The invention relates to compounds of formula (1), and salts thereof. In some embodiments, the invention relates to inhibitors or modulators of Pim-1 and/or Pim-2, and/or Pim-3 protein kinase activity or enzyme function. In still further embodiments, the invention relates to pharmaceutical compositions comprising compounds disclosed herein, and their use in the prevention and treatment of Pim kinase related conditions and diseases, preferably cancer.
MACROCYCLES AS PIM INHIBITORS

FIELD OF THE INVENTION

The present invention relates to certain macrocycles that are Pirn inhibitors, pharmaceutical compositions containing such compounds, and processes for preparing such compounds. Provided herein also are methods of treating disorders or diseases treatable by inhibition of Pims, such as cancer, and the like.

BACKGROUND

The role of Pirn serine/threonine kinases in the pathogenesis and therapy of hematological malignancies and solid cancers is of interest to the medical community. Pirn proteins are constitutively active and are over-expressed in a subset of human cancers, many of hematological origin. Pirn kinases also regulate aspects of transformation and drug resistance in hematological malignancies such as DLBCL, MM, and AML where they are overexpressed or mutated. Aberrant expression of Pim-1 or Pim-2 promotes tumor development in mouse models of lymphoma and prostate cancer. Elevated Pim-1 levels correlate with poor prognosis in DLBCL and mantle cell lymphoma. Pims play a role in some solid tumors (e.g. prostate cancer, and head and neck cancer). Whereas elevated levels of Pim-1 and Pim-2 were mostly found in hematological malignancies and prostate cancer, increased Pirn-3 expression was observed in different solid tumors. Pirn kinases are constitutively active and their activity supports in vitro and in vivo tumour cell growth and survival through modification of an increasing number of common as well as isoform-specific substrates including several cell cycle regulators and apoptosis mediators. Pim-1 mediates homing and migration of normal and malignant hematopoietic cells by regulating chemokine receptor surface expression. Knockdown experiments by RNA interference or dominant-negative acting mutants suggested that Pirn kinases are important for maintenance of a transformed phenotype and therefore potential therapeutic targets.

There exists a need for compounds that inhibit the growth of tumors, treat cancer, modulate cell cycle arrest, and/or inhibit molecules such as Pim-1, Pim-2, or Pim-3 and pharmaceutical formulations and medicaments that contain such compounds.
SUMMARY OF THE INVENTION

The present invention comprises a new class of macrocyclic compounds useful in the treatment of diseases, such as Pim-mediated diseases, for example cancer. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds, methods for the treatment of Pim-mediated diseases and other maladies, such as treatment of hematological malignancies and of solid tumors, for example prostate cancer, and head and neck cancer, using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds of the invention are represented by the following general structure:

![Chemical Structure](image)

and a pharmaceutically acceptable salt thereof; wherein Q, X, Z, a, b, c, q, w, s, r, R, R²; and R² are defined below.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents, patent applications and other publications recited herein are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the current invention relates to compounds having the general structure of formula 1:
wherein
ring a is a ring that together with the 2 carbon atoms to which it attaches, forms a phenyl ring or a 5-6 membered heterocyclic ring;

X is N or CH;
Z is O, S, NR\textsubscript{R\textsuperscript{b}}, CO, CHR\textsubscript{b} or C(R\textsubscript{b})\textsubscript{2};
Q is a linker saturated or unsaturated chain;
q is NH or CH;
ris CH\textsubscript{2} or N;
s is N or C;
w is CH or N;
ring b is unsaturated, or partially saturated;
ring c is saturated, or partially saturated;
R\textsuperscript{1} is H, or halo;
R\textsuperscript{2} is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxycarbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;
R\textsuperscript{b} is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonylaminoalkyl, alkylcyanobalactaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl; and
R\textsuperscript{e} is H, -PO(OCH\textsubscript{3})\textsubscript{2}, alkylcyanobalactaminoalkyl or hydroxyalkyl;
and a pharmaceutically acceptable salt thereof.

In another embodiment, ring a is
wherein $R_1$ is H, or halo; and a pharmaceutically acceptable salt thereof.

In another embodiment, the compounds of Formula I comprise

wherein $X$ is N or CH;
$Z$ is O, S, NR, CO, CHR or C(R)$_2$;
Q is a 3-8 membered linker that attaches with $Z$;
ring a is $R_1$ is H, or halo;
$R_2$ is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;
R^6 is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonylaminoalkyl, alkylcarbonylaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl; wherein R^6 is H; and

wherein R^7 is H or C1-3 alkyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, the compounds of Formula I comprise

![Chemical Structures]

wherein

X is N or CH;
Z is O, S, NR^3, C=0, CHR or C(R^3)^2;
Q is optionally substituted C_4-C_5 alkenylenyl, or optionally substituted phenyl-C_1-C_2 alkenylenyl, or optionally substituted C_4-C_5 alkenylenyl, optionally substituted C_4-C_5 alkenylenyl, or optionally substituted C_4-C_5 alkenylenyl, or optionally substituted C_1-C_2 alkenylenyl or (CH_2)_n-O-(CH_2)_m, optionally substituted C_4-C_5 alkenylenyl, or optionally substituted C_1-C_2 alkenylenyl-amino carbonyl-C_1-C_2 alkenylenyl, or optionally substituted C_3-C_4 alkenylenyl; when Q attaches to Z; or wherein Q is optionally substituted 5-7 membered heterocyclyl-alkenyl, or optionally substituted 5-7 membered heterocyclyl-alkenyl; when Q incorporates Z into the heterocyclic ring;

ring α is

R^1 is H, or halo;
R^2 is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;

R^b is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonylaminoalkyl, alkylcarbonylaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl;
substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl;
wherein \( R^6 \) is H; and
wherein \( R^7 \) is H;
and a pharmaceutically acceptable salt thereof.

In another embodiment, \( Z \) is O, S, NR\(^{10} \), or CHR\(^{10} \); and \( R^8 \) is H, Cl\(_2\) alkyl, Cl\(_2\) hydroxyalkyl, C\(_{1-2}\) alkylsulfonyl-Cu alkyl, BOC-amino-C\(_{1-2}\) alkyl, amino-C\(_{1-2}\) alkyl, C\(_{1-2}\) alkylsulfonyl-C\(_{1-2}\) alkyl, C\(_{1-2}\) alkylsulfonylamino-C\(_{1-2}\) alkyl or C\(_{1-2}\) alkylcarbonylamino-C\(_{1-2}\) alkyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R^1 \) is H or fluoro; and a pharmaceutically acceptable salt thereof.

In another embodiment, ring a is ; and \( R^2 \) is H or fluoro; and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R^9 \) is H, methylcarbonyl or hydroxymethyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, \( Q \) and \( Z \) together form
In another embodiment, \( R^2 \) is H, \( \text{Ci}_2 \) alkyl, \( \text{HC}(=\text{O})- \) or \( \text{Ci}_2 \) hydroxyalkyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R^2 \) is H, methyl, \( \text{HC}(=\text{O})- \) or hydroxymethyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R^2 \) is H; and a pharmaceutically acceptable salt thereof.

Another aspect of the current invention relates to compounds having the general structure of Formula 2
wherein $Z$ is $O$ or $NH$; and

wherein $Q$ is optionally substituted $C_4$-$C_9$ alkenylenyl, or optionally substituted phenyl-$C_1$-$C_2$ alkylenyl;

and a pharmaceutically acceptable salt thereof.

In another embodiment, $Z$ is $O$; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Z$ is $NH$; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Q$ is but-2-enylenyl, 4-methylbut-2-enylenyl, 3-methylbut-2-enylenyl, 2-methylbut-2-enylenyl or phenylmethylenyl; and a pharmaceutically acceptable salt thereof.

A family of specific compounds of particular interest within Formula 1 consists of compounds and a pharmaceutically-acceptable salt thereof as follows:

(11E)-1 1-methyl-14-oxa-3,7,23-

triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1~8,22~]tetracosa-

l(2 l),2(24),4, 11,15,17, 19,22-octaen-6-one;

(9R, 11E)-11-methyl- 14-oxa-3,7,23-

triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1~8,22~]tetracosa-

l(2 l),2(24),4, 11,15,17, 19,22-octaen-6-one;

(9S, 11E)-11-methyl- 14-oxa-3,7,23-

triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1~8,22~]tetracosa-

l(2 l),2(24),4, 11,15,17, 19,22-octaen-6-one;

16-oxa-3,7,25-triazahexacyclo[15.6.2.1~2,5~.1~1~1.15~.0~4,9~.0~20,24~]heptacosa-

l(23),2(27),4, 11(26), 12, 14, 17,19,21, 24-decaen-6-one;

(11E)-12-methyl-14-oxa-3,7,23-

triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1~8,22~]tetracosa-

l(2 l),2(24),4, 11,15,17, 19,22-octaen-6-one;

(11E)-12-methyl-3,7,14,23-tetrazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~1~8,22~]tetracosa-

l(2 l),2(24),4, 11,15,17, 19,22-octaen-6-one;
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(9R, 11E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one ;
(9S,1 IE)-12-methyl-3,7,14,23-
5 tetraazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;
(9R,1 iz)-14-oxa-3,7,23-triazapentacylo[13.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;
(9S,1 iz)-14-oxa-3,7,23-triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;
(9R,1 IE)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one; and
(9S,1 IE)-14-oxa-3,7,23-triazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(2 l),2(24),4,11,15,17,19,22-octaen-6-one.

Another aspect of the current invention relates to compounds having the general 
structure of Formula 3

![Chemical Structure](image)

wherein \( R^1 \) is H or fluoro;
20 wherein \( R^2 \) is H, HC(=0)-, Ci_2 alkyl or Ci_2 hydroxyalkyl;
wherein \( Z \) is O, S or NR^3;
wherein \( R^3 \) is H, Ci_2 alkyl, Ci_2 hydroxyalkyl, Ci_2 alkylsulfonyl-Cu alkyl, BOC-amino-
Ci_2 alkyl, amino-Ci_2 alkyl, Ci_2 alkylsulfonyl-Cu alkylamino-Ci_2 alkyl, Ci_2 
alkylsulfonylamino-Ci_2 alkyl or Ci_2 alkylcarbonylamino-Ci_2 alkyl;
25 wherein \( Q \) is optionally substituted C_4-C_5 alkylenyl, optionally substituted C_4-C_5 
alkenylenyl, optionally substituted C_4-C_5 alkynylenyl, optionally substituted phenyl-
Ci_2 alkylenyl or -(CH_2)_m-0-(CH_2)_n-; and
wherein \( n \) is 1-2; wherein \( m \) is 1-2; provided \( n+m = 3 \) or 4;
and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R^1 \) is H; and a pharmaceutically acceptable salt thereof.
In another embodiment, R² is H, HC(=0)-, methyl or hydroxymethyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, R² is H or methyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, Z is O or S; and a pharmaceutically acceptable salt thereof.

In another embodiment, Q is butylenyl, 4-methylbutylenyl, 4-hydroxymethylbutylenyl, 2,3-dihydroxy-4-methylbutylenyl, but-2-enylenyl, 4-hydroxymethylbut-2-enylenyl, 4-hydroxyethylbut-2-enylenyl, 4-methylbut-2-enylenyl, 4,4-dimethylbut-2-enylenyl, 4-trifluoromethylbut-2-enylenyl, 4-(methylsulfonyl)but-2-enylenyl, 3-methylbut-2-enylenyl, 2-methylbut-2-enylenyl, but-2-ynylenyl, 4-methylbut-2-ynylenyl, pentylenyl, pent-2-enylenyl, -(CH₂)₂, -(CH₂)₂, or phenylmethyl; and a pharmaceutically acceptable salt thereof.

A family of specific compounds of particular interest within Formula 1 consists of compounds and a pharmaceutically-acceptable salt thereof as follows:

(lIE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1,3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;

(9S,1 IE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1,3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;

(9R,1 IE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1,3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;

(9S,11Z)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1,3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;

(11IE)-12-methyl-3,7,14,17,23-pentaazapentacyclo[1,3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(2 l),2(24),4,11,15,17,19,22-octaen-6-one;
(9R, 11E)-12-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
1(2 1),2(24),4, 11,15,17,19,22-octaen-6-one;

(9S, 11E)-12-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
1(2 1),2(24),4, 11,15,17,19,22-octaen-6-one;

(9S, 11E)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
1(2 1),2(24),4, 11,15,17,19,22-octaen-6-one

(9R, 11Z)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
1(2 1),2(24),4, 11,15,17,19,22-octaen-6-one

(9R, 11E)-17-methyl-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
1(22),2(25),4, 11,16,18,20,23-octaen-6-one

(9S, 11E)-17-methyl-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
1(22),2(25),4, 11,16,18,20,23-octaen-6-one

(9R, 11Z)-17-methyl-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
1(22),2(25),4, 11,16,18,20,23-octaen-6-one
(9S, 11Z)-1 7-methyl-3, 7, 15, 18, 24-
pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
l(22), 2(25), 4, 11, 16, 18, 20, 23 -octaen-6-one;
(9R, 11E, 13R)-13, 16-dimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-nonaen-6-one
(9S, 11E, 13R)-13, 16-dimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-nonaen-6-one;
(9S, 11E, 13S)-13, 16-dimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-nonaen-6-one;
(9S, 11E)-13, 13, 16-trimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-nonaen-6-one;
(9R, 11E, 13S)-13, 16-dimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-nonaen-6-one;
(9S)-16-methyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 11, 15, 17, 18, 20, 22-octaen-6-one;
(9R)-16-methyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 15, 17, 18, 20, 22-octaen-6-one;
(9S, 13R)-13, 16-dimethyl-3, 7, 14, 17, 23-
pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22), 2(24), 4, 15, 17, 18, 20, 22-octaen-6-one;
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(9S,13S)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 15,17,1 8,20,22-octae1-6-one;
(9R,11E)-12,16-dimethyl- 14-thia-3,7,17,23-
tetraazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one;
(11E)-1 1,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one;
(9S,11E)-12,16-dimethyl- 14-thia-3,7,17,23-
tetraazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one;
(9S,13R)-12-dihydroxy-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(22),2(24),4, 15,17,18,20,22-octae1-6-one;
17-methyl-3,7,15,1 8,24-
pentaazahexacyclo[1 4.6.2.2-1 1,14-.1-2,5-.0-4,9-.0-19,23-]heptacosa-
l(23),2(27),4, 11,13,16,18,19,21,23,25-undecaen-6-one;
(9R,11E)-14,16-dimethyl-3 ,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one;
(9R,11Z)-14,16-dimethyl-3 ,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one;
(9S,11E,13R)-13-methyl-6-oxo-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaene- 16-carbaldehyde;
(9S,11E)-12-methyl-6-oxo-3 ,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 11,15,17,18,20,22-nonaene- 16-carbaldehyde;
(9R,13R)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(22),2(24),4, 15,17,18,20,22-octae1-6-one;
(9R, 11Z, 13R)-13, 16-dimethyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E, 13R)-13-(hydroxymethyl)- 16-methyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E)- 14, 16-dimethyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E)- 17-methyl-4,7, 12,15,18,24-
heaxazapentacyclo[1.4.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,19,23\textsuperscript{0}]-pentacosa-
l(22),2,5(25), 16,18,20,23-heptaene-6, 11-dione;
(9R)- 17-methyl-4,7, 12,15,18,24-
heaxazapentacyclo[1.4.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,19,23\textsuperscript{0}]-pentacosa-
l(22),2,5(25), 16,18,20,23-heptaene-6,II-dione;
(9S, 13R)- 13-(hydroxymethyl)- 16-methyl-3,7,1 4,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 15,17,18,20,22-octaen-6-one;
(9S, 11E, 13S)- 13-(hydroxymethyl)- 16-methyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11Z, 13S)- 13-(hydroxymethyl)- 16-methyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E)- 12, 14, 16-trimethyl-3, 7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E, 13S)- 13-(2-hydroxy ethyl)- 16-methyl-3,7, 14,17,23-
pentaazapentacyclo[1.3.6.2.1\textsuperscript{2},5\textsuperscript{0},4,9\textsuperscript{0},0,18,22\textsuperscript{0}]-tetracosa-
l(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one;
(9S, 11E, 13R)-13-(2-hydroxy ethyl)-16-methyl-3, 7, 14, 17, 23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;

(9S, 11E)-2 1-fluoro-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;

17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20-heptaen-11-yn-6-one;

(9S, 11E)-16-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one;

(9S, 11E)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one;

(9S, 11Z)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one;

(9S, 11E, 13S)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one;

(9S, 11E, 13R)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one;
(9R)-17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2(25),4,16,18,20,23-heptaen-6-one;

(9S)-17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2(25),4,16,18,20,23-heptaen-6-one;

(9R,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one;

(9S,11E,13S)-2-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,19,22-octaen-6-one;

(9S)-17-methyl-3,7,15,18,24-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(23),2(25),4,16(24),17,19,21-heptaen-6-one;

(9S,11E,13S)-16-methyl-13-(2-(methylsulfonyl)ethyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;

(9S,11E,13R)-16-methyl-13-(2-(methylsulfonyl)ethyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;

(lIE,13R)-16-methyl-13-(trifluoromethyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,19,22-octaen-6-one;

(9S,13S)-2-fluoro-13,16-dimethyl-1-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,19,22-heptaen-6-one;

tert-butyl (2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2(25),4,16,18,20,23-heptaen-6-one;

(9S,11E,13S)-2-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,19,22-octaen-6-one;

tert-butyl (2-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2(25),4,16,18,20,23-heptaen-6-one;

(9S)-17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[4.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2(25),4,16,18,20,23-heptaen-6-one;
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(9S,11Z)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one;
(9S)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one;
(9S,11Z)-16-methyl-14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one;
(9S,11E)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one;
N-(2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)acetamide;
N-(2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)methanesulfonamide;
(9S,11E,13S)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;
(9S,11Z)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;
(9S,11E,13R)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;
(9S,11E)-16-(hydroxymethyl)-12-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one;
(9S,11E)-16-methyl-14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one; and
N-(2-((9S, 11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-1(2 1),2(24),4, 11,15,17,1 9,22-octaen-14-yl)ethyl)acetamide.

Another aspect of the current invention relates to compounds having the general structure of Formula 4

![Formula 4](image)

wherein $R^1$ is H;
wherein $R^2$ is $C_{1-2}$ alkyl;
wherein $Z$ is $CH_2$ or NH; and
wherein $Q$ is optionally substituted $C_4$-$C_5$ alkenylenyl, or optionally substituted $C_{1-2}$ alkenylenyl-aminocarbonyl-$C_{1-2}$ alkenylenyl, and a pharmaceutically acceptable salt thereof.

In another embodiment, $R^2$ is methyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Z$ is NH; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Q$ is 3-methylbut-2-enylenyl, ethylenylaminocarbonylmethylene, (2-methylethylenyl)aminocarbonylmethylene, or methylenylaminocarbonylmethylene; and a pharmaceutically acceptable salt thereof.

A family of specific compounds of particular interest within Formula 1 consists of compounds and a pharmaceutically-acceptable salt thereof as follows:

(9S, 14R)-14,17-dimethyl-4,7, 12,1 5,1 8,24-
hexaazapentacyclo[1 4.6.2.1~2,5~.0~4,9~.0~19,23~] pentacosa-
l(22),2,5(25),1 6,1 8,20,23-heptaene-6,1 l-dione;

(9R, 14R)-14,17-dimethyl-4,7, 12,1 5,1 8,24-
hexaazapentacyclo[1 4.6.2.1~2,5~.0~4,9~.0~19,23~] pentacosa-
l(22),2,5(25),1 6,1 8,20,23-heptaene-6,1 l-dione;

17-methyl-4,7, 12, 15,1 8,24-
hexaazapentacyclo[1 4.6.2.1~2,5~.0~4,9~.0~1 9,23~]pentacosa-
l(22),2,5(25),1 6,1 8,20,23-heptaene-6,1 l-dione;
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16-methyl-4,7,12,17,23-pentaazapentacyclo[2.2.1.2.5.0.4.9.0.1.8,22]tetracosa-1(21),2,5(24),15,17,19,22-heptaene-6,11-dione; and
(11E)-1,2,16-dimethyl-4,7,14,17,23-pentaazapentacyclo[3.6.2.1.2.5.0.4.9.0.1.8,22]tetracosa-1(21),2,5(24),11,15,17,19,22-octaen-6-one.

Another aspect of the current invention relates to compounds having the general structure of Formula 5

![Formula 5](image)

wherein ring d forms a 4-7 membered nitrogen containing heterocyclyl;
wherein R^1 is H;
wherein R^2 is H or C_1-2 alkyl; and
wherein Q is optionally substituted C_3-C_4 alkenylenyl;
and a pharmaceutically acceptable salt thereof.

In another embodiment, R^2 is methyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, ring d is morpholinyl or 2-oxo-oxazolidinyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, ring d is or ; and a pharmaceutically acceptable salt thereof.

In another embodiment, Q is 2-propenylenyl, or 3-propenylenyl; and a pharmaceutically acceptable salt thereof.

A family of specific compounds of particular interest within Formula 1 consists of compounds and a pharmaceutically-acceptable salt thereof as follows:
Another aspect of the current invention relates to compounds having the general structure of Formula 1’:

\[
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9
\]

wherein

- ring \( a \) is a ring that together with the 2 carbon atoms to which it attaches, forms a phenyl ring or a 5-6 membered heterocyclic ring;
- \( X \) is \( N \) or \( CH \);
- \( Z \) is \( O, S, NR^b, C=O \) or \( C(R^b)_2 \);
- \( Q \) is a linker saturated or unsaturated chain;
- \( q \) is \( N, NH, CH \) or \( CH_2 \);
- \( r \) is \( CH, NH, CH_2 \) or \( N \);
- \( s \) is \( N \) or \( CH \);
- \( w \) is \( CH, CH_2, N \) or \( NH \);
- ring \( b \) is unsaturated, or partially saturated;
- ring \( c \) is saturated, or partially saturated;
- \( R^1 \) is \( H \), or halo;
$R^2$ is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;

$R^b$ is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonylaminoalkyl, alkylcarbonylaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl; and

$R^c$ is H, -PO(Oalkyl)$_2$, alkylcarbonyl, alkylcarbonyloxyalkoxycarbonyl, alkoxy carbonyl, aminoalkylcarbonyloxyalkoxycarbonyl or hydroxyalkyl;

and a pharmaceutically acceptable salt thereof.

In another embodiment, ring a is

$R^1$ is H, or halo; and a pharmaceutically acceptable salt thereof.

Another aspect of the current invention relates to compounds having the general structure of Formulas l’a-l’f.
wherein $X$ is $N$ or $CH$; $Z$ is $O$, $S$, $NR$, $C=0$, or $C\left(R^b\right)_2$; $Q$ is a 3-8 membered linker that attaches with $Z$;

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$\alpha$ ring is $H$, or halo; $R^1$ is $H$, $Cl_{1-6}$ haloalkyl, $Cl_{1-6}$ hydroxyalkyl, $Cl_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $HC\left(=0\right)$, carboxy, $Cl_{1-6}$ alkoxy carbonyl, $C_{1-6}$ cycloalkyl, or substituted or unsubstituted heterocycle; $R^b$ is $H$, $Cl_{1-6}$ alkyl, $Cl_{1-6}$ haloalkyl, $Cl_{1-6}$ hydroxyalkyl, $C_{1-6}$ alkylsulfonyl-$Cl_{1-6}$ alkyl, $BOC$-amino-$Cl_{1-6}$ alkyl, amino-$Cl_{1-6}$ alkyl, cyano-$Cl_{1-6}$-alkyl, $Cl_{1-6}$-alkoxy-$Cl_{1-6}$-alkyl, $Cl_{1-6}$-alkylsulfonyl-$Cl_{1-6}$-alkylaminocarbonyl-$Cl_{1-6}$-alkyl, unsubstituted or substituted $C_{1-6}$-cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-$Cl_{1-6}$-alkyl or unsubstituted or substituted heterocycle; $R^6$ is $H$, and $R^7$ is $H$ or $C_{1-6}$ alkyl; and a pharmaceutically acceptable salt thereof.

Another aspect of the current invention relates to compounds having the general structure of Formulas 1'b and 1'e

wherein $X$ is $N$ or $CH$; $Z$ is $O$, $S$, $NR$, $C=0$, or $C\left(R^b\right)_2$; $Q$ is optionally substituted $C_2-C_6$ alkenylenyl, optionally substituted $C_4-C_5$ alkenylenyl, optionally substituted $C_4-C_5$ alkenylenyl, optionally substituted cycloalkyl-$C_2-C_4$ alkenylenyl, optionally substituted phenyl-$Cl_{1-2}$ alkenylenyl, $-\left(CH_2\right)_n-0-\left(CH_2\right)_{m-n}$, or optionally substituted $Cl_{1-2}$ alkenylenyl-aminocarbonyl-$Cl_{1-2}$ alkenylenyl, when $Q$ attaches to $Z$; or wherein $Q$ is
optionally substituted 5-7 membered heterocyclyl-alkyl, or optionally substituted 5-7
membered heterocyclyl-alkenyl, when Q incorporates Z into the heterocyclic ring;

\[
\begin{align*}
\text{ring a is} & \quad ; \\
R^1 & \text{is } H, \text{or halo; } R^2 \text{is } H, \text{haloalkyl, hydroxyalkyl, alkyl, alkoxy,}
\end{align*}
\]

HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted
heterocyclyl; \( R^3 \) is \( \text{H, } \text{Ci}_4 \text{-alkyl, } \text{Ci}_4 \text{-hydroxyalkyl, C}_1 \text{C}_4 \text{-alkylsulfonyl-Ci} \text{.}
\]

4-alkyl, BOC-amino-Ci 4-alkyl, C1 4-aminoalkyl, C1 4-cyanoalkyl, C4-alkoxy-Ci 4-alkyl,
C1 4-alkylsulfonfyl-Ci 4-alkylamino-Ci 4-alkyl, Ci1 4-alkylcarbonylamino-Ci 4-alkyl, unsubstituted or substituted C1 4-cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl-Ci 2-alkyl or unsubstituted or
substituted 4-6 membered heterocyclyl; \( R^6 \) is \( \text{H; and } R^7 \text{is } \text{H;} \) and a pharmaceutically acceptable salt thereof.

In another embodiment, \( Z \) is O, S, NR, or CHR; \( R^3 \) is \( \text{H, } \text{Ci}_2 \text{-alkyl, } \text{Ci}_2 \text{-hydroxyalkyl, } \text{Ci}_2 \text{-alkylsulfonfyl-Cu-alkyl, BOC-amino-Ci} \text{2-alkyl, amino-Ci}_2 \text{-alkyl, Ci}_2 \text{-alkylsulfonfyl-Ci} \text{2-alkylamino-Ci} \text{2-alkyl, cyan-C} \text{2-alkyl, Ci}_2 \text{-alkylsulfonfylamino-Ci} \text{2-alkyl, Ci}_2 \text{-alkylcarbonylamino-Ci} \text{2-alkyl, unsubstituted or substituted Ci} \text{2,6-cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl-Ci} \text{2-alkyl or unsubstituted or substituted 4-6 membered heterocyclyl; } R^6 \text{is } \text{H; and } R^7 \text{is } \text{H; and a pharmaceutically acceptable salt thereof.}

In another embodiment, \( R^1 \) is \( \text{H or fluoro; and a pharmaceutically acceptable salt thereof.}

In another embodiment, ring a is \( ; \) and \( R^1 \) is \( \text{H or fluoro; and a}
pharmaceutically acceptable salt thereof.

In another embodiment, \( R^5 \) is \( \text{H, methylcarbonyl, -PO(0-methyl)}_2, -PO(0-tert-
butyl)}_2, \text{methylcarbonyloxy -methoxycarbonyl, tert-butylcarbonyloxy-methoxycarbonyl,}
isopropylcarbonyloxy-methoxycarbonyl, 1,5-diaminopentyl-carbonyloxy-
methoxycarbonyl, butoxycarbonyl or hydroxymethyl; and a pharmaceutically acceptable
salt thereof.

In another embodiment, \( Q \) and \( Z \) together form

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and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R_2 \) is \( H, \text{Cl}_2 \text{alkyl, HC(=0)-} \) or \( \text{C}_1\text{-2 hydroxyalkyl} \); and a pharmaceutically acceptable salt thereof.

In another embodiment, \( R_2 \) is \( H, \text{methyl, HC(=0)-} \) or \( \text{hydroxy} \text{methyl} \); and a pharmaceutically acceptable salt thereof.

In another embodiment, \( Z \) is \( O \); and a pharmaceutically acceptable salt thereof.

In another embodiment, \( Z \) is \( \text{NH} \); and a pharmaceutically acceptable salt thereof.

The current invention relates to compounds of Formula 3'

wherein \( R^1 \) is \( H \) or fluoro; \( R^2 \) is \( H, \text{HC(=0)-} \), \( \text{Cl}_2 \text{alkyl or Cl}_2 \text{hydroxyalkyl} \); \( Z \) is \( O, S \) or \( \text{NR}^3 \); \( R^5 \) is \( H, \text{Cl}_2 \text{alkyl, Cl}_2 \text{hydroxyalkyl, Cl}_2 \text{alkylsulfonyl-C}_{1,3}-\text{alkyl, BOC} \)
amino-$\text{Ci}_2$-alkyl, amino-$\text{Ci}_2$-alkyl, $\text{Ci}_2$-alkylsulfonyl-$\text{Ci}_3$-alkylamino-$\text{Ci}_2$-alkyl, $\text{C}_1$-$\text{alkylsulfonylamino-}$-$\text{Ci}_2$-alkyl, cyano-$\text{Ci}_4$-alkyl or $\text{C}_1$-$\text{alkylcarbonylamino-}$-$\text{Ci}_2$-alkyl;

$R^1$ is $H$, -$\text{PO}(\text{O-}$-$\text{C}_2$-alkyl)$_2$, $\text{C}_1$-$\text{alkylcarbonyloxy-}$-$\text{C}_2$-$\text{alkylcarbonyloxy-}$-$\text{C}_1$-$\text{alkoxycarbonyl,}$

$Q$ is optionally substituted $\text{C}_4$-$\text{C}_4$ alkenylenyl, optionally substituted $\text{C}_3$-$\text{C}_4$ alkenylenyl, optionally substituted $\text{C}_2$-$\text{C}_3$ alkylenyl, optionally substituted phenyl-$\text{C}_2$-$\text{alkylcarbonyloxy-}$-$\text{C}_2$-$\text{alkenylenyl,}$

$n$ is 1-2; and $m$ is 1-2; provided $n+m=3$ or 4;

and a pharmaceutically acceptable salt thereof.

In another embodiment, $R^1$ is $H$; and a pharmaceutically acceptable salt thereof.

In another embodiment, $R^2$ is $H$, $\text{HC}(=\text{O})-$, methyl or hydroxymethyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, $R^2$ is $H$ or methyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Z$ is $O$ or $S$; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Z$ is $\text{HN, methylamino, hydroxyethylamino, BOC-}$

$a$minoethylamino, $\text{a}$minoethylamino, $\text{c}$yanopropylamino,

$\text{m}$ethylsulfonylethylaminoethy lamino, $\text{m}$ethylsulfonylethylaminoethy lamino,

$\text{m}$ethylcarbonylaminoethylamino or $\text{m}$ethylsulfonylethylpropylamino; and a pharmaceutically acceptable salt thereof.

In another embodiment, $Q$ is butylenyl, 2-methylbutylenyl, 3-methylbutylenyl, 4-methylbutylenyl, 4-hydroxybutylenyl, 4-hydroxyethylbut-2-enylenyl, 4-hydroxyethylbut-2-enylenyl, 4-methylbut-2-enylenyl, 2-methylbut-2-enylenyl, 3-methylbut-2-enylenyl, 4-methylbut-2-enylenyl, 4,4-dimethylbut-2-enylenyl, 4-trifluoromethylbut-2-enylenyl, 4-(methylsulfonylethyl)but-2-enylenyl, 3-methylbut-2-enylenyl, 2-methylbut-2-enylenyl, but-2-enylenyl, pentenyl, pent-2-enylenyl, 2-methylpent-2-enylenyl, $-(\text{CH}_2)_2$-$0$-$\text{CH}_3$, 3-($\text{eth-2-enylenyl}$)cyclobutyl or phenylethynyl; and a pharmaceutically acceptable salt thereof.

In another embodiment, $R^6$ is $H$; and a pharmaceutically acceptable salt thereof.

Another family of specific compounds of particular interest within Formula 1 and 1’ consists of compounds and a pharmaceutically-acceptable salt thereof as follows:
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(9S, 11Z, 13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-
4,9~.0~18,22~]tetracosa-l(22),2(24),4,II,15,17,18,20,22-nonaen-6-one;
(9S, HE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-
4,9~.0~1 8,22~]tetracosa- l(21),2(24),4,1 1,15,17,19,22-octaen-6-one;

(9S, 11Z)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-
4,9~.0~18,22~]tetracosa-l(22),2(24),4,II,15,17,18,20,22-nonaen-6-one;
(9S, 13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-
4,9~.0~18,22~]tetracosa-l(22),2(24),4,II,15,17,18,20,22-octaen-6-one;  and
(9S, HZ)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-
4,9~.0~18,22~]tetracosa-l(22),2(24),4,II,15,17,18,20,22-nonaen-6-one.

Another aspect of the invention relates to a pharmaceutical composition
comprising a compound of formulas (1 and 1′) and a pharmaceutically-acceptable
diluent or carrier.

Another aspect of the invention relates to the use of a compound according to any
of the above embodiments as a medicament.

Another aspect of the invention relates to the use of a compound according to any
of the above embodiments in the manufacture of a medicament for the treatment of
cancer.

The compounds of this invention may have in general several asymmetric centers
and are typically depicted in the form of racemic mixtures. This invention is intended to
encompass racemic mixtures, partially racemic mixtures and separate enantiomers and
diastereomers.

The present invention includes all pharmaceutically acceptable isotopically-
labelled compounds of the present invention wherein one or more atoms are replaced by
atoms having the same atomic number, but an atomic mass or mass number different from
the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention
include, but are not limited to, isotopes of hydrogen, such as 2H and 3H, carbon, such as
13C, 14C and 15C, chlorine, such as 35Cl, fluorine, such as 18F, iodine, such as 123I and 125I,
nitrogen, such as 15N and 15N, oxygen, such as 16O, 17O and 18O, phosphorus, such as 32P,
and sulphur, such as 35S.

Certain isotopically-labelled compounds of the present invention, for example,
those incorporating a radioactive isotope, are useful in drug and/or substrate tissue
distribution studies. The radioactive isotopes tritium, i.e. 3H, and carbon-14, i.e. 14C, are
particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e. $^2$H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as $^1$C, $^{18}$F, $^{15}$O and $^{15}$N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the present invention 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 reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. $D_2O$, de-acetone, de-DMSO.

Specific embodiments of the present invention include the compounds exemplified in the Examples below and their pharmaceutically acceptable salts, complexes, solvates, polymorphs, stereoisomers, metabolites, prodrugs, and other derivatives thereof. Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, $t$-butyl, pentyl, isoamyl, hexyl and the like.

Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkenylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most
preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "alkenylenyl" embraces bridging divalent alkenyl radicals.

The term "alkynyl" embraces linear or branched radicals having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Examples of such radicals include ethynyl and the like. Even more preferred are lower alkynyl radicals having two to three carbon atoms. The term "alkynylenyl" embraces bridging divalent alkynyl radicals.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyland dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "cyanoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more cyano
radicals. More preferred cyanoalkyl radicals are "lower cyanoalkyl" radicals having one to six carbon atoms and one or more cyano radicals. Examples of such radicals include cyanomethyl, cyanopropyl, and cyanohexyl.

The term "alkoxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, fluoroethoxy and fluoropropoxy.

The term "alkoxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more alkoxy radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or more alkoxy radicals. Examples of such radicals include methoxymethyl, ethoxyethyl, propoxypropyl and methoxyethyl. Even more preferred are lower alkoxyalkyl radicals having one to three carbon atoms.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred are phenyl. Said "aryl" group may have 1 to 3 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino. Phenyl substituted with -O-CH₂-O- forms the aryl benzdioxolyl substituent.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered
heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclic radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiazadiazolyl [e.g., 1,2,4-thiazadiazolyl, 1,3,4-thiazadiazolyl, 1,2,5-thiazadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isodindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoimidazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thiophenyl, oxazolyl, furyl, and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrollyl, indazolyl,
pyrazolyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

Particular examples of non-nitrogen containing heteroaryl include pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzofuryl, benzothienyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofurly, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-R'-benzo[d]isothiazol-6-yl, dihdropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

"Heterocycle" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:
The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes \(-\text{C}_2\text{H}_2\).

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes \(-(\text{C}=\text{O})\)-.

The term "alkylcarbonyl" denotes a carbonyl radical substituted with an alkyl group.

The term "alkoxycarbonyl" denotes an ester group, containing an alkoxy substituted carbonyl.

The term "aminocarbonyl" denotes an amide group of the formula \(-\text{C}(=\text{O})\text{NH}_2\).

The terms "aralkyl" or "arylalkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "optionally substituted phenylalkylenyl" when used in a linker may be divalent on either the alkyl portion or the phenyl ring and the alkyl portion.

The terms "arylalkenyl" embraces aryl-substituted alkenyl radicals. Preferable aralkyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having two to six carbon atoms. Even more preferred are "phenylalkenyl" where a phenyl ring is attached to alkenyl portions having two to three carbon atoms. The aryl in said arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The terms "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are \(\text{C}_{3,6}\) cycloalkyl-\(\text{C}_{6}\) alkyl" radicals having \(\text{C}_{3,6}\)
cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. The cycloalkyl in said cycloalkylalkyl may be additionally substituted with halo, alkyl, and the like.

The terms "cycloalkylalkenyl" embraces cycloalkyl-substituted alkenyl radicals. Preferable cycloalkylalkenyl radicals are "C3-6 cycloalkyl-C2-6 alkenyl" radicals having C3-6 cycloalkyl radicals attached to alkenyl radicals having two to six carbon atoms. The cycloalkyl in said cycloalkylalkenyl may be additionally substituted with halo, alkyl, and the like.

The terms "heterocyclylalkyl" embraces heterocyclyl-substituted alkyl radicals. Preferable heterocyclylalkyl radicals are "3-7 membered heterocyclyl-C6 alkyl" radicals having 3-7 membered heterocyclyl radicals attached to alkyl radicals having one to six carbon atoms. Other heterocyclylalkyl radicals are "5-7 membered heterocyclyl-Cu alkyl" radicals having 5-6 membered heterocyclyl radicals attached to alkyl radicals having one to six carbon atoms. The heterocyclyl in said 3-7 membered heterocyclylalkyl may be additionally substituted with halo, alkyl, and the like.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Suitable aryloxy radicals may be phenyloxy and the like.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are substituted with one alkyl radical and with two independent alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "alkenylamino" embraces "N-alkenylamino" where amino groups are substituted with one alkenyl radical. More preferred alkenylamino radicals are "lower alkenylamino" radicals having an alkenyl radical of two to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkenylamino radicals having two to three carbon atoms.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.
The term "cycloalkylamino" denotes amino groups which have been substituted with one or two cycloalkyl radicals, such as N-cyclohexylamino. The cycloalkylamino radicals may be further substituted on the cycloalkyl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "heterocyclylamino" denotes amino groups which have been substituted with one or two heterocyclyl radicals, such as N-piperidinylamino. The "heterocyclylamino" radicals may be further substituted on the heterocyclyl ring portion of the radical.

The term "alkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C1-3-alkylamino radicals, such as N-benzyllamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The term "cycloalkylalkylamino" denotes amino groups which have been substituted with one or two cycloalkylalkyl radicals. More preferred are C1-3 cycloalkyl-C1-3-alkylamino radicals. The cycloalkylalkylamino radicals may be further substituted on the cycloalkyl portion.

The term "heterocyclylalkylamino" denotes amino groups which have been substituted with one or two heterocyclylalkyl radicals. More preferred are C1-3 cycloalkyl-C1-3-alkylamino radicals. The heterocyclylalkylamino radicals may be further substituted on the cycloalkyl portion.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminooethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable
alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethyldimethylaminoethyl and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH₂ groups.

The term "carboxyalkylamino" embraces amino groups substituted with a carboxyalkyl radical. More preferred carboxyalkylamino radicals are "lower carboxyalkylamino" radicals having one to six carbon atoms. Other preferred carboxyalkylamino groups have alkyl portions with one to three carbon atoms.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO₂⁻.

The term "alkylsulfonyl" includes sulfonyl radicals substituted with an alkyl radical. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylsulfonyl radicals having one to three carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl and ethylsulfonyl.

The term "alkylsulfonylamino" embraces amino groups substituted with an alkylsulfonyl radical. More preferred alkylsulfonylamino radicals are "lower alkylsulfonylamino" radicals having one to six carbon atoms. Other preferred alkylsulfonylamino groups have alkyl portions of one to three carbon atoms.

The term "alkylsulfonylalkylamino" embraces alkylamino groups substituted with an alkylsulfonyl radical. More preferred alkylsulfonylalkylamino radicals are "lower alkylsulfonylalkylamino" radicals having alkyl groups of one to six carbon atoms. Other preferred alkylsulfonylalkylamino groups have alkyl portions of one to three carbon atoms.

The term "alkoxyalkylamino" embraces amino groups substituted with an alkoxyalkyl radical, as previously described. More preferred alkoxyalkylamino radicals are "lower alkoxyalkylamino" radicals having alkyl radicals of one to six carbon atoms.
Other preferred alkoxyalkylamino groups have alkyl portions of one to three carbon atoms.

The term "hydroxyalkylamino" embraces amino groups substituted with an hydroxyalkyl radical, as previously described. More preferred hydroxyalkylamino radicals are "lower hydroxyalkylamino" radicals having alkyl radicals of one to six carbon atoms. Other preferred hydroxyalkylamino groups have alkyl portions of one to three carbon atoms.

The term "haloalkylamino" embraces amino groups substituted with a haloalkyl radical, as previously described. More preferred haloalkylamino radicals are "lower haloalkylamino" radicals having alkyl radicals of one to six carbon atoms. Other preferred haloalkylamino groups have alkyl portions of one to three carbon atoms.

The term "aminoalkylamino" embraces alkylamino groups substituted with an amino (-NH₂) group. More preferred aminoalkylamino radicals are "lower aminoalkylamino" radicals having alkyl groups of one to six carbon atoms. Other preferred aminoalkylamino groups have alkyl portions of one to three carbon atoms.

The term "aminocarbonylalkylamino" embraces amino groups substituted with an aminocarbonyl radical, as previously described. More preferred aminocarbonylalkylamino radicals are "lower aminocarbonylalkylamino" radicals having alkyl radicals of one to six carbon atoms. Other preferred aminocarbonylalkylamino groups have alkyl portions of one to three carbon atoms.

The term "alkoxycarbonylalkylamino" embraces amino groups substituted with an alkoxy carbonyl radical, as previously described. More preferred alkoxy carbonylalkylamino radicals are "lower alkoxy carbonylalkylamino" radicals having alkyl radicals of one to six carbon atoms. Other preferred alkoxy carbonylalkylamino groups have alkyl portions of one to three carbon atoms.

"Benzo group", alone or in combination, means the divalent radical C₆H₄=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring—for example tetrahydronaphthalene, indole and the like.

The term "oxo" represents the groups =O (as in carbonyl).

"Pharmacologically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid,
lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," see infra and Berge et al., J. Pharm. Sci. 66:1 (1977).

"Saturated, partially-saturated or unsaturated" includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.

"Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

"Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, isobutoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, trichloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a
heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-trisilyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzylxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can
readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups, and the like, for example as illustrated in the following examples:

\[
\begin{align*}
\text{amine} & \quad \leftrightarrow \\
\text{amide}
\end{align*}
\]

and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug 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 patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxyalkyl substituted derivatives which are cleaved by esteras in vivo releasing the free drug and formaldehyde (Bungard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-aclyloxyethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/1 1/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is
meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

Utility and Methods of Use

An aspect of the present invention is a method for inhibiting Pim kinase activity in a cell, comprising contacting the cell with an effective amount of a compound of Formulas 1-5, 1’ and 3’.

Another aspect of the present invention provides a method for treating a condition by modulation of Pim kinase activity comprising administering to a patient in need of such treatment an effective amount of a compound of Formulas 1-5, 1’ and 3’.

Another embodiment of the present invention provides a method for treating a cancer disorder in a patient, comprising administering to the patient a composition comprising an amount of a compound of Formulas 1-5, 1’ and 3’ effective to inhibit Pim kinase activity in the patient.

Another embodiment of the present invention provides a method for treating a cancer disorder in a patient, wherein the cancer is prostate, head and neck or lymphoma, comprising administering to the patient a composition comprising an amount of a compound of Formulas 1-5, 1’ and 3’ effective to inhibit Pim kinase activity in the patient.

Another aspect of the present invention provides the use of any one of the compounds of Formulas 1-5, 1’ and 3’ in the manufacture of a medicament for the treatment of cancer.

Administration and Pharmaceutical Compositions

In general, the compounds of this invention can be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of a compound of this invention, i.e., the active ingredient, depends upon numerous factors, such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of formula (1) may range from approximately 0.1-1000 mg per day.

In general, compounds of this invention can be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or
subcutaneous) administration. The preferred manner of administration is oral using a
convenient daily dosage regimen, which can be adjusted according to the degree of
affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders,
sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other
appropriate compositions.

The choice of formulation depends on various factors, such as the mode of drug
administration (e.g., for oral administration, formulations in the form of tablets, pills or
capsules are preferred) and the bioavailability of the drug substance. Recently,
pharmaceutical formulations have been developed especially for drugs that show poor
bioavailability based upon the principle that bioavailability can be increased by increasing
the surface area, i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288
describes a pharmaceutical formulation having particles in the size range from 10 to 1,000
nm in which the active material is supported on a crosslinked matrix of macromolecules.
U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in
which the drug substance is pulverized to nanoparticles (average particle size of 400 nm)
in the presence of a surface modifier and then dispersed in a liquid medium to give a
pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of, in general, a compounds of the present
invention in combination with at least one pharmaceutically acceptable excipient.

Acceptable excipients are non-toxic, aid administration, and do not adversely affect the
therapeutic benefit of the compounds of the present invention. Such excipient may be any
solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is
generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose,
sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate,
glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and
semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and
various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g.,
peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly
for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in
aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation contains, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compounds of the present invention based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.
Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acenthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, fludaridine, fludarabine phosphate, 5-fluorouracil, N-(2′-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uracytin.

A second family of antineoplastic agents which may be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakanaga CA-102, carboplatin, carmustine, Chinoind-139, Chinoind-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba
A-1700-WO-PCT


A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents.


A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic

Alternatively, the present compounds may also be used in co-therapies with other antineoplastic agents, such as acemannan, aclarubicin, aldesleukin, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, anecstim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capcitabine, cetromelukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), dacizumab, denileukin difitox, deslorelin, dexamethasone, dilazep, docetaxel, docosanol, doxencalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, efomithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gentuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-NI, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural interferon alpha, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interferon gamma-1 beta, iobenguane, irinotecan, irosogadine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentaran sulfate, letrozole, leukocyte alpha interferon, leuprolerin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprolol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitokactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, naragrostim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentoan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a,
porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfm, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, strontium-89 chloride, suramin, tasonermin, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazarotene, tazaroteme...
Synthetic Methods

The following abbreviations may be used herein:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH or HOAc</td>
<td>acetic acid</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>argon</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine 5'-triphosphate</td>
</tr>
<tr>
<td>A-Phos or Amphos</td>
<td>di-t-butyl-(4-dimethylaminophenyl)phosphine</td>
</tr>
<tr>
<td>BBr₃</td>
<td>boron tribromide</td>
</tr>
<tr>
<td>(BPin)₂</td>
<td>bis(pinacolato)diboron</td>
</tr>
<tr>
<td>BrettPhos</td>
<td>dicyclohexyl(2',4',6'-triisopropoxy-3,6-dimethoxy-1,1'-biphenyl)-2-yl)phosphine</td>
</tr>
<tr>
<td>BrettPhos precatalyst</td>
<td>Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4'-6'-triisopropoxy-3,6-dimethoxy-2',4'-]</td>
</tr>
<tr>
<td>nBuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>chloroform</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>C₀₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>Calcd or Calc’d</td>
<td>calculated</td>
</tr>
<tr>
<td>Cone.</td>
<td>concentrated</td>
</tr>
<tr>
<td>Cul</td>
<td>copper (I) iodide</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEA</td>
<td>diethylamine</td>
</tr>
<tr>
<td>DIPEA, DIEA</td>
<td>diisopropylethyl amine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DTT</td>
<td>dithiothreitol</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediamine tetraacetic acid</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et₃N or TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Symbol</td>
<td>Name</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethyl alcohol</td>
</tr>
<tr>
<td>FBS</td>
<td>fetal bovine serum</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs II Catalyst (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene) (tricyclohexyl phosphine)ruthenium</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>¾</td>
<td>hydrogen</td>
</tr>
<tr>
<td>10</td>
<td>HCl</td>
</tr>
<tr>
<td>HCO(_2)H</td>
<td>formic acid</td>
</tr>
<tr>
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<td>water</td>
</tr>
<tr>
<td>H(_2)O(_2)</td>
<td>hydrogen peroxide</td>
</tr>
<tr>
<td>HNO(_3)</td>
<td>nitric acid</td>
</tr>
<tr>
<td>15</td>
<td>H(_2)SO(_4)</td>
</tr>
<tr>
<td>Hex</td>
<td>hexanes</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>IPA or iPrOH</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>KHSO(_4)</td>
<td>potassium bisulfate</td>
</tr>
<tr>
<td>20</td>
<td>KHMDS or KHMD S</td>
</tr>
<tr>
<td>KOAc</td>
<td>potassium hydroxyacetate</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>K(_3)PO(_4)</td>
<td>potassium phosphate</td>
</tr>
<tr>
<td>L</td>
<td>liter</td>
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<tr>
<td>25</td>
<td>LCMS, LC-MS or LC/MS</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LHMD S or LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m/z</td>
<td>mass divided by charge</td>
</tr>
<tr>
<td>MeOH</td>
<td>methyl alcohol</td>
</tr>
<tr>
<td>30</td>
<td>MePPh(_3)Br</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mL</td>
<td>milliliters</td>
</tr>
<tr>
<td>MgSQ(_4)</td>
<td>magnesium sulfate</td>
</tr>
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</table>
**Mass** spectra

*MS*

N$_2$  nitrogen

NH$_3$  ammonia

NH$_4$OH  ammonium hydroxide

5  NH$_4$OAc  ammonium acetate

NH$_4$Cl  ammonium chloride

NMO  n-methylmorpholine oxide

NaH  sodium hydride

NaOH  sodium hydroxide

10  NaHCO$_3$  sodium bicarbonate

Na$_2$CO$_3$  sodium carbonate

Na$_2$SO$_4$  sodium sulfate

NBS  N-bromosuccinimide

NMP  l-methyl-2-pyrrolidinone

15  **NMR**  nuclear magnetic resonance

POCl$_3$  phosphorous oxychloride

Pd/C  palladium on carbon

Pd(PPh$_3$)$_4$  tetrakis(triphenylphosphine)-palladium (0)

PdCl$_2$(PPh$_3$)$_2$  dichloro bis(triphenylphosphine)-palladium (II)

20  Pd$_2$dba$_3$  tris(dibenzylideneacetone) dipalladium (0)

Pd(dppf)Cl$_2$  [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)

PdCl$_2$  palladium chloride

P  protecting group

25  Pos. ion  positive ion

Pt/C  platinum on carbon

rt or RT  room temperature

Sat.  saturated

SFC  supercritical fluid chromatography

30  TFA  trifluoroacetic acid

THF  tetrahydrofuran

Ts or tosyl  para-toluene sulfonyl

wt  weight

Xphos  2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
The compounds of the invention can be prepared according to the following procedures of Schemes 1-10, wherein the substituents are as defined for formulas 1-5, 1' and 3' above, except where noted.

**Scheme 1**

Substituted 6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-ones 4 can be prepared according to the method set out in Scheme 1. A strong alkyl metal, such as an organolithium reagents (e.g. butyllithium) is added to a solution of a dihalo-bicyclic ring 1 at a temperature below 0 °C, preferably below -50 °C, even more preferably at about -72 °C. Treatment with an acetamide at a temperature below 0 °C, preferably below -50 °C, even more preferably at about -70 °C yields the acetyl derivative 2. Bromination of the acetyl derivative 2, such as with a base, e.g. Et₃N, teri-butyltrimethylsilyl trifluoromethanesulfonate, and bromination such as with NBS, provides the desired bromoacetyl compound 2a. Treatment of the bromoacetyl compound 2a with an ammonia salt, such as NH₄OAc, and piperidine-2,4-dione at a temperature above RT, preferably at about 50 °C affords the 6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one 3. Substitution of the remaining halo group provides further compounds 4. For example, treatment with arylamines such as aniline, in the presence of a strong non-nucleophilic base, e.g. LHMDS, provides the desired amine derivatives. Alternatively, where the chloro substituent is methyl ester substituent, treatment of compound 1 with a palladium
catalyst, such as Pd(PPh\(_3\))\(_4\) and a tin reagent, such as tributyl(l-ethoxyvinyl)tin, at a temperature higher than RT, preferably above about 50 °C, more preferably at about 100 °C provides the corresponding the acetyl derivative 2 [with the ester substitution]. Grubbs catalyst 2nd generation is added to 4 and heated such as to reflux to form the macrocycle 5.

Scheme 2

Similarly, ether substituted compounds 4, where Z is oxygen, can be prepared according to the method set out in Scheme 2. Alcohols [Z\(^\circ\)OH] are treated with strong base, such as NaH, then added to the chloro substituted compounds 3 furnished substituted 6,7-dihydro-l//-pyrrolo[3,2-c]pyridin-4(5//)-ones 4.

Scheme 3

Amino substituted compounds 4, where R\(^1\) is alkylamino, arylamino and the like, are prepared by the method described in Scheme 3. Fluoro-substituted compounds 6 and an optionally substituted amine [Z\(^\circ\)NH\(_2\)] are heated at a temperature higher than RT, preferably above about 50 °C, more preferably at about 80 °C to furnish the desired amines 4.

Scheme 4
Compounds 8, where where R₄ is phenylalkyl and the like, are prepared by the
method described in Scheme 4. Halo-substituted compounds 7 having an optionally
substituted MeZ-phenyl portion are treated with boron tribromide. The resulting material
is treated with a base, such as NaH, preferably above about 50 °C, more preferably at
about 80 °C to furnish the desired macrocycles 8.

**Scheme 5**

Similarly, compounds 12, where where R₄ is phenylalkyl and the like, are
prepared by the method described in Scheme 5. Halo-phenylalkyl substituted
quinazolines 11 are prepared by methods described above. Halo-phenylalkyl substituted
quinazolines 11 are cyclized using a catalyst such as Brettphos, preferably above about 50
°C, more preferably at about 110 °C, to furnish the desired macrocycles 12.
Other cyclic amides can be prepared such as the 3,4-dihydropyrrolo[1,2-
\text{a}]pyrazin-1 (2H)-ones 15 as described in Scheme 6. Methyl 4-bromo-IH-pyrrole-2-
carboxylate 13 is reacted with base, such as NaH, and 1,2 dibromoethane at a temperature
higher than RT, preferably above about 50 °C, more preferably at about 70 °C to afford
the bromoethyl derivative 14. Cyclization, such as with treatment with (2,4-
dimethoxyphenyl)methanamine, at a temperature higher than RT, preferably above
100 °C, more preferably at about 150 °C yields the protected bromo-3,4-
dihydropyrrolo[1,2-a]pyrazin-1 (2H)-one 15.

8-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalines 17 can be prepared
similar to that shown in Scheme 7. Treatment of the bromo compound 16 with
bis(pinacolato)diboron, a palladium catalyst such as PdCl$_2$(dppf)$_2$, and a base, such as potassium acetate, at a temperature higher than RT, preferably above about 75 °C, more preferably at about 105 °C, affords the desired boron derivative 17.

**Scheme 8**

Other cyclic amides of the present invention can be prepared such as the 3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-ones 23 as described in Scheme 8. Substituted amines are coupled to the 8-bromo-2-chloroquinoline through treatment with base, such as LiHMDS, at a temperature of about RT, to afford the desired 8-bromoquinolin-2-amine 19. The bromo compound 20 is converted to the boronic acid 21 via treatment with a palladium catalyst, such as Pd(dppf)$_2$Cl$_2$, bis(pinacolato)diboron, and a base such as KOAc, at a temperature higher than RT, preferably above about 75 °C, more preferably at about 115 °C. Coupling of the boronic acid 21 with the protected 7-bromo-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one 16 such as in the presence of a palladium catalyst, such as Pd$_2$(dba)$_3$ or bis(di-2-ethylhexyl(4-dimethylaminophenyl)phosphine)-dichloro-palladium(II), and dicyclohexyl(2’,4’,6’-triisopropyl-[1,1’-biphenyl]-2-yl)phosphine and a base such as K$_3$PO$_4$, at a temperature higher than RT, preferably above about 75 °C, more preferably at about 130 °C, gave the protected 7-(quinolin-8-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one 22. Deprotection, such as with acid, at a
A temperature higher than RT, preferably at about 50 °C, affords the desired 7-(quinolin-8-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one 23.

Scheme 9

Macrocycles with amide containing linkers can be prepared as described in Scheme 9. Deprotection of protected amines and esters, such as with base or with acid, provides the desired amino acid. Amide formation such as with treatment with PyBop yields the desired amides 26.

Scheme 10

Macrocycle prodrug intermediates 27 can be prepared according to the method set out in Scheme 10. Treatment of the 6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one 3 with an acyl halide, phosphate ester, and the like provides the substituted amides 27. Subsequent steps as described in Scheme 1 provides the complete macrocycle prodrug.
The starting compounds defined in Schemes 1-10 may also be present with functional groups in protected form if necessary and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible. If so desired, one compound of formulas 1-5, 1’ and 3’ can be converted into another compound of formulas 1-5, 1’ and 3’ or a N-oxide thereof; a compound of formulas 1-5, 1’ and 3’ can be converted into a salt; a salt of a compound of formulas 1-5, 1’ and 3’ can be converted into the free compound or another salt; and/or a mixture of isomeric compounds of formulas 1-5, 1’ and 3’ can be separated into the individual isomers.

