0.1 – 1 µM; compounds having an activity designated as "B" provided an IC_{50} of 1 – 5 µM; compounds having an activity designated as "C" provided an IC_{50} of 5 – 10 µM; and compounds having an activity designated as "D" provided an IC_{50} of > 10 µM. The term $pIC_{50} = -\log(IC_{50})$. Compounds having an activity designated as "E" provided a pIC_{50} of 1 – 4; compounds having an activity designated as "F" provided a pIC_{50} of 4 – 5; and compounds having an activity designated as "G" provided a pIC_{50} of > 5. "NA" stands for "not assayed."

[00345] Example 18. Covalent modification study using MS (Mass Spectrometry)

[00346] Mass spectrometry was used to analyze covalent modification of protein by selected inhibitors. Recombinant human PAD4 was used at 4 mg/ml in 20 mM Tris pH7.6, 400 mM NaCl, 5 mM TCEP. Where applicable, buffer was supplemented with 5mM $CaCl_2$ to determine Calcium sensitivity of modification. Inhibitors were dissolved in DMSO at final concentrations of 0.2 mM to 5 mM and incubated with protein at 27°C for 16 hours prior to analysis. Control experiments were performed with protein and DMSO in absence of inhibitor. Samples were centrifuged for 15 seconds at 10000 rpm at room temperature immediately prior to analysis using a Waters LCT-Premier TOF mass spectrometer, using a mobile phase from 5% to 80% acetonitrile in water supplemented by 0.1% formic acid.

[00347] Example 19. Inactivation kinetics

[00348] Covalent binding of an active compound to the target enzyme leads to time dependent loss of the enzyme activity. The rate of inactivation depends on the inhibitor concentration ([I]) and can be quantified under pseudo-first order conditions ([I]>>[hPAD4]).

[00349] Inactivation kinetics experiments were performed in 384-well polystyrene plates at 37 °C. Compounds (10 - 200 µM) and hPAD4 (4 µM) solutions were pre-incubated in assay buffer (100 mM Tris-HCl, pH 7.6) containing 10 mM $CaCl_2$ and 2 mM DTT for 10 minutes to reach a temperature of 37 °C. Equal volumes (10 µl) of compound and hPAD4 solutions were mixed at various time points between 0 and 70 minutes. At 70 minutes time point, the inactivation solution was diluted 10-fold in enzymatic reaction buffer (100 mM Tris-HCl, pH 7.6) containing 166.7 µM peptide substrate (H-TSTGGRQGSHH-$CONH_2$), 1.1 mM $CaCl_2$ and 2 mM DTT. After 30 minutes of incubation at 37 °C the enzymatic reaction was quenched by 3-fold dilution in 5% TCA solution in ACN. Substrate peptide arginine citrullination was determined by solid phase extraction mass spectrometry (SPE-MS). An Agilent RapidFire 300 equipped with a HILIC (H1) cartridge was used for sampling with solvents 0.1% TFA in H_2O/ACN (20/80) for P1 and 0.1% TFA in H_2O/ACN (50/50) for P2 and P3. Substrate and product peptide were detected using a coupled Agilent 6460 QQQ and multiple reaction monitoring (MRM) on transitions 562.3/969.4 and 562.8/541, respectively, in positive ion mode. DMSO content of the inactivation reaction was 1%. Cl-amidine (100 mM, final concentration during enzyme inactivation reaction) and 1% DMSO were used as positive and negative controls of the inactivation reaction, respectively.

[00350] Pseudo-first order rate constants of inactivation reaction, k_{obs}, were determined by fitting the time dependent loss of residual hPAD4 activity, A_{res}, with equation: $A_{res}(t) =$

$e^{-kobs * t}$. A plot of the pseudo-first order rate constants versus molar concentrations of the inhibitors allowed determination of the kinetic reaction constants: k_{inact} – maximum rate of inactivation at infinite [I]; K_I – inhibitor concentration, at which rate of inactivation is equal to $1/2k_{inact}$; k_{inact}/ K_I.

