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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/002057 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *A61K 31/4439* (2006.01)
C07D 403/14 (2006.01) *A61P 27/00* (2006.01)
C07D 471/04 (2006.01) *A61P 9/00* (2006.01)
C07D 417/14 (2006.01) *A61P 11/00* (2006.01)
A61K 31/444 (2006.01) *A61P 19/00* (2006.01)
A61K 31/4745 (2006.01) *A61P 37/00* (2006.01)
A61K 31/497 (2006.01) *A61P 3/00* (2006.01)

(21) International Application Number:
PCT/IB2013/055299

(22) International Filing Date:
27 June 2013 (27.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/665,477 28 June 2012 (28.06.2012) US
61/774,241 7 March 2013 (07.03.2013) US

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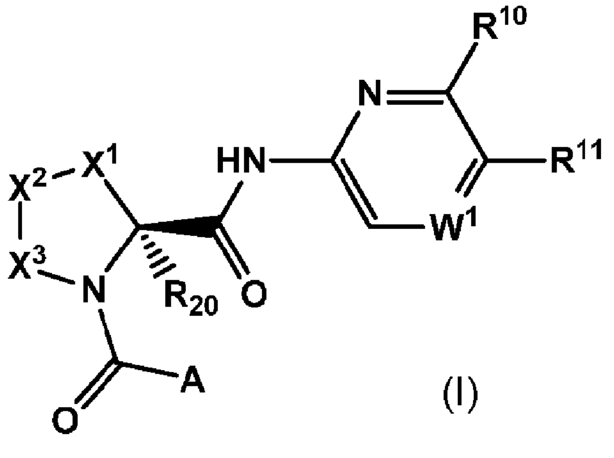
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,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

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

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: PYRROLIDINE DERIVATIVES AND THEIR USE AS COMPLEMENT PATHWAY MODULATORS



(I)

(57) **Abstract**: The present invention provides a compound of formula I: (I) a method for manufacturing the compounds of the invention, and its therapeutic uses as complement alternative inhibitors for the treatment of ocular diseases. The present invention further provides a combination of pharmacologically active agents and a pharmaceutical composition.

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PYRROLIDINE DERIVATIVES AND THEIR USE AS COMPLEMENT PATHWAY MODULATORS

FIELD OF THE INVENTION

The invention relates to the inhibition of the complement alternative pathway and particularly to inhibition of Factor D, in patients suffering from conditions and diseases associated with \complement alternative pathway activation such as age-related macular degeneration, diabetic retinopathy and related ophthalmic diseases.

BACKGROUND OF THE INVENTION

The complement system is a crucial component of the innate immunity system and comprises a group of proteins that are normally present in an inactive state. These proteins are organized in three activation pathways: the classical, the lectin, and the alternative pathways (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363-391). Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertase and the C5-convertase. The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including gram-negative bacteria. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials).

Factor D may be a suitable target for the inhibition of this amplification of the complement pathways because its plasma concentration in humans is very low (about 1.8 μg/mL), and it has been shown to be the limiting enzyme for activation of the alternative complement pathway (P.H. Lesavre and H.J. Müller-Eberhard. J. Exp. Med., 1978; 148: 1498-1510; J.E. Volanakis et al., New Eng. J. Med., 1985; 312:395-401).

Macular degeneration is a clinical term that is used to describe a family of diseases that are characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. In the center of the retina is the macula lutea, which is about 1/3 to ½ cm in diameter. The macula provides detailed vision, particularly in the center (the fovea), because the cones are higher in density and because of the high ratio of ganlion cells to photoreceptor cells. Blood vessels, ganglion cells, inner nuclear layer and cells, and the plexiform layers are all displaced to the side (rather than resting above the photoreceptor cells), thereby allowing light a more direct path to the cones. Under the retina is the choroid, a part of the uveal tract, and the retinal pigmented epithelium (RPE), which is between the neural retina and the choroid. The choroidal blood vessels provide nutrition to the retina and its visual cells.

Age-related macular degeneration (AMD), the most prevalent form of macular degeneration, is associated with progressive loss of visual acuity in the central portion of the visual field, changes in color vision, and abnormal dark adaptation and sensitivity. Two principal clinical manifestations of AMD have been described as the dry, or atrophic, form and the neovascular, or exudative, form. The dry form is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. About 10-20% of these AMD patients progress to the second form of AMD, known as neovascular AMD (also referred to as wet AMD).

Neovascular AMD is characterized by the abnormal growth of blood vessels under the macula and vascular leakage, resulting in displacement of the retina, hemorrhage and scarring. This results in a deterioration of sight over a period of weeks to years. Neovascular AMD cases originate from intermediate or advanced dry AMD. The neovascular form accounts for 85% of legal blindness due to AMD. In neovascular AMD, as the abnormal blood vessels leak fluid and blood, scar tissue is formed that destroys the central retina.

The new blood vessels in neovascular AMD are usually derived from the choroid and are referred to as choroidal neovascularizaton (CNV). The pathogenesis of new choroidal vessels is poorly understood, but such factors as inflammation, ischemia, and local production of angiogenic factors are thought to be important. A published study suggests that CNV is caused by complement activation in a mouse laser model (Bora P.S., J. Immunol. 2005;174; 491-497).

Human genetic evidence implicates the involvement of the complement system, particularly the alternative pathway, in the pathogenesis of Age-related Macular Degeneration (AMD). Significant associations have been found between AMD and polymorphisms in complement factor H (CFH) (Edwards AO, et al. Complement factor H polymorphism and age-related macular degeneration. Science. 2005 Apr 15;308(5720):421-4; Hageman GS, et al Acommon haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7227-32; Haines JL, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005 Apr 15;308(5720):419-21; Klein RJ, et al Complement factor H polymorphism in age-related macular degeneration. Science. 2005 Apr 15;308(5720):385-9; Lau LI, et al. Association of the Y402H polymorphism in complement factor H gene and neovascular age-related macular degeneration in Chinese patients. Invest Ophthalmol Vis Sci. 2006 Aug;47(8):3242-6; Simonelli F, et al. Polymorphism p.402Y>H in the complement factor H protein is a risk factor for age related macular degeneration in an Italian population.Br J Ophthalmol. 2006 Sep;90(9):1142-5; and Zareparsi S, et al Strong association of the Y402H variant in complement factor H at 1q32with susceptibility to age-related macular degeneration. Am J Hum Genet. 2005 Jul;77(1):149-53. Complement factor B (CFB) and complement C2 (Gold B, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006 Apr;38(4):458-62 and Jakobsdottir J, et al. C2 and CFB genes inage-related maculopathy and joint action with CFH and LOC387715 genes. PLoS One. 2008 May 21;3(5):e2199), and most recently in complement C3 (Despriet DD, et al Complement component C3 and risk of age-related macular degeneration. Ophthalmology. 2009 Mar;116(3):474-480.e2; Maller JB, et al Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007 Oct;39(10):1200-1 and Park KH, et al Complement component 3 (C3) haplotypes and risk of advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009 Jul;50(7):3386-93. Epub 2009 Feb 21. Taken together, the genetic variations in the alternative pathway components CFH, CFB, and C3 can predict clinical outcome in nearly 80% of cases.

Currently there is no proven medical therapy for dry AMD and many patients with neovascular AMD become legally blind despite current therapy with anti-VEGF agents such as Lucentis. Thus, it would be desirable to provide therapeutic agents for the treatment or prevention of complement mediated diseases and particularly for the treatment of AMD.

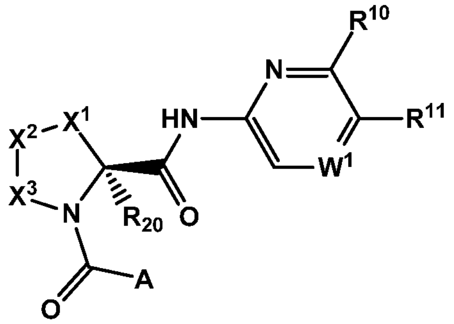
SUMMARY OF THE INVENTION

The present invention provides compounds that modulate, and preferably inhibit, activation of the alternative complement pathway. In certain embodiments, the present invention provides compounds that modulate, and preferably inhibit, Factor D activity and/or Factor D mediated complement pathway activation. Such Factor D modulators are preferably high affinity Factor D inhibitors that inhibit the catalytic activity of complement Factor Ds, such as primate Factor D and particularly human Factor D.

The compounds of the present invention inhibit or suppress the amplification of the complement system caused by C3 activation irrespective of the inital mechanism of activation (including for example activation of the classical, lectin or ficolin pathways).

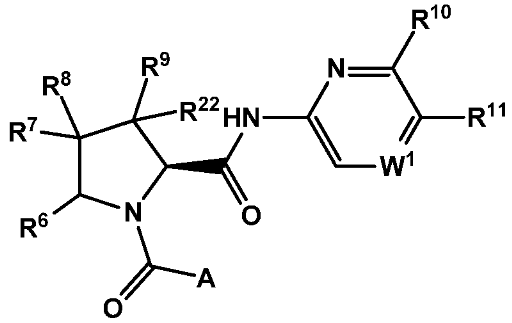
Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

Within certain aspects, Factor D modulators provided herein are compounds of Formula I and salts thereof:



(I)

Within certain other aspects, Factor D modulators provided herein are compounds of Formula I and salts thereof:



(II)

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the definition of formula (I) or formula (II) or subformulae thereof and one or more pharmaceutically acceptable carriers.

In another embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I) or formula (II) or subformulae thereof and one or more therapeutically active.

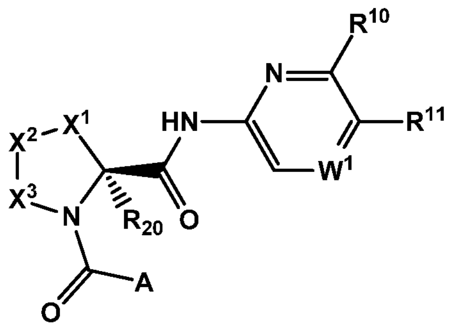
The invention further provides methods of treating or preventing complement mediated diseases, the method comprising the steps of identifying a patient in need of complement modulation therapy and administering a compound of Formula (I) or formula (II) or a subformulae thereof. Complement mediated diseases include ophthalmic diseases (including early or neovascular age-related macular degeneration and geographic atrophy), autoimmune diseases (including arthritis, rheumatoid arthritis), Respiratory diseases, cardiovascular diseases.

Other aspects of the invention are discussed *infra*.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention provides compounds that modulate Factor D activation and/or Factor D-mediated signal transduction of the complement system. Such compounds may be used *in vitro* or *in vivo* to modulate (preferably inhibit) Factor D activity in a variety of contexts.

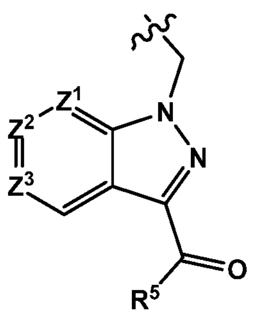
In a first embodiment, the invention provides compounds of Formula I and pharmaceutically acceptable salts thereof, which modulate the alternative pathway of the complement system. Compounds of Formula I are represented by the structure:



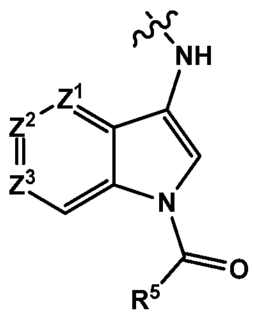
(I)

wherein

A is a group selected from:



and



;

Z^1 is $C(R^1)$ or N;

Z^2 is $C(R^2)$ or N;

Z^3 is $C(R^3)$ or N, wherein at least one of Z^1, Z^2 or Z^3 is not N;

R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^AR^B$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^CR^D, cyano, CO_2H, $CONR^AR^B$, SO_2C_1-C_6alkyl, and SO_2NH_2, $SO_2NR^AR^B$, C_1-C_6alkoxycarbonyl, $-C(NR^A)NR^CR^D$, C_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, cyano, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl,

$C(O)NR^AR^B$, NR^CR^D, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 or 3 ring heteroatoms selected from N, O or S, and wherein optional phenyl and heteroaryl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 is C_1-C_4alkyl, hydroxyC_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, amino, methylamino;

X^1 is CR^9R^{22} or sulfur;

X^2 is CR^7R^8, oxygen, sulfur, N(H) or N(C_1-C_6alkyl), wherein at least one of X^1 and X^2 is carbon; or

X^1 and X^2, in combination, forms an olefin of the formula $-C(R^7)=C(H)$- or $-C(R^7)=C(C_1$-C_4alkyl)-, wherein the $C(R^7)$ is attached to X^3;

X^3 is $(CR^6R^{21})_q$ or N(H) wherein q is 0,1 or 2, wherein X^3 is CR^6R^{21} or $(CR^6R^{21})_2$ when either X^1 or X^2 is sulfur or X^2 is oxygen; or

X^2 and X^3, taken in combination, are –N=C(H)– or –N=C(C_1-C_4alkyl)– in which the C(H) or C(C_1-C_4alkyl) is attached to X^1;

R^6 is selected at each occurrence from hydrogen and C_1-C_6alkyl;

R^7 is hydrogen, halogen, hydroxy, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, haloC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^8 is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^AR^B, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^AR^B, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^9 is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^AR^B, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and OC(O)NR^CR^D each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^AR^B;

R^{20} is hydrogen or C_1-C_6alkyl;

R^{21} is selected at each occurrence from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{22} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

CR^7R^8, taken in combination forms a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^7 and R^8, taken in combination, form an exocyclic methylidene (=CH_2);

R^7 and R^{22} or R^8 and R^9, taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^AR^B;

R^6 and R^7 or R^8 and R^{21}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^AR^B; or

R^{20} and R^{22} taken in combination form a fused 3 carbocyclic ring system;

R^9 and R^{21} taken in combination form a form 1 to 3 carbon alkylene linker;

R^7 and R^{20} taken in combination form 1 to 3 carbon alkylene linker;

R^{10} is halogen, C_1-C_4alkyl, haloC_1-C_2alkyl or haloC_1-C_2alkoxy or C_1-C_2alkoxy;

R^{11} is hydrogen, halogen or C_1-C_4alkyl;

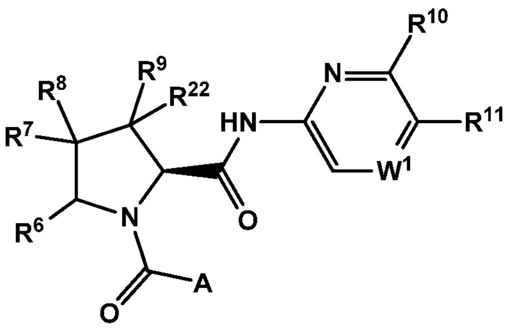
W^1 is $C(R^{12})$ or N;

R^{12} is halogen, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, hydroxy and CO_2H, CO_2Me, or $CONR^AR^B$;

R^A and R^B are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^AR^B, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy; and

R^C and R^D, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl.

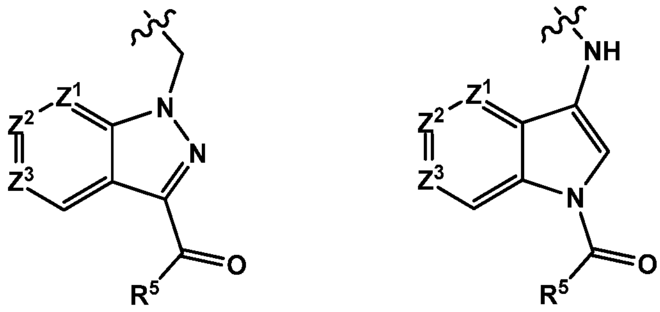
In a second embodiment, the invention provides compounds of Formula II and pharmaceutically acceptable salts thereof, which modulate the alternative pathway of the complement system. Compounds of Formula II are represented by the structure:



(II)

wherein

A is a group selected from:



and ;

Z^1 is $C(R^1)$ or N;

Z^2 is $C(R^2)$ or N;

Z^3 is $C(R^3)$ or N, wherein at least one of Z^1, Z^2 or Z^3 is not N;

R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^AR^B$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^CR^D, cyano, CO_2H, $CONR^AR^B$, SO_2C_1-C_6alkyl, and SO_2NH_2, $SO_2NR^AR^B$, C_1-C_6alkoxycarbonyl, -$C(NR^A)NR^CR^D$, C_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, cyano, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^AR^B$, NR^CR^D, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 or 3 ring heteroatoms selected from N, O or S, and wherein optional phenyl and heteroaryl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 is C_1-C_4alkyl, hydroxyC_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, amino, methylamino;

R^6 is hydrogen;

R^7 is hydrogen or fluoro;

R^8 is hydrogen, methyl or hydroxymethyl;

R^9 is hydrogen, halogen, hydroxy or C_1-C_4alkoxy ; or

R^6 and R^7, taken in combination, form a cyclopropane ring; or

R^8 and R^9, taken in combination, form a cyclopropane ring;

R^{22} is hydrogen or fluoro;

R^{10} is halogen, C_1-C_4alkyl, haloC_1-C_2alkyl or haloC_1-C_2alkoxy

R^{11} is hydrogen, halogen or C_1-C_4alkyl;

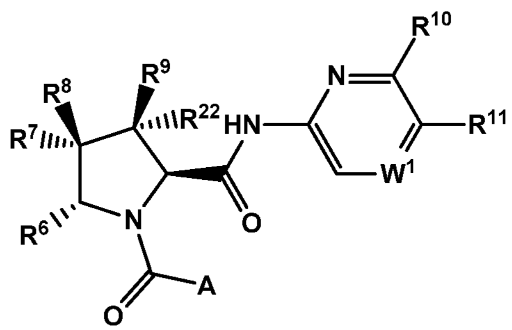
W^1 is N or CR^{12};

R^{12} is halogen, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, hydroxy and CO_2H, CO_2Me, or $CONH_2$;

R^A and R^B are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^AR^B, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy; and

R^C and R^D, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl.

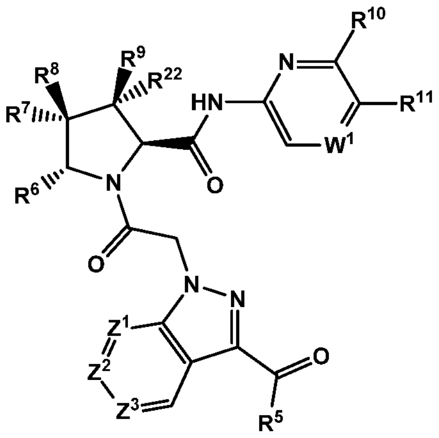
In certain aspects of embodiments one or two, compounds of Formula II are provided which are represented by Fromula IIa



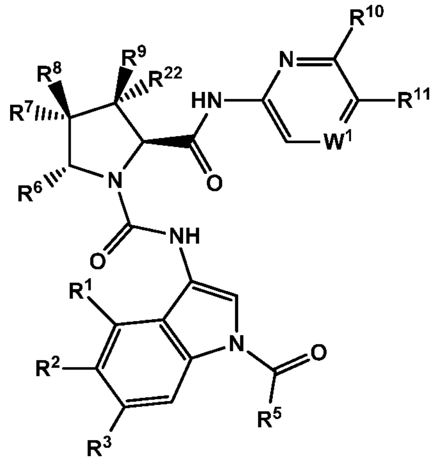
(IIa).

Certain compounds of Formula IIa include those in which R^6, R^8 and R^9 are hydrogen and R^7 and R^{22} are halogen, preferably fluorine.

In a third embodiment, compounds, or salts thereof, according to embodiment one or two are provided. Compounds of the third embodiment are represented by Formula III or Formula IV:



or



(III) (IV).

In a fourth embodiment, a compound or salt thereof according to any one of embodiments one to three is provided in which Z^1 is N or CR^1; Z^2 is N or CR^2 and Z^3 is N or CR^3 wherein at least one of Z^1, Z^2 and Z^3 are not N;

R^1 is hydrogen, halogen or C_1-C_4alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, CO_2H, C_1-C_4alkyl and C_1-C_4alkoxy;

R^3 is selected from the group consisting of hydrogen, halogen, CO_2H, C_1-C_4alkyl, C_3-C_5cycloalkyl, haloC_1-C_4alkyl and C_1-C_4alkoxy, wherein the alkoxy is optionally substituted by pyridyl or pyrimidinyl and

R^5 is amino or C_1-C_4alkyl.

In a fifth embodiment, a compound or salt thereof according to any one of embodiments one to four is provided in which R^6 and R^7 taken in combination form a cyclopropane ring;

R^8 is hydrogen, methyl or hydroxymethyl; and

R^9 is hydrogen.

In a sixth embodiment, a compound or salt thereof according to any one of embodiments one to four is provided in which R^6 and R^7 are hydrogen; and

R^8 and R^9 taken in combination form a cyclopropane ring

In a seventh embodiment, a compound or salt thereof according to any one of embodiments one to four is provided in which R^6 is hydrogen;

R^8 is hydrogen or methyl;

R^7 is fluoro;

R^9 is hydrogen or methoxy; and

R^{22} is hydrogen or fluoro.

In an eighth embodiment, a compound or salt thereof according to any one of embodiments one to six is provided in which W^1 is CH or C(OMe);

R^{10} is bromo, chloro, iodo, trifluoromethyl or difluoromethoxy; and

R^{11} is hydrogen.