N-Oxides can be obtained in a known manner by reacting a compound of formulas 1-5, 1’ and 3’ with H₂O₂ or a peracid, e.g. 3-chloroperoxy-benzoic acid, in an inert solvent, e.g. dichloromethane, at a temperature between about -10-35°C, such as about 0°C - RT.

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a compound of formulas 1-5, 1’ and 3’ or in the synthesis of a compound of formulas 1-5, 1’ and 3’, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.


In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned above under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of formulas 1-5, 1' and 3' with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of formulas 1-5, 1' and 3' may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formulas 1-5, 1' and 3') may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from about 130°C to about 170°C, one molecule of the acid being expelled per molecule of a compound of formulas 1-5, 1' and 3'.

Salts can usually be converted to free compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers, for example in the H+ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from about -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at about -80 to about 60°C, at RT, at about -20 to about 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.
Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective reactions, allowing for example easier recovery of individual isomers.

The solvents from which those can be selected which are suitable for the reaction in question include for example water, esters, typically lower alkyl-lower alkanoates, e.g., ethyl acetate, ethers, typically aliphatic ethers, e.g., diethylether, or cyclic ethers, e.g., THF, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically MeOH, EtOH or 1-propanol, 2-propanol, nitriles, typically ACN, halogenated hydrocarbons, typically DCM, acid amides, typically DMF, bases, typically heterocyclic nitrogen bases, e.g., pyridine, carboxylic acids, typically lower alkanecarboxylic acids, e.g., AcOH, carboxylic acid anhydrides, typically lower alkane acid anhydrides, e.g., acetic anhydride, cyclic, linear, or branched hydrocarbons, typically cyclohexane, hexane, or isopentane, or mixtures of these solvents, e.g., aqueous solutions, unless otherwise stated in the description of the process. Such solvent mixtures may also be used in processing, for example in chromatography.

The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound in situ. In the preferred embodiment, one starts from those starting materials which lead to the compounds described above as preferred.

The compounds of formulas 1-5, 1' and 3', including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of the invention, are known, are commercially available, or can be synthesized in analogy to or according to methods that are known in the art.
In the preparation of starting materials, existing functional groups which do not participate in the reaction should, if necessary, be protected. Preferred protecting groups, their introduction and their removal are described above or in the examples.

All remaining starting materials are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described in the examples.

Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzyloltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, scalemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention.

The compounds may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Substituents on ring moieties (e.g., phenyl, thienyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn
unattached to a specific atom, whereby they are intended to be attached at any available atom that is not already substituted by an atom other than H (hydrogen).

The compounds of this invention may contain heterocyclic ring systems attached to another ring system. Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

Alternatively, a compound of any of the formulas delineated herein may be synthesized according to any of the processes delineated herein. In the processes delineated herein, the steps may be performed in an alternate order and may be preceded, or followed, by additional protection/deprotection steps as necessary. The processes may further comprise use of appropriate reaction conditions, including inert solvents, additional reagents, such as bases (e.g., LDA, DIPEA, pyridine, K₂C₀₃, and the like), catalysts, and salt forms of the above. The intermediates may be isolated or carried on in situ, with or without purification. Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, simulated moving bed ("SMB")), extraction, distillation, trituration, reverse phase HPLC and the like. Reactions conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the inhibitor compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); A. Katritzky and A. Pozharski, Handbook of Heterocyclic Chemistry, 2nd Ed. (2001); M. Bodanszky, A. Bodanszky: The practice of Peptide Synthesis Springer-Verlag, Berlin Heidelberg 1984; J. Seyden-Penne: Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd Ed., Wiley-VCH, 1997; and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).
The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas 1-5 and 1’ and 3’. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. All microwave assisted reactions were conducted with a Initiator™ Microwave Synthesizer from Biotage™. All compounds showed NMR spectra consistent with their assigned structures. Melting points were determined on a Buchi apparatus and are uncorrected. MS data was determined by electrospray ionization technique. All examples were purified to >90% purity as determined by high-performance liquid chromatography. Unless otherwise stated, reactions were run at RT.

Analytical Methods:

Unless otherwise indicated, HPLC analyses were run on an Agilent Model 1100 system with an Agilent Technologies Zorbax SB-C₈ (5 μ) reverse phase column (4.6 x 150 mm) run at 30 °C with a flow rate of about 1.50 mL/min (Agilent Technologies, Santa Clara, CA). The mobile phase used solvent A (H₂O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a 11 min gradient from 5% to 100% ACN. The gradient was followed by a 2 min. return to 5% ACN and about a 2.5 min. re-equilibration (flush).

LC-MS Methods:
Unless otherwise indicated, samples were run on an Agilent model-1100 LC-MSD system with an Agilent Technologies XDB-C$_8$ (3.5µ) reverse phase column (4.6 x 75 mm) at 30 °C. The flow rate was constant and ranged from about 0.75 mL/min to about 1.0 mL/min. The mobile phase used a mixture of solvent A (H$_2$O/0.1% HCO$_2$H or TFA) and solvent B (ACN/0.1% HCO$_2$H or TFA) with a 5 to for a gradient from 10% to 90% solvent B. The gradient was followed by a 0.5 min period 9 min time period to return to 10% solvent B and a 2.5 min 10% solvent B re-equilibration (flush) of the column.

**Preparative HPLC Methods:**

Where indicated, compounds of the present invention were purified via reverse phase HPLC using a Gilson (Gilson, Middleton, WI) or Shimadzu (Columbia, MD) workstation utilizing one of the following two protocols: (A) Using a 50 x 100 mm column (Waters, Exterra, C$_{18}$, 5µ) (Waters, Milford, MA) at 50 mL/min. The mobile phase used was a mixture of solvent A (H$_2$O/10 mM ammonium carbonate at pH about 10, adjusted with cone. NH$_4$OH) and solvent B (85:15 ACN/water, 10 mM ammonium carbonate at pH of about 10 adjusted with cone. NH$_4$OH). Each purification run utilized a >10 min gradient from 40% to 100% solvent B followed by a 5 min flow of 100% solvent B. The gradient was followed by a 2 min return to 40% solvent B; or (B) Using a Waters 20 x 50 mm column at 20 mL/min or Phenomenex Gemini 5µ C$_{18}$ 100 x 30mm (Phenomenex, Torrance, CA). The mobile phase used was a mixture of solvent A (H$_2$O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a >10 min gradient from 5% to 100% solvent B. The gradient is followed by a 2 min return to 5% ACN.

**Mass Spectra (MS)**

Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an (M+H$^+$) or (M-FT) molecular ion, depending on the ionization mode (positive or negative). The molecular ion reported was obtained by electrospray detection method.

Compounds having an isotopic atom, such as bromine and the like, are reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

**Intermediates**
Intermediate A: 5-allylpiperidine-2,4-dione

Step 1: tert-butyl 5-allyl-2,4-dioxopiperidine-1-carboxylate

To a solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharma, Libertyville, IL, 8.50 g, 39.9 mmol) and allyl chloride (Acros Organics, 12.99 ml, 159 mmol) in 400 mL THF at -20 °C (acetone bath with dry ice added periodically) was added LiHMDS, 1.0 M solution in THF (Sigma Aldrich, St. Louis, MO, 100 ml, 100 mmol) dropwise via addition funnel, with the internal temperature of the reaction kept at -18 to -20 °C. A thick precipitate was observed, which disappeared on complete addition. The clear, yellow-orange reaction was stirred for 1 h and was quenched by addition of water and 400 mL Et₂O. The aqueous layer was acidified with 5 M HCl, and the organic layer was washed 1 x brine, and the combined organics were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (330 g) eluting with 0-100% EtOAc/hexanes. The product containing fractions were combined and concentrated to afford tert-butyl 5-allyl-2,4-dioxopiperidine-1-carboxylate (7.00 g, 27.6 mmol, 69.3 % yield): ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.23 (1 H, br. s.), 5.65 - 5.90 (1 H, m), 5.01 - 5.17 (2 H, m), 4.93 (1 H, s), 3.75 (1 H, dd, J=13.1, 4.3 Hz), 3.58 (1 H, dd, J=13.2, 4.4 Hz), 2.30 - 2.49 (2 H, m), 2.04 - 2.18 (1 H, m), 1.42 (9 H, s).

Step 2: 5-allylpiperidine-2,4-dione

In a 1-L round-bottomed flask tert-butyl 5-allyl-2,4-dioxopiperidine-1-carboxylate (35.60 g, 141 mmol) was treated with 4 M HCl in 1,4-dioxane (Sigma Aldrich, 176 ml, 703 mmol). The mixture was stirred under inert atmosphere overnight. The progress of the reaction was monitored by TLC (eluent: 100% EtOAc) and LC/MS, which showed reaction completion. The mixture was concentrated in-vacuo. The residue was diluted with DCM (500 ml). Then solid NaHCO₃ (125 g) was added slowly into the mixture. The overall mixture was stirred vigourously for 1.5 h, then filtered through a fine-fritted
To the filtrate, was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was triturated with EtOAc (200 ml) and hexanes (800 ml). The mixture was filtered and the filtrate was concentrated in vacuo. This gave 5-allylpiperidine-2,4-dione (16.98 g, 111 mmol, 79 % yield) as a tan oil, which was used without further purification: m/z (ESI, +ve) 154.0 (M+H)⁺.

Intermediate B: (S)-7-allyl-2-bromo-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

Step 1: (S)-7-allyl-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

To a solution of aminoacetaldehyde dimethyl acetal (58 g, 553.3 mmol, Sigma-Aldrich) in THF (150 mL) was added tert-butyl 5-allyl-2,4-dioxopiperidine-1-carboxylate (Intermediate A, Step 1; 70 g, 276.6 mmol.). The reaction was heated at 100 °C for 45 min. The solvent was removed in vacuo and the residue was washed with Et₂O. The crude material was dissolved in DCM (200 mL) and cooled to 0 °C. TFA (200 mL) was added and the mixture was slowly warmed to RT and stirred for 8 h. The solvent was then removed in vacuo and the residue was diluted with DCM and treated with solid NaHCO₃ (200 g). The suspension was filtered and the filtrate was concentrated. The residue was purified with silica gel chromatography (eluted with 2% MeOH in DCM) to give 7-allyl-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (8.8 g, 18.1 %) as an off white solid. ¹H-NMR (400MHz, DMSO-ｄ₆): δ 11.20 (s, 1H), 6.80 (s, 1H), 6.70 (t, J = 2.8 Hz, 1H), 6.22 (t, J = 2.4 Hz, 1H), 5.78 - 5.86 (m, 1H), 5.07 - 5.12 (m, 2H), 3.31 - 3.42 (m, 1H), 3.09 - 3.14 (m, 1H), 2.95 - 2.99 (m, 1H), 2.20 - 2.28 (m, 1H). MS (ESI, pos. ion) m/z: 171.1 (M+). The racemic mixture was resolved by SFC (20% MeOH, Chiralpak ICH (250x20 mm), 70ml/min, 262-nm, 81/158 Bar) to give separated enantiomers (S)-7-allyl-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (first eluting peak), and (R)-7-allyl-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (second eluting peak).
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Step 2: (S)-7-allyl-2-bromo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

To a 250-mL round-bottomed flask was added (S)-7-allyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (2.50 g, 14.19 mmol) in DMF (50 mL). The solution was cooled to -60 °C and 1,3-dibromo-5,5-dimethylhydantoin (2.028 g, 7.09 mmol, Sigma-Aldrich) was added. The reaction was stirred at -60 °C for 20 min. The mixture was poured into ice/water (300 mL) and a solid formed. The suspension was filtered and the solid was washed with EtOAc (80 mL). The solid was dried to give 3.0 g of the product. The filtrate was extracted with EtOAc (150 mL x 3) and the combined organic layers were washed with water (80 mL x 3), brine (50 mL), dried (MgSO₄), filtered and concentrated. The residue was purified with silica gel chromatography (eluted with 1-3% MeOH in DCM) to give the product 390 mg. Overall (S)-7-allyl-2-bromo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3.39 g, 13.29 mmol, 94% yield) was obtained: ¹H NMR (400 MHz, DMSO-d6) δ ppm 11.83 (1 H, br. s.), 6.96 (1 H, br. s.), 6.23 (1 H, d, J=2.0 Hz), 5.73 - 5.87 (1 H, m), 5.04 - 5.15 (2 H, m), 3.40 (1 H, ddd, J=12.3, 5.5, 2.3 Hz), 3.12 (1 H, ddd, J=12.4, 6.6, 2.9 Hz), 2.89 - 2.99 (1 H, m), 2.46 - 2.49 (1 H, m), 2.18 - 2.30 (1 H, m). MS (ESI, pos. ion) m/z: 255.0/257.0 (M+).

**Intermediate C:** 7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

NH₄OAc (Fisher Scientific, Fair Lawn, NJ, 7.76 g, 101 mmol), 5-allylpiperidine-2,4-dione (Intermediate A, 3.86 g, 25.2 mmol), 2-bromo-1-(3-fluoro-2-methylquinaxalin-5-yl)ethanone (4.75 g, 16.78 mmol) were combined in 160 mL EtOH, sealed, and heated at 50 °C for 5 h. The reaction was concentrated to 1/2 volume, then partitioned between saturated aqueous NaHCO₃ (caution, gas evolution) and DCM. The aqueous layer was extracted with DCM 3x, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with a minimal volume of MeOH, sonicated, and filtered, rinsing 2x MeOH, to give 1.6 g (28% yield) 7-allyl-2-(3-fluoro-2-methylquinaxalin-5 -yl)-6,7-dihydro- 1H-pyrrolo[3,2-c]pyridin-4(5H)-one as an
Intermediate D: 2(S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one
Intermediate E: 2(R)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

Intermediate C was resolved by SFC (Chiralpak ASH, 5 µ, 250x30, 30% IPA containing 0.2% DEA, 120mL/min, 268 nm, 96/21 3 Bar) to give separated enantiomers 2(S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (first eluting peak, intermediate D), and 2(R)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (second eluting peak, intermediate E).


Step 1: 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline
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A 500 mL rbf was charged with a stir bar, KOAc (Sigma Aldrich, 29.3 g, 299 mmol), PdCl₂(PPh₃)₂DCM adduct (Strem Chemicals, Newburyport, MA, 3.05 g, 3.73 mmol), bis(pinacolato) diboron (Sigma Aldrich, 37.9 g, 149 mmol), 5-bromo-3-fluoro-2-methylquinoxaline (18.0 g, 74.7 mmol), and 100 mL anhydrous THF. Argon was bubbled into the mixture for 1 min, and the reaction was fitted with a water-cooled reflux condensor and was heated to reflux under argon. After 4 h the reaction was judged complete, was cooled, diluted with 100 mL EtOAc, filtered through Celite, rinsing 3 x 100 mL EtOAc, and concentrated in vacuo. The material was treated with DCM and adsorbed onto 100 g silica gel and purified by silica gel chromatography (split into two batches) (240 g column) using 0 - 70% EtOAc/hexane. The product-containing fractions were concentrated to afford 27.9 g of an orange semi-solid, which was used without further purification. A portion of this material was used in the next step.

Step 2: (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

Argon was bubbled into a mixture of 1,1-bis[(di-t-butyl-p-methylaminophenyl)palladium(ii) chloride (Sigma Aldrich, 1.227 g, 1.733 mmol), potassium phosphate, dibasic (EMD Chemicals, Gibbstown, NJ, 21.12 g, 121 mmol), (S)-7-allyl-2-bromo-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate B, 8.84 g, 34.7 mmol), 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-y1)quinoxaline (19.97 g, 69.3 mmol) (impure, from previous step) in 200 mL DMF and 100 mL water for 2 min. The orange slurry was placed in a 70 °C oil bath under argon. After 2 h the reaction was checked by LCMS and judged complete. The reaction was poured onto ice, and the resulting solid was collected by filtration (glass frit), rinsing 3 x 100 mL water. The slightly wet filter cake was transferred to a 500 mL rbf with MeOH/DCM and concentrated in vacuo to give 11.6 g material. The material was treated with 20% MeOH in DCM and adsorbed onto 55 g silica gel and purified by silica gel chromatography (220 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (7.40 g, 22.00 mmol, 63.5 % yield) as a orange solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.59 (1 H, s), 8.08 (1 H, dt, J=1A, 0.7 Hz), 7.86 - 7.96 (1 H, m), 7.72 - 7.84 (1 H, m), 7.19 (1 H, d, J=2.3 Hz), 7.00 (1 H, t, J=2.6 Hz), 5.83 - 6.04 (1 H, m), 5.02 - 5.28 (2 H, m), 3.40 - 3.55

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(1 H, m), 3.03 - 3.26 (3 H, m), 2.69 (3 H, s), 2.53 - 2.61 (1 H, m), 2.28 - 2.41 (1 H, m),
m/z (ESI, +ve) 337.1 (M+H)^+.

Intermediate F: 7-allyl-2-(2-chloroquinolin-8-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

2-Bromo-l-(2-chloroquinolin-8-yl)ethanone (0.900 g, 3.16 mmol), 5-allylpiperidine-2,4-dione (Intermediate A, 0.581 g, 3.80 mmol), NH₄OAC (Fisher Scientific, 0.975 g, 12.65 mmol) were combined in 15 mL EtOH, sealed, and heated in a 50 °C bath for 4 h. The reaction was partitioned between saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted with DCM 3x, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (80 g column) using 0 - 60% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to give 7-allyl-2-(2-chloroquinolin-8-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.365 g, 1.081 mmol, 34.2 % yield) as a sticky orange-brown oil: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.70 (1 H, d, J=0.6 Hz), 8.50 (1 H, d, J=8.6 Hz), 8.13 (1 H, dt, J=IA, 0.8 Hz), 7.90 (1 H, dt, J=8.0, 0.8 Hz), 7.58 - 7.73 (2 H, m), 7.20 (1 H, d, J=0.4 Hz), 7.00 (1 H, br. s.), 5.87 - 6.05 (1 H, m), 5.12 - 5.24 (2 H, m), 3.43 - 3.58 (1 H, m), 3.04 - 3.27 (2 H, m), 2.53 - 2.62 (1 H, m), 2.30 - 2.43 (1 H, m). m/z (ESI, +ve) 338.1 (M+H)^+.

Intermediate G and H: (S)-but-3-en-2-amine hydrochloride and (R)-but-3-en-2-amine hydrochloride
Step 1: 2-(but-3-en-2-yl)isoindoline-1,3-dione

A mixture of phthalimide potassium (39.3 g, 212 mmol), K₂CO₃ (5.9 g, 42.5 mmol), and DMF (354 ml) was set stirring at RT before adding 3-chloro-1-butene (25.00 ml, 276 mmol). The suspension was fitted with a reflux condenser and heated to 140 °C for 7 h before cooling to RT and pouring in 1.5 L water at 0 °C with rapid stirring. The resulting white precipitate was collected by filtration and was rinsed with cold water. After drying under air for 1 h, the material was transferred to a bottle and dried under vacuum at 50 °C overnight to give 2-(but-3-en-2-yl)isoindoline-1,3-dione (41.05 g, 204 mmol, 96% yield):

1H NMR (400 MHz, DMSO-d₆) δ ppm: 7.75 - 7.94 (4 H, m), 6.11 (1 H, ddd, J=17.3, 10.4, 5.8 Hz), 5.05 - 5.25 (2 H, m), 4.72 - 4.89 (1 H, m), 1.50 (3 H, d, J=7.0 Hz), m/z (ESI, +ve) 202.1 (M+H)+.

Step 2: (R)-2-(but-3-en-2-yl)isoindoline-1,3-dione and (S)-2-(but-3-en-2-yl)isoindoline-1,3-dione

2-(But-3-en-2-yl)isoindoline-1,3-dione (351 g, 1.7 mol) was resolved by chiral SFC (Column: Chiralpak AD-H, 50 x 250 mm, 5 μm, Mobile Phase A: CO₂, Mobile Phase B: MeOH, Isocratic: 10% B with CO₂ recycler on, Flow Rate: 225 g/min) to give first eluting peak (R)-2-(but-3-en-2-yl)isoindoline-1,3-dione (135 g, 672 mmol) and second eluting peak (S)-2-(but-3-en-2-yl)isoindoline-1,3-dione (140 g, 698 mmol).

Preparation of intermediate G (S)-but-3-en-2-amine hydrochloride:

(S)-2-(But-3-en-2-yl)isoindoline-1,3-dione (97.70 g, 486 mmol) was treated with ethanolamine (Sigma Aldrich, 122 ml, 2039 mmol) and EtOH (211 ml) in a 1L round-bottom flask. The flask was sealed with cap/parafilm and placed into a pre-heated (30 °C) bath, then stirred the mixture overnight. The flask was fitted with a water-cooled short path and heated in an oil bath (95 °C). A single fraction was collected boiling at 78 °C. The fraction was added slowly via pipette to a rapidly stirring solution of HCl, 1.0 M solution in Et₂O (Sigma Aldrich, 864 ml, 864 mmol) at 0 °C (a white precipitate formed). After 30 min, the reaction mixture was concentrated in vacuo. Hexanes were added into the mixture, then concentrated in vacuo. The residue was placed under high-vac for 2 h. The semi-solid was diluted with Et₂O (100 ml) and placed into a sonicator for 3 min. The precipitate was collected by filtration and the flask was rinsed with Et₂O and collected precipitate. The solid was dried in reduced-pressure oven (50 °C) 2 h. This gave (S)-but-
3-en-2-amine hydrochloride (28.89 g, 269 mmol, 55.3 % yield) as white solid: $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 5.92 (t, $J=6.65$ Hz, 1 H) 5.32 - 5.58 (m, 2 H) 3.87 (s, 1 H) 1.39 (d, $J=6.65$ Hz, 3 H).

Preparation of intermediate H (R)-but-3-en-2-amine hydrochloride:
(R)-2-(But-3-en-2-yl)isoindoline-1,3-dione (14.5 g, 72.1 mmol) in a 250 mL rbf was treated with 30 mL EtOH and ethanolamine (Sigma-Aldrich, 18.16 ml, 303 mmol). The slurry was sealed and placed in a 30 °C bath for 12 h. The clear, light yellow reaction was fitted with a short path distillation apparatus and heated. A single fraction boiling at about 77 °C, 20.5 g, was collected. The material was added slowly via pipette to a stirring solution of HCl, 1.0 M solution in Et$_2$O (Sigma Aldrich; 100 ml, 100 mmol) at 0 °C. A thick white precipitate was evident. After 1 h, the mixture was concentrated in vacuo to give a waxy material. This was treated with 30 mL anhydrous toluene and concentrated in vacuo to give a white solid. Dried overnight on hood pump to give (R)-but-3-en-2-amine hydrochloride (6.07 g, 56.4 mmol, 78 % yield). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 5.92 (t, $J=6.65$ Hz, 1 H) 5.32 - 5.58 (m, 2 H) 3.87 (s, 1 H) 1.39 (d, $J=6.65$ Hz, 3 H).

Intermediate I: 3-methyl-N-(2-methylallyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-amine

Step 1: 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine
A sealed bottle was charged with 2-methylallylamine (6.74 g, 95 mmol, Matrix Scientific, Columbia, SC), 5-bromo-3-chloro-2-methylquinoxaline (6.10 g, 23.69 mmol) in DMSO (40 mL). The reaction was heated at 100 °C for 1 h, then cooled to RT. The mixture was poured into ice/water (200 mL) and stirred for 10 min. The suspension was filtered and the solid was dried. The solid was further treated with 10% Et$_2$O in hexanes (50 mL) and the suspension was filtered and the solid was dried to give the product 4.2 g. The filtrate was concentrated and the residue was purified with silica gel chromatography (eluted
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with 15-25% EtOAc in Hexanes) to give another 2.6 g of the product. Overall 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (6.8 g, 23.27 mmol, 98 % yield) was obtained: 1H NMR (400 MHz, CDCl3) δ ppm 9.48 (1 H, br. s.), 6.89 - 7.01 (2 H, m), 6.58 (1 H, dd, J=2.7, 1.4 Hz), 5.89 - 6.05 (1 H, br. s.), 5.03 (1 H, s), 4.94 (1 H, s), 4.30 (2 H, d, J=5.7 Hz), 2.62 (3 H, s), 1.88 (3 H, s). MS (ESI, pos. ion) m/z: 292.0/294.0 (M+).

Step 2: 3-methyl-N-(2-methylallyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-amine

A mixture of 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (10.128 g, 34.7 mmol), bis(pinacolato)diboron (17.61 g, 69.3 mmol, Sigma-Aldrich), PdCl2(PPh3)2 (1.415 g, 1.733 mmol, Sigma-Aldrich) and KOAc (13.61 g, 139 mmol, Alfa Aesar) in THF (69.3 mL) was heated at 100 °C in a sealed vessel for 14 h, then cooled to RT. The mixture was diluted with EtOAc (200 mL) and filtered through a pad of Celite. The filtrate was dried, filtered and concentrated. The crude product was purified with silica gel chromatography (eluted with 0-40% EtOAc in Hexanes) to give 3-methyl-N-(2-methylallyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-amine (10.31 g, 30.4 mmol, 88 % yield) as a brown oil: 1H NMR (400 MHz, DMSO-d6) δ ppm 7.75 (dd, J=8.0, 1.4 Hz, 1 H), 7.65 (dd, J=6.9, 1.3 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 7.16 - 7.23 (m, 1 H), 4.87 - 4.93 (m, 1 H), 4.77 (s, 1 H), 4.16 (d, J=5.9 Hz, 2 H), 2.52 (s, 3 H), 1.78 (s, 3 H), 1.33 (s, 12 H). MS (ESI, pos. ion) m/z: 258 (M+) (the mass of boronic acid was observed).

Intermediate J: ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate

![Diagram of Intermediate J]

Step 1: (is)-ethyl 4-(4-bromo-1H-pyrrrole-2-carboxamido)but-2-enoate

The title compound was prepared according to WO20 10/03 1816. 1H NMR (400 MHz, CDCl3) δ ppm 9.48 (1 H, br. s.), 6.89 - 7.01 (2 H, m), 6.58 (1 H, dd, J=2.7, 1.4 Hz), 5.89 -
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6.02 (2 H, m), 4.16 - 4.24 (2 H, m), 1.23 - 1.32 (3 H, m). m/z (ESI, +ve ion) 301.0/302.9 (M+H)^+.

Step 2: ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate

(is)-Ethyl 4-(4-bromo-1H-pyrrole-2-carboxamido)but-2-enoate (2.35 g, 7.80 mmol) was treated with ACN (30 mL) under argon and treated with DBU (0.27 mL, 1.795 mmol) and stirred at RT for 1 h 45 min. The mixture was concentrated on the rotovap and the crude residue purified on the ISCO Combiflash Rf (40 g Thomson SingleStep column, using a gradient of 30-50% EtOAc in hexanes) affording ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (1.24 g, 4.12 mmol, 52.8 % yield) as a colorless viscous oil which crystallized to a white solid overnight under vacuum.

HNMR (400 MHz, CDCl3) δ ppm 6.93 (1 H, d, J=1.6 Hz), 6.84 (1 H, d, J=1.8 Hz), 5.87 (1 H, br. s.), 4.65 (1 H, t, J=6.8, 3.4 Hz), 4.11 - 4.24 (2 H, m), 3.92 (1 H, dd, J=12.8, 4.0 Hz), 3.46 - 3.54 (1 H, m), 2.74 - 2.90 (2 H, m), 1.26 (3 H, t, J=7.1 Hz), m/z (ESI, +ve ion) 301.0/303.0 (M+H)^+.

Intermediate K: 5-bromo-3-chloro-6-fluoro-2-methylquinoxaline

Step 1: 2-bromo-1,3-difluoro-4-nitrobenzene

1-Bromo-2,6-difluorobenzene (Oakwood Products Inc., West Columbia, SC, 15.4 mL, 104 mmol) was treated with H2SO4, 95-98% (77 mL, 1445 mmol) and cooled in an ice bath. It was then treated with HNO3 69-70% (68 mL, 1050 mmol) slowly dropwise via a dropping funnel and stirred for and additional 30 min. The mixture was poured onto ice (500 mL) and stirred vigorously for 3 min. The resulting suspension was extracted with DCM (4 x 100 mL), washed with brine (500 mL) and dried over Na2SO4, filtered and concentrated affording crude 2-bromo-1,3-difluoro-4-nitrobenzene (32.55 g, 137 mmol)
as a bright yellow crystalline solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.13 (1 H, ddd, $J=9.8$, 8.1, 5.5 Hz), 7.13 (1 H, ddd, $J=9.3$, 7.1, 2.0 Hz). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ ppm -92.06 (1 F, s), -104.31 (1 F, s). $m/z$ (ESI, +ve ion) 259.1/261.1 (M+Na)$^+$. 

Step 2: 2-bromo-3-fluoro-6-nitroaniline

Prepared according to WO 2010/046388. 2-Bromo-1,3-difluoro-4-nitrobenzene (27.15 g, 114 mmol) was treated with ammonium carbonate (Sigma Aldrich, 10.96 g, 114 mmol) and DMF (200 mL) followed by Et$_3$N (47.7 mL, 342 mmol) and stirred at RT for 48 h. The mixture was treated with water and extracted with DCM (300 mL). The DCM layer was washed with water (3 x 200 mL) and brine (3 x 200 mL), dried over MgSO$_4$, filtered and concentrated affording crude 2-bromo-3-fluoro-6-nitroaniline (25.99 g, 111 mmol, 97% yield) as a bright yellow amorphous solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.22 (1 H, dd, $J=9.6$, 5.9 Hz), 6.81 (2 H, br. s), 6.56 (2 H, dd, $J=9.6$, 7.2 Hz). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ ppm -90.92 (1 F, s). $m/z$ (ESI, +ve ion) 234.9/236.9 (M+H)$^+$. 

Step 3: 3-bromo-4-fluorobenzene-1,2-diamine

A 500 mL round-bottomed flask containing 5% Pt/C (6.00 g, 1.54 mmol) and 2-bromo-3-fluoro-6-nitroaniline (20.85 g, 89 mmol) were treated with EtOH (250 mL) and stirred under an atmosphere of H$_2$ (balloon) for 22 h. LC-MS indicated ca. 35% conversion to the desired material ($M+1=204.9/206.9$). Another balloon of H$_2$ was added and it was stirred for another 16 h resulting in >90% conversion to the desired product ($M+1=204.9/207.1$) by LC-MS. The suspension was filtered through a plug of Celite washing with EtOH and concentrated affording crude 3-bromo-4-fluorobenzene-1,2-diamine (18 g, 88 mmol, 99% yield) as a black/purple viscous oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.60 (1 H, dd, $J=8.5$, 5.2 Hz), 6.42 - 6.50 (1 H, m). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ ppm -116.48 (1 F, s). $m/z$ (ESI, +ve ion) 204.9/206.9 (M+H)$^+$. 

Step 4: 8-bromo-7-fluoro-3-methyl-3,4-dihydroquinoxalin-2(1H)-one

A 500 mL round-bottomed flask charged with 3-bromo-4-fluorobenzene-1,2-diamine (18 g, 88 mmol), DMF (100 mL), ethyl 2-bromopropionate (Sigma Aldrich, 11.54 mL, 89 mmol) and NaHCO$_3$ powder (7.60 g, 90 mmol) was heated to 90 °C with a reflux condenser for 30 min, then at 120 °C for 15 h. The reaction was cooled to RT, treated with brine and extracted with EtOAc (2 x 200 mL), washed with brine (3 x) and dried
over Na₂S₂O₄, filtered and concentrated affording crude 8-bromo-7-fluoro-3-methyl-3,4-dihydroquinoxalin-2(1H)-one (2.175 g, 84 mmol, 96 % yield) as an orange-brown viscous oil. The material was used in the subsequent step without further purification: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.67 (s, 1 H) 6.78 - 6.89 (m, 1 H) 6.48 - 6.78 (m, 1 H) 6.07 - 6.35 (m, 1 H) 1.25 (d, J=6.46 Hz, 3 H). ¹³F NMR (377 MHz, DMSO-d₆) δ ppm -120.49 (1 F, s). m/z (ESI, +ve ion) 257.0/259.0, 259.0/261.0 (M+H)+.

Step 5: 8-bromo-7-fluoro-3-methylquinoxalin-2(1H)-one
A mixture of water (14 mL) and 30% H₂O₂ (30.0 mL, 294 mmol) was added slowly dropwise to a solution of 8-bromo-7-fluoro-3-methyl-3,4-dihydroquinoxalin-2(1H)-one (2.17 g, 84 mmol) in IN NaOH (168 mL, 168 mmol) and MeOH (140 mL). The flask was fitted with a reflux condenser and heated at 85 °C for 3 h. LC-MS indicated ca. 87% conversion to the desired product (M+H=257.0/259.0). The reaction mixture was cooled to RT and acidified with 2N HCl to ca. pH 6 and was diluted with CHCl₃/IPA(4:1) (100 mL), added to a separatory funnel. The resulting suspension was filtered through a sintered glass frit, washing with water and dried affording 8-bromo-7-fluoro-3-methylquinoxalin-2(1H)-one (5.83 g, 22 mmol, 22 % yield) as a light brown solid. m/z (ESI, +ve ion) 257.0/259.0 (M+H)+. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.83 (1 H, br. s.), 7.67 - 7.88 (1 H, m), 7.34 (1 H, t, J=8.4 Hz), 2.43 (3 H, s). ¹³F NMR (377 MHz, DMSO-d₆) δ ppm -104.13 (1 F, s). The aqueous solution was extracted with CHCl₃:i-PrOH 9:1 (6 x 100 mL), dried over MgSO₄, filtered and concentrated affording additional 8-bromo-7-fluoro-3-methylquinoxalin-2(1H)-one (12.5 g, 49 mmol, 58 % yield) as a dark brown amorphous solid (ca. 80% purity). The material was used in the subsequent step without further purification.

Step 6: 5-bromo-3-chloro-6-fluoro-2-methylquinoxaline
In a 500-mL round-bottomed flask, 8-bromo-7-fluoro-3-methylquinoxalin-2(1H)-one (3.57 g, 13.89 mmol) and POCl₃ (20.0 mL, 215 mmol) were heated at 90 °C for 1.5 h with a reflux condenser. The reaction was cooled to RT and most of the excess POCl₃ was removed under reduced pressure (rotary evaporator). The mixture was treated with EtOAc (100 mL), cooled in an ice bath, treated with ice chips and IN NaOH slowly. After phase separation, the organic layer was washed with brine (50 mL), dried over MgSO₄, filtered and concentrated to afford the crude product as a brown solid. The crude residue was
poured by chromatography on the ISCO Combiflash RF (80 g Redisep column, using a
gradient of 0-100% DCM in hexanes (eluted with ca. 35-60% DCM)) affording 5-bromo-
3-chloro-6-fluoro-2-methylquinoxaline (1.88 g, 6.82 mmol, 49.1% yield) as a light
orange crystalline solid, m/z (ESI, +ve ion) 275.0/277.0 (M+H)+. 1H NMR (400 MHz,
CZX¾) δ ppm 8.01 (1 H, dd, J=9.3, 5.4 Hz), 7.58 (1 H, dd, J=9.1, 8.1 Hz), 2.86 (3 H, s).
[19]F NMR (376 MHz, CDCl¾) δ ppm -99.07 (1 F, s).

Intermediate L: (S)-7-allyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-
dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

A glass microwave reaction vessel was charged with (S)-7-allyl-2-bromo-6,7-dihydro-
IH-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 228 mg, 0.894 mmol),
bis(pinacolato)diboron (Sigma Aldrich, 454 mg, 1.787 mmol), PdCl₂(dppf) DCM adduct
(Sigma Aldrich, 36 mg, 0.045 mmol) and KOAc (Sigma Aldrich, 351 mg, 3.57 mmol) in
THF (4.00 mL). The reaction mixture was stirred and heated in a Initiator microwave
reactor (Personal Chemistry, Biotage AB, Inc., Upssala, Sweden) at 100 ºC for 50 min.
EtOAc was added and the mixture was filtered through Celite and the filtrate was
concentrated. The crude material was purified by silica gel chromatography (12 g),
eluting with 100% EtOAc, to give (S)-7-allyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-
2-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (130 mg, 0.430 mmol, 48% yield) as an off-white solid, m/z (ESI, +ve) 303.2 (M+H)+.

Intermediate M: 7-(but-2-yn-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-
IH-pyrrolo[3,2-c]pyridin-4(5H)-one
Step 1: tert-butyl 5-(but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate
To a solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharma, Libertyville, IL, 1.0 g, 4.69 mmol) and 1-bromo-2-butyne (2.49 g, 18.76 mmol) in 80 mL THF at -25 to -20 °C (a few pieces of dry ice tossed in an acetone bath till desired temperature was reached) was added dropwise LiHMDS (11.72 mL of 1.0 M solution in THF, 11.72 mmol) such that the internal temperature did not exceed -20 °C. The yellow clear reaction mixture was stirred for 1 h (final temp -20 °C); then quenched by addition of 25 mL of ice cold 0.5 N HCl, and extracted with 2X75 mL of EtOAc. The combined organic solution was washed with brine (2X10 mL), dried over Na₂SO₄ and concentrated. The brown residue was purified by silica gel chromatography (15-60% EtOAc/hexanes) to give tert-butyl 5-(but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (809 mg, 65% yield) as a viscous brown oil: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.29 (1 H, br. s), 4.95 (1 H, s), 3.88 (1 H, m), 3.73 (1 H, m), 2.57 (1 H, m), 2.46 (1 H, m), 2.30 (1 H, m), 1.75 (3 H, s), 1.45 (9 H, s). m/z (ESI, +ve) 288.0 (M+Na)⁺.

Step 2: 5-(but-2-yn-1-yl)piperidine-2,4-dione
A solution of tert-butyl 5-(but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (4.25 g, 16.02 mmol) in 25 mL of DCM at 0 °C was treated with TFA (5.95 mL, 80 mmol) and the resulting mixture was stirred at RT for 30 min. The mixture was concentrated under reduced pressure to give a brown viscous oil, which was treated with 5 mL of toluene and evaporated again under reduced pressure. The remaining brown oil was treated with 100 mL of DCM and an excess of solid NaHCO₃ and stirred rapidly for 10 min. The reaction
A mixture was filtered, rinsed with 2X25 mL of DCM, and concentrated under reduced pressure to give a tan solid, 5-(but-2-yn-1-yl)piperidine-2,4-dione (2.1 g, 79% yield), which was used without further purification: m/z (ESI, +ve) 166.1 (M+H)^+.

5 Step 3: 7-(but-2-yn-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one
A solution of aminoacetaldehyde dimethyl acetal (Sigma-Aldrich, 5.54 mL, 50.9 mmol) and 5-(but-2-yn-1-yl)piperidine-2,4-dione (2.1 g, 12.71 mmol) in THF (30 mL) was heated in an oil bath at 75 °C for 15 min. The solvents were then removed and the residue was treated with Et₂O (5 mL) and hexanes (15 mL) and stirred in an ice bath for 15 min resulting in precipitation of white free-flowing solid. The solid was filtered, rinsed with a mixed solvents of Et₂O (3 mL)/hexanes (5 mL), collected and dried to give 5-(but-2-yn-1-yl)-4-((2,2-dimethoxyethyl)amino)-5,6-dihydropyridin-2(1H)-one as a pale yellow amorphous solid, m/z (ESI, +ve) 253.0 (M+H)^+. To the yellow amorphous solid in DCM (40 mL) at RT was added TFA (4.72 mL, 63.6 mmol); and the resulting brown solution was stirred at RT for 2 h; then heated in an oil bath at 45 °C for 2 h. The solvents were removed on the rotovap and the crude residue was diluted with DCM (150 mL) and treated with solid NaHCO₃ (25 g). The suspension was vigorously stirred for 10 min, filtered, and rinsed with 2x25 mL of DCM. The filtrate was concentrated. The brown viscous oil was chromatographed on a silica gel column (1-7% MeOH in DCM) affording 7-(but-2-yn-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (1.32 g, 55% yield) as a brown amorphous solid: ^1^H NMR (400 MHz, DMSO-d₆) δ ppm 11.16 (1 H, br. s), 6.90 (1 H, br. s), 6.71 (1 H, t, J=2.4 Hz), 6.21 (1 H, t, J=2.4 Hz), 3.49 (1 H, m), 3.29 (1 H, m), 3.01 (1 H, m), 2.56 (1 H, m), 2.37 (1 H, m), 1.78 (3 H, t, J=2.4 Hz), m/z (ESI, +ve) 190.1 (M+H)^+.

20 Step 4: 2-bromo-7-(but-2-yn-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one
A solution of 7-(but-2-yn-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (1.32 g, 7.01 mmol) in DMF (25 mL) was cooled to -60 °C and 1,3-dibromo-5,5-dimethylhydantoin (Sigma-Aldrich, 1.0 g, 3.51 mmol) was added in one portion. The resulting green solution was stirred at -55 °C for 30 min. The mixture was poured into ice/water (35 mL) and a solid was formed. The suspension was filtered and the solid was washed with water (2x2.5 mL) followed by EtOAc (2x5 mL). The solid was collected and dried to give 1.59 g of the title compound, in >95% pure of m/z (ESI, +ve) 267.0/269.0 (M+H)^+. The filtrate was extracted with EtOAc (3x50 mL). The aqueous layer was
discarded. The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified on a silica gel column (1-10% MeOH in DCM) to give 400 mg of the title compound, which contained some DMF. The combined material of 2-bromo-7-(but-2-yn-1-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (1.99 g), was used in the subsequent Suzuki coupling reaction without further purification: ¹H NMR (400 MHz, DMSO-de) δ ppm 11.86 (1 H, br. s), 7.01 (1 H, br. s), 6.23 (1 H, d, J=2.2 Hz), 3.47 (1 H, m), 3.28 (1 H, m), 2.98 (1 H, m), 2.55 (1 H, m), 2.39 (1 H, m), 1.76 (3 H, t, J=2.2 Hz). m/z (ESI, +ve) 267.0/269.0 (M+H)⁺.

Step 5: 7-(but-2-yn-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

In a 500 mL round bottomed flask, 2-bromo-7-(but-2-yn-1-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (1.87 g, 7.01 mmol), potassium phosphate dibasic (3.66 g, 21.03 mmol), 1,1-bis(di-t-butyl-p-methylaminophenyl)palladium(ii) chloride (Sigma-Aldrich, 0.24 g, 0.35 mmol) and 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (Intermediate D Step 1, 2.96 g, 10.27 mmol) were treated with DMF (26.3 mL) and water (8.76 mL), and argon was bubbled through the solution for 10 min then it was heated to 70 °C in an oil bath for 18 h. The reaction mixture was cooled to RT and treated with water (10 mL) and extracted with EtOAc (3 x 50 mL). The organic solution was washed with brine (10 mL) and concentrated. The brown residue was purified on a silica gel column (1-10% MeOH in DCM) affording 7-(but-2-yn-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (1.50 g, 61% yield) as a bright yellow amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 11.64 (1 H, br. s), 8.10 (1 H, d, J=7.4 Hz), 7.90 (1 H, d, J=7.6 Hz), 7.73 (1 H, t, J=8.0 Hz), 7.23 (1 H, d, J=2.3 Hz), 5.33 (1 H, br.), 3.72 (1 H, ddd, J=12.1, 1.5, 3.5 Hz), 3.46 (1 H, ddd, J=12.1, 7.0, 2.6 Hz), 3.34 (1 H, m), 2.9 (3 H, s), 2.58 (1 H, m), 1.93 (1 H, s), 1.87 (3 H, m). ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -72.40. m/z (ESI, +ve) 349.1 (M+H)⁺.

Intermediate N: (S)-7-(but-2-yn-1-yl)-2-(2-methyl-3-(/?)-pent-3-yn-2-ylamino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

Intermediate O: (?)-7-(but-2-yn-1-yl)-2-(2-methyl-3-(/?)-pent-3-yn-2-ylamino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one
A mixture of 7-(but-2-yn-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate M, 200 mg, 0.57 mmol) and (R)-pent-3-yn-2-amine hydrochloride (prepared according to WO 200505 1914, 85% ee, 137 mg, 1.14 mmol), and DIPEA (0.2 mL, 1.14 mmol) in 2 mL DMSO was heated at 80 °C in an oil bath for 3.5 h. The reaction was partitioned between sat. NaHCO₃ (10 mL) and EtOAc (100 mL). The organic layer was separated, washed with water (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified on a silica gel column (50-100% EtOAc in DCM followed by 1-5% MeOH in DCM) to give material which by LCMS had two peaks with m/z (ESI, +ve) 412.3 (M+H)+, indicating a mixture of diastereomers in about 85% to 15% ratio. In an analytical SFC (Chiralpak IC (15 x 4.6), 5 µ, 50% C02 and 50% MeOH containing 0.2% DEA, flow rate 4.0 mL/min, 100 Bar, oven temperature 40 °C), the material showed 4 peaks, with retention time (peak area %) Peak 1 at 3.70 min (42%), Peak 2 at 3.95 min (7.5%), Peak 3 at 4.59 min (7.5%) and Peak 4 at 4.96 min (42%). The material was separated by preparative SFC chromatography (Chiralpak IC (250 x 21), 5 µ, 55% C02 and 45% MeOH containing 20 mM NH₃, flow rate 60 mL/min, 120 Bar, oven temperature 40 °C) to give 3 fractions: the 1st fraction contained Peak 1 and Peak 2, which was further purified (see below); the 2nd fraction contained Peak 3 (6.6 mg of yellow crystalline solid, structure characterization was not carried out); the 3rd fraction contained Peak 4: (7R)-7-(but-2-yn-1-yl)-2-(2-methyl-3-((7R)-pent-3-yn-2-ylamino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate O, 41 mg) was obtained as a yellow crystalline solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.00 (1 H, br. s), 7.93 (1 H, dd, J=7.5, 1.3 Hz), 7.63 (1 H, dd, J=8.0, 1.2 Hz), 7.45 (1 H, d, J=7.4 Hz), 7.38 (1 H, t, J=7.8 Hz), 7.01 (1 H, s), 7.40 (1 H, m), 4.97 (1 H, td, J=7.1, 2.2 Hz), 3.57 (1 H, m), 3.44 (1 H, dt, J=12.7, 3.9 Hz), 3.16 (1 H, m), 2.58 (3 H, s), 2.54 (2 H, m), 1.81 (3 H, s), 1.61 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 349.1 (M+H)+. The 1st fraction containing Peak 1 and Peak 2 was further separated by preparative SFC chromatography (Chiralpak OD-H (250 x 21), 5 µ, 75% C02 and 25% MeOH containing 20 mM NH₃,
flow rate 70 mL/min, 158 Bar, oven temperature 40 °C) to give 2 fractions: 1st fraction contained Peak 1: (S)-7-(but-2-yn-1-yl)-2-(2-methyl-3-(2-aminoo)quinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate N, 38 mg) was obtained as a yellow crystalline solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 12.33 (1 H, br. s), 7.97 (1 H, d, J=7.6 Hz), 7.62 (1 H, d, J=8.0 Hz), 7.40 (1 H, m), 7.35 (1 H, m), 7.10 (1 H, d, J=7.4 Hz), 6.99 (1 H, m), 3.59 (1 H, dd, J=11.7, 4.7 Hz), 3.40 (1 H, m), 3.13 (1 H, m), 2.66 (2 H, m), 2.58 (3 H, s), 1.83 (3 H, s), 1.76 (3 H, s), 1.62 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 349.1 (M+H)+.

Intermediate O 2-bromo-l-(2-chloroquinolin-8-yl)ethanone

To a solution of 8-bromo-2-chloroquinoline (Biofine International, Vancouver, BC; 10.0 g, 41.2 mmol) in 200 mL THF in a dry ice/aceton bath was added nBuLi solution (2.5 M in hexanes; 18.14 ml, 45.4 mmol) slowly (dropwise) via addition funnel such that the internal temperature did not exceed -72 °C. After 15 min, N-methoxy N-methylacetamide (Aldrich; 5.05 ml, 49.5 mmol) was added via syringe such that the internal temperature did not exceed -72 °C. The dry ice/aceton bath was removed and the reaction was quenched with 200 mL saturated aq. NH4Cl and diluted with 300 mL Et2O. The organic layer was washed 1x brine, dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (240 g column) using 0-20 % EtOAc/hexanes until less polar impurities elute, then 20-40% EtOAc/hexanes to elute desired material. Fractions were combined and concentrated to give 1-(2-chloroquinolin-8-yl)ethanone (3.63 g, 17.65 mmol, 43% yield) as a peach-colored solid: 1H NMR (400 MHz, CDCl3) δ ppm 8.16 (1 H, d, J=8.6 Hz), 8.06 (1 H, d, J=7.2, 1.6 Hz), 7.96 (1 H, dd, J=8.0, 1.6 Hz), 7.59 - 7.66 (1 H, m), 7.46 (1 H, d, J=8.6 Hz), 7.28 (3 H, s). m/z (ESI, +ve) 206.0 (M+H)+. To a solution of 1-(2-chloroquinolin-8-yl)ethanone (3.25 g, 15.80 mmol) in 3 mL DCM at 0 °C was added Et3N (2.86 ml, 20.55 mmol) followed by TBSOTf (3.99 ml, 17.38 mmol), dropwise. The reaction was stirred for 1 h, and then was partitioned between saturated aq. NaHCO3 and DCM. The aq. layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to give 5.71 g of an orange oil. This oil was taken up in 70 mL THF, treated with water (4.56 ml, 253 mmol) and NBS (2.95 g, 16.59 mmol), and stirred at 25 °C for 15 min. The reaction was then partitioned between water and Et2O. The organic layer was sequentially washed with
A saturated aq. NaHCO₃, water, and saturated aq. NaCl, and the organics layer was dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give 6 g of 2-bromo-l-(2-chloroquinolin-8-yl)ethanone as a yellow solid.

5 Intermediate Q 5-bromo-3-chloro-2-methylquinoxaline

A slurry of 8-bromo-3-methylquinoxalin-2(1H)-one (6.33 g, 26.5 mmol) in POCl₃ (20 mL, 219 mmol) was heated at reflux for 1.5 h in a round-bottomed flask fitted with a water-cooled reflux condenser and drying tube. Excess POCl₃ was removed in vacuo (16 Torr, 36 ºC), and the residue was taken up in DCM (50 mL), transferred to an Erlenmeyer flask, cooled to 0 ºC, and saturated aq. NaHC0₃ (ca. 80 mL) was added (cautiously, with rapid stirring). The resulting biphasic mixture was stirred rapidly for 5 min. Upon cessation of gas evolution, the mixture was extracted with DCM (3 x 200 mL), and the combined extracts were dried over Na₂SO₄, filtered, and concentrated onto silica gel. Chromatographic purification of the residue (silica gel, 0-30% EtOAc/hexanes) furnished 5-bromo-3-chloro-2-methylquinoxaline (5.12 g, 19.85 mmol, 75% yield) as a light-yellow solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 (1 H, d, J=7.6 Hz), 8.00 (1 H, dd, J=8.4, 1.2 Hz), 7.60 (1 H, t, J=7.9 Hz), 2.87 (3 H, s). m/z (ESI, +ve) 256.9 (M+H)⁺.

20 Intermediate R 5-bromo-3-fluoro-2-methylquinoxaline

A 1-L, three-necked round-bottomed flask equipped with a mechanical stirrer, a nitrogen gas inlet, and a temperature probe was charged 5-bromo-3-chloro-2-methylquinoxaline (21.5 g, 83 mmol), DMSO (21.5 mL) and KF (4.85 mL, 209 mmol), and the resulting mixture was heated at 90 ºC for 2.5 h. The mixture was cooled to RT and ice/water (430 mL) was added. The precipitated solid was collected by vacuum filtration and then washed with water (100mL) and dried in vacuo to afford 5-bromo-3-fluoro-2-methylquinoxaline (21 g) as a brown solid, which was used without further purification in the subsequent step. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.03 (1 H, d, J=2.2 Hz), 8.01 (1 H, d, J=1.2 Hz), 7.59 (1 H, t, J=7.9 Hz), 2.79 (3 H, d, J=1.4 Hz). ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -70.61 (1 F, br. s.). m/z (ESI, +ve) 240.9 (M+H)⁺.
Intermediate S l-(3-fluoro-2-methylquinoxalin-5-yl)ethanone

A 1-L, three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, nitrogen gas inlet, and a temperature probe was charged with 5-bromo-3-fluoro-2-methylquinoxaline (30 g, 124 mmol), Pd(PPh₃)₄ (4.31 g, 3.73 mmol), toluene (300 mL), and tributyl(l-ethoxyvinyl)tin (Synthox, Wake Forest, NC; 46.2 mL, 137 mmol), and the resulting mixture was heated under N₂ atmosphere at 90 °C for 18 hours. The mixture was cooled to RT, HCl (6.0 N, aq.; 12.45 mL, 74.7 mmol) was added, and the resulting mixture was stirred at RT for 10 min. The mixture was extracted with EtOAc (500 mL). The organic layer was separated and sequentially washed with brine (2 × 200 mL) and saturated aq. NaHCO₃ (100 mL) and then concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0-1 00% DCM/heptane followed by repurification with silica gel, 0-75% EtOAc/heptane) furnished l-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (16.0 g, 78.4 mmol, 63% yield) as an orange solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.20 (1 H, dd, J=8.3, 1.3 Hz), 8.10 (1 H, dd, J=7.3, 1.1 Hz), 7.77 (1 H, t, J=7.8 Hz), 2.92 (3 H, s), 2.79 (3 H, d, J=1.6 Hz). ¹³F NMR (377 MHz, CDCl₃) δ ppm -69.81 (1 F, s). m/z (ESI, +ve) 205.1 (M+H)+.

Intermediate T 2-bromo-l-(3-fluoro-2-methylquinoxalin-5-yl)ethanone

TBSOTf (2.92 mL, 12.73 mmol) was added (dropwise, over 3 min) to a mixture 1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (2.00 g, 9.79 mmol) and TEA (2.05 mL, 14.7 mmol) in DCM (100 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. The mixture was diluted with DCM (50 mL), washed with saturated aq. NaHCO₃ (2 × 100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to provide 5-(1-((2-tert-butyldimethylsilyl)oxy)vinyl)-3-fluoro-2-methylquinoxaline (3.451 g) as an orange-brown oil. This oil was taken up in THF (100 mL) and cooled to 0 °C, water (2.82 mL, 157 mmol) and NBS (1.743 g, 9.79 mmol) were sequentially added, and the resulting solution was stirred at 0 °C for 2 min. The mixture was diluted with Et₂O (100 mL) and sequentially washed with water (80 mL), saturated aq. NaHCO₃ (80 mL), water (80 mL), and brine (80 mL). The resulting solution was dried over Na₂SO₄, filtered, and concentrated onto silica gel. Chromatographic purification (silica gel, 0-20% EtOAc/heptanes) provided 2-bromo-l-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (2.77 g, 9.78 mmol, 100 % yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.27 (1 H, d, J=5.3 Hz), 8.25 (1 H, d, J=4.3 Hz), 7.82 (1 H, t, J=7.8 Hz), 5.02 (2 H, s), 2.80 (3 H, s).
Intermediate U l-(3-chloro-2-methylquinoxalin-5-yl)ethanone

1-(3-Fluoro-2-methylquinoxalin-5-yl)ethanone (2.00 g, 9.79 mmol) was treated with HCl (4.0 M solution in 1,4-dioxane; 24.49 ml, 98 mmol), and the homogeneous reaction was fitted with a drying tube. After 6 h the reaction was concentrated in vacuo, and the solid was taken up in DCM. Solid NaHCO₃ was added cautiously with rapid stirring, and saturated aq. NaHCO₃ was sequentially added cautiously with rapid stirring. The mixture was partitioned between saturated NaHCO₃ and DCM. The aq. layer was extracted with DCM (2x), and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give l-(3-chloro-2-methylquinoxalin-5-yl)ethanone (99% yield) as an orange-brown solid. MS (ESI, pos. ion) m/z: 221.0 (M+1).

Example 1: (lIIE)-ll-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,Ll,15,17,19,22-octaen-6-one

Step 1: 2-(allyloxy)quinolin-8-yl)-7-(2-methylallyl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

To a solution of 3-bromo-2-methylpropene (Aldrich, 1.891 ml, 18.76 mmol) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharm inc, Libertyville IL, 1.00 g, 4.69 mmol) in 50 mL THF at -17 °C (ice/salt bath) was added LiHMDS, 1.0 M solution in THF (11.72 ml, 11.72 mmol) via syringe such that the temperature did not exceed -16 °C. After 1 h, the reaction was treated with water and DCM, and the aqueous layer was acidified with 1 N aq. KHSO₄. The aqueous layer was extracted 3 x DCM, and the
combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give 1.8 g of a yellow oil. This was treated with HCl, 4.0 M solution in 1,4-dioxane (Aldrich; 11.72 ml, 46.9 mmol) and was fitted with a drying tube. After 30 min the reaction was judged complete by LCMS and was placed in the freezer overnight. In the morning the reaction was concentrated in vacuo to a thick oil. This material was treated with 2-bromo-1-(2-chlorquinolin-8-yl)ethanone (0.534 g, 1.876 mmol), NH₄OAc (Fisher Scientific, 0.723 g, 9.38 mmol), and 10 mL EtOH, sealed, and heated to 50 °C for 4 h. The material was treated with DCM and purified by silica gel chromatography (80 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.199 g impure material. In a separate flask, a slurry of NaH 60% in mineral oil (Aldrich; 0.13 g, 2.81 mmol) in 2 mL DMF was prepared and to this slurry was added allyl alcohol (Alfa Aesar; 0.191 mL, 2.81 mmol) dropwise. After 10 min, the 0.199 g material was added to the reaction. The orange reaction was sealed and heated to 70 °C for 1 h. The reaction was cooled and partitioned between saturated aqueous NH₄Cl and EtOAc. The organic layer was washed with water once, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (40 g column) using 0- 90% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.146 g of a 9:1 mixture of isomers; data for major isomer 2-(2-(allyloxy)quinolin-8-yl)-7-(2-methylallyl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.79 (1 H, br. s), 8.31 (1 H, d, J=8.8 Hz), 8.03 (1 H, dt, J=7.5, 0.6 Hz), 7.76 (1 H, dt, J=8.0, 0.7 Hz), 7.47 (1 H, t, J=7.7 Hz), 7.13 (1 H, d, J=8.8 Hz), 7.00 - 7.07 (1 H, m), 6.94 (1 H, br. s.), 6.12 - 6.28 (1 H, m), 5.47 (1 H, dd, J=1.2, 1.6 Hz), 5.32 (1 H, dt, J=10.6, 0.8 Hz), 5.08 - 5.18 (1 H, m), 4.99 - 5.07 (1 H, m), 4.87 (1 H, s), 4.77 (1 H, s), 3.38 - 3.49 (1 H, m), 3.10 - 3.25 (2 H, m), 2.44 - 2.48 (1 H, m), 2.20 - 2.37 (1 H, m), 1.77 (3 H, s) m/z (ESI, +ve) 374.0 (M+H)+. 