[00351] Certain compounds of the present invention were assayed according to the procedures described above and were found to covalently modify PAD4.

[00352] **Table 3**, below, shows the activity of selected compounds of this invention in the covalent modification assay described above. The compound numbers correspond to the compound numbers in **Table 1**.

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	B	G	B	G
I-2	A	G	A	G
I-3	D	E	D	F
I-4	D	F	D	F
I-5	B	G	A	G

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-6	D	E	NA	NA
I-7	D	E	NA	NA
I-8	C	G	C	F
I-9	B	G	A	G
I-10	D	F	D	F
I-11	D	F	NA	NA
I-12	D	F	NA	NA
I-13	D	E	NA	NA

Compound #	hPAD4 RFMS IC_{50} μM	hPAD4 RFMS pIC_{50}	mPAD4 RFMS IC_{50} μM	mPAD4 RFMS pIC_{50}
I-14	B	G	A	G
I-15	A	G	NA	NA
I-16	D	E	NA	NA
I-17	D	E	NA	NA

Table 3. Covalent Modification Study: Inactivation Kinetics*

Compound #	k_{inact} (min^{-1})	K_i (μM)	k_{inact}/K_i ($min^{-1}M^{-1}$)
I-1	0.3414	182.3	1872
I-2	0.6469	89.9	7801
I-5	0.9225	181.4	5085

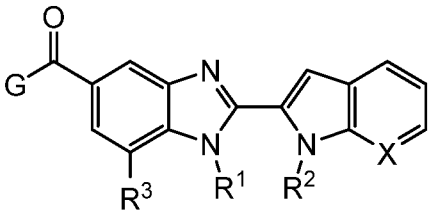
Compound #	k_{inact} (min^{-1})	K_i (μM)	k_{inact}/K_i ($min^{-1}M^{-1}$)
I-8	0.0563	39.63	1420
I-9	0.368	165	2231

*hPAD4 isoform; Ca^{++} concentration = 10 mM

CLAIMS

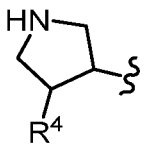
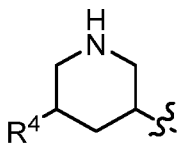
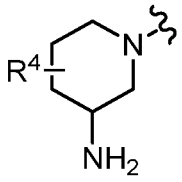
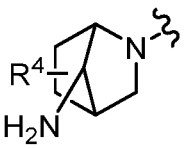
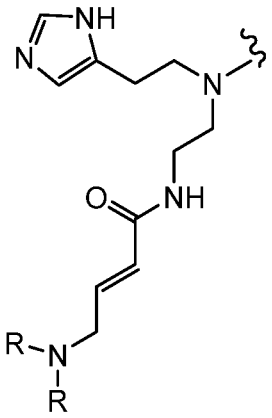
We claim:

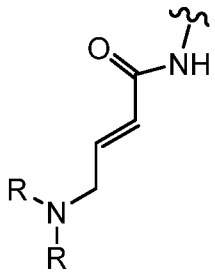
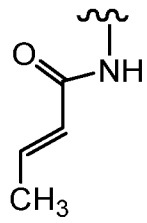
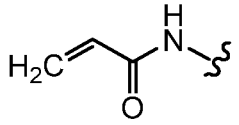
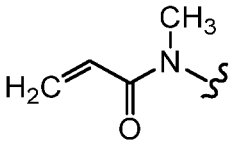
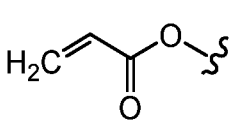
1. A compound of formula **I**



I

or a pharmaceutically acceptable salt thereof, wherein:

G is  ,  ,  ,  , or  ;

each R^4 is independently selected from  ,  ,  ,  , or  ;