In a ninth embodiment, a compound or salt thereof according to any one of embodiments one to six is provided in which W^1 is N;

R^{10} is bromo or trifluoromethyl; and

R^{11} is hydrogen or methyl.

In a tenth embodiment, a compound or salt thereof according to any one of embodiments one or two is provided in which the compound is selected from the group consisting of

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide;

5-Ethyl-1-{2-oxo-2-[(1R,3S,5R)-3-(6-trifluoro methyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridazine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-fluoromethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide;

(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-difluoro methoxy-pyridin-2-yl)-amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-5-methyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-methyl-1H-indazole-3-carboxylic acid amide;

1-{2-Oxo-2-[(1R,3S,5R)-3-(6-trifluoromethyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-fluoro-1H-indazole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-5-methyl-pyrazin-2-yl)-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-trifluoro methyl-pyrazin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-trifluoromethyl-pyrazin-2-yl)-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

1-{2-[(2S,4R)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Chloro-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Iodo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-4-methoxy-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-5-methyl-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyridin-2-yl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide]-1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyrazin-2-yl)-amide];

(1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyridin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(fluoromethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

(S)-N-(6-bromopyridin-2-yl)-3-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl) thiazolidine-2-carboxamide;

1-(2-((1R,3S,5R)-3-((6-bromopyridin-2-yl) carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-N-methyl-1H-indazole-3-carboxamide;

1-(2-((2R,3S)-2-((6-bromopyridin-2-yl) carbamoyl)-3-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide;

N-(6-bromopyridin-2-yl)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl)-2-azabicyclo[2.1.1]hexane-3-carboxamide;

5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyrazin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

(2R,3R,4S)-N2-(6-bromopyridin-2-yl)-N1-(1-carbamoyl-1H-indol-3-yl)-3,4-difluoropyrrolidine-1,2-dicarboxamide; and

(S)-N2-(6-bromopyridin-2-yl)-N3-(1-carbamoyl-1H-indol-3-yl)thiazolidine-2,3-dicarboxamide.

Some of the compounds listed *supra* have been prepared in enantiopure form (i.e., greater than about 80%, greater than 90% or greater than 95% enantiomeric purity). Other compounds have been isolated as mixtures of stereoisomers, e.g., diastereoisomeric mixtures of two or more diastereoisomers. Each compound isolated as a mixture of stereoisomers has been marked as mixture in the foregoing list.

In one embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I), (II), (III), (IV) or subformulae thereof or any one of the specifically disclosed compounds of the invention and one or more therapeutically active agents (preferably selected from those listed *infra*).

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term “alkyl” refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

As used herein, the term “alkylene” refers to divalent alkyl group as defined herein above having 1 to 20 carbon atoms. It comprises 1 to 20 carbon atoms, Unless otherwise provided, alkylene refers to moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkylene include, but are not limited to, methylene, ethylene, *n*-propylene, *iso*-propylene, *n*-butylene, *sec*-butylene, *iso*-butylene, *tert*-butylene, *n*-pentylene, isopentylene, neopentylene, *n*-hexylene, 3-methylhexylene, 2,2-dimethylpentylene, 2,3-dimethylpentylene, *n*-heptylene, *n*-octylene, *n*-nonylene, *n*-decylene and the like.

As used herein, the term “haloalkyl” refers to an alkyl as defined herein, that is substituted by one or more halo groups as defined herein. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the polyhaloalkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

The term "aryl" refers to an aromatic hydrocarbon group having 6-20 carbon atoms in the ring portion. Typically, aryl is monocyclic, bicyclic or tricyclic aryl having 6-20 carbon atoms.

Furthermore, the term "aryl” as used herein, refers to an aromatic substituent which can be a single aromatic ring, or multiple aromatic rings that are fused together.

Non-limiting examples include phenyl, naphthyl or tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as alkyl, trifluoromethyl, cycloalkyl, halogen, hydroxy, alkoxy, acyl, alkyl-C(O)-O-, aryl-O-, heteroaryl-O-, amino, thiol, alkyl-S-, aryl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, carbamoyl, alkyl-S(O)-, sulfonyl, sulfonamido, phenyl, and heterocyclyl.

As used herein, the term “alkoxy” refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1-7, more preferably about 1-4 carbons.

As used herein, the term “heterocyclyl” or “heterocyclo” refers to a saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-

membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, and the like.

The term “heterocyclyl” further refers to heterocyclic groups as defined herein substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;
(b) hydroxy (or protected hydroxy);
(c) halo;
(d) oxo, i.e., =O;
(e) amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxyl;
(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;
(j) alkyl-O-C(O)-;
(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl or sulfonamido;
(o) aryl;
(p) alkyl-C(O)-O-;
(q) aryl-C(O)-O-;
(r) aryl-S-;
(s) aryloxy;
(t) alkyl-S-;
(u) formyl, i.e., HC(O)-;
(v) carbamoyl;
(w) aryl-alkyl-; and
(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 9 ring carbon atoms or between 3 and 7 ring carbon atoms, each of which can be optionally substituted by one, or two, or three, or more substituents independently selected from the group consisting of alkyl, halo, oxo, hydroxy, alkoxy, alkyl-C(O)-, acylamino, carbamoyl, alkyl-NH-, $(alkyl)_2N$-, thiol, alkyl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, sulfonyl, sulfonamido, sulfamoyl, and heterocyclyl. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like. Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like. Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

As used herein, the term “aryloxy” refers to both an -O-aryl and an -O-heteroaryl group, wherein aryl and heteroaryl are defined herein.

As used herein, the term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring system (e.g., 5-7 membered monocycle or an 8-10 memberred bicycle) or a 5-7 membered ring system. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl.

The term “heteroaryl” also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include 1-, 2-, 3-, 5-, 6-, 7-, or 8- indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8- purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9- benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroary groups include, but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, and 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

A heteroaryl group may be substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;
(b) hydroxy (or protected hydroxy);
(c) halo;
(d) oxo, i.e., =O;
(e) amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxyl;
(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;
(j) alkyl-O-C(O)-;
(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl or sulfonamido;
(o) aryl;
(p) alkyl-C(O)-O-;
(q) aryl-C(O)-O-;
(r) aryl-S-;
(s) aryloxy;
(t) alkyl-S-;
(u) formyl, i.e., HC(O)-;
(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the term “optionally substituted” unless otherwise specified refers to a group that is unsubstituted or is substituted by one or more, typically 1, 2, 3 or 4, suitable non-hydrogen substituents, each of which is independently selected from the group consisting of:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term “isomers” refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate. The asterisk (*) indicated in the name of a compound designate a racemic mixture. "Diastereoisomers” or “diastereomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, , hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

In certain embodiments, selective deuteration of compounds of Formula (I) or formula (II) include deuteration of R^5, when R^5 is alkanoyl, e.g., $C(O)CD_3$. In other embodiments, certain substitutents on the proline ring are selectively deuterated. For example, when any of R^8 or R^9 are methyl or methoxy, the alkyl residue is preferably deuterated, e.g., CD_3 or OCD_3. In other compounds, when R^{11} is methyl, the alkyl residue is deuterated. In certain other compounds, when R^{10} is partially halogenated alkyl, e.g., 2,2,2-trifluoroethyl, the remaining hydrogen substiutents are deuterated, e.g., CD_2CF_3. In certain other compounds, when two substituents of the proline ring are combined to form a cyclopropyl ring, the unsubstituted methylene carbon is selectively deuterated.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

The compounds of the present invention may inherently or by design form solvates with solvents (including water). Therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term “solvate” refers to a molecular complex of a compound of the present invention (including salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to a recipient, e.g., water, ethanol, dimethylsulfoxide, acetone and other common organic solvents. The term “hydrate” refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder, or a disease or biological process (e.g., tissue regeneration and reproduction) (i) mediated by Factor D, or (ii) associated with Factor D activity, or (iii) characterized by activity (normal or abnormal) of the complement alternative pathway; or (2) reducing or inhibiting the activity of Factor D; or (3) reducing or inhibiting the expression of Factor D; or (4) reducing or inhibiting activation of the complement system and particularly reducing or inhibiting generation of C3a, iC3b, C5a or the membrane attack complex generated by activation of the complement alternative pathway. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of Factor D and/or the complement alternative pathway; or at least partially reducing or inhibiting the expression of Factor D and/or the complement alternative pathway. The meaning of the term “a therapeutically effective amount” as illustrated in the above embodiment for Factor D and/or the complement alternative pathway.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a,” "an,” "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or

(*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds of the present invention that converts *in vivo* to the compounds of the present invention. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

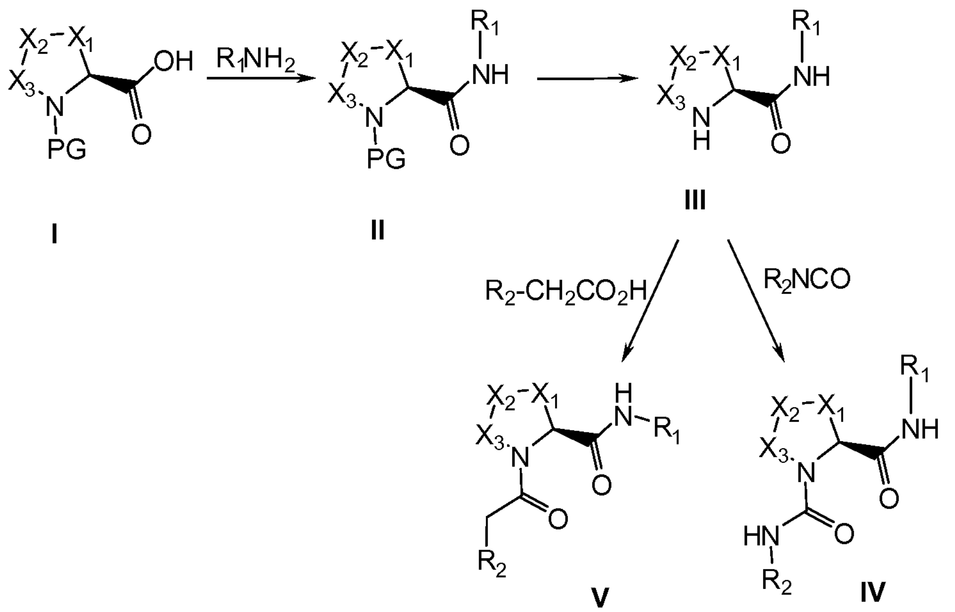
The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

Typically, the compounds of formula (I) can be prepared according to the Schemes provided *infra*.

A compound of the formula IV or V can, for example, be prepared from a corresponding N-protected aminoacid as described below:



By reacting an N-protected aminoacid I wherein PG is a protecting group or a reactive derivative thereof with an amino compound, under condensation conditions to obtain a compound of the formula II. Removing the protecting group and reacting the compound of the formula III with an isocyanate to obtain a compound of the formula IV or with an acid or a reactive derivative thereof under condensation conditions to obtain a compound of the formula V.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure materials.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *to those skilled in the art*.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and ophthalmic administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions, emulsions, each of which may be suitable for ophthalmic administration). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for ophthalmic application, *e.g.*, for the treatment of eye diseases *e.g.*, for therapeutic or prophylactic use in treating age related macular degeneration and other complement mediated ophthalmic disorders. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be desirable.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

Prophylactic and Therapeutic Uses

The compounds of formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. Factor D modulating properties, complement pathway modulating properties and modulation of the complement alternative pathway properties, e.g. as indicated in *in vitro* and *in vivo* tests as provided in the next sections and are therefore indicated for therapy.

The present invention provides methods of treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, methods are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, methods of treating or preventing compelment mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the compound of Formula (I) of the invention. In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The methods of treating or preventing AMD include, but are not limited to, methods of treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macuar degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet’s disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, anca vasculitis, cryoglobulinemia, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), dense deposit disease, blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

In other embodiments, the compounds of the invention are suitable for use in the treatment of diseases and disorders associated with fatty acid metabolism, including obesity and other metabolic disorders.

In another embodiment, the compounds of the invention may be used in blood ampules, diagnostic kits and other equipment used in the collection and sampling of blood. The use of the compounds of the invention in such diagnostic kits may inhibit the ex vivo activation of the complement pathway associated with blood sampling.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

The activity of a compound according to the present invention can be assessed by the following *in vitro* & *in vivo* methods.

The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents.

In one embodiment, the invention provides a product comprising a compound of formula (I) and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by alternative complement pathway. Products provided as a combined preparation include a composition comprising the compound of formula (I) and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of formula (I) and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I). In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of formula (I) for treating a disease or condition mediated by the complement alternative pathway, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the complement alternative pathway, wherein the medicament is administered with a compound of formula (I).

The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the complement alternative pathway, wherein the compound of formula (I) is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the other therapeutic agent is prepared for administration with a compound of formula (I). The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the compound of formula (I) is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the other therapeutic agent is administered with a compound of formula (I).

The invention also provides the use of a compound of formula (I) for treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the complement alternative pathway and/or Factor D wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

The pharmaceutical compositions can be administered alone or in combination with other molecules known to have a beneficial effect on retinal attachment or damaged retinal tissue, including molecules capable of tissue repair and regeneration and/or inhibiting inflammation. Examples of useful, cofactors include anti-VEGF agents (such as an antibody or FAB against VEGF, e.g., Lucentis or Avastin), basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), axokine (a mutein of CNTF), leukemia inhibitory factor (LIF), neutrotrophin 3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), insulin-like growth factor II, prostaglandin E2, 30 kD survival factor, taurine, and vitamin A. Other useful cofactors include symptom-alleviating cofactors, including antiseptics, antibiotics, antiviral and antifungal agents and analgesics and anestheticsSuitable agents for combination treatment with the compounds of the invention include agents known in the art that are able to modulate the activities of complement components.

A combination therapy regimen may be additive, or it may produce synergistic results (*e.g.*, reductions in complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/or treating AMD or another complement related ocular disease as described above with a compound of the invention and an anti-angiogenic, such as anti-VEGF agent (including Lucentis and Avastin) or photodynamic therapy (such as verteporfin).

In some embodiments, the present invention provide a combination therapy for preventing and/or treating autoimmune disease as described above with a compound of the invention and a B-Cell or T-Cell modulating agent (for example cyclosporine or analogs thereof, rapamycin, RAD001 or analogs thereof, and the like). In particular, for multimple sclerosis therapy may include the combination of a compound of the invention and a second MS agent selected from fingolimod, cladribine, tysarbi, laquinimod, rebif, avonex and th elike.

In one embodiment, the invention provides a method of modulating activity of the complement alternative pathway in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of formula (I). The invention further provides methods of modulating the activity of the complement alternative pathway in a subject by modulating the activity of Factor D, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of Formula (I).

In one embodiment, the invention provides a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for use as a medicament.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for the treatment of a disorder or disease in a subject mediated by complement activation. In particular, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for the treatment of a disorder or disease mediated by activation of the complement alternative pathway.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), in the manufacture of a medicament for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly in the manufacture of a medicament for the treatment of a disease or disorder in a subject characterized by over activiation of the complement alternative pathway.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), or subformulae thereof for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly, the invention provides uses of the compounds provided herein in the treatment of a disease or disorder characterized by over activiation of the complement alternative pathway or the C3 amplification loop of the alternative pathway. In certain embodiments, the use is in the treatment of a disease or disorder is selected from retinal diseases (such as age-related macular degeneration).

The present invention provides use of the compounds of the invention for treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, uses are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, uses of treating or preventing compelment mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating or preventing age-related macular degeneration (AMD). In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The use in treating or preventing AMD include, but are not limited to, uses in treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch’s membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macuar degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides uses for treating a complement related disease or disorder. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating a complement related disease or disorder, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating glomerulonephritis. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides use of the compounds of the invention for reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade (°C). If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Inter Alia the following *in vitro* tests may be used

Human complement factor D assay: Method 1

Recombinant human factor D (expressed in *E. coli* and purified using standard methods) at 10 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 0.1 M Hepes buffer, pH 7.5, containing 1 mM $MgCl_2$, 1 M NaCl and 0.05 % CHAPS. A synthetic substrate Z-Lys-thiobenzyl and 2,4-dinitrobenzenesulfonyl-fluoresceine are added to final concentrations of 200 μM and 25 μM, respectively. The increase in fluorescence is recorded at excitation of 485 nm and emission at 535 nm in a microplate spectrofluorimeter. IC_{50} values are calculated from percentage of inhibition of complement factor D-activity as a function of test compound concentration.

Human complement factor D assay: Method 2

Recombinant human factor D (expressed in *E. coli* and purified using standard methods) at a 10 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 0.1 M PBS pH 7.4 containing 7.5 mM $MgCl_2$ and 0.075% (w/v) CHAPS. Cobra venom factor and human complement factor B substrate complex is added to a final concentration of 200 nM. After 1 hour incubation at room temperature, the enzyme reaction was stopped by addition of 0.1 M sodium carbonate buffer pH 9.0 containing 0.15 M NaCl and 40 mM EDTA. The product of the reaction, Ba, was quantified by means of an enzyme-linked-immunosorbent assay. IC_{50} values are calculated from percentage of inhibition of factor D-activity as a function of test compound concentration.

The following Examples, while representing preferred embodiments of the invention, serve to illustrate the invention without limiting its scope.

<u>Abbreviations</u>:

abs.	Absolute
Ac	acetyl
AcOH	acetic acid
aq.	aqueous
cc	concentrated
c-hexane	cyclohexane
CSA	Camphor sulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	N,N'-dicyclohexylcarbodiimide
DCE	Dichloroethane
DEA	Diethylamine
DIBALH	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMME	dimethoxymethane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	triethylamine
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
Flow	flow rate
h	hour(s)
HATU	2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium
HMPA	hexamethylphosphoroamide
HOBt	1-hydroxybenzotriazole
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
HPLC	High Performance Liquid Chromatography
i-PrOH	isopropanol
L	liter(s)
LC/MS	Liquid Chromatography/Mass Spectrometry
LDA	lithium diisopropylamine
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
MesCl	Mesyl Chloride
min	minute(s)
mL	milliliter
MS	Mass Spectrometry
NBS	N-Bromo succinimide
NMM	4-methylmorpholine

NMP	N-methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
Pd/C	palladium on charcoal
Prep	Preparative
Ph	phenyl
RP	reverse phase
RT	room temperature
sat.	saturated
TBAF	tetra-butylammonium fluoride
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDMS	tert-butyldimethylsilyl
TBME	tert-butylmethylether
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	Thin Layer Chromatography
TMEDA	tetramethylethylenediamine
T_3P	Propylphosphonic anhydride
t_R	retention time

Trademarks

Celite	= Celite® (The Celite Corporation) = filtering aid based on diatomaceous earth
NH_2 Isolute	(= Isolute® NH_2, Isolute® is registered for Argonaut Technologies, Inc.) = ion exchange with amino groups based on silica gel
Nucleosil	= Nucleosil®, trademark of Machery & Nagel, Düren, FRG for HPLC materials
PTFE membrane	= Chromafil O-45/15MS Polytetrafluoroethylene Machereynagel)
PL Thiol Cartridge	= Stratosphere® SPE, PL-Thiol MP SPE+, 500mg per 6 mL tube, 1.5 mmol (nominal)

Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at RT.

Phase separator: Biotage - Isolute Phase separator (Part Nr: 120-1908-F for 70 mL and Part Nr: 120-1909-J for 150 mL)

TLC conditions: R_f values for TLC are measured on 5 x 10 cm TLC plates, silica gel F_{254}, Merck, Darmstadt, Germany.