Step 2: (lIIE)-II-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1-2,5-,.0-4,9-,.0-18,22-]tetracosa-l(21),2(24),4,1 1,15,17,19,22-octea-6-one

To a solution of 2-(2-(allyloxy)quinolin-8-yl)-7-(2-methylallyl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.16 g, 0.311 mmol) in 15 mL DCM was added Grubbs catalyst 2nd generation (Aldrich; 0.026 g, 0.031 mmol). The light pink reaction
was flushed with argon for 2 min, then fitted with a water-cooled reflux condensor, and was heated to reflux. After 1 h, the reaction is nearly complete. After 30 min additional, the reaction was concentrated in vacuo. The resulting material was dissolved in DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 10-100 % ACN/H2O with 0.1% TFA; product-containing fractions were treated with saturated aqueous NaHCO3 and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na2SO4, filtered, and concentrated in vacuo to give (11E)-11-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (0.045 g, 42% yield) as a light yellow solid.

H NMR (400 MHz, DMSO-d6) δ ppm 13.39 (1 H, br. s), 8.32 (1 H, d, J=9.0 Hz), 8.17 (1 H, dt, J=7.9, 0.7 Hz), 7.71 (1 H, dt, J=7.9, 0.7 Hz), 7.44 (1 H, t, J=7.7 Hz), 7.14 (1 H, d, J=9.0 Hz), 7.10 (1 H, d, J=4.7 Hz), 6.95 (1 H, d, J=1.8 Hz), 5.99 (1 H, d, J=7.0 Hz), 4.97 - 5.17 (2 H, m), 3.30 - 3.50 (3 H, m), 3.08 - 3.16 (1 H, m), 2.35 (1 H, t, J=12.0 Hz), 1.81 (3 H, s). m/z (ESI, +ve) 346.3 (M+H)+.


A portion of the material prepared in Example 1 was separated by SFC chromatography (ADH (4.6 x 150 mm), 5 μ, 45% MeOH containing 0.2% DEA, 4 ml/min,100 Bar) to give separated enantiomers (9R,11E)-11-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one and (9S,11E)-11-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one. Example 2 was the first eluting product, Example 3 was the second eluting product.
Example 4: 16-oxa-3,7,25-triazahexacyclo[15.6.2.1\(^{-2,5}\).1\(^{-15}\)\,-0\(^{-4,9}\)\,-0\(^{-20,24}\)\,-]heptacosa-
l(23),2(27),4,ll(26),12,14,17,19,21,24-decaen-6-one

Step 1: 2-(2-chloroquinolin-8-yl)-7-(3-methoxybenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

To a solution of 1-(bromomethyl)-3-methoxybenzene (2.63 ml, 18.76 mmol) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharm, Libertyville, IL; 1.00 g, 4.69 mmol) in 50 mL THF at -17 °C (ice/salt) was added LiHMDS 1.0 M in THF (11.72 ml, 11.72 mmol) dropwise via syringe such that the internal temperature did not exceed -14 °C. A precipitate formed during the first 1/2 addition, then disappeared upon further LiHMDS addition. The resulting clear yellow solution was stirred 30 min. The reaction was treated with water and DCM, and 5% KHSO\(_4\) was added to acidify the aqueous layer. The aqueous layer was extracted 3 x DCM. The combined extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (40 g column) using 0 - 50% EtOAc/hexane. The product-containing fractions were concentrated to afford 1.34 g of a foam. This material was treated with 40 mL 4.0 M HCl in dioxane (Aldrich) and fitted with a drying tube. After 2 h, the reaction was checked by LCMS and judged complete, and was concentrated in vacuo to a thick oil which was placed on hood pump overnight. This material was treated with 2-bromo-l-(2-chloroquinolin-8-yl)ethanone (0.534 g, 1.876 mmol), NH\(_4\)OAC (Fisher Scientific, 1.446 g, 18.76 mmol), and 20 mL EtOH, sealed, and heated to 50 °C. After 3 h, the reaction was judged complete by LCMS. The reaction was carefully quenched with saturated aqueous NaHCO\(_3\) and partitioned between saturated aqueous NaHCO\(_3\) and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (80
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g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford impure 2-(2-chloroquinolin-8-yl)-7-(3-methoxybenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.42 g, 1.005 mmol, 21.43 % yield) as an orange solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 11.72 (1 H, s), 8.50 (1 H, d, J=8.6 Hz), 8.08 - 8.19 (1 H, m), 7.85 - 7.95 (1 H, m), 7.61 - 7.76 (2 H, m), 7.20 - 7.31 (2 H, m), 6.97 (1 H, br. s), 6.72 - 6.90 (3 H, m), 3.74 (3 H, s), 3.04 - 3.31 (4 H, m), 2.74 (1 H, dd, J=12.8, 10.3 Hz), m/z (ESI, +ve) 418.1 (M+H)+.

Step 2: 16-oxa-3,7,25-triazahexacyclo[15.6.2.1~1,1~-1,11,15,~,0~4,9~0~20,24~l]heptacosa-
l(23),2(27),4,11(26),12,14,17,19,2(14-decaen-6-one
To a solution of 2-(2-chloroquinolin-8-yl)-7-(3-methoxybenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.40 g, 0.957 mmol) in 5 mL DCM under N2 was added BBr3, 1.0 M in DCM (Sigma-Aldrich; 1.053 ml, 1.053 mmol) dropwise via syringe. A thick orange precipitate resulted. 5 mL DCM was added to promote stirring. The orange slurry was stirred for 1 h. An additional 0.5 mL BBr3 (1.0 M in DCM) was added and stirring continued. After 1 h, the reaction was judged complete, was cooled to 0 °C and quenched carefully with dropwise addition of 4 mL MeOH to give a homogeneous solution. 4 g silica gel was added and the mixture concentrated in vacuo, and the residue purified by silica gel chromatography (40 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford impure material (0.210 g) as an orange solid. The solid was treated with 25 mL DMF and NaH 60% in mineral oil (Aldrich; 0.153 g, 3.83 mmol) under N2. The reaction was heated to 80 °C for 4 h. The reaction was cooled in an ice/water bath and TFA (0.295 ml, 3.83 mmol) was added. This material was concentrated in vacuo, was dissolved in 3.5 mL DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 15-100 % ACN/H2O with 0.1% TFA; the product-containing fraction was treated with saturated aqueous NaHCO3 and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na2SO4, filtered, and concentrated in vacuo to give 16-oxa-3,7,25-triazahexacyclo[15.6.2.1~1,1~-1,11,15,~,0~4,9~0~20,24~l]heptacosa-
l(23),2(27),4,11(26),12,14,17,19,2(14-decaen-6-one (0.018 g, 0.049 mmol, 5% yield) as a yellow solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 12.90 (1 H, br. s), 8.48 (1 H, d, J=8.8 Hz), 8.15 (1 H, dt, J=7.5, 0.7 Hz), 7.92 (1 H, t, J=2.1 Hz), 7.70 - 7.81 (1 H, m),
To a slurry of NaH 60% in mineral oil (Aldrich; 0.112 g, 2.81 mmol) in 1 mL DMF was added 2-methyl-2-propen-1-ol (Aldrich; 0.237 ml, 2.81 mmol) dropwise via syringe. After 10 min, 7-allyl-2-(2-chloroquinolin-8-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate F; 0.190 g, 0.562 mmol) was added as a solution in 1 mL DMF (0.5 mL rinse). The reaction was sealed and heated to 80 °C for one h. The reaction was cooled and partitioned between saturated aqueous NH₄Cl and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (25 g column) using 0 - 100% 90/10 DCM/MeOH in DCM; the product-containing fractions were concentrated to afford impure 7-allyl-2-(2-(2-methylallyloxy)quinolin-8-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.133 g). This material was treated with Grubbs 2nd generation catalyst (Aldrich; 0.030 g, 0.036 mmol) and 18 mL anhydrous DCM, and argon was bubbled through the orange solution for 2 min. The reaction was fitted with a water-cooled reflux condensor and heated to reflux in an oil bath. The reaction was heated overnight. The reaction was concentrated, the resulting material was dissolved in DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 15-100 % ACN/H₂O with 0.1% TFA; product-containing fractions were concentrated in vacuo. The material was treated with Et₂O, sonicated, and filtered, rinsing with Et₂O to give the (IIE)-12-methyl-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one (0.012 g, 0.035 mmol, 9.76 % yield) as an off-white solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.28 (1 H, br. s.), 8.32 (1 H, d, J=8.8 Hz), 8.18 (1 H, dd, J=7.5, 1.5 Hz), 7.71 (1 H, dt, J=7.9, 0.8 Hz), 7.44 (1 H, t, J=7.7 Hz),

Example 5: (IIE)-12-methyl-14-oxa-3,7,23-
triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
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7.15 (1 H, d, J=8.8 Hz), 7.02 - 7.10 (1 H, m), 6.98 (1 H, dd, J=2.0, 0.4 Hz), 5.93 (1 H, d, J= 10.6 Hz), 4.88 - 5.09 (2 H, m), 3.11 - 3.47 (4 H, m), 2.36 - 2.46 (1 H, m), 1.74 (3 H, s).

\( m/z \) (ESI, +ve) 346.1 (M+H)+.

5  Example: (HE)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(21),2(24),4,11,15,17,19,22-octaen-6-one

![Chemical Structure]

Step 1: 7-allyl-2-(2-((2-methylallyl)amino)quinolin-8-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

Argon was bubbled through a slurry of sodium tert-butoxide (0.939 g, 9.77 mmol), 2-methylallylamine (Matrix Scientific, Columbia, SC, 0.347 ml, 4.88 mmol), BrettPhos (0.026 g, 0.049 mmol), 7-allyl-2-(2-chloroquinolin-8-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate F, 0.330 g, 0.977 mmol), BrettPhos precatalyst (0.039 g, 0.049 mmol) in 3 mL dioxane for 30 sec. The reaction was sealed and heated to 80 °C. After 2 h, the reaction was cooled and judged complete by LCMS. The reaction was partitioned between saturated aqueous NH₄CеЛ and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (40 g column) using 0 - 50% 90/10/1 DCM/MeOH/conc. NH₄OH in DCM The product-containing fractions were concentrated to afford 7-allyl-2-(2-((2-methylallyl)amino)quinolin-8-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.126 g, 0.338 mmol, 34.6 % yield) as a yellow foam: \(^1\)H NMR (400 MHz, DMSO-de) \( \delta \) ppm 12.51 (1 H, br. s.), 7.88 - 7.98 (2 H, m), 7.54 (1 H, t, \( J=5.6 \) Hz), 7.49 (1 H, dt, \( J=7.9, 0.8 \) Hz), 7.18 (1 H, t, \( J=7.6 \) Hz), 6.96 - 7.00 (1 H, m), 6.88 - 6.95 (2 H, m), 5.79 - 5.92 (1 H, m), 5.06 - 5.17 (2 H, m), 4.99 (1 H, s), 4.88 (1 H, s), 4.02 - 4.09 (2 H, m), 3.43 - 3.55 (1 H, m), 3.16 - 3.26 (1 H, m), 3.00 - 3.10 (1 H, m), 2.53 - 2.60 (1 H, m), 2.26 - 2.41 (1 H, m), 1.84 (3 H, s). m/z (ESI, +ve) 373.1 (M+H)+.
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Step 2: (1E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1^2,5~.0^4,9~.0^18,22~]tetracosa-\[l(21),2(24),4,11,15,17,19,22\]-octaen-6-one

7-Allyl-2-(2-((2-methylallyl)amino)quinolin-8-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridi^ with purified Grubbs II Catalyst (Aldrich; 0.029 g, 0.034 mmol) were dissolved in 17 mL anhydrous DCM; the flask was fitted with a water cooled reflux condenser and the reaction was heated to reflux under N₂ for 3 h. The reaction was cooled, judged complete by LCMS, and adsorbed onto 1.5 g silica gel from MeOH/DCM and dried. The material was purified by silica gel chromatography (25 g column) using 30 - 70 % 90/10/1 DCM/MeOH/conc. NH₄OH in DCM. The product-containing fractions were concentrated to give 79 mg yellow solid. This material was dissolved in DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C₁₈ column, 10-70 % ACN/H₂O with 0.1% TFA; product-containing fraction was treated with saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na₂SO₄, filtered, and concentrated in vacuo to give (1E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1^2,5~.0^4,9~.0^18,22~]tetracosa-\[l(21),2(24),4,11,15,17,19,22\]-octaen-6-one as a light yellow solid:

\(^{1}\text{H} \text{NMR} (400 \text{ MHz, DMSO-\text{d}_6) \delta ppm} \text{ 13.65 (1 H, br. s.), 7.99 (1 H, dt, \text{J}=7.5, 0.7 Hz), 7.89 (1 H, d, \text{J}=9.0 Hz), 7.64 (1 H, t, \text{J}=4.8 Hz), 7.40 - 7.49 (1 H, m), 7.17 (1 H, t, \text{J}=7.6 Hz), 6.99 (1 H, d, \text{J}=4.5 Hz), 6.88 (2 H, d, \text{J}=6.7 Hz), 5.64 - 5.93 (1 H, m), 3.97 (2 H, d, \text{J}=4.5 Hz), 3.33 - 3.40 (1 H, m), 3.18 - 3.30 (2 H, m), 2.34 - 2.46 (2 H, m), 1.63 (3 H, s).} \text{m/z (ESI, +ve) 345.2 (M+H)^+.} \n
Examples 7 and 8: (9R,11E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1^2,5~.0^4,9~.0^18,22~]tetracosa-\[l(21),2(24),4,11,15,17,19,22\]-octaen-6-one and (9S,11E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1^2,5~.0^4,9~.0^18,22~]tetracosa-\[l(21),2(24),4,11,15,17,19,22\]-octaen-6-one
A portion of the material prepared in Example 6 was separated by SFC chromatography (ASH (250 x 20), 5 µ, 40% MeOH containing 20 mM NH₃, 70 ml/min, 128/200 Bar) to give separated enantiomers (9R,11E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaaen-6-one and (9S,11E)-12-methyl-3,7,14,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaaen-6-one. Example 7 was the first eluting product. Example 8 was the second eluting product.

Example 9: (HE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaaen-6-one

Step 1: 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine

A solution of 5-bromo-3-chloro-2-methylquinoxaline (0.633 g, 2.458 mmol) in 2-methylprop-2-en-1-amine (Matrix Scientific, Columbia, SC; 3.50 g, 49.2 mmol) was stirred at RT overnight. The reaction was judged complete by LCMS and the orange solution was partitioned between water and EtOAc. The organic layer was washed with water 3 times, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (0.591 g, 2.023 mmol, 82 % yield) as a red oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 - 7.87 (2 H, m), 7.22 (1 H, t, J=7.9 Hz), 5.00 - 5.05 (1 H, m), 4.92 - 4.97 (1 H, m), 4.30 (2 H, d, J=5.7 Hz), 2.59 (3 H, br. s.), 1.89 (3 H, s). m/z (ESI, +ve) 292.0 (M+H)⁺.
Step 2: 8-(1-ethoxyvinyl)-3-methyl-N-(2-methylallyl)quinoxalin-2-amine
Argon was bubbled through a mixture of tributyl(l-ethoxyvinyl)tin (Aldrich; 1.025 ml, 3.03 mmol), Cul (Riedel-de-Haen; 0.077 g, 0.405 mmol), cesium fluoride (Aldrich; 0.922 g, 6.07 mmol), Pd2(dba)3 (Strem, 0.185 g, 0.202 mmol), X-Phos (Strem, 0.096 g, 0.202 mmol), 8-bromo-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (0.591 g, 2.023 mmol) in 10 mL dioxane for 2 min. The dark reaction was sealed and placed in an 80 °C oil bath. After 5 h, the reaction was judged complete by LCMS. The reaction was transferred to a flask with DCM and adsorbed onto 5 g silica gel and dried in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 50% EtOAc/hexane. The major product-containing fractions were concentrated to afford 8-(1-ethoxyvinyl)-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (0.304 g, 1.073 mmol, 53.0 % yield): 

\[ \text{H NMR (400 MHz, DMSO-d_6)} \delta \text{ ppm 7.65 - 7.71 (2 H, m), 7.36 - 7.42 (1 H, m), 7.27 (1 H, t, J=7.7 Hz), 5.28 (1 H, s), 4.84 (1 H, br. s), 4.72 - 4.78 (1 H, m), 4.54 - 4.60 (1 H, m), 3.99 - 4.08 (2 H, m), 3.89 (2 H, q, J=7.0 Hz), 2.53 (3 H, s), 1.76 (3 H, s), 1.33 (3 H, t, J=6.9 Hz).} \]

Step 3: 7-allyl-2-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5 H)-one

To a solution of 8-(l-ethoxyvinyl)-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (0.302 g, 1.066 mmol) in 10 mL THF and water (0.307 ml, 17.05 mmol) was added NBS (0.190 g, 1.066 mmol). The orange reaction was stirred for 30 min, at which point it was partitioned between saturated aqueous NaHCO3 and EtOAc. The organic layer was washed with saturated aqueous NaHCO3, once, brine once, and the organics were dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to give 0.396 g of an orange solid. The material was treated with NH4OAc (0.329 g, 4.26 mmol) and 5-allylpiperidine-2,4-dione (Intermediate A; 0.196 g, 1.279 mmol) and 10 mL EtOH, sealed, and placed in a 50 °C oil bath for 5 h. The reaction was cooled and placed in a freezer over the weekend. The reaction was carefully quenched with saturated aqueous NaHCO3. The reaction was partitioned between saturated aqueous NaHCO3 and DCM. The aequous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (40 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated
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to afford 7-allyl-2-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.060 g, 0.155 mmol, 14.53 % yield) as an orange solid:

1H NMR (400 MHz, DMSO-d₆) δ ppm 11.76 (1 H, br. s.), 7.88 (1 H, dt, J=7.5, 0.7 Hz), 7.53 - 7.62 (1 H, m), 7.50 (1 H, t, J=6.0 Hz), 7.28 - 7.37 (1 H, m), 7.06 - 7.14 (1 H, m), 6.90 (1 H, br. s.), 5.78 - 5.97 (1 H, m), 5.06 - 5.17 (2 H, m), 4.79 - 4.93 (2 H, m), 4.01 - 4.18 (2 H, m), 3.45 - 3.55 (1 H, m), 3.18 - 3.25 (1 H, m), 3.17 (1 H, d, J=5.1 Hz), 2.98 - 3.07 (1 H, m), 2.57 (3 H, s), 2.27 - 2.39 (1 H, m), 1.85 (3 H, s). m/z (ESI, +ve) 388.1 (M+H)⁺.

Step 4: (1E)-12,1 6-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0=4.9-.0=1 8,22-]tetracosa-
l(21),2(24),4 l,11,15,17,19,22-octaen-6-one

Argon was flushed through a suspension of 7-allyl-2-(2-methyl-3-((2-
methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.060 g, 0.155 mmol) and Grubbs catalyst 2nd generation (Aldrich; 6.57 mg, 7.74 μηο) and 10 mL DCM for 1 min. The reaction was fitted with a water-cooled reflux condenser and placed in an oil bath and heated to reflux. After 4 h, additional Grubbs catalyst 2nd generation (Aldrich; 6.57 mg, 7.74 μηο) was added and heating continued. After 2 h, the reaction was concentrated in vacuo, then treated with DMSO. A bright yellow ppt did not dissolve, even with 3 mL DMSO and sonication or heating. The slurry was filtered through a 0.45 uM nylon membrane and the yellow solid was collected and dried in vacuo overnight to give 12 mg yellow solid. The filtrate was purified by preparative HPLC, 10-80 % ACN/H₂O with 0.1% TFA; product-containing fractions were treated with saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na₂SO₄, filtered, and concentrated in vacuo, and the material was combined with the solid isolated by filtration to give a total of (1E)-12,16-dimethyl-
3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0=4.9-.0=1 8,22-]tetracosa-
l(21),2(24),4 l,11,15,17,19,22-octaen-6-one (0.030 g, 0.083 mmol, 54% yield): 1H NMR
(400 MHz, DMSO-de) δ ppm 13.38 (1 H, br. s.), 7.97 (1 H, d, J=7.6 Hz), 7.56 - 7.62 (1 H, m), 7.51 - 7.55 (1 H, m), 7.31 (1 H, t, J=7.8 Hz), 7.01 (1 H, d, J=4.7 Hz), 6.87 - 6.92 (1 H, m), 5.82 (1 H, d, J=9.0 Hz), 4.06 - 4.22 (1 H, m), 3.92 - 4.05 (1 H, m), 3.34 - 3.43 (1 H, m), 3.10 - 3.29 (2 H, m), 2.57 (3 H, s), 2.26 - 2.46 (2 H, m), 1.61 (3 H, s). m/z (ESI, +ve) 360.2 (M+H)⁺.
Examples 10-13: (9R,11Z)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1\(2,5\).0\(4,9\).0\(18,22\)]tetracosa-l(21),2(24),4,15,17,19,22-octaen-6-one, (9S,11Z)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1\(2,5\).0\(4,9\).0\(18,22\)]tetracosa-l(21),2(24),4,15,17,19,22-octaen-6-one, (9R,11E)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1\(2,5\).0\(4,9\).0\(18,22\)]tetracosa-l(21),2(24),4,15,17,19,22-octaen-6-one, (9S,11E)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1\(2,5\).0\(4,9\).0\(18,22\)]tetracosa-l(21),2(24),4,15,17,19,22-octaen-6-one

To a slurry of NaH 60% in mineral oil (Aldrich; 0.112 g, 2.81 mmol) in 1 mL DMF was added allyl alcohol (Alfa Aesar; 0.191 ml, 2.81 mmol) dropwise via syringe. After 10 min, 7-allyl-2-(2-chloroquinolin-8-yl)-6,7-dihydro-H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate F, 0.190 g, 0.562 mmol) was added as a solution in 1 mL DMF (0.5 mL rinse). The reaction was sealed and heated to 80 °C for one h. The reaction was cooled and partitioned between saturated aqueous NH\(_4\)Cl and EtOAc. The organic layer was washed 1 x water, 1 x brine, and the organics were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (25 g column) using 0 - 80% 90/10 DCM/MeOH in DCM. The product containing fractions were concentrated in vacuo to give 0.100 g of impure material. This material was treated with Grubbs 2nd generation catalyst (0.024 g, 0.028 mmol) and 15 mL anhydrous DCM, and argon was bubbled through the reaction for 2 min. The reaction was sealed and heated to 50 °C in an oil bath overnight. The reaction was concentrated, and this material was dissolved in DMSO and purified by Shimadzu RPHPLC,
Phenomenex Gemini 150x30 mm C18 column, 10-100 % ACN/H₂O with 0.1% TFA; product-containing fractions were concentrated in vacuo to give (0.030 g, 0.09 mmol, 33% yield) as a mixture of isomers. A portion of this material was further resolved into four components by preparative SFC chromatography (OJ-H (5 um, 21 x 250 mm, 60 ml/min), 40% IPA/40 mM NH₃, T = 40 °C, P = 193 bar) to give:

First (Example 10) and third (Example 12) eluting peaks, separate enantiomers of (11Z)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one: 

\[ ^1H \text{ NMR (400 MHz, } \text{CDCl}_3:MeOH-d_4) \delta \]

ppm: 13.77 (1 H, br. s.), 8.36 (1 H, d, J=8.8 Hz), 8.12 - 8.28 (1 H, m), 7.83 - 7.90 (1 H, m), 7.65 (1 H, t, J=7.7 Hz), 7.25 (1 H, d, J=8.8 Hz), 7.07 - 7.18 (1 H, m), 5.99 - 6.17 (2 H, m), 5.71 - 5.81 (1 H, m), 4.96 - 5.05 (1 H, m), 3.73 - 3.82 (1 H, m), 3.59 - 3.67 (2 H, m), 2.87 - 3.03 (1 H, m), 2.53 - 2.66 (1 H, m), \( m/z \) (ESI, +ve) 332.1 (M+H)^+.

Second (Example 11) and fourth (Example 13) eluting peaks, separate enantiomers of (11E)-14-oxa-3,7,23-triazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one: 

\[ ^1H \text{ NMR (400 MHz, } \text{CDCl}_3:MeOH-d_4) \delta \]

ppm: 13.86 (1 H, br. s.), 8.26 - 8.38 (2 H, m), 7.75 - 7.87 (1 H, m), 7.57 - 7.68 (1 H, m), 7.15 - 7.31 (2 H, m), 6.33 - 6.51 (1 H, m), 6.17 - 6.32 (1 H, m), 5.27 - 5.40 (1 H, m), 5.08 - 5.23 (1 H, m), 3.62 - 3.81 (3 H, m), 2.91 (1 H, d, J=14.1 Hz), 2.45 - 2.72 (1 H, m), \( m/z \) (ESI, +ve) 332.1 (M+H)^+.

Example 14: (9S,HE)-12,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

Example 15: (9R,HE)-12,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

![Diagram](attachment:image.png)
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first eluting peak, Example 14, (9S,11E)-12,16-dimethyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one and second eluting peak, Example 15 (9R,11E)-12,16-dimethyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one: 

Example 14, alternative procedure: (9S,11E)-12,16-dimethyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

Example 16: (9S,11Z)-12,16-dimethyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

Step 1: (S)-7-allyl-2-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A glass microwave reaction vessel was charged with (2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)boronic acid (Intermediate I, 40 mg, 0.156 mmol) and (S)-7-allyl-2-bromo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 39.7 mg, 0.156 mmol) in 1,4-dioxane (1.0 mL)/water (0.25 mL) followed by Pd2dba3(7.12 mg, 7.78 µmol, Strem), 2-(dicyclohexylphosphino)-2′,4′,6′-tri-isopropylr-biphenyl (7.42 mg, 0.016 mmol, Sigma-Aldrich) and K3PO4 (66.1 mg, 0.311 mmol, Sigma-Aldrich). The reaction mixture was stirred and heated in an oil bath at 100 °C for 40 min, then cooled to RT. The mixture was diluted with DCM (80 mL) and washed with water
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(15 mL), brine (10 mL). The organic layers was dried (MgSO₄), filtered and concentrated.

The residue was purified with silica gel chromatography (eluted with 1-4% MeOH in DCM) to give (S)-7-allyl-2-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (32 mg, 0.083 mmol, 53.1% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm
11.76 (1 H, br. s.), 7.88 (1 H, d, J=7.6 Hz), 7.57 (1 H, dd, J=8.0, 1.2 Hz), 7.49 (1 H, t, J=5.7 Hz), 7.32 (1 H, t, J=7.7 Hz), 7.10 (1 H, d, J=2.2 Hz), 6.89 (1 H, br. s.), 5.78 - 5.92 (1 H, m), 5.08 - 5.16 (2 H, m), 4.89 (1 H, s), 4.82 (1 H, s), 4.09 (2 H, t, J=4.8 Hz), 3.49 (1 H, dd, J=12.6, 3.6 Hz), 3.21 (1 H, dt, J=12.6, 4.1 Hz), 3.02 (1 H, dd, J=9.5, 4.8 Hz), 2.57 (3 H, s), 2.1 - 2.38 (1 H, m), 1.85 (3 H, s). MS (ESI, pos. ion) m/z: 388.3 (M+H)+.

Step 2: (9S,1E)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0.0-0.0-0.0-1 8.22-]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one and (9S,11Z)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0.0-0.0-0.0-1 8.22-]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

To a 150-mL round-bottomed flask was added (S)-7-allyl-2-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3.50 g, 9.03 mmol) in DCM (400 mL) followed by tricyclohexylphosphine[1 3.3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidine]ruthenium (0.767 g, 0.903 mmol, Sigma-Aldrich). The mixture was bubbled with Ar for 5 min, then equiped with a reflux condenser and heated in an oil bath at 50 °C for 90 min, then cooled to RT. The solvent was removed and the residue was purified with silica gel chromatography (eluted with 1-7% MeOH in DCM) to give the product (2.99 g, 92% yield). The product was further purified with preparative supercritical fluid chromatography (SFC) (Chiralcel ODH (250x30), 5 μ, 40% MeOH, 286-nm, 119/193 bar) to give (9S,1E)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0.0-0.0-0.0-1 8.22-]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (the major peak) and (9S,11Z)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0.0-0.0-0.0-1 8.22-]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (the minor peak).

Analytical data:
Example 14, (9S,1E)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0.0-0.0-1 8.22-]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.40 (1 H, br. s.), 7.96 - 8.02 (1 H, m), 7.52 - 7.63 (2 H, m), 7.33 (1 H, t, J=7.7 Hz), 7.02 (1 H, d, J=4.5 Hz), 6.91 (1 H, d,
$$J=2.0 \text{ Hz}) \text{, } 5.84 \text{ (1 H, d, } J=8.4 \text{ Hz) } , \text{ } 4.13 \text{ (1 H, br. s.) } , \text{ } 3.98 - 4.06 \text{ (1 H, m) } , \text{ } 3.40 \text{ (1 H, dt, } J=10.4 \text{, } 5.0 \text{ Hz) } , \text{ } 3.26 - 3.30 \text{ (1 H, m) } , \text{ } 3.17 - 3.25 \text{ (1 H, m) } , \text{ } 2.59 \text{ (3 H, s) } , \text{ } 2.37 - 2.48 \text{ (2 H, m) } , \text{ } 1.63 \text{ (3 H, s)}$$

Example 16, (9S,1LZ)-12,16-dimethyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),41 1,15,17,19,22-octaen-6-one: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 7.94 (1 H, br. s.), 7.83 - 7.90 (1 H, m), 7.58 (1 H, d, $J=6.5$ Hz), 7.29 - 7.38 (1 H, m), 6.96 (1 H, br. s.), 6.75 (1 H, br. s.), 5.63 (1 H, d, $J=11.3$ Hz), 4.53 (1 H, d, $J=15.8$ Hz), 3.64 - 3.77 (1 H, m), 3.36 (1 H, br. s.), 3.17 (2 H, br. s.), 2.70 - 2.82 (1 H, m), 2.58 (3 H, br. s.), 2.45 - 2.24 (1 H, m), 1.71 (3 H, br. s).

MS (ESI, pos. ion) m/z: 360.1 (M+H)$^+$. 

Example 17: (HE)-12-methyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),41,15,17,19,22-octaen-6-one

Step 1: 8-chloro-N-(2-methylallyl)quinoxalin-2-amine
2,8-Dichloroquinoxaline (Pharmabridge Inc., Doylestown, PA; 2.00 g, 10.05 mmol) and 2-methylallylamine (Matrix, Columbia, SC; 4.29 ml, 60.3 mmol) were combined in a tube, sealed, and heated to 80 °C in an oil bath. After 4 h, the reaction was cooled and the reaction was partitioned between saturated aqueous NaHCO$_3$ and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over
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anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give 8-chloro-N-(2-methylallyl)quinoxalin-2-amine (2.40 g, 10.27 mmol, quantitative yield) as an orange semi-solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.28 (1 H, s), 7.77 - 7.85 (1 H, m), 7.69 (1 H, d, J=7.7 Hz), 7.29 - 7.34 (1 H, m), 5.04 (1 H, s), 4.96 (1 H, s), 4.20 (2 H, d, J=5.9 Hz), 1.88 (3 H, s). m/z (ESI, +ve) 320.0 (M+H)⁺.

Step 2: 8-(1-ethoxyvinyl)-N-(2-methylallyl)quinoxalin-2-amine

Argon was bubbled through a mixture of tributyl(1-ethoxyvinyl)tin (Aldrich; 5.20 ml, 15.40 mmol), Cul (Riedel-de-Haen; 0.391 g, 2.054 mmol), cesium fluoride (Aldrich; 4.68 g, 30.8 mmol), Pd₂(dba)₃ (Strem; 2.351 g, 2.57 mmol), X-Phos (Strem; 1.224 g, 2.57 mmol), 8-chloro-N-(2-methylallyl)quinoxalin-2-amine (2.40 g, 10.27 mmol) in 20 mL dioxane in a scalable pressure vessel for 2 min. The reaction was sealed and heated to 120 °C in an oil bath overnight. The reaction was transferred to a 500 mL rfb with DCM, and adsorbed onto 20 g silica gel in vacuo. The material was purified by silica gel chromatography (160 g column) using 0 - 50% EtOAc/hexane to give 8-(1-ethoxyvinyl)-N-(2-methylallyl)quinoxalin-2-amine (2.85 g, 10.6 mmol, quantitative yield): ¹H NMR (400 MHz, DMSO-de) δ ppm 8.36 (1 H, s), 7.90 (1 H, t, J=5.9 Hz), 7.73 (1 H, d, J=7.8 Hz), 7.30 (1 H, t, J=7.8 Hz), 5.22 (1 H, s), 4.91 (1 H, s), 4.81 (1 H, s), 4.58 (1 H, s), 3.98 (2 H, m), 3.90 (2 H, q, J=6.9 Hz), 1.77 (2 H, s), 1.33 (3 H, t, J=6.9 Hz).

Step 3: 2-bromo-1-(3-((2-methylallyl)amino)quinoxalin-5-yl)ethanone

8-(1-ethoxyvinyl)-N-(2-methylallyl)quinoxalin-2-amine (2.82 g, 10.47 mmol) was dissolved in 50 mL THF and water (3.02 ml, 168 mmol) was added followed by 1-bromopyrrolidin-2,5-dione (Fluka; 1.770 g, 9.95 mmol). After 30 min, the reaction was partitioned between saturated aqueous NaHCO₃ and Et₂O. The organic layer was washed with saturated aqueous NaHCO₃ once, water once, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (80 g column) using 0 - 30% EtOAc/hexane to give 2-bromo-1-(3-((2-methylallyl)amino)quinoxalin-5-yl)ethanone (0.96 g, 3.00 mmol, 28.6 % yield): ¹H NMR (400 MHz, CDCl₃) δ ppm 8.32 (1 H, br. s), 8.04 - 8.19 (2 H, m), 7.41 - 7.51 (1 H, m), 5.07 (1 H, br. s), 4.96 (1 H, br. s), 4.12 (2 H, d, J=5.7 Hz), 1.88 (3 H, s). m/z (ESI, +ve) 320.0 (M+H)⁺.
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Step 4: 7-allyl-2-(3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A slurry of NH₄OAC (Fisher Scientific, 0.924 g, 11.99 mmol), 5-allylpiridine-2,4-dione (Intermediate A, 0.574 g, 3.75 mmol), 2-bromo-1-(3-((2-methylallyl)amino)quinoxalin-5-yl)ethanone (0.96 g, 3.00 mmol) in 30 mL EtOH was sealed and stirred rapidly. The reaction was placed in a 60 °C oil bath, then the oil bath was turned off and the reaction cooled slowly overnight. In the morning, the reaction was heated to 60 °C. After 2 h, the reaction was judged complete by LCMS. The reaction was partitioned between saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 60% 90/10 DCM/MeOH in DCM to give 7-allyl-2-(3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.140 g, 0.375 mmol, 12.50% yield) as an orange solid; ¹H NMR (400 MHz, DMSO-de) δ ppm: 11.89 (1 H, br. s.), 8.45 (1 H, s), 8.05 - 8.12 (1 H, m), 7.95 (1 H, dt, J=7.5, 0.7 Hz), 7.63 (1 H, dt, J=8.1, 0.6 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.06 - 7.12 (1 H, m), 6.92 (1 H, br. s.), 5.79 - 5.98 (1 H, m), 5.05 - 5.17 (2 H, m), 4.98 (1 H, s), 4.88 (1 H, s), 4.06 (2 H, dd, J=6.1, 0.4 Hz), 3.44 - 3.52 (1 H, m), 3.15 - 3.25 (1 H, m), 3.00 - 3.10 (1 H, m), 2.53 - 2.60 (1 H, m), 2.27 - 2.40 (1 H, m), 1.84 (3 H, s). m/z (ESI, +ve) 374.1 (M+H)⁺.

Step 5: (11E)-12-methyl-3,7,14,1 7,23-pentaaza-pentacyclo[1 3.6.2.1 2.5-0.4.9-0-1 8,22-7tetracosa-l(21),2(24),4(1 1.15,1 7.1 9,22-octan-6-one

Argon was bubbled into a slurry of 7-allyl-2-(3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.140 g, 0.375 mmol) and Grubbs catalyst 2nd generation (Aldrich; 0.032 g, 0.037 mmol) in 19 mL DCM for 2 min. The reaction was fitted with a water-cooled reflux condenser and heated to reflux. The reaction became a brown homogeneous solution. After 6 h, additional Grubbs catalyst 2nd generation (Aldrich; 0.032 g, 0.037 mmol) and 5 mL DCM was added and reflux continued overnight. In the morning, 3 g silica gel was added and the reaction concentrated in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 70% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (11E)-12-methyl-3,7,14,1 7,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,5,17,19,22-octaen-6-one (0.054 g, 0.16 mmol, 42% yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.50 (1 H, br. s.), 8.43 (1 H, s), 8.19 - 8.26 (1 H, m), 8.03 (1 H, dt, 7=7.6, 0.7 Hz), 7.59 (1 H, dt, 7=8.0, 0.7 Hz), 7.33 (1 H, t, 7=7.8 Hz), 7.01 (1 H, d, 7=4.7 Hz), 6.89 - 6.93 (1 H, m), 5.78 - 5.87 (1 H, m), 3.94 - 4.14 (2 H, m), 3.35 - 3.43 (1 H, m), 3.13 - 3.29 (2 H, m), 2.32 - 2.46 (2 H, m), 1.61 (3 H, s). m/z (ESI, +ve) 346.3 (M+H)⁺.

Examples 18 and 19: (9R, llE)-12-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one and (9S, llE)-12-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one

The individual enantiomers of Example 17 were obtained by chiral SFC (Column: Chiralpak AS-H (250 x 21 mm, 5 µ) Mobile Phase: 75:25 (A:B); A: Liquid CO₂ B: MeOH (40 mM NH₃), Flow Rate: 75 mL/min; Oven Temp: 40 °C; Inlet Pressure: 100 bar) to give Example 18 (first eluting product) and Example 19 (second eluting product).

Example 20: (9S,llZ)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
Example 21: (9S,llE)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
Example 22: (9R,llZ)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
Example 23: (9R,11E)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0.4,9^0.0^18,22^0.8,22]tetracosa-1(21),2(24),4,11,15,19,22-octaen-6-one

Step 1: 7-allyl-2-(3-(allylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A slurry of 7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate C, 0.322 g, 0.957 mmol) in allylamine (Aldrich; 5.02 ml, 67.0 mmol) was sealed and heated to 60 °C for 2 h. The reaction was cooled to RT, judged complete and diluted with ~ 5 mL saturated aqueous NaHCO₃ and 5 mL water. The thick suspension was filtered, rinsing with water and MeOH, and was dried in vacuo to give 7-allyl-2-(3-(allylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.289 g, 0.774 mmol, 81 % yield) as a bright yellow solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 12.05 (1 H, br. s.), 7.91 (1 H, dt, J=7.5, 0.8 Hz), 7.54 - 7.61 (2 H, m), 7.33 (1 H, t, J=7.7 Hz), 7.03 (1 H, dd, J=1.8, 0.4 Hz), 6.91 - 6.96 (1 H, m), 6.04 - 6.16 (1 H, m), 5.79 - 5.95 (1 H, m), 5.25 - 5.34 (1 H, m), 5.08 - 5.20 (3 H, m), 4.18 (2 H, t, J=5.3 Hz), 3.50 (1 H, ddt, J=12.4, 5.7, 0.7, 0.7 Hz), 3.18 - 3.24 (1 H, m), 3.01 - 3.08 (1 H, m), 2.57 (3 H, s), 2.44 - 2.51 (1 H, m), 2.28 - 2.40 (1 H, m). m/z (ESI, +ve) 374.1 (M+H)⁺.

Step 2: (9S,11Z)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0.4,9^0.0^18,22^0.8,22]tetracosa-1(21),2(24),4,11,15,19,22-octaen-6-one,
(9R, 11Z)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one,

(9R, 11E)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one

Argon was bubbled through a slurry of 7-allyl-2-(3-(allylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.289 g, 0.774 mmol) and Grubbs II Catalyst (Aldrich; 0.131 g, 0.155 mmol) for 2 min. The reaction was sealed and placed in a 50 °C oil bath overnight (~ 12 h). The green heterogeneous reaction was judged complete by LCMS. The reaction was concentrated onto 3 g silica gel from MeOH/DCM and dried in vacuo, and was purified by silica gel chromatography (40 g column) using 0 - 100% 90/10 DCMeOH in DCM to give 0.234 g of a mixture of products as a light green solid. The material was purified by SFC: Column: Cellulose-1 (21 mm x 25 cm, 5 μ, phenomenex, Lux-1, PO-AX (OD-H clone column), 60% C02 and MeOH 40% with 40 mM NH3, flow rate 70 ml/min, P=193 bar, 40 °C, to give Example 20 (9S,1 lZ)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (first eluting peak, 26 mg containing an impurity, material was sonicated in 0.5 mL MeOH and filtered, rinsing 1 x 0.5 mL MeOH, to give 17 mg, 0.051 mmol, 7% yield), Example 21 (9S,1 lE)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (second eluting peak, 51 mg, 0.15 mmol, 19% yield), and a mixture of (9R,1 lZ) - and (9R, 11E)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (first eluting peak, 28 mg, 0.081 mmol, 10% yield) and Example 23 (9R,1 lE)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (second eluting peak, 44 mg, 0.13 mmol, 16% yield).

Analytical data for Example 20 (9S,1 lZ)-16-methyl-3,7,14,17,23-pentaazapentacyclo[3.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one
octaen-6-one: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 13.79 (1 H, s), 7.95 - 8.03 (1 H, m), 7.88 (1 H, dt, $J=7.9$, 0.8 Hz), 7.58 (1 H, dt, $J=7.9$, 0.8 Hz), 7.34 (1 H, t, $J=7.8$ Hz), 6.99 (1 H, d, $J=4.5$ Hz), 6.78 (1 H, dd, $J=1.8$, 0.4 Hz), 5.72 - 5.89 (1 H, m), 5.51 - 5.66 (1 H, m), 4.40 (1 H, ddd, $J=1.8$, 0.4 Hz), 3.74 - 3.92 (1 H, m), 3.37 (1 H, t, $J=5.2$ Hz), 3.18 - 3.25 (2 H, m), 2.69 - 2.81 (1 H, m), 2.56 (3 H, s), 2.26 (1 H, d, $J=13.9$ Hz). m/z (ESI, +ve): 346.1 (M+H)+.

Analytical data for Example 21 (9S,11E)-16-methyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracon-6-one: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 13.54 (1 H, br. s), 7.98 (1 H, dt, $J=7.5$, 0.7 Hz), 7.53 (2 H, dd, $J=8.0$, 1.4 Hz), 7.31 (1 H, t, $J=7.8$ Hz), 7.02 (1 H, d, $J=4.5$ Hz), 6.89 (1 H, dd, $J=2.0$, 0.4 Hz), 6.00 - 6.14 (1 H, m), 5.83 - 5.94 (1 H, m), 4.14 - 4.28 (1 H, m), 3.98 - 4.09 (1 H, m), 3.34 - 3.38 (1 H, m), 3.22 - 3.30 (1 H, m), 3.07 - 3.16 (1 H, m), 2.52 - 2.62 (4 H, m), 2.15 - 2.28 (1 H, m). m/z (ESI, +ve): 346.1 (M+H)+.

Analytical data for Example 22 (9R,11Z)-1 6-methyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracon-6-one: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 13.79 (1 H, s), 7.95 - 8.03 (1 H, m), 7.88 (1 H, dt, $J=7.4$, 0.8 Hz), 7.58 (1 H, dt, $J=7.9$, 0.8 Hz), 7.34 (1 H, t, $J=7.8$ Hz), 6.99 (1 H, d, $J=4.5$ Hz), 6.78 (1 H, dd, $J=1.8$, 0.4 Hz), 5.72 - 5.89 (1 H, m), 5.51 - 5.66 (1 H, m), 4.40 (1 H, ddd, $J=15.8$, 10.4, 4.9 Hz), 3.74 - 3.92 (1 H, m), 3.37 (1 H, t, $J=5.2$ Hz), 3.18 - 3.25 (2 H, m), 2.69 - 2.81 (1 H, m), 2.56 (3 H, s), 2.26 (1 H, d, $J=13.9$ Hz), m/z (ESI, +ve): 346.1 (M+H)+.

Analytical data for Example 23 (9R,11E)-1 6-methyl-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracon-6-one: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 13.54 (1 H, br. s), 7.98 (1 H, dt, $J=7.5$, 0.7 Hz), 7.53 (2 H, dd, $J=8.0$, 1.4 Hz), 7.31 (1 H, t, $J=7.8$ Hz), 7.02 (1 H, d, $J=4.5$ Hz), 6.89 (1 H, dd, $J=2.0$, 0.4 Hz), 6.00 - 6.14 (1 H, m), 5.83 - 5.94 (1 H, m), 4.14 - 4.28 (1 H, m), 3.98 - 4.09 (1 H, m), 3.34 - 3.38 (1 H, m), 3.22 - 3.30 (1 H, m), 3.07 - 3.16 (1 H, m), 2.52 - 2.62 (4 H, m), 2.15 - 2.28 (1 H, m), m/z (ESI, +ve): 346.1 (M+H)+.

Example 24: (9S,11E)-12,16-dimethyl-14-oxa-3,7,17,23-
tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracon-
l(21),2(24),4(11),15,17,19,22-octaen-6-one
Example 25: (9R,11E)-12,16-dimethyl-14-oxa-3,7,17,23-
tetraazapentacyclo[13.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(21),2(24),4,11,15,19,22-octaen-6-one

Step 1:

7-allyl-2-(2-methyl-3-((2-methylallyl)oxy)quinoxalin-5-yl)-6,7-dihydro-1H-
pyrrolo[3,2-c]pyridin-4(5H)-one

To a slurry of NaH, 60% dispersion in mineral oil (Aldrich; 0.059 g, 1.486 mmol) in 1
mL DMF at 0 °C was added 2-methyl-2-propen-1-ol (TCI America; 0.125 ml, 1.486
mmol) slowly dropwise (bubbling). After 5 min the reaction was warmed to RT. After
10 min, 7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-
c]pyridin-4(5H)-one (Intermediate C, 0.050 g, 0.149 mmol) was added as a solid. The
reaction became red. After 30 min, the reaction was treated with saturated aqueous
NH₄Cl and EtOAc. The organic layer was washed 1x water, 1x brine, dried over
anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The yellow solid was suspended
in 5 mL Et₂O, sonicated, and filtered, rinsing 3 x 1 mL Et₂O, and the solid collected and
dried in vacuo to give 7-allyl-2-(2-methyl-3-((2-methylallyl)oxy)quinoxalin-5-yl)-6,7-
dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.052 g, 0.134 mmol, 90 % yield) as a
bright yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.56 (1 H, br. s.), 7.98 (1 H,
d., J=6.8 Hz), 7.79 (1 H, d, J=7.4 Hz), 7.58 - 7.65 (1 H, m), 7.10 (1 H, d., J=2.2 Hz), 6.95
(1 H, br. s.), 5.81 - 5.95 (1 H, m), 4.90 - 5.18 (7 H, m), 3.47 (1 H, ddd, J=12.2, 5.3, 1.7
Hz), 3.20 (1 H, ddd, J=12.3, 6.1, 2.9 Hz), 3.06 - 3.15 (1 H, m), 2.60 - 2.69 (4 H, m), 2.35
(1 H, dt, J=14.0, 8.7 Hz), 1.88 (3 H, s). m/z (ESI, +ve) 389.1 (M+H)+.

Step 2: (9S,11E)-12,16-dimethyl-14-oxa-3,7,17,23-
tetraazapentacyclo[13.6.2.1-2,5-.0-4,9-.0-18,22-]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one and (9R,11E)-
12,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1
3.6.2.1-2,5-.0-4,9-.0-1 8,22-]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
Argon was bubbled into a mixture of 7-allyl-2-(2-methyl-3-(2-methylallyl)oxy)quinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.052 g, 0.134 mmol) and Grubbs catalyst 2nd generation (Aldrich; 0.023 g, 0.027 mmol) in 6.7 mL anhydrous DCM for 1 min. The reaction was sealed and heated to 45 °C. After 4 h, the reaction was concentrated in vacuo, taken up in 3.5 mL DMSO and filtered through a 0.45 μ filter, and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 15-80 % ACN/H2O with 0.1% TFA; product-containing fractions were combined and concentrated in vacuo to give 0.028 g material. This was further purified by chiral SFC (Chiralpak AS-H (250 x 21 mm, 5 μ); Mobile Phase: 78:22 (A:B) A: Liquid CO2; B: MeOH (20 mM NH3); Flow Rate: 75 mL/min; Oven Temp: 40 °C; Inlet Pressure: 100 bar) to give: first eluting peak Example 24 (9S,1 IE)-12,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~12,5~.0~4,9~.0~19,23]tetracosa-l(21),2(24),4,1 l,l 5,1 7,1 9,22-octena~en-6-one (0.008 g, 0.022 mmol, 17% yield) and second eluting peak Example 25 (9R,1 IE)-12,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~12,5~.0~4,9~.0~19,23]tetracosa-l(21),2(24),4,1 l,l 5,1 7,1 9,22-octena~en-6-one (0.008 g, 0.022 mmol, 17% yield). Analytical data: 1H NMR (400 MHz, DMSO-d6) δ ppm 13.05 (1 H, br. s.), 8.12 (1 H, d, J=6.8 Hz), 7.72 (1 H, d, J=7.8 Hz), 7.51 - 7.62 (1 H, m), 7.06 (1 H, d, J=3.9 Hz), 6.99 (1 H, d, J=2.0 Hz), 5.96 (1 H, d, J=8.0 Hz), 5.16 (1 H, d, J=13.3 Hz), 5.00 (1 H, d, J=13.5 Hz), 3.36 - 3.46 (2 H, m), 3.18 - 3.27 (1 H, m), 2.63 (3 H, s), 2.43 - 2.48 (2 H, m), 1.69 (3 H, s). m/z (ESI, +ve) 361.1 (M+H)+.

Example 26: (9R,1IE)-17-methyl-3,7,15,18,24-pentaaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23]pentacos-1(22),2(25),4,11,16,18,20,23-octena~en-6-one

Example 27: (9S,1IE)-17-methyl-3,7,15,18,24-pentaaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23]pentacos-1(22),2(25),4,11,16,18,20,23-octena~en-6-one

Example 28: (9R,1HZ)-17-methyl-3,7,15,18,24-pentaaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23]pentacos-1(22),2(25),4,11,16,18,20,23-octena~en-6-one

Example 29: (9S,1HZ)-17-methyl-3,7,15,18,24-pentaaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23]pentacos-1(22),2(25),4,11,16,18,20,23-octena~en-6-one
Step 1: 7-allyl-2-(3-(but-3-en-1-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A thick orange mixture of 7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate C; 0.113 g, 0.336 mmol) in 3-buten-1-amine (Alfa-Aesar; 2.172 ml, 23.52 mmol) was sealed and heated to 70 °C. After 2 h, the reaction was judged complete by LCMS. The reaction was diluted with DCM/MeOH, adsorbed onto 1.5 g silica gel, dried, and purified by silica gel chromatography (25 g column) using 0 - 50% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 7-allyl-2-(3-(but-3-en-1-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.140 g, 0.361 mmol, quantitative yield) as a yellow solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 12.01 (1 H, br. s.), 7.90 (1 H, d, J=7.6 Hz), 7.57 (1 H, d, J=7.8 Hz), 7.22 - 7.40 (2 H, m), 7.09 (1 H, d, J=2.0 Hz), 6.93 (1 H, br. s.), 5.79 - 6.10 (2 H, m), 4.99 - 5.26 (4 H, m), 3.43 - 3.69 (3 H, m), 3.18 - 3.25 (1 H, m), 2.98 - 3.11 (1 H, m), 2.50 - 2.62 (6 H, m), 2.21 - 2.40 (1 H, m). m/z (ESI, +ve) 388.1 (M+H)$^+$. 

Step 2: (9R,11E)-1 7-methyl-3,7,15,18,24-pentaaazapentacyclo[1 4.6.2.1-2,5-0-4,9-0-1 9,23-]pentacosa-l(22),2(25),4,1 11,6,1 8,10,23-octaen-6-one, (9S,11E)-1 7-methyl-3,7,15,18,24-pentaaazapentacyclo[1 4.6.2.1-2,5-0-4,9-0-1 9,23-]pentacosa-l(22),2(25),4,1 11,16,18,20,23-octaen-6-one, (9R,11Z)-1 7-methyl-3,7,15,18,24-
A-1700-WO-PCT

pentaazapentacyclo[1 4.6.2.1-2.5-.0-.4.9-.0-.1] 9,23-pentacosa-
l(22),2(25),4,11 l,6,1,8,20,23-octaen-6-one, (9S,11 lZ)-1 7-methyl-3,7,1 l,5,8,24-
pentaazapentacyclo[1 4.6.2.1-2.5-.0-.4.9-.0-.1] 9,23-pentacosa-
l(22),2(25),4,11 l,6,1,8,20,23-octaen-6-one

Argon was flushed through a slurry of 7-allyl-2-(3-(but-3-en-1-ylamino)-2-
methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

(0.130 g, 0.336 mmol) and Grubbs catalyst 2nd generation (Aldrich; 0.057 g, 0.067 mmol) in 17 mL
anhydrous DCM for 1 min. The reaction was sealed and heated to 45 °C. After 2 h, the
reaction was treated with MeOH to give a solution and was adsorbed onto 1.3 g silica gel
and dried in vacuo. The material was purified by silica gel chromatography (25 g
column) using 0 - 100% 90/10 DCM/MeOH in DCM, to give 0.099 g yellow-green solid.
This material was further purified by chiral SFC (AS-H (2 x 15 cm) 40% (1:1:1 mixture
of MeOH:EtOH:IPA with 0.1% NH₄OH)/60% C0₂, 100 bar, 65 mL/min) to give three
materials: peak 1, 2, and 3. Peak 2 was further purified by chiral SFC (AD-H (2 x 15 cm),
35% MeOH(NH₄OH)/C0₂, 100 bar, 60 mL/min) to give first eluting (peak 2a) and
second eluting (peak 2b) materials:

Example 26, (9R,1 lE)-1 7-methyl-3,7,1 l,5,8,24-
pentaazapentacyclo[1 4.6.2.1-2.5-.0-.4.9-.0-.1] 9,23-pentacosa-
l(22),2(25),4,11 l,6,1,8,20,23-octaen-6-one (Peak 1, 0.033 g, 0.092 mmol, 27.4 % yield):

1H NMR (400 MHz, DMSO-d₆) δ ppm 12.13 (1 H, br. s.), 7.94 (1 H, d, J=7.6 Hz), 7.41-
7.59 (2 H, m), 7.27 (1 H, t, J=7.8 Hz), 7.04 (1 H, d, J=3.1 Hz), 6.91 (1 H, d, J=1.8 Hz),
6.05 (1 H, dt, J=14.9, 7.3 Hz), 5.85 (1 H, ddd, J=1.5, 10.3, 4.8 Hz), 3.64 - 3.77 (1 H, m),
3.49 - 3.60 (1 H, m), 3.33 - 3.41 (1 H, m), 3.14 - 3.25 (1 H, m), 3.01 - 3.13 (1 H, m), 2.52
(3 H, s), 2.13 - 2.47 (4 H, m). m/z (ESI, +ve) 360.2 (M+H)⁺.

Example 27, (9S,1 lE)-17-methyl-3,7,1 l,5,8,24-
pentaazapentacyclo[1 4.6.2.1-2.5-.0-.4.9-.0-.1] 9,23-pentacosa-
l(22),2(25),4,11 l,6,1,8,20,23-octaen-6-one (Peak 3, 0.031 g, 0.086 mmol, 25.7 % yield):

1H NMR (400 MHz, DMSO-d₆) δ ppm 12.13 (1 H, br. s.), 7.94 (1 H, d, J=7.6 Hz), 7.41-
7.59 (2 H, m), 7.27 (1 H, t, J=7.8 Hz), 7.04 (1 H, d, J=3.1 Hz), 6.91 (1 H, d, J=1.8 Hz),
6.05 (1 H, dt, J=14.9, 7.3 Hz), 5.85 (1 H, ddd, J=1.5, 10.3, 4.8 Hz), 3.64 - 3.77 (1 H, m),
3.49 - 3.60 (1 H, m), 3.33 - 3.41 (1 H, m), 3.14 - 3.25 (1 H, m), 3.01 - 3.13 (1 H, m), 2.52
(3 H, s), 2.13 - 2.47 (4 H, m). m/z (ESI, +ve) 360.2 (M+H)⁺.

Example 28, (9R,1 lZ)-1 7-methyl-3,7,1 l,5,8,24-
pentaazapentacyclo[1 4.6.2.1-2.5-.0-.4.9-.0-.1] 9,23-pentacosa-
A-1700-WO-PCT

l(22),2(25),4,11,16,18,20,23-octaen-6-one (Peak 2a, 0.0025 g, 0.0069 mmol, 2.1 % yield): \(^1\)H NMR (400 MHz, \(\text{CDCl}_3:\text{MeOH-d}_4\)) \(\delta\) ppm 7.89 (1 H, d, \(J=6.5\) Hz), 7.61 - 7.69 (1 H, m), 7.37 (1 H, t, \(J=7.8\) Hz), 7.02 (1 H, d, \(J=2.0\) Hz), 6.45 (1 H, t, \(J=6.2\) Hz), 5.64 - 5.83 (2 H, m), 3.87 - 4.02 (1 H, m), 3.39 - 3.61 (4 H, m), 2.70 - 2.91 (2 H, m), 2.59 (3 H, s), 2.26 - 2.42 (2 H, m). \(m/z\) (ESI, +ve) 360.2 (M+H)+.