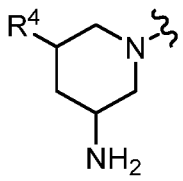
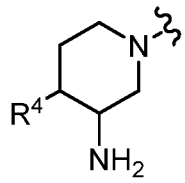
R^1 is hydrogen or C_{1-6} aliphatic;

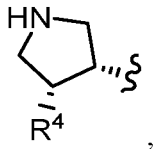
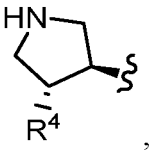
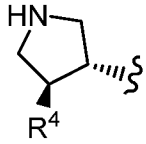
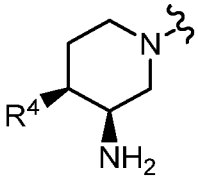
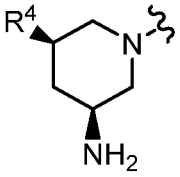
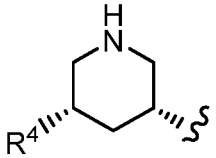
R^2 is hydrogen or C_{1-10} aliphatic;

X is selected from N or CH;

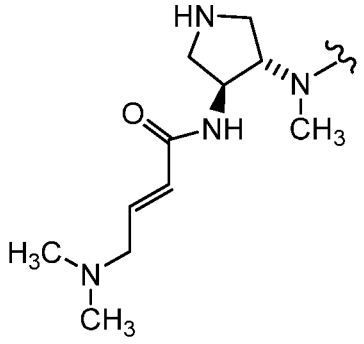
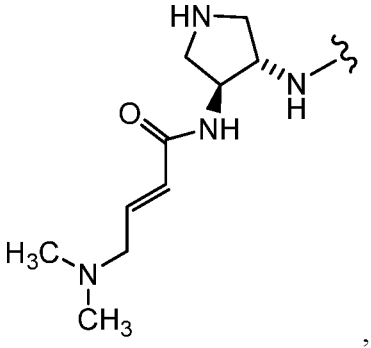
R^3 is –R, or –OR; and

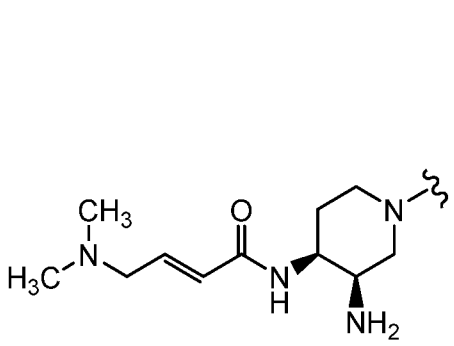
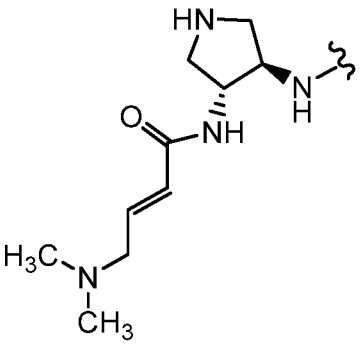
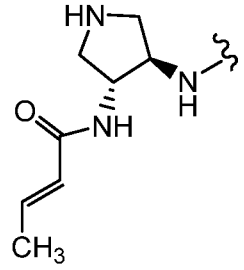
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with 1-3 fluorine atoms.