HPLC conditions:

HPLC were performed using an Agilent 1100 or 1200 series instrument. Mass spectra and LC/MS were determined using an Agilent 1100 series instrument.

a: Waters Symmetry C18, 3.5 µm, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min

b: Agilent Eclipse XDB-C18; 1.8 µm; 2.1x30mm 5-100% CH_3CN/H_2O/3 min, 100% CH_3CN/0.75 min, CH_3CN and H_2O containing 0.1% of TFA, flow: 0.6 mL/min

c: Agilent Eclipse XDB-C18; 1.8 µm; 2.1x30mm 20-100% CH_3CN/H_2O/3 min, 100% CH_3CN/0.75 min, CH_3CN and H_2O containing 0.1% of TFA, flow: 0.6 mL/min

d: Agilent Eclipse XDB-C18, 1.8 µm, 4.6x50mm, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min

e: Waters Sunfire C18, 2.5 µm, 3x30mm, 0-10% in 0.5 min, 10-98% CH_3CN in H_2O in 2.5 min, 98% CH_3CN in H_2O for 0.7 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.4 mL/min

f. Waters XBridge C18, 2.5 µm, 3x30mm, 10-98% CH_3CN in H_2O in 3 min, 98% CH_3CN in H_2O for 0.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.4 mL/min, T = 40°C

g. Waters X-Bridge C18, 2.5 µm, 3x50mm, 10-98% CH_3CN in H_2O in 8.6 min then 98% CH_3CN in H_2O for 1.4 min, CH_3CN and H_2O both containing 0.73 mM NH_4OH, flow 1 mL/min, T = 30°C

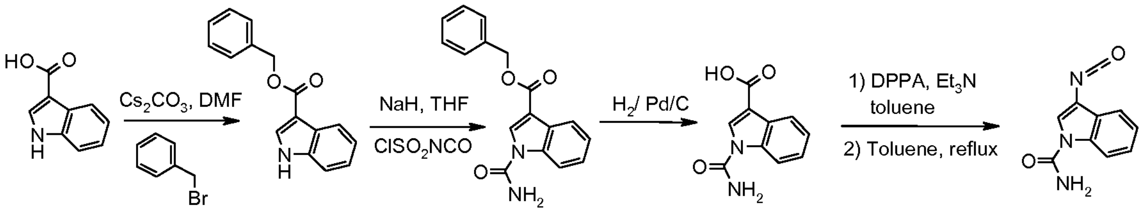
h. Waters X-Bridge C18, 2.5 µm, 3x50mm, 10-98% CH_3CN in H_2O in 8.6 min then 98% CH_3CN in H_2O for 1.4 min, CH_3CN and H_2O both containing 0.1% TFA, flow 1 mL/min, T = 40°C

UPLC conditions:

i. UPLC/MS: Waters Acquity; Waters Acquility HSS T3; 1.8 µm; 2.1x50mm 2-98% CH_3CN/H_2O/1.4 min, H_2O containing 0.05% HCOOH + 3.75 mM NH_4OAc and CH_3CN containing 0.04% HCOOH, flow : 1.4 mL/min

Part A: Synthesis of substituted aromatic or heteroromatic building blocks:

Scheme A1: Preparation of 3-isocyanato-indole-1-carboxylic acid amide



A. 1H-Indole-3-carboxylic acid benzyl ester

To a solution of 1H-indole-3-carboxylic acid (5 g, 31 mmol) in DMF (70 mL) under a nitrogen atmosphere at 0°C was added cesium carbonate (11 g, 31 mmol) and benzyl bromide (4.05 mL, 34.1 mmol). The reaction mixture was stirred at RT for 48 h and poured into water. EtOAc was added and the layers were separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was taken up in Et_2O and the resulting precipitate was filtered-off to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.55; MS (LC-MS): 252.1 [M+H]+, 274.0 [M+Na]+, 525.1 [2M+Na]+, 250.1 [M-H]-; t_R (HPLC conditions a) 3.77 min.

B. 1-Carbamoyl-1H-indole-3-carboxylic acid benzyl ester

To a solution of 1H-indole-3-carboxylic acid benzyl ester (3.5 g, 13.9 mmol) in THF (70 mL) at 5°C, was added NaH (60 % in mineral oil, 557 mg, 13.9 mmol). The mixture was stirred at 5°C for 30 min before slow dropwise addition of chlorosulfonyl isocyanate (2.42 mL, 27.9 mmol) maintaining the temperature between 5°C and 10°C. The pale yellow solution was further stirred at RT for 3.5 h. Acetic acid (22.5 mL) was added (exothermic), and the resulting solution was stirred at RT for 1.5 h before addition of ice and water (100 mL). The white thick suspension was stirred at RT for 30 min and the precipitate was filtered-off, taken up in MeOH and filtered-off again to afford the title compound. ^{1}H-NMR (400 MHz, DMSO): δ (ppm) 8.64 (s, 1H), 8.29 (d, 1H), 8.04 (d, 1H), 7.90 (m, 2H), 7.50 (d, 2H), 7.42 (t, 2H), 7.36-7.30 (m, 3H), 5.38 (s, 2H).

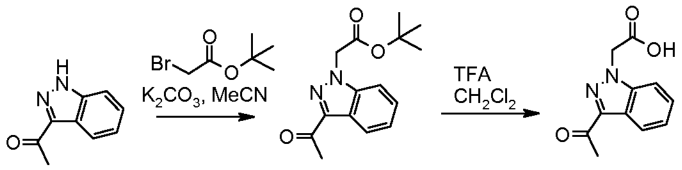
C. 1-carbamoyl-1H-indole-3-carboxylic acid

1-Carbamoyl-1H-indole-3-carboxylic acid benzyl ester (1.33 g, 4.52 mmol) was dissolved in a mixture of DMF/THF 1:1 (28 mL), Pd/C (10 %, 250 mg) was added and the solution was degassed 3 times replacing air with nitrogen then nitrogen with hydrogen. The reaction mixture was further stirred under hydrogen atmosphere overnight and the catalyst was removed through a pad of Celite and washed with THF. The solvents were concentrated under high vacuum to give a yellow solid which was taken up in Et_2O and filtered-off to afford the title compound. ^{1}H-NMR (400 MHz, DMSO): δ (ppm) 12.6 (m, 1H), 8.54 (bs, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.85 (m, 2H), 7.34-7.27 (m, 2H).

D. 3-isocyanato-indole-1-carboxylic acid amide

To a suspension of 1-carbamoyl-1H-indole-3-carboxylic acid (1.31 g, 6.42 mmol) in toluene (30 mL, *CH_2Cl_2 can also be used instead of toluene*) under a nitrogen atmosphere was added Et_3N (893 µl, 6.42 mmol). After 15 min DPPA (1.54 mL, 6.42 mmol) was added and the reaction mixture was further stirred at RT overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 and the precipitate was filtered-off to give the acyl azide intermediate (565 mg). Toluene (20 mL) was added and the suspension refluxed under a nitrogen atmosphere until diseaperance of the acyl azide by TLC (1h30). Toluene was concentrated under vacuum and the title isocyanate was directly used in the next step without further purification. ^{1}H-NMR (400 MHz, CDCl3): δ (ppm) 8.18 (d, 1H), 7.61 (d, 1H), 7.44 (t, 1H), 7.35 (t, 1H), 7.23 (s, 1H), 5.39 (bs, 2H).

Scheme A2 : Preparation of 2-(3-acetyl-1H-indazol-1-yl)acetic acid



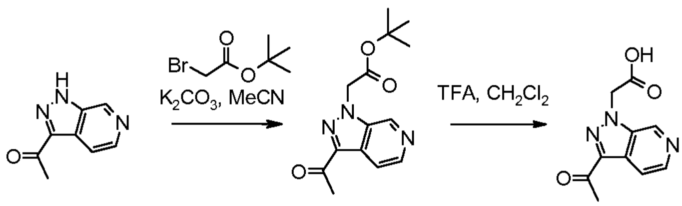
A. Tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate

To a solution of 1-(1H-indazol-3-yl)ethanone [4498-72-0] (2 g, 12.46 mmol) in CH_3CN (50 mL) was added K_2CO_3 (3.97 g, 28.7 mmol) and tert-butyl 2-bromoacetate (2.58 mL, 17.48 mmol). The reaction mixture was stirred at 90°C overnight. The reaction mixture was filtered, the residue was washed with CH_3CN and the filtrate was concentrated under vacuum. The material thus obtained was used directly in the next step without further purification. MS: 275 [M+H]+; t_R (HPLC conditions b): 3.78 min.

B. 2-(3-Acetyl-1H-indazol-1-yl)acetic acid

To a solution of tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate (4 g, 12.4 mmol) in CH_2Cl_2 (45 mL) was added TFA (15 mL, 195.0 mmol). The reaction mixture was stirred at RT overnight. Then was then diluted with CH_2Cl_2 and MeOH, and volatiles were evaporated under reduced pressure to afford the title compound : MS: 219 [M+H]+; t_R (HPLC conditions b): 2.78 min.

Scheme A3: Preparation of (3-acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate



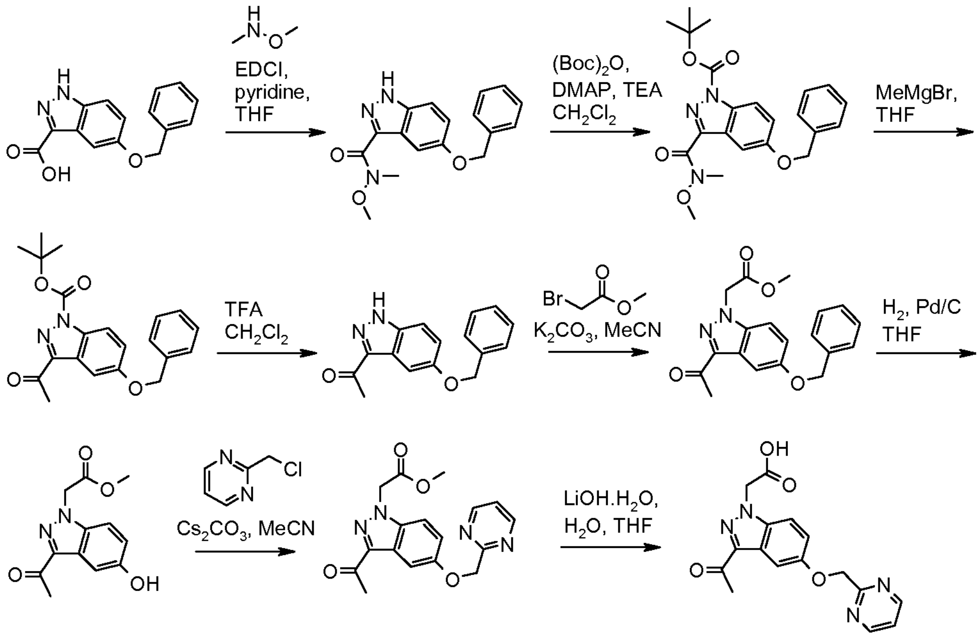
A. (3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid tert-butyl ester

To a solution of 1-(1H-pyrazolo[3,4-c]pyridin-3-yl)-ethanone (Sphinx Scientific Laboratory LLC, catalog number: PPY-1-CS01) (2.45 g 14.4 mmol) in CH_3CN (50 mL) were added potassium carbonate (3.99 g, 28.9 mmol) and tert-butyl bromoacetate (2.34 mL, 15.9 mmol). The reaction mixture was stirred at RT overnight. The crude product was poured into water and extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 1:0 to 0:1) to give the title compound. TLC, Rf (EtOAc) = 0.7; MS: 276 [M+H]+; t_R (HPLC conditions c): 2.06 min.

B. (3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate

The title compound was prepared from (3-acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid tert-butyl ester in a similar manner as described in step B, Scheme A2, for the preparation of 2-(3-acetyl-1H-indazol-1-yl)acetic acid. MS : 220 [M+H]+; t_R (HPLC conditions c): 0.69 min.

Scheme A4: Preparation of 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetic acid



A. 5-(Benzyloxy)-N-methoxy-N-methyl-1H-indazole-3-carboxamide

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428. To 5-(benzyloxy)-1H-indazole-3-carboxylic acid [177941-16-1] (3.50 g, 13.1 mmol) in THF (70 mL) was added N,O-dimethylhydroxylamine (1.40 g, 14.4 mmol). The mixture was cooled to 0°C before the addition of pyridine (2.30 mL, 28.7 mmol). The solution was stirred at 0°C for 1.5 h, and then at RT for 1 h. Pyridine (2.10 mL, 26.1 mmol) and EDCI (5.00 g, 26.1 mmol) were added and the mixture was stirred at RT overnight. Water was added to the reaction mixture followed by extraction (x3) with CH_2Cl_2. The combined organics were washed with saturated aqueous $NaHCO_3$ solution, dried (Phase separator) and concentrated to give the title compound. MS (LC/MS): 312.0 [M+H]+, 334.0 [M+Na]+, 645.1 [2M+Na]+, 310.0 [M-H]-; t_R (HPLC conditions d): 4.44 min.

B. Tert-butyl 5-(benzyloxy)-3-(methoxy(methyl)carbamoyl)-1H-indazole-1-carboxylate

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428. To a solution of 5-(benzyloxy)-N-methoxy-N-methyl-1H-indazole-3-carboxamide (3.40 g, 10.9 mmol) in CH_2Cl_2 (70 mL) was added DMAP (0.13 g, 1.09 mmol), Et_3N (1.67 mL, 12.0 mmol) and Boc-anhydride (3.80 mL, 16.4 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h and allowed to return to RT overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 50 mL of 0.1 M aqueous HCl solution and water. The organic phase was dried (Phase separator) and concentrated to give the title compound. MS (LC/MS): 434.0 [M+Na]+, 845.0 [2M+Na]+; t_R (HPLC conditions d): 5.79 min.

C. Tert-butyl 3-acetyl-5-(benzyloxy)-1H-indazole-1-carboxylate and 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428. To tert-butyl 5-(benzyloxy)-3-(methoxy(methyl)carbamoyl)-1H-indazole-1-carboxylate (4.70 g, 11.4 mmol) in THF (60 mL), cooled to -78°C, was added MeMgBr (3M solution in Et_2O, 22.9 mL, 68.5 mmol). The reaction mixture was stirred at -78°C for 1 h. A saturated aqueous NH_4Cl solution was added to the reaction mixture and the temperature was allowed to raise to RT. The mixture was extracted twice with CH_2Cl_2, the combined organics were dried (Phase separator) and concentrated to give the title mixture which was used without purification in the next step. 1-(5-(Benzyloxy)-1H-indazol-3-yl)ethanone: MS (LC/MS): 267.0 [M+H]+, 289.0 [M+Na]+, 265.1 [M-H]-; t_R (HPLC conditions d): 4.72 min. Tert-butyl 3-acetyl-5-(benzyloxy)-1H-indazole-1-carboxylate: MS (LC/MS): 389.0 [M+Na]+, 310.9 [M-tBu]+, 267.1 [M-Boc]+; t_R (HPLC conditions d): 6.12 min.

D. 1-(5-(Benzyloxy)-1H-indazol-3-yl)ethanone

To the mixture of tert-butyl 3-acetyl-5-(benzyloxy)-1H-indazole-1-carboxylate and 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone (3.80 g, 10.4 mmol) in CH_2Cl_2 (50 mL) was added TFA (7.99 mL, 104 mmol). The reaction mixture was stirred at RT overnight, then was diluted with CH_2Cl_2 and washed with 100 mL of 2N aqueous NaOH solution. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried (Phase separator) and concentrated to give the title compound. MS (LC/MS): 267.0 [M+H]+, 289.0 [M+Na]+, 265.1 [M-H]-; t_R (HPLC conditions d): 4.71 min.

E. Methyl 2-(3-acetyl-5-(benzyloxy)-1H-indazol-1-yl)acetate

To 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone (3.50 g, 13.1 mmol) in CH_3CN (100 mL) was added K_2CO_3 (4.54 g, 32.9 mmol) and methyl 2-bromoacetate (1.33 mL, 14.5 mmol). The reaction mixture was stirred at 90°C for 90 min. After filtration, the solid was washed with CH_3CN. Volatiles of the filtrate were evaporated and the crude mixture was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 1:1 to 1:3). TLC, R_f (c-hexane/EtOAc 1:3) = 0.64; MS (LC/MS): 339.0 [M+H]+, 361.0 [M+Na]+; t_R (HPLC conditions d): 5.09 min.

F. Methyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate

To methyl 2-(3-acetyl-5-(benzyloxy)-1H-indazol-1-yl)acetate (3.70 g, 10.9 mmol) in THF (80 mL) was added Pd/C (10%, 400 mg). The reaction mixture was stirred at 50°C overnight under a H_2 atmosphere and then was filtered over a pad of Celite. The residue washed with CH_2Cl_2 and the filtrate was concentrated under reduced pressure to give the title compound. MS (LC/MS): 248.9 [M+H]+, 271.0 [M+Na]+; t_R (HPLC conditions d): 3.36 min.

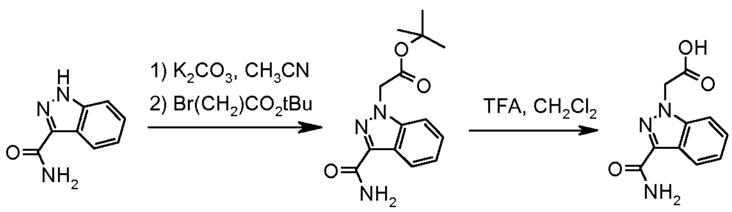
G. Methyl 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetate

To methyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1.80 g, 7.25 mmol) in CH_3CN (75 mL) was added 2-(chloromethyl)pyrimidine hydrochloride (1.32 g, 7.98 mmol) and Cs_2CO_3 (5.91 g, 18.1 mmol). The reaction mixture was stirred at 70°C for 2 h. The reaction mixture was filtered and washed with CH_3CN. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 1:1 to 1:3) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:3) = 0.35; MS (LC/MS): 340.9 [M+H]+, 363.0 [M+Na]+; t_R (HPLC conditions d): 3.64 min.

H. 2-(3-Acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetic acid

To methyl 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetate (1.93 g, 5.67 mmol) in THF (15 mL) and water (15 mL) was added $LiOH.H_2O$ (0.25 g, 5.95 mmol). The reaction mixture was stirred at RT for 1.5 h. Volatiles were evaporated and the residue was freeze-dried overnight to give the title compound as a lithium salt. MS (LC/MS): 327.0 [M+H]+, 325.1 [M+H]+; t_R (HPLC conditions d): 3.24 min.

<u>**Scheme A5: Preparation of (3-carbamoyl-indazol-1-yl)-acetic acid**</u>



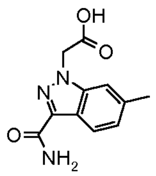
A. Tert-butyl 2-(3-carbamoyl-1H-indazol-1-yl)acetate

To a suspension of 1H-indazole-3-carboxamide [90004-04-9] (2.00 g, 12.4 mmol) and potassium carbonate (4.12 g, 29.8 mmol) in CH_3CN (60 mL) was added tert-butyl bromoacetate (2.20 mL, 14.9 mmol) dropwise at RT, and the resulting mixture was refluxed for 16 h. The mixture was then cooled to RT and filtered, the solid was washed with CH_3CN and the filtrate was concentrated under vacuum. The residual oil was used directly in the next step without further purification. MS (LC/MS): 276.0 [M+H]+; t_R (HPLC conditions b): 3.22 min.

B. (3-Carbamoyl-indazol-1-yl)-acetic acid

To a solution of tert-butyl 2-(3-carbamoyl-1H-indazol-1-yl)acetate (3.42 g, 12.4 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL, 130 mmol) and the resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated in vacuo, the residual solid was suspended in MeOH and concentrated again in vacuo to give the title compound. MS (UPLC/MS): 220 [M+H]+; t_R (HPLC conditions b): 1.79 min.

(3-Carbamoyl-6-methyl-indazol-1-yl)-acetic acid

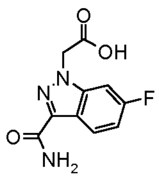


The title compound was prepared from 6-methyl-1H-indazole-3-carboxamide by using the same procedures as for the preparation of (3-carbamoyl-indazol-1-yl)-acetic acid. MS (UPLC-MS): 234 [M+H]+; t_R (HPLC conditions e): 1.33 min.

6-methyl-1H-indazole-3-carboxamide

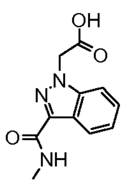
To a solution of 6-methyl-1H-indazole-3-carboxylic acid (440 mg, 2.50 mmol), ammonium chloride (401 mg, 7.49 mmol) and HBTU (1.42 g, 3.75 mmol) in DMF (10 ml) was added DIPEA (1.31 ml, 7.49 mmol) and the reaction mixture was stirred for 16 h at RT. The reaction mixture was concentrated, diluted in EtOAc, washed with 1N HCl, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 1:0 to 8:2). MS (UPLC-MS): 176 [M+H]+; t_R (HPLC conditions e): 1.30 min.

(3-Carbamoyl-6-fluoro-indazol-1-yl)-acetic acid



The title compound was prepared from 6-fluoro-1H-indazole-3-carboxylic acid by using the same procedure as described for the preparation of (3-carbamoyl-6-methyl-indazol-1-yl)-acetic acid. MS (UPLC/MS): 238.1 [M+H]+; t_R (UPLC conditions i): 0.55 min.

2-(3-(methylcarbamoyl)-1H-indazol-1-yl)acetic acid

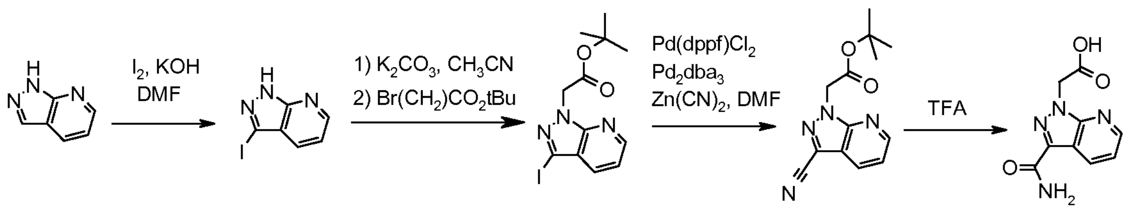


The title compound was prepared from N-methyl-1H-indazole-3-carboxamide by using the same procedures as for the preparation of (3-carbamoyl-indazol-1-yl)-acetic acid (Scheme A5). MS (LC/MS): 234.1 [M+H]+, 232.1 [M-H]-, t_R (HPLC conditions f): 0.95 min.