Example 29: (9S,11Z)-17-methyl-3,7,15,18,24-pentaazapentacyclo[14.6.2.1~4,9~.0~19,23~]tetraconta-l(22),2(25),4,11,16,18,20,23-octaen-6-one

Example 2b, 0.0031 g, 0.0087 mmol, 2.6 % yield): \(^1\)H NMR (400 MHz, 4:1 CDCl\(_3\):MeOH-d\(_4\)) \(\delta\) ppm 7.89 (1 H, d, \(J=6.5\) Hz), 7.61 - 7.69 (1 H, m), 7.37 (1 H, t, \(J=7.8\) Hz), 7.02 (1 H, d, \(J=2.0\) Hz), 6.45 (1 H, t, \(J=6.2\) Hz), 5.64 - 5.83 (2 H, m), 3.87 - 4.02 (1 H, m), 3.39 - 3.61 (4 H, m), 2.70 - 2.91 (2 H, m), 2.59 (3 H, s), 2.26 - 2.42 (2 H, m). \(m/z\) (ESI, +ve) 360.2 (M+H)+.

Example 30: (9R,11E,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Example 31: (9S,11,E,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Example 32: (9S,11Z,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

![Chemical Structure](image-url)
Step 1: 7-allyl-2-(3-((R)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo [3,2-c]pyridin-4(5H)-one

A mixture of (R)-but-3-en-2-amine hydrochloride (Intermediate H; 0.288 g, 2.68 mmol), 7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate C; 0.300 g, 0.892 mmol) in 4 mL THF was treated with DIPEA (Aldrich, 0.931 ml, 5.35 mmol) and the reaction was sealed and heated to 60 °C. 1.5 mL DMSO was added to give a cloudy mixture. After 2 h, the temperature was increased to 80 °C. After 6 h the reaction was partitioned between water and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The solid was adsorbed onto 2 g silica gel from DCM/MeOH and dried in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 70% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 7-allyl-2-(3-((R)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.230 g, 0.594 mmol, 66.6 % yield) as a yellow solid: m/z (ESI, +ve) 388.1 (M+H)*.


Ar was bubbled through a solution of Grubbs catalyst 2nd generation (Aldrich; 0.099 g, 0.16 mmol) and 7-allyl-2-(3-((R)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.225 g, 0.581 mmol) in 30 mL anhydrous DCM for 1 min, the reaction was sealed, and placed in a 50 °C oil bath. After 2 h, the reaction was judged complete and was adsorbed onto 3 g silica gel and dried in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. Combined fractions to give 0.188 g of a green-yellow solid. This material was further purified by chiral SFC (ODH (21x250mm, 5 µ), 45% MeOH with 20 mM NH₃, 65 ml/min total flow) to give first eluting peak (peak 1, mixture of two components) and pure second eluting peak (peak 2). Peak 1 was further purified by SFC
(Pyridine column (2.1x250mm, 5 µ), 27% MeOH with 20 mM NH₃, 70 ml/min) to give first eluting peak (peak la) and second eluting peak (peak lb).

Example 30: (9R,1E,13R)-1 3,16-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[1 3.6.2.1^2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4l 1,5.1.7,1 8,20,22-nonaen-6-one (Peak 2, 0.083 g, 39.8 % yield): ^1H NMR (400 MHz, DMSO-d$_6$) δ ppm 13.57 (1 H, br. s.), 7.86 - 8.09 (1 H, m), 7.54 (1 H, dd, J=7.8, 1.0 Hz), 7.33 (1 H, t, J=7.8 Hz), 7.02 (1 H, d, J=4.3 Hz), 6.89 (1 H, d., J=2.0 Hz), 6.50 (1 H, s), 5.85 - 6.09 (2 H, m), 4.26 (1 H, t, J=6.7 Hz), 3.01 - 3.36 (3 H, m), 2.57 (4 H, d, J=13.5 Hz), 2.04 - 2.25 (1 H, m), 1.50 (3 H, d, J=7.0 Hz), m/z (ESI, +ve) 360.2 (M+H)$^+$.  

Example 31: (9S,1E,13R)-1 3,16-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[l 3.6.2.1^2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4l 1,5.1,7,1 8,20,22-nonaen-6-one (Peak la, 0.063 g, 0.175 mmol, 30.2 % yield): ^1H NMR (400 MHz, DMSO-d$_6$) δ ppm 13.46 (1 H, br. s.), 7.96 (1 H, d, J=6.7 Hz), 7.59 (1 H, d, J=6.3 Hz), 7.48 - 7.54 (1 H, m), 7.30 (1 H, t, J=7.8 Hz), 7.01 (1 H, d, J=4.1 Hz), 6.86 (1 H, d, J=2.0 Hz), 6.25 (1 H, d, J=16.0 Hz), 5.77 - 5.95 (1 H, m), 4.28 (1 H, br. s.), 3.28 - 3.42 (2 H, m), 3.04 - 3.18 (1 H, m), 2.52 - 2.70 (4 H, m), 2.14 - 2.37 (1 H, m), 1.48 (3 H, d, J=6.5 Hz). m/z (ESI, +ve) 360.1 (M+H)$^+$.  

Example 32: (9S,1Z,13R)-1 3,16-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[l 3.6.2.1^2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4l 1,5.1,7,1 8,20,22-nonaen-6-one (Peak lb, 0.0057 g, 0.016 mmol, 2.73 % yield): ^1H NMR (400 MHz, DMSO-d$_6$) δ ppm 13.80 (1 H, br.), 7.88 (1 H, m), 7.52 (1 H, m), 7.36 (2 H, m), 7.01 (1 H, d, J=4.5 Hz), 6.80 (1 H, d, J=2.0 Hz), 5.78 (1 H, m), 5.65 (1 H, m), 4.75 (1 H, m), 3.39 (1 H, m), 3.18 (2 H, m), 2.70 (1 H, m), 2.63 (3 H, s), 2.33 (1 H, m), 1.44 (3 H, d, J=7.0 Hz). m/z (ESI, +ve) 360.2 (M+H)$^+$.  

Example 32, alternative preparation: (9S,1Z,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4l,15,17,18,20,22-nonaen-6-one
Step 1: (9S,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-l 1-yn-6-one

In a glove box, to a solution of (S)-7-(but-2-yn-1-yl)-2-(2-methyl-3-((R)-pent-3-yn-2-
ylemino)quinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate
N, 38 mg, 0.092 mmol) in toluene (2.3 mL) in a glass tube was added tri-tert-butoxy(2,2-
dimethylpropyldyne)tungsten (Strem Chemicals Inc.; 17 mg, 0.03 mmol). The glass tube
was sealed and transferred out of the glove box. It was heated in an oil bath at 80 °C for
3.5 h. The reaction mixture was concentrated under reduced pressure and the residue
was purified on a silica gel column (50-100% EtOAc in DCM followed by 5% MeOH in
DCM) to give 18 mg of yellow crystalline solid that was about 85% pure (by LCMS) of
m/z (ESI, +ve) 358.1 (M+H)+. The solid was dissolved in 2 mL of DMSO and purified on
a reversed phase HPLC [20-95% of 0.1% TFA in CH3CN in 0.1% TFA in water]. The
desired fractions were collected, concentrated, and the residue was partitioned between
15 mL of EtOAc and 5 mL of 0.5 N NaOH. The organic layer was separated, washed with 2
mL of brine, dried over Na2SO4 and concentrated to give (9S,13R)-13,16-dimethyl-
3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-l 1-yn-6-one (8 mg, 24% yield) as a yellow
crystalline solid: 1H NMR (400 MHz, MeOH-d4) δ ppm 8.01 (1 H, d, J=7.6 Hz), 7.62 (1
H, d, J=8.0 Hz), 7.42 (1 H, t, J=7.9 Hz), 7.01 (1 H, d, J=2.0 Hz), 4.56 (1 H, qd, J=6.8, 3.0
Hz), 3.53 (2 H, m), 3.23 (1 H, m), 2.72 (1 H, m), 2.58 (3 H, s), 2.47 (1 H, m), 1.65 (3 H,
d, J=6.8 Hz). m/z (ESI, +ve) 358.1 (M+H)+.

Step 2: (9S,1 IZ,13R)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

A solution of (9S,13R)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-l 1-yn-6-one (8 mg, 0.022 mmol) in 2 mL of MeOH
was treated with quinoline (10 mg, 0.08 mmol) and palladium (Sigma-Aldrich Chemicals,
8 mg of 5% wt on calcium carbonate, poisoned with lead). The mixture was
hydrogenated with a H2 balloon for 4 h. It was diluted with MeOH, filtered through a pad
of Celite and the filtrate was concentrated. Purification on a silica gel column (1-10%
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MeOH in DCM) gave (9S,11Z,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (5.0 mg, 62% yield) as a yellow crystalline solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 13.80 (1 H, br.), 7.88 (1 H, m), 7.52 (1 H, m), 7.36 (2 H, m), 7.01 (1 H, d, $J$=4.5 Hz), 6.80 (1 H, d, $J$=2.0 Hz), 5.78 (1 H, m), 5.65 (1 H, m), 4.75 (1 H, m), 3.39 (1 H, m), 3.18 (2 H, m), 2.70 (1 H, m), 2.63 (3 H, s), 2.33 (1 H, m), 1.44 (3 H, d, $J$=7.0 Hz), $m/z$ (ESI, +ve) 360.2 (M+H)$^+$. 

Example 32 Alternative Preparation: (9S,11Z,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: Acetaldehyde (Sigma-Aldrich, 285 ml, 5074 mmol) and MgSO$_4$ (Sigma-Aldrich, 660 g, 5480 mmol) were added to a solution of (R)-2-methylpropane-2-sulfinamide (AK Scientific, Inc., Union City, CA, 246 g, 2.03 mol) in DCM (1.2 L). The slurry was stirred at RT for 16 h. The reaction mixture was filtered and concentrated to give product.
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contaminated with starting material. A slurry with MgSO₄ (660 g, 5480 mmol) in a solution of the resulting oil and acetaldehyde (285 ml, 5074 mmol) in DCM (1200 ml) was stirred at RT for 16 h. The reaction mixture was filtered and concentrated to give (R,E)-N-ethylidene-2-methylpropane-2-sulfamide (248.14 g, 1685 mmol, 83 % yield) as an amber oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.18 (s, 9 H) 2.22 (d, J=5.09 Hz, 3 H) 8.07 (q, J=5.09 Hz, 1 H). MS (ESI, pos. ion) m/z: 399.0 (M+l).

Step 2: LiHMDS in THF (1.0 M, Sigma-Aldrich, 235 ml, 235 mmol) was added over 30 min via addition funnel to a solution of 3-chloroprop-1-yne (Sigma-Aldrich, 16.84 ml, 235 mmol) in pentane (400 ml) in a three neck 5 L rbf fixed with a mechanical stirrer and temperature probe at -72 °C. The yellow solution was stirred at -72 °C for 15 min; (R,E)-N-ethylidene-2-methylpropane-2-sulfamide (34.6 g, 235 mmol) in THF (20 ml) was then added to the reaction mixture. The brown solution was stirred at -78 °C for 15 min and was warmed to 17 °C over 3 h when mostly MS (ESI, pos. ion) m/z: 222.1 (M+i) was observed.

Step 3: Tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharma, Libertyville, IL, 37.6 g, 176 mmol) in THF (400 ml) was added to the reaction mixture; this was cooled to -20 °C (an acetone bath was adjusted to the desired temperature by addition of dry ice), and LiHMDS in THF (1.0 M in THF; Sigma-Aldrich, 564 ml, 564 mmol) was added via addition funnel over 10 min (the internal temperature was kept below -20 °C). The brown solution was stirred at -20 °C for 1 h. The reaction mixture was quenched with water (500 mL) and acidified with 1 N aq. KHSO₄ (1.5 L). The organic layer was separated in a separatory funnel and was washed with water (2 x 400 mL); the aqueous layer was extracted with ether (2 x 250 mL); the combined organics were dried over Na₂SO₄ and concentrated to give a red oil. The crude product was directly injected onto a column and was purified via automated flash chromatography (1.5 kg RediSep Rf Gold, silica gel initially eluted with hexanes) with 100% DCM to 30% acetone/DCM to give tert-butyl 5-((R)-4-((R)-1,1-dimethylethylsulfinamido)pent-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (54.09 g, 32.3% yield over two steps) as a yellow foam. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.19 (s, 9 H) 1.37 - 1.42 (m, 3 H) 1.56 (s, 9 H) 2.49 - 2.65 (m, 2 H) 2.66 - 2.74 (m, 1 H) 3.19 - 3.30 (m, 1 H) 3.37 - 3.49 (m, 1 H) 3.88 - 4.02 (m, 1 H) 4.02 - 4.09 (m, 2 H) 4.43 (dd, J=14.08, 4.89 Hz, 1 H). MS (ESI, pos. ion) m/z: 399.0 (M+i).
Step 4: Hydrogen chloride in dioxane (Sigma-Aldrich, 109 ml, 437 mmol) was added to a solution of tert-butyl 5-((R)-4-((R)-1,1-dimethylethylsulfinamido)pent-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (57.99 g, 146 mmol) in dioxane (500 ml)/water (31.5 ml, 1746 mmol) at RT for 75 min. The reaction mixture was concentrated to give a red oil. MS (ESI, pos. ion) m/z: 195.1 (M+1).

Step 5: An exotherm was observed after making a solution of the red oil from step 4, acetic acid, ammonia salt (Sigma-Aldrich, 22.43 g, 291 mmol), and ammonia in methanol (Sigma-Aldrich, 728 ml, 1455 mmol) (max. 31 °C); 2-chloroacetaldehyde in water (Sigma-Aldrich, 18.48 ml, 146 mmol) was then added when another exotherm was observed via internal temperature probe (max. 29 °C). The red solution was placed on the rotory evaporator at ambient pressure with the bath at 50 °C for 1 h. The reaction mixture was concentrated to give a red oil. MS (ESI, pos. ion) m/z: 218.1 (M+1).

Step 6: A solution of the resulting red oil, di-tert-butyl dicarbonate (Sigma-Aldrich, 95 g, 437 mmol), and N-ethyl-N-isopropylpropan-2-amine (Sigma-Aldrich, 127 ml, 728 mmol) in DCM (500 ml)/MeOH (250 ml) was stirred at rt for 30 min when MS (ESI, pos. ion) m/z: 318.0 (M+1) was observed. The reaction mixture was washed with saturated aqueous NaHCO₃ (2 x 400 mL) in a separatory funnel; the aqueous layer was extracted with DCM (2 x 200 mL), then the combined organics were dried over Na₂SO₄, and concentrated to give a red oil. The crude product was dissolved in DCM, was directly injected onto a column, and was purified via automated flash chromatography (1.5 kg RediSep Rf Gold, silica gel initially eluted with hexanes) with 100% DCM to 4% methanol in DCM to give tert-butyl ((2R)-5-((4-oxo-4,5,6,7-tetrahydro-IH-pyrrolo[3,2-c]pyridin-7-yl)pent-3-yn-2-yl)carbamate (17.29 g, 54.5 mmol, 37.4 % yield over three steps) as a pale yellow foam. The diastereomers were separated by chiral SFC (Column: Chiralpak AD (20 μm, 21 mm x 250 mm), F = 120 ml/min, 35% MeOH 20 mM NH₃/carbon dioxide. Sample dissolved in MeOH (50 mg/mL), P = 131 bar, 3.5 ml injection, 262 nm) to give tert-butyl ((R)-5-((S)-4-oxo-4,5,6,7-tetrahydro-IH-pyrrolo[3,2-c]pyridin-7-yl)pent-3-yn-2-yl)carbamate (26.38 g, 83 mmol, 46.5 % yield) as a pale yellow foam. ¹H NMR (400 MHz, CDCl₃, δ ppm) 1.37 (d, J=7.04 Hz, 3 H) 1.47 (s, 9 H) 2.34 - 2.45 (m, 1 H) 2.49 - 2.60 (m, 1 H) 3.11 (dq, J=10.69, 5.11 Hz, 1 H) 3.22 - 3.31 (m, 1 H) 3.71 (ddd, J=12.18, 5.43, 1.56 Hz, 1 H) 4.25 - 4.35 (m, 1 H) 4.77 (d, J=6.06 Hz,
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1 H 5.26 (br. s., 1 H) 6.59 (t, J=2.54 Hz, 1 H) 6.78 (t, J=2.54 Hz, 1 H) 10.20 (br. s., 1 H).

MS (ESI, pos. ion) m/z: 318.0 (M+l).

Step 7: NanoSelect LF 200 (BASF, Iselin, NJ, 1 g) was stirred in a yellow solution of tert-butyl ((R)-5-((S)-4-oxo-4,5,6,7-tetrahydro-II-pyrrolo[3,2-c]pyridin-7-yl)pent-3-yn-2-y)carbamate (10 g, 31 mmol) in 2 M NH₃ in MeOH (200 ml) at rt under H₂ (15 psig) for 1.5 h. The mixture was filtered to remove the palladium catalyst; activated carbon (16.8 g) was stirred in the yellow solution at rt for 16 h. After filtration and concentration, tert-butyl ((R,Z)-5-((S)-4-oxo-4,5,6,7-tetrahydro-II-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-y)carbamate was isolated as a light yellow foam. MS (ESI, pos. ion) m/z: 320.1 (M+l).

Step 8: 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (Sigma-Aldrich, 3.24 g, 11.35 mmol) was added to a solution of tert-butyl ((R,Z)-5-((S)-4-oxo-4,5,6,7-tetrahydro-II-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-y)carbamate (7.63 g, 23.89 mmol) in DMF (200 ml) in a 500 mL rbf at -60 °C (dry ice/acetone bath temperature monitored). The yellow solution was stirred at -60 °C for 30 min. The combined reaction mixtures were diluted with DCM (500 mL), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (2 x 100 mL) and water (5 x 200 mL); the organic layer was separated, dried over Na₂SO₄, and concentrated to give a greenish oil. The crude product in DCM was purified via automated flash chromatography (silica gel) with 100% hexanes to 100% EtOAc in hexanes to give tert-butyl ((R,Z)-5-((S)-2-bromo-4-oxo-4,5,6,7-tetrahydro-II-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-y)carbamate (7.48 g, 18.78 mmol, 52.2 % yield over two steps) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.19 (d, J=6.65 Hz, 3 H) 1.48 (s, 9 H) 2.16 - 2.26 (m, 1 H) 2.67 - 2.78 (m, 1 H) 2.86 - 2.98 (m, 1 H) 3.37 (dd, J=12. 13, 7.24 Hz, 1 H) 3.57 (dd, J=12. 13, 5.48 Hz, 1 H) 4.46 - 4.58 (m, 1 H) 4.67 (d, J=6.46 Hz, 1 H) 5.37 (t, J=9.98 Hz, 1 H) 5.55 (id, J=11.10, 4.40 Hz, 1 H) 5.62 (br. s., 1 H) 6.49 (d, J=2.35 Hz, 1 H) 10.26 (br. s., 1 H). MS (ESI, pos. ion) m/z: 398.1/400.1 (M+l).

Step 9: A solution of tert-butyl ((R,Z)-5-((S)-2-bromo-4-oxo-4,5,6,7-tetrahydro-II-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-y)carbamate (12.31 g, 30.9 mmol), 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (Intermediate D, Step 1, 17.81 g, 61.8 mmol), and potassium hydrogenphosphate (Sigma-Aldrich, 18.84 g, 108 mmol) in DMF (281 ml)/water (28.1 ml) at 70 °C was sparged with nitrogen for 3 min;
PdCl$_2$(Amphos)$_2$ (Sigma-Aldrich, 1.094 g, 1.545 mmol) was then added, and the solution soon turned red. This was stirred at 70 °C for 30 min. The reaction mixture was diluted with EtOAc (500 mL), added to a separatory funnel, and washed with water (5 x 200 mL); the combined aqueous layers were back extracted with DCM (2 x 200 mL); the combined organic layers were separated, dried over Na$_2$SO$_4$, and concentrated; a small amount of product was observed in the aqueous layer. The crude product in DCM was loaded onto the column and was purified via automated flash chromatography (1.5 kg RediSep R$_f$ Gold, silica gel initially eluted with hexanes) with 100% DCM to 5% MeOH in DCM to give tert-butyl ((R,Z)-5-((S)-2-(3-fluoro-2-methylquinolin-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-yl)carbamate (12.07 g, 25.2 mmol, 75% yield) as a yellow foam. $^1$H NMR (400 MHz, CDC$_1$_3) $\delta$ ppm 1.20 - 1.23 (m, 3 H), 1.24 (s, 9 H) 2.46 - 2.58 (m, 1 H) 2.74 (d, $J$=7.04 Hz, 1 H) 2.79 (s, 3 H) 3.19 - 3.29 (m, 1 H) 3.40 - 3.47 (m, 1 H) 3.67 (ddd, $J$=12.08, 5.53, 2.74 Hz, 1 H) 4.46 - 4.63 (m, 2 H) 5.38 (br. s., 1 H) 5.54 - 5.63 (m, 1 H) 5.63 - 5.70 (m, 1 H) 7.22 (d, $J$=2.15 Hz, 1 H) 7.68 - 7.76 (m, 1 H) 7.85 - 7.91 (m, 1 H) 8.07 (d, $J$=7.43 Hz, 1 H) 11.41 (br. s., 1 H). $^{19}$F NMR (377 MHz, CDC$_1$_3) $\delta$ ppm -72.31 (s, 1 F). MS (ESI, pos. ion) m/z: 480.0 (M+1).

Step 10: A solution of tert-butyl ((R,Z)-5-((S)-2-(3-fluoro-2-methylquinolin-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-7-yl)pent-3-en-2-yl)carbamate (12.07 g, 25.2 mmol) and 2,2,2-trifluoroacetic acid (Sigma-Aldrich, 78 ml, 1007 mmol) in DCM (503 ml) was stirred at rt for 30 min. The dark red solution was concentrated. MS (ESI, pos. ion) m/z: 380.1 (M+1).

Step 11: A solution of the resulting red oil from Step 10 and N-ethyl-N-isopropylpropan-2-amine (Sigma-Aldrich, 88 ml, 503 mmol) in DMSO (755 ml) was stirred at 100 °C for 1 h. The reaction mixture was diluted with water (2000 mL), added to a separatory funnel, and extracted with DCM/IPA (3:2) (8 x 200 mL); the combined organic layers were washed with water (4 x 200 mL), separated, dried over Na$_2$SO$_4$, and concentrated. The crude product in DCM/MeOH was loaded onto the column and was purified via automated flash chromatography (1.5 kg RediSep R$_f$ Gold, silica gel) with 100% hexanes to 100% EtOAc in hexanes (removes phosphine ligand) then 100% DCM to 5% MeOH in DCM to give the Z-macrocycle as a yellow slurry (contaminated with DMSO via NMR) with a slightly acrid smell. The yellow slurry was suspended in methanol (100 mL, removes impurities), sonicated for 5 min, filtered, sonicated in absolute ethanol (50 mL,
removes residual methanol), and dried in vacuo to give (9S,1 lZ,1 3R)-13,16-dimethyl-
3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (6.09 g, 16.94 mmol, 67.3 % yield over
two steps) as a yellow solid. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 1.42 (d, \(J=7.04\) Hz,
3 H) 2.29 (d, \(J=13.69\) Hz, 1 H) 2.60 - 2.76 (m, 1 H) 3.14 - 3.25 (m, 2 H)
3.37 (t, \(J=4.99\) Hz, 1 H) 4.71 (tt, \(J=13.30, 7.04\) Hz, 1 H) 5.60 - 5.68
(m, 1 H) 5.70 - 5.78 (m, 1 H) 6.78 (d, \(J=1.96\) Hz, 1 H) 6.98 (d, \(J=4.50\) Hz, 1 H) 7.30 -
7.38 (m, 2 H) 7.58 (dd, \(J=8.12, 1.08\) Hz, 1 H) 7.88 (dd, \(J=7.43, 1.17\) Hz, 1 H) 13.77 (br.
s., 1 H). MS (ESI, pos. ion) m/z: 360.0 (M+1).

Example 33: (9S,1 lE,13S)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-
IH-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-
pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 4.57 g, 13.60 mmol), (5)-but-3-en-2-
amine hydrochloride (Intermediate G, 3.07 g, 28.6 mmol), and DIPEA (10.0 ml, 57.5
mmol) in DMSO (28.5 ml) was stirred under argon at 60 °C for 7.5 h. The reaction
mixture was then partitioned between EtOAc (300 mL) and sat. aqueous NaHCO\(_3\) (200
mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc
(300 mL). The combined organic extracts were sequentially washed with water (2 x 300
mL) and brine (200 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to
provide (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-
IH-pyrrolo[3,2-c]pyridin-4(5H)-one (5.46 g, 14.09 mmol, quantitative yield) as a yellow-
orange solid: \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 1.12 (1 H, br. s.), 7.90 (1 H, dd,
\(J=7.4, 0.8\) Hz), 7.56 - 7.61 (1 H, m), 7.33 (1 H, t, \(J=7.8\) Hz), 7.11 (1 H, d, \(J=7.4\) Hz), 7.04
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(1 H, d, J=2.0 Hz), 6.94 (1 H, br. s.), 6.10 (1 H, ddd, J=17.3, 10.4, 4.8 Hz), 5.88 (1 H, ddt, J=16.8, 9.8, 7.2, 7.2 Hz), 5.23 (1 H, d, J=17.2 Hz), 5.14 (1 H, s), 5.07 - 5.12 (2 H, m), 4.74 - 4.87 (1 H, m), 3.45 - 3.55 (1 H, m), 3.22 (1 H, dt, J=7.6, 3.9 Hz), 3.07 (1 H, dq, J=9.6, 4.8 Hz), 2.59 (3 H, s), 2.28 - 2.39 (1 H, m), 1.45 (3 H, d, J=6.8 Hz), 0.95 (1 H, d, J=6.5 Hz), m/z (ESI, +ve) 388.3 (M+H)+.

Step 2: (9S,11E,3S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Grubbs Catalyst - 2nd generation (Aldrich; 2.00 g, 2.356 mmol) was added to a solution of (S)-7-allyl-2-(3 -((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (5.27 g, 13.60 mmol) in DCM (550 mL). The resulting solution was stirred under argon at 40 °C for 5 h. Additional Grubbs Catalyst - 2nd generation (330 mg, 0.389 mmol) was added, and the resulting solution was stirred under argon at 40 °C for 1 h. MeOH (10 mL) and silica gel (30 g) were added, and the resulting mixture was concentrated in vacuo. Chromatographic purification (dry-load, ISCO, 330g, Redi-Sep Gold, 0-10% MeOH/DCM, 30 min, 254 nm) furnished a yellow-green solid (4.42 g). MeOH (30 mL) was added to this solid, and the resulting suspension was sonicated for 30 sec, then vacuum filtered, rinsing the collected material with with MeOH (1 x 10 mL). The collected material was then dried in vacuo to provide (95,11s,13s)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (3.2 g, 8.90 mmol, 65% yield) as a yellow-green solid. 1H NMR (400 MHz, DMSO-d6) δ ppm 13.51 - 13.63 (1 H, m), 7.99 (1 H, d, J=7.4 Hz), 7.54 (1 H, d, J=7.8 Hz), 7.33 (1 H, t, J=7.7 Hz), 7.02 (1 H, d, J=4.3 Hz), 6.89 (1 H, d, J=4.3 Hz), 6.50 (1 H, s), 5.96 - 6.05 (1 H, m), 5.87 - 5.96 (1 H, m), 4.21 - 4.32 (1 H, m), 3.32 - 3.37 (1 H, m), 3.20 - 3.30 (1 H, m), 3.06 - 3.16 (1 H, m), 2.61 (3 H, s), 2.57 (1 H, d, J=14.9 Hz), 2.12 - 2.24 (1 H, m), 1.51 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 360.2 (M+H)+.

Example 34: (9S,11E)-13,13,16-trimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one
Step 1: tert-butyl (2-methylbut-3-en-2-yl)carbamate
To a slurry of methyl triphenylphosphonium bromide (Fluka Chemie, Gmbh; 3.53 g, 9.88 mmol) in 50 mL THF under N₂ at -78 °C was added KHMD 0.5 M in toluene (Aldrich; 19.76 mL, 9.88 mmol) dropwise via syringe over ~ 2 min. The reaction became yellow. An ice/water bath was added and the reaction stirred for 30 min. The reaction was re-cooled to -78 °C and tert-butyl 2-formylpropan-2-yl carbamate (BetaPharma Inc., Branford, CT; 1.85 g, 9.88 mmol) was added as a solution in 10 mL THF via syringe. The cooling bath was warmed to RT and the reaction stirred over the weekend. The reaction was partitioned between water and EtOAc. The organic layer was washed with water once, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and 10 g silica gel, dried in vacuo, and purified by silica gel chromatography (80 g column) using 0 - 20% EtOAc/hexane. The product-containing fractions were concentrated to afford tert-butyl (2-methylbut-3-en-2-yl)carbamate (0.750 g, 4.05 mmol, 41.0 % yield) as a clear/colorless oil: ¾ NMR (400 MHz, CDCl₃) δ ppm 5.97 (1 H, dd, J=17.4, 10.6 Hz), 4.98 - 5.17 (2 H, m), 4.57 (1 H, br. s.), 1.38 (6 H, s).

Step 2: 2-methylbut-3-en-2-amine hydrochloride
tert-Butyl (2-methylbut-3-en-2-yl)carbamate (0.750 g, 4.05 mmol) was treated with HCl, 4.0 M solution in 1,4-dioxane (Aldrich; 10.12 ml, 40.5 mmol) and the reaction was fitted with a drying tube and stirred at RT for 1 h. The reaction was judged complete by TLC (20% EtOAc/hexanes, visualize with KMnO₄). The reaction was treated with 10 mL...
anhydrous toluene and concentrated in vacuo, then treated with 5 mL anhydrous toluene
and concentrated again and dried on hood pump to give 2-methylbut-3-en-2 -amine
hydrochloride (0.447 g, 3.68 mmol, 91 % yield) as a white solid: \(^1\)H NMR (400 MHz,
\(CDCl_3\) \(\delta\) ppm 8.62 (4 H, br. s), 6.01 (1 H, dd, \(J=17.4, 11.0\) Hz), 5.43 (1 H, d, \(J=17.6\)
Hz), 5.28 (1 H, d, \(J=10.8\) Hz), 1.62 (6 H, br. s).

Step 3: (S)-7-allyl-2-(2-methyl-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-
dihydro-\(1\)H-pyrrolo[3,2-c]pyridin-4(5H)-one

(S)-7-Allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-\(1\)H-pyrrolo[3,2-c]pyridin-
4(5H)-one (Intermediate B; 0.130 g, 0.386 mmol) and 2-methylbut-3-en-2-amine
hydrochloride (0.235 g, 1.932 mmol) were combined in a sealable vessel and 3 mL
DMSO and DIPEA (Aldrich; 0.504 ml, 2.90 mmol) were added. The reaction was sealed
and heated 12 h at 60 °C, and was then heated approximately 3 h at 100 °C. The reaction
was partitioned between saturated aqueous NaHCO\(_3\) and EtOAc. The organic layer was
washed with water once, brine once, and the organics were dried over anhydrous Na\(_2\)SO\(_4\),
filtered, and concentrated in vacuo. The material was treated with DCM and purified by
silica gel chromatography (40 g column) using 0 - 70% 90/10 DCM/MeOH in DCM. The
product-containing fractions were concentrated to give 0.118 g orange solid. This material
was dissolved in DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C\(_18\)
column, 15-100 % ACN/H\(_2\)O with 0.1% TFA; product-containing fractions were treated
with saturated aqueous NaHCO\(_3\) and DCM. The aqueous layer was extracted 3 x DCM
and combined organics dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to give (S)-
7-allyl-2-(2-methyl-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-dihydro-\(1\)H-pyrrolo[3,2-c]pyridin-
4(5H)-one (0.072 g, 0.179 mmol, 46.4 % yield) as a yellow glass:

\(^1\)H NMR (400 MHz, \(DMSO-d_6\) \(\delta\) ppm 11.76 (1 H, br. s), 7.91 (1 H, dd, \(J=7.6, 1.2\) Hz),
7.57 (1 H, dd, \(J=8.0, 1.2\) Hz), 7.34 (1 H, t, \(J=7.8\) Hz), 6.99 (1 H, d, \(J=2.0\) Hz), 6.92 (1 H,
d, \(J=3.7\) Hz), 6.37 (1 H, s), 6.20 (1 H, dd, \(J=17.5, 10.7\) Hz), 5.83 - 6.00 (1 H, m), 5.05 -
5.31 (4 H, m), 3.54 (1 H, dd, \(J=12.4, 5.0\) Hz), 3.19 - 3.29 (1 H, m), 2.93 - 3.06 (1 H, m),
2.63 (3 H, s), 2.27 - 2.43 (2 H, m), 1.60 (3 H, s), 1.59 (3 H, s) m/z (ESI, +ve) 402.2

(M+H)+.

Step 4: (9S,1 LE)-1 3.1 1.6-trimethyl-3.7,14,17,23-
pentaazapentacyclo[1 3.6.2.1 2.5.0 4.9.0-0 8.22]-tetracosa-
1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one

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Argon was bubbled through a solution of Grubbs catalyst 2nd generation (Aldrich; 0.030 g, 0.036 mmol) and (S)-7-allyl-2-(2-methyl-3-((2-methylbut-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.072 g, 0.179 mmol) in 9 mL DCM for 2 min. The reaction was sealed and heated to 45 °C for 6 h. Grubbs catalyst 2nd generation (Aldrich; 0.030 g, 0.036 mmol) was added; the reaction was sealed, and heating continued for 1 h. The reaction was placed in the freezer over the weekend, then concentrated in vacuo and treated with DMSO, filtered (0.45 µ filter) to give 3 mL dark brown liquid. This material was purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 10-100 % ACN/H2O with 0.1% TFA. The combined product containing fractions were treated with saturated aqueous NaHCO3 and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na2SO4, filtered, and concentrated in vacuo to give (9S,11E)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.12,5.04,9.018,22]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (0.009 g, 0.024 mmol, 13.44 % yield) as a yellow green solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 13.50 (1 H, br. s), 7.98 (1 H, dd, J=7.5, 1.1 Hz), 7.53 (1 H, dd, J=8.0, 1.2 Hz), 7.33 (1 H, t, J=7.8 Hz), 7.01 (1 H, d, J=4.3 Hz), 6.87 (1 H, d, J=2.2 Hz), 6.32 (1 H, s), 6.23 (1 H, d, J=15.8 Hz), 5.78 - 5.95 (1 H, m), 3.00 - 3.35 (2 H, m), 2.54 - 2.73 (4 H, m), 2.12 - 2.41 (2 H, m), 1.56 (3 H, s), 1.51 (3 H, s). m/z (ESI, +ve) 374.1 (M+H)+.

Example 35: (9R,11E,13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.12,5.04,9.018,22]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Example 36: (9R,11Z,13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.12,5.04,9.018,22]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one
(R)-7-Allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c
4(5H)-one (Intermediate E; 0.100 g, 0.297 mmol) was treated with (S)-but-3-en-2-amine hydrochloride (Intermediate G; 0.160 g, 1.486 mmol) and DIPEA (Aldrich; 0.388 ml, 2.230 mmol) in 3 mL DMSO. The orange reaction was sealed and heated to 60 °C overnight. The light yellow reaction was analyzed by LCMS and judged complete. The reaction was partitioned between saturated aqueous NaHCO₃ and EtOAc. The organic layer was washed with water once, brine once, and the organics were dried over anhydrous Na₂S₀₄, filtered, and concentrated in vacuo, to give 0.113 g yellow solid. This material was treated with Grubbs catalyst 2nd generation (Aldrich; 0.050 g, 0.059 mmol), and 15 mL DCM. Argon was bubbled through the solution for 1 min, the reaction was sealed, and heated to 45 °C. After 1 h, the reaction was judged complete by LCMS and 1 g silica gel was added and the reaction concentrated in vacuo. The material was purified by silica gel chromatography (40 g column) using 0 - 70% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.091 g material that was further purified by chiral SFC (ADH (21x250 mm, 5 µ), 35% EtOH + 20 mM NH₃ in supercritical CO₂, Flow = 65 mL/min) to give

Second eluting peak - Example 35: (9R,11E,13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0-4.9-0-1 8.22-]tetracosa-
1(22),2(24).4,1 1,1,5,7,1 8,20,22-nonaen-6-one (0.071 g, 0.198 mmol, 66.4 % yield): 

$^1$H NMR (400 MHz, DMSO-$_d$_6) δ ppm 13.46 (1 H, br. s.), 7.96 (1 H, d, J=6.7 Hz), 7.59 (1 H, d., J=6.3 Hz), 7.48 - 7.54 (1 H, m), 7.30 (1 H, t, J=7.8 Hz), 7.01 (1 H, d, J=4.1 Hz), 6.86 (1 H, d., J=2.0 Hz), 6.25 (1 H, d, J=16.0 Hz), 5.77 - 5.95 (1 H, m), 4.28 (1 H, br. s.), 3.28 -
Example 36: (9R,11Z,13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.2.5-\ldots 0-4,9-\ldots 0-1 8,22-]tetracosa-
1(22),2(24),4,11,15,17,18,20,22-octaen-6-one.

Example 37: (9S)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1.2.5-\ldots 0-4,9-\ldots 0-18,22-]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-6-one.

(9S,11E)-16-Methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1.2.5-\ldots 0-4,9-\ldots 0-1
8,22-]tetracosa-
l(21),2(24),4,1
l(22),2(24),4,1,1,5,1,7,1,9,22-octan-6-one (Example 21; 0.021 g, 0.061 mmol) and
palladium hydroxide 10 wt. % (dry basis) on activated carbon, wet (Strem; 0.065 g) were
combined in a sealable vial and flushed with N\textsubscript{2}. 2 mL MeOH was added and the
atmosphere replaced with H\textsubscript{2} from a balloon. The reaction was stirred rapidly at RT.
After 1 h, the reaction was flushed with N\textsubscript{2}, filtered through a 0.45 µ syringe filter, rinsing
1 x MeOH, and concentrated down to a 2 mL volume. NaOH 1.0 N aqueous (VWR;
0.304 mL, 0.304 mmol) was added, the reaction was placed in a 60 °C bath, and H\textsubscript{2}O\textsubscript{2}
30% aqueous (Aldrich; 0.062 ml, 0.608 mmol) was added dropwise via syringe. After 30
min, a yellow precipitate had formed. The reaction was cooled and filtered, rinsing 2 x 1
mL MeOH, and the solid dried in vacuo to give (9S)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1.2.5-\ldots 0-4,9-\ldots 0-1
8,22-]tetracosa-
l(22),2(24),4,15,1,7,1,8,20,22-octan-6-one (0.005 g, 0.014 mmol, 23.67 % yield) a
yellow solid: \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \(\delta\) ppm 7.95 (1 H, d, \(J=7.4\) Hz), 7.83 (1 H, t, \(J=4.7\) Hz), 7.56 (1 H, d, \(J=8.0\) Hz), 7.33 (1 H, t, \(J=7.8\) Hz), 6.99 (1 H, d, \(J=4.1\) Hz), 6.90
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(1 H, s), 3.47 - 3.73 (1 H, m), 2.91 - 3.41 (4 H, m), 2.52 (3H, s), 2.02 - 2.18 (1 H, m), 1.55 - 1.99 (5 H, m). m/z (ESI, +ve) 348.0 (M+H)+.

Example 38: (9R)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one

Example 39: (9R,11E)-16-Methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one

Example 39: (9S,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one

Example 39: (9S,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one

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(9S, 11E, 13R)-13, 16-Dimethyl-3, 7, 14, 17, 23-pentaaza-
opentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-6-one (Example 31; 0.019 g, 0.053 mmol) and palladium hydroxide 10 wt. % (dry basis) on activated carbon, wet (Strem; 0.056 g) were combined in a vial and flushed with N2. 2 mL MeOH was added, and the atmosphere replaced with H2 from a balloon. After 3 h, the reaction was flushed with N2, and filtered through a 0.45 μ syringe filter, rinsing with MeOH, then concentrated down to 2 mL volume. NaOH 1 N volumetric solution (VWR; 0.264 ml, 0.264 mmol) was added and the reaction was heated to 60 °C. H2O2 30% in water (Aldrich; 0.027 ml, 0.264 mmol) was added dropwise via syringe. After 30 min, additional H2O2 30% in water (Aldrich; 0.027 ml, 0.264 mmol) was added. After 30 min additional H2O2 30% in water (Aldrich; 0.027 ml, 0.264 mmol) was added and the reaction stirred 10 min. The reaction was concentrated, and the residue taken up in 1.5 mL DMSO and several drops TFA were added to neutralize the NaOH. The solution was filtered through a 0.45 μ filter and was purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 10-70 % ACN/H2O with 0.1% TFA; product-containing fraction was treated with saturated aqueous NaHCO3 and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na2SO4, filtered, and concentrated in vacuo to give (9S,13R)-13,16-dimethyl-3,7,14,17,23-
opentaaza-pentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-6-one (0.004 g, 0.011 mmol, 20.94 % yield) as a yellow solid: H NMR (400 MHz, DMSO-d6) δ ppm 7.87 (1 H, dd, J=7.4, 1.0 Hz), 7.57 (1 H, dd, J=8.1, 1.1 Hz), 7.33 (1 H, t, J=7.8 Hz), 7.08 (1 H, d, J=5.3 Hz), 6.94 (1 H, d, J=4.1 Hz), 6.81 (1 H, d, J=1.8 Hz), 3.92 (1 H, br. s), 3.23 - 3.29 (1 H, m), 3.08 - 3.19 (1 H, m), 2.91 - 3.05 (1 H, m), 2.56 (3 H, s), 2.36 - 2.47 (1 H, m), 1.55 - 1.97 (4 H, m), 1.41 - 1.37 (4 H, m) m/z (ESI, +ve) 362.1 (M+H)+.
A suspension of (9S,11E,13S)-3,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-nonaen-6-one (950 mg, 2.64 mmol) and 10 wt% (dry basis) palladium, on activated carbon (wet, degussa type eOl ne/w) (Aldrich; 2813 mg, 1.322 mmol) in THF (55 mL) was stirred under a H₂ atmosphere (1 atm) at 55 °C for 17 h. The reaction flask was then flushed with argon, palladium, 10 wt% (dry basis), on activated carbon (wet, degussa type eOl ne/w) (1.97 g, 0.924 mmol) was added, and the resulting mixture was stirred under argon at 55 °C for 15 min. Additional Pd/C, 10 wt% (dry basis, wet, degussa type e1 Ol ne/w) (563 mg, 0.264 mmol) was added, and the resulting mixture was stirred under argon at 55 °C for 15 min. The reaction mixture was subsequently filtered through Celite, and the Celite pad was washed with (1:1) MeOH/DCM (100 mL). The combined filtrates were concentrated onto silica gel and chromatographically purified (silica gel, 0-10% MeOH/DCM) to provide (9S,13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one (430.0 mg, 1.190 mmol, 45% yield) as a yellow solid: ³¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.47 (1 H, br. s.), 8.01 (1 H, d, J=7.4 Hz), 7.57 (1 H, d, J=8.0 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.08 (1 H, d, J=4.5 Hz), 7.03 (1 H, d, J=4.1 Hz), 6.96 (1 H, d, J=4.1 Hz), 3.55 - 3.66 (1 H, m), 3.19 - 3.27 (1 H, m), 3.11 - 3.19 (1 H, m), 2.96 - 3.06 (1 H, m), 2.57 (3 H, s), 2.34 - 2.44 (1 H, m), 2.19 - 2.32 (1 H, m), 1.94 - 2.05 (1 H, m), 1.58 - 1.73 (1 H, m), 1.42 - 1.52 (1 H, m), 1.39 (3 H, d, J=6.5 Hz), 1.21 - 1.31 (1 H, m). m/z (ESI +ve) 362.1 (M+H)⁺.

Example 41: (9R,11E)-12,16-dimethyl-14-thia-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-nonanen-6-one
Step 1: (R)-7-allyl-2-(2-methyl-3-((2-methylallyl)thio)quinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one

A slurry of NaH as 60% dispersion in mineral oil (Sigma Aldrich, 137 mg, 3.43 mmol) in DMF (3.4 mL) was set stirring under N₂ before adding 2-methylprop-2-ene-1-thiol (Oakwood Products, West Columbia, SC, 302 mg, 3.43 mmol). After 15 min, a solution of (R)-4-allyl-6-(3-fluoro-2-methylquinoxalin-5-yl)-2,3,4,5-tetrahydro-1H-cyclopenta[c]pyridin-1-one (Intermediate E, 115 mg, 0.343 mmol) in 3 mL DMF was added, and the reaction was stirred for 3 h. The mixture was diluted with water and extracted with DCM, drying over Na₂SO₄, filtering, and concentrating under reduced pressure. The material was triturated with Et₂O to give a bright yellow solid. The material was sonicated with DCM and filtered using gravity to give a yellow solution that, when concentrated, gave (R)-7-allyl-2-(2-methyl-3-((2-methylallyl)thio)quinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (98 mg, 71%) as a yellow solid: 1H NMR (CDCl₃) δ: 7.91 - 7.99 (m, 1H), 7.81 - 7.87 (m, 1H), 7.65 - 7.75 (m, 1H), 6.93 - 7.04 (m, 2H), 5.80 - 5.97 (m, 1H), 5.06 - 5.16 (m, 2H), 4.97 - 5.02 (m, 1H), 4.84 - 4.91 (m, 1H), 4.04 - 4.24 (m, 2H), 3.44 - 3.52 (m, 1H), 3.17 - 3.25 (m, 1H), 3.02 - 3.12 (m, 1H), 2.67 - 2.71 (m, 1H), 2.65 (s, 3H), 2.26 - 2.37 (m, 2H), 1.83 (s, 3H). m/z (ESI, +ve) 405.2 (M+H)^+.

Step 2: (9R,1 IE)-12,16-dimethyl-14-thia-3, 7,17,23-tetraaza-pentacyclo[13.6.2.1^22.24^22]tetracosa-1(22),2(24),4,11,15,17,18,20,22-non-6-one

A solution of Grubbs catalyst 2nd generation (Sigma Aldrich, 50.4 mg, 0.059 mmol), (R)-7-allyl-2-(2-methyl-3-((2-methylallyl)thio)quinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (120 mg, 0.297 mmol), and DCM (5.9 mL) was set stirring at 65°C for 1.5 h. The reaction was concentrated under reduced pressure before being solubilized in DMSO and purified by reverse-phase preparative HPLC. The product fractions were concentrated in a Genevac EZ-2 evaporator at 55°C over night. The dried fractions were solubilized in 10:1 MeOFL/DCM (5 mL) and percolated through a Silicycle Si-carbonate...
cartridge (pre-washed with MeOH). The resulting yellow solution was transferred to a round bottom flask and concentrated under reduced pressure to a yellow residue that was dried further under high vacuum to afford (9R,11E)-12,16-dimethyl-14-thia-3,7,17,23-tetraazapentacyclo[13.6.2.1\(2\),5\(0\),4,9\(0\),18,22\(0\)]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (0.015 g, 13% yield) as a yellow solid: \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 12.37 (br. s, 1H), 8.02 - 8.10 (m, 1H), 7.74 - 7.79 (m, 1H), 7.56 - 7.65 (m, 1H), 7.18 - 7.26 (m, 1H), 7.10 - 7.17 (m, 1H), 5.78 - 5.87 (m, 1H), 4.16 - 4.28 (m, 1H), 3.74 - 3.85 (m, 1H), 3.52 - 3.64 (m, 1H), 3.37 - 3.48 (m, 2H), 2.76 (s, 3H), 2.40 - 2.66 (m, 2H), 1.92 (s, 3H). m/z (ESI, +ve) 377.1 (M+H)+.

Example 42: (HE)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1\(2\),5\(0\),4,9\(0\),18,22\(0\)]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: tert-butyl 5-(2-methylallyl)-2,4-dioxopiperidine-1-carboxylate

To a solution of 3-bromo-2-methylpropene (Aldrich; 3.78 ml, 37.5 mmol) and 1-boc-piperidine-2,4-dione (Ark Pharma, Libertyville, IL; 2.00 g, 9.38 mmol) in 80 mL THF at 17 °C (ice/salt) was added LiHMDS, 1.0 M solution in THF (Aldrich; 23.45 ml, 23.45 mmol) slowly via syringe over 10 min. The reaction became thick with a precipitate that dissolved upon complete addition of LiHMDS. After 45 min, water and DCM were added, and the aqueous layer was acidified with 5 N HCl. The aqueous layer was extracted with DCM 2 times, and the combined organics were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The material was treated with DCM and...
purified by silica gel chromatography (80 g column) using 0 - 60% EtOAc/hexane. The product-containing fractions were concentrated to afford tert-butyl 5-(2-methylallyl)-2,4-dioxopiperidine-1-carboxylate (2.0 g, 7.48 mmol, 80 % yield) as a light yellow oil: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.23 (1 H, br. s.), 4.92 (1 H, s), 4.85 (1 H, br. s.), 4.68 (1 H, s), 3.73 (1 H, dd, $J$=13.1, 3.1 Hz), 3.50 (1 H, dd, $J$=12.9, 3.9 Hz), 2.53 - 2.59 (1 H, m), 2.25 - 2.34 (1 H, m), 2.01 - 2.11 (1 H, m), 1.71 (3 H, s), 1.42 (9 H, s).

Step 2: 2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

Tert-butyl 5-(2-methylallyl)-2,4-dioxopiperidine-1-carboxylate (1.95 g, 7.29 mmol) in 36 mL DCM at 0 °C was treated with TFA (Aldrich; 2.71 ml, 36.5 mmol). The ice bath was removed and the reaction stirred for 30 min. The reaction was concentrated in vacuo to give an oil. The material was treated with 10 mL DCM and an excess of solid NaHCO$_3$ and stirred rapidly for 10 min. The reaction was filtered, rinsing with DCM, and concentrated in vacuo to give 1.4 g of an oil. This material was treated with 2-bromo-1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (1.45 g, 5.12 mmol), and NH$_4$OAc (Fisher, 2.369 g, 30.7 mmol), and 50 mL EtOH, the reaction was sealed, and placed in a 50 °C bath. The reaction became orange and homogeneous. After 4 h, the reaction was heterogeneous. The reaction was concentrated to 1/4 volume and partitioned between saturated aqueous NaHCO$_3$ and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was adsorbed onto 10 g silica gel from DCM and dried, and purified by silica gel chromatography (80 g column) using 0 - 70% 90/10 DCM/MeOH in DCM. Product-containing fractions were concentrated to give 0.88 g of a red semisolid. This material was treated with 5 mL Et$_2$O, sonicated 20 min, then filtered, rinsing 2 x 1 mL Et$_2$O, the solid was collected and dried in vacuo to give 2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.474 g, 1.353 mmol, 26.4 % yield) as an orange solid: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.61 (1 H, br. s.), 8.09 (1 H, d, $J$=7.4 Hz), 7.87 - 7.99 (1 H, m), 7.72 - 7.87 (1 H, m), 7.20 (1 H, d, $J$=2.2 Hz), 7.02 (1 H, br. s.), 4.93 (1 H, s), 4.84 (1 H, s), 3.38 - 3.52 (1 H, m), 3.12 - 3.28 (2 H, m), 2.71 (3 H, s), 2.45 (1 H, dd, $J$=13.8, 5.0 Hz), 2.28 (1 H, dd, $J$=13.8, 9.3 Hz), 1.82 (3 H, s)). m/z (ESI, +ve) 351.0 (M+H)$^+$. 

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Step 3: 2-(3-(allylamino)-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

2-(3-Fluoro-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.214 g, 0.611 mmol) was treated with allylamine (Aldrich; 4.12 ml, 55.0 mmol) and a stir bar and sealed and stirred rapidly for 4 h. The reaction was partitioned between saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted with DCM 2x, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The solid was suspended in MeOH and filtered, rinsing 1 x MeOH, and the solid dried in vacuo to give 2-(3-(allylamino)-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.170 g, 0.439 mmol) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 12.03 (1 H, s), 7.91 (1 H, d, J=7.6 Hz), 7.51 - 7.63 (2 H, m), 7.33 (1 H, t, J=7.8 Hz), 7.03 (1 H, d, J=2.0 Hz), 6.92 (1 H, br. s.), 6.01 - 6.21 (1 H, m), 5.29 (1 H, dd, J=17.2, 1.4 Hz), 5.17 (1 H, d,J=10.4 Hz), 4.88 (1 H, s), 4.78 (1 H, s), 4.18 (2 H, br. s.), 3.38 - 3.51 (1 H, m), 3.07 - 3.23 (2 H, m), 2.57 (3 H, s), 2.20 - 2.43 (2 H, m), 1.78 (3 H, s). m/z (ESI, +ve) 388.1 (M+H)⁺.

Step 4: (1E)-1,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1²,5.0⁴,9.0¹⁸,22]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonahex-6-one

Argon was bubbled through a slurry of Grubbs catalyst 2nd generation (Aldrich; 0.055 g, 0.065 mmol) and 2-(3-(allylamino)-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.125 g, 0.323 mmol) in 16 mL DCM for 2 min. The reaction was sealed with a cap and parafilm and placed in a 45 °C bath and heated overnight. The reaction was charged with fresh catalyst (Grubbs catalyst 2nd generation (Aldrich; 0.055 g, 0.065 mmol)) and fitted with a water-cooled reflux condenser and heated to reflux. After 8 h, the reaction was cooled, treated with 2 mL MeOH and adsorbed onto 2 g silica gel and dried. The material was purified by silica gel chromatography (40 g column) using 0 - 60% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.009 g of impure material. Additional material was obtained from the following reaction: Argon was bubbled through a slurry of Grubbs catalyst 2nd generation (0.074 g, 0.088 mmol) and 2-(3-(allylamino)-2-methylquinoxalin-5-yl)-7-(2-methylallyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Aldrich; 0.170 g, 0.439 mmol) in 22 mL DCE for 60 sec. The reaction was sealed and
heated to 80 °C. After 2 h, additional Grubbs catalyst 2nd generation (Aldrich; 0.150 g, 0.176 mmol) was added, and heating was continued for 1 h. The bath was turned off and cooled slowly to RT. The reaction was stirred overnight. The reaction was adsorbed onto 1.5 g silica gel and dried in vacuo. Purified by silica gel chromatography (40 g redisep gold column) using 0 - 100% 90/1 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 59 mg impure product-containing material. This was combined with the 0.009 g impure material isolated in the prior reaction, and the combined materials were dissolved in DMSO and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 15-85 % ACN/H2O with 0.1% TFA; product-containing fractions were treated with saturated aqueous NaHCO3 and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na2SO4, filtered, and concentrated in vacuo to give (HE)-l 1.16-dimethyl-3,7,14,17,23-

tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~.0~22~]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (0.010 g, 0.028 mmol, 3% yield) as a yellow solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 13.47 (1 H, br. s.), 7.97 (1 H, d, 

$J=7.4$ Hz), 7.63 (1 H, d, $J=5.3$ Hz), 7.53 (1 H, d, $J=7.8$ Hz), 7.31 (1 H, d, $J=15.5$ Hz), 7.06 (1 H, d, $J=4.1$ Hz), 6.88 (1 H, s), 5.70 (1 H, d, $J=6.7$ Hz), 3.95 - 4.21 (2 H, m), 3.26 - 3.47 (2 H, m), 3.01 - 3.15 (1 H, m), 2.55 (3 H, s), 2.53-2.46 (1 H, m), 2.23 - 2.32 (1 H, m), 1.82 (3 H, s). m/z (ESI, +ve) 360.2 (M+H)+.

Example 43: (9S,11E)-12,16-dimethyl-14-thia-3,7,17,23-

tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~.0~22~]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: (S)-7-allyl-2-(2-methyl-3-((2-methylallyl)thio)quinoxalin-5-yl)-6,7-dihydro-1H-

pyrrolo[3,2-c]pyridin-4(5H)-one

A slurry of NaH as a 60% dispersion in mineral oil (Sigma Aldrich. 119 mg, 2.97 mmol) was set stirring in DMF (2.9 mL) at RT under N2. Methallyl mercaptan was added (Oakwood Scientific, 262 µL, 2.97 mmol), and the mixture was set stirring for 30 min.
Solid (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 100 mg, 0.297 mmol) was added, and the resulting reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with water and extracted with DCM. The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was triturated with Et$_2$O and sonicated for 5 minutes to give a solid that was isolated by filtration and used in the next step without further purification. m/z (ESI, +ve) 405.2 (M+H)$^+$.  

Step 2: (9S,1lE)-12,16-dimethyl-14-thia-3,7,17,23-tetraazapentacyclo[13.6.2.1-2,5.0-4,9.0-18,22]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one  
A solution of (S)-7-allyl-2-(2-methyl-3-((2-methylallyl)thio)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (40 mg, 0.099 mmol), Grubbs 2nd generation catalyst (Sigma Aldrich; 16.79 mg, 0.020 mmol), and DCM (2 mL) was set stirring at 65°C for 1.5 h. The reaction was concentrated under reduced pressure, diluted with DMSO, and purified by reverse-phase preparative HPLC (Phenomenex Gemini column, 10 µ, C$_{18}$, 100 A, 150 x 30 mm, 0.1% TFA in ACN/water, gradient 5% to 95%). The product fractions were concentrated in a Genevac EZ-2 evaporator at 55°C. The dried fractions were solubilized in 10:1 MeOH:DCM (5 mL) and filtered through a Silicycle Si-carbonate cartridge (pre-washed within MeOH). The filtrate was concentrated under reduced pressure to give (9S,1lE)-12,16-dimethyl-14-thia-3,7,17,23-tetraazapentacyclo[13.6.2.1-2,5.0-4,9.0-18,22]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (23 mg, 22%, 2 steps): $\frac{3}{4}$ NMR (DMSO-de) δ: 12.08 - 12.22 (m, 1H), 8.19 - 8.27 (m, 1H), 7.70 - 7.78 (m, 1H), 7.57 - 7.69 (m, 1H), 7.05 - 7.18 (m, 2H), 5.86 - 5.98 (m, 1H), 4.23 - 4.36 (m, 1H), 3.94 - 4.10 (m, 1H), 3.33 - 3.45 (m, 2H), 3.17 - 3.28 (m, 2H), 2.69 (s, 3H), 2.36 - 2.47 (m, 1H), 1.83 (s, 3H); m/z (ESI, +ve) 377.1 (M+H)$^+$.  