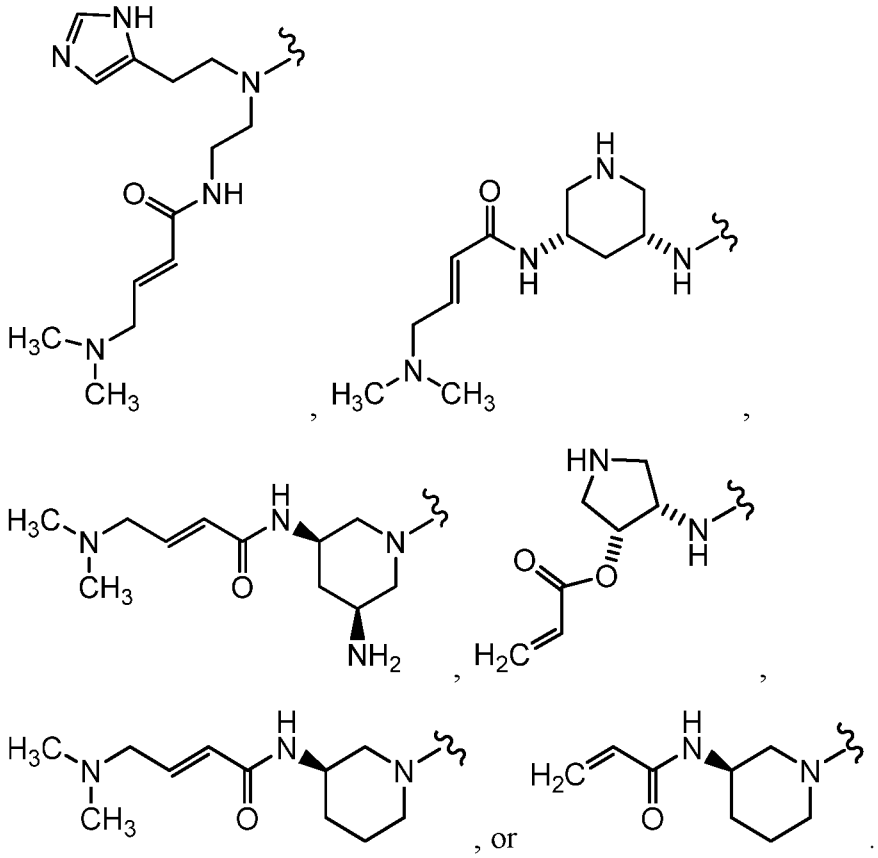
2. The compound according to claim 1, wherein G is  or  .

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

4. The compound according to claim 1, wherein G is selected from

 ,  ,

 ,  ,  ,



5. The compound according to any one of claims 1 through 4, wherein R^1 is methyl.

6. The compound according to any one of claims 1 through 5, wherein R^2 is C_{1-10} aliphatic.

7. The compound according to claim 6, wherein R^2 is -CH_2-cyclopropyl.

8. The compound according to any one of claims 1 through 7, wherein X is N.

9. The compound according to any one of claims 1 through 7, wherein X is CH.

10. The compound according to claim 1, wherein said compound is selected from those set forth in Table 1, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutically acceptable composition comprising the compound according to any of claims 1 through 10, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

12. The composition according to claim 11, in combination with an additional therapeutic agent.

13. 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 10.

14. 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 12.

15. The method according to claim 14, wherein said subject is a human subject.

18. The method according to claim 14, wherein said subject is a veterinary subject.

19. The method according to claim 15, 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.

20. The method according to claim 15, 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/US2017/044194

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D401/14 A61K31/437 A61K31/4545 A61K31/4184
A61P35/00 A61P35/02 A61P37/00 A61P31/18 A61P29/00
A61P17/00 A61P9/00 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

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 LTD [GB]; ATKINSON STEPHEN JOHN [GB]; BARKER MICHAEL DAVID) 30 January 2014 (2014-01-30) claims 1, 20-22 page 1, line 3 - line 9 page 27, line 21 - line 24 -----	1-20
A	HUW D LEWIS ET AL: "Inhibition of PAD4 activity is sufficient to disrupt mouse and human NET formation", NATURE CHEMICAL BIOLOGY, vol. 11, no. 3, 26 January 2015 (2015-01-26), pages 189-191, XP055293192, Basingstoke ISSN: 1552-4450, DOI: 10.1038/nchembio.1735 page 190; figure 1 -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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
13 November 2017	06/12/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brandstetter, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/044194

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CN 104470919 A	25-03-2015
		CY 1118524 T1	12-07-2017
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		US 2017119750 A1	04-05-2017
		WO 2014015905 A1	30-01-2014