N-methyl-1H-indazole-3-carboxamide

To a mixture of indazole-3-carboxylic acid (1 g, 6.17 mmol), methylamine hydrochloride (1.25 g, 18.50 mmol) and HBTU (3.51 g, 9.25 mmol) in DMF (15 mL) under nitrogen atmosphere was added DIPEA (4.31 ml, 24.67 mmol) and the mixture was stirred at RT overnight. EtOAc and aqueous HCL (1N) were added, the layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (c-hexane/ EtOAc 100/0 to 0/100) to afford the title compound. MS (LC/MS): 176.1 [M+H]+, 174.1 [M-H]-; t_R (HPLC conditions f): 0.87 min.

Scheme A6: General protocol for the preparation of (3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid



A. 3-Iodo-1H-pyrazolo[3,4-b]pyridine

To a solution of 1H-pyrazolo[3,4-b]pyridine (2.00 g, 16.8 mmol) in DMF (35 mL) were added iodine (6.39 g, 25.2 mmol) and potassium hydroxide (2.35 g, 42.0 mmol). The reaction mixture was stirred at RT for 16 h. The mixture was diluted with 10% sodium thiosulfate and water and the resulting suspension was filtered to give the title compound as a yellow powder. TLC, R_f (EtOAc) = 0.8; MS (UPLC/MS): 246.0 [M+H]+, 243.9 [M-H]-; t_R (HPLC conditions f): 1.31 min.

B. (3-Iodo-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid tert-butyl ester

To a suspension of 3-iodo-1H-pyrazolo[3,4-b]pyridine (3.6 g, 14.7 mmol) and potassium carbonate (4.87 g, 35.3 mmol) in CH_3CN (100 mL) was added dropwise at RT tert-butyl 2-bromoacetate (2.61 mL, 17.6 mmol). The resulting mixture was refluxed for 16 h. After cooling to RT, the mixture wasfiltered and the solid was washed with CH_3CN to give, after drying in vacuo, the title compound. TLC, R_f (c-hexane/EtOAc) = 0.7; MS (UPLC/MS): 360.0 [M+H]+; t_R (HPLC conditions f): 2.28 min.

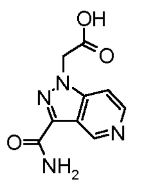
C. (3-Cyano-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid tert-butyl ester

A mixture of tert-butyl (3-iodo-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid tert-butyl ester (4.70 g, 13.1 mmol), $Zn(CN)_2$ (1.69 g, 14.4 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (1.07 mg, 1.31 mmol), $Pd_2(dba)_3$ (1.12 mg, 1.31 mmol) in water (6.5 mL) and DMF (50 mL) was stirred at 120°C for 4 h under argon. After cooling to RT, the reaction mixture was diluted with EtOAc and washed with water, sat. aq. $NaHCO_3$ (2x) and brine, dried (Na_2SO_4), filtered, concentrated and purified by flash column chromatography on silica gel (c-hexane/EtOAc 7:3) to give the title compound. MS (LC/MS): 259.0 [M+H]+; t_R (HPLC conditions d): 3.20 min.

D. (3-Carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid

A solution of (3-cyano-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid tert-butyl ester (1.43 g, 5.54 mmol) in TFA (6 mL) was subjected to microwave irradiation at 140°C for 90 min. The reaction mixture was concentrated in vacuo, the residual solid was suspended in MeOH and volatiles were removed again in vacuo. MS: 221.0 [M+H]+, 219.0 [M+H]+; ^{1}H-NMR (400 MHz, DMSO): δ (ppm) 13.35 (m, 1H), 8.65 (d, 1H), 8.57 (d, 1H), 7.89 (s, 1H), 7.57 (s, 1H), 7.41 (dd, 1H), 5.33 (s, 2H).

<u>(3-Carbamoyl-pyrazolo[4,3-c]pyridin-1-yl)-acetic acid</u>



The title comound was prepared from 1H-pyrazolo[4,3-c]pyridine [271-52-3] by using the same procedures as in Scheme A6 for the preparation of 2(3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid. MS (LC/MS): 221 [M+H]+, t_R (HPLC conditions b): 0.19 min.

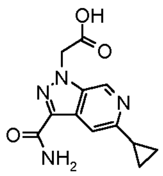
<u>(3-Carbamoyl-5-ethyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid</u>

The title compound was prepared from 5-ethyl-1H-pyrazolo[3,4-c]pyridine by using the same procedures as for the preparation of 2(3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid (Scheme A6). MS (LC/MS): 249 [M+H]+, t_R (HPLC conditions b): 0.49 min.

5-Ethyl-1H-pyrazolo[3,4-c]pyridine

Triethylaluminum (21.7 mL, 40.4 mmol; 25 wt% solution in toluene) was added to a vigorously stirred solution of 5-bromo-1H-pyrazolo[3,4-c]pyridine [929617-35-6] (4.00 g, 20.2 mmol) and $Pd(PPh_3)_4$ (1.17 g, 1.01 mmol) in THF (100 mL) under argon. The reaction mixture was stirred at 65°C for 60 h, cooled to RT and poured into sat. aq. NH_4Cl. The resulting suspension was filtered, the solid was washed with water and discarded. The filtrate and combined washings were extracted with EtOAc (3x). The combined organic extracts were washed with brine, then dried (phase separator), concentrated and purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 5:5 to 0:10) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:3) = 0.22; MS (LC/MS): 148 [M+H]+, t_R (HPLC conditions b): 0.71 min.

(3-Carbamoyl-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid



The title compound was prepared by using the same procedures as in Scheme A6 for the preparation of 2(3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid and by starting from 5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine. MS (LC-MS): 261 [M+H]+, t_R (HPLC conditions d): 1.84 min.

5-Cyclopropyl-1H-pyrazolo[3,4-c]pyridine

A solution of 6-cyclopropyl-4-methylpyridin-3-amine (130 mg, 0.88 mmol) in AcOH (10 mL) was treated with a solution of sodium nitrite (61 mg, 0.88 mmol) in water (0.5 mL). The reaction mixture was stirred at RT for 15 min and then was allowed to stand at RT for 24 h. AcOH was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic solution was washed with water and brine, then dried (Phase separator) and concentrated under reduced pressure to give the title compound. MS (LC-MS): 160 [M+H]+, t_R (HPLC conditions d): 2.07 min.

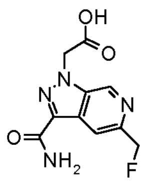
6-Cyclopropyl-4-methylpyridin-3-amine

To a solution of 2-cyclopropyl-4-methyl-5-nitropyridine (201 mg, 0.96 mmol) in MeOH (5 mL) were added 3N aqueous HCl (9.60 mL, 28.8 mmol) and Zn powder (376 mg, 5.75 mmol). The mixture was stirred 18 h at RT. The solution was neutralized with a sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x). The combined organics were dried (Phase Separator) and concentrated under reduced pressure to give the title compound. MS (LC-MS): 149 [M+H]+, t_R (HPLC conditions d): 2.22 min.

2-Cyclopropyl-4-methyl-5-nitropyridine

Potassium cyclopropyltrifluoroborate (857 mg, 5.79 mmol), 2-chloro-4-methyl-5-nitropyridine (500 mg, 2.90 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), Cs_2CO_3 (2.83 g, 8.69 mmol), and n-butyl-di-adamantylphosphine (62 mg, 0.17 mmol) were charged into a capped vial. The vial was purged with argon and then sealed with a septum cap. Toluene/H_2O 10:1 (11 mL) was added by syringe and the mixture was heated at 100°C for 16 h. More potassium cyclopropyltrifluoroborate (857 mg, 5.79 mmol) was added to the mixture which was further heated at 100°C for 72 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The filtrate was dried (Phase separator) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/30 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound. MS (LC-MS): 179 [M+H]+, t_R (HPLC conditions d): 4.26 min.

<u>(3-Carbamoyl-5-fluoromethyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid</u>



The title compound was prepared by using the same procedures as in Scheme A6 for the preparation of 2(3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid and by starting from 5-fluoromethyl-1H-pyrazolo[3,4-c]pyridine. MS (UPLC-MS): 253.1 [M+H]+, t_R (HPLC conditions h): 0.41 min.

5-Fluoromethyl-1H-pyrazolo[3,4-c]pyridine

To a solution of 2-(fluoromethyl)-4-methyl-5-nitropyridine (1.12 g, 5.71 mmol) in AcOH (40 mL) was added at 0°C Zn powder (3.74 g, 57.1 mmol). The mixture was stirred 30 min at 0°C and then 30 min at RT. The suspension was filtered through a pad of Celite and the filtrate was treated with a solution of sodium nitrite (552 mg, 8.00 mmol) in water (2 mL). The reaction mixture was stirred at RT for 1 h. AcOH was evaporated under reduced pressure and the residue was diluted with EtOAc and washed (2x) with a sat. aq. solution of $NaHCO_3$. The aqueous washings were back-extracted with EtOAc and the combined organics were dried (Phase separator) and concentrated under reduced pressure to give the title compound. MS (UPLC-MS): 151.8 [M+H]+, t_R (HPLC conditions h): 0.29 min.

2-(Fluoromethyl)-4-methyl-5-nitropyridine

To a solution of (4-methyl-5-nitropyridin-2-yl)methanol (1.07 g, 6.06 mmol) in dry CH_2Cl_2 (30 mL) was added DAST (1.00 mL, 7.64 mmol) dropwise at -78°C. The reaction mixture was stirred at -78°C for 30 min and then at RT for 4 h. The mixture was diluted with CH_2Cl_2, the suspension was filtered through a phase separator (the solid was discarded) and the filtrate was washed with a sat. aq. solution of $NaHCO_3$ (2x). The aqueous washings were back-extracted with CH_2Cl_2 and the combined organics were dried (phase separator) and concentrated under vacuum. The crude product was used directly in the next step. MS (UPLC-MS): 171.0 [M+H]+, t_R (HPLC conditions h): 2.28 min.

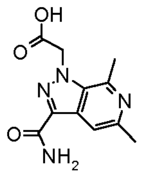
(4-Methyl-5-nitropyridin-2-yl)methanol

To a solution of methyl 4-methyl-5-nitropicolinate (4.66 g, 23.8 mmol) in methanol (160 mL) was added $NaBH_4$ (4.49 g, 119 mmol) slowly at 0°C (gas evolution) and the reaction was stirred at RT for 2 h. Additional $NaBH_4$ (900 mg, 23.76 mmol) was added to the mixture which was further stirred at RT for 30 min. The reaction mixture was concentrated in vacuo and the residual oil was diluted with cold water and extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (phase separator) and concentrated under reduced pressure. The residual pale-brown solid was used directly in the next step. MS (UPLC-MS): 169.1 [M+H]+, t_R (HPLC conditions h): 0.86 min.

Methyl 4-methyl-5-nitropicolinate

To a solution of 4-methyl-5-nitropicolinic acid (5.0 g, 27.5 mmol) in methanol (60 mL) was slowly added concentrated sulfuric acid (4.39 mL, 82 mmol) and the mixture was refluxed under argon for 18 h. The volatiles were evaporated and a sat. aq. solution of $NaHCO_3$ was added slowly until the aqueous phase showed a pH of 7-8. The resultant mixture was extracted with CH_2Cl_2 (x3), the combined organic extracts were dried (phase separator) and concentrated under vacuum. MS (UPLC-MS): 197.0 [M+H]+, t_R (HPLC conditions h): 1.99 min.

<u>(3-Carbamoyl-5,7-dimethyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid</u>



The title compound was prepared from 5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine by using the same procedures as described for the preparation of 2(3-carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid (Scheme A6). MS (LC-MS): 249 [M+H]+, t_R (HPLC conditions d): 0.9 min.

5,7-Dimethyl-1H-pyrazolo[3,4-c]pyridine

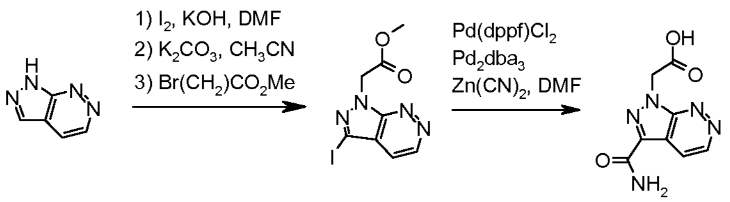
To a vigorously stirred solution of 7-bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine (3.65 g, 14.6 mmol) and $Pd(PPh_3)_4$ (845 mg, 0.73 mmol) in THF (65 mL) was added trimethylaluminum (14.6 mL, 29.3 mmol; 2 M sol. in toluene) under argon. The reaction mixture was stirred at 65°C for 60 h, and then was cooled to RT and poured into a sat. aq. NH_4Cl solution. The resulting suspension was filtered, the solid was washed with water and discarded. The filtrate and the combined washings were extracted with EtOAc (3x). The combined organics were washed with brine, then dried (Phase separator) and concentrated under reduced pressure to give 5,7-

dimethyl-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 148 [M+H]+, t_R (HPLC conditions b): 0.50 min.

7-Bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine

A solution of 2-bromo-4,6-dimethylpyridin-3-amine [104829-98-3] (4.00 g, 19.9 mmol) in acetic acid (300 mL) was treated with a solution of sodium nitrite (1.37 g, 19.9 mmol) in water (2.5 mL). The reaction mixture was stirred at RT for 15 min and was then allowed to stand at ambient temperature for 24 h. An additional solution of sodium nitrite (500 mg, 7.25 mmol) in water (1 mL) was added to the mixture which was allowed to stand at RT for 16 h. Acetic acid was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The precipitate was filtered off, washed and discarded. The combined filtrates were washed with water and brine, then dried (Phase separator) and concentrated under vacuum to give 7-bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 212 [M+H]+, t_R (HPLC conditions b): 2.49 min.

Scheme A7: Preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetic acid



A. Methyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetate

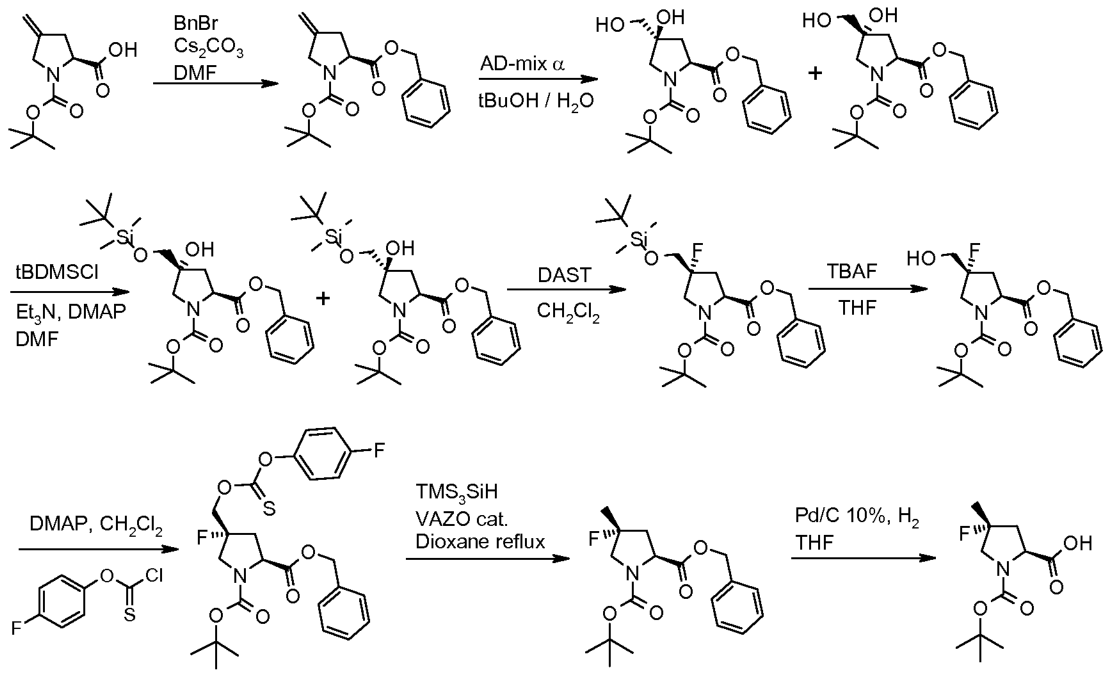
To a solution of 1H-pyrazolo[3,4-c]pyridazine [271-75-0] (450 mg, 3.75 mmol) in DMF (10 mL) was added iodine (951 mg, 3.75 mmol) and KOH (525 mg, 9.37 mmol). The mixture was stirred at RT for 16 h until completion of the reaction. Methyl 2-bromoacetate (0.380 mL, 4.12 mmol) was then added to the reaction mixture and stirring was continued at RT for 2 h. The mixture was diluted with EtOAc and washed with water (10 mL), the organic phase was dried (Na_2SO_4), filtered and evaporated under vacuum. The crude mixture was purified by flash column chromatography on silica gel (c-Hex/EtOAc 66:33) to afford the title compound as a brown solid. TLC, R_f (c-Hex/EtOAc 1:1) = 0.40; MS (LC/MS): 318.9 [M+H]+; t_R (HPLC conditions d): 3.35 min.

B. 2-(3-Carbamoyl-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetic acid

To a solution of methyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetate (675 mg, 2.12 mmol) in DMF (7.5 mL) and water (1.5 mL) was added $Zn(CN)_2$ (274 mg, 2.33 mmol), Pd_2dba_3 (194 mg, 0.21 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (173 mg, 0.21 mmol). The reaction mixture was stirred at 100°C for 16 h. The resulting suspension was filtered and the filtrate was evaporated under vacuum. The residue was suspended in CH_3CN/MeOH 1:1, the solid was filtered off and the filtrate was purified by preparative HPLC (Macherey Nagel, VP250/40, C18 Nucleosil 100-10, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound after lyophilisation. MS (LC/MS): 222.1 [M+H]+; t_R (HPLC conditions d): 1.34 min.

Part B: Synthesis of various 5-membered heterocycles :

Scheme B1: Preparation of (R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



A. (S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To (S)-1-(tert-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (4 g, 17.60 mmol) dissolved in DMF (100 mL) at 0°C were added benzyl bromide (2.51 mL, 21.12 mmol) and cesium carbonate (6.31 g, 19.36 mmol). The solution was stirred 16 h at RT then was concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) afforded the title compound. MS (UPLC/MS): 218 [MH-tBu]+, t_R (HPLC conditions e): 2.44 min.

B. (2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4R)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

A solution of AD-mix-alpha (30 g, 21.43 mmol) in tBuOH (120 mL) and Water (120 mL) was stirred until both phases were clear and then cooled to 0°C. (S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (6.48 g, 20.42 mmol) was added and the reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched at 0°C by addition of sodium sulfite (14.5 g), then allowed to reach RT and stirred for 1 h. After extraction with CH_2Cl_2 (3 x 100 mL), the organic phases were joined, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) gave the title compounds as an unseparable mixture. MS (UPLC/MS): 352 [M+H]+, t_R (HPLC conditions e): 1.50 min.

C. (2S,4R)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4S)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4S)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4R)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (5.46 g, 15.54 mmol) in DMF (80 mL) were added tert-butyl dimethylchlorosilane (2.45 g, 16.32 mmol), triethylamine (2.16 mL, 15.54 mmol) and DMAP (0.19 g, 1.55 mmol). The solution was stirred for 16 h at RT then was washed with sat $NaHCO_3$ (2 x 100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 9:1) gave (2S,4R)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 466 [M+H]+]+, 510 [M+HCOO]-; t_R (HPLC conditions f): 2.83 min and (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 466 [M+H]+ , 510 [M+HCOO]-; t_R (HPLC conditions e): 2.95 min.

D. (2S,4R)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (5.20 g, 11.17 mmol) in CH_2Cl_2 (100 mL) at -78°C under a nitrogen atmosphere was added DAST (2.21 mL, 16.75 mmol). The solution was stirred for 16 h at RT then was washed with a sat. aq. solution of $NaHCO_3$ (2 x 100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 9:1) afforded the title compound. MS (UPLC/MS): 468 [M+H]+ , 512 [M+HCOO]-; t_R (HPLC conditions e): 3.00 min.

E. (2S,4R)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (4.10 g, 8.77 mmol) in THF (80 mL) at RT was added TBAF (1M in THF, 17.53 mL, 17.53 mmol). The reaction was stirred at RT for 30 min then poured into water and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc

3:2) afforded th title compound. MS (UPLC/MS): 354 [M+H]+, 398 [M+HCOO]-; t_R (HPLC conditions e): 2.07 min.

F. (2S,4R)-4-Fluoro-4-(4-fluoro-phenoxythiocarbonyloxymethyl)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (300 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added 4-fluorophenylthionochloroformate (0.18 mL, 1.27 mmol) and DMAP (311 mg, 2.55 mmol). The reaction mixture was stirred at RT for 2 days then was diluted with CH_2Cl_2 (40 mL), washed with aq. 0.5 HCl (50 mL), water (50 mL) and brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 3:1) gave the title compound. MS (UPLC/MS): 508 [M+H]+; t_R (HPLC conditions e): 2.73 min.