**Example 44:** (HE)-12,16-dimethyl-4,7,14,17,23-pentaazapentacyclo[13.6.1.1-2,5.0-4,9.0-18,22]tetracosa-l(21),2,5(24),ll,15,17,19,22-octaen-6-one
Step 1: 7-bromo-4-(2-hydroxyethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

Ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate

(Intermediate J; 1.23 g, 4.08 mmol) was treated with THF (30 mL), cooled to 0 °C and treated with lithium aluminum hydride, 1.OM solution in THF (4.08 mL, 4.08 mmol) and stirred at 0 °C for 30 min. The reaction mixture was quenched by slow dropwise addition of an aqueous solution of sodium potassium tartrate and stirred at RT for 30 min. The reaction mixture was extracted with EtOAc (3 x 25 mL), washed with brine and dried over MgSO₄, filtered and concentrated affording crude 7-bromo-4-(2-hydroxyethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (987 mg, 3.81 mmol, 93 % yield) as a white crystalline solid: ¹H NMR (400 MHz, MeOH-d₄) δ ppm 7.10 (1 H, s), 6.83 (1 H, s), 4.47 (1 H, tt, J=7.1, 3.7 Hz), 3.85 (1 H, dd, J=13.2, 4.2 Hz), 3.68 (1 H, dt, J=1.2, 5.6 Hz), 3.46 - 3.56 (2 H, m), 1.91 - 2.07 (2 H, m). m/z (ESI, +ve ion) 259.0/261.0 (M+H)⁺.

Step 2: 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetaldehyde

7-Bromo-4-(2-hydroxyethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (908 mg, 3.50 mmol) and Dess-Martin periodinane (1.86 g, 4.38 mmol) were treated with DCM (20 mL) and found to be insoluble so it was treated with THF (10 mL) and stirred at RT overnight (16 h). LC-MS showed little advancement of the reaction. Additional Dess-Martin periodinane (1.00 g, 2.35 mmol) was added and the solution heated to reflux at 70 °C for 2.5 h. The reaction mixture was cooled to RT, treated with water and EtOAc (100 mL) and washed with sodium thiosulfate (2 x 25 mL) and NaHCO₃ (2 x 25 mL) and brine. The aqueous layer was back extracted with DCM (3 x 50 mL) and the combined organic extracts were dried over MgSO₄, filtered and concentrated affording crude 2-(7-bromo-1 -
A-1700-WO-PCT

oxo-1,2,3,4-tetrahydropyrrolo[1',2-a]pyrazin-4-yl)acetaldehyde (788 mg, 3.07 mmol, 87% yield) as a yellow foam which was used in the subsequent step without further purification: \[ ^1H \text{NMR} (400 \text{ MHz}, DMSO-d_6) \delta \text{ppm} 9.68 (1 \text{ H, s}), 7.78 (1 \text{ H, br. s}), 7.16 (1 \text{ H, d, } J=1.6 \text{ Hz}), 6.67 (1 \text{ H, d, } J=1.6 \text{ Hz}), 4.74 (1 \text{ H, t, } J=4.7 \text{ Hz}), 3.65 (1 \text{ H, ddd, } J=13.1, 4.1, 2.0 \text{ Hz}), 3.26 - 3.31 (1 \text{ H, m}), 3.01 (2 \text{ H, d, } J=6.5 \text{ Hz}). m/z (ESI, +ve ion) 257.0/259.0 (M+H)^+.

Step 3: 4-allyl-7-bromo-3,4-dihydropyrrolo[1,2-a]pyrazin-1 (2H)-one
Methyl triphenylphosphonium bromide (1.54 g, 4.31 mmol) in THF (20 mL) was cooled to 0 °C and treated with LiHMDS, 1.0M solution in THF (4.31 mL, 4.31 mmol) slowly dropwise resulting in a bright yellow solution. The solution was stirred for 30 min then 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetaldehyde (554 mg, 2.155 mmol) in THF (5 mL) was added and the solution stirred at 0 °C for 1 h. The reaction mixture was quenched with water and extracted with EtOAc (2 x 50 mL), washed with brine and dried over MgSO₄, filtered and concentrated. Purification on the ISCO Combiflash Rf (40 g Thomson SingleStep column, using a gradient of 0-100% EtOAc in hexanes) afforded 4-allyl-7-bromo-3,4-dihydropyrrolo[1',2-a]pyrazin-1(2H)-one (97.2 mg, 0.381 mmol, 17.7 % yield) as a light yellow film: \[ ^1H \text{NMR} (400 \text{ MHz}, CDCl}_3) \delta \text{ppm} 7.13 (1 \text{ H, br. s}), 6.91 (1 \text{ H, d, } J=1.6 \text{ Hz}), 6.83 (1 \text{ H, d, } J=1.8 \text{ Hz}), 5.74 (1 \text{ H, ddt, } J=17.1, 10.0, 7.1, 7.1 \text{ Hz}), 5.10 - 5.23 (2 \text{ H, m}), 4.09 - 4.20 (1 \text{ H, m}), 3.76 (1 \text{ H, ddd, } J=12.9, 4.2, 2.0 \text{ Hz}), 3.42 - 3.52 (1 \text{ H, m}), 2.59 - 2.69 (1 \text{ H, m}), 2.48 - 2.59 (1 \text{ H, m}). m/z (ESI, +ve ion) 255.0/257.0 (M+H)^+.

Step 4: 4-allyl-7-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-3,4-
dihydropyrrolo[1,2-a]pyrazin-1(2H)-one
A 5-mL glass microwave tube was charged with 4-allyl-7-bromo-3,4-dihydropyrrolo[1,2-a]pyrazin-1 (2H)-one (97 mg, 0.380 mmol), dicyclohexyl[2',4',6'-trisopropyl-[1',1'-biphenyl]-2-yl]phosphine (Strem Chemicals, 10.9 mg, 0.023 mmol), Pd₂dba₃ (Strem Chemicals, 10.5 mg, 0.011 mmol), potassium phosphate (Riedel de Haen, Buchs, Switzerland, 242 mg, 1.14 mmol) and 3-methyl-N-(2-methylallyl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-amine (Intermediate 1, 155 mg, 0.456 mmol). The solids were purged with argon and treated with 1,4-dioxane (2.5 mL) and water (0.83 mL) and heated in a microwave reactor at 130 °C for 20 min. The reaction mixture was treated with water, extracted with EtOAc, washed with brine and concentrated.
Purification on the ISCO Combiflash Rf (25 g Thomson SingleStep column, using a gradient of 20-100% EtOAc in hexanes) afforded 4-allyl-7-(2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (57.9 mg, 0.149 mmol, 79% yield) as a light yellow amorphous solid: $^1$H NMR (400 MHz, MeOH-d$_4$) δ ppm 8.07 (1 H, d, $J$=1.4 Hz), 7.81 (1 H, d, $J$=7.4 Hz), 7.63 (1 H, d, $J$=8.0 Hz), 7.47 - 7.51 (1 H, m), 7.32 - 7.39 (1 H, m), 5.83 - 5.96 (1 H, m), 5.21 (1 H, d, $J$=7.8 Hz), 5.17 (1 H, s), 4.96 (2 H, br. s.), 4.34 - 4.42 (1 H, m), 4.15 - 4.28 (2 H, m), 3.83 (1 H, dd, $J$=13.1, 4.3 Hz), 3.55 (1 H, dd, $J$=13.0, 3.8 Hz), 2.63 - 2.76 (2 H, m), 2.61 (3 H, s). m/z (ESI, $^{+}$ve ion) 388.1 (M+H)$^+$.  

Step 5: (11E)-1,2,1 6-dimethyl-4,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2,5(24),11,15,17,19,22-octaen-6-one afforded (11E)-12,1 6-dimethyl-4,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2,5(24),11,15,17,19,22-octaen-6-one as its mono-2,2,2-trifluoroacetate salt (4.4 mg, 9.3 µmol, 6.8% yield) as an orange amorphous solid after drying in a Genevac Series II evaporator overnight. $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.47 - 7.64 (4 H, m), 7.27 - 7.35 (1 H, m), 7.08 - 7.22 (1 H, m), 6.75 (1 H, s), 5.41 (1 H, br. s.), 4.40 (1 H, br. s.), 3.70 (1 H, d, $J$=11.0 Hz), 3.49 (1 H, d, $J$=11.1, 6.9 Hz), 2.68 (1 H, br. s.), 2.52 (3 H, br. s.), 2.40 - 2.49 (1 H, m), 1.37 (3 H, br. s.). m/z (ESI, $^{+}$ve ion) 360.2 (M+H)$^+$. 

Example 45: (9S, 13R)-ll,12-dihydroxy-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one
A cloudy mixture of (9S,11E,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (Example 31; 0.050 g, 0.139 mmol) and NMO (Aldrich; 0.049 g, 0.417 mmol) and methanesulfonamide (TCI America; 0.013 g, 0.139 mmol) in 2 mL acetone, 0.5 mL THF, and 0.4 mL water was treated with osmium tetroxide 4 wt% in water (Aldrich; 0.088 ml, 0.014 mmol). The reaction was sealed and stirred rapidly at RT. After 12 h, observe 15% conversion. Additional osmium tetroxide 4 wt% in water (Aldrich, 0.088 ml, 0.014 mmol) was added and the reaction stirred over the weekend. The reaction was concentrated to ~1/4 original volume; this material was dissolved in DMSO, filtered, and purified by RPHPLC, Phenomenex Gemini 150x30 mm Ci8 column, 5-50% ACN/H₂O with 0.1% TFA; product-containing fractions were treated with saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted 3 x DCM and combined organics dried over Na₂SO₄, filtered, and concentrated in vacuo to give a single Cn,Ci₂ isomer (9S,13R)-1,12-dihydroxy-1,3,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-1(22),2(24),4,11,15,17,18,20,22-octaen-6-one (0.006 g, 0.015 mmol, 10.96 % yield) as an orange solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.84 (1 H, d, J=7.4 Hz), 7.54 (1 H, d, J=7.8 Hz), 7.31 (1 H, t, J=7.8 Hz), 6.80 - 6.95 (2 H, m), 6.75 (1 H, s), 5.08 (1 H, d, J=5.1 Hz), 4.96 (1 H, br. s.), 4.44 (1 H, br. s.), 3.97 - 4.09 (1 H, m), 3.09 - 3.41 (3 H, m), 2.57 (3 H, s), 2.03 - 2.16 (1 H, m), 1.54 (1 H, dd, J=14.3, 5.5 Hz), 1.38 (3 H, d, J=6.8 Hz). m/z (ESI, +ve) 394.1 (M+H)⁺.

Example 46: 17-methyl-3,7,15,18,24-pentaazaheptacyclo[14.6.2.2^11,14.1^2,5.0^4,9.0^19,23]heptacosa-1(23),2(27),4,11,13,16,18,19,21,23,25-undecaen-6-one
Step 1: tert-butyl 5-(4-chlorobenzyl)-2,4-dioxopiperidine-1-carboxylate
4-Chlorobenzyl chloride (Fluka Chemie GmbH; 6.04 g, 37.5 mmol) and 1-boc-piperidine-2,4-dione (Ark Pharma, Libertyville, IL; 2.00 g, 9.38 mmol) were combined in 75 mL THF under N₂ and were cooled in an ice/salt bath. LiHMDS, 1.0 M solution in THF (Aldrich, 23.45 ml, 23.45 mmol) was added slowly dropwise via syringe. After addition of about 5-10 mL, a thick solid formed, which disappeared as additional LiHMDS was added. The reaction was stirred for 15 min. The reaction was stirred for an additional 15 min, then quenched with water, DCM was added, and the aqueous phase was acidified with 5 N HCl. The aqueous layer was extracted 3 x DCM. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (160 g column) using 0 - 100% EtOAc/DCM. The product-containing fractions were concentrated to afford tert-butyl 5-(4-chlorobenzyl)-2,4-dioxopiperidine-1-carboxylate (2.30 g, 6.81 mmol, 72.6 % yield) as a white foam: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.31 (1 H, br. s.), 7.37 (2 H, d, J=8.4 Hz), 7.21 (2 H, d, J=8.2 Hz), 4.95 (1 H, s), 3.52 - 3.64 (1 H, m), 3.40 - 3.51 (1 H, m), 2.98 (1 H, d, J=10.4 Hz), 2.53 - 2.72 (2 H, m), 1.42 (9 H, br. s.).

Step 2: 7-(4-chlorobenzyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5 H)-one
TFA (2.53 ml, 34.0 mmol) was added to a stirring solution of tert-butyl 5-(4-chlorobenzyl)-2,4-dioxopiperidine-1-carboxylate (2.30 g, 6.81 mmol) in 20 mL DCM. Gas evolution observed. After 30 min, the reaction was concentrated in vacuo and the resulting off-white solid was treated with NH₄OAc (Fisher Scientific, 2.178 g, 28.3 mmol), 2-bromo-l-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (1.00 g, 3.53 mmol), and
35 mL EtOH under N₂. The reaction was sealed and heated to 50 °C for 6 h. The reaction was partitioned between saturated aqueous NaHCO₃ and DCM. The aqueous layer was extracted with DCM 3 times, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and adsorbed onto 10 g silica gel, dried, and purified by silica gel chromatography (80 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 7-(4-chlorobenzyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.630 g, 1.497 mmol, 42.4 % yield) as an orange foam: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.59 (1 H, br. s.), 8.07 (1 H, d, J=7.4 Hz), 7.88 - 7.97 (1 H, m), 7.77 - 7.87 (1 H, m), 7.37 - 7.43 (2 H, m), 7.30 (2 H, d, J=8.2 Hz), 7.21 (1 H, d, J=2.0 Hz), 6.97 (1 H, br. s.), 3.3 - 3.39 (1 H, m), 3.24 - 3.29 (1 H, m), 3.05 - 3.15 (2 H, m), 2.79 (1 H, dd, J=13.4, 10.1 Hz), 2.72 (3 H, s). m/z (ESI, +ve) 421.1 (M+H)+.

Step 3: 2-(3-amino-2-methylquinoxalin-5-yl)-7-(4-chlorobenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A slurry of 7-(4-chlorobenzyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.270 g, 0.642 mmol) in NH₃, 2 M solution in 2-propanol (Aldrich, 6.42 ml, 12.83 mmol) was sealed and heated to 70 °C overnight. The reaction was adsorbed onto 2 g silica gel from DCM and dried in vacuo. Purified by silica gel chromatography (40 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 2-(3-amino-2-methylquinoxalin-5-yl)-7-(4-chlorobenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.103 g, 0.246 mmol, 38.4 % yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.34 (1 H, s), 7.91 (1 H, d, J=7.6 Hz), 7.56 (1 H, d, J=7.4 Hz), 7.21 - 7.45 (5 H, m), 7.09 (2 H, br. s.), 7.00 (1 H, d, J=1.8 Hz), 6.90 (1 H, br. s.), 3.31 - 3.39 (2 H, m), 3.17 (1 H, dd, J=13.4, 4.4 Hz), 3.09 (1 H, dd, J=8.3, 3.6 Hz), 2.77 (1 H, dd, J=13.2, 10.3 Hz), 2.53 (3 H, s). m/z (ESI, +ve) 418.1 (M+H)+.

Step 4: 17-methyl-3,7,15,18,24-pentaazahexacyclo[14.6.2.2-1,14-1-2,5-0-4,9-0-19,23-]heptacosa-
(l23),2(27),4,11,3,1,6,1,8,19,2,1,23,25-undecaen-6-one

Argon was bubbled through a slurry of potassium carbonate (0.111 g, 0.804 mmol) (finely ground in a mortar and pestle), Brettphos precatalyst (Strem; 0.048 g, 0.060
mmol), Brettphos (Strem; 0.032 g, 0.060 mmol), and 2-(3-amino-2-methylquinazolin-5-yl)-7-(4-chlorobenzyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.084 g, 0.201 mmol) in 12 mL t-butanol for 1 min. The reaction was sealed and heated to 110 °C overnight. The reaction was partitioned between water and DCM and the aqueous layer was extracted 4 x DCM. The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. This material was dissolved in DMSO, filtered, and purified by RPHPLC, Phenomenex Gemini 150x30 mm C18 column, 10-80% ACN/H₂O with 0.1% TFA; product-containing fractions were concentrated in vacuo to give 0.015 g of a red film. The material was further purified by SFC (Column: Chiralcel OD-H (Sepax) (250 x 21 mm, 5 µ); Mobile Phase: 60:40 (A:B); A: Liquid CO₂, B: EtOH (0.2% DEA); Flow Rate: 70 mL/min; Oven Temp: 40 °C; Inlet Pressure: 100 bar). The product containing fractions were combined to give 17-methyl-3,7,15,17,23-pentaaza-hexacyclo[14.6.2.2~11,1~4,9~12,5~04,9~19,23~0]heptacosa-l(23),2(27),4,1,1,3,1,6,1,8,1,9,2,1,23,25-undecaen-6-one (0.0024 g, 0.006 mmol, 3.1% yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.34 (1 H, s), 8.95 (1 H, s), 7.84 (1 H, d, J=7.2 Hz), 7.72 (1 H, d, J=8.4 Hz), 7.57 (1 H, d, J=8.0 Hz), 7.24 - 7.40 (3 H, m), 7.10 (1 H, br. s.), 7.04 (1 H, d, J=6.3 Hz), 6.79 (1 H, s), 3.53 - 3.64 (1 H, m), 3.34 - 3.47 (3 H, m), 2.59 - 2.72 (4 H, m). m/z (ESI, +ve) 382.1 (M+H)⁺.

Example 47: (9R,llE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~04,9~018,22~0]tetracosa-l(22),2(24),4,(ll,15,17,18,20,22-nonaen-6-one

Example 48: (9R,llZ)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~04,9~018,22~0]tetracosa-l(22),2(24),4,(ll,15,17,18,20,22-nonaen-6-one
A-1700-WO-PCT

Step 1: (R)-7-allyl-2-(3-(allyl(methyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo [3,2-c]pyridin-4(5 H)-one

A solution of N-methylallylamine (Sigma Aldrich, 21 µL, 0.297 mmol), (R)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro- lH-pyrrolo [3,2-c]pyridin-4(5H)-one (Intermediate E, 100 mg, 0.297 mmol), and DMSO (3.0 mL) was sealed and heated to 100 °C for 1.5 h. The reaction was cooled to RT and diluted with water and saturated aqueous NaCl. The crude mixture was extracted with DCM (3x15 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a bright yellow solid that was used without purification: m/z (ESI, +ve) 388.3 (M+H)⁺.

Step 2: (9R,1 IE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1.2.1.1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

A solution of (R)-7-allyl-2-(3-(allyl(methyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (85 mg, 0.219 mmol) in DCM (Sigma Aldrich, 4.4 mL) was set stirring before adding Grubbs catalyst 2nd generation (Sigma Aldrich, 186 mg, 0.219 mmol) and heating to 65 °C for 2 h. The reaction was cooled and concentrated onto silica gel and purified by silica gel chromatography (eluent: 0 to 6% MeOH/DCM), giving a single peak. The material was further purified by preparative SFC (solubilized in 1:1 MeOH at 4 mg/mL, 292 nm, Phenomenex, Lux-1, repack-S/N=1204 ODH Column, 5 urn at 21x150 mm length, 60% CO₂ with IPA/40 mM NH₃, P = 186 bar at 1 mL/min) to give (9R,1 IE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1.2.1.1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Analytical data for (9R,1 IE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1.2.1.1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one: ¹H NMR (400 MHz, DMSO-δ₆) δ ppm 13.24 - 13.45 (1 H, m) 7.98 - 8.08 (1 H, m) 7.71 - 7.82 (1 H, m) 7.50 - 7.61 (1 H, m) 7.11 - 7.22 (1 H, m)
A-1700-WO-PCT

- 7.19 (1 H, m) 6.39 - 6.41 (1 H, m) 5.86 - 6.12 (1 H, m) 4.37 - 4.51 (1 H, m) 4.05 - 4.17 (1 H, m) 3.56 - 3.63 (2 H, m) 3.41 - 3.55 (2 H, m) 3.25 (3 H, s) 2.89 (3 H, s) 2.68 - 2.76 (1 H, s) 2.31 - 2.45 (1 H, m). m/z (ESI, +ve) 360.2 (M+H)+.

Analytical data for (9R,11Z)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,13,17,18,20,22-nonaen-6-one:

NMR (400 MHz, DMSO-d6) δ ppm
13.15 - 13.28 (1 H, m) 7.88 - 7.94 (1 H, m) 7.70 - 7.84 (1 H, m) 7.48 - 7.56 (1 H, m) 6.99 - 7.03 (1 H, m) 5.84 - 5.96 (2H, m) 4.86 - 4.95 (1H, m) 3.71 - 3.82 (1H, m) 3.50 - 3.65 (3H, m) 3.35 - 3.49 (4 H, m) 2.86 - 2.93 (3H, m) 2.69 - 2.84 (1 H, m) 2.24 - 2.36 (1 H, m): m/z (ESI, +ve) 360.2 (M+H)+.

Example 49: 16-methyl-4,7,12,17,23-pentaazapentacyclo[13.6.2.1--2,5--0--4,9--0--18,22--]tetracosa-1(21),2,5(24),15,17,19,22-heptaene-6,11-dione

Step 1: tert-butyl (2-(8-bromo-3-methylquinoxalin-2-yl)ethyl)carbamate

A mixture of PdCl2(PPh3)2 (Aldrich, 15.9 mg, 0.019 mmol), cesium carbonate (Aldrich, 380 mg, 1.165 mmol), potassium tert-butyl N-[2-(trifluoroboranuinydyl)ethyl] carbamate (Frontier Scientific, Newark, DE, 102 mg, 0.408 mmol) and 5-bromo-3-chloro-2-methylquinoxaline (100 mg, 0.388 mmol) in toluene (1.2 mL), dioxane (0.6 mL) and water (0.4 mL) was heated in an oil bath at 85 °C for 18 h (reference, see: Molander, G. A. et al. Org. Lett. 2007, 9, 203-206). The resulting mixture of products was purified on a ISCO Companion (12 g Redisep column, using a gradient 10-35% EtOAc in hexanes)
affording tert-butyl (2-(8-bromo-3-methylquinoxalin-2-yl)ethyl)carbamate (25 mg, 0.068 mmol, 17.58 % yield) as a brown solid, m/z (ESI, +ve ion) 366.0/368.0 (M+H)^+.

Step 2: ethyl 2-(7-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate
A mixture of tert-butyl (2-(8-bromo-3-methylquinoxalin-2-yl)ethyl)carbamate (88 mg, 0.240 mmol), bis(pinacolato)diboron (Aldrich, 122 mg, 0.481 mmol), KOAc (Aldrich, 94 mg, 0.961 mmol) and PdCl_2(PPh_3)_2 (Aldrich, 9.8 mg, 0.012 mmol) in DMF (1.5 mL) was heated at 105 °C for 2 h. The reaction mixture was diluted with 50 mL of EtOAc, washed with water (2 x 15 mL). The organic layer was dried over MgSO_4 and concentrated to give the crude product as a gooey black solid. The crude material was treated with ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (Intermediate J, 87 mg, 0.290 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,l'-biphenyl]-2-yl)phosphine (Strem Chemicals, 6.9 mg, 0.014 mmol), Pd(OAc)_2 (Strem Chemicals, 6.6 mg, 7.25 μmol), potassium phosphate (Riedel de Haen, Buchs, Switzerland, 154 mg, 0.725 mmol) in a 20-mL glass microwave tube, purged with argon and treated with dioxane (2.50 mL) and water (0.83 mL) and heated in a microwave reactor at 130 °C for 25 min. The reaction mixture was treated with water, extracted with EtOAc, washed with brine and concentrated. Purification of the crude residue on the ISCO CombiFlash RF (25 g Thomson SingleStep column, using a gradient of 20-100% EtOAc in hexanes) afforded ethyl 2-(7-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (40 mg, 0.079 mmol, 32.6 % yield) as a white amorphous solid: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.97 (1 H, br. s.), 7.86 (2 H, d, J=7.8 Hz), 7.65 - 7.71 (1 H, m), 7.48 - 7.53 (1 H, m), 5.51 (1 H, br. s.), 5.23 (1 H, s), 4.84 (1 H, br. s.), 4.10 - 4.25 (2 H, m), 3.98 - 4.05 (1 H, m), 3.81 (2 H, br. s.), 3.60 (1 H, d, J=12.9 Hz), 3.23 (2 H, t, J=6.3 Hz), 2.97 (2 H, d, J=6.8 Hz), 2.76 (3 H, s), 1.35 (9 H, s), 1.21 - 1.28 (3 H, m). m/z (ESI, +ve ion) 508.1 (M+H)^+.

Step 3: 2-(7-(3-(2-aminoethyl)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetic acid hydrochloride
Ethyl 2-(7-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (26.7 mg, 0.053 mmol) was treated with THF (0.5 mL) and EtOH (0.5 mL) then with 1N NaOH (0.4 mL, 0.40 mmol) and stirred at RT for 45 min. The reaction mixture was concentrated in vacuo (rotary...
evaporater) and then treated with 4M HCl in dioxane (0.25 mL, 1.00 mmol) and stirred at RT for 30 min at which point LC-MS indicated clean conversion to the desired amino acid as its hydrochloride salt. The reaction mixture was dried under high vacuum overnight and the resulting red solid and was used directly in the macrolactamization step without further purification assuming quantitative yield, m/z (ESI, +ve ion) 380.1 (M+H)+.

Step 4: 16-methyl-4,7, 12,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-1 (2 1),2,5(24),15, 17,19,22-heptaene-6, 11-dione

2-(7-(3-(2-Aminoethyl)-2-methylquinoxalin-5 -yl)-1-oxo-1,2,3,4-tetrahydropyrrolo [1,2-alpyrazin-4-yl)acetic acid hydrochloride (20 mg, 0.048 mmol) was treated with THF (4 mL), DMF (1.0 mL) and the resulting suspension was stirred at RT. It was then treated with several drops of DIPEA and the suspension turned light yellow. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (59 mg, 0.113 mmol) was added in one portion and stirred at RT for 5 h. The reaction mixture was treated with water and extracted with DCM (4 x 15 mL). The crude residue was dissolved in DMSO and purified on the Gilson (Silicycle Silichrome XT C18 column; 30 x 150 mm, 5 μη; 5-95% 0.1%TFA/ACN in 0.1%TFA/water) affording 16-methyl-4,7, 12,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-1 (2 1),2,5(24),15, 17,19,22-heptaene-6, 11-dione 2,2,2-trifluoroacetate (8.9 mg, 9.36 μη; 19.46 % yield) as an orange amorphous solid after drying in a Genevac Series II evaporator overnight: 1H NMR (400 MHz, DMSO-d6) δ ppm 8.52 (1 H, br. s.), 8.19 (1 H, s), 7.87 (1 H, d, J=6.8 Hz), 7.79 (1 H, d, J=7.6 Hz), 7.72 (1 H, t, J=7.7 Hz), 7.62 (1 H, br. s.), 7.00 (1 H, s), 4.63 (1 H, d, J=4.3 Hz), 3.92 - 4.02 (2 H, m), 3.46 - 3.57 (5 H, m), 3.30 (2 H, d, J=5.5 Hz), 2.93 (1 H, dd, J=14.5, 4.1 Hz), 2.70 (3 H, s), 2.61 (1 H, dd, J=14.3, 5.5 Hz), m/z (ESI, +ve ion) 362.0 (M+H)+.
Example 50: (9S,11E,13R)-13-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaene-16-carbaldehyde

A slurry of (9S,11E,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaene-16-carbaldehyde (Example 31; 0.017 g, 0.047 mmol) and selenium dioxide (Aldrich; 7.87 mg, 0.071 mmol) in 0.7 mL of 4% water in dioxane was sealed and heated to 60 °C. The reaction was stirred overnight. The reaction was treated with DCM/MeOH; insoluble red precipitate was observed. 0.500 g silica gel was added and the reaction concentrated in vacuo. The material was purified by silica gel chromatography (12 g column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (9S,11E,13R)-13-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaene-16-carbaldehyde (0.0045 g, 0.012 mmol, 25.5% yield) as a red solid: 1H NMR (400 MHz, CDCl₃) δ ppm 13.30 (1H, br. s.), 10.15 (1H, s), 8.57 (1H, d, J=7.0 Hz), 7.79 (1H, dd, J=8.2, 1.0 Hz), 7.48 (1H, t, J=7.8 Hz), 7.08 (1H, d, J=2.0 Hz), 6.32 (1H, d, J=16.0 Hz), 5.75 - 5.96 (1H, m), 5.52 (1H, br. s.), 4.25 - 4.46 (1H, m), 3.23 - 3.65 (3H, m), 2.66 (1H, d, J=13.3 Hz), 2.26 - 2.48 (1H, m), 1.61 (4H, d, J=6.5 Hz), m/z (ESI, +ve) 374.1 (M+H)+.

Example 51: (9S,11E)-12-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaene-16-carbaldehyde

A mixture of selenium dioxide (Aldrich; 0.023 g, 0.209 mmol) and (9S,11E)-12,16-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaene-16-carbaldehyde...
l(21),2(24),4,l l,1 5,1 7,1 9,22-octaen-6-one (Example 14; 0.050 g, 0.139 mmol) in 1.4 mL dioxane and 0.056 mL water was stirred rapidly at RT. The reaction was sealed and heated to 60 °C. After 2 h, the reaction was treated with DCM and MeOH, silica gel was added (0.5 g) and the slurry was concentrated in vacuo. The material was purified by silica gel chromatography (12 g gold column) using 0-100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (9S,1lE)-12-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,l 1,1 5,1 7,1 9,22-octaen-6-carbaldehyde (0.0038 g, 10.18 µmol, 7.32 % yield) as a red solid: 1H NMR (400 MHz, CDCl3) δ ppm 13.20 (1H, br. s.), 10.17 (1H, s), 8.40 (1H, d, J=5.3 Hz), 8.13 (1H, d, J=7.4 Hz), 7.81 (1H, d, J=8.2 Hz), 7.45 - 7.56 (1H, m), 7.12 (1H, d, J=2.0 Hz), 5.81 (1H, d, J=10.8 Hz), 5.52 (1H, br. s.), 4.05 - 4.30 (2H, m), 3.35 - 3.62 (3H, m), 2.35 - 2.64 (2H, m), 1.67 - 1.74 (3H, m). m/z (ESI, +ve) 374.1 (M+H)+.

Example 53 17-methyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-l(22),2,5(25),16,18,20,23-heptaene-6,11-dione

Step 1: tert-butyl (2-((8-bromo-3-methylquinoxalin-2-yl)amino)ethyl)carbamate
A solution of 5-bromo-3-fluoro-2-methylquinoxaline (0.956 g, 3.97 mmol), N-Boc-ethylenediamine (Aldrich, 0.81 mL, 5.16 mmol) and DIPEA (1.38 mL, 7.93 mmol) in DMSO (8.0 mL) was heated at 80 °C for 5 h. The mixture was diluted with EtOAc (100 mL) and washed with water (10 mL) and brine (2 x 25 mL). The organic layer was dried
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over MgSO₄, filtered and concentrated. The residue was purified on the ISCO Combiflash Rf (40 g Thomson SingleStep column, using a gradient of 20-100% EtOAc in hexanes) allowing tert-butyl (2-((8-bromo-3-methylquinoxalin-2-yl)amino)ethyl)carbamate (1.30 g, 3.40 mmol, 86 % yield) as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 7.81 (1 H, d, J=7.6 Hz), 7.77 (1 H, dd, J=8.2, 1.2 Hz), 7.21 (1 H, t, J=7.9 Hz), 6.31 1 (1 H, br. s.), 5.26 (1 H, br. s.), 3.72 - 3.80 (2 H, m), 3.51 - 3.59 (2 H, m), 2.58 (3 H, s), 1.42 (9 H, s). m/z (ESI, +ve ion) 381.0/383.1 (M+H)⁺.

Step 2: tert-butyl (2-((3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-yl)amino)ethyl)carbamate

A mixture of tert-butyl (2-((8-bromo-3-methylquinoxalin-2-yl)amino)ethyl)carbamate (397 mg, 1.041 mmol), bis(pinacolato)diboron (Alrich, 529 mg, 2.083 mmol), Pd(dppf)Cl₂ (Alrich, 42.5 mg, 0.052 mmol) and KOAc (Alrich, 409 mg, 4.17 mmol) in THF (4.00 mL) was heated at 100 °C in a sealed vessel for 4 h. The mixture was diluted with EtOAc (50 mL) and treated with water. It was then washed with brine (2 x 25 mL), dried over MgSO₄, filtered and concentrated. The crude was purified on an ISCO CombiFlash Rf (40 g Thomson SingleStep column, using a gradient of 0-100% EtOAc in DCM, then 0-20% MeOH in DCM) to give tert-butyl (2-((3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxalin-2-yl)amino)ethyl)carbamate (342 mg, 0.798 mmol, 77 %, yield) as a tan amorphous solid upon concentration of the product containing fractions: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.12 (1 H, d, J=6.1 Hz), 7.84 - 7.95 (1 H, m), 7.65 (2 H, br. s.), 7.42 (1 H, br. s.), 7.67 (1 H, br. s.), 6.76 (1 H, br. s.), 6.05 (1 H, br. s.), 3.83 (1 H, br. s.), 3.58 (5 H, br. s.), 3.49 (2 H, br. s.), 2.59 (3 H, br. s.), 1.47 (12 H, br. s.), 1.26 (3 H, d, J=7.2 Hz), m/z (ESI, +ve ion) 347.1 (M+H)⁺ (the pinacol ester is labile under the conditions used to run the LC-MS and the observed mass corresponded to the corresponding boronic acid).

Step 3: ethyl 2-((7-((tert-butoxycarbonyl)amino)ethyl)amino)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate

A 20-mL glass microwave tube was charged with ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (Intermediate J, 2.17 mg, 0.721 mmol), dicyclohexyl(2′,4′,6′-trisopropyl-[1,1′-biphenyl]-2-yl)phosphine (Strem Chemicals, 20.6 mg, 0.043 mmol), Pd₂(db)₃ (Strem Chemicals, 19.8 mg, 0.022 mmol), K₃PO₄ (Riedel de Haen, Buchs, Switzerland, 459 mg, 2.162 mmol) and tert-butyl (2-((3-methyl-8-(4,4,5,5-
tetramethyl-l,3,2-dioxaborolan-2-yl)quinoxalin-2-yl)amino)ethyl) carbamate (340 mg, 0.793 mmol) and purged with argon. The solids were then treated with dioxane (5.0 mL) and water (1.65 mL) and heated in a microwave reactor at 130 °C for 30 min. The reaction mixture was treated with water, extracted with EtOAc, washed with brine and concentrated. Purification on the ISCO CombiFlash RF (40 g Thomson SingleStep column, using a gradient of 20-100% EtOAc in hexanes, then 0-15% MeOH in DCM) afforded ethyl 2-(7-(3-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-2-methylquinoxalin-5-yl)-1-oxo-l,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (165 mg, 0.316 mmol, 43.8 % yield) as a light yellow film: 1H NMR (400 MHz, CDCl3) δ ppm 7.90 (1 H, br. s), 7.66 - 7.80 (3 H, m), 7.32 - 7.40 (1 H, m), 5.89 (1 H, br. s), 5.67 (1 H, br. s), 5.49 (1 H, br. s), 4.80 (1 H, br. s), 4.08 - 4.21 (3 H, m), 4.02 (1 H, d, J=12.7 Hz), 3.74 (2 H, br. s), 3.46 - 3.63 (3 H, m), 2.88 - 2.97 (2 H, m), 2.57 (3 H, br. s), 2.04 (2 H, br. s), 1.45 (9 H, br. s), m/z (ESI, +ve ion) 523.2 (M+H)+.

Step 4: 2-((8-(4-(carboxymethyl)-1-oxo-l,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)-3-methylquinoxalin-2-yl)amino)ethanaminium chloride

Ethyl 2-((7-(3-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-2-methylquinoxalin-5-yl)-1-oxo-l,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (165 mg, 0.316 mmol) was treated with THF (5.0 mL) and EtOH (5.0 mL) then treated with IN NaOH (0.95 mL, 0.95 mmol) and stirred at RT for 30 min. The reaction mixture was concentrated in vacuo (rotary evaporator) and then treated with 4M HCl in dioxane (1.56 mL, 6.31 mmol) and THF (3 mL) and stirred at RT for 30 min. The volatiles were removed in vacuo (rotary evaporator) yielding crude 2-((8-(4-(carboxymethyl)-1-oxo-l,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)-3-methylquinoxalin-2-yl)amino)ethanaminium chloride as a bright orange amorphous solid which was then dried under vacuum for 2 h. The material was used in the subsequent step without further purification, m/z (ESI, +ve ion) 395.1 (M+H)+.

Step 5: 17-methyl-4,7,12,15,18,24-hexazapentacyclo[14.6.2.1.2-5.0-4.9.0-19.23-]pentacosa-l(22),2,5(25),16,18,20,23-heptaene-6,11-dione

2-((8-(4-(Carboxymethyl)-1-oxo-l,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)-3-methylquinoxalin-2-yl)amino)ethanaminium chloride (136 mg, 0.316 mmol) was treated with THF (10 mL) and DMF (3.75 mL) and the resulting suspension was stirred at RT. It was then treated with DIPEA (0.55 mL, 3.16 mmol) and the suspension turned light
pink/purple and (benzotriazol-1-yl oxy)tripyrrolidinophosphonium hexafluorophosphate (411 mg, 0.789 mmol) was added in one portion and the resulting solution stirred at RT for 1 h. The reaction mixture was treated with water and extracted with EtOAc (50 mL), DCM (4 x 15 mL) and 10% IPA in CHCl₃ (3 x 40 mL). A portion of the crude residue was dissolved in DMSO and purified on the Gilson (Silichrome XT C₁₈ column; 30 x 150 mm, 5 μ; 5-95% 0.1% TFA/CH₃CN in 0.1% TFA/water) affording 17-methyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1₂,₅.0₄,₉.0₁₈,₂₂]tetracosa-l(22),2(24),4,11,15,17,18,20,22-octaen-11-yn-6-one (400 MHz, DMSO-d₆) δ ppm 8.87 (1 H, br. s.), 8.75 (1 H, br. s.), 7.79 (1 H, d, J=7.0 Hz), 7.73 (1 H, br. s.), 7.51 (1 H, d, J=7.6 Hz), 7.20 - 7.32 (2 H, m), 7.17 (1 H, br. s.), 4.67 (1 H, br. s.), 3.95 (1 H, br. s.), 3.68 (2 H, br. s.), 3.03 (1 H, br. s.), 2.64 - 2.76 (1 H, m), 2.60 (1 H, d, J=11.7 Hz), m/z (ESI, +ve ion) 377.1 (M+H)⁺.

Example 54: (9R,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-11-yn-6-one

The title compound (31 mg, 89% yield) was prepared and isolated as a yellow crystalline solid from (R)-7-(but-2-ynyl)-2-(2-methyl-3-((R)-pent-3-yn-2-ylamino)quinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(3H)-one (Intermediate O, 40 mg, 0.09 mmol) following an analogous procedure to Example 32, Alternative Preparation, Step 1: ¹H NMR (400 MHz, MeOH-d₄) δ ppm 8.00 (1 H, d, J=7.6 Hz), 7.63 (1 H, d, J=8.2 Hz), 7.43 (1 H, m), 7.01 (1 H, s), 4.65 (1 H, m), 3.54 (2 H, m), 3.23 (1 H, m), 2.66 (1 H, m), 2.64 (3 H, s), 2.46 (1 H, m), 1.71 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 358.3 (M+H)⁺.

Example 55. (9R,13Z,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-nonena-6-one
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The title compound (6.5 mg, 21% yield) was prepared and isolated as a yellow crystalline solid from (9R,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (Example 54, 30 mg, 0.08 mmol) following an analogous procedure to Example 32, Alternative Preparation, Step 2: 

\[
\begin{align*}
\text{H NMR} &\ (400 \text{ MHz, DMSO-}d_6) \delta \text{ ppm } 13.81 \ (1 \text{ H, br. s}), 7.85 \ (1 \text{ H, d, } J=6.7 \text{ Hz}), 7.56 \ (1 \text{ H, d, } J=7.4 \text{ Hz}), 7.34 \ (1 \text{ H, t, } J=7.8 \text{ Hz}), 7.18 \ (1 \text{ H, d, } J=4.1 \text{ Hz}), 6.97 \ (1 \text{ H, d, } J=4.3 \text{ Hz}), 6.70 \ (1 \text{ H, d, } J=1.8 \text{ Hz}), 5.50 \ (1 \text{ H, m}), 5.41 \ (1 \text{ H, m}), 4.89 \ (1 \text{ H, m}), 3.25 \ (1 \text{ H, d, } J=6.8 \text{ Hz}). \ m/z \ (ESI, +ve) 360.2 \ (M+H)^+.
\end{align*}
\]

Example 56: (9S,1E,13R)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: (R)-tert-butyl 2,2-dimethyl-4-vinyloxazolidine-3-carboxylate

To a slurry of MePPh₃Br (Fluka Chemie GmbH; 3.74 g, 10.47 mmol) in 50 mL THF at 78 °C was added nBuLi solution, 2.5 M in hexanes (Aldrich; 3.84 ml, 9.60 mmol) dropwise via syringe. After 10 min, the reaction was warmed to RT, then recooled to 0 °C. (S)-(e)-3-(tert-butoxycarbonyl)-(s)-4-formyl-2,2-dimethyl-1,3-oxazolidine (TCI America; 2.00 g, 8.72 mmol) dissolved in 8 mL THF was added dropwise via syringe. The reaction was stirred for several hours. The reaction was partitioned between saturated aqueous NH₄Cl and Et₂O. The organic layer was washed with brine once and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and adsorbed onto 15 g silica gel, dried, and purified by
silica gel chromatography (120 g) using 0 - 30% EtOAc/hexane to give (R)-tert-butyl 2,2-dimethyl-4-vinylazolidine-3-carboxylate (1.2 g, 5.32 mmol, 61.0 % yield) as a clear/colorless oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 5.69 - 5.96 (1 H, m), 5.06 - 5.27 (2 H, m), 4.20 - 4.47 (1 H, m), 4.05 (1 H, dd, J=8.8, 6.3 Hz), 3.76 (1 H, dd, J=8.8, 2.2 Hz), 3.17 - 1.71 (15 H, m).

Step 2: (R)-2-aminobut-3-en-l -ol hydrochloride
(R)-tert-Butyl 2,2-dimethyl-4-vinylazolidine-3-carboxylate (1.2 g, 5.28 mmol) was treated with HCl, 5 N (Ricca Chemical Company; 4.81 ml, 158 mmol). The reaction was stirred rapidly, and HCl, 4.0 M solution in 1,4-dioxane (Aldrich; 5.04 ml, 145 mmol) was added and bubbling was observed. The reaction was stirred for 1 h, at which point the stir bar was removed and the reaction concentrated in vacuo. The resulting oil was treated with anhydrous toluene and concentrated in vacuo. This was repeated, and the oil was placed on the hood pump, resulting in (R)-2-aminobut-3-en-l -ol hydrochloride (0.696 g, 5.63 mmol, quantitative yield) as a waxy solid: ¹H NMR (400 MHz, MeOH-d₄) δ ppm 5.89 (1 H, ddd, J=17.5, 10.5, 7.0 Hz), 5.42 - 5.53 (2 H, m), 3.74 - 3.84 (2 H, m), 3.52 - 3.64 (1 H, m).

Step 3: (S)-7-allyl-2-(3-(((R)-1 -hydroxybut-3-en-2-yl)amino)-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one
A mixture of (S)-7-allyl-2-(3-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.150 g, 0.446 mmol), (R)-2-aminobut-3-en-l -ol hydrochloride (0.165 g, 1.338 mmol), and DIPEA (Aldrich; 0.465 ml, 2.68 mmol) in 2 mL DMSO was sealed and placed in a 70 °C oil bath. After 2 h, the reaction was nearly complete, and was stirred at 45 °C overnight. The reaction was partitioned between saturated aqueous NaHCO₃ and EtOAc. The aqueous layer was extracted 1 x EtOAc, and the combined organic layers were washed with water once, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The resulting semisolid (0.220 g) was treated with DCM and purified by silica gel chromatography (25 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (S)-7-allyl-2-(3-(((R)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.157 g, 0.389 mmol, 87 % yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.00 (1 H, br. s), 7.87 - 7.94 (1 H, m), 7.53 - 7.61 (1 H, m), 7.33 (1 H, t, J=7.8 Hz)
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Hz), 7.00 - 7.06 (1 H, m), 6.87 - 7.00 (2 H, m), 6.02 - 6.14 (1 H, m), 5.82 - 5.97 (1 H, m), 5.75 (1 H, s), 5.26 - 5.36 (1 H, m), 5.03 - 5.22 (4 H, m), 4.71 - 4.85 (1 H, m), 3.66 - 3.77 (2 H, m), 3.46 - 3.56 (1 H, m), 3.18 - 3.27 (1 H, m), 3.03 - 3.13 (1 H, m), 2.60 (3 H, s), 2.43 - 2.48 (1 H, m), 2.29 - 2.41 (1 H, m). m/z (ESI, +ve) 404.1 (M+H)⁺.

Step 4: (9S,1E,3R)-13-(hydroxymethyl)-1 6-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,1 1,15,17,18,20,22-nonaen-6-one

Argon was bubbled through a solution of Grubbs catalyst 2nd generation (Aldrich; 0.064 g, 0.075 mmol) and (S)-7-allyl-2-(3-((R)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinaxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.152 g, 0.377 mmol) in 19 mL anhydrous DCM for 60 sec. The homogeneous reaction was sealed and heated to 45 °C. After 2 h, the reaction was treated with MeOH and 1.5 g silica gel and dried in vacuo, purified by silica gel chromatography (24 g) using 0 - 100% 90/10 DCM/MeOH. The product-containing fractions were concentrated to afford 0.085 g of a yellow-green solid. This material was suspended in MeOH, sonicated 1 min, filtered, rinsing 1 x MeOH. The bright yellow solid was collected and dried in vacuo to give (9S,11E,13R)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-l (22),2(24),4,1 1,15,17,18,20,22-nonaen-6-one (0.061 g, 0.162 mmol, 43.1 % yield) as a bright yellow solid. ¹H NMR (400 MHz, DMSO-de) δ ppm 13.55 (1 H, br. s.), 8.01 (1 H, d, J=7.4 Hz), 7.57 (1 H, d, J=7.8 Hz), 7.35 (1 H, t, J=7.8 Hz), 7.02 (1 H, d, J=4.1 Hz), 6.91 (1 H, d, J=2.0 Hz), 6.35 (1 H, s), 5.98 - 6.17 (1 H, m), 5.79 (1 H, dd, J=15.7, 7.5 Hz), 5.43 (1 H, t, J=5.9 Hz), 4.14 - 4.26 (1 H, m), 3.57 - 3.76 (2 H, m), 3.32 - 3.38 (1 H, m), 3.22 - 3.30 (1 H, m), 3.06 - 3.18 (1 H, m), 2.60 (3 H, s), 2.56 (1 H, br. s.), 2.14 - 2.26 (1 H, m). m/z (ESI, +ve) 376.1 (M+H)⁺.

Example 57: (9S,11E)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Example 58: (9S,11Z)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one
Step 1: (S)-7-allyl-2-(3-(allyl(methyl)amino)-2-methylquinoxaline-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of N-methylprop-2-en-1-amine (Sigma Aldrich, 85 mg, 1.192 mmol), (S)-7-allyl-2-(3-fluoro-2-methylquinoxaline-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 133.7 mg, 0.397 mmol), and DMSO (4.0 mL) was stirred at 100 °C in a sealed tube for 3 h. The material was cooled to RT, diluted with water, and extracted with EtOAc (3x20 mL). The organics were washed with saturated aqueous NH₄Cl (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a yellow solid that was used without purification: m/z (ESI, +ve) 388.3 (M+H)⁺.

Step 2: (9S,1LE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,ll,15,17,18,20,22-nonaen-6-one

A solution of Grubbs 2nd generation catalyst (Sigma Aldrich, 114 mg, 0.134 mmol) and (S)-7-allyl-2-(3-(allyl(methyl)amino)-2-methylquinoxaline-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (260 mg, 0.671 mmol) was stirred in DCM (6.7 mL) at 50 °C for 2 h. The mixture was cooled to RT, adsorbed onto silica, and concentrated under reduced pressure. The material was purified on by silica gel chromatography (eluent: 0 to 9% MeOH/DCM). The product fractions were combined and concentrated. The resulting residue was purified a second time by SFC (solubilized in 1:1 MeOH at 4 mg/mL, 292 nm, Phenomenex, Lux-1, repack-S/N= 1204 ODH Column, 5 μ at 21x150 mm length, 60% CO₂ with IPA/40 mM NH₃, P = 186 bar at 1 mL/min, giving (9S,1IE)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,ll,15,17,18,20,22-nonaen-6-one (33.6 mg, 28%, 2 steps) as the first eluting peak and (9S,1IZ)-14,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,l l,1 5,1 7,1 8,20,22-nonaen-6-one (30.7 mg, 23%) as the second eluting peak.

Analytical data for (9S,l lE)-14,1 6-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[13.6.2. 1~2,5~.0~4,9~.0~1 8,22~]tetracosa-1 (22),2(24),4,l l,1 5,1 7,1 8,20,22-nonaen-6-one: 

$^1$H NMR (DMSO-d$_6$) δ ppm 13.15 - 13.23 (IH, m) 7.98 - 8.13 (IH, m) 7.58 - 7.69 (1H, m) 7.41 - 7.52 (1H, m) 7.06 - 7.13 (1H, m) 6.91 - 7.01 (1H, m) 6.14 - 6.26 (1H, m) 5.93 - 6.06 (1H, m) 4.21 - 4.33 (1H, m) 3.96 - 4.10 (1H, m) 3.34 - 3.40 (1H, m) 3.24 - 3.29 (1H, m) 3.21 (3H, s) 3.08 - 3.18 (1H, m) 2.69 (3H, s), 2.59 - 2.67 (1H, m) 2.20 - 2.36 (1H, m); m/z (ESI, +ve) 360.2 (M+H)$^+$. 

Analytical data for (9S,l lZ)-14,1 6-dimethyl-3,7,14,1 7,23-pentaazapentacyclo[13.6.2. 1~2,5~.0~4,9~.0~1 8,22~]tetracosa-1 (22),2(24),4,l l,1 5,1 7,1 8,20,22-nonaen-6-one: 

$^1$H NMR (DMSO-d$_6$) δ ppm 13.21 - 13.31 (1H, m) 7.87 - 7.98 (1H, m) 7.59 - 7.66 (1H, m) 7.36 - 7.47 (1H, m) 6.96 - 7.08 (1H, m) 6.76 - 6.88 (1H, m) 5.75 - 5.92 (2H, m), 4.71 - 4.84 (1H, m), 3.70 - 3.83 (1H, m), 3.41 (3H, s), 3.35 - 3.39 (1H, m), 3.19 - 3.25 (2H, m), 2.79 (3H, s), 2.61 - 2.73 (1H, m), 2.22 - 2.35 (1H, m); m/z (ESI, +ve) 360.2 (M+H)$^+$. 

Examples 59-60: (9S)-17-methyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-1 (22),2,5(25),16,18,20,23-heptaene-6,ll-dione and (9R)-17-methyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-1 (22),2,5(25),16,18,20,23-heptaene-6,ll-dione 

Separated enantiomers were obtained by dissolving 41 mg of racemic Example 53 in 20 mL 1:1 MeOH:DCM and subjecting to chiral separation using a preparatory SFC (Conditions: 25% MeOH containing 20 mM NH$_3$ as a cosolvent in supercritical CO$_2$ on a Chiralcel OJ-H column (20 x 250 mm i.d., 5 µm) with a flow rate of 70 mL/min using injections of 1.2 mL of racemic material). The separated material was then subject to analytical SFC (Conditions: 25% MeOH containing 0.1% DEA as a modifier in
supercritical CO₂ on a Chiralcel OJ-H column (4.6 mm x 15 cm i.d., 5 µ) with a flow rate of 4.0 mL/min. Example 59 eluted as the second peak under the analytical SFC conditions: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.83 (1 H, br. s.), 8.74 (1 H, br. s.), 7.78 (1 H, br. s.), 7.70 (1 H, br. s.), 7.51 (1 H, d, J=6.3 Hz), 7.19 - 7.34 (2 H, m), 7.17 (1 H, br. s.), 4.68 (1 H, br. s.), 3.95 (1 H, br. s.), 3.67 (1 H, br. s.), 3.55 (1 H, d, J=10.2 Hz), 3.43 (2 H, d, J=9.0 Hz), 3.03 (1 H, br. s.), 2.65 - 2.75 (1 H, m), 2.56 - 2.65 (1 H, m), m/z (ESI, +ve ion) 377.1 (M+H)+. Example 60 eluted as the first peak under the analytical SFC conditions described above: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.84 (1 H, br. s.), 8.75 (1 H, br. s.), 7.79 (1 H, d, J=7.0 Hz), 7.66 - 7.75 (1 H, m), 7.52 (1 H, d, J=7.6 Hz), 7.27 - 7.33 (1 H, m), 7.20 - 7.27 (1 H, m), 7.17 (1 H, s), 4.62 - 4.74 (1 H, m), 3.88 - 4.02 (1 H, m), 3.63 - 3.77 (1 H, m), 3.55 (1 H, dt, J=12.7, 4.0 Hz), 3.38 - 3.51 (2 H, m), 2.96 - 3.10 (1 H, m), 2.65 - 2.75 (1 H, m), 2.60 (1 H, dd, J=14.5, 10.2 Hz), m/z (ESI, +ve ion) 377.1 (M+H)+.

Examples 61-62: (9S,14R)-14,17-dimethyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1₂⁻²⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻ifetimeaazaheptaene-6,11-dione and (9R,14R)-14,17-dimethyl-4,7,12,15,18,24-hexaazapentacyclo[14.6.2.1₂⁻²⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻::-] pentacosa-
(22),2,5(25),16,18,20,23-heptaene-6,11-dione

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Step 1: (7S)-tert-butyl (2-((8-bromo-3-methylquinolin-2-yl)amino)propyl)carbamate

A solution of 5-bromo-3-chloro-2-methylquinoline (1.00 g, 3.88 mmol), (P)-1-N-Boc-
propane-1,2-diamine HCl (Acesys Pharmatech, North Brunswick, NJ, Cat#: A1032R,
1.24 g, 5.89 mmol) and DIPEA (2.02 mL, 11.65 mmol) in DMSO (8.0 mL) was heated at
80 °C for 16 h. The mixture was diluted with EtOAc (100 mL) and washed with water (2
x 30 rriL) and brine (25 mL). The organic layer was dried over MgSO₄, filtered and concentrated. The crude residue was purified on an ISCO CombiFlash Rf (80 g Thomson SingleStep column, using a gradient of 30-60% EtOAc in hexanes) to give (R)-tert-butyl (2-((8-bromo-3-methylquinoxalin-2-yl)amino)propyl)carbamate (1.23 g, 3.11 mmol, 80 % yield) as an orange viscous oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.78 - 7.83 (1 H, m), 7.76 (1 H, d, J=8.0 Hz), 7.19 (1 H, t, J=7.9 Hz), 6.08 (1 H, d, J=4.7 Hz), 5.20 (1 H, br. s.), 4.33 - 4.47 (1 H, m), 3.41 - 3.52 (1 H, m), 3.29 - 3.41 (1 H, m), 2.56 (3 H, s), 1.40 (9 H, s), 1.38 (3 H, d). m/z (ESI, +ve ion) 395.1/397.0 (M+H)+.

Step 2: (R)-tert-butyl (2-((3-methyl-8-(4,4,5,5-tetramethyl-1,2,3,4-tetrahydro-2H-pyrazin-4-yl)acetate)prop-2-yl)quinoxalin-2-yl)amino)propyl)carbamate

A mixture of (75)-tert-butyl (2-((8-bromo-3-methylquinoxalin-2-yl)amino)propyl)carbamate (1.20 g, 3.04 mmol), bis(pinacolato) diboron (Aldrich, 1.54 g, 6.07 mmol), Pd(dppf)Cl₂ (Aldrich, 0.124 g, 0.152 mmol) and KOAc (Aldrich, 1.19 g, 12.14 mmol) in THF (12 mL) was heated at 100 °C in a sealed vessel for 2 h then stirred at RT overnight (16 h). The mixture was diluted with EtOAc (50 mL) and treated with water. It was then washed with brine (2 x 25 mL), dried over MgSO₄, filtered and concentrated. The crude was purified with an ISCO CombiFlash Rf (40 g Thomson SingleStep column, using a gradient of 0-10% MeOH in DCM) to give (R)-tert-butyl (2-((3-methyl-8-(4,4,5,5-tetramethyl-1,2,3,4-tetrahydro-2H-pyrazin-4-yl)acetate)prop-2-yl)quinoxalin-2-yl)amino)propyl)carbamate (1.28 g, 2.90 mmol, 96 % yield) as a light brown foam, m/z (ESI, +ve ion) 317.1 (M+H)+ (the pinacol ester is labile under the conditions used to run the LC-MS and the observed mass corresponded to the corresponding boronic acid).

Step 3: ethyl 2-(7-(3-(((R)-1-((tert-butoxycarbonyl)amino)propan-2-yl)amino)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate

A 20-mL glass microwave tube was charged with ethyl 2-(7-bromo-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (Intermediate J, 350 mg, 1.162 mmol), dicyclohexyl(2',4',6'-triisopropyl-1',1'-biphenyl-2-yl)phosphine (Strem Chemicals, 33.2 mg, 0.070 mmol), Pd₂(db₃)₃ (Strem Chemicals, 31.9 mg, 0.035 mmol), potassium phosphate tribasic (Riedel de Haen, Buchs, Switzerland, 740 mg, 3.49 mmol) and (R)-tert-butyl (2-((3-methyl-8-(4,4,5,5-tetramethyl-1,2,3,4-tetrahydro-2H-pyrazin-4-yl)acetate)prop-2-yl)quinoxalin-2-yl)amino)propyl)carbamate (643 mg, 1.453 mmol) were purged with argon and treated with dioxane (5.0 mL) and water (1.65 mL) and heated in a heating block at 130 °C for 30
The reaction mixture was diluted with water and extracted with EtOAc (2 x 50 mL), washed with brine and dried over MgSO₄, filtered and concentrated. Purification of the crude residue on the ISCO CombiFlash RF (40 g Thomson SingleStep column, using a gradient of 30-100% EtOAc in hexanes, then with 0-20% MeOH in DCM) afforded ethyl 2-(7-(3-((R)-1-((tert-butoxycarbonyl)amino)propan-2-yl)amino)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (434.9 mg, 0.810 mmol, 69.7% yield) as a tan foam: m/z (ESI, +ve ion) 537.2 (M+H)+ as two closely eluting peaks.

Step 4: (277)-2-((8-(4-(carboxymethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)-3-methylquinoxalin-2-yl)amino)propan-1-amine chloride

Ethyl 2-(7-(3-((7S)-1-((tert-butoxycarbonyl)amino)propan-2-yl)amino)-2-methylquinoxalin-5-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-4-yl)acetate (430 mg, 0.801 mmol) was treated with THF (7.5 mL) and EtOH (7.5 mL) then with IN NaOH (2.4 mL, 2.40 mmol) and stirred at RT for 30 min. LC-MS indicated clean conversion to the desired carboxylic acids m/z (ESI, +ve ion) 509.1 (M+H)+. The reaction mixture was concentrated in vacuo (rotary evaporator) and then treated with 4M HCl in dioxane (4.0 mL, 16.03 mmol) and THF (3 mL) and stirred at RT for 30 min at which point LC-MS indicated clean conversion to the desired amino acid m/z (ESI, +ve ion) 409.1 (M+H)+. The volatiles were removed on the rotary evaporator and the bright orange amorphous solid was further dried in the vacuum oven for 2 h at 40 °C. The mixture of diastereomers were used in the subsequent step without further purification.

Step 5: (9S,14R)-14,17-dimethyl-4,7,12,1 5,1 8,24-hexaazapenta-cyclo[14.6.2. 1-2,5-0,4,9-0,1 9,23-] pentacosa-1(22),2,5(25),1 6,1 8,20,23-heptaene-6,1 1-dione and (9R,14R)-14,1 7-dimethyl-4,7,12,1 5,1 8,24-hexaazapenta-cyclo[14.6.2. 1-2,5-0,4,9-0,1 9,23-] pentacosa-1(22),2,5(25),1 6,1 8,20,23-heptaene-6,1 1-dione (27S)-2-((8-(4-(Carboxymethyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)-3-methylquinoxalin-2-yl)amino)propan-1-amine chloride (357 mg, 0.802 mmol) was treated with THF (20.0 mL) and DMF (6.3 mL) and the resulting suspension was stirred at RT. It was then treated with DIPEA (1.4 mL, 8.02 mmol) and the suspension turned light pink/purple and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (1.04 g, 2.01 mmol) was added in two portions (separated by 30 min). The reaction mixture was diluted with water and extracted with EtOAc (2 x 50 mL), washed with brine and dried over MgSO₄, filtered and concentrated.
min) and the resulting solution stirred at RT for an additional 45 min. The reaction mixture was treated with water and extracted with DCM (4 x 25 mL) and 10% IPA in CHCl₃ (4 x 50 mL). The crude residue was dissolved in DMSO and purified on the Gilson (Silichrome XT C₁₈ column; 30 x 150 mm, 5 μm; 5-95% 0.1%TFA/CH₂CN in 0.1%oTFA/water). The mixture of diastereomers were separated using preparatory SFC (Conditions: 30% MeOH as a cosolvent in supercritical CO₂ on a Chiralcel OJ-H column (20 x 250 mm i.d., 5 μm) with a flow rate of 70 mL/min using injections of 4.9 mg/mL material). Example 61 eluted as the first peak under these conditions and was isolated as a yellow amorphous solid as its 2,2,2-trifluoroacetate salt upon drying under vacuum: ^1H NMR (400 MHz, DMSO-d₆) δ ppm 8.85 - 8.89 (1 H, m), 8.81 (1 H, t, J=5.4 Hz), 7.81 (1 H, d, J=6.7 Hz), 7.70 (1 H, br. s.), 7.51 (1 H, d, J=7.0 Hz), 7.28 (1 H, t, J=7.7 Hz), 7.14 - 7.20 (1 H, m), 6.76 (1 H, d, J=7.6 Hz), 4.71 - 4.82 (1 H, m), 4.36 (1 H, br. s.), 3.60 (1 H, dt, J=12.5, 3.6 Hz), 3.13 - 3.27 (1 H, m), 2.64 - 2.74 (1 H, m), 1.39 (3 H, d, J=7.0 Hz). m/z (ESI, +ve ion) 391.2 (M+H)^+. Example 62 eluted as the second peak under these conditions and was isolated as a yellow amorphous solid as its 2,2,2-trifluoroacetate salt upon drying under vacuum: ^1H NMR (400 MHz, DMSO-d₆) δ ppm 8.24 (1 H, br. s.), 7.58 - 7.67 (2 H, m), 7.56 (1 H, d, J=7.2 Hz), 7.32 (1 H, t, J=7.7 Hz), 7.21 (1 H, s), 6.91 (1 H, d, J=6.7 Hz), 6.86 (1 H, d, J=6.7 Hz), 4.57 (1 H, dd, J=8.9, 3.6 Hz), 3.80 - 3.93 (1 H, m), 3.61 - 3.74 (2 H, m), 2.95 - 3.06 (1 H, m), 2.83 (1 H, dd, J=13.7, 9.2 Hz), 2.68 (1 H, dd, J=13.5, 2.9 Hz), 2.53 (3 H, s), 1.31 (3 H, d, J=7.0 Hz). m/z (ESI, +ve ion) 391.2 (M+H)^+.

**Example 63:** (9S,13R)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5-.0-4.9-.0-18,22-.]tetracosa-1(22),2(24),4,15,17,18,20,22-octaen-6-one

Palladium hydroxide 10 wt.% (dry basis) on activated carbon, wet (Strem, 0.669 g) and (9S, 11E, 13R)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaaza-pentacyclo[1 3.6.2.1-2,5-.0-4.9-.0-1 8,22-.]tetracosa-1(22),2(24),4,1 1.15,1 7.1 8.20,22-
nonaen-6-one (Example 56; 0.118 g, 0.314 mmol) were combined and flushed with N₂. 3 mL MeOH was added, and the atmosphere was replaced with H₂ from a balloon. After 5 h, the reaction was diluted with MeOH and filtered through a pad of Celite, rinsing with 50 mL MeOH and 50 mL 1:1 DCM/MeOH. The yellow solution was concentrated in vacuo to give 0.079 g orange solid. This material was treated with 2 mL MeOH and a stir bar, and stirred rapidly open to air overnight. After about 24 h total the reaction was concentrated and treated with 20% MeOH in DCM and adsorbed onto 0.75 g silica gel and purified by silica gel chromatography (12 g column) using 50 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 22 mg of a yellow solid. The material was sonicated in 1 mL MeOH, filtered, rinsing with 0.5 mL MeOH. The solid was collected and dried in vacuo to give (9S,13R)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-octaen-6-one (0.0135 g, 0.036 mmol, 11.38 % yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-de) δ ppm 13.47 (1 H, br. s.), 8.02 (1 H, d, J=7.6 Hz), 7.58 (1 H, d, J=8.0 Hz), 7.35 (1 H, t, J=7.8 Hz), 7.03 (1 H, d, J=4.1 Hz), 6.96 (1 H, d, J=1.4 Hz), 6.81 (1 H, d, J=4.1 Hz), 4.96 (1 H, t, J=6.1 Hz), 3.62 - 3.81 (2 H, m), 3.55 (1 H, br. s.), 3.09 - 3.27 (2 H, m), 2.93 - 3.07 (1 H, m), 2.58 (3 H, s), 2.09 - 2.30 (2 H, m), 1.92 - 2.06 (1 H, m), 1.78 - 1.92 (1 H, m), 1.44 - 1.59 (1 H, m), 1.15 - 1.32 (1 H, m). m/z (ESI, +ve) 378.2 (M+H)+.

Example 64: (9S,11E,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-octaen-6-one

Example 65: (9S,11Z,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-octaen-6-one
Step 1: (S)-tert-butyl 2,2-dimethyl-4-vinyloxazolidine-3-carboxylate
A suspension of MePPh₃Br (Fluka, 8.57 g, 23.99 mmol) in THF (218 ml) was stirred and cooled to -78 °C. A solution of 2.5 M n-BuLi in hexanes (Sigma Aldrich, 10.47 ml, 26.2 mmol) was added dropwise over 5 min, and the reaction was slowly warmed to RT. (R)-(+)-3-Boc-2,2-dimethyloxazolidine-4-carboxaldehyde (Sigma Aldrich; 5 g, 21.81 mmol) was added dropwise via syringe, and the resulting suspension was stirred at RT for 18 h. The reaction was carefully quenched with sat. aq. NH₄Cl and extracted with Et₂O. The combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo. DCM was added, and the crude reaction was adsorbed onto silica and chromatographically purified (eluent: 0 to 30% EtOAc/hexanes), giving the product, (S)-tert-butyl 2,2-dimethyl-4-vinyloxazolidine-3-carboxylate, as a colorless oil (3.8 g, 77%): ¹H NMR (MeOH-d₄) δ: 5.75 - 5.89 (m, 1H), 5.10 - 5.25 (m, 2H), 4.32 (br. s., 1H), 4.03 - 4.12 (m, 1H), 3.73 (d, J = 8.4 Hz, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H).

Step 2: (S)-2-aminobut-3-en-l-ol hydrochloride
A solution of (S)-tert-butyl 2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (3.8 g, 16.72 mmol) in 5.0 N aqueous HCl (Sigma Aldrich, 100 ml, 502 mmol) and a 4.0 M solution of HCl in 1,4-dioxane (Sigma Aldrich, 104 ml, 418 mmol) was stirred at RT. Upon addition of the dioxane solution, gas evolution was noted. The reaction was stirred for 2 h at which point the colorless solution was concentrated in vacuo to give a tan oil that was azeotroped with MeOH and toluene. A tan, waxy solid that resulted was dried further under high vacuum, giving (S)-2-aminobut-3-en-l-ol as a hydrochloride salt (1.84 g,
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89%): ¹H NMR (400 MHz, MeOD) δ ppm 5.81 - 5.95 (1 H, m) 5.39 - 5.54 (2 H, m) 3.73 - 3.86 (2 H, m) 3.51 - 3.65 (2 H, m). Step 3: (S)-7-allyl-2-(3-(((S)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A mixture of DIPEA (EMD Biosciences, 778 µL, 4.47 mmol), (S)-2-aminobut-3-en-1-ol hydrochloride (276 mg, 2.236 mmol), and (S)-7-allyl-2-(3-(((S)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 250.6 mg, 0.621 mmol) was stirred in DMSO (4.9 mL) at 80°C for 2.5 h. The reaction mixture was cooled to RT with stirring over 1.5 h. It was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organics were washed with brine and dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was taken up in DCM and chromatographically purified (eluent: 0 to 10% MeOH/DCM), giving (S)-7-allyl-2-(3-(((S)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (251 mg, 83%).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.03 (1 H, br. s.) 7.90 - 8.01 (1 H, m) 7.58 - 7.64 (1 H, m) 7.33 (1 H, br. s.) 7.04 (1 H, br. s.) 6.94 (2 H, br. s.) 6.00 - 6.15 (1 H, m) 5.90 - 5.97 (1 H, m) 5.34 (1 H, m) 5.20 - 5.24 (1 H, m) 5.08 - 5.18 (2 H, m) 4.96 - 5.07 (1 H, m) 4.74 (1 H, br. s.) 3.80 - 3.85 (1 H, m) 3.52 - 3.61 (1 H, m) 3.35 - 3.40 (1 H, m) 2.97 - 3.13 (1 H, m) 2.61 (3 H, s) 2.27 - 2.43 (1 H, m). m/z (ESI, +ve) 404.1 (M+H)+.

Step 4: (9S,1E,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0,4,9-0-1 8,22]-tetracosa-1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one and (9S,1I,13S)-13-(hydroxy methyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0,4,9-0-18,22]-tetracosa-1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one

A suspension of Grubbs 2nd Generation Catalyst (Sigma Aldrich, 105 mg, 0.124 mmol), (S)-7-allyl-2-(3-(((S)-1-hydroxybut-3-en-2-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (250 mg, 0.620 mmol), and DCM (31 mL) was bubbled through with argon gas for two min. The mixture was sealed and stirred at 45 °C for 1.5 h. The reaction was removed from heat and adsorbed onto silica gel. The adsorbed crude mixture was chromatographically purified on silica gel (eluent: 5 to 10% MeOH/DCM). The product fractions were dried in vacuo, and the isomeric mixture was further purified by SFC (282 nm, Chiralpak ADH Column, 5 µ, 250 x 30mm, 42%
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MeOH containing 20 mM NH₃, 120 mL/min, affording (9S,11E,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1₂,₅.0⁴,₉.₀¹₈,₂₂.]tetracosa-l(22),2(24),4,1 1,1,5,17,18,20,22-nonaen-6-one (56.7 mg, 48%) as the first eluting peak and (9S,11Z,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1₂,₅.0⁴,₉.₀¹₈,₂₂.]tetracosa-l(22),2(24),4,1 1,1,5,17,18,20,22-nonaen-6-one (16.2 mg, 14%) as the second eluting peak.

Analytical data for (9S,11E,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1₂,₅.0⁴,₉.₀¹₈,₂₂.]tetracosa-l(22),2(24),4,1 1,1,5,17,18,20,22-nonaen-6-one: ¾ NMR (DMSO-d₆) δ: 13.42 (br. s, 1H), 7.89 - 8.00 (m, 1H), 7.50 - 7.56 (m, 1H), 7.42 - 7.49 (m, 1H), 7.24 - 7.37 (m, 1H), 6.96 - 7.04 (m, 1H), 6.81 - 6.90 (m, 1H), 6.10 - 6.24 (m, 1H), 5.85 - 5.99 (m, 1H), 4.84 - 4.92 (m, 1H), 4.04 - 4.25 (m, 2H), 3.73 - 4.04 (m, 2H), 3.04 - 3.28 (m, 3H), 2.65 - 2.78 (m, 1H, m/z (ESI, +ve) 376.3 (M+H)+.

Analytical data for (9S,11Z,13S)-13-(hydroxymethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1₂,₅.0⁴,₉.₀¹₈,₂₂.]tetracosa-l(22),2(24),4,1 1,1,5,17,18,20,22-nonaen-6-one: ¾ NMR (DMSO-d₆) δ: 13.68 - 13.80 (1H, m) 7.85 - 7.93 (1H, m) 7.54 - 7.63 (1H, m) 7.31 - 7.40 (1H, m) 7.16 - 7.23 (1H, m) 6.99 (1H, s) 6.79 (1H, s) 5.83 - 5.94 (1H, m) 5.47 - 5.57 (1H, m) 4.92 - 5.01 (1H, m) 4.58 - 4.68 (1H, m) 3.68 - 3.80 (1H, m) 3.54 - 3.64 (1H, m) 3.36 - 3.42 (1H, m) 3.17 - 3.28 (2H, m) 2.65 - 2.78 (1H, m) 2.61 (3H, s) 2.22 - 2.37 (1H, m): m/z (ESI, +ve) 376.3 (M+H)+.

Example 66: (9S,11E)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1₂,₅.0⁴,₉.₀¹₈,₂₂.]tetracosa-l(22),2(24),4,115,17,18,20,22-nonaen-6-one

Step 1: A solution of N,2-dimethylprop-2-en-l -amine (Frontier Scientific, 440 mg, 5.17 mmol), (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-
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c\pyridin-4(5H)-one (Intermediate D, 579 mg, 1.723 mmol), and DMSO (17.2 ml) was sealed under N₂ and stirred at 85 °C for 3 h. The reaction was cooled to RT. The reaction was diluted with water and extracted with DCM (3x). The combined organics were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo to a residue with spectral data consistent with the target diolefin product (680 mg, 98%): \( \text{\textsuperscript{1}H NMR (DMSO-dg) \( \delta \): 11.77 (br. s, 1H), 7.88 - 7.95 (1H, m) 7.60 - 7.67 (1H, m) 7.40 - 7.49 (1H, m) 7.05 - 7.11 (1H, m) 6.89 - 6.98 (1H, m) 5.76 - 5.88 (1H, m) 4.93 - 5.12 (4H, m) 3.95 - 4.01 (2H, m) 3.40 - 3.49 (1H, m) 3.12 - 3.21 (2H, m) 3.01 - 3.06 (4H, m), 2.61 - 2.67 (3H, m) 2.25 - 2.37 (1H, m) 1.69 (3H, s): m/z (ESI, +ve) 402.2 (M+H)\textsuperscript{+}.}

Step 2: (9S,1\textit{E})-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1.6.2.1^2-2.5^-0^-4.9^-0^-18.22^-]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one
A solution of Grubbs 2\textsuperscript{nd} Generation Catalyst (Sigma Aldrich, 288 mg, 0.339 mmol), (S)-7-allyl-2-(2-methyl-3-(methyl(2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-II-pyrrolo[3,2-c]pyridin-4(5H)-one (680 mg, 1.694 mmol), and DCM (33.6 ml) was bubbled with argon for 3 min, and the reaction mixture was sealed and heated to 55 °C for 2 h. An additional 10 mol% catalyst was added, and the reaction was resealed and heated to 55 °C for 18 h. It was cooled to RT, and silica was added. The silica mixture was concentrated in vacuo, and the reaction was chromatography purified on silica gel (eluent: 0 to 5% MeOH/DCM). The product fractions were combined and concentrated under reduced pressure. Addition of MeOH and sonication afforded the product as a solid that was collected by filtration. The filtrate was concentrated in vacuo and purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 \( \mu \text{m}, C\text{\textsubscript{18}}, 100 \text{ A}, 150 \times 30 \text{ mm}, 0.1\% \text{TFA in ACN/water}, \text{gradient 10\% to 95\% over 10 min (8 x 500 \mu l, injections, compound elution at \~8 min). The fractions were concentrated in vacuo on a Genevac EZ-2 Evaporator at 55 °C. The fractions were solubilized in MeOH, and the free base was generated by allowing the compound to filter through a Silicycle Si-carbonate cartridge (pre-washed with 10 mL MeOH). The yellow filtrate was concentrated under reduced pressure to a yellow residue. The residue was taken up in DCM, combined with the solid collected by filtration, and concentrated under reduced pressure to a give (9S,1\textit{E})-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1.6.2.1^2-2.5^-0^-4.9^-0^-18.22^-]tetracosa-1(22),2(24),4,11,15,17,18,20,22-nonaen-6-one as a solid (105 mg, 17%). \( \text{\textsuperscript{1}H NMR (400 MHz, DMSO-dg) \( \delta \): \~14.1, 8.0, 7.5, 7.0, 6.8, 5.8, 4.9, 3.9, 3.4, 3.0, 2.6, 2.2, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.0}.\]
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MHz, DMSO-d$_6$ δ ppm 12.98 - 13.03 (1 H, m) 8.00 - 8.05 (1 H, m) 7.55 - 7.61 (1 H, m) 7.35 - 7.41 (1 H, m) 7.05 - 7.11 (1 H, m) 6.91 - 6.95 (1 H, m) 5.73 - 5.79 (1 H, m) 4.25 - 4.33 (1 H, m) 4.08 - 4.18 (1 H, m) 3.41 (3 H, s) 3.14 - 3.26 (3 H, m) 2.73 (3 H, s) 2.31 - 2.43 (2 H, m) 1.68 (3 H, s): m/z (ESI, +ve) 374.1 (M+H)$^+$.  

Example 67: (9S,11E,13S)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1$^2$2,5$^2$.0$^4$9$^4$.0$^18$22$^2$.]tetracosa-$l$(22),2(24),4,11,15,17,18,20,22-nonaen-6-one  

Example 68: (9S,11E,13R)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1$^2$2,5$^2$.0$^4$9$^4$.0$^18$22$^2$.]tetracosa-$l$(22),2(24),4,11,15,17,18,20,22-nonaen-6-one

Step 1: (7S)-7-allyl-2-(3-((5-hydroxypent-1-en-3-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one  

A suspension of DIPEA (EMD Biosciences, 1089 μl, 6.26 mmol), 3-aminopent-1-en-1-ol hydrochloride (Squarix Biotechnology, 431 mg, 3.13 mmol), and (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-indol-4(5H)-one (Intermediate D, 420 mg, 1.252 mmol) in DMSO (8349 μl) was sealed and heated to 85 °C for 2 h. The reaction mixture was cooled, diluted with water and saturated aqueous NH$_4$Cl and extracted with DCM (3x). The combined organics were dried over Na$_2$SO$_4$, silica gel was added, and the mixture was concentrated in vacuo. The crude reaction was chromatographically purified on silica gel (eluent: 0.5 to 10% MeOH/DCM). The product fractions were combined and concentrated under reduced pressure to give (7S)-7-allyl-2-(3-((5-hydroxypent-1-en-3-yl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one:  

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 11.89 - 12.13 (1 H, m) 7.71 - 7.97 (1 H, m) 7.43 - 7.65 (1 H, m) 7.19 - 7.32 (1 H, m) 7.05 - 7.16 (1 H, m) 6.86 - 7.04 (3 H, m) 5.63 - 6.12 (2 H, m) 5.07 - 5.30 (4 H, m) 4.69 - 4.96 (2 H, m) 3.45 - 3.68 (3 H, m) 3.03 - 3.30 (4 H, m) 2.28 - 2.42 (1 H, m) 1.84 - 2.06 (2 H, m): m/z (ESI, +ve) 418.2 (M+H)$^+$.  

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Step 2: (9S,1 lE,13S)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4, 11,15,17, 1 8,20,22-nonaen-6-one and (9S, 1 lE, 13R)- 13-(2-hydroxy ethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4, 11,15,17, 18,20,22-nonaen-6-one
A solution of Grubbs 2nd Generation Catalyst (Sigma Aldrich, 252 mg, 0.297 mmol), (7S)-7-allyl-2-(3-(5-hydroxypent-1-en-3-yl)amino)-2-methylquinoxalin-5-yl)-6,7-
dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (620 mg, 1.485 mmol), and DCM (74.300 mL) was bubbled through with argon gas for 60 s. The reaction was sealed and stirred at 50 °C for 2 h. The reaction was cooled, silica gel was added, and the mixture was concentrated in vacuo. The crude reaction was purified on silica gel (eluent: 5% MeOH/DCM) to give a mixture of isomers. The isomers were further purified by SFC (AD-H Column, 5 µm in width at 21x150 mm, P = 200 bar, T = 40 °C with 40% EtOH at 1 mL/min, solubilized in 1:1 DCM/MeOH), affording (9S, l lE, 13S)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (54 mg, 19%) as the first eluting peak and (9S, l lE, 13R)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (86 mg, 30%) as the second eluting peak.

Analytical data for (9S, l lE, 13S)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one: ¾NMR (DMSO-d₆) δ: 13.63 - 13.67 (m, 1H), 7.98 - 8.03 (m, 1H), 7.54 - 7.59 (m, 1H), 7.32 - 7.38 (m, 2H), 7.03 - 7.07 (m, 1H), 6.90 - 6.93 (m, 1H), 5.86 - 6.07 (m, 2H), 5.28 - 5.32 (m, 1H), 4.30 - 4.39 (m, 1H), 3.70 - 3.86 (m, 2H), 3.24 - 3.31 (m, 1H), 3.08 - 3.21 (m, 1H), 2.57 - 2.70 (m, 2H), 2.57 (s, 3H), 2.19 - 2.27 (m, 1H), 2.04 - 2.16 (m, 1H), 1.75 - 1.84 (m, 1H): m/z (ESI, +ve) 390.2
(M+H)+.

Analytical data for (9S, l lE, 13R)-13-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm
13.37 - 13.44 (1 H, m) 7.93 - 7.97 (1 H, m) 7.46 - 7.53 (2 H, m) 7.27 - 7.33 (1 H, m) 7.00 - 7.04 (1 H, m) 6.83 - 6.87 (1 H, m) 6.18 - 6.26 (1 H, m) 5.85 - 5.96 (1 H, m) 4.21 - 4.30 (1 H, m) 3.41 - 3.51 (2 H, m) 3.23 - 3.38 (2 H, m) 3.08 - 3.15 (1 H, m) 2.57 - 2.62 (1 H
Example 69: (9S,11E)-21-fluoro-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^{2,5}.0^{4,9}.0^{18,22}]nortetracosa-l(22),2(24),4,11,15,18,20,22-nonaen-6-one.

Step 1: 8-bromo-7-fluoro-3-methyl-N-(2-methylallyl)quinoxalin-2-amine

5-Bromo-3-chloro-6-fluoro-2-methylquinoxaline (Intermediate K, 674 mg, 2.45 mmol) and 2-methylallylamine (Matrix Scientific, Columbia, SC, 0.87 mL, 12.23 mmol) in DMSO (10 mL) was stirred at 100 °C for 4 h. The reaction mixture was treated with DCM (50 mL), and washed with saturated aqueous NaHCO₃ (2 x 25 mL) and then with brine (1 x 25 mL). The organic layer was dried over MgSO₄, filtered and concentrated.

The crude product was adsorbed onto silica gel and was purified using an ISCO Combiflash Rf (40 g Thomson SingleStep column, using a gradient of 0-60% EtOAc in hexanes) affording 8-bromo-7-fluoro-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (670 mg, 2.16 mmol, 88 % yield) as an orange crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 (1 H, br. s.), 7.17 (1 H, t, J=8.5 Hz), 5.06 (1 H, br. s.), 5.02 (1 H, br. s.), 4.94 (1 H, br. s.), 4.30 (2 H, br. s.), 2.58 (3 H, br. s.), 1.88 (3 H, br. s.), 1.54 (2 H, br. s.). ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -103.10 (1 F, s). m/z (ESI, +ve ion) 310.0/312.0 (M+H)*.

Step 2: (S)-7-allyl-2-(6-fluoro-2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yi)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A glass microwave tube was charged with (5)-7-allyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate L, 117 mg, 0.387 mmol), K₂P₂O₇ (Aldrich , 246 mg, 1.16 mmol), Pd₂(dba)₃ (Strem Chemicals, 17.71 mg, 0.019 mmol), XPhos (Strem Chemicals, 18.44 mg, 0.039 mmol) and 8-bromo-
7-fluoro-3-methyl-N-(2-methylallyl)quinoxalin-2-amine (120 mg, 0.387 mmol) in 1,4-dioxane (3.0 mL) and water (1.1 mL). The reaction was stirred and heated in a heating block at 110 °C for 1 h. The mixture was treated with water and extracted with EtOAc (2 x 25 mL), washed with brine and concentrated. The residue was purified on the Gilson 5 (Silicycle Silichrome XT C18 column; 30 x 150 mm, 5 μ, 20-95% 0.1%TFA/CH3CN in 0.1%TFA/water) affording (5)-7-allyl-2-(6-fluoro-2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one 2,2,2-trifluoroacetate (36.3 mg, 0.070 mmol, 18.06% yield) as a yellow-orange amorphous solid after drying in the genevac overnight: 1H NMR (400 MHz, MeOD) δ ppm 7.62 (1 H, br. s.), 7.23 (1 H, t, J=10.2 Hz), 7.17 (1 H, br. s.), 5.81 - 5.96 (1 H, m), 5.10 - 5.20 (2 H, m), 4.98 (2 H, d, J=16.6 Hz), 4.10 - 4.24 (2 H, m), 3.69 (1 H, d, J=12.3 Hz), 3.46 (1 H, d, J=13.1 Hz), 3.09 (1 H, br. s.), 2.60 (3 H, br. s.), 2.54 (1 H, d, J=13.9 Hz), 2.36 - 2.48 (1 H, m), 1.91 (3 H, br. s.). m/z (ESI, +ve ion) 406.1 (M+H)⁺. The material was treated with DCM and washed with a saturated solution of NaHCO3 to provide the free-base for submission to the subsequent step.

Step 3: (S)-7-allyl-2-(6-fluoro-2-methyl-3-((2-methylallyl)amino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (30.9 mg, 0.076 mmol) and Grubbs Second Generation RCM catalyst (Aldrich, 12.9 mg, 0.015 mmol) were combined under argon and treated with DCM (5.0 mL). The reaction vessel was fitted with a water-cooled reflux condenser, and the reaction was heated to reflux for 1 h. The reaction mixture was concentrated and the crude residue taken up in DMSO (4 mL) and purified on the Gilson (Silicycle Silichrome XT C18 column; 30 x 150 mm, 5 μ, 20-95% 0.1%TFA/CH3CN in 0.1%TFA/water) affording the title compound (29.5 mg, 0.049 mmol, 63.9% yield) as its bis(TFA) salt as a rust-colored amorphous solid after drying in the genevac overnight: 1H NMR (400 MHz, MeOD) δ ppm 13.48 (1 H, br. s.), 7.52 (1 H, dd, J=9.0, 5.7 Hz), 7.15 - 7.24 (2 H, m), 5.80 (1 H, d, J=9.8 Hz), 4.15 - 4.23 (1 H, m), 4.04 - 4.13 (1 H, m), 3.55 (1 H, d, J=5.9 Hz), 2.59 (3 H, s), 2.41 - 2.55 (2 H, m), 2.33 - 2.40 (1 H, m), 1.69 (3 H, s). 19F NMR (376 MHz, MeOD) δ ppm -77.64 (6 F, s), -108.4 (1 F, s). m/z (ESI, +ve ion) 378.0 (M+H)⁺.
Example 70: (9S,12Z,13S)-20-methyl-15-oxa-3,7,18,21,27-pentaazahexacyclo[17.6.2.1~2,5~.0~4,9~.0~13,18~.0~22,26~]octacosa-l(26),2(28),4,11,19(27),20,22,24-octaen-6-one

Example 71: (9S,12E,13S)-20-methyl-15-oxa-3,7,18,21,27-pentaazahexacyclo[17.6.2.1~2,5~.0~4,9~.0~13,18~.0~22,26~]octacosa-l(26),2(28),4,11,19(27),20,22,24-octaen-6-one

TFA (Aldrich, 0.883 ml, 11.89 mmol) was added to a stirring solution of (S)-tert-butyl 3-vinylmorpholine-4-carboxylate (Synthesized from (R)-4-tert-butyl 3-methyl morpholine-3,4-dicarboxylate (Acesys Pharmatech, North Brunswick, NJ) according to WO05080386; 0.469 g, 2.200 mmol) in 2 mL DCM at RT. After 1 h, the reaction was concentrated. The material was combined with (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.200 g, 0.595 mmol) and DIPEA (Aldrich; 0.827 ml, 4.76 mmol) in 2 mL DMSO, was sealed, and heated to 70 °C for 36 h. The reaction was partitioned between saturated aqueous NaHCO₃ and EtOAc. The organic layer was washed with brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (24 g) using 0 - 100 % 90/10 DCM/MeOH. The product containing fractions were concentrated in vacuo to give 0.236 g of an orange foam. This material was combined with Grubbs catalyst, 2nd generation (Aldrich; 0.233 g, 0.275 mmol) and 27 mL DCM, and argon was bubbled through the solution for 1 min. The reaction was sealed and heated to 50 °C for 1 h. 1 mL MeOH was added followed by 2 g silica gel and the mixture was concentrated in vacuo. The material was purified by silica gel chromatography (24 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to give 0.091...
g. This was further purified by chiral SFC (Column: Chiralcel OD-H (Sepax) (250 x 21 mm, 5 µ); Mobile Phase: 50:50 (A:B); A: Liquid C0, B: MeOH (20 mM NH3); Flow Rate: 55 mL/min; Oven Temp: 40 °C; Inlet Pressure: 206 bar) to give:

(9S,1Z,13S)-20-methyl-15-oxa-3,7,18,2,12,27-pentaaazaheptacyclo[17.6.2.1~2,5~.0~4,9~.0~13,1~8~.0~22,26~]octacosa-1(26),2(28),4,1,19(27),20,22,24-octaen-6-one (Example 70, first eluting peak; 0.011 g, 0.027 mmol, 4.5 % yield) as a yellow solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 13.02 (1 H, br. s.), 7.97 (1 H, dd, J=7.4, 1.2 Hz), 7.69 (1 H, dd, J=8.1, 1.1 Hz), 7.49 - 7.61 (1 H, m), 7.03 (1 H, d, J=4.3 Hz), 6.82 (1 H, d, J=2.0 Hz), 5.97 - 6.09 (1 H, m), 5.85 - 5.97 (1 H, m), 4.57 - 4.70 (1 H, m), 3.76 - 3.97 (3 H, m), 3.56 - 3.69 (2 H, m), 3.42 - 3.51 (1 H, m), 3.35 - 3.42 (1 H, m), 3.15 - 3.28 (2 H, m), 2.72 (3 H, s), 2.62 - 2.71 (1 H, m), 2.34 - 2.43 (1 H, m). m/z (ESI, +ve) 402.2 (M+H)+.

(9S,1IE,13S)-20-methyl-15-oxa-3,7,18,2,12,27-pentaaazaheptacyclo[17.6.2.1~2,5~.0~4,9~.0~13,1~8~.0~22,26~]octacosa-1(26),2(28),4,1,19(27),20,22,24-octaen-6-one (Example 71, second eluting peak; 0.070 g, 0.174 mmol, 29.2 % yield) as a yellow solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 11.37 (1 H, br. s.), 7.83 (1 H, d, J=7.2 Hz), 7.72 (1 H, d, J=7.2 Hz), 7.50 - 7.59 (1 H, m), 6.99 (1 H, d, J=3.9 Hz), 6.60 (1 H, s), 6.40 (1 H, dd, J=15.6, 6.3 Hz), 5.68 (1 H, t, J=11.2 Hz), 3.97 (1 H, br. s.), 3.73 - 3.88 (3 H, m), 3.66 (1 H, dd, J=11.1, 5.2 Hz), 3.49 - 3.61 (1 H, m), 3.34 - 3.42 (3 H, m), 3.22 - 3.30 (1 H, m), 2.79 - 2.93 (1 H, m), 2.67 (3 H, s), 2.28 - 2.39 (1 H, m). m/z (ESI, +ve) 402.2 (M+H)+.

Example 72: 16-methyl-3,7,14,17,23-pentaaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,15(23),16,18,20-heptaen-ll-yn-6-one

Step 1: tert-butyl (4-chlorobut-2-yn-1 -yl)carbamate
To a stirring solution of l-amino-4-chloro-2-butyne hydrochloride (Aldrich; 5.00 g, 35.7 mmol) in 125 mL 5:1 H₂O/MeOH was added di-tert-butyl dicarbonate (Aldrich; 8.57 g, 39.3 mmol) and NaOH 10.0 N (Ricca Chemical; 4.29 ml, 42.9 mmol). After 3 h, the reaction was extracted 3 x DCM, and the combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (160 g column) using 0 - 100% DCM/hexane. The product-containing fractions were concentrated to afford tert-butyl (4-chlorobut-2-yn-1-yl)carbamate (3.7 g, 18.17 mmol, 50.9 % yield) as a clear/colorless oil. ³¹H NMR (400 MHz, CDCl₃) δ ppm 4.69 (1 H, br. s.), 4.14 (2 H, t, J=2.1 Hz), 3.99 (2 H, br. s.), 1.48 (9 H, br. s).

Step 2: tert-butyl 5-(4-((tert-butoxycarbonyl)amino)but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate
A solution of tert-butyl (4-chlorobut-2-yn-1-yl)carbamate (0.764 g, 3.75 mmol) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (0.200 g, 0.938 mmol) in 9 mL THF under N₂ was cooled in an ice/salt bath (~10 °C). LiHMDS solution 1.0 M in THF (3.28 ml, 3.28 mmol) was added slowly dropwise. A thick precipitate formed, which disappeared upon complete addition of LiHMDS. After 1 h, additional 2 mL LiHMDS 1.0 M in THF was added. After 30 min additional 2 mL LiHMDS 1.0 M in THF was added. After 30 min, the reaction was treated with water and EtOAc, and 5 N HCl was added to acidify the aqueous layer. The layers were separated, and organic layer was washed 1x brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (24 g) using 0 - 100% EtOAc/hexane. The product-containing fractions were concentrated to afford tert-butyl 5-(4-((tert-butoxycarbonyl)amino)but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (0.245 g, 0.644 mmol, 68.7 % yield) as a glass: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.33 (1 H, br. s.), 7.14 (1 H, br. s.), 4.94 (1 H, s), 3.79 (2 H, d, J=4.7 Hz), 3.69 (2 H, br. s.), 2.50 - 2.70 (2 H, m), 2.19 - 2.43 (1 H, m), 1.44 (9 H, s), 1.37 (9 H, s).

Step 3: 16-methyl-3,7,14,17,23-pentaazapentacyclo[1.3.6.2.1~2,5~,.0~4,9~.0~1~8,22~]tetracosa-l(22),2(24),4,15(23),16,18,20-heptaen-11-yn-6-one
TFA (Aldrich; 0.957 ml, 12.88 mmol) was added to a solution of tert-butyl 5-(4-((tert-butoxycarbonyl)amino)but-2-yn-1-yl)-2,4-dioxopiperidine-1-carboxylate (0.245 g, 0.644
mmol) in 6 mL DCM. The reaction was fitted with a drying tube and stirred rapidly at RT for 1.5 h. The reaction was concentrated in vacuo to give an orange oil. This material was treated with NH₄OAc (Fisher, 0.298 g, 3.86 mmol), 2-bromo-1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (0.182 g, 0.644 mmol), and 6 mL EtOH. The homogeneous reaction was sealed and heated at 50 °C for 4 h. A precipitate had formed. The reaction was cooled and treated with 3:1 chloroform/IPA and MeOH, and stirred rapidly for 30 min. The layers were separated and the aqueous layer was extracted 3x DCM/IPA. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with 10% MeOH in DCM and adsorbed onto 1 g silica gel and purified by silica gel chromatography (24 g) using 0-100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.020 g material. This was sonicated in MeOH, filtered, rinsing with MeOH, and the solid was collected and dried in vacuo to give 16-methyl-3,7,14,17,23-pentaazapentacyclo[12.6.2.1.2,5.0.4,9.0.19,23]tetracosa-1(22),2(25),4,16,18,20,23-heptaen-6-one (0.013 g, 0.038 mmol, 5.88% yield):

Mass spectrum (ESI, +ve) m/z 344.1 (M+H)⁺.

Example 73: 17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[14.6.2.1.2,5.0.4,9.0.19,23]pentacosa-1(22),2(25),4,16,18,20,23-heptaen-6-one

Step 1: tert-butyl 5-(2-(2-bromoethoxy)ethyl)-2,4-dioxopiperidine-1-carboxylate
To a solution of tert-butyl 2,4-dioxopiperidine-l-carboxylate (Ark Pharma, Libertyville, IL, 1.32 g, 6.19 mmol) and bis(2-bromoethyl) ether (Sigma-Aldrich, 5.74 g, 24.76 mmol) in 30 mL of THF at -25 to -20 °C was added LiHMDS (15.48 mL of 1.0 M in THF, 15.48 mmol) slowly such that the internal temperature did not exceed -20 °C. The clear yellow reaction mixture was stirred for 1 h (final temperature at -20 °C) and was quenched by the addition of 20 mL of ice cold 0.5 N HCl, and extracted with 2X75 mL of EtOAc. The combined organic solution was washed with brine, dried over Na2SO4 and concentrated. The residue of was purified on a silica gel column (20-65% EtOAc in hexanes) to give tert-butyl 5-(2-(2-bromoethoxy)ethyl)-2,4-dioxopiperidine-l-carboxylate (750 mg, 33% yield) as an amorphous solid: 1H NMR (400 MHz, DMSO-d6) δ ppm 11.16 (1 H, br. s), 4.85 (1 H, s), 3.97-3.63 (4 H, m), 3.52-3.42 (5 H, m), 1.55 (1 H, m), 1.53 (1 H, m), 1.36 (9 H, s). m/z (ESI, +ve) 386/388 (M+Na)+.

Step 2: 5-(2-(2-azidoethoxy)ethyl)piperidine-2,4-dione

A mixture of tert-butyl 5-(2-(2-bromoethoxy)ethyl)-2,4-dioxopiperidine-l-carboxylate (750 mg, 2.05 mmol) and sodium azide (268 mg, 4.12 mmol) in 4 mL of DMF was stirred at RT for 18 h. Additional 134 mg of sodium azide was added to the reaction mixture and stirring was continued for 18 h. The reaction mixture was filtered through a pad of Celite and rinsed with 2X1.5 mL of EtOAc. The filtrate was washed with 10 mL of water. The water layer was extracted with 2X25 mL of EtOAc. The combined organic extracts were concentrated and the residue was purified on a silica gel column (30-50% EtOAc in hexanes) to give tert-butyl 5-(2-(2-azidoethoxy)ethyl)-2,4-dioxopiperidine-l-carboxylate (430 mg) as a viscous clear oil: m/z (ESI, +ve) 349.1 (M+Na)+. A solution of tert-butyl 5-(2-(2-azidoethoxy)ethyl)-2,4-dioxopiperidine-l-carboxylate (430 mg, 1.31 mmol) in 5 mL of DCM at RT was treated with 0.5 mL of TFA and stirred for 1 h. It was concentrated under reduced pressure and the residue was dissolved in 50 mL of DCM and vigorously stirred with 15 g of NaHCO3 for 15 min. It was filtered and rinsed with 2X10 mL of DCM. The filtrate was concentrated to give 5-(2-(2-azidoethoxy)ethyl)piperidine-2,4-dione (300 mg, 64% yield) as a brown oil, which was used in next step without further purification: m/z (ESI, +ve) 227.0 (M+H)+.

Step 3: 7-(2-(2-azidoethoxy)ethyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one
A mixture of 2-bromo-1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (313 mg, 1.10 mmol), 5-(2-(2-azidoethoxy)ethyl)piperidine-2,4-dione (300 mg, 1.32 mmol), and NH₄OAc (511 mg, 6.63 mmol) in 10 mL EtOH in a sealed glass tube was heated in an oil bath at 50 °C for 4 h. The reaction was concentrated to 1/4 of its volume; then partitioned between saturated NaHCO₃ (15 mL) and CH₂Cl₂ (15 mL). The aqueous layer was extracted with 3X10 mL of CH₂Cl₂, and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (50% EtOAc in DCM followed by 2-10% MeOH in DCM) to give 7-(2-(2-azidoethoxy)ethyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (134 mg, 29% yield) as a brown amorphous solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.56 (1 H, br. s), 8.10 (1 H, d, J=7.4 Hz), 7.92 (1 H, d, J=8.2 Hz), 7.82 (1 H, t, J=7.8 Hz), 7.19 (1 H, d, J=2.2 Hz), 7.02 (1 H, br.), 3.51 - 3.70 (5 H, m), 3.44 (2 H, m), 3.26 (1 H, m), 3.14 (1 H, m), 2.72 (3 H, s), 2.09 (1 H, m), 1.80 (1 H, m). m/z (ESI, +ve) 410.1 (M+H)⁺.

Step 4: 17-methyl-12-oxa-3,7,15, 18,24-pentaazapentacyclo[1 4.6.2.1.25.3.0.4.9.3.0.1.9.23.1]pentacosal[22],2(25),4,16,1 8,20,23-heptaen-6-one

A mixture of 7-(2-(2-azidoethoxy)ethyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (100 mg, 0.244 mmol) and palladium on activated carbon (10% wt, 26.0 mg, 0.024 mmol) in 7.5 mL of THF and 0.5 mL of EtOH was hydrogenated with a balloon filled with H₂ for 18 h. Additional palladium on activated carbon (10% wt, 26.0 mg, 0.024 mmol) was added to the reaction mixture and hydrogenation with a balloon filled with H₂ was continued for 18 h. It was filtered through a pad of Celite and rinsed with 10 mL of EtOAc followed by 10 mL of EtOH. The filtrate was concentrated and the residue was purified on a silica gel column (1-5% DCM in MeOH) to give 17-methyl-12-oxa-3,7,15, 18,24-pentaazapentacyclo[1 4.6.2.1.25.3.0.4.9.3.0.1.9.23.1]pentacosal[22,2(25),4,16,1 8,20,23-heptaen-6-one (34 mg, 38% yield) as a yellow crystalline solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.72 (1 H, br.), 7.96 (1 H, dd, J=7.6, 1.2 Hz), 7.60 (1 H, m), 7.57 (1 H, m), 7.34 (1 H, t, J=7.8 Hz), 6.95 (1 H, m), 3.78 (2 H, m), 3.65 (3 H, m), 3.38 - 3.56 (3 H, m), 3.05 - 3.28 (2 H, m), 2.57 (3 H, s), 1.71 (2 H, m). m/z (ESI, +ve) 364.1 (M+H)⁺.
Example 74: (9S,11E)-16-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one

Example 75: (9S,11Z)-16-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one

Step 1: N-(3-(methylsulfonyl)propyl)prop-2-en-1-amine

A solution of 1-bromo-3-(methylsulfonyl)propane (0.355 g, 1.765 mmol)/l-chloro-3-(methylsulfonyl)propane (WO09021965, 0.277 g, 1.765 mmol) in allylamine (2.65 ml, 35.3 mmol) was stirred at RT for 16 h. The crude product was directly injected onto the column and was purified via automated flash chromatography (silica gel) with 100% DCM to 5% 2 M NH₃ in MeOH/DCM to give A^-(3-(methylsulfonyl)propyl)prop-2-en-1-amine (0.219 g, 1.235 mmol, 70.0 % yield) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 1.56 (br. s., 1 H) 1.88 (tt, J=14.28, 7.43 Hz, 2 H) 2.64 (t, J=6.75 Hz, 2 H) 2.81 (s, 3 H) 3.03 (t, J=7.63 Hz, 2 H) 3.12 (d, J=5.87 Hz, 2 H) 4.98 (d, J=10.17 Hz, 1 H) 5.06 (d, J=17.21 Hz, 1 H) 5.75 (ddt, J=16.87, 10.61, 5.82, 5.82 Hz, 1 H). MS (ESI, pos.) m/z: 178.2 (M+H)^+.

Step 2: (S)-7-allyl-2-(3-(allyl(3-(methylsulfonyl)propyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 163 mg, 0.485 mmol) and N-(3-
A-1700-WO-PCT

(methylsulfonyl)propyl)prop-2-en-l-amine (172 mg, 0.969 mmol) in DMSO (4846 µl) was stirred at 70 °C for 16 h. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (2 x 100 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% hexanes/EtOAc (2:1) to 30% EtOH/hexanes/EtOAc (2:1) to give (S)-7-allyl-2-(3-(methylsulfonyl)propyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (180 mg, 0.365 mmol, 75% yield) as a yellow solid: 1H NMR (400 MHz, CDCl₃) δ ppm 2.21 (quin, J=7.38 Hz, 2 H) 2.42 - 2.52 (m, 1 H) 2.54 - 2.60 (m, 1 H) 2.76 (s, 3 H) 2.86 (s, 3 H) 3.04 - 3.10 (m, 2 H) 3.10 - 3.16 (m, 1 H) 3.42 (ddd, J=12.18, 5.72, 3.23 Hz, 1 H) 3.56 - 3.66 (m, 1 H) 3.66 - 3.76 (m, 2 H) 4.04 (d, J=6.06 Hz, 2 H) 5.13 - 5.22 (m, 2 H) 5.32 - 5.42 (m, 3 H) 5.81 - 6.01 (m, 2 H) 7.19 (d, J=2.15 Hz, 1 H) 7.56 (t, J=7.82 Hz, 1 H) 7.77 (dd, J=8.22, 1.17 Hz, 1 H) 7.96 (dd, J=7.63, 1.17 Hz, 1 H) 11.58 (br. s., 1 H). MS (ESI, pos. ion) m/z: 494.4 (M+H)+.

Step 3: A solution of (S)-7-allyl-2-(3-(methylsulfonyl)propyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (0.180 g, 0.365 mmol) and Grubbs catalyst 2nd generation (0.062 g, 0.073 mmol) in DCM (18.23 ml) was sparged with N₂ before it was heated to 50 °C for 2 h. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 6% 2 M NH₃ in MeOH/DCM to give a mixture of products (13.1 mg, 0.281 mmol, 77% yield) as a ~2:1 mixture of isomers via NMR as a yellow solid. MS (ESI, pos. ion) m/z: 466.2 (M+H)+. The material was further purified by SFC:

Column: AS-H (5 μm, 21 mm x 250 mm, S/N = 5172), F = 50 ml/min, 50% MeOH 20 mM NH₃/CO₂. All sample dissolved in 12 ml MeOH/DCM 1/1 P = 206 bar, 1.1 ml injection, 290 nm, to give (9S,1 IE)-16-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-l(22),2(24),4,1 1,5(23),1 6,1 8,20-octaen-6-one (first eluting peak, 46 mg, 0.10 mmol, 35%) and (9S,1 II)-1 6-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-l(22),2(24),4,1 1,5(23),1 6,1 8,20-octaen-6-one (second eluting peak, 58 mg, 0.13 mmol, 44%).

Analytical data for (9S,1 IE)-16-methyl-14-(3-(methylsulfonyl)propyl)-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5-0-4,9-0-1 8,22-]tetracosa-
A-1700-WO-PCT

l(22),2(24),4,l,1 l 5(23),1 6,1 8,20-octaen-6-one: ¾ N M (400 MHz, CDCh) δ ppm 2.3 1 -
2.47 (m, 3 H ) 2.65 (d, = 1 3.89 ... mg, 2.05 1 mmol) in DMSO
(6838 µ ΐ) was stirred a t 7 0 ° C for 2 4 h . The reaction mixture was diluted with DCM (150

Example 76: (9S,1Z)-16-methyl-14-(3-(methylsulfonyl)propyl)-7,23-
pentaazapentacyclo[l 3.6.2.1~2,5~.0~4,9~.0~18,22~
tetracosa-
l(22),2(24),4,l,1 l 5(23),1 6,1 8,20-octaen-6-one: ¹H N M R (400 MHz, CDCh) δ ppm 2.17 -
2.29 (m, 1 H ) 2.32 (d, J=14.87 Hz, 1 H ) 2.40 (dt, J=14.82, 7.36 Hz, 1 H ) 2.68 - 2.80 (m, 1
H) 2.81 (s, 3 H ) 2.95 (s, 3 H ) 3.06 (t, J=7.34 Hz, 2 H ) 3.30 - 3.42 (m, 1 H ) 3.42 - 3.52 (m,
2 H ) 3.65 - 3.78 (m, 3 H ) 4.84 (dd, J=16.53, 8.90 Hz, 1 H ) 5.26 (d, J=3.13 Hz, 1 H ) 5.74
(dd, J=10.76, 9.00 Hz, 1 H ) 5.83 (dd, J=12.52, 11.54 Hz, 1 H ) 6.99 (d, J=2.35 Hz, 1 H )
7.51 (t, J=8.02 Hz, 1 H ) 7.72 (dd, J=8.12, 1.08 Hz, 1 H ) 7.88 (dd, J=7.24, 1.17 Hz, 1 H )
12.77 (br. s., 1 H ). MS (ESI, pos. ion) m/z: 466.2 (M+H)+.

Example 77: (9S,HZ)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~
tetracosa-
l(22),2(24),4,l,1 l 5(23),1 6,1 8,20-octaen-6-one

Step 1: (S)-7-allyl-2-(3-(allyl(2-hydroxyethyl)amino)-2-methylquinaxin-5-yl)-6,7-
dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one
A solution of (S)-7-allyl-2-(3-fluoro-2-methylquinaxin-5-yl)-6,7-dihydro-1H-
pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 230 mg, 0.684 mmol) and 2-
allylamino)ethanol (Ryan Scientific, Mt. Pleasant, SC, 207 mg, 2.05 l mmol) in DMSO
(6838 µι) was stirred at 70 °C for 24 h. The reaction mixture was diluted with DCM (150
ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (3 x 100 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 6% 2 M NH₃ in MeOH/DCM to give (S)-7-allyl-2-(3-(allyl(2-hydroxyethyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-H-pyrrolo[3,2-c]pyridin-4(5H)-one (264 mg, 0.632 mmol, 92% yield) as a yellow foam: ¹H NMR (400 MHz, CDCl₃) δ ppm: 2.36 - 2.47 (m, 1 H) 2.51 - 2.59 (m, 1 H) 2.67 (t, J=5.18 Hz, 1 H) 2.75 (s, 3 H) 3.02 - 3.10 (m, 1 H) 3.30 - 3.37 (m, 1 H) 3.60 - 3.69 (m, 1 H) 3.69 - 3.75 (m, 1 H) 3.75 - 3.83 (m, 1 H) 3.93 (q, J=5.67 Hz, 2 H) 4.12 (d, J=5.48 Hz, 2 H) 5.10 (s, 1 H) 5.14 (d, J=6.46 Hz, 1 H) 5.31 - 5.42 (m, 3 H) 5.76 - 5.89 (m, 1 H) 5.92 - 6.04 (m, 1 H) 7.10 (d, J=2.15 Hz, 1 H) 7.46 (t, J=7.82 Hz, 1 H) 7.70 (dd, J=8.02, 0.98 Hz, 1 H) 7.88 (dd, J=7.53, 1.08 Hz, 1 H) 11.86 (br. s., 1 H) MS (ESI, pos. ion) m/z: 418.4 (M+H)+.

Step 2: (9S,1lE)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0-.4.9-.0-1 8.22-.]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one and (9S,1lZ)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0-.4.9-.0-18.22-.]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one.

A solution of (S)-7-allyl-2-(3-(allyl(2-hydroxyethyl)amino)-2-methylquinoxalin-5-yl)-6,7-dihydro-H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.264 g, 0.632 mmol) (sonicated to dissolve in DCM) and Grubbs catalyst 2nd generation (0.107 g, 0.126 mmol) in DCM (31.6 ml) was stirred at 40 °C in a sealed flask for 2 h. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 6% 2 M NH₃ in MeOH/DCM to give a mixture of E and Z isomers (188 mg, 0.483 mmol, 76% yield) as a yellow solid. The material was purified by SFC: Column: AS-H (5 μm, 21 mm x 250 mm, S/N = 5172). F = 60 ml/min, 45% MeOH 20 mM NH₃/CO₂. All sample dissolved in 50 ml MeOH/DCM 1/4, P = 220 bar, 1.1 ml injection, 288 nm, to give (9S,1lE)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0-.4.9-.0-18.22-.]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one (first eluting peak, 52 mg, 0.13 mmol, 28%) and (9S,1lZ)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-.0-.4.9-.0-1 8.22-.]tetracosa-
l(22),2(24),4,11,15(23),16,18,20-octaen-6-one (second eluting peak, 92 mg, 0.24 mmol, 49%).

Analytical data for (9S,1lE)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one: 

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm

2.19 - 2.37 (m, 1 H) 2.62 (d, J=12.52 Hz, 1 H) 2.70 (s, 3 H) 3.12 - 3.20 (m, 1 H) 3.22 - 3.31 (m, 1 H) 3.35 - 3.40 (m, 1 H) 3.51 - 3.60 (m, 1 H) 3.62 - 3.71 (m, 1 H) 3.73 - 3.80 (m, 2 H) 4.28 (br. s., 2 H) 4.84 (t, J=5.18 Hz, 1 H) 5.91 - 6.03 (m, 1 H) 6.28 (d, J=15.45 Hz, 1 H) 6.97 (d, J=2.15 Hz, 1 H) 7.10 (d, J=4.50 Hz, 1 H) 7.48 (t, J=7.8 Hz, 1 H) 7.63 (dd, J=8.0, 1.3 Hz, 1 H) 8.09 (dd, J=7.5, 1.2 Hz, 1 H) 13.18 (br. s., 1 H). MS (ESI, pos. ion) m/z: 390.2 (M+H)$^+$. 

Analytical data for (9S,1lZ)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one: 

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm

2.31 (dd, J=12.91, 2.93 Hz, 1 H) 2.63 - 2.74 (m, 1 H) 2.80 (s, 3 H) 3.18 (d, J=5.28 Hz, 3 H) 3.39 (t, J=5.09 Hz, 1 H) 3.63 - 3.75 (m, 3 H) 3.81 - 3.87 (m, 1 H) 3.90 (d, J=16.24 Hz, 1 H) 4.77 (dd, J=16.43, 7.43 Hz, 1 H) 5.74 - 5.88 (m, 2 H) 6.84 (d, J=2.15 Hz, 1 H) 7.05 (d, J=4.50 Hz, 1 H) 7.44 (t, J=7.8 Hz, 1 H) 7.63 (dd, J=8.2, 1.7 Hz, 1 H) 7.94 (dd, J=7.4, 1.17 Hz, 1 H) 13.08 (br. s., 1 H). MS (ESI, pos. ion) m/z: 390.2 (M+H)$^+$. 

Example 78-80: (9S,1lE,13S)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one, (9S,1lE,13R)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one, (9S,1lZ)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15(23),16,18,20-octaen-6-one
Step 1: NaH (60% in mineral oil, 27.7 mg, 0.693 mmol) was added to a solution of but-3-en-2-ol (ASDI 500014001, 50 mg, 0.693 mmol) in DMF (2311 μL) at 0 °C; this was stirred for 10 min at 0 °C before solid (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 78 mg, 0.231 mmol) was added. The reaction mixture was warmed to RT and stirred for 2 h; more (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (62 mg) was added and stirred at RT (2 h); more (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (62 mg) was added and stirred at RT for 16 h. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO$_3$ (2 x 100 ml) before the organic layer was separated, dried over Na$_2$SO$_4$, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 4% 2 M NH$_3$ in MeOH/DCM to give (7S)-7-allyl-2-(3-(but-3-en-2-yloxy)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (111 mg, 0.286 mmol, 48% yield) as a yellow oil. $^1$H NMR (400 MHz, CDC$_3$) δ ppm: 1.64 (t, J=6.06 Hz, 3 H) 2.43 - 2.64 (m, 2 H) 2.69 (s, 3 H) 3.00 - 3.10 (m, 1 H) 3.43 (dq, J=12.30, 4.25 Hz, 1 H) 3.76 (dd, J=12.23, 5.18 Hz, 1 H) 5.14 (d, J=5.87 Hz, 1 H) 5.17 (t, J=6.65 Hz, 1 H) 5.30 (d, J=10.76 Hz, 1 H) 5.37 (dd, J=17.41, 4.30 Hz, 1 H) 5.63 - 5.71 (m, 1 H) 5.79 (br. s., 1 H) 5.93 (m, 1 H) 6.16 (ddt, J=17.31, 10.76, 4.55, 4.55 Hz, 1 H) 7.14 - 7.18 (m, 1 H) 7.55 (t, J=7.92 Hz, 1 H) 7.79 (d, J=8.22 Hz, 1 H) 7.98 (d, J=7.63 Hz, 1 H) 11.61 (d, J=43.04 Hz, 1 H). MS (ESI, pos. ion) m/z: 389.3 (M+H)$^+$.  