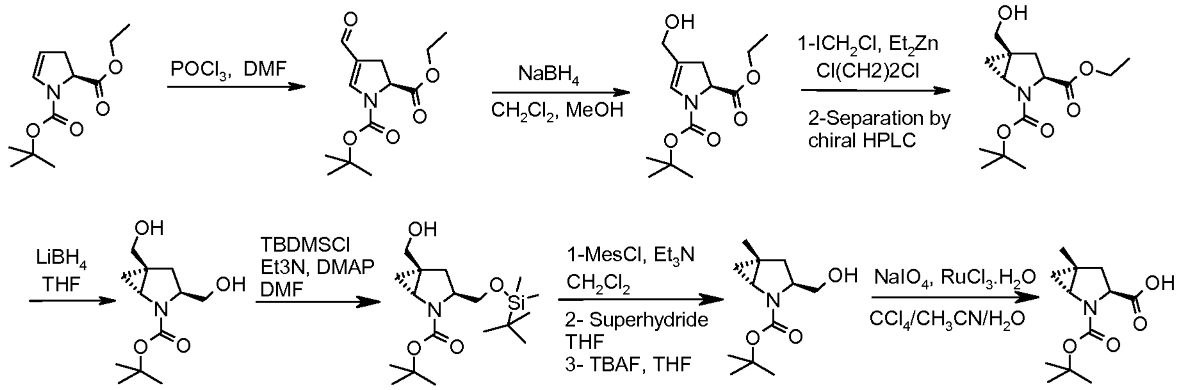
G. (2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-fluoro-4-(4-fluoro-phenoxythiocarbonyloxymethyl)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (290 mg, 0.57 mmol) in dioxane (5 mL) were added VAZO (69 mg, 0.28 mmol) and tris(trimethylsilyl) silane (0.24 mL, 0.77 mmol). The reaction mixture was refluxed for 30 min then was stirred for 16 h at RT and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 4:1) afforded the title compound. MS (UPLC/MS): 338 [M+H]+; t_R (HPLC conditions e): 2.38 min.

H. (2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

A solution containing (2S,4R)-4-fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (700 mg, 2.075 mmol) and Pd/C 10% (221 mg, 2.075 mmol) in THF (6 mL) was placed under a nitrogen atmosphere and stirred for 5 h. The catalyst was removed through a pad of Celite and washed with MeOH. Solvents were removed under vacuum to give the title compound as a colorless oil which was used without further purification in the next step. MS (UPLC/MS): 246,2 [M-H]-, 292,2 [M+HCOO-]-, 493,4 [2M-H]-.

Scheme B2: Preparation of (1R,3S,5R)-5-methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester



A. (S)-4-Formyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

$POCl_3$ (7.59 mL, 83 mmol) was added in 25 min at 0°C under N_2 atmosphere to DMF (6.39 mL, 83 mmol) and the mixture was stirred at RT for 20 min. Dry CH_2Cl_2 (150 mL) was added at 0°C, followed by a solution of (S)-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (10 g, 41.4 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred 30 min at RT until completion. Then slowly poured into an ice cold aqueous solution of NaOH 10 N (150 mL) and extracted with CH_2Cl_2 (x3). The combined organic extracts were washed with brine (x2), with water, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 9:1) to give the title compound as a yellow oil. R_f, TLC (c-hexane/EtOAc 4:1) = 0.2; MS (UPLC-MS): 270 [M+H]+, 170 [M-Boc]-; t_R (HPLC conditions e): 1.93 min.

B. (S)-4-Hydroxymethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

A solution of (S)-4-formyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (3.32 g, 12.3 mmol) in CH_2Cl_2 (51.4 mL) was cooled at -78°C under a nitrogen atmosphere, solid $NaBH_4$ (1 g, 24.7 mmol) was added portionwise maintaining the temperature at -78°C. MeOH (25.7 mL) was added dropwise and the reaction mixture was allowed to reach 0°C and was stirred 1h30 at 0°C. The reaction mixture was quenched with an aq. sat. solution of NH_4Cl and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1 to EtOAc) to give the title compound as a yellow oil. R_f, TLC (c-hexane/EtOAc 1:1) = 0.30; MS (UPLC-MS): 272.2 [M+H]+, 316 [M+HCOO]-; t_R (HPLC conditions e): 1.74 min.

C. (1R,3S,5S) and (1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

To a solution of (S)-4-hydroxymethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (1.12 g, 4.13 mmol) in CH_2Cl_2 (115 mL) under argon at -20°C were slowly added diethylzinc (1M in hexanes, 8.26 mL, 8.26 mmol) and diiodomethane (0.73 mL, 9.08 mmol) and the reaction mixture was further stirred at -10°C for 2 h. Diethylzinc (1M in hexanes, 8.26 mL, 8.26 mmol) and diiodomethane (0.73 mL, 9.08 mmol) were again added and the reaction mixture was further stirred at -10°C for 2 h to complete the reaction. A sat. aq. solution of NH_4Cl was added slowly (exothermic) at -20°C followed by CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x2). To the combined organic layers were added few crystals of Na_2S and water (ratio CH_2Cl_2/H_2O 20:1) and the biphasic mixture was stirred for 30 min. Water was added, the layers were separated, dried (Na_2SO_4), filtered and concentrated to give a mixture of diastereoisomers. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) to give a mixture of diastereoisomers (4:6 (1R,3S,5S)/(1S,3S,5R)): R_f, TLC (c-hexane/EtOAc 1:1) = 0.25; MS (UPLC-MS): 186.1[MH-Boc]+, 230.2 [MH-tBu]+, 286.3 [MH+H]+, 308.2 [MH+Na]+, 330.3 [M+HCOO]-; t_R (HPLC conditions e): 1.75 min. The two diastereoisomers were separated by preparative chiral HPLC (column: 8 SMB columns Chiralpak AD, 20 um, 250 x 30 mm; eluent: heptane–EtOH 80:20) to give (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester: t_R (Chiralpak AD-prep, 20 uM, 250 x 4.6 mm, n-heptane/EtOH 80/20, flow rate 1 mL/min, detection: UV at 210 nm): 6.94 min and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester: t_R (Chiralpak AD-prep, 20 uM, 250 x 4.6 mm, n-heptane/EtOH 80/20, flow rate 1 mL/min, detection: UV at 210 nm): 4.20 min.

D. (1R,3S,5S)-3,5-Bis-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (3 g, 10.51 mmol) in THF (50 mL) at 0°C under a nitrogen atmosphere was added $LiBH_4$ (2M in THF, 10.51 mL, 21.03 mmol) and the resulting solution was stirred at RT 2 h. The reaction mixture was slowly poured into a cold sat. solution of $NaHCO_3$ and extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound which was used in the next step without purification. R_f, TLC (CH_2Cl_2/MeOH 95:5) = 0.35; MS (UPLC-MS): 244.1 [M+H]+, 188.1 [MH-tBu]+, 509.3 [2M+Na]+, 288.2 [M+HCOO]-.

E. (1R,3S,5S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5S)-3,5-bis-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (9.76 mmol) in DMF (100 mL) at 0°C under a nitrogen atmosphere was added TBDMSCl (1.54 g, 10.25 mmol), Et_3N (1.43 mL, 10.25 mmol) and DMAP (119 mg, 0.98 mmol). The reaction mixture was stirred at RT under nitrogen for 2 h, then poured into water and extracted with EtOAc (x3). The combined organic layers were washed with water (x3), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1-1 to EtOAc) to give the title compound as a yellow oil. R_f, TLC (c-hexane/EtOAC 2:1) = 0.40; MS (UPLC-MS): 358.3 [M+H]+, 302.2 [MH-tBu]+, 258.2 [MH-Boc]+, 402.3 [M+HCOO]-; t_R (HPLC conditions f): 2.81 min.

F. (1R,3S,5R)-3-Hydroxymethyl-5-methyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

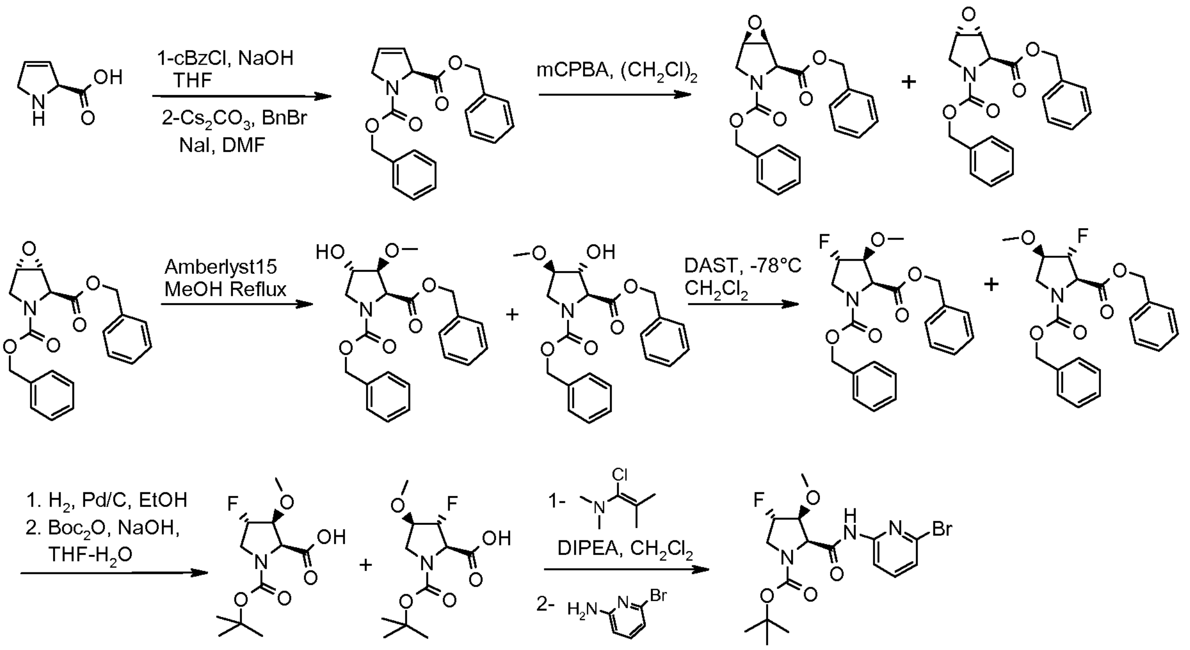
To a solution of (1R,3S,5S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester (755 mg, 2.11 mmol) and Et_3N (441 µL, 3.17 mmol) in CH_2Cl_2 (20 mL) at 0°C under a nitrogen atmosphere was added methanesulfonyl chloride (247 µL, 3.17 mmol) and the resulting solution was allowed to reach RT and stirred for 4 h. The reaction mixture was poured into a sat. aq. solution of $NaHCO_3$, extracted with CH_2Cl_2 (x2), dried (Na_2SO_4), filtered and concentrated to give (1R,3S,5S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester as a yellow oil: R_f, TLC (c-hexane/EtOAc 2:1) = 0.4. To a solution of (1R,3S,5S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (2.09 mmol) in THF (20 mL) at 0°C under an argon atmosphere was added lithium triethylborohydride (1M in THF, 4.18 mL, 4.18 mmol) and the reaction mixture was stirred at 0°C for 6 h. Then poured into cold water and extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. To a solution of the crude reaction mixture containing (1R,3S,5R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (2.1 mmol) in THF (4.5 mL) was added tetrabutylammonium fluoride trihydrate (1M in THF, 4.16 mL, 4.16 mmol) and reaction mixture was stirred at RT under an argon atmosphere for 1 h. Then was poured into water and extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 3-2) to give the title compound. R_f, TLC (c-hexane/EtOAC 2:1) = 0.35; MS (UPLC-MS): 228.2 [M+H]+, 172.1 [MH-tBu]+, 272.4 [M+HCOO]-;]-; t_R (HPLC conditions f): 1.91 min.

G. (1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester

To a solution of (1R,3S,5R)-3-hydroxymethyl-5-methyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (130 mg, 0.57 mmol) in CCl_4/ CH_3CN/ H_2O (ratio 2/2/3; 4 mL) were successively added $NaIO_4$ (367 mg, 1.72 mmol) and $RuCl_3.H_2O$ (4.8 mg, 0.02 mmol). The dark reaction mixture was stirred vigorously at RT until completion (2.5 h). CH_2Cl_2 was added (+ a few drops of aqueous 1 M HCl, to acidify the mixture) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (x2) and the combined organic extracts were dried

(Na_2SO_4), filtered and concentrated to give the title compound which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.46 (m, 1H), 3.86 (m, 1H), 3.06 (m, 1H), 2.40 (dd, 1H), 1.86 (m, 1H), 1.37 (m, 9H), 1.18 (s, 3H) 0.65 (m, 2H).

Scheme B3: Preparation of (2S,3S,4S)-2-(6-bromo-pyridin-2-ylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid 1-benzyl ester

To a solution of (S)-2,5-dihydro-1H-pyrrole-2-carboxylic acid (15 g, 133 mmol) and sodium hydroxide (10.6 g, 265 mmol) in THF (150 mL) cooled at 0°C was added benzylchloroformate (32.0 mL, 166 mmol). The mixture was allowed to reach RT overnight. The reaction mixture was concentrated, water was added and the aqueous layer was extracted with Et_2O (2 x 200 mL), acidified (6N HCl) and extracted with AcOEt (2 x 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was used in the next step without purification. MS (UPLC/MS): 248 [M+H]+; t_R (HPLC conditions e): 1.66 min.

B. (S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid dibenzyl ester

To a solution of (S)-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 1-benzyl ester (29.6 g, 120 mmol) in DMF (250 mL) were added cesium carbonate (42.9 g, 132 mmol) followed by benzyl bromide (17.09 mL, 144 mmol) and sodium iodide (2.15 g, 14.37 mmol) and the mixture was stirred at RT for 48 h. The reaction mixture was quenched with water (500 mL) and extracted with EtOAc (3 x 200 mL). The organic extracts were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 4:1) to give the title compound. MS (UPLC/MS): 338 [MH-Boc]+; t_R (HPLC conditions e): 2.31 min.

C. (1S,2S,5R)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester and (1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester

Were prepared according to the procedure described in *Tetrahedron,* **1998**, *54*, 981-1186 from (S)-2,5-dihydro-pyrrole-1,2-dicarboxylic acid dibenzyl ester. To a solution of (S)-2,5-dihydro-pyrrole-1,2-dicarboxylic acid dibenzyl ester (7.5 g, 22.23 mmol) in DCE (80 mL) were added mCPBA (7.67 g, 44.5 mmol) and 4,4'-thiobis(6-tert-butyl-m-cresol) (0.797 g, 2.22 mmol). The reaction mixture was then heated to 90°C overnight. Then was concentrated. The crude residue was diluted in CH_2Cl_2 (200 mL) and washed with an aq. solution of $Na_2S_2O_5$ 5% and with a sat. aq. solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 10:0 to 8:2) give (1S,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester: MS (UPLC/MS): 354 [M+H]+, t_R (HPLC conditions e): 2.24 min and (1S,2S,5R)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester: MS (UPLC/MS): 354 [M+H]+, t_R (HPLC conditions e): 2.15 min.

D. (2S,3S,4S)-4-Hydroxy-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2S,3R,4R)-3-hydroxy-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

To a solution of (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester (30 g, 85 mmol) in MeOH (150 mL) was added Amberlyst 15 (30 g). The reaction mixture was heated overnight at 65°C, then allowed to cool to RT and filtered. Amberlyst 15 residue was washed with MeOH. The combined filtrates were concentrated and purified by flash column chromatography on silica gel (c-hexane 100% to EtOAc 100%) to give a mixture of the 2 regioisomers as a yellow oil. R_f, TLC (c-hexane/EtOAc 1:1) = 0.5; MS (UPLC/MS): 386.2 [M+H]+, 430.2 [M+HCOO]-; t_R (HPLC conditions a): 1.93 min.

E. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

A solution of (2S,3S,4S)-4-hydroxy-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2S,3R,4R)-3-hydroxy-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (17.8 g, 46.2 mmol) in CH_2Cl_2 (250 mL) was cooled under Argon at -78°C and DAST (12.2 mL, 92 mmol) was added dropwise. The reaction mixture was allowed to reach RT and further stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and carefully quenched with a sat. aq. solution of $NaHCO_3$. The layers were separated, the aqueous layer extracted twice with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 10:0 to 0:10) gave a mixture of the 2 regioisomers as a yellow solid. R_f, TLC (EtOAc) = 0.5; MS (UPLC/MS): 388.3 [M+H]+, 405.3 $[M+NH_4]$+; t_R (HPLC conditions e): 2.15 min.

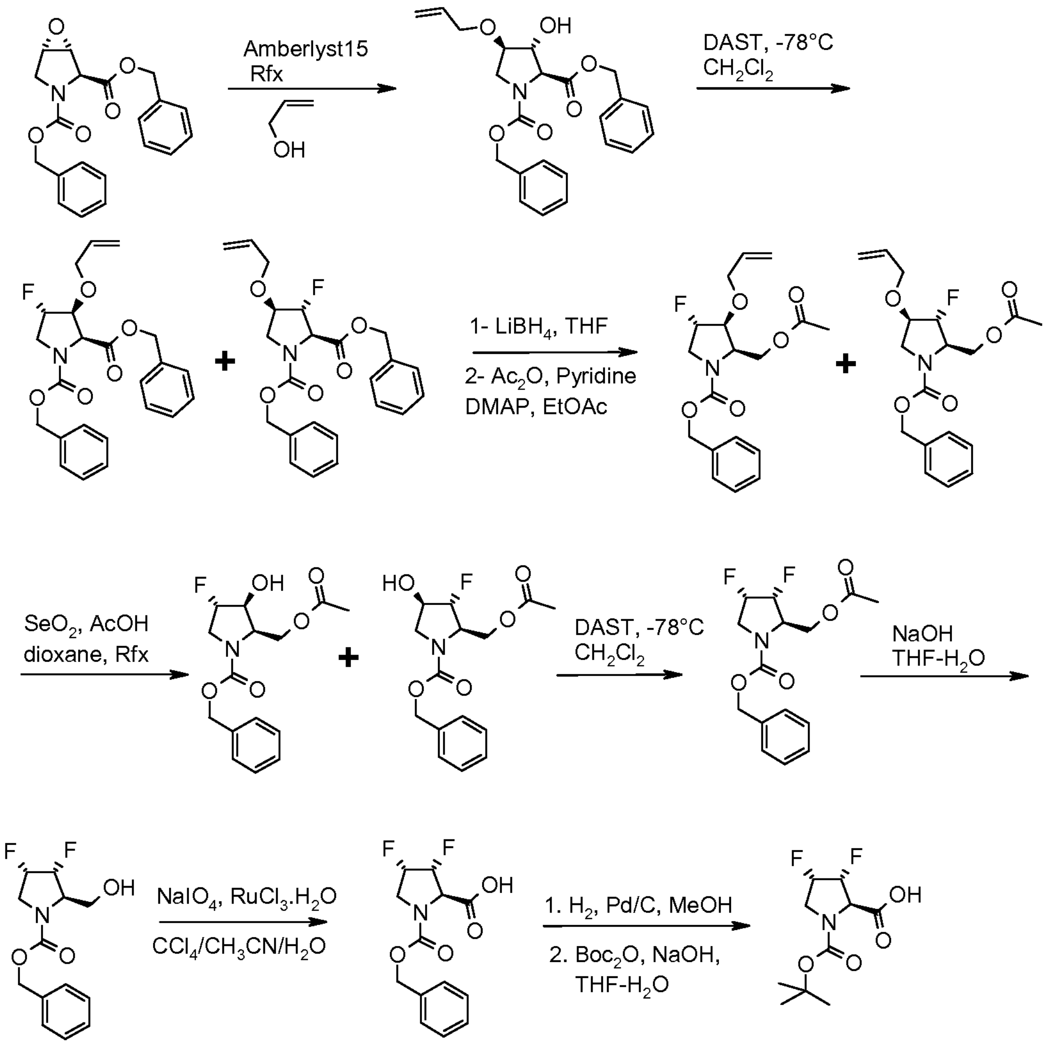
F. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-Fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (13.6 g, 35.1 mmol) in MeOH (110 mL) was added Pd/C 10% (1.3 g). The reaction was placed under hydrogen atmosphere (by degassing 3 times replacing air with nitrogen then nitrogen with hydrogen) and was stirred for 16 h. The mixture was placed under a nitrogen atmosphere and the catalyst was removed through a pad of Celite and washed with MeOH. After concentration, the residue was dissolved in a mixture of THF (110 mL) and water (55 mL) then aq. 1N NaOH (70.2 mL) and Boc anhydride (16.3 g, 70.2 mmol) were added and the reaction mixture was stirred at RT for 72 h. After concentration, the crude residue was dissolved in water and extracted twice with Et_2O. The aqueous layer was acidified to pH = 1 by addition of HCl 2N and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the desired mixture of regioisomers which was used without further purification in the next step. R_f, TLC (EtOAc) = 0.1; MS (UPLC/MS): 264 [M+H]+.