Step 2: A solution of (7S)-7-allyl-2-(3-(but-3-en-2-yloxy)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.111 g, 0.286 mmol) and Grubbs catalyst 2nd generation (0.049 g, 0.057 mmol) in DCM (28.6 ml) was stirred at 40 °C for 1 h. The
A crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 4% 2 M NH₃ in MeOH/DCM to give a yellow solid as a mixture of isomers. The mixture was dissolved in 1:1 MeOH/DCM (~20 mg/ml) and injected (5 x 1.0 ml) onto the Shimadzu preparatory LC (Phenomenex Gemini C₈ column (150 * 30 mm, 10 µm), 35 mL/min, 5-100% CH₃CN/H₂O + 0.1% TFA) before the pure fractions were combined, basicified with NaHCO₃ (saturated, aqueous), extracted with DCM, separated, dried over Na₂SO₄, and concentrated via rotary evaporation to give a single C₁₃ diastereomer of (9S,1IE)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1,2,2,4,1,1,15(23),16,18,20-octanen-6-one (Example 78, 16 mg, 0.044 mmol, 18% yield) and a mixture of isomers (24 mg). SFC purification of the mixture: Column: AS-H (5 µm, 21 mm x 250 mm, S/N = 5172), F = 60 ml/min, 35% MeOH 20 mM NH₃/CO₂. All sample dissolved in 4 ml MeOH/DCM 1/1, P = 213 bar, 1.1 ml injection, 288 nm, gave a single C₁₃ diastereomer of (9S,1IE)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1,2,2,4,1,1,15(23),16,18,20-octanen-6-one (Example 79, 15 mg, 0.042 mmol, 17%) and a single C₁₃ diastereomer of (9S,1IE)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1,2,2,4,1,1,15(23),16,18,20-octanen-6-one (Example 80, 2 mg, 0.005 mmol, 2%).

Analytical data for first isolated C₁₃ diastereomer of (9S,1IE)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1,2,2,4,1,1,15(23),16,18,20-octanen-6-one Example 78: ³¹NMR (400 MHz, DMSO-d₆) δ ppm 1.63 (d, J=6.65 Hz, 3 H) 2.27 - 2.39 (m, 1 H) 2.62 (s, 3 H) 2.71 (d, J=13.50 Hz, 1 H) 3.19 - 3.25 (m, 1 H) 3.31 - 3.40 (m, 3 H) 5.40 (br. s., 1 H) 5.86 - 5.97 (m, 1 H) 6.44 (d, J=16.04 Hz, 1 H) 6.92 (s, 1 H) 7.59 (t, J=8.02 Hz, 1 H) 7.74 (dd, J=8.22, 1.17 Hz, 1 H) 8.08 (d, J=6.65 Hz, 1 H) 12.74 (br. s., 1 H). MS (ESI, pos. ion) m/z: 361.1 (M+H)⁺.

Analytical data for second isolated C₁₃ diastereomer (9S,1IE)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[1,2,2,4,1,1,15(23),16,18,20-octanen-6-one Example 79: ³¹NMR (400 MHz, DMSO-d₆) δ ppm 1.60 (d, J=6.46 Hz, 3 H) 2.19 - 2.29 (m, 1 H) 2.61 (s, 3 H) 2.62 - 2.70 (m, 1 H) 3.10 - 3.19 (m, 1 H) 3.26 - 3.33 (m, 1 H) 3.36 - 3.42 (m, 1 H) 5.24 (quin, J=6.60 Hz, 1 H) 6.03 - 6.19 (m, 2 H) 7.00 (d, J=2.15 Hz, 1 H) 7.10 (d, J=4.30 Hz, 1 H) 7.58 (t,
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J=7.82 Hz, 1 H) 7.72 (dd, J=8.02, 1.17 Hz, 1 H) 8.14 (dd, J=7.63, 1.17 Hz, 1 H) 13.29 (br. s., 1 H). MS (ESI, pos. ion) m/z: 361.4 (M+H)+.

Analytical data for the single isolated C$_3$ diastereomer of (9S,11Z)-13,16-dimethyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20-octaen-6-one, Example 80: ¾NMR (400 MHz, CDCl$_3$)

δ ppm 1.58 - 1.60 (m, 3 H) 2.37 (d, J=15.06 Hz, 1 H) 2.62 - 2.73 (m, 1 H) 2.70 (s, 3 H)
3.35 - 3.48 (m, 2 H) 3.48 - 3.55 (m, 1 H) 5.30 (br. s., 1 H) 5.72 (quin, J=6.75 Hz, 1 H)
5.77 - 5.90 (m, 2 H) 6.97 (s, 1 H) 7.57 (t, J=8.02 Hz, 1 H) 7.79 (d, J=8.22 Hz, 1 H) 7.89 (d, J=7.43 Hz, 1 H) 13.14 (br. s., 1 H). MS (ESI, pos. ion) m/z: 361.2 (M+H)+.

Examples 81 and 82: (9tf)-17-methyl-12-oxa-3,7,15,18,24-pentaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
l(22),2(25),4,16,18,20,23-heptaen-6-one and (9S)-17-methyl-12-oxa-3,7,15,18,24-
pentaazapentacyclo[14.6.2.1~2,5~.0~4,9~.0~19,23~]pentacosa-
l(22),2(25),4,16,18,20,23-heptaen-6-one

A portion of Example 73 was separated by preparative SFC chromatography (Chiralpak AS-H (250 x 21), 5 μ, 60% CO$_2$ and 40% MeOH containing 0.2% DEA, flow rate 70 mL/min, 100 Bar, oven temperature 40 ºC) to give separated enantiomers with ee values greater than 99%, each. The 1st eluent was assigned as Example 82 and 2nd eluent was assigned as Example 81. Retention time was 2.04 min for 1st eluent and 2.99 min for 2nd eluent, using analytical SFC (Chiralpak AS-H (150 x 4.6), 5 μ, 60% CO$_2$ and 40% MeOH containing 0.2% DEA, flow rate 4.0 mL/min, 100 Bar, oven temperature 40 ºC).

Example 83: (9R,13R)-13,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,15,17,18,20,22-octaen-6-one
A suspension of (9R,11E,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.2.5.0.4,9.0.18,22-]tracosa-
(22),2(24),4,11,15,17,18,20,22-nonaen-6-one (Example 30; 33.0 mg, 0.092 mmol) and palladium on carbon (10% w/w) (Aldrich; 98 mg, 0.092 mmol) in THF (1.5 mL) was stirred under a H₂ atmosphere (45 psi) at 25 °C for 20 h. The reaction flask was flushed with argon, additional Pd/C (10% w/w) (49 mg, 0.046 mmol) was added, and the resulting suspension was stirred under a H₂ atmosphere (45 psi) at 25 °C for 1 d. The reaction flask was flushed with argon, and the resulting suspension was filtered through Celite, sequentially washing with MeOH (10 mL) and 1:1 MeOH/DCM (10 mL). The combined filtrates were concentrated in vacuo to provide a yellow solid. This solid was taken up in MeOH (2.0 mL), NaOH (1.0N, aqueous) (0.184 mL, 0.184 mmol) and H₂O₂ (30%, w/w) (0.014 mL, 0.138 mmol) were sequentially added, and the resulting mixture was stirred at 25 °C for 10 min. The reaction mixture was then partitioned between 5% MeOH/DCM (40 mL) and 10:1 water/brine (30 mL). The organic layer was separated, and the aqueous layer was extracted with 5% MeOH/DCM (2 × 30 mL). All organic layers were then combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 20-100% EtOAc/hexanes, then 0-100% MeOH/DCM) furnished (9R,13R)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.2.5.0.4,9.0.18,22-]tracosa-
(22),2(24),4,11,15,17,18,20,22-octaen-6-one (12.1 mg, 0.033 mmol, 36% yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.39 - 13.53 (1 H, m), 8.00 (1 H, dd, J=7.0, 2.8 Hz), 7.56 (1 H, dd, J=8.0, 1.2 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.06 (1 H, d, J=4.9 Hz), 7.01 (1 H, d, J=4.3 Hz), 6.95 (1 H, d, J=2.0 Hz), 3.54 - 3.67 (1 H, m), 3.19 - 3.26 (1 H, m), 3.14 (1 H, br. s.), 3.01 (1 H, t, J=12.0 Hz), 2.57 (3 H, s), 2.39 (1 H, t, J=12.0 Hz), 2.18 - 2.29 (1 H, m), 1.93 - 2.06 (1 H, m), 1.60 - 1.70 (1 H, m), 1.41 - 1.52 (1 H, m), 1.39 (3 H, d, J=6.7 Hz), 1.20 - 1.27 (1 H, m). m/z (ESI, +ve) 362.1 (M+H)⁺.
Example 84: (9S,11E,13S)-21-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1\(^2\).5\(^2\).0\(^4\).9\(^2\).0\(^18\).22\(^2\)]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one

Step 1: (S)-8-bromo-N-(but-3-en-2-yl)-7-fluoro-3-methylquinoxalin-2-amine

A mixture of 5-bromo-3-chloro-6-fluoro-2-methylquinoxaline (Intermediate K; 1.00 g, 3.63 mmol), (S)-but-3-en-2-amine hydrochloride (Intermediate G; 781 mg, 7.26 mmol) and DIPEA (Sigma Aldrich, 2.53 mL, 14.52 mmol) in DMSO (5.2 mL) was stirred at 90 °C for 13 h. The reaction was partitioned between saturated NaHCO\(_3\) (aq.) and Et\(_2\)O.

The organic layer was washed with water and brine and dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (80 g) eluting with a gradient of 0-40% EtOAc/hexane to afford (S)-8-bromo-N-(but-3-en-2-yl)-7-fluoro-3-methylquinoxalin-2-amine (790 mg, 2.55 mmol, 70% yield) as an orange solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ ppm 7.74 (dd, \(J=9.00, 5.67\) Hz, 1 H), 7.17 (t, \(J=8.61\) Hz, 1 H), 5.99 (ddd, \(J=17.21, 10.27, 5.77\) Hz, 1 H), 5.40 (dt, \(J=17.21, 1.47\) Hz, 1 H), 5.18 (dt, \(y=10.37, 1.37\) Hz, 1 H), 5.00 - 5.11 (m, 1 H), 4.86 (d, \(J=8.22\) Hz, 1 H), 2.55 (s, 3 H), 1.47 (d, \(J=6.65\) Hz, 3 H). m/z (ESI, +ve) 310.1, 312.1 (M+H\(^+\)).

Step 2: (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-6-fluoro-2-methylquinazolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A glass microwave reaction vessel was charged with (S)-8-bromo-N-(but-3-en-2-yl)-7-fluoro-3-methylquinazolin-2-amine (152 mg, 0.491 mmol), (S)-7-allyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate L, 267 mg, 0.663 mmol), Pd\(_2\)(dba)\(_3\) chloroform adduct (Strem Chemicals Inc., 25 mg, 0.025 mmol), XPhos (Strem Chemicals Inc., 23 mg, 0.049 mmol) and K\(_3\)PO\(_4\) (Riedel de Haen AG, 0.122 mL, 1.473 mmol) in dioxane (2.0 mL) and water (0.5 mL).
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The reaction mixture was stirred and heated in an Initiator microwave reactor (Personal Chemistry, Biotage AB, Inc., Upssala, Sweden) at 100 °C for 30 min. Water was added and the mixture was extracted with EtOAc (3X). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude material was purified by preparatory HPLC, 5-100 % ACN/H₂O with 0.1% TFA over 15 min; product-containing fraction was treated with saturated NaHCO₃ (aq.) and CH₂Cl₂. The aqueous layer was extracted 3 x CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-6-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (80 mg, 40%):

1H NMR (400 MHz, CDCl₃) δ ppm 12.49 (br. s., 1 H), 7.63 (dd, 7=9.00, 5.48 Hz, 1 H), 7.35 - 7.39 (m, 1 H), 7.23 (dd, 7=1.54, 9.00 Hz, 1 H), 6.11 (dddd, 7=17.21, 10.56, 3.91 Hz, 1 H), 5.83 (ddt, 7=16.46, 10.73, 7.14, 7.14 Hz, 1 H), 5.55 (br. s., 1 H), 5.24 - 5.36 (m, 2 H), 5.16 (dd, 7=6.94, 1.66 Hz, 1 H), 5.12 (s, 1 H), 4.99 (d, 7=6.85 Hz, 1 H), 4.69 - 4.80 (m, 1 H), 3.77 (dd, 7=12.1, 5.48 Hz, 1 H), 3.44 (dt, 7=12.23, 4.06 Hz, 1 H), 2.95 - 3.04 (m, 1 H), 2.61 (s, 3 H), 2.46 - 2.52 (m, 2 H), 2.01 (s, 3 H), 1.56 (d, 7=6.85 Hz, 3 H), m/z (ESI, +ve) 406.1 (M+H)+.

Step 3: (9S,1IE,13S)-2 1-fluoro-13,16-dimethyl-3,7,14,17-tetraconta-1(21),2(24),4,11,15,17,19,22-octacos-6-one Argon was bubbled for 2 min through a solution of (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-6-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.054 g, 0.133 mmol) and Grubbs catalyst, 2nd generation (Sigma Aldrich, 5.65 mg, 0.66 μmol) in CH₂Cl₂ (7 mL). The reaction was sealed and heated to 45 °C for 1 h. The crude material was absorbed onto a plug of silica gel and purified by silica gel chromatography (4 g), eluting with a gradient of 0-7% MeOH in CH₂Cl₂, to provide (9S,1IE,13S)-2 1-fluoro-13,16-dimethyl-3,7,14,17-tetraconta-1(21),2(24),4,11,15,17,19,22-octacos-6-one (0.040 g, 0.106 mmol, 80 % yield) as a yellow solid; 1H NMR (400 MHz, DMSO-d₆) δ ppm 13.53 - 13.65 (1 H, m), 7.58 (1 H, dd, 7=9.0, 5.9 Hz), 7.32 (1 H, dd, 7=12.1, 9.0 Hz), 7.11 (1 H, d, 7=4.3 Hz), 6.89 (1 H, dd, 7=5.4, 1.9 Hz), 6.61 (1 H, d, 7=1.2 Hz), 5.84 - 6.05 (2 H, m), 4.25 (1 H, t, 7=6.4 Hz), 3.34 - 3.40 (1 H, m), 3.20 - 3.31 (1 H, m), 3.06 - 3.17 (2 H, m), 2.60 (6 H, s), 2.54 - 2.59 (1 H, m), 2.13 - 2.26 (2 H, m), 1.51 (3 H, d, 7=6.8 Hz), m/z (ESI, +ve) 378.1 (M+H)+.
Example 85: (9S,11E,13R)-19-methyl-15-oxa-3,7,17,20,26-pentaazahexacyclo[16.6.2.1^2,5^2.0^4,9^2.0^13,17^2.0^21,25]heptacosa-1(25),2(27),4,11,18(26),19,21,23-octaene-6,16-dione


Example 87: (9S,11Z,13S)-19-methyl-15-oxa-3,7,17,20,26-pentaazahexacyclo[16.6.2.1^2,5^2.0^4,9^2.0^13,17^2.0^21,25]heptacosa-1(25),2(27),4,11,18(26),19,21,23-octaene-6,16-dione

To a solution of 4-vinlyloxazolidin-2-one (Prepared from tert-butyl 2,2-dimethyl-4-vinlyloxazolidine-3-carboxylate, Annova Chem Inc., San Diego, CA, according to J. Org. Chem. Vol. 74, 2009, 8852-8855, 0.235 g, 2.081 mmol) in 1 mL DMF at 0 °C was added NaH 60% in mineral oil (Aldrich; 0.083 g, 2.081 mmol) in 2 equal portions separated by 5 min. Gas evolution observed. The ice bath was removed and the reaction stirred rapidly at RT 10 min. The foamy mixture was treated with (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.100 g, 0.297 mmol), 1 mL DMF, and the reaction was sealed and heated to 90 °C. After 2 h, the reaction was cooled and partitioned between saturated aqueous NH₄Cl and EtOAc. The layers were separated, and the aqueous layer was extracted 1 x EtOAc, and the combined organic layers were washed with water once, brine once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (24 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.080 g of a mixture of isomers. This was treated with Grubbs catalyst 2nd generation (Aldrich; 0.032 g, 0.037 mmol) and 9 mL DCM and argon was bubbled into the solution for 30 sec. The reaction was sealed and placed in a 45 °C bath for 2 h. Additional Grubbs
catalyst 2nd generation (Aldrich; 0.032 g, 0.037 mmol) was added, the reaction was sealed, and heated to 45 °C for 1 h. The reaction was cooled, MeOH was added and the reaction was adsorbed onto 1 g silica gel, dried, and purified by silica gel chromatography (12 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford a mixture of isomeric products and impurities (0.035 g) as a yellow-brown solid. The material was further purified by chiral SFC (Column: Chiralcel OJ-H (Sepax) (250 x 21 mm, 5 µ); Mobile Phase: 70:30 (A:B); A: Liquid CO2, B: MeOH (20 mM NH3); Flow Rate: 65 mL/min; Inlet Pressure: 158 bar) to give:

(9S,1 IE,13R)-1 9-methyl-1,5-oxa-3,7,17,20,26-pentaazahexacyclo[16.6.2.1~2,5~.0~4.9~.0~1~3,17~.0~2~1.25~]heptacosa-1(25),2(27),4,11,18(26),19,21,23-octae-6,16-dione (First eluting, Example 85, 0.0046 g, 0.011 mmol, 6.15 % yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 12.59 (1 H, br. s.), 8.21 (1 H, dd, J=7.2, 1.4 Hz), 7.66 - 7.88 (2 H, m), 7.01 - 7.19 (2 H, m), 6.44 (1 H, dd, J=14.6, 10.3 Hz), 6.12 - 6.29 (1 H, m), 5.16 - 5.31 (1 H, m), 4.86 (1 H, t, J=7.8 Hz), 4.31 (1 H, d, J=8.4 Hz), 3.36 - 3.44 (1 H, m), 3.23 - 3.29 (1 H, m), 3.12 - 3.21 (1 H, m), 2.59 - 2.71 (4 H, m), 2.30 - 2.46 (1 H, m). m/z (ESI, +ve) 402.2 (M+H)+.

(9S,1 IZ,13R)-1 9-methyl-1,5-oxa-3,7,17,20,26-pentaazahexacyclo[16.6.2.1~2,5~.0~4.9~.0~1~3,17~.0~2~1.25~]heptacosa-1(25),2(27),4,11,18(26),19,21,23-octae-6,16-dione (Second eluting, Example 86, 0.0034 g, 8.47 µmol, 4.55 % yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 12.32 (1 H, br. s.), 8.06 (1 H, dd, J=7.3, 1.1 Hz), 7.78 - 7.87 (1 H, m), 7.68 - 7.77 (1 H, m), 7.04 (1 H, d, J=4.3 Hz), 6.77 (1 H, d, J=2.0 Hz), 6.14 - 6.30 (1 H, m), 5.71 - 5.84 (1 H, m), 5.55 - 5.68 (1 H, m), 4.74 (1 H, t, J=7.8 Hz), 4.19 (1 H, t, J=8.9 Hz), 3.29 - 3.54 (4 H, m), 2.70 (3 H, s), 2.28 (1 H, d, J=14.5 Hz). m/z (ESI, +ve) 402.2 (M+H)+.

(9S,1 IZ,13S)-19-methyl-15-oxa-3,7,17,20,26-pentaazahexacyclo[16.6.2.1~2,5~.0~4.9~.0~1~3,17~.0~2~1.25~]heptacosa-1(25),2(27),4,11,18(26),19,21,23-octae-6,16-dione (Third eluting, Example 87, 0.0057 g, 0.014 mmol, 7.62 % yield): 1H NMR (400 MHz, DMSO-d6) δ ppm 12.03 (1 H, br. s.), 8.08 (1 H, d, J=6.7 Hz), 7.80 - 7.90 (1 H, m), 7.68 - 7.80 (1 H, m), 7.09 (1 H, d, J=4.3 Hz), 6.92 (1 H, d, J=2.2 Hz), 6.03 - 6.17 (1 H, m), 5.80 - 5.99 (2 H, m), 4.68 (1 H, t, J=7.7 Hz), 4.15 - 4.30 (1 H, m), 3.43 (1 H, dt, J=10.4, 5.0 Hz), 3.08 - 3.28 (2 H, m), 2.79 - 2.94 (1 H, m), 2.74 (3 H, s), 2.37 (1 H, d, J=13.9 Hz). m/z (ESI, +ve) 402.2 (M+H)+.
Example 88: (9S)-17-methyl-3,7,15,18,24-pentaazapentacyclo[14.6.2.1\(2,5\)-.0\(4,9\)-.0\(19,23\)-]pentacos(23),2(25),4,16(24),17,19,21-heptaen-6-one

Step 1: (S)-7-allyl-2-(3-(but-3-en-1-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

3-Buten-1-amine (Alfa Aesar, 0.275 ml, 2.97 mmol) and (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.109 g, 0.281 mmol) were combined in 1.5 mL DMSO, sealed, and heated to 70 °C overnight. The reaction was treated with ~ 6 mL saturated aqueous NaHCO₃, and the precipitate was collected by filtration, rinsing 1 x water. Solid was collected and dried in vacuo to give (S)-7-allyl-2-(3-(but-3-en-1-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.109 g, 0.281 mmol, 95 % yield): 

\[
\text{HNMR (400 MHz, DMSO-}d_6\text{) } \delta \text{ ppm: } 12.01 (1 \text{ H, br. s}), 7.90 (1 \text{ H, d, } J=7.6 \text{ Hz}), 7.57 (1 \text{ H, d, } J=7.8 \text{ Hz}), 7.22 - 7.40 (2 \text{ H, m}), 7.09 (1 \text{ H, d, } J=2.0 \text{ Hz}), 6.93 (1 \text{ H, br. s}), 5.79 - 6.10 (2 \text{ H, m}), 4.99 - 5.26 (4 \text{ H, m}), 3.43 - 3.69 (3 \text{ H, m}), 3.18 - 3.25 (1 \text{ H, m}), 2.98 - 3.11 (1 \text{ H, m}), 2.50 - 2.62 (6 \text{ H, m}), 2.21 - 2.40 (1 \text{ H, m}). \text{ } m/z (\text{ESI, +ve}) 388.1 (M+H)^+.
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Step 2: Argon was bubbled through a slurry of Grubbs catalyst 2nd generation (Aldrich; 0.048 g, 0.056 mmol) and (S)-7-allyl-2-(3-(but-3-en-1-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.109 g, 0.281 mmol) in 14 mL DCM for 30 sec. The reaction was sealed, heated to 45 °C and stirred rapidly. Upon completion, the reaction was treated with MeOH, and silica gel, and dried in vacuo. The residue was purified by silica gel chromatography using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.080 g material. This material and palladium on carbon 10%, wetted (50 wt % water) (0.118 g) were combined under N₂ and 4 mL THF was added. The atmosphere was replaced with H₂ from a balloon and the reaction was stirred rapidly overnight. The reaction was flushed...
with N\(_2\) and filtered through Celite, rinsing with 100 mL of 1:1 DCM/MeOH. The filtrate was concentrated in vacuo to give 0.074 g yellow solid. This material was treated with 4 mL MeOH to give a suspension, and H\(_2\)O \(_2\) 30% in water (Aldrich; 0.025 mL, 0.245 mmol) was added followed by iron (ii) chloride (Alfa Aesar, Ward Hill, MA, 0.846 mg, 6.68 µmol). The reaction was stirred rapidly for 2 h. Additional H\(_2\)O \(_2\) 30% in water (Aldrich; 0.025 mL, 0.245 mmol) was added. After 30 min, the reaction was treated with DCM to give a solution and was adsorbed onto 1 g silica gel, dried, and purified by silica gel chromatography (24 g) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford (9S)-17-methyl-3,7,15,18,24-pentaazapentacyclo[4.6.2.1^2,5.0^4,9.0^18,23]pentacosa-1(23),2(25),4,16(24),17.9.2.1-heptaen-6-one (0.031 g, 0.086 mmol, 38.5% yield) as a yellow solid: \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 12.02 (1 H, br. s.), 7.91 (1 H, d, \(J=6.7\) Hz), 7.51 - 7.69 (2 H, m), 7.30 (1 H, t, \(J=7.7\) Hz), 7.03 (1 H, d, \(J=4.1\) Hz), 6.85 (1 H, d, \(J=1.8\) Hz), 3.56 (1 H, m), 3.01 - 3.35 (4 H, m), 1.56 - 1.96 (6 H, m), 1.47 (2 H, br. s.). m/z (ESI, +ve) 362.2 (M+H).
Step 1: 5-(methylthio)pent-l-en-3-amine hydrochloride

A slurry of anhydrous MgSO₄ (Sigma Aldrich, 52.1 g, 433 mmol) and (R)-(++)-2-methyl-2-propanesulfinamide (AK Scientific, Union City, CA, 0.5 g, 87 mmol) was stirred in DCM (61.9 ml). 3-(methylthio) propionaldehyde (Sigma Aldrich, 17.52 ml, 173 mmol) was added, and the reaction was stirred under N₂. After stirring for 26 h, the reaction mixture was filtered with DCM rinsing and concentrated under reduced pressure to a liquid. A portion of the liquid (2.5 g) was treated with DCM (121 ml), and this solution was cooled to -30 °C and a 1.0 M solution of vinylmagnesium bromide in THF (Sigma Aldrich, 15.67 ml, 15.67 mmol) was added dropwise over 10 min, taking care to maintain an internal temperature less than -15 °C. Upon complete addition, the mixture was stirred for 1.5 h at -30 °C. The reaction was warmed to RT and saturated aqueous NH₄Cl was added. The mixture was extracted with DCM. The organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was stirred with MeOH (10 mL) and 4 M HCl in 1,4-dioxane (Sigma Aldrich, 27 mL, 120 mmol). The mixture was stirred for 2 h and was subsequently concentrated in vacuo to afford a residue. It was sonicated with toluene after initial concentration under reduced pressure and concentrated in vacuo from toluene a second time, to give 5-(methylthio)pent-l-en-3-amine hydrochloride (1.2 g) as a viscous residue: ¹H NMR

(DMSO-d₆) δ: 8.40 - 8.57 (2H, m) 5.75 - 5.88 (1H, m) 5.35 - 5.45 (2H, m) 3.77 - 3.86 (1H, m) 3.64 - 3.74 (1H, m) 3.15 - 3.23 (2H, m) 3.02 (3H, s) 2.12 - 2.25 (1H, m).

Step 2: tert-butyl (5-(methylthio)pent-l-en-3-yl)carbamate

A solution of 5-(methylthio)pent-l-en-3-amine hydrochloride (2.3 g, 13.71 mmol) in dioxane (18.29 ml) was stirred, and saturated aqueous NaHCO₃ (EMD Biosciences, 2.304 ml, 27.4 mmol) and di-tert-butyl dicarbonate (Sigma Aldrich, 5.87 ml, 27.4 mmol) were subsequently added. The monophasic solution was stirred at RT overnight. An additional 2 mL saturated aqueous NaHCO₃ and 0.5 equivalents of DMAP were added, and the reaction was stirred for 30 min. The reaction was diluted with water, extracted with DCM, and the organic layer was washed with saturated aqueous NaHCO₃. The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give tert-butyl (5-(methylthio)pent-l-en-3-yl)carbamate (865 mg, 31%) as an oil: ¾ NMR (CDCl₃) δ: 5.69 - 5.84 (1H, m) 5.08 - 5.23 (2H, m) 4.12 - 4.29 (1H, m) 2.47 - 2.58 (2H, m) 2.12 (3H, s) 1.74 - 1.90 (2H, m) 1.45 (9H, s).
Step 3: 5-(methylsulfonyl)pent-1-en-3-amine hydrochloride

A solution of tert-butyl (5-(methylthio)pent-1-en-3-yl)carbamate (1.62 g, 7.00 mmol) in DMF (35.0 mL) was stirred, and 77% 3-chloroperoxybenzoic acid (Sigma Aldrich, 3.38 g, 14.70 mmol) was added as a solution in 5 mL DMF. The mixture was stirred overnight at RT. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ and extracted with EtOAc. The combined organics were washed with IN NaOH and dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to an oil. The oil was diluted with water and extracted with EtOAc. The combined organics were washed with IN aqueous HCl, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to yield a residue that was carried forward without purification. The residue was stirred in 4 M HCl/dioxane (15 mL) for 1 h. The resulting solution was concentrated under reduced pressure and sonicated twice with toluene. It was concentrated in vacuo then dried under high vacuum to give 5-(methylsulfonyl)pent-1-en-3-amine hydrochloride (534 mg, 19%, 2 steps): $^1$H NMR (DMSO-$d_6$) δ: 8.40 - 8.57 (2H, m) 5.75 - 5.88 (1H, m) 5.35 - 5.45 (1H, m) 3.77 - 3.86 (1H, m) 3.64 - 3.74 (1H, m) 3.15 - 3.23 (2H, m) 3.02 (3H, s) 2.12 - 2.25 (1H, m) 1.94 - 2.06 (IH, m).

Step 4: (7S)-7-allyl-2-(2-methyl-3-(5-(methylsulfonyl)pent-1-en-3-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of (S)-7-allyl-2-(3-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 300 mg, 0.892 mmol), 5-(methylsulfonyl)pent-1-en-3-amine hydrochloride (534 mg, 2.68 mmol), diisopropylethylamine (EMD Biosciences, 931 µL, 5.35 mmol), and DMSO (891.9 µL) was sealed and stirred at 80°C for 3 h. An additional 200 mg of 5-(methylsulfonyl)pent-1-en-3-amine hydrochloride was added as a solution in DMSO, and the reaction was stirred for an additional 2 h at 80°C. The reaction was cooled to RT, diluted with water, and extracted with DCM. The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The mixture was adsorbed onto silica and purified by column chromatography (eluent: 0 to 8% MeOH/DCM over 20 min). The combined product fractions were concentrated under reduced pressure to give (7S)-7-allyl-2-(2-methyl-3-(5-(methylsulfonyl)pent-1-en-3-yl)amino)quinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (184 mg, 43%): $^1$H NMR (CDCl$_3$) δ: 11.59 - 11.89 (1H, m) 7.90 - 7.94 (1H, m) 7.72 - 7.78 (1H, m) 7.40 - 7.46 (1H, m) 7.09 - 7.14 (1H, m) 5.81 - 6.05 (3H, m).
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m) 5.63 - 5.74 (1H, m) 5.33 - 5.41 (2H, m) 5.13 - 5.20 (2H, m) 4.86 - 5.00 (1H, m) 3.72 - 3.81 (1H, m) 3.42 - 3.51 (1H, m) 3.23 - 3.39 (2H) 3.05 - 3.14 (1H, m) 3.01 (2H, s) 2.97 - 3.00 (2H, m) 2.70 (3H, s) 2.44 - 2.58 (3H, m): m/z (ESI, +ve) 452.2 (M+H)+.

Step 5: (9S,1IE,13S)-1 6-methyl-13-(2-(methylsulfonyl)ethyl)-3,7,14,1 7,23-pentaazapentacyclo[1 3.6.2.1-2.5-0~·~0-4.9-0~·~0-1 8,22-]tetracosa-

l(22),2(24),4, 11,1 5,17,1 8,20,22-nonaen-6-one and (9S,1IE,13R)- 16-methyl- 13-(2- (methylsulfonyl)ethyl)-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2.5-0~·~0-4.9-0~·~0-1 8,22-]tetracosa-
l(22),2(24),4, 11,1 5,17,1 8,20,22-nonaen-6-one

A solution of (7S)-7-allyl-2-(2-methyl-3-((5-(methylsulfonyl)pentyl)-3-yl)amino)quinolizin-5-yl)-6,7-dihydro-IH-pyrololo[3,2-c]pyridin-4(5H)-one (184 mg, 0.384 mmol), Grubbs’ 2nd generation catalyst (Sigma Aldrich, 65.1 mg, 0.077 mmol), and DCM (7673 µl) was purged with argon. It was subsequently sealed and heated to 50°C for 3 h. The reaction mixture was cooled to RT, and the mixture was concentrated in vacuo. The mixture of isomers was subsequently purified by SFC SFC (AD-H Column, 5 µm in width at 21 x 150 mm, P = 200 bar, T = 40 °C with 40% EtOH at 1 mL/min, solubilized in 1:1 DCM/MeOH), affording both C15 diastereomers of (9S,1IE)-16-
methyl-13-(2-(methylsulfonyl)ethyl)-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1-2.5-0~·~0-4.9-0~·~0-1 8,22-]tetracosa-
l(22),2(24),4, 11,1 5,17,1 8,20,22-nonaen-6-one:

First eluting diastereomer. Example 89 (49.5 mg, 56%): 1/4 NMR (400 MHz, DMSO-δ6) δ ppm 13.38 - 13.44 (1H, m) 7.94 - 8.00 (1H, m) 7.56 - 7.61 (1H, m) 7.51 - 7.56 (1H, m) 7.26 - 7.36 (1H, m) 7.00 - 7.06 (1H, m) 6.88 (1H, s) 6.18 - 6.28 (1H, m) 5.94 - 6.09 (1H, m) 4.19 - 4.28 (1H, m) 3.13 - 3.24 (3H, m) 2.95 (3H, s) 2.59 - 2.69 (1H, m) 2.57 (3H, s) 2.36 - 2.43 (2H, m) 2.21 - 2.36 (2H, m) 1.45 (1H, s): m/z (ESI, +ve) 452.1 (M+H)+. Second eluting diastereomer, Example 90 (32 mg, 37%): 1H NMR (400 MHz, DMSO-δ6) δ ppm 13.37 - 13.42 (1H, m) 7.94 - 8.00 (1H, m) 7.55 - 7.59 (1H, m) 7.50 - 7.54 (1H, m) 7.22 - 7.30 (1H, m) 6.99 - 7.06 (1H, m) 6.86 (1H, s) 6.12 - 6.19 (1H, m) 5.90 - 6.08 (1H, m) 4.19 - 4.26 (1H, m) 3.14 - 3.23 (3H, m) 2.91 (3H, s) 2.57 - 2.66 (1H, m) 2.53 (3H, s) 2.37 - 2.41 (2H, m) 2.20 - 2.35 (2H, m) 1.43 (1H, s): m/z (ESI, +ve) 452.1 (M+H)+.
Example 91: (lIlE,13R)-16-methyl-13-(trifluoromethyl)-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1^2,5^-0^4,9^-0^18,22^-]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one

Step 1: (7?)-1-(2-methyl-3-((l,l^-1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-yl)ethanone
A mixture of 1-(3-chloro-2-methylquinoxalin-5-yl)ethanone (0.394 g, 1.786 mmol), (R)-
l,l^-1-trifluorobut-3-en-2-amine hydrochloride (WO201 1053821, 0.346 g, 2.143 mmol),
bis(tri-tert-butylphosphine)palladium (Strem Chemicals, 0.091 g, 0.179 mmol), and
K$_3$PO$_4$ (1.327 g, 6.25 mmol) in iBuOH (17.86 ml) was sparged with N$_2$ before it was
heated in a sealed flask at 120 °C for 3 h. The crude product was adsorbed onto silica and
was purified via automated flash chromatography (silica gel) with 100% hexanes to 40%
EtOAc in hexanes to give (7?)-1-(2-methyl-3-((l,l^-1-trifluorobut-3-en-2-
yl)amino)quinoxalin-5-yl)ethanone (50 mg, 0.162 mmol, 9.05 % yield) as a red oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.67 (s, 3 H) 2.87 (s, 3 H) 5.10 (d, J=9.00 Hz, 1 H) 5.47 -
5.59 (m, 2 H) 5.68 - 5.80 (m, 1 H) 6.04 (ddd, J=16.87, 10.81, 5.58 Hz, 1 H) 7.48 (t, J=7.82 Hz, 1 H) 7.93 (ddd, J=7.34, 1.47 Hz, 1 H) 8.00 (dd, J=8.22, 1.37 Hz, 1 H). $^{19}$F
NMR (377 MHz, CDCl$_3$) δ ppm -75.24 (s, 3 F). MS (ESI, pos. ion) m/z: 310.1 (M+H)$^+$.  

Step 2: (7?)-2-bromo-1-(2-methyl-3-((l,l^-1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-
yl)ethanone
A solution of (7?)-1-(2-methyl-3-((l,l^-1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-
yl)ethanone (50 mg, 0.162 mmol), tert-butyldimethylsilyl trifluoromethanesulfonate
(Aldrich, 64.1 mg, 0.242 mmol), and TEA (49.1 mg, 0.485 mmol) in DCM (1617 µl) was
stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (2 x 75 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated to give an oil: MS (ESI, pos. ion) m/z: 424.2 (M+I). A solution of this material, 1-bromopyrrolidine-2,5-dione (Aldrich, 28.8 mg, 0.162 mmol), and water (46 µl) in THF (1617 µl) was stirred at RT for 1 h. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (2 x 75 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% hexanes to 30% EtOAc in hexanes to give (7S)-bromo-1-(2-methyl-3-((1,1,1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-yl)ethanone (33 mg, 0.085 mmol, 52.6 % yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.69 (s, 3 H) 4.81 - 4.87 (m, 1 H) 4.94 - 5.00 (m, 1 H) 5.12 (d, J=9.00 Hz, 1 H) 5.52 - 5.61 (m, 2 H) 5.65 - 5.76 (m, 1 H) 6.05 (ddd, J=16.82, 10.76, 5.48 Hz, 1 H) 7.52 (t, J=7.73 Hz, 1 H) 8.06 (s, 1 H) 8.08 (s, 1 H). ¹³C NMR (377 MHz, CDCl₃) δ ppm -75.11 (s, 3 F). MS (ESI, pos. ion) m/z: 388.0/390.0 (M+H)⁺.

Step 3: 7-allyl-2-(2-methyl-3-((7S)-1,1,1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of 5-allylpyrrolidine-2,4-dione (Intermediate A, 19.53 mg, 0.128 mmol), (R)-2-bromo-1-(2-methyl-3-((1,1,1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-yl)ethanone (33 mg, 0.085 mmol), and NH₄OAc (Aldrich, 32.8 mg, 0.425 mmol) in MeOH (850 µl) was heated to 50 °C for 16 h. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (75 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 5% 2 M NH₃ in MeOH/DCM to give 7-allyl-2-(2-methyl-3-((7S)-1,1,1-trifluorobut-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-dihydro-IH-pyrrolo[3,2-c]pyridin-4(5H)-one (5 mg, 0.011 mmol, 13%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 2.43 - 2.56 (m, 2 H) 2.70 (s, 3 H) 2.98 - 3.07 (m, 1 H) 3.40 - 3.48 (m, 1 H) 3.73 - 3.80 (m, 1 H) 5.07 (d, J=7.43 Hz, 1 H) 5.10 - 5.21 (m, 2 H) 5.39 - 5.49 (m, 2 H) 5.57 - 5.65 (m, 2 H) 5.77 - 5.90 (m, 1 H) 6.12 (ddt, J=16.77, 11.00, 5.38, 5.38 Hz, 1 H) 7.13 (dd, J=6.46, 2.15 Hz, 1 H) 7.48 (t, J=7.92 Hz, 1 H) 7.75 (d, J=8.22 Hz, 1 H) 7.93 -
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7.99 (m, 1 H) 11.46 (d, J=53.21 Hz, 1 H). $^1$F NMR (376 MHz, $CDCl_3$) δ ppm -74.60 (s, 3 F) -74.34 (s, 3 F). MS (ESI, pos. ion) m/z: 442.2 (M+H)⁺.

Step 4: (1E,1 3°)-1 6-methyl-13-(trifluoromethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaaen-6-one

A solution of 7-allyl-2-(2-methyl-3-((7°)-1,1-triflorobut-3-en-2-yl)amino)quinoxalin-5-yl)-6,7-dihydro-lH-pyrrolo[3,2-c]pyridin-4(5H)-one (5 mg, 0.011 mmol) and Grubbs catalyst 2nd generation (1.923 mg, 2.265 μmol) in $DCM$ (227 μl) was stirred at 50 °C in a sealed tube for 2 h. The reaction mixture was concentrated and dissolved in DCE (1.5 ml) before adding more Grubbs catalyst 2nd generation (1.923 mg, 2.265 μmol); the reaction mixture was sparged with $N_2$ then heated in a sealed tube at 80 °C for 16 h when some product was observed. The crude product was dissolved in MeOH and injected (3 x 1.000 ml) onto the Shimadzu preparatory LC (Phenomenex Gemini C$_{18}$ column (150 × 30 mm, 10 μm), 35 mL/min, 5-100% CH$_3$CN/H$_2$O + 0.1% TFA) before the pure fractions were combined, basicified with NaHCO$_3$ (saturated, aqueous), extracted with DCM, separated, dried over Na$_2$SO$_4$, and concentrated via rotary evaporation to give impure product. A preparatory TLC plate was loaded with the impure mixture and run 1 time in 30% EtOH/[hexanes/EtOAc (2:1)]; after scraping the plate, extraction with DCM/MeOH, filtration, and concentration via rotary evaporation, (1E,1 3°)-16-methyl-1 3-(trifluoromethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-heptaen-6-one

Example 92: (9S,13S)-21-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,15,17,19,22-heptaen-6-one
A heterogenous solution of (9S,11E,13S)-21-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1.3.6.2.8.2.5.7.3.4]octadeca-1(21),2(24),4(1) 1,1 5,1 7,1 9,22-octen-6-one (Example 84, 88 mg, 0.233 mmol) in THF (12 mL) was degassed by bubbling N₂ through the solution for 10 min. 10% Pd/C (Sigma Aldrich, 248 mg, 0.233 mmol) was added to the reaction mixture. A gas bag with a 3-way stopcock filled with H₂ was attached to the flask. The flask was evacuated under vacuum and then back-filled with H₂ (3X). The mixture was stirred for 21 h at RT. The solution was degassed by bubbling N₂ through the solution for 10 min and then filtered through Celite and concentrated. The crude product was resubjected to the reaction conditions. The crude product was dissolved in THF (12 mL) and the solution was degassed by bubbling N₂ through the solution for 10 min. 10% Pd/C (Sigma Aldrich, 50 mg, 0.047 mmol, 0.2 eq) was added. A gas bag with a 3-way stopcock filled with H₂ was attached to the flask. The flask was evacuated under vacuum and then back-filled with H₂ (3X). The mixture was stirred for 21 h at RT. The solution was degassed by bubbling N₂ through the solution for 10 min and then filtered through Celite and concentrated. The yellow solid was dissolved in 4 mL of MeOH and H₂O (Sigma Aldrich, 30 wt. % solution in water, 0.026 mL, 0.256 mmol) and FeCl₂ (Alfa Aesar, Ward Hill, MA, 1.5 mg, 0.012 mmol) were added at RT. The mixture was stirred at RT for 1 h and then brine and CH₂Cl₂ were added. The layers were separated and the aqueous layer was extracted with 10% MeOH in CH₂Cl₂ (2X). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to give 120 mg of crude product. The crude material was absorbed onto a plug of silica gel and purified by silica gel chromatography (12 g), eluting with a gradient of 0-5% MeOH in CH₂Cl₂, to provide (9S,13S)-21-fluoro-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1.3.6.2.8.2.5.7.3.4]octadeca-1(21),2(24),4(1) 1,1 5,1 7,1 9,22-heptaten-6-one (32 mg, 0.084 mmol, 36 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.59 (br. s., 1 H), 7.61 (dd, J=8.90, 5.58 Hz, 1 H), 7.33 (dd, J=11.64, 9.10 Hz, 1 H), 7.25 (d, J=4.89 Hz, 1 H), 7.13 (d, J=4.11 Hz, 1 H), 6.96 (d, J=4.11 Hz, 1 H), 3.12 - 3.30 (m, 2 H), 2.99 - 3.09 (m, 1 H), 2.57 (s, 3 H), 2.32 - 2.42 (m, 1 H), 2.18 - 2.31 (m, 1 H), 1.94 - 2.07 (m, 1 H), 1.60 - 1.74 (m, 1 H), 1.42
Example 93: tert-butyl (2-((9S,H2)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate

Step 1: tert-butyl (2-(allylamino)ethyl)carbamate

3-Bromoprop-1-ene (Aldrich, 1.685 ml, 19.47 mmol) was added to a mixture of tert-butyl (2- aminoethyl)carbamate (Fluka, 3.08 ml, 19.47 mmol) and KOAc (2.293 g, 23.37 mmol) in THF (97 ml) at 65 °C; the reaction mixture was stirred at 65 °C for 2 h. The reaction mixture was diluted with DCM (200 ml), added to a separatory funnel, and washed with water (2 x 100 ml). The aqueous layer was extracted with CHC₃/IPA (3:2) (4 x 100 ml) before the combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% EtOAc to 30% MeOH in EtOAc to give tert-butyl (2-(allylamino)ethyl)carbamate (650 mg, 3.25 mmol, 16.67 % yield) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 1.31 (br. s., 1 H) 1.45 (s, 9 H) 2.74 (t, J=5.87 Hz, 2 H) 3.18 - 3.29 (m, 4 H) 4.96 (br. s., 1 H) 5.10 (dd, J=10.17, 1.37 Hz, 1 H) 5.18 (dq, J=17.12, 1.5 Hz, 1 H).
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1.60 Hz, 1 H) 5.88 (ddt, J=16.95, 10.54, 6.02, 6.02 Hz, 1 H). MS (ESI, pos. ion) m/z: 201.2 (M+H)+.

Step 2: (S)-tert-butyl (2-(allyl(8-(7-allyl-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-methylquinoxalin-2-yl)amino)ethyl)carbamate

A solution of (S)-7-allyl-2-(3-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 672 mg, 1.997 mmol), tert-butyl (2-(allylamino)ethyl)carbamate (600 mg, 3.00 mmol), and N-ethyl-N-isopropylpropan-2-amine (1044 µL, 5.99 mmol) in DMSO (3994 µL) was stirred at 80 °C for 16 h. The reaction mixture was diluted with DCM (150 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO₃ (3 x 100 ml) before the organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 3% 2 M NH₃ in MeOH/DCM to give (S)-tert-butyl (2-(allyl(8-(7-allyl-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-methylquinoxalin-2-yl)amino)ethyl)carbamate (930 mg, 1.800 mmol, 90 % yield) as a yellow amorphous solid: 1H NMR (400 MHz, CDCl₃) δ ppm 1.28 (s, 9 H) 2.42 - 2.53 (m, 1 H) 2.60 - 2.68 (m, 1 H) 2.77 (s, 3 H) 3.07 - 3.15 (m, 1 H) 3.32 - 3.45 (m, 3 H) 3.56 - 3.67 (m, 3 H) 4.13 (d, J=5.09 Hz, 2 H) 4.59 (t, J=5.97 Hz, 1 H) 5.09 - 5.20 (m, 2 H) 5.28 - 5.45 (m, 3 H) 5.79 - 5.91 (m, 1 H) 5.91 - 6.04 (m, 1 H) 7.15 (d, J=1.56 Hz, 1 H) 7.52 (t, J=7.92 Hz, 1 H) 7.74 (dd, J=8.22, 1.17 Hz, 1 H) 7.96 (d, J=7.43 Hz, 1 H) 11.86 (br. s., 1 H). MS (ESI, pos. ion) m/z: 517.4 (M+H)+.

Step 3: tert-butyl (2-((9S,1 Iz)-1 6-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0-4.9-0-1 8,22-]tetracosa-1(21),2(24),4,11,15,17,19,22-octae-14-(y)ethyl)carbamate and tert-butyl (2-((9S,1 1E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0-4.9-0-1 8,22-]tetracosa-1(21),2(24),4,11,15,17,19,22-octae-14-(y)ethyl)carbamate

A solution of (S)-tert-butyl (2-(allyl(8-(7-allyl-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-methylquinoxalin-2-yl)amino)ethyl)carbamate (0.930 g, 1.800 mmol) and Grubbs catalyst 2nd generation (0.306 g, 0.360 mmol) in DCM (36.0 ml) was sparged with N₂ before it was heated to reflux under N₂ for 1.5 h. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel)

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with 100% DCM to 5% 2 M NH₃ in MeOH/DCM to give a mixture of E/Z macrocycle isomers as a rust colored solid. SFC purification of the mixture:

Column: AS-H (10 µm, 21 mm x 250 mm), F = 70 ml/min, 55% MeOH/C0₂. Entire sample dissolved in 420 ml MeOH/DCM 6/1, P = 100 bar, 7 ml injection, 290 nm, gave tert-butyl (2-((9S,1 lZ)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate: (0.40 g, 0.819 mmol, 45.5% yield) as a brown solid and tert-butyl (2-((9S,1 lE)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate: (0.28 g, 0.573 mmol, 31.8% yield) as a brown solid.

Analytical data for tert-butyl (2-((9S,1 lZ)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1.3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate: ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (s, 9 H) 2.25 - 2.38 (m, 1 H) 2.60 (d, J=13.69 Hz, 1 H) 2.76 (s, 3 H) 3.28 - 3.39 (m, 3 H) 3.43 - 3.56 (m, 3 H) 3.62 (d, J=6.06 Hz, 1 H) 4.13 - 4.23 (m, 1 H) 4.25 - 4.34 (m, 1 H) 5.02 (br. s., 1 H) 5.42 (d, J=2.15 Hz, 1 H) 5.92 (dd, J=13.89, 11.93 Hz, 1 H) 6.20 (dd, J=15.94, 7.34 Hz, 1 H) 7.07 (d, J=1.96 Hz, 1 H) 7.49 (t, J=7.82 Hz, 1 H) 7.69 (d, J=7.82 Hz, 1 H) 7.96 (d, J=7.43 Hz, 1 H) 13.12 (br. s., 1 H). MS (ESI, pos. ion mix: 489.4 (M+H)*.

Analytical data for tert-butyl (2-((9S,1 lE)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1.3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate: ¹H NMR (400 MHz, CDCl₃) δ ppm 1.34 (s, 9 H) 2.31 (d, J=14.08 Hz, 1 H) 2.68 - 2.80 (m, 1 H) 2.81 (s, 3 H) 3.28 - 3.39 (m, 2 H) 3.40 - 3.47 (m, 2 H) 3.54 - 3.61 (m, 2 H) 3.73 (d, J=16.04 Hz, 1 H) 3.82 (dt, J=14.23, 7.07 Hz, 1 H) 4.53 (t, J=5.67 Hz, 1 H) 4.83 (dd, J=16.33, 8.12 Hz, 1 H) 5.33 (br. s., 1 H) 5.69 - 5.86 (m, 2 H) 6.99 (d, J=1.96 Hz, 1 H) 7.49 (t, J=7.82 Hz, 1 H) 7.71 (dd, J=8.22, 0.98 Hz, 1 H) 7.86 (d, J=6.65 Hz, 1 H) 12.82 (br. s., 1 H). MS (ESI, pos. ion mix: 489.2 (M+H)*.

Example 95: (9S,1lZ)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one
A brown solution of tert-butyl (2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)carbamate (Example 93, 0.40 g, 0.819 mmol) and TFA (6.31 ml, 8.2 mmol) in DCM (8.19 ml) was stirred at RT for 15 min. The reaction mixture was concentrated to give (9S,11Z)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (0.368 g, 0.732 mmol, 89% yield) as a yellow solid. Pure (9S,11Z)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-6-one (27 mg) was obtained after suspension of the solid in DCM/MeOH, filtration, and drying the solid in vacuo. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ ppm 2.32 (d, J=13.30 Hz, 1H), 2.69 (d, J=1.93 Hz, 1H), 2.79 (s, 3H), 3.20-3.27 (m, 2H), 3.32-3.42 (m, 3H), 3.68-3.79 (m, 1H), 3.79-3.89 (m, 2H), 4.75 (dd, J=16.63, 8.61 Hz, 1H), 5.76 (dd, J=10.95, 7.63 Hz, 1H), 5.87 (t, J=11.35 Hz, 1H), 6.85 (d, J=1.76 Hz, 1H), 7.05 (d, J=4.30 Hz, 1H), 7.50 (t, J=7.82 Hz, 1H), 7.67 (d, J=7.83 Hz, 1H), 7.87 (br. s., 2H), 7.97 (d, J=7.43 Hz, 1H), 12.95 (br. s., 1H). $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ ppm -73.48 (s, 3F). MS (ESI, pos. ion) m/z: 389.1 (M+H)$^+$. 

Example 96: (9S)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(22),2(24),4,15,17,18,20,22-octaen-6-one

A suspension of (9S,11E)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,11,15(23),16,18,20-octae-6-one (Example 76; 35 mg, 0.090 mmol) and Pd/C (10 wt% (dry basis), wet, degussa type eIOI ne/w) (Aldrich; 106 mg, 0.045 mmol) in THF (3.0 mL) was stirred under a H₂ atmosphere (1 atm) at 55 °C for 2 h. The reaction mixture was then filtered through Celite, and the Celite pad was washed with (1:1)

MeOH/DCM (10 mL). The combined filtrates were concentrated in vacuo to provide a yellow oil. This oil was taken up in MeOH (0.9 mL), iron(II) chloride (Alfa Aesar, Ward Hill, MA; 0.338 mg, 2.67 μmol) and 30% aqueous H₂O₂ (9.99 μL, 0.098 mmol) were sequentially added, and the resulting solution was stirred at 23 °C for 1 h. The reaction mixture was then diluted with DCM (100 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 75 mL). The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated onto silica gel. Chromatographic purification (silica gel, 0-4% (2 M NH₃ in MeOH)/DCM) followed by rpHPLC purification of product-containing fractions (Phenomenex Gemini C₁₈ column (150 × 30 mm, 10 mm), 35 mL/min, 5-100% CH₃CN/H₂O + 0.1% TFA) afforded the TFA salt of the product, which was partitioned between DCM and saturated aqueous NaHCO₃ solution. The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated in vacuo to provide (9S)-14-(2-hydroxyethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(22),2(24),4,11,15,17,19,22-octade-6-one (2.04 mg, 5.21 μmol, 6% yield) as a yellow-green solid: ^1^H NMR (400 MHz, DMSO-d₆) δ ppm 7.99 (1 H, d, J=7.6 Hz), 7.61 (1 H, d, J=8.2 Hz), 7.42 (1 H, t, J=7.7 Hz), 7.02 (1 H, d, J=3.7 Hz), 6.92 (1 H, s), 4.88 (1 H, t, J=4.9 Hz), 3.87 (1 H, br. s.), 3.68 - 3.77 (4 H, m), 3.37 - 3.47 (2 H, m), 3.11 - 3.18 (1 H, m), 3.05 (1 H, br. s.), 2.77 (3 H, s), 2.08 - 2.20 (1 H, m), 1.95 - 2.08 (1 H, m), 1.87 (1 H, br. s.), 1.71 (3 H, br. s.). m/z (ESI, +ve) 392.1 (M+H)⁺.

Example 97: (9S,lIZ)-16-methyl-14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octane-6-one
A mixture of (9S,1lZ)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one (Example 95, 76 mg, 0.151 mmol), TEA (3.16 µl, 0.227 mmol), and (methylsulfonyl)ethene (Aldrich, 132 µl, 1.512 mmol) in THF (504 µl)/IPA (1008 µl) was heated in the microwave at 120 °C for 10 min (x3). The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 7% 2 M NH3 in MeOH/DCM to give (9S,1lZ)-1 6-methyl-
14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one (49 mg, 0.099 mmol, 65.5% yield) as a yellow solid: 1H NMR (400 MHz, CDCl3) δ ppm 2.31 (d, J=14.08 Hz, 1 H) 2.69 - 2.80 (m, 1 H) 2.82 (s, 3 H) 2.87 (s, 3 H) 2.91 - 3.01 (m, 2 H) 3.03 - 3.08 (m, 2 H) 3.10 - 3.15 (m, 2 H) 3.29 - 3.39 (m, 1 H) 3.43 - 3.52 (m, 2 H) 3.56 - 3.65 (m, 1 H) 3.68 (t, J=6.94 Hz, 1 H) 3.71 - 3.80 (m, 1 H) 4.84 (dd, J=16.33, 7.92 Hz, 1 H) 5.35 (d, J=3.52 Hz, 1 H) 5.70 - 5.86 (m, 2 H) 6.98 (dd, J=2.15 Hz, 1 H) 7.48 (dd, J=8.12, 7.53 Hz, 1 H) 7.70 (dd, J=8.22, 1.17 Hz, 1 H) 7.86 (dd, J=7.43, 1.17 Hz, 1 H) 12.84 (br. s., 1 H). MS (ESI, pos. ion) m/z: 495.2 (M+H)+.

Example 98: (9S,1lE)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-6-one
A solution of tert-butyl (2-((9S,1 lE)-16-methyl-6-oxo-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,1 1,5,17,19,22-octaen-14-yl)ethyl)carbamate (Example 94, 0.28 g, 0.573 mmol) and TFA (2.208 ml, 28.7 mmol) in DCM (5.73 ml) was stirred at RT for 30 min.

The reaction mixture was concentrated to give (9S,1 lE)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,1 1,5,17,19,22-octaen-6-one (0.28 g, 0.557 mmol, 97 % yield) as a brown solid:

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\text{H NMR (400 MHz, DMSO-}d_6) \delta \text{ ppm 2.24 - 2.35 (m, 1 H) 2.59 - 2.67 (m, 1 H) 2.71 (s, 3 H) 2.97 - 2.98 (m, 1 H) 3.10 - 3.20 (m, 2 H) 3.21 - 3.33 (m, 2 H) 3.61 (t, J=7.73 Hz, 2 H) 4.20 (br. s., 2 H) 5.95 - 6.07 (m, 1 H) 6.22 (d, J=15.26 Hz, 1 H) 6.98 (d, J=2.15 Hz, 1 H) 7.10 (br. s., 1 H) 7.48 - 7.56 (m, 1 H) 7.66 (d, J=8.22 Hz, 1 H) 7.87 (br. s., 2 H) 8.11 (d, J=7.63 Hz, 1 H) 13.07 (br. s., 1 H). M S (ESI, pos. ion) m/z: 389.1 (M+H)^+.
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Example 99: N-(2-((9S,HZ)-16-methyl-6-oxo-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)acetamide

A solution of (9S,l lZ)-14-(2-aminoethyl)-1 6-methyl-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,1 1,5,17,19,22-octaen-6-one (Example 95, 46 mg, 0.092 mmol), acetic anhydride (Fluka Chemie GmbH, 43.2 µl, 0.458 mmol), and TEA (89 µl, 0.641 mmol) in DCM (915 µl) was stirred at RT for 2 h. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 7% 2 M NH₃ in MeOH/DCM to give N-(2-((9S, 1IZ)-16-methyl-6-oxo-3,7,14,17,23-
pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-
l(21),2(24),4,1 1,15,17,19,22-octaen-14-yl)ethyl)acetamide as a red oil contaminated with Et₃N. The impure product was dissolved in DMSO (~20 mg/ml) and injected (2 x 1.000 ml) onto the Shimadzu preparatory LC (Phenomenex Gemini C₁₈ column (150 x 30 mm,
10 µι), 35 mL/min, 5-100% CH₃CN/H₂O + 0.1% TFA) before the pure fractions were combined, basicified with NaHCO₃ (saturated, aqueous), extracted with DCM, separated, dried over Na₂SO₄, and concentrated via rotary evaporation to give N-(2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[l3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,15,17,19,22-octaen-14-yl)ethyl)acetamide (18 mg, 0.042 mmol, 45.7 % yield) as a yellow solid.