G. (2S,3S,4S)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of(2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (900 mg, 3.42 mmol) in dry CH_2Cl_2 (21.5 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (0.452 ml, 3.42 mmol) at 0°C under a nitrogen atmosphere. Formation of the acyl chloride intermediate was monitored by TLC after quenching of an aliquot with MeOH to form the corresponding methyl ester. After completion (2 h), 6-bromo-pyrazin-2-ylamine (1774 mg, 10.26 mmol) was added at 0°C, followed by DIPEA (3.58 mL, 20.51 mmol) and the reaction mixture further stirred 2 h at RT. The reaction mixture was concentrated, MeOH was added and the solution was concentrated again. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5µm, 30x100mm, gradient: 0-0.5 min 5% CH_3CN in H_2O, Flow: 5mL/min; 0.5-18.5 min 5 to 100% CH_3CN in H_2O, Flow: 40mL/min; 18.5-20 min 100% CH_3CN, Flow: 40mL/min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, neutralized with an aq. sat. solution of $NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated to give the title compound as a white powder. R_f, TLC (EtOAc) = 0.8; MS (UPLC-MS): 418.1/420.1 [M+H]+, 416.2/418.1 [M-H]-; t_R (HPLC conditions f): 2.18 min.

Scheme B4: Preparation of (2R,3R,4S)-1-(tert-Butoxycarbonyl)-3,4-difluoropyrrolidine-2-carboxylic acid



A. (2S,3R,4R)-Dibenzyl 4-(allyloxy)-3-hydroxypyrrolidine-1,2-dicarboxylate

To a solution of (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester (20 g, 53.8 mmol) in allyl alcohol (73.5 mL) was added Amberlyst 15 (20 g). The reaction mixture was refluxed for 3 h, then allowed to cool to RT and filtered. Amberlyst 15 residue was washed with CH_2Cl_2. The combined filtrates were concentrated and purified by flash column chromatography on silica gel (c-hexane 100% to c-hexane/EtOAc 1/1) to give the title compound. R_f, TLC (c-hexane/EtOAc 2:1) = 0.3; MS (UPLC/MS): 412.2 [M+H]+, 429.2 [M+NH$_4$]+, 456.2 [M+HCOO]-, 867.4 [2M+HCOO]-; t_R (HPLC conditions f): 2.37 min.

B. (2S,3S,4S)-Dibenzyl 3-(allyloxy)-4-fluoropyrrolidine-1,2-dicarboxylate and (2R,3R,4R)-dibenzyl 4-(allyloxy)-3-fluoropyrrolidine-1,2-dicarboxylate

A solution of (2S,3R,4R)-dibenzyl 4-(allyloxy)-3-hydroxypyrrolidine-1,2-dicarboxylate (5.86 g, 13.82 mmol) in CH_2Cl_2 (50 mL) was cooled under nitrogen at -78°C and DAST (6.08 mL, 41.4 mmol) was added dropwise. The reaction mixture was allowed to reach RT in 4.5 h and further stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and carefully quenched with a sat. aq. solution of $NaHCO_3$. The layers were separated, the aqueous layer extracted twice with

CH_2Cl_2, the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 10:0 to 8:2) gave the title compounds as a mixture of 2 regioisomers as a yellow oil. R_f, TLC (c-hexane/EtOAc 2:1) = 0.6; MS (UPLC/MS): 414.3 [M+H]+, 431.2 [M+NH_4]+, 844.4 [2M+NH_4]+; t_R (HPLC conditions f): 2.69 min.

C. (2R,3S,4S)-Benzyl 3-(allyloxy)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 4-(allyloxy)-3-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate

To a solution of (2S,3S,4S)-dibenzyl 3-(allyloxy)-4-fluoropyrrolidine-1,2-dicarboxylate and (2R,3R,4R)-dibenzyl 4-(allyloxy)-3-fluoropyrrolidine-1,2-dicarboxylate (4.1 g, 9.92 mmol) in THF (50 mL) at 0°C under a nitrogen atmosphere, was added $LiBH_4$ (2 M in THF, 9.92 mL, 19.83 mmol). The resulting yellow solution was stirred at 0°C for 2 h and then at RT for 18 h. The reaction mixture was slowly poured into a cold aqueous solution of $NaHCO_3$ and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1/1) to give the title compounds as a mixture of 2 regioisomers. R_f, TLC (c-hexane/EtOAc 2:1) = 0.3; MS (UPLC/MS): 310.2 [M+H]+, 354.2 [M+HCOO]-.

D. (2R,3S,4S)-Benzyl 2-(acetoxymethyl)-3-(allyloxy)-4-fluoropyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 2-(acetoxymethyl)-4-(allyloxy)-3-fluoropyrrolidine-1-carboxylate

To a solution of (2R,3S,4S)-benzyl 3-(allyloxy)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 4-(allyloxy)-3-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.35 g, 4.15 mmol) in EtOAc (40 mL) cooled at 0°C under a nitrogen atmosphere were added acetic anhydride (392 μL, 4.15 mmol), pyridine (334 μL, 4.15 mmol) and 4-dimethylaminopyridine (253 mg, 2.07 mmol). The reaction mixture was allowed to reach RT and was stirred for 2 h. EtOAc and water were added, the layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1/1) to give the title compounds as a mixture of 2 regioisomers a colorless oil. R_f, TLC (c-hexane/EtOAc 2:1) = 0.5; MS (UPLC/MS): 352.2 [M+H]+, 369.2 [M+NH_4]+; t_R (HPLC conditions f): 2.39 and 2.43 min.

E. (2R,3S,4S)-Benzyl 2-(acetoxymethyl)-4-fluoro-3-hydroxypyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 2-(acetoxymethyl)-3-fluoro-4-hydroxypyrrolidine-1-carboxylate

To a solution of (2R,3S,4S)-benzyl 2-(acetoxymethyl)-3-(allyloxy)-4-fluoropyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 2-(acetoxymethyl)-4-(allyloxy)-3-fluoropyrrolidine-1-carboxylate (1.12 g, 3.17 mmol) and selenium dioxide (387 mg, 3.49 mmol) in dioxane (15 mL) was added acetic acid (272 μL, 4.76 mmol). The dark reaction mixture was stirred at reflux for

2.5 h. EtOAc was added and the reaction mixture was filtered, the filtrate was concentrated and purified by flash column chromatography on silica gel (RediSep-Gold column, c-hexane to c-hexane/EtOAc 1/1) to afford a mixture of the title compounds as a yellow oil. MS (UPLC/MS): 312.1 [M+H]+, 329.2 [M+NH4]+, 356.1 [M+HCOO]-; t_R (HPLC conditions f): 1.83 and 1.86 min.

F. (2R,3R,4S)-Benzyl 2-(acetoxymethyl)-3,4-difluoropyrrolidine-1-carboxylate

A solution of (2R,3S,4S)-benzyl 2-(acetoxymethyl)-4-fluoro-3-hydroxypyrrolidine-1-carboxylate and (2R,3R,4R)-benzyl 2-(acetoxymethyl)-3-fluoro-4-hydroxypyrrolidine-1-carboxylate (540 mg, 1.735 mmol) in CH_2Cl_2 (6 mL) was cooled under nitrogen at -78°C and DAST (1.15 mL, 8.67 mmol) was added dropwise. The reaction mixture was allowed to reach RT in 2 h and further stirred for 21 h. The reaction mixture was diluted with CH_2Cl_2 and carefully poured into a sat. aq. solution of $NaHCO_3$. The layers were separated, the aqueous layer extracted twice with CH_2Cl_2, the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (RediSep Gold column-40 g, c-hexane to c-hexane/EtOAc 1/1) afforded the title compound as a yellow oil. The relative stereochemistry (2R,3R,4S) was attributed based on Roesy NMR experiments. R_f, TLC (c-hexane/EtOAc 2:1) = 0.4; MS (UPLC/MS): 314.1 [M+H]+, 331.1 [M+NH_4]+, 358.2 [M+HCOO]-; t_R (HPLC conditions f): 2.12 min.

F. (2R,3R,4S)-Benzyl 3,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate

To a solution of (2R,3R,4S)-Benzyl 2-(acetoxymethyl)-3,4-difluoropyrrolidine-1-carboxylate (295 mg, 0.94 mmol) in THF (8.5 mL) and water (850 µL) was added NaOH (1N, 1.88 mL, 1.88 mmol) and the reaction mixture was stirred at RT for 2 h. EtOAc and water were added. The layers were separated and and the aqueous layer was extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was used without purification in the next step. MS (UPLC/MS): 272.1 [M+H]+, 289.1 [M+H_2O]+, 565.2 [2M+H]+, 316.1 [M-H]-; t_R (HPLC conditions f): 1.82 min.

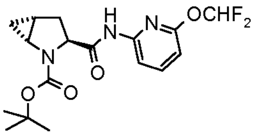
G. (2R,3R,4S)-1-(Benzyloxycarbonyl)-3,4-difluoropyrrolidine-2-carboxylic acid

To a solution of (2R,3R,4S)-benzyl 3,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (245 mg, 0.90 mmol) in CCl_4/ CH_3CN/ H_2O (ratio 2/2/3; 6.3 mL) were successively added $NaIO_4$ (580 mg, 2.71 mmol) and $RuCl_3.H_2O$ (7.5 mg, 0.04 mmol). The dark reaction mixture was stirred vigorously at RT until completion (3 h). CH_2Cl_2 was added (+ a few drops of aqueous 1 M HCl, to acidify the mixture) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (x2) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to afford the title compound which was used in the next step without further purification. MS (UPLC/MS): 286.1 [M+H]+, 303.1 [M+H_2O]+, 284.1 [M-H]-, 569.2 [2M-H]-; t_R (HPLC conditions f): 1.80 min.

H. (2R,3R,4S)-1-(tert-Butoxycarbonyl)-3,4-difluoropyrrolidine-2-carboxylic acid

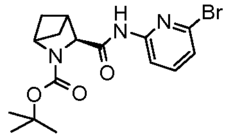
To a solution of (2R,3R,4S)-1-(benzyloxycarbonyl)-3,4-difluoropyrrolidine-2-carboxylic acid (175 mg, 0.58 mmol) in MeOH (7 mL) was added Pd/C 10% (35 mg). The reaction mixture was placed under hydrogen atmosphere (by degassing 3 times replacing air with nitrogen then nitrogen with hydrogen) and was stirred for 1 h. The mixture was placed under a nitrogen atmosphere and the catalyst was removed through a pad of Celite and washed with MeOH. After concentration, the residue was dissolved in a mixture of THF (7 mL) and water (3.5 mL) then 10% aq. NaOH (1.17 mmol) and Boc anhydride (254 mg, 1.17 mmol) were added and the reaction mixture was stirred at RT for 16 h. After concentration, the crude residue was dissolved in water and extracted twice with Et_2O. The aqueous layer was acidified to pH = 1 by addition of HCl 1N and extracted twice with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 8/2) to give the title compound. R_f, TLC (CH_2Cl_2/MeOH 8/2) = 0.2. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 5.30-5.12 (m, 2H), 4.10 (bt, 1H), 3.78 (m, 1H), under water signal (m, 1H), 1.41 (s, 3H), 1.36 (s, 6H).

<u>(1R,3S,5R)-3-(6-Difluoromethoxy-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester</u>



To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (121 mg, 0.53 mmol) in dry THF (3 mL) at -20°C was added triethylamine (85 µL, 0.61 mmol) followed by ethylchloroformate (0.051 mL, 0.53 mmol) dropwise under argon. The reaction mixture was stirred at -20°C for 80 min. A solution of 6-difluoromethoxy-pyridin-2-ylamine hydrochloride (prepared as described in Part C, 100 mg, 0.509 mmol) and triethylamine (85 µL, 0.61 mmol) in dry DMF (1 mL) was added, the reaction mixture was stirred at the same temperature for an additional 1 h, warmed up to room temperature and stirred for 60 h at 50°C. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound. MS (UPLC-MS): 370 [M+H]+; t_R (HPLC conditions d): 4.90 min.

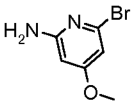
<u>tert-Butyl 3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate</u>



To an ice-cooled solution of 2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-3-carboxylic acid (prepared in a similar manner as described by K. L. Gorres et al., *Biochemistry*, **2008**, *47*, 9447)(45 mg, 0.198 mmol) in CH_2Cl_2 (1.5 mL) under nitrogen atmosphere was added 1-methylimidazole (0.039 mL, 0.495 mmol) and the mixture was stirred for 10 min. Methanesulfonyl chloride (0.017 mL, 0.218 mmol) was added and the mixture was stirred at 0°C for 20 min. 2-Amino-6-bromopyridine (34.3 mg, 0.198 mmol) was added and the dark solution was stirred at RT overnight. Water was added and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAC 7:3) to afford the title compound as a powder. R_f, TLC (c-hexane/EtOAc 7/3) = 0.5; MS (UPLC-MS): 382.2/384.2 [M+H]+, 380.1/382.2 [M-H]-; t_R (HPLC conditions f): 2.38 min.

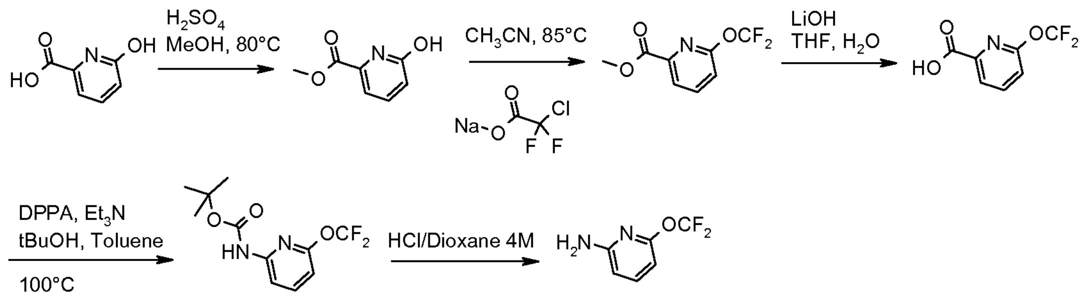
Part C: Synthesis of 2-phenyl-cyclopropylamine intermediates:

6-Bromo-4-methoxy-pyridin-2-ylamine



A solution of 6-bromo-4-chloro-pyridin-2-ylamine (200 mg, 0.964 mmol) and sodium methanolate (0.5 M in MeOH, 12.5 ml, 6.25 mmol) was subjected to microwave irradiation at 120°C for 2 h, then at 140°C for 1 h. Et_2O and water were added, the layers were separated and the aqueous layer was extracted with Et_2O (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5μm, 30x100mm, gradient: 0-0.5 min 5% CH_3CN in H_2O, Flow: 5mL/min; 0.5-18.5 min 5 to 100% CH_3CN in H_2O, Flow: 40mL/min; 18.5-20 min 100% CH_3CN, Flow: 40mL/min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, neutralized with a sat. aq. solution of Na_2CO_3 and extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound as white solid. R_f, TLC (EtOAc) = 0.75; MS (UPLC-MS): 203.0/205.0 [M+H]+; t_R (HPLC conditions g): 0.76 min.

Scheme C1: Preparation of 6-difluoromethoxy-pyridin-2-ylamine hydrochloride



A. Methyl 6-hydroxypicolinate

To a solution of 6-hydroxypicolinic acid (3.0 g, 21.6 mmol) in methanol (50 mL) was added concentrated sulfuric acid (2.70 mL, 50.7 mmol) slowly and the mixture was then refluxed under argon for 18 h. The volatiles were evaporated and a sat. aq. solution of $NaHCO_3$ was added slowly until the aqueous phase showed a pH of 7-8. The resultant mixture was extracted with CH_2Cl_2 (x3), the combined organic extracts were dried (phase separator) and concentrated under vacuum to give the title compound as a pale-brown solid. MS (LC-MS): 154 [M+H]+; t_R (HPLC conditions d): 1.96 min.

B. Methyl 6-(difluoromethoxy)picolinate

To a stirred solution of methyl 6-hydroxypicolinate (1.38 g, 9.01 mmol) in dry acetonitrile (25 mL) at RT was added sodium 2-chloro-2,2-difluoroacetate (2.75 g, 18.0 mmol). The reaction mixture was stirred at 85°C for 78 h. The reaction mixture was diluted with CH_3CN and filtered, the filtrate was concentrated under reduced pressure (40 mbar). The residual oil was used directly in the next step. MS (LC-MS): 204 [M+H]+; t_R (HPLC conditions d): 3.88 min.

C. 6-(Difluoromethoxy)picolinic acid

To a solution of methyl 6-(difluoromethoxy)picolinate (1.83 g, 9.01 mmol) in THF (30 mL) was added 2N aq. LiOH (18.0 mL, 36.0 mmol) and the reaction was stirred at RT for 2 h. 1M HCl was added to acidify the reaction mixture to pH = 2-3 and the resulting aqueous solution was concentrated under reduced pressure. The residue was purified by preparative HPLC (Macherey-Nagel Nucleosil 100-10 C18, 5 µm, 40x250 mm, flow: 40 ml/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound. MS (LC-MS): 190 [M+H]+; t_R (HPLC conditions d): 3.23 min.

D. *tert*-Butyl 6-(difluoromethoxy)pyridin-2-ylcarbamate

A suspension of 6-(difluoromethoxy)picolinic acid (1.30 g, 4.30 mmol) in a mixture of toluene (40 mL) and *tert*-butanol (4 mL) was treated successively with Et_3N (2.40 mL, 17.2 mmol) and DPPA

(1.40 mL, 6.46 mmol) and the solution was stirred at 100°C for 16 h. After cooling to RT, the reaction mixture was diluted with EtOAc. The organic layer was washed with a sat. aq. solution of $NaHCO_3$ and brine, dried (phase separator), and concentrated. The residual oil was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 ml/min, eluent: 15-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound. MS (LC-MS): 261 [M+H]+; t_R (HPLC conditions d): 5.15 min.

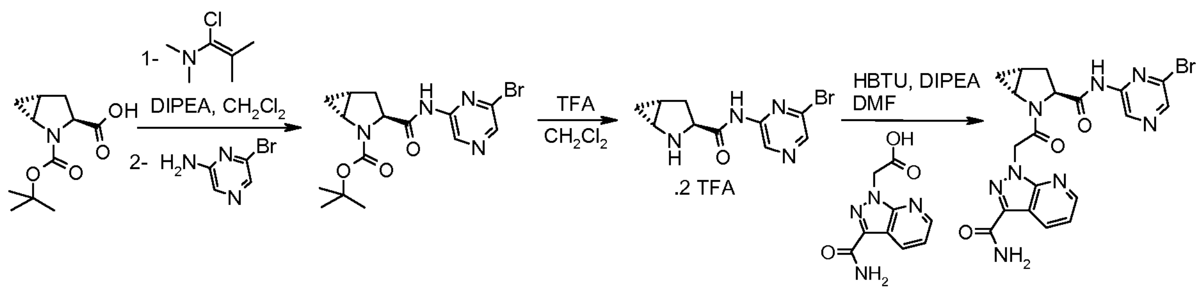
E. 6-(Difluoromethoxy)pyridin-2-ylamine hydrochloride

Tert-butyl 6-(difluoromethoxy)pyridin-2-ylcarbamate (780 mg, 3.00 mmol) was dissolved in 4M HCl in dioxane (16.0 mL, 64.0 mmol) and the resulting solution was stirred at RT for 16 h. The solvent was evaporated, the material was redissolved in dichloromethane and evaporated again to recover the title compound as a hydrochloride salt. MS (LC-MS): 161 [M+H]+; t_R (HPLC conditions d): 3.22 min.

Part D: Synthesis of examples 1 to 39

[1]H NMR data for selected compounds can be found at the end of Part D.

Scheme D1: General protocol described for the preparation of Example 1: 1-{2-[(1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide



A. (1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (680 mg, 2.99 mmol) in dry CH_2Cl_2 (16 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (0.435 ml, 3.29 mmol) at 0°C under a nitrogen atmosphere. Formation of the acyl chloride intermediate was monitored by TLC after quenching of an aliquot with MeOH to form the corresponding methyl ester. After completion (2 h), 6-bromo-pyrazin-2-ylamine (573 mg, 3.29 mmol) was added at 0°C, followed by DIPEA (1.05 ml, 5.98 mmol) and the reaction mixture was further stirred 2 h at RT. The reaction mixture was concentrated, MeOH was added and the solution was concentrated again. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 0:1) to give the title compound. TLC, R_f (EtOAc) = 0.90; MS (UPLC-MS): 383.1/385.1 [M+H]+, 381.2/383.0 [M-H]-; t_R (HPLC conditions f): 2.12 min.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide di(trifluoroacetate) salt

To a solution of (1R,3S,5R)-3-(6-bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (720 mg, 1.88 mmol) in CH_2Cl_2 (15 mL) was added TFA (1.45 ml, 18.79 mmol) and the solution was stirred at RT for 2 h. Volatils were evaporated and the crude residue was dried under high vacuum to give the title compound which was stored in the freezer and used without further purification in the next step. MS (UPLC/MS): 283.0/285.0 [M+H]+, 281.0/283.0 [M-H]-; t_R (HPLC conditions f): 0.45 min.

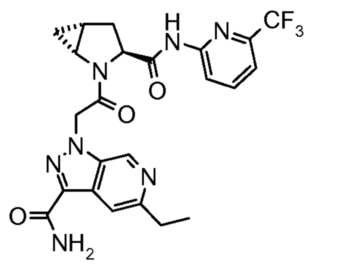
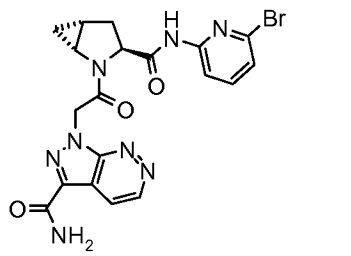
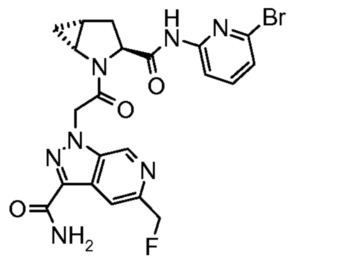
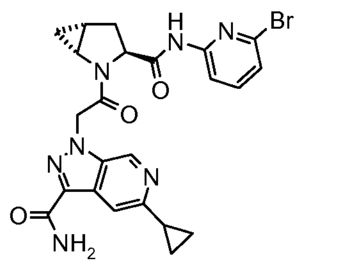
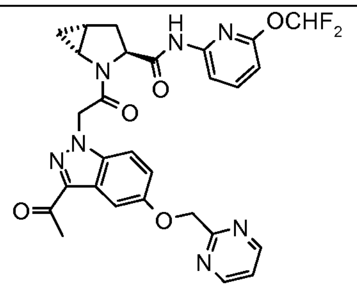
C. Example 1: 1-{2-[(1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide

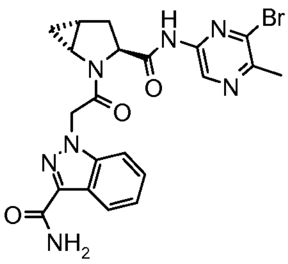
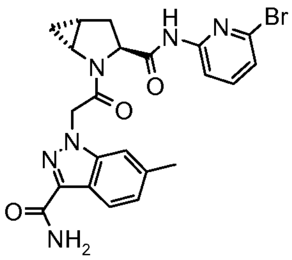
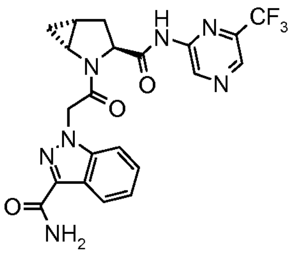
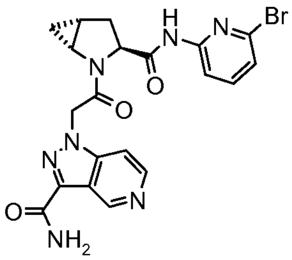
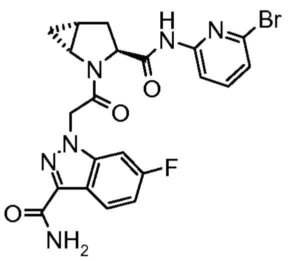
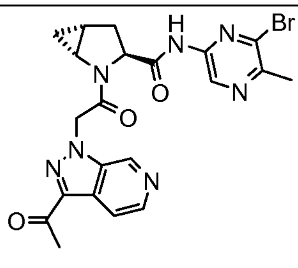
(3-Carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid (68.3 mg, 0.204 mmol, prepared as described in Part A), (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide (2 TFA salt, 110 mg, 0.204 mmol) and HBTU (116 mg, 0.307 mmol) were dissolved in DMF (0.8 mL). DIPEA (214 µL, 1.23 mmol) was added and the reaction mixture was stirred at 25°C for 2 h. The crude reaction mixture was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 5% to 100% CH_3CN in H_2O in 18 min, 100% CH_3CN for 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, neutralized with an aq. sat. solution of $NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated to give the title compound as a white powder. TLC, R_f (EtOAc) = 0.25; MS (UPLC/MS): 485.0/487.1 [M+H]+, 483.1/485.0 [M-H]-; t_R (HPLC conditions g): 2.57 min.

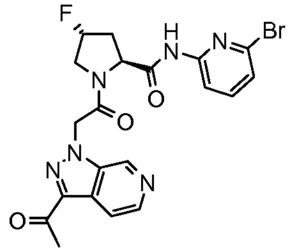
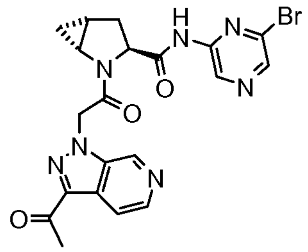
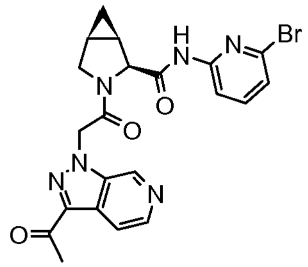
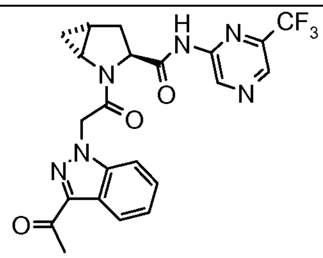
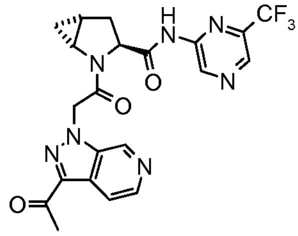
The examples below were prepared according to the general procedures described in Scheme D1 for **Example 1** *using commercially available building blocks if not otherwise stated (see notes at the end of table 1):*

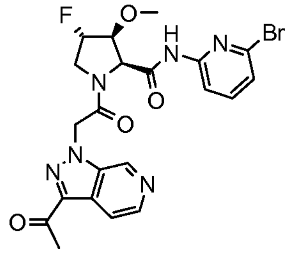
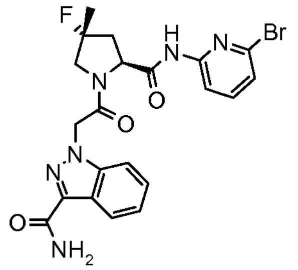
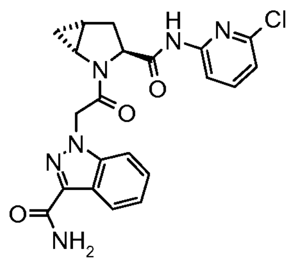
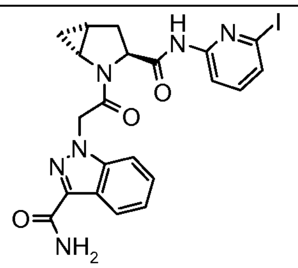
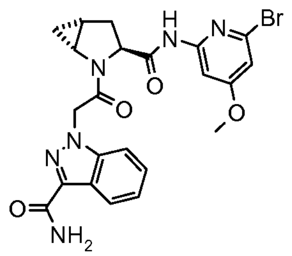
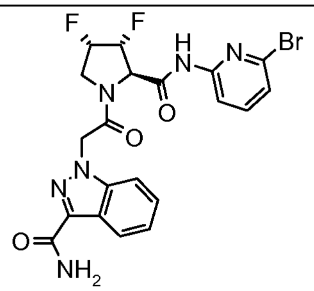
Table 1:

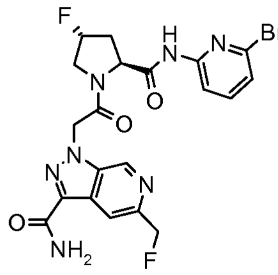
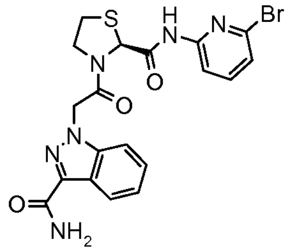
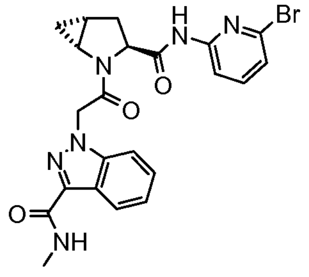
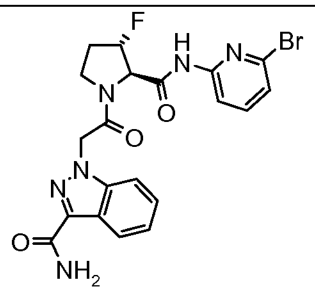
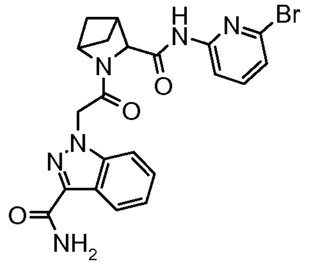
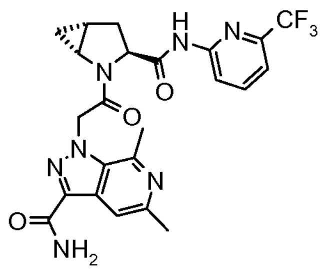
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)

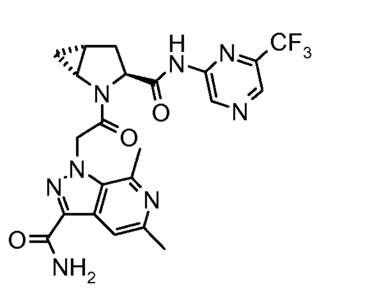
2		5-Ethyl-1-{2-oxo-2-[(1R,3S,5R)-3-(6-trifluoro methyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.50 ; 489.1/191.0 [M+H]+, 487.1/489.0 [M-H]-; t_R (a): 2.22 min.
3		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridazine-3-carboxylic acid amide	(1) 487.1/485.1 [M+H]+, 485.3/483.1 [M-H]-; t_R (d): 3.62 min.
4		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-fluoromethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 485.2 [M+Na]+;]-; t_R (d): 3.47 min.
5		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 524/526 [M+H]+; t_R (d): 3.53 min.
6		(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-difluoro methoxy-pyridin-2-yl)-amide	(1,2) 578 [M+H]+; t_R (d): 4.50 min.

7		1-{2-[(1R,3S,5R)-3-(6-Bromo-5-methyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (EtOAc) = 0.45 ; 498.1/500.1 [M+H]+, 496.1/498.1 [M-H]-; t_R (a): 2.73 min.
8		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-methyl-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.75; 497.1/499.1 [M+H]+, 514.2/516.1 [M+NH4]+, 541.3/543.0 [M+HCOO]-; t_R (a): 2.70 min.
9		1-{2-Oxo-2-[(1R,3S,5R)-3-(6-trifluoromethyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.60; 474.3 [M+H]+, 491.3 [M+NH_4]+, 472.3 [M-H]-, 518.3 [M+HCOO]-; t_R (a): 2.51 min.
10		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[4,3-c] pyridine-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0; 484.1/486.1 [M+H]+, 482.1/482/484.1 [M-H]-; t_R (g): 2.00 min.
11		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-fluoro-1H-indazole-3-carboxylic acid amide	(1) 501.1/503.1 [M+H]+, 523.1/525.1 [M+Na]+, 499.0/501.1 [M-H]-, 545.6/547.0 [M+HCOO]- ; t_R (a): 3.05 min.
12		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid (6-bromo-5-methyl-	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 498.1/500.1 [M+H]+, 520.1/522.1 [M+Na]+, 496.1/498.1 [M-H]-; t_R

		pyrazin-2-yl)-amide	(g): 2.52 min.
13		(2S,4R)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 489.1/491.1 [M+H]+, 511.0/513.1 [M+Na]+, 487.1/489.1 [M-H]-; t_R (g): 2.41 min.
14		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.6; 484.2/486.3 [M+H]+, 967.4/969.3 [2M+H]+, 482.2/484.2 [M-H]-, 965.2/967.4 [2M-H]-; t_R (g): 2.31 min.
15		(1R,2S,5S)-3-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo [3.1.0]hexane-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.65; 483.1/485.1 [M+H]+, 965.2/967.2 [2M+H]+, 481.1/483.1 [M-H]-, 527.0/529.1 [M+HCOO]-, 963.2/965.2 [2M-H]-; t_R (g): 2.71 min.
16		(1R,3S,5R)-2-[2-(3-Acetyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-trifluoro methyl-pyrazin-2-yl)-amide	(1) R_f (EtOAc) = 0.75; 473.3 [M+H]+, 471.3 [M-H]-; t_R (g): 4.27 min.
17		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid (6-trifluoromethyl-pyrazin-2-yl)-amide	(1) R_f (EtOAc) = 0.22; 0.45 ;474.2 [M+H]+, 472.2 [M-H]-; t_R (g): 2.66 min.

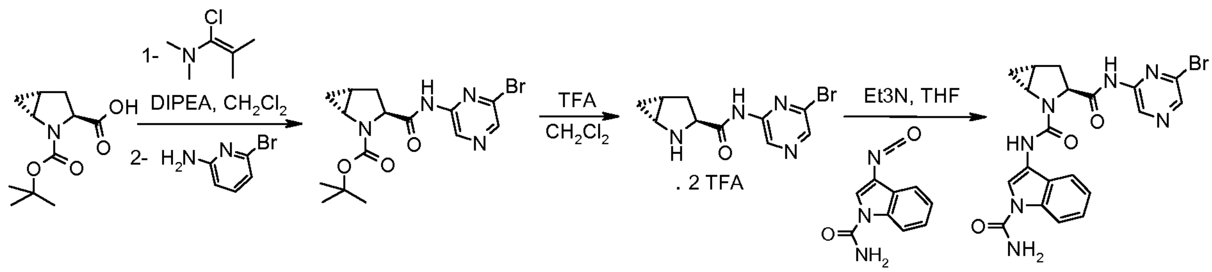
18		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1,2) R_f (EtOAc) = 0.25; 519.1/521.1 [M+H]+, 517.2/519.0 [M-H]-; t_R (g): 2.69 min.
19		1-{2-[(2S,4R)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,3) R_f (EtOAc) = 0.55; 503.1/505.1 [M+H]+, 501.1/503.0 [M-H]-; t_R (g): 3.31 min.
20		1-{2-[(1R,3S,5R)-3-(6-Chloro-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.40; 439.2/441.1 [M+H]+, 456.2/458.1 [M+NH_4]+, 894.3/896.3 [2M+NH_4]+, 437.1/439.1 [M-H]-; t_R (g): 3.29 min.
21		1-{2-[(1R,3S,5R)-3-(6-Iodo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.45; 531.1 [M+H]+, 553.0 [M+Na]+, 529.1 [M-H]; t_R (g): 3.63 min.
22		1-{2-[(1R,3S,5R)-3-(6-Bromo-4-methoxy-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,4) R_f (EtOAc) = 0.40; 513.1/515.1 [M+H]+, 511.1/513.1 [M-H]-; t_R (g): 3.68 min.
23		1-{2-[(2R,3R,4S)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-3,4-difluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 95:5) = 0.55; 507.1/509.1 [M+H]+, 524.1/526.2 [M+NH_4]+, 505.1/507.1 [M-H]-; t_R (h): 3.25 min.

24		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(fluoromethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	(1) 522.1/524.1 [M+H]+, 520.1/522.1 [M-H]-; t_R (h): 2.55 min.
25		(S)-N-(6-bromopyridin-2-yl)-3-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl) thiazolidine-2-carboxamide	(1) R_f (AcOEt) = 0.5; 489.1/491.1 [M+H]+ 487.1/489.1 [M-H]-; t_R (h): 3.23 min.
26		1-(2-((1R,3S,5R)-3-((6-bromopyridin-2-yl) carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-N-methyl-1H-indazole-3-carboxamide	(1) R_f (AcOEt) = 0.55; 497.2/499.2 [M+H]+, 495.2/497.1 [M-H]-; t_R (h): 3.47 min.
27		1-(2-((2R,3S)-2-((6-bromopyridin-2-yl) carbamoyl)-3-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide	(1,5) R_f (CH_2Cl_2/MeOH 95/5) = 0.55; 489.1/491.1 [M+H]+, 487.1/489.1 [M-H]-; t_R (h): 3.32 min.
28		N-(6-bromopyridin-2-yl)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl)-2-azabicyclo [2.1.1]hexane-3-carboxamide	(1,2) R_f (CH_2Cl_2/MeOH 95/5) = 0.55; 483.1/485.2 [M+H]+ 481.2/483.2 [M-H]-; t_R (h): 3.65 min.
29		5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	(1,6) R_f (CH_2Cl_2/MeOH 9/1) = 0.50; 502.3 [M+H]+, 500.2 [M-H]-; t_R (h): 2.45 min.

30		5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyrazin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	(1,6) R_f (CH_2Cl_2/MeOH 9/1) = 0.45; 503.2 [M+H]+, 1005.5 [2M+H], 501.3 [M-H]-, 1003.5 [2M-H]-; t_R (h): 2.07 min.

(1) The acid derivative used is step C was prepared as described in Part A; (2) The title compound was prepared according to the general procedure described in Scheme D1 steps B and C starting from the substituted proline derivative prepared as described in Part B; (3) The acid derivative used in step A was prepared as described in Part B; (4) The amine derivative used in step A was prepared as described in Part C; (5) (2R,3R)-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester used in step A was prepared according to the procedure described in WO2012/093101; (6) Step C was performed in CH_2Cl_2 using T_3P (50% in AcOEt) instead of HBTU in DMF.

Scheme D2: General protocol described for the preparation of Example 31: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]



A. (1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (680 mg, 2.99 mmol) in dry CH_2Cl_2 (16 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (435 µL, 3.29 mmol) at 0°C under nitrogen atmosphere. Formation of the acyl chloride intermediate was monitored by TLC after quenching of an aliquot with MeOH to form the corresponding methyl ester. After completion (1-1.5 h), 2-bromo-6-aminopyrazine (573 mg, 3.29 mmol) was added at 0°C, followed by DIPEA (1.045 mL, 5.98 mmol) and the reaction mixture further stirred 2 h at RT. The reaction mixture was concentrated and purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 0:1) to give the title compound. TLC, R_f (EtOAc) = 0.85; MS: 383.1/385.1 [M+H]+, 381.2/383.0 [M-H]-; t_R (HPLC conditions f): 2.12 min.

B. (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide di(trifluoroacetate) salt

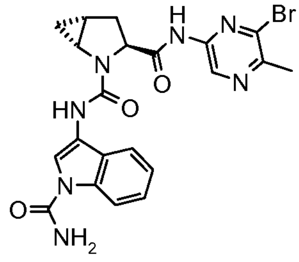
To a solution of (1R,3S,5R)-3-(6-bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (720 mg, 1.88 mmol) in CH_2Cl_2 (15 mL) was added TFA (1.45 mL, 18.79 mmol) and the solution was stirred 2 h at RT. CH_2Cl_2 was concentrated and the crude residue was dried under high vacuum to give the title compound as a yellow oil which was stored in the freezer and used without further purification in the next step. MS: 283.0/285.0 [M+H]+, 281.0/283.0 [M-H]-; t_R (HPLC conditions f): 0.45 min.

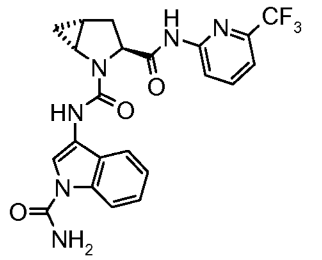
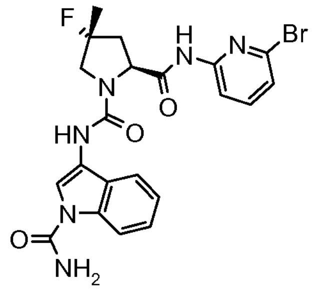
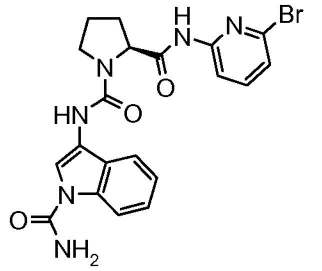
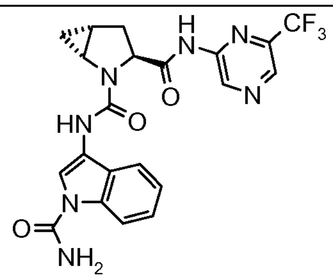
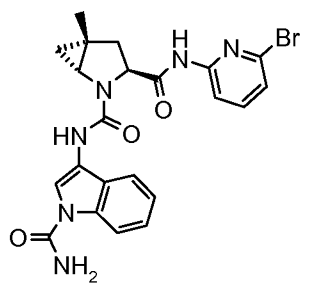
C. Example 31: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]

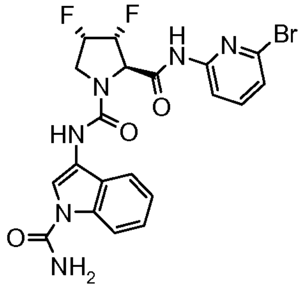
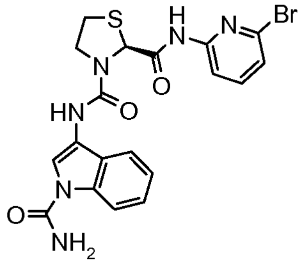
To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide (2 TFA salt, 700 mg, 1.30 mmol) and 3-isocyanato-indole-1-carboxylic acid amide (262 mg, 1.30 mmol, prepared as described in Part A) in THF (9 mL) was added Et_3N (0.907 mL, 6.50 mmol) under a nitrogen atmosphere. The resulting solution was stirred at RT under nitrogen for 20 min, then poured into water and extracted EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 30x100mm, eluent: 0-0.5 min 5% CH_3CN in H_2O, flow: 5mL/min; 0.5-18.5 min 5 to 100% CH_3CN in H_2O, flow: 40mL/min; 18.5-20 min 100% CH_3CN, CH_3CN and H_2O both containing 0.1% TFA) to give the title compound after neutralization (saturated aqueous solution of $NaHCO_3$) and extraction (CH_2Cl_2) of the purified fractions. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45; MS (UPLC/MS): 484.1/486.1 [M+H]+, 501.1/503.1 [M+18]+, 482.2/484.2 [M-H]-; t_R (HPLC conditions g): 3.45 min.

The examples below were prepared according to the general procedures described in Scheme D2 for **Example 31** *using commercially available building blocks if not otherwise stated (see notes at the end of table 2):*

Table 2:

Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)
32		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-5-methyl-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-	R_f (CH_2Cl_2/MeOH 95:5) = 0.3; 498.1/500.0 [M+H]+, 496.2/498.1 [M-H]-; t_R (g): 3.52 min.

		amide]	
33		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyridin-2-yl)-amide]	473.2 [M+H]+, 945.3 [2M+H]+, 471.1 [M-H]-, 943.3 [2M-H]-; t_R (g): 3.91 min
34		(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) R_f (EtOAc) = 0.75; 503.1/505.1 [M+H]+, 501.0/503.1 [M-H]-; t_R (g): 3.54 min
35		(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide]-1-[(1-carbamoyl-1H-indol-3-yl)-amide]	R_f (EtOAc) = 0.60; 471.1/473.1 [M+H]+, 469.2/471.0 [M-H]-; t_R (g): 3.42 min
36		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyrazin-2-yl)-amide]	R_f (CH_2Cl_2/MeOH 95:5) = 0.35; 474.1 [M+H]+, 491.2 [$M+NH_4$]+, 472.2 [M-H]-, 945.4 [2M-H]-; t_R (g): 3.76 min.
37		(1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyridin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) R_f (CH_2Cl_2/MeOH 95:5) = 0.55; 497.1/499.1 [M+H]+, 993.2/995.2 [2M+H]+, 495.1/497.1 [M-H]-; t_R (g): 4.31 min.

38		(2R,3R,4S)-N2-(6-bromopyridin-2-yl)-N1-(1-carbamoyl-1H-indol-3-yl)-3,4-difluoropyrrolidine-1,2-dicarboxamide	(1) R_f (CH_2Cl_2/MeOH 95:5) = 0.55; 507.1/509.1 [M+H]+, 529.2/531.2 [M+Na]+, 505.1/507.1 [2M-H]-; t_R (h): 3.80 min.
39		(S)-N2-(6-bromopyridin-2-yl)-N3-(1-carbamoyl-1H-indol-3-yl)thiazolidine-2,3-dicarboxamide	489.1/491.2 [M+H]+ 487.1/489.2 [M-H]-; t_R (h): 3.64 min.

(1) The acid derivative used is step A was prepared as described in Part B.

[1]H NMR data for selected compounds:

Example 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.16 (s, 1H), 9.27 (s, 1H), 8.62 (d, 1H), 8.56 (m, 2H), 7.87 (s, 1H), 7.54 (s, 1H), 7.39 (dd, 1H), 5.83 (d, 1H), 5.54 (d, 1H), 4.46 (m, 1H), 3.88 (m, 1H), 2.34 (m, 1H), 2.25 (m, 1H), 1.95 (m, 1H), 1.06 (m, 1H), 0.70 (m, 1H).

Example 4: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.81 (s, 1H), 9.19 (s, 1H), 8.20 (s, 1H), 8.03 (d, 1H), 7.92 (s, 1H), 7.72 (t, 1H), 7.60 (s, 1H), 7.33 (d, 1H), 6.00 (d, 1H), 5.60 - 5.72 (m, 2H), 5.54 (s, 1H), 4.47 (dd, 1H), 3.83 (m, 1H), 2.34 (dd, 1H), 2.17 - 2.28 (m, 1H), 1.82 - 1.97 (m, 1H), 0.97 - 1.09 (m, 1H), 0.77 - 0.87 (m, 1H).

Example 6: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.48 (s, 1H), 8.84 (d, 2H), 7.84 - 7.92 (m, 2H), 7.72 - 7.36 (m, 4H), 7.22 (dd, 1H), 6.72 - 6.81 (m, 1H), 5.90 (d, 1H), 5.54 (d, 1H), 5.35 (s, 2H), 4.51 (dd, 1H), 3.80 - 3.87 (m, 1H), 2.58 (s, 3H), 2.27 - 2.38 (m, 1H), 2.16 - 2.27 (m, 1H), 1.84 - 1.97 (m, 1H), 0.96 - 1.08 (m, 1H), 0.78 (m, 1H).

Example 15: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.90 (s, 1H), 9.18 (s, 1H), 8.42 (d, 1H), 8.05 (m, 2H), 7.70 (t, 1H), 7.31 (d, 1H), 5.71 (s, 2H), 4.65 (m, 1H), 4.02 (m, 1H), 3.91 (d, 1H), 2.65 (s, 3H), 2.01 (m, 1H), 1.89 (m, 1H), 0.80 (m, 1H), 0.73 (m, 1H).

Example 22: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.73 (s, 1H), 8.19 (d, 1H), 8.67 (m, 3H), 8.45 (t, 1H), 7.39 (m, 1H), 7.27 (t, 1H), 6.97 (s, 1H), 5.81 (d, 1H), 5.49 (d, 1H), 4.45 (m, 1H), 3.80 (m, 1H), 2.31 (m, 1H), 2.20 (m, 1H), 1.89 (m, 1H), 1.01 (m, 1H), 0.74 (m, 1H).

Example 26: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.78 (s, 1H), 8.32 (m, 1H), 8.19 (d, 1H), 8.03 (d, 1H), 7.73 (t, 1H), 7.67 (d, 1H), 7.45 (t, 1H), 7.34 (d, 1H), 7.27 (d, 1H), 5.81 (d, 1H), 5.49 (d, 1H), 4.45 (m, 1H), 3.81 (m, 1H), 2.82 (d, 3H), 2.32 (m, 1H), 2.21 (m, 1H), 1.90 (m, 1H), 1.01 (m, 1H), 0.70 (m, 1H).

Example 31: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.10 (s, 1H), 9.33 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.28 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.39 (m, 2H), 7.27 (t, 1H), 7.20 (t, 1H), 4.37 (t, 1H), 3.94 (m, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 1.82 (m, 1H), 0.87 (m, 1H), 0.58 (m, 1H).

Example 36: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.28 (s, 1H), 9.65 (s, 1H), 8.89 (s, 1H), 8.68 (s, 1H), 8.28 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.39 (m, 2H), 7.27 (t, 1H), 7.20 (t, 1H), 4.42 (t, 1H), 3.95 (m, 1H), 2.41 (m, 1H), 2.22 (m, 1H), 1.83 (m, 1H), 0.87 (m, 1H), 0.58 (m, 1H).

Example 38: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.32 (s, 1H), 8.49 (s, 1H), 8.27 (d, 1H), 8.10 (d, 1H), 7.97 (s, 1H), 7.77 (m, 2H), 7.40 (m, 3H), 7.27 (t, 1H), 7.19 (t, 1H), 5.52-5.33 (m, 2H), 4.87 (m, 1H), 4.18 (m, 1H), 3.90 (m, 1H).

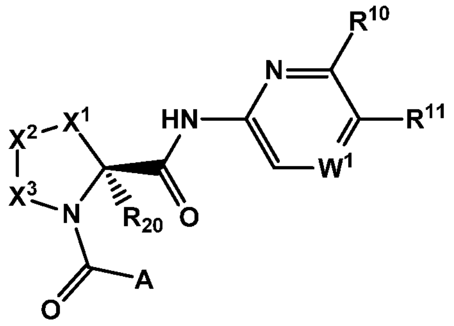
Factor D inhibition data using Method 1 to determine the IC_{50} values

Example	IC_{50} (μM)	Example	IC_{50} (μM)

1	0.019	**21**	0.003
2	0.018	**22**	0.005
3	0.024	**23**	0.008
4	0.002	**24**	0.007
5	0.004	**25**	0.010
6	0.038	**26**	0.040
7	0.006	**27**	0.080
8	0.005	**28**	0.120
9	0.032	**29**	0.006
10	0.009	**30**	0.080
11	0.005	**31**	0.004
12	0.016	**32**	0.005
13	0.009	**33**	0.013
14	0.011	**34**	0.014
15	0.014	**35**	0.020
16	0.017	**36**	0.055
17	0.064	**37**	0.008
18	0.007	**38**	0.010
19	0.011	**39**	0.020
20	0.004		

What is claimed is:

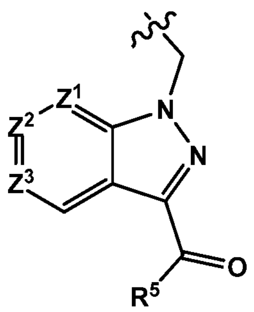
1. A compound, or a salt thereof, according to formula (I):



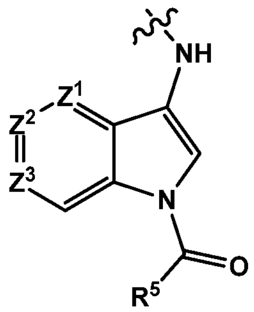
(I)

wherein

A is a group selected from:



and



;

Z^1 is $C(R^1)$ or N;

Z^2 is $C(R^2)$ or N;

Z^3 is $C(R^3)$ or N, wherein at least one of Z^1, Z^2 or Z^3 is not N;

R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^AR^B$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^CR^D, cyano, CO_2H, $CONR^AR^B$, SO_2C_1-C_6alkyl, and SO_2NH_2, $SO_2NR^AR^B$, C_1-C_6alkoxycarbonyl, -$C(NR^A)NR^CR^D$, C_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, cyano, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^AR^B$, NR^CR^D, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 or 3 ring heteroatoms selected from N, O or S, and wherein optional phenyl and heteroaryl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 is C_1-C_4alkyl, hydroxyC_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, amino, methylamino;

X^1 is CR^9R^{22} or sulfur;

X^2 is CR^7R^8, oxygen, sulfur, N(H) or N(C_1-C_6alkyl), wherein at least one of X^1 and X^2 is carbon; or

X^1 and X^2, in combination, forms an olefin of the formula –C(R^7)=C(H)- or –C(R^7)=C(C_1-C_4alkyl)-, wherein the C(R^7) is attached to X^3;

X^3 is $(CR^6R^{21})_q$ or N(H) wherein q is 0,1 or 2, wherein X^3 is CR^6R^{21} or $(CR^6R^{21})_2$ when either X^1 or X^2 is sulfur or X^2 is oxygen; or

X^2 and X^3, taken in combination, are –N=C(H)– or –N=C(C_1-C_4alkyl)– in which the C(H) or C(C_1-C_4alkyl) is attached to X^1;

R^6 is selected at each occurrence from hydrogen and C_1-C_6alkyl;

R^7 is hydrogen, halogen, hydroxy, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, haloC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^8 is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^AR^B, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^AR^B, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^9 is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^AR^B, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and OC(O)NR^CR^D each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^AR^B;

R^{20} is hydrogen or C_1-C_6alkyl;

R^{21} is selected at each occurrence from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{22} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

CR^7R^8, taken in combination forms a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^7 and R^8, taken in combination, form an exocyclic methylidene (=CH_2);

R^7 and R^{22} or R^8 and R^9, taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^AR^B;

R^6 and R^7 or R^8 and R^{21}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^AR^B; or

R^{20} and R^{22} taken in combination form a fused 3 carbocyclic ring system;

R^9 and R^{21} taken in combination form a form 1 to 3 carbon alkylene linker;

R^7 and R^{20} taken in combination form 1 to 3 carbon alkylene linker;

R^{10} is halogen, C_1-C_4alkyl, haloC_1-C_2alkyl or halo C_1-C_2alkoxy

R^{11} is hydrogen, halogen or C_1-C_4alkyl;

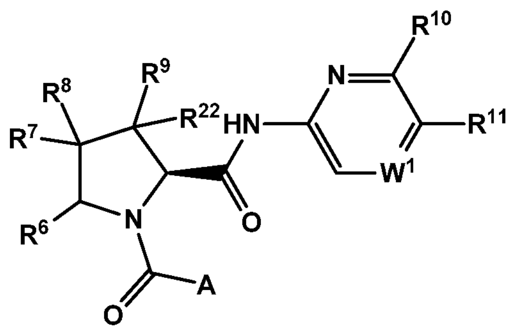
W^1 is $C(R^{12})$ or N;

R^{12} is halogen, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, hydroxy and CO_2H, CO_2Me, or $CONR^AR^B$;

R^A and R^B are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^AR^B, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy; and

R^C and R^D, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl.

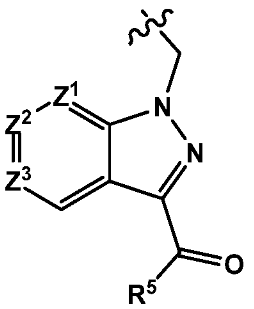
2. A compound, or a salt thereof, according to formula (II):



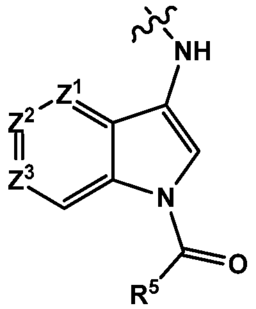
(II)

wherein

A is a group selected from:



and



;

Z^1 is $C(R^1)$ or N;

Z^2 is $C(R^2)$ or N;

Z^3 is $C(R^3)$ or N, wherein at least one of Z^1, Z^2 or Z^3 is not N;

R^1 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^AR^B$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^CR^D, cyano, CO_2H, $CONR^AR^B$, SO_2C_1-C_6alkyl, and SO_2NH_2, $SO_2NR^AR^B$, C_1-C_6alkoxycarbonyl, $-C(NR^A)NR^CR^D$, C_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, cyano, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^AR^B$, NR^CR^D, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 or 3 ring heteroatoms selected from N, O or S, and wherein optional phenyl and heteroaryl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 is C_1-C_4alkyl, hydroxyC_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, amino, methylamino;

R^6 is hydrogen;

R^7 is hydrogen or fluoro;

R^8 is hydrogen, methyl or hydroxymethyl;

R^9 is hydrogen, halogen, hydroxy or C_1-C_4alkoxy ; or

R^6 and R^7, taken in combination, form a cyclopropane ring; or

R^8 and R^9, taken in combination, form a cyclopropane ring;

R^{22} is hydrogen or fluoro;

R^{10} is halogen, C_1-C_4alkyl, haloC_1-C_2alkyl or haloC_1-C_2alkoxy

R^{11} is hydrogen, halogen or C_1-C_4alkyl;

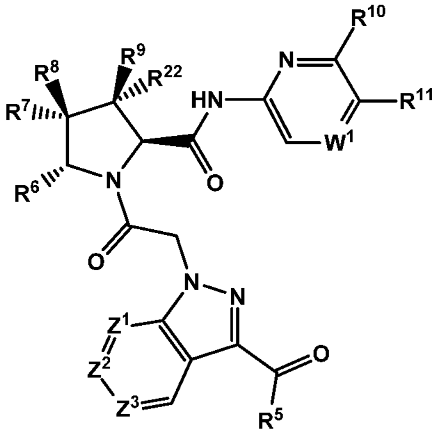
W^1 is N or CR^{12};

R^{12} is halogen, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, hydroxy and CO_2H, CO_2Me, or $CONH_2$;

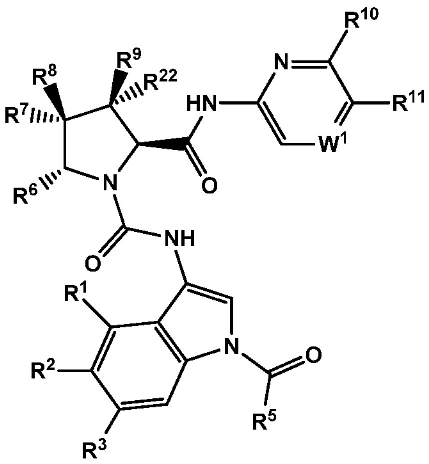
R^A and R^B are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^AR^B, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy; and

R^C and R^D, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl.

3. The compound of claim 1 or 2, or a salt thereof, according to formula (III) or (IV):



or



(III) (IV).

4. The compound of any one of claims 1 to 3, or a salt thereof, wherein Z^1 is N or CR^1; Z^2 is N or CR^2 and Z^3 is N or CR^3 wherein at least one of Z^1, Z^2 and Z^3 are not N;

R^1 is hydrogen, halogen or C_1-C_4alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, CO_2H, C_1-C_4alkyl and C_1-C_4alkoxy;

R^3 is selected from the group consisting of hydrogen, halogen, CO_2H, C_1-C_4alkyl, C_3-C_5cycloalkyl, haloC_1-C_4alkyl and C_1-C_4alkoxy, wherein the alkoxy is optionally substituted by pyridyl or pyrimidinyl and

R^5 is amino or C_1-C_4alkyl.

5. The compound of any one of claims 1 to 4, or a salt thereof, wherein

R^6 and R^7 taken in combination form a cyclopropane ring;

R^8 is hydrogen, methyl or hydroxymethyl; and

R^9 is hydrogen.

6. The compound of any one of claims 1 to 4, or a salt thereof, wherein
R^6 and R^7 are hydrogen; and
R^8 and R^9 taken in combination form a cyclopropane ring.

7. The compound of any one of claims 1 to 4, or a salt thereof, wherein
R^6 is hydrogen;
R^8 is hydrogen or methyl;
R^7 is fluoro;
R^9 is hydrogen or methoxy; and
R^{22} is hydrogen or fluoro.

8. The compound of any one of claims 1 to 7, or a salt thereof, wherein
W^1 is CH or C(OMe);
R^{10} is bromo, chloro, iodo, trifluoromethyl or difluoromethoxy; and
R^{11} is hydrogen.

9. The compound of any one of claims 1 to 7, or a salt thereof, wherein
W^1 is N;
R^{10} is bromo or trifluoromethyl; and
R^{11} is hydrogen or methyl.

10. The compound of claim 1 or claim 2, or a salt thereof, selected from the group consisting of

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide;

5-Ethyl-1-{2-oxo-2-[(1R,3S,5R)-3-(6-trifluoro methyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridazine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-fluoromethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide;

(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-difluoro methoxy-pyridin-2-yl)-amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-5-methyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-methyl-1H-indazole-3-carboxylic acid amide;

1-{2-Oxo-2-[(1R,3S,5R)-3-(6-trifluoromethyl-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-fluoro-1H-indazole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-5-methyl-pyrazin-2-yl)-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-trifluoro methyl-pyrazin-2-yl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-trifluoromethyl-pyrazin-2-yl)-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide;

1-{2-[(2S,4R)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Chloro-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Iodo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(6-Bromo-4-methoxy-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-5-methyl-pyrazin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyridin-2-yl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide]-1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-trifluoromethyl-pyrazin-2-yl)-amide]; and

(1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo-pyridin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide].

11. The compound of claim 1 or claim 2, or a salt thereof, selected from the group consisting of

1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(fluoromethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

(S)-N-(6-bromopyridin-2-yl)-3-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl) thiazolidine-2-carboxamide;

1-(2-((1R,3S,5R)-3-((6-bromopyridin-2-yl) carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-N-methyl-1H-indazole-3-carboxamide;

1-(2-((2R,3S)-2-((6-bromopyridin-2-yl) carbamoyl)-3-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide;

N-(6-bromopyridin-2-yl)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetyl)-2-azabicyclo[2.1.1]hexane-3-carboxamide;

5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

5,7-dimethyl-1-(2-oxo-2-((1R,3S,5R)-3-((6-(trifluoromethyl)pyrazin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide;

(2R,3R,4S)-N2-(6-bromopyridin-2-yl)-N1-(1-carbamoyl-1H-indol-3-yl)-3,4-difluoropyrrolidine-1,2-dicarboxamide; and

(S)-N2-(6-bromopyridin-2-yl)-N3-(1-carbamoyl-1H-indol-3-yl)thiazolidine-2,3-dicarboxamide.

12. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of claims 1-11.

13. A combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to any one of claims 1-11 and a second therapeutically active agent.

14. A method of modulating complement alternative pathway activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-11.

15. A method of treating a disorder or a disease in a subject mediated by complement activation, in particular mediated by activation of the complement alternative pathway, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-11.

16. The method of claim 15, in which the disease or disorder is selected from the group consisting of age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet’s uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration, neural regeneration, dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity.

17. A method of treating age related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising a compound of any one of claims 1-11.

18. A compound according to any one of claims 1-11, for use as a medicament.

19. Use of a compound according to any one of claims 1-11 in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement alternative pathway.

20. A compound according to any one of claims 1-11 for use in the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement alternative pathway.

21. Use of a compound according to any one of claims 1-11, for the treatment of age-related macular degeneration.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/055299

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/14 C07D471/04 C07D417/14 A61K31/444 A61K31/4745 A61K31/497 A61K31/4439 A61P27/00 A61P9/00 A61P11/00 A61P19/00 A61P37/00 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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2010/066684 A2 (NOVARTIS AG [CH]; ARTMAN III GERALD DAVID [US]; ELLIOTT JASON MATTHEW) 17 June 2010 (2010-06-17) claims 1-33 page 33 -----	1-21
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2013	21/10/2013

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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