Example 100: N-(2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[l3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,15,17,19,22-octaen-14-yl)ethyl)methanesulfonamide

A solution of (9S,11Z)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[l3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-1(21),2(24),4,15,17,19,22-octaen-1-one (Example 95, 60 mg, 0.119 mmol), methanesulfonyl chloride (Acros, 46.2 µι, 0.597 mmol), and TEA (116 µι, 0.836 mmol) in DCM (194 µι) was stirred at RT for 24 h. The reaction mixture was concentrated, charged with pyridine (5 ml) and more methanesulfonyl chloride (46.2 µι, 0.597 mmol) and the reaction was stirred at RT for 1 h then at 50 °C for 16 h. The reaction mixture was concentrated, diluted with DCM (100 ml), added to a separatory funnel, and washed with 1 N aqueous citric acid (2 x 75 ml) before the material was dissolved in MeOH (~20 mg/ml) and injected (3 x 1.000 ml) onto the Shimadzu preparatory LC (Phenomenex Gemini C₁₈ column (150 * 30 mm, 10 µπι), 35 mL/min, 5-100% CH₃CN/H₂O + 0.1%
TFA) before organic layer was separated, dried over Na₂SO₄, and concentrated. The crude product the pure fractions were combined, basicified with NaHCO₃ (saturated, aqueous), extracted with DCM, separated, dried over Na₂SO₄, and concentrated via rotary evaporation to give N-(2-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaaza-pentacyclo[13.6.2.1.2,5.0.4,9.0.1.8,22]tetracosa-l(21),2(24),4,11,15,17,19,20,22-nonaen-14-yl)ethyl)methanesulfonamide (6 mg, 0.013 mmol, 10.77 % yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ ppm: 2.22 (d, J=13.11 Hz, 1 H) 2.56 - 2.67 (m, 1 H) 2.85 (s, 3 H) 2.95 (s, 3 H) 3.16 - 3.28 (m, 2 H) 3.32 - 3.39 (m, 1 H) 3.45 (quin, J=6.16 Hz, 2 H) 3.71 - 3.84 (m, 2 H) 3.88 - 3.98 (m, 1 H) 4.86 (dd, J=16.24, 6.85 Hz, 1 H) 5.42 (d, J=4.30 Hz, 1 H) 5.74 (d, J=8.80 Hz, 2 H) 6.78 (d, J=2.15 Hz, 1 H) 7.46 (t, J=7.82 Hz, 1 H) 7.71 (dd, J=8.22, 1.17 Hz, 1 H) 7.75 (dd, J=7.43, 1.17 Hz, 1 H) 12.76 (br. s., 1 H).

MS (ESI, pos. ion) m/z: 467.1 (M+H)⁺.

Example 101: (9S,11E,13S)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraaza-pentacyclo[13.6.2.1.2,5.0.4,9.0.1.8,22]tetracosa-l(21),2(24),4,11,15,17,19,20,22-nonaen-6-one

Example 102: (9S,11Z)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraaza-pentacyclo[13.6.2.1.2,5.0.4,9.0.1.8,22]tetracosa-l(21),2(24),4,11,15,17,19,20,22-nonaen-6-one

Example 103: (9S,11E,13R)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraaza-pentacyclo[13.6.2.1.2,5.0.4,9.0.1.8,22]tetracosa-l(21),2(24),4,11,15,17,19,20,22-nonaen-6-one

Step 1: 1-((tert-butyldimethylsilyl)oxy)but-3-en-2-ol
A solution of (tert-butyldimethylsilyloxy)acetaldehyde (Sigma Aldrich, 2.186 ml, 11.47 mmol) in THF (57.4 ml) at 0 °C was stirred under N₂. A 1.0 M solution of vinylmagnesium bromide in THF (Sigma Aldrich, 20.08 ml, 20.08 mmol) was added dropwise and the reaction was stirred for 45 min. A saturated aqueous solution of NH₄Cl was added to quench the reaction. It was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude reaction mixture was diluted with DCM, adsorbed onto silica, and purified by silica gel chromatography (eluent: 5 to 100% EtOAc/hexanes). The product fractions were combined and concentrated in vacuo to give 1-((tert-butyldimethylsilyl)oxy)but-3-en-2-ol (1.97 g, 84%).

As an oil: ¹H NMR (DMSO-d₆) δ: 5.79 - 5.90 (1H, m) 5.17 - 5.31 (1H, m) 5.03 - 5.13 (1H, m) 3.89 - 4.05 (1H, m) 3.32 - 3.62 (2H, m), 0.86 (9H, s), 0.03 (6H, s).

Step 2: (9S,1E,13S)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~1 8,22~]tetracosa-
1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one, (9S,11Z)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~−1 8,22~]tetracosa-
1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one, (9S,1E,13R)-13-(hydroxymethyl)-16-
methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~−1 8,22~]tetracosa-
1(22),2(24),4, 11,15,17,18,20,22-nonaen-6-one

A slurry of NaH as a 60% dispersion in mineral oil (Strem Chemicals, 35.7 mg, 0.892 mmol) in DMF (2477 μl) was stirred, and 1-((tert-butyldimethylsilyloxy)but-3-en-2-ol (180 mg, 0.892 mmol) was added in one aliquot. The mixture was stirred until gas evolution ceased, and (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-IH-
pyrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 100 mg, 0.297 mmol) was added as a solid. The solution was stirred for 1 h. The reaction was diluted with water and extracted with DCM. The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a solid. This material was treated with THF (1.9 mL) under N₂ and was stirred at RT. A 1.0 M solution of tetra-N-butyllammonium fluoride in THF (386 μL, 0.386 mmol) was added in one portion, and the resulting suspension was stirred for 1 h. The mixture was diluted with water and extracted with DCM. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The mixture was suspended in DCM, adsorbed onto silica, and purified by silica gel chromatography (eluent: 0 to 10% MeOH/DCM) to give the product with impurities. This material was treated with Grubbs 2nd generation catalyst (Sigma
Aldrich, 84 mg, 0.099 mmol) and DCM (9.9 mL), and the suspension was sealed at stirred at 50 °C for 3 h. The material was cooled, adsorbed onto silica, and purified by silica gel chromatography (eluent: 0 to 10% MeOH/DCM). The product fractions were combined and concentrated under reduced pressure. The material was further purified by SFC (AD-H Column, 5 μ, 21x150 mm, P = 200 bar, T = 40 °C with 40% EtOH at 1 mL/min, solubilized in 1:1 DCM/MeOH), to give:

First eluting peak, a single C₁₃ diastereomer of (9S,1lE)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1₂,₅.₀₄,₉.₀₁₈,₂₂₆]tetracasons(22),2(24),4,11,17,18,20,22-nonaen-6-one (Example 101, 3.2 mg, 5%, 3 steps): ¹H NMR (400 MHz, CDCl₃) δ ppm 11.99 - 12.13 (1 H, m) 7.96 - 8.09 (1 H, m) 7.75 - 7.84 (1 H, m) 7.50 - 7.62 (1 H, m) 7.13 - 7.23 (1 H, m) 6.24 - 6.28 (2 H, m) 6.10 - 6.13 (1 H, dd, m) 5.31 (1 H, s) 4.91 - 4.98 (1 H, m) 4.61 - 4.68 (1 H, m) 4.51 - 4.57 (1 H, m) 3.30 - 3.45 (4 H, m) 2.74 (3 H, s) 2.43 - 2.48 (1 H, m): m/z (ESI, +ve) 377.1 (M+H)⁺.

Second eluting peak, a single C₁₃ diastereomer of (9S,1lZ)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1₂,₅.₀₄,₉.₀₁₈,₂₂₆]tetracasons(22),2(24),4,11,17,18,20,22-nonaen-6-one (Example 102, 2.2 mg, 4%, 3 steps): ¹H NMR (400 MHz, CDCl₃) δ ppm 11.93 - 12.11 (1 H, m) 7.98 - 8.08 (1 H, m) 7.73 - 7.86 (1 H, m) 7.50 - 7.63 (1 H, m) 7.10 - 7.20 (1 H, m) 6.17 - 6.31 (1 H, m) 5.99 - 6.15 (1 H, m) 4.86 - 4.98 (1 H, m) 4.60 - 4.71 (1 H, m) 4.51 - 4.57 (2 H, m) 3.22 - 3.38 (3 H, m) 2.73 (4 H, s) 2.35 - 2.53 (2 H, m): m/z (ESI, +ve) 377.1 (M+H)⁺.

Third eluting peak, a single C₁₃ diastereomer of (9S,1lE)-13-(hydroxymethyl)-16-methyl-14-oxa-3,7,17,23-tetraazapentacyclo[13.6.2.1₂,₅.₀₄,₉.₀₁₈,₂₂₆]tetracasons(22),2(24),4,11,17,18,20,22-nonaen-6-one (Example 103, 2.3 mg, 4%, 3 steps): ¹H NMR (400 MHz, CDCl₃) δ ppm 11.98 - 12.10 (1 H, m) 7.96 - 8.10 (1 H, m) 7.75 - 7.82 (1 H, m) 7.51 - 7.64 (1 H, m) 7.13 - 7.20 (1 H, m) 6.21 - 6.29 (1 H, m) 6.09 - 6.13 (1 H, m) 5.31 (1 H, s) 4.94 - 5.03 (1 H, m) 4.60 - 4.63 (1 H, m) 4.49 - 4.54 (1 H, m) 3.30 - 3.40 (4 H, m) 2.65 (3 H, s) 2.32 - 2.38 (2 H, m): m/z (ESI, +ve) 377.1 (M+H)⁺.

Example 104: (9S,lIE)-16-(hydroxymethyl)-12-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1₂,₅.₀₄,₉.₀₁₈,₂₂₆]tetracasons(22),2(24),4,11,17,18,20,22-nonaen-6-one
A solution of (9S,1lE)-12-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l1,15,17,19,22-octaen-6-one (Example 5; 40.3 mg, 0.108 mmol) and sodium triacetoxyhydroborate (Aldrich; 34.3 mg, 0.162 mmol) in a mixture of THF (3.0 mL) and MeOH (0.300 mL) was stirred at 25 °C for 10 min. Additional sodium triacetoxyhydroborate (34.3 mg, 0.162 mmol) was added, and the resulting mixture was stirred at 25 °C for 10 min. Saturated aqueous NaHCO₃ solution (10 mL) was then added, and the resulting mixture was partitioned between 5% MeOH/DCM (50 mL) and half-saturated aqueous NaHCO₃ solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with 5% MeOH/DCM (30 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to provide (9S,1lE)-16-(hydroxymethyl)-12-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,l1,15,17,19,22-nonaen-6-one (31.9 mg, 0.085 mmol, 79% yield) as a yellow-orange solid.

\[ \text{Example 105: } (9S,1lE)-16-methyl-14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l1,15,17,19,22-octaen-6-one \]
A solution of (9S,11E)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (Example 98, 57 mg, 0.113 mmol), (methylsulfonyl)ethene (Aldrich, 99 µl, 1.134 mmol), and triethylamine (23.72 µl, 0.170 mmol) in THF (378 µl) was heated in the microwave for 30 min at 120 °C. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 7% 2 M NH₃ in MeOH/DCM to give (9S,11E)-16-methyl-14-(2-((2-(methylsulfonyl)ethyl)amino)ethyl)-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (25 mg, 0.051 mmol, 44.6 % yield) as a yellow solid: ^1^H NMR (400 MHz, CDCl₃) δ ppm 2.31 - 2.43 (m, 1 H) 2.63 (d, J= 13.11 Hz, 1 H) 2.74 (s, 3 H) 2.88 (s, 3 H) 2.97 - 3.10 (m, 2 H) 3.10 - 3.16 (m, 2 H) 3.16 - 3.22 (m, 2 H) 3.33 - 3.41 (m, 2 H) 3.41 - 3.52 (m, 2 H) 3.53 - 3.63 (m, 1 H) 4.14 - 4.32 (m, 2 H) 5.43 (d, J= 4.1 Hz, 1 H) 5.87 - 5.98 (m, 1 H) 6.18 - 6.28 (m, 1 H) 7.10 (d, J= 2.15 Hz, 1 H) 7.50 (t, J= 3.2 Hz, 1 H) 7.69 (dd, J= 8.12, 1.27 Hz, 1 H) 7.98 (dd, J= 7.63, 1.37 Hz, 1 H) 13.14 (br. s., 1 H). MS (ESI, pos. ion) m/z: 495.2 (M+H)^+.

Example 106: N-(2-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5.0^4,9.0^18,22]tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)acetamide
A mixture of (9S,11E)-14-(2-aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0,4^9,0^18,22^]
tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (Example 98, 66 mg, 0.131 mmol), acetic anhydride (Fluka Chemie GmbH, 62.0 µl, 0.657 mmol), and TEA (341 µl, 0.919 mmol) in DCM (1313 µl) was stirred at RT for 30 min. The reaction mixture was diluted with DCM (100 ml), added to a separatory funnel, and washed with saturated aqueous NaHCO_3 (2 x 50 ml) before the organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was adsorbed onto silica and was purified via automated flash chromatography (silica gel) with 100% DCM to 4% 2 M NH_3 in MeOH/DCM to give N-(2-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0,4^9,0^18,22^]
tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)acetamide (21 mg, 0.049 mmol, 37.1% yield) as a yellow solid:

H NMR (400 MHz, CDCl_3) δ ppm 1.96 (s, 3 H) 2.09 - 2.20 (m, 1 H) 2.52 (d, J=12.91 Hz, 1 H) 2.73 (s, 3 H) 3.10 - 3.28 (m, 2 H) 3.34 - 3.40 (m, 1 H) 3.44 - 3.52 (m, 2 H) 3.53 - 3.68 (m, 2 H) 4.13 - 4.20 (m, 2 H) 5.71 - 5.82 (m, 2 H) 6.08 (dd, J=15.75, 2.84 Hz, 1 H) 6.47 (t, J=6.26 Hz, 1 H) 7.01 (d, J=1.96 Hz, 1 H) 7.47 (t, J=7.82 Hz, 1 H) 7.66 (dd, J=8.22, 0.98 Hz, 1 H) 7.94 (dd, J=7.53, 1.08 Hz, 1 H) 13.00 (br. s., 1 H). MS (ESI, pos. ion) m/z: 431.1 (M+H)^+.

Example 107: N-(2-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0,4^9,0^18,22^]
tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-14-yl)ethyl)methanesulfonamide

(9S,11Z)-14-(2-Aminoethyl)-16-methyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1^2,5^0,4^9,0^18,22^]
tetracosa-l(21),2(24),4,11,15,17,19,22-octaen-6-one (95, 20 mg, 0.051 mmol), methanesulfonyl chloride (Sigma-Aldrich, 15.94 µl, 0.206 mmol), and Et_3N (Sigma-Aldrich, 28.7 µl, 0.206 mmol) were combined in a
manner similar to that described in Example 106 to give N-(2-((9S,1 1E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2.5-0-4.9-0-1 8.22-]tetracosa-l(21),2(24),4,ll,15,17,19,22-octaan-14-yl)ethyl)methanesulfonamide (3 mg, 6.43 µmol, 12% yield) as a yellow solid. $^1$H NMR (400 MHz, CDC$_3$) δ ppm 2.25 (td, $J$=12.32, 7.71 Hz) 7.58 (1 H, dd, $J$=8.02, 7.82 Hz) 1.17 Hz) 7.49 (1 H, dd, $J$=5.87 Hz) 7.34 (1 H, t, $J$=7.73 Hz) 7.04 (1 H, d, $J$=2.15 Hz) 6.96 (1 H, br. s.) 5.75 - 5.94 (1 H, m) 5.03 - 5.15 (2 H, m) 4.89 (2 H, d, $J$=9.39 Hz) 4.50 - 4.64 (1 H, m) 3.44 - 3.53 (1 H, m) 3.13 - 3.27 (5 H, m) 2.86 - 2.97 (3 H, m) 2.64 - 2.72 (2 H, m) 2.28 - 2.40 (1 H, m). m/z (ESI, +ve) 400.2 (M+H)$^+$. 

Example 108: (9S)-17-methyl-3,7,15,18,24-pentaazahexacyclo[14.6.2.1-2.5-1-12.14-0-4.9-0-19.23-]hexacosa-l(23),2(26),4,ll,16,18,19,22-octaen-14-yl)ethyl)methanesulfonamide hydrochloride (Sigma Aldrich, 0.049 g, 0.595 mmol), and DIEA (EMD Biosciences, 207 µL, 1.189 mmol) were combined in a manner similar to that described in Example 30 to give (S)-7-allyl-2-(3-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.100 g, 0.297 mmol), 3-methylenehexacyclobutaminate residue: $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 12.07 (1 H, s) 7.91 (1 H, dd, $J$=7.63, 1.37 Hz) 7.58 (1 H, dd, $J$=8.02, 1.17 Hz) 7.49 (1 H, d, $J$=5.87 Hz) 7.34 (1 H, t, $J$=7.73 Hz) 7.04 (1 H, d, $J$=2.15 Hz) 6.96 (1 H, br. s.) 5.75 - 5.94 (1 H, m) 5.03 - 5.15 (2 H, m) 4.89 (2 H, d, $J$=9.39 Hz) 4.50 - 4.64 (1 H, m) 3.44 - 3.53 (1 H, m) 3.13 - 3.27 (5 H, m) 2.86 - 2.97 (3 H, m) 2.64 - 2.72 (2 H, m) 2.28 - 2.40 (1 H, m). m/z (ESI, +ve) 400.2 (M+H)$^+$. 

Step 1: (S)-7-allyl-2-(3-(but-3-en-1-yl)amino)-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (S)-7-allyl-2-(3-fluoro-2-methylquinolin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D; 0.100 g, 0.297 mmol), 3-methylenehexacyclobutaminate
Step 2: (9S)-17-methyl-3,7,15,18,24-pentaazahexacyclo[14. 6.2.1-2, 5-. 1-12,1 4-.0-4,9-.0-1 9,23~]hexacosa-
l(23),2(26),4, 11,16,18,19,2,123-nonaen-6-one.
((S)-7-Allyl-2-(2-methyl-3-((3-methylenecyclobutyl)amino)quinoxalin-5-yl)-6,7-di hydro-
IH-pyridin[3,2-clpyridin-4(5H)-one (Step 1, 0.130 g, 0.325 mmol) and Grubbs’ Catalyst
2nd Generation (Sigma Aldrich, 0.055 mg, 0.065 mmol) were combined in a manner
similar to that described in Example 30 to give (9S)-17-methyl-3,7,15,
18,24-pentaazahexacyclo[14. 6.2.1-2, 5-. 1-12,14-. 0-4, 9-.0-1 9,23~]hexacosa-
l(23),2(26),4,11,16,18,19,21,23-nonaen-6-one (0.017 g, 0.046 mmol, 17%) as a yellow-
brown solid: 'H NMR (400 MHz, DMSO-d6) δ ppm 11.51 (1 H, s) 7.97 (1 H, d, J=6.26
Hz) 7.57 (1 H, d, J=6.65 Hz) 7.46 (1 H, d, J=7.63 Hz) 7.31 (1 H, t, J=7.73 Hz) 7.13 (1 H,
d, J=4.9 Hz) 6.85 (1 H, d, J=4.35 Hz) 5.65 (1 H, br. s.) 4.35 (1 H, br. s.) 4.10 (1 H, br.
s.) 3.27 (2 H, m) 3.18 (2 H, d, J=7.73 Hz) 3.05 (3 H, br. s.) 2.28 - 2.39 (2 H, m) 2.16 -
2.28 (2 H, m). m/z (ESI, +ve) 372.2 (M+H)+.
Examples 109-110: (9R,llE)-ll,17-dimethyl-3,7,15,18,24-
pentaazapentacyclo [1462-1,25-0-4,9-0-19,23-] pentacosa-
l(22),2(25),4,11,16,18,20,23-octaen-6-one and (9S,HE)-ll,17-dimethyl-3,7,15,18,24-
pentaazapentacyclo [1462-1,25-0-4,9-0-19,23-] pentacosa-
l(22),2(25),4,11,16,18,20,23-octaen-6-one

(9R, 11E)-11,17-dimethyl-3,7,15,18,24-
pentaazapentacyclo[1 462 1-2,5-0-4,9-0-1 9,23~]pentacosa-
l(22),2(25),4, 11,16,18,20,23-octaen-6-one and (9S, 11E)-11,17-dimethyl-3,7,15,18,24-
pentaazapentacyclo[1 462 1-2,5-0-4,9-0-1 9,23~]pentacosa-
l(22),2(25),4, 11,16,18,20,23-octaen-6-one were synthesized in a manner similar to
Example 1 using but-3-en-l -amine. Individual enantiomers were obtained by chiral SFC
(Column: Chiralpak AS-H Sepax (150 x 21 mm, 5 micron); Mobile Phase: 60:40 (A:B)
A: Liquid C02; B: MeOH (20 mM NH3); Flow Rate: 75 mL/min; Oven Temp: 40 °C;
A-1700-WO-PCT

Outlet Pressure: 100 bar: $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 12.12 (1 H, br. s.) 7.93 (1 H, d, J=6.8 Hz) 7.44 - 7.63 (2 H, m) 7.26 (1 H, t, J=7.8 Hz) 7.04 (1 H, br. s.) 6.92 (1 H, d, J=2.0 Hz) 5.83 (1 H, t, J=7.4 Hz) 3.46 - 3.72 (2 H, m) 3.27 - 3.44 (2 H, m) 3.01 - 3.14 (1 H, m) 2.56 - 2.72 (1 H, m) 2.59 (3 H, s), 2.16 - 2.29 (2 H, m) 2.06 (1 H, dt, J=7.0, 3.5 Hz) 1.60 (3 H, s). m/z (ESI, +ve) 374.1 (M+H)$^+$.

Example 111-114: (9S, llZ)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13621-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,ll,15(23),16,18,20-octaen-6-one; (9S, llZ)-ll,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13621-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,ll,15(23),16,18,20-octaen-6-one; (9R, llZ)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13621-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,ll,15(23),16,18,20-octaen-6-one; (9R, HZ)-ll,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13621-2,5-0-4,9-0-18,22-]tetracosa-l(22),2(24),4,ll,15(23),16,18,20-octaen-6-one.
A-1700-WO-PCT

Step 1: mixture of tert-butyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate and tert-butyl 5-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate

To a 500-mL three neck round-bottomed flask was added n-boc-hydroxylamine (Sigma Aldrich, 5.0 g, 37.6 mmol) in DCM (75 mL) followed by copper (i) chloride (Sigma Aldrich, 186 mg, 1.878 mmol), ethanolamine (Sigma Aldrich, 0.338 mL, 5.63 mmol) and isoprene (Sigma Aldrich, 3.76 mL, 37.6 mmol). The green mixture was stirred at RT for 10 min, then H$_2$O$_2$ 30% in H$_2$O (Sigma Aldrich, 26.9 mL, 263 mmol) was added dropwise through syringe pump in 30 min. The reaction was stirred at RT for 2 h, then quenched with H$_2$O (50 mL). The mixture was extracted with DCM (80 mL X3) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated. The residue was purified with silica gel chromatography (eluted with 2-5% EtOAc in DCM) to give a mixture of tert-butyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate and tert-butyl 5-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (2.35 g, 5.90 mmol, 31.4 % yield) as a colorless oil. MS (ESI, pos. ion) m/z: 222.1 (M+Na).

Step 2: (Z)-tert-butyl (4-hydroxy-2-methylbut-2-en-1-yl)carbamate and (Z)-tert-butyl (4-hydroxy-3-methylbut-2-en-1-yl)carbamate

To a 500-mL round-bottomed flask was added a mixture of tert-butyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate and tert-butyl 5-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (3.00 g, 7.53 mmol) and molybdenum carbonyl (Strem, 3.18 g, 12.05 mmol) in ACN (105 mL)/H$_2$O (15 mL). The mixture was stirred at RT for 10 min, then sodium borohydride (Riedel de Hsen AG, 0.142 g, 3.76 mmol) was added. The reaction was heated at 85 °C for 15 h, then cooled to RT. Et$_2$O (100 mL) was added and the mixture was filtered through a plug of Celite and washed with Et$_2$O (30 mL x3). The filtrate was concentrated and the residue was purified with silica gel chromatography (eluted with 5-25% EtOAc in hexanes) to give (Z)-tert-butyl (4-hydroxy-2-methylbut-2-en-1-yl)carbamate and (Z)-tert-butyl (4-hydroxy-3-methylbut-2-en-1-yl)carbamate (2.60 g, 6.46 mmol, 86 % yield) as a light yellow oil. MS (ESI, pos. ion) m/z: 224.1 (M+Na).

Step 3: (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)carbamate and (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)carbamate

To a 100-mL round-bottomed flask was added a mixture of (Z)-tert-butyl (4-hydroxy-2-methylbut-2-en-1-yl)carbamate and (Z)-tert-butyl (4-hydroxy-3-methylbut-2-en-1-yl)carbamate (1.00 g, 2.484 mmol) and tert-butyldimethylchlorosilane (Acros, 0.936 g,
6.21 mmol) in DCM (10 mL) followed by Et₃N (0.864 mL, 6.21 mmol) and 4-(dimethylamino)pyridine (Sigma Aldrich, 0.061 g, 0.497 mmol). The reaction was stirred at RT for 2 h, then quenched with water. The mixture was extracted with DCM (50 mL x2). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified with silica gel chromatography (eluted with 0-5% EtOAc in Hexanes) to give (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)carbamate and (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)carbamate (1.42 g, 2.250 mmol, 91% yield) as a colorless oil. MS (ESI, pos. ion) m/z: 338 (M+Na).

Step 4: (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)(methyl)carbamate

To a 100-mL round-bottomed flask was added a mixture of (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)(methyl)carbamate (1.30 g, 2.060 mmol) in THF (15 mL) and the solution was cooled to 0 °C. NaH, 60% dispersion in mineral oil (Sigma Aldrich, 0.173 g, 4.33 mmol) was added followed by iodomethane (0.320 mL, 5.15 mmol). The reaction was stirred at 0 °C for 1 h, then warmed to RT for 2 h. The reaction was quenched with water and the mixture was extracted with DCM (50 mL X3). The combined organic layers were dried (MgSO₄), filtered and concentrated to give the crude mixture, which was used in the next reaction without further purification. MS (ESI, pos. ion) m/z: 352.1 (M+Na).

Step 5: (Z)-tert-butyl (4-hydroxy-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-hydroxy-3-methylbut-2-en-1-yl)(methyl)carbamate

To a 100-mL round-bottomed flask was added a mixture of (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)(methyl)carbamate (1.50 g, 2.276 mmol) in THF (10 mL) followed by tetrabutylammonium fluoride, 1.0 M in THF (Sigma Aldrich, 5.69 mL, 5.69 mmol). The reaction was stirred at RT for 30 min, then quenched with water. The mixture was extracted with DCM (50 mL X3) and the combined organic layers were dried (MgSO₄), filtered and concentrated to give the crude mix, which was
used in the next reaction without further purification. MS (ESI, pos. ion) m/z: 238.1 (M+Na).

Step 6: (Z)-tert-butyl (4-chloro-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-chloro-3-methylbut-2-en-1-yl)(methyl)carbamate

To a 150-mL round-bottomed flask was added a mixture of (Z)-tert-butyl (4-hydroxy-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-hydroxy-3-methylbut-2-en-1-yl)(methyl)carbamate (0.98 g, 2.276 mmol) in DCM (50 mL) and the solution was cooled to 0 °C. Triphenylphosphine (Sigma Aldrich, 2.388 g, 9.10 mmol) was added followed by slow addition of chlorosuccinimide (Alfa Aesar, 1.033 g, 7.74 mmol). The mixture was stirred at 0 °C for 30 min, then the solvent was removed. The residue was purified with silica gel chromatography (eluted with 2-5% EtOAc in Hexanes) to give (Z)-tert-butyl (4-chloro-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-chloro-3-methylbut-2-en-1-yl)(methyl)carbamate (925 mg, 1.979 mmol, 87% yield) as a colorless oil. MS (ESI, pos. ion) m/z: 256.1 (M+Na).

Step 7: (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate and (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate

To a 100-mL round-bottomed flask was added a mixture of (Z)-tert-butyl (4-chloro-2-methylbut-2-en-1-yl)(methyl)carbamate and (Z)-tert-butyl (4-chloro-3-methylbut-2-en-1-yl)(methyl)carbamate (438 mg, 0.938 mmol) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (400 mg, 1.876 mmol) in THF (10 mL). The solution was cooled to -30 °C and LiHMDS, 1.0m solution in THF (Sigma Aldrich, 4.69 mL, 4.69 mmol) was added dropwise. The reaction was stirred at -20-30 °C for 1 h, then diluted with DCM and 5% KHSO₄. The mixture was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified with silica gel chromatography (eluted with 20-40% EtOAc in Hexanes) to give (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate and (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate (1:1) (560 mg, 0.682 mmol, 72.7% yield) as a solid. MS (ESI, pos. ion) m/z: 433.1 (M+Na).
Step 8: (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate and (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate

A glass microwave reaction vessel was charged with a mixture of (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate and (Z)-tert-butyl 5-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2,4-dioxopiperidine-1-carboxylate (750 mg, 0.914 mmol) and 2-bromo-1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (517 mg, 1.827 mmol) in EtOH (10 mL) followed by NH₄OAc (563 mg, 7.31 mmol). The reaction was stirred at RT for 15 h. The mixture was diluted with water and the suspension was filtered. The resulting solid was purified with silica gel chromatography (eluted with 20-40% EtOAc in hexanes) to give (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate and (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate (227 mg, 0.191 mmol, 20.93 % yield) as a yellow solid. MS (ESI, pos. ion) m/z: 616.1 (M+Na).

Step 9: (Z)-2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methyl-4-(methylamino)but-2-en-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one and (Z)-2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methyl-4-(methylamino)but-2-en-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

To a 25-mL round-bottomed flask was added a mixture of (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-2-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate and (Z)-tert-butyl 7-(4-((tert-butoxycarbonyl)(methyl)amino)-3-methylbut-2-en-1-yl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate (225 mg, 0.189 mmol) and TFA (Sigma Aldrich, 0.146 mL, 1.895 mmol) in DCM (2 mL). The reaction was stirred at RT for 30 min, then the solvent was removed to give the crude mixture, which was used in the next reaction without further purification. MS (ESI, pos. ion) m/z: 394.1 (M+H).
Step 10: \((1\mathrm{I}Z)\)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4,1 1,1 1,5(23),1 6,1 8,20-octaen-6-one, (HZ)-1 1,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4,1 1,1 5(23),1 6,1 8,20-octaen-6-one, (HZ)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4, 11,15(23),16, 18,20-octaen-6-one: and (1\mathrm{I}Z)-11,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4,11,15(23),16,18,20-octaen-6-one

A glass microwave reaction vessel was charged with a mixture of (Z)-2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methyl-4-(methylamino)but-2-en-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one and (Z)-2-(3-fluoro-2-methylquinoxalin-5-yl)-7-(2-methyl-4-(methylamino)but-2-en-1-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (179 mg, 0.455 mmol) in DMSO (4 mL) followed by Et$_3$N (0.633 mL, 4.55 mmol). The reaction mixture was stirred and heated in an oil bath at 100 °C for 90 min. The mixture was cooled to RT and water (50 mL) was added. The suspension was filtered and the resulting solid was purified first with preparative SFC chromatography (OJ-H (5 um, 21 x 150 mm, 75 mL/min), 20% Methanol (20 mM NH$_3$). T = 40 °C, P = 100 bar) then the first peak was further purified with preparative SFC chromatography (Column: Chiralpak AS-H Sepax (150 x 21 mm, 5 micron), 30% MeOH (20 mM NH$_3$), T = 40 °C, P = 100 bar) to give the following compounds in sequence:

Example 111: single enantiomer of (1\mathrm{I}Z)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4,1 1,1 5(23),1 6,1 8,20-octaen-6-one: MS (ESI, pos. ion) m/z: 374.1 (M+H);

$^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 13.09 (1 H, br. s.), 7.90 (1 H, dd, J=7.4, 1.4 Hz), 7.61 (1 H, dd, J=8.1, 1.3 Hz), 7.40 (1 H, t, J=7.8 Hz), 6.98 (1 H, d, J=4.3 Hz), 6.78 (1 H, d, J=2.2 Hz), 5.56 - 5.65 (1 H, m), 4.91 (1 H, d, J=16.8 Hz), 3.66 - 3.76 (1 H, m), 3.43 (3 H, s), 3.34 - 3.38 (1 H, m), 3.14 - 3.19 (2 H, m), 2.82 (3 H, s), 2.15 - 2.25 (1 H, m), 1.70 (3 H, s)

Example 112: single enantiomer of (1\mathrm{I}Z)-1 1,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[1362 1-2,5,0-4,9,0-18,22-]tetracosane-1(22),2(24),4,1 1,1 5(23),1 6,1 8,20-octaen-6-one: MS (ESI, pos. ion) m/z: 374.1 (M+H);
$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 13.12 (1 H, br. s.), 7.87 (1 H, dd, $J=7.4$, 1.4 Hz), 7.61 (1 H, dd, $J=8.1$, 1.3 Hz), 7.40 (1 H, t, $J=7.8$ Hz), 7.03 (1 H, d, $J=4.5$ Hz), 6.76 (1 H, d, $J=2.2$ Hz), 5.57 (1 H, d, $J=7.8$ Hz), 4.78 (1 H, dd, $J=16.1$, 8.9 Hz), 3.67 - 3.76 (1 H, m), 3.42 - 3.50 (1 H, m), 3.40 (3 H, s), 3.33 - 3.38 (1 H, m), 3.22 (1 H, d, $J=1.7$ Hz), 2.74 - 2.83 (4 H, m), 2.12 - 2.21 (1 H, m), 1.87 (3 H, s)

Example 113: single enantiomer of (1Z)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13621~2,5~0~4,9~0~18,22~]tetracosa-l(21),2(24),4,15,17,19,22-heptaen-6-one

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 13.09 (1 H, br. s.), 7.90 (1 H, dd, $J=7.4$, 1.2 Hz), 7.61 (1 H, dd, $J=8.1$, 1.1 Hz), 7.40 (1 H, t, $J=7.7$ Hz), 6.98 (1 H, d, $J=4.3$ Hz), 6.78 (1 H, d, $J=2.2$ Hz), 5.53 - 5.67 (1 H, m), 4.91 (1 H, d, $J=16.6$ Hz), 3.65 - 3.77 (1 H, m), 3.43 (3 H, s), 3.34 - 3.38 (1 H, m), 3.13 - 3.20 (2 H, m), 2.82 (3 H, s), 2.16 - 2.24 (1 H, m), 1.70 (3 H, s)

Example 114: single enantiomer of (HZ)-1,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[3621~2,5~0~4,9~0~18,22~]tetracosa-l(22),2(24),4,15,17,19,22-heptaen-6-one

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 13.12 (1 H, br. s.), 7.84 - 7.89 (1 H, m), 7.61 (1 H, d, $J=7.8$ Hz), 7.36 - 7.43 (1 H, m), 7.03 (1 H, d, $J=3.9$ Hz), 6.76 (1 H, d, $J=1.8$ Hz), 5.52 - 5.61 (1 H, m), 4.79 (1 H, dd, $J=16.3$, 8.9 Hz), 3.67 - 3.78 (1 H, m), 3.42 - 3.50 (1 H, m), 3.40 (3 H, s), 3.35 (1 H, d, $J=6.3$ Hz), 3.16 - 3.25 (1 H, m), 2.74 - 2.83 (4 H, m), 2.13 - 2.20 (1 H, m), 1.87 (3 H, s)

Example 115 (9S,12S)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13621~2,5~0~4,9~0~18,22~]tetracosa-l(21),2(24),4,15,17,19,22-heptaen-6-one

Example 116 (9S,HR)-H,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13621~2,5~0~4,9~0~18,22~]tetracosa-l(21),2(24),4,15,17,19,22-heptaen-6-one

Example 117 (9R,12S)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13621~2,5~0~4,9~0~18,22~]tetracosa-l(21),2(24),4,15,17,19,22-heptaen-6-one

Example 118 (9R,HR)-Il,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13621~2,5~0~4,9~0~18,22~]tetracosa-l(21),2(24),4,15,17,19,22-heptaen-6-one
A-1700-WO-PCT

Step 1: (S)-1,4-dibromo-2-methylbutane

To a slurry of triphenylphosphine (Aldrich, 50.6 g, 193 mmol) in 280 mL ACN at 3 °C under N₂ in a 3 neck flask fitted with internal temperature monitor and mechanical stirrer was added bromine (Aldrich, 9.94 ml, 193 mmol) slowly dropwise via addition funnel, such that the internal temperature did not exceed 12 °C. The resulting yellow suspension was stirred for 15 min, at which point (S)-2-methylbutane-1,4-diol (TCI America; 10.0 g, 96 mmol) was added as a solution in 20 mL ACN, dropwise via addition funnel at a rate such that the temperature did not exceed 5 °C. The reaction became clear upon complete addition. The ice bath was removed and the clear, colorless reaction was stirred overnight. In the morning, a white crystalline material was evident. The reaction was filtered through a glass frit, rinsing 1 x 100 mL ACN. The filtrate was concentrated in vacuo, and the resulting residue was treated with 300 mL pentane and stirred rapidly about an hour. The reaction was filtered, rinsing 1 x 100 mL pentane, and the filtrate was concentrated in vacuo. At about 1/2 volume, a precipitate formed. This was removed by filtration, rinsing 3 x 30 mL pentane, and the filtrate was concentrated in vacuo to give (S)-1,4-dibromo-2-methylbutane (18.5 g, 80 mmol, 84 % yield) as a clear/colorless oil: ¹H NMR (400 MHz, CDC1₃) δ ppm 3.37 - 3.54 (8 H, m) 1.98 - 2.18 (4 H, m) 1.81 (2 H, dq, J=13.9, 6.9 Hz) 1.07 (3 H, s) 1.05 (3 H, s).

Step 2: tert-butyl 5-((S)-4-bromo-3-methylbutyl)-2,4-dioxopiperidine-1-carboxylate and tert-butyl 5-((R)-4-bromo-2-methylbutyl)-2,4-dioxopiperidine-1-carboxylate

A 1 L 3 neck rbf was charged with tert-butyl 2,4-dioxopiperidine-1-carboxylate (Ark Pharma; Libertyville, IL; 4.00 g, 18.76 mmol) and (S)-1,4-dibromo-2-methylbutane (21.57 g, 94 mmol) and 150 mL THF, and fitted with atemperature probe, mechanical stirrer, and addition funnel. The reaction was cooled to -20 °C (periodic addition of dry ice chunks to acetone) and LiHMDS, 1.0 M solution in THF (Aldrich, 46.9 ml, 46.9 mmol) was added dropwise via addition funnel such that the temperature of the reaction
did not exceed -19 °C. The reaction became thick with a precipitate during addition, which dissolved upon complete addition. The temperature of the reaction was maintained between -11 and -20 °C for 1 h. The reaction was quenched with water, HCl 5.0 N solution (18.76 ml, 94 mmol), and Et₂O was added. The organic layer was washed with saturated aq NaCl and the organics were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The material was treated with DCM and purified by silica gel chromatography (330 g ISCO redisep gold column) using 0 - 100% EtOAc/hexane to give a mixture of tert-butyl 5-((S)-4-bromo-3-methylbutyl)-2,4-dioxopiperidine-1-carboxylate and tert-butyl 5-((R)-4-bromo-2-methylbutyl)-2,4-dioxopiperidine-1-carboxylate (3.40 g, 9.39 mmol, 50.0 % yield), as an oil with solid: m/z (ESI, +ve) 384.0/386.0 (M+Na)+.

Step 3: tert-butyl 5-((S)-4-azido-3-methylbutyl)-2,4-dioxopiperidine-1-carboxylate and tert-butyl 5-((R)-4-azido-2-methylbutyl)-2,4-dioxopiperidine-1-carboxylate

The mixture of isomers from step 2 (3.40 g, 9.39 mmol) and sodium azide (Fluka; 3.30 ml, 94 mmol) were combined in 19 mL DMF, the reaction was flushed with nitrogen and sealed, and stirred for 48 h at RT. The reaction was judged complete and the reaction was treated with ice, partitioned between H₂O and Et₂O. The aq layer was extracted 1 x Et₂O, and the organic layers were washed with water once, saturated aqueous NaCl once, and the organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a mixture of tert-butyl 5-((S)-4-azido-3-methylbutyl)-2,4-dioxopiperidine-1-carboxylate and tert-butyl 5-((R)-4-azido-2-methylbutyl)-2,4-dioxopiperidine-1-carboxylate (2.64 g, 8.14 mmol, 87 % yield), m/z (ESI, +ve) 347.1 (M+Na)+.

Step 4: 7-((S)-4-azido-3-methylbutyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one and 7-((R)-4-azido-2-methylbutyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

A solution of the mixture from Step 3 (2.64 g, 8.14 mmol) in 30 mL DCM was fitted with a Drierite-filled drying tube and the reaction was cooled to 0 °C. TFA (Aldrich, 6.05 ml, 81 mmol) was added dropwise by syringe, and the ice bath was removed. The reaction was stirred at RT for 1 h and concentrated in vacuo to give 3.62 g of a yellow oil. The material was treated with NH₄OAc (5.02 g, 65.1 mmol), 2-bromo-1-(3-fluoro-2-methylquinoxalin-5-yl)ethanone (Intermediate U; 3.00 g, 10.58 mmol), and 75 mL EtOH, sealed, and heated in a 50 °C bath for 6 h. The reaction was quenched by addition of
saturated aqueous NaHCO$_3$ with rapid stirring (bubbling) and DCM. The aqueous layer was extracted with DCM 3x, and the combined organics were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. The material was treated with 10% MeOH in DCM and adsorbed onto 15 g silica gel and purified by silica gel chromatography (80 g ISCO gold column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford a mixture of 7-((S)-4-azido-3-methylbutyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one and 7-((R)-4-azido-2-methylbutyl)-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.880 g, 2.160 mmol, 26.5 % yield) as an orange solid. m/z (ESI, +ve) 408.2 (M+H)$^+$. 


To a solution of the mixture from Step 4 (0.880 g, 2.160 mmol) in 18 mL THF under argon was added water (0.389 ml, 21.60 mmol) followed by trimethylphosphine, 1.0 M solution in THF (Aldrich, 3.24 ml, 3.24 mmol). The clear, orange solution was stirred for 2 h. The reaction was concentrated in vacuo and concentrated from anhydrous toluene 3 x, and dried in vacuo for 20 min. The residue was treated with anhydrous DMSO (50 mL) and DIEA (1.878 ml, 10.80 mmol) and placed in a 70 °C oil bath. After 1 h, the reaction was poured into 500 mL ice/water, and a precipitate formed. This was collected by filtration through a 0.45 micron membrane under vacuum. The semisolid was transferred to a flask with DCM/MeOH and adsorbed onto 4.5 g silica gel and dried. The material was purified by silica gel chromatography (40 g ISCO gold column) using 0 - 100% 90/10 DCM/MeOH in DCM. The product-containing fractions were concentrated to afford 0.107 g containing a mixture of isomers. This was further purified by chiral SFC: 1st SFC Purification: AS-H (5 micron, 21x 250 mm, S/N=5172), F=60ml/min, 70% carbon dioxide and 30% MeOH with 20mM ammonia; 282nm, bpr=100 bar, column
A-1700-WO-PCT

p=172. Three peaks were collected named by order of elution: peaks 1, 2 and 3. 2nd SFC Purification of peak 3: AD-H (5um, 21x250 mm, S/N=5271), F=60/min, 75% carbon dioxide and 25% MeOH with 20mM ammonia. 282nm, bpr=100 bar to give peak 3-1 and 3-2 (named by order of elution).

Example 115 (9S,12S)-12,16-dimethyl-3,7,14,1 7,23-pentaaza-
pentacyclo[1 21,2(24),4,15,1 7,19,22-heptaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.86 - 7.98 (2 H, m) 7.57 (1 H, dd, J=8.1, 1.1 Hz) 7.33 (1 H, t, J=7.8 Hz) 6.96 (1 H, d, J=4.1 Hz) 6.87 (1 H, d, J=1.8 Hz) 3.88 (1 H, d, J=14.7 Hz) 3.25 - 3.30 (1 H, m) 3.09 - 3.20 (1 H, m) 2.98 (1 H, dt, J=13.6, 7.1 Hz) 2.70 - 2.84 (1 H, m) 2.56 (3 H, s) 2.40 (1 H, br. s) 1.88 - 2.05 (1 H, m) 1.50 - 1.71 (3 H, m) 1.01 (3 H, d, J=6.3 Hz), m/z (ESI, +ve) 362.1 (M+H)⁺.

Example 116 (9S,11R)-11,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 21,2(24),4,15,1 7,19,22-heptaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.89 (1 H, dd, J=7.4, 1.2 Hz) 7.84 (1 H, t, J=5.0 Hz) 7.57 (1 H, dd, J=8.1, 1.1 Hz) 7.33 (1 H, t, J=7.8 Hz) 7.00 (1 H, br. s) 6.83 (1 H, d, J=1.8 Hz) 3.62 (1 H, t, J=13.2 Hz) 3.08 - 3.31 (4 H, m) 2.52 (3 H, s) 1.86 - 2.23 (3 H, m) 1.59 (1 H, dd, J=15.1, 5.3 Hz) 1.38 - 1.53 (1 H, m) 1.05 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 362.1 (M+H)⁺.

Example 117 (9R,12S)-12,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 21,2(24),4,15,1 7,19,22-heptaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.48 (1 H, br. s) 7.99 (1 H, d, J=7.4 Hz) 7.88 (1 H, br. s) 7.56 (1 H, d, J=7.8 Hz) 7.33 (1 H, t, J=7.7 Hz) 7.03 (1 H, d, J=3.9 Hz) 6.95 (1 H, s) 3.49 (1 H, d, J=12.7 Hz) 2.94 - 3.28 (4 H, m) 2.54 (3 H, s) 2.29 - 2.44 (1 H, m) 1.99 (1 H, br. s) 1.74 (2 H, br. s) 1.19 - 1.37 (1 H, m) 1.06 (3 H, d, J=5.9 Hz), m/z (ESI, +ve) 362.1 (M+H)⁺.

Example 118 (9R,11R)-11,16-dimethyl-3,7,14,17,23-
pentaazapentacyclo[1 21,2(24),4,15,1 7,19,22-heptaen-6-one: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.98 (1 H, dd, J=7.6, 1.0 Hz) 7.78 (1 H, t, J=5.0 Hz) 7.56 (1 H, dd, J=8.0, 1.0 Hz) 7.33 (1 H, t, J=7.8 Hz) 7.02 (1 H, d, J=4.3 Hz) 6.93 (1 H, d, J=1.6 Hz) 3.54 - 3.69 (1 H, m) 2.95 - 3.28 (3 H, m) 2.52 (3 H, s) 2.20 (1 H, br. s) 1.93 (1 H, br. s) 1.80 (1 H, br. s) 1.55 - 1.70 (1 H, m) 1.43 (1 H, d, J=13.9 Hz) 1.11 (3 H, d, J=6.7 Hz), m/z (ESI, +ve) 362.1 (M+H)⁺.
A-1700-WO-PCT

Example 119: \((9S,11E,13R)-13-(methoxymethyl)-16-methyl-3,7,14,17,23-
pentaazapentacyclo[13.6.2.1^{2,5} \cdot 0 \cdot 4,9 \cdot 0 \cdot 18,22-]tetracosa-
l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one\)

Step 1: (R)-tert-butyl (l-methoxy-3-oxopropan-2-yl)carbamate
A solution of (R)-tert-butyl (l-hydroxy-3-methoxypropan-2-yl)carbamate (CNH Technologies, 2.49 g, 12.13 mmol) in DCM (121 ml) was stirred, and Dess-Martin periodinane (Sigma Aldrich 5.66 g, 13.34 mmol) was added, giving a milky white suspension. Stirring under N\(_2\) for 30 min gave a transparent solution with a purple hue. The reaction was stirred more rapidly, and 15 mL saturated aqueous Na\(_2\)CO\(_3\) and 15 mL saturated aqueous sodium thiosulfate were added. The milky mixture was stirred for 1 h. The resulting biphasic solution was extracted with DCM (3x), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to give (R)-tert-butyl (1-methoxy-3-oxopropan-2-yl)carbamate as a milky white residue (2.19 g, 10.78 mmol, 89%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 9.65 (1 H, s) 5.40 (1 H, br. s.) 4.22 - 4.39 (1 H, m) 3.93 (1 H, dd, J=9.59, 2.93 Hz) 3.63 (1 H, dd, J=9.59, 4.11 Hz) 3.35 (3 H, s) 1.47 (9 H, s). \(m/z\) (ESI, +ve) 400.2 (M+H)+.

Step 2: (R)-l-methoxybut-3-en-2-amine hydrochloride
A suspension of methyltriphenylphosphonium bromide (Sigma Aldrich, 2.53 g, 7.09 mmol) in anhydrous THF (30 mL) was stirred under N\(_2\) and cooled to -78°C. n-butyllithium solution, 2.5m in hexanes (Sigma Aldrich, 2.83 mL, 7.09 mmol) was added dropwise over 10 min, and the mixture was warmed to RT. It was cooled to 0°C, and (R)-tert-butyl (1-methoxy-3-oxopropan-2-yl)carbamate (Step 1, 1.2 g, 5.90 mmol) in 10 mL
anhydrous THF was added dropwise over 5 min. The mixture was stirred at 0°C as the ice bath expired. The reaction was diluted with saturated aqueous NH_4Cl. Et_2O was added, and the reaction mixture was washed 3x. The organic partition was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a viscous brown-yellow residue.

The mixture was diluted with DCM and adsorbed onto silica. It was purified on 24 g SiO_2 (eluent: 0 to 50% EtOAc/hexanes then 50 to 80% EtOAc/hexanes). The material was concentrated in vacuo. HCl in 1,4-dioxane, 4 N (Sigma Aldrich, 7.38 mL, 29.5 mmol) was added to the mixture and stirred for 2 h. The mixture was diluted with MeOH and concentrated in vacuo to a brown residue that was used without additional purification. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 6.11 (2 H, br. s.) 5.67 - 5.81 (1 H, m) 5.01 - 5.18 (2 H, m) 3.33 - 3.42 (1 H, m) 3.24 - 3.28 (2 H, m) 3.22 - 3.24 (3 H, m).


A solution of DIEA (EMD Biosciences, 326 μL, 1.873 mmol), (R)-1-methoxybut-3-en-2-amine hydrochloride (Step 2, 0.129 g, 0.936 mmol), (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Intermediate D, 0.105 mg, 0.312 mmol), and DMSO (3.1 mL) was sealed and stirred at 80 °C for 60 h.

The mixture was cooled, diluted with water, and extracted with DCM. The combined organics were dried over Na_2SO_4, filtered, and adsorbed onto silica in vacuo. The reaction mixture was purified on 12 g SiO_2 (eluent: 0 to 4% MeOH/DCM over 30 minutes, RediSep Gold). The product fractions were combined and concentrated in vacuo to an orange residue that contained the product with impurities (0.039 g isolated material).

The isolated material was combined with Grubbs’ catalyst, 2nd generation (Sigma Aldrich, 0.016 g, 0.019 mmol) and DCM (1.9 mL) and bubbled with argon for 30 s, sealed, and heated to 50 °C for 30 min. The reaction was cooled to RT, transferred to a round bottom flask, and concentrated in vacuo. The residue was taken up in 2 mL DMSO and purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 μ, C18, 100 A, 150 x 30 mm, 0.1% TFA in ACN/H_2O_2, gradient 5% to 90% over 10 min. The product fractions were dried in a Genevac EZ-2 evaporator at 55 °C. The resulting TFA salts were diluted with MeOH and applied to a pre-washed (MeOH) Silicycle Si-carbonate cartridge. The compound eluted in MeOH as a yellow solution. It was concentrated under reduced pressure to give (9S,11E,13R)-13-(methoxymethyl)-16-methyl-
Example 120: 4-((9S,IIE)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2.5~.0~4.9~.0~18.22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-14-yl)butanenitrile

Example 121: 4-((9S,IIZ)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2.5~.0~4.9~.0~18.22~]tetracosa-1(21),2(24),4,11,15,17,19,22-octaen-14-yl)butanenitrile

Step 1: 4-(allylamino)butanenitrile

A solution of 4-chlorobutyronitrile (Sigma-Aldrich, 2.0 mL, 20.86 mmol) in prop-2-en-1-amine (Sigma-Aldrich, 3.13 mL, 417 mmol) was stirred at RT for 16 h. The reaction mixture was concentrated to remove excess allylamine. The crude product was directly injected onto a column and was purified via automated flash chromatography (silica gel) with 100% DCM to 4% MeNH3 in MeOH/DCM to give 4-(allylamino)butanenitrile (427 mg, 3.44 mmol, 16.48 % yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.18 (br. s., 1 H) 1.82 (quin, J=6.94 Hz, 2 H) 2.46 (t, J=7.14 Hz, 2 H) 2.75 (t, J=6.75
Hz, 2 H) 3.25 (dt, J=6.02, 1.30 Hz, 2 H) 5.11 (dd, J=10.27, 1.47 Hz, 1 H) 5.18 (dq, J=17.21, 1.56 Hz, 1 H) 5.83 - 5.93 (m, 1 H). MS (ESI, pos. ion) m/z: 125.2 (M+1).

Steps 2-3: Synthesized over two steps from (S)-7-allyl-2-(3-fluoro-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrololo[3,2-c]pyridin-4(5H)-one (Intermediate D, 150 mg, 0.446 mmol), 4-(allylamino)butanenitrile (111 mg, 0.892 mmol), and N-ethyl-N-isopropylpropan-2-amine (Sigma-Aldrich, 155 µL, 0.892 mmol) according to Example 75 to give, after chiral SFC, 4-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l,5,15,17,19,22-octaen-14-yl)butanenitrile (12 mg, 0.029 mmol, 29.3% yield, first eluting isomer) and 4-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l,5,15,17,19,22-octaen-14-yl)butanenitrile (14 mg, 0.034 mmol, 34% yield, second eluting isomer).

Analytical data for 4-((9S,11E)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l,5,15,17,19,22-octaen-14-yl)butanenitrile: 1H NMR (400 MHz, CDCl3) δ ppm 2.15 - 2.24 (m, 2 H) 2.31 - 2.42 (m, 1 H) 2.48 (td, J=6.94, 4.50 Hz, 2 H) 2.65 (d, J=13.30 Hz, 1 H) 2.75 (s, 3 H) 3.32 - 3.50 (m, 4 H) 3.51 - 3.61 (m, 1 H) 4.12 - 4.21 (m, 1 H) 4.24 - 4.33 (m, 1 H) 5.32 (d, J=3.13 Hz, 1 H) 5.91 - 6.02 (m, 1 H) 6.22 (ddt, J=15.63, 7.46, 1.96, 1.96 Hz, 1 H) 7.11 (d, J=2.35 Hz, 1 H) 7.53 (t, J=8.02 Hz, 1 H) 7.71 (dd, J=8.12, 1.27 Hz, 1 H) 8.00 (dd, J=7.53, 1.27 Hz, 1 H) 13.12 (br. s., 1 H). MS (ESI, pos. ion) m/z: 413.3 (M+1).

Analytical data for 4-((9S,11Z)-16-methyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(21),2(24),4,l,5,15,17,19,22-octaen-14-yl)butanenitrile: 1H NMR (400 MHz, CDCl3) δ ppm 1.98 - 2.11 (m, 1 H) 2.11 - 2.23 (m, 1 H) 2.28 - 2.37 (m, 1 H) 2.42 (td, J=6.80, 2.45 Hz, 2 H) 2.68 - 2.78 (m, 1 H) 2.82 (s, 3 H) 3.37 (t, J=9.39 Hz, 1 H) 3.42 - 3.53 (m, 2 H) 3.65 (t, J=7.92 Hz, 2 H) 3.71 (d, J=17.80 Hz, 1 H) 4.86 (dd, J=16.43, 8.41 Hz, 1 H) 5.28 (d, J=2.93 Hz, 1 H) 5.70 - 5.79 (m, 1 H) 5.79 - 5.89 (m, 1 H) 6.99 (d, J=2.15 Hz, 1 H) 7.51 (t, J=7.43 Hz, 1 H) 7.73 (dd, J=8.22, 1.17 Hz, 1 H) 7.88 (dd, J=7.43, 1.17 Hz, 1 H) 12.76 (s, 1 H). MS (ESI, pos. ion) m/z: 413.3 (M+1).
The Compounds were prepared according to a procedure similar to that described Examples 115-118 starting from (R)-2-methylbutane-1,4-diol (TCI America).

Analytical data:

Example 122 (9S,12R)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.0^4,9.0^18,22]tetracosa-1(21),2(24),4,15,17,19,22-heptaen-6-one: ¾ NMR (400 MHz, DMSO-d_6) δ ppm 13.48 (1 H, br. s.) 7.99 (1 H, d, J=7.4 Hz)
  7.88 (1 H, br. s.) 7.56 (1 H, d, J=8.0 Hz) 7.26 - 7.38 (1 H, m) 7.03 (1 H, d, J=3.9 Hz) 6.95 (1 H, s) 3.49 (1 H, d, J=1.9 Hz) 2.89 - 3.27 (4 H, m) 2.54 (3 H, s) 2.37 (1 H, br. s.) 1.99 (1 H, br. s.) 1.74 (2 H, br. s.) 1.18 - 1.37 (1 H, m) 1.06 (2 H, d, J=5.9 Hz), m/z (ESI, +ve) 362.1 (M+H)^+.

Example 123 (9R,12R)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.0^4,9.0^18,22]tetracosa-1(21),2(24),4,15,17,19,22-heptaen-6-one: ¾ NMR (400 MHz, DMSO-d_6) δ ppm 7.91 (2 H, d, J=6.5 Hz) 7.56 (1 H, d, J=8.0, 0.8 Hz) 7.33 (1 H, t, J=7.8 Hz) 6.96 (1 H, d, J=4.3 Hz) 6.86 (1 H, d, J=1.4 Hz) 3.87 (1 H, d, J=14.3 Hz) 3.24 - 3.30 (1 H, m) 3.07 - 3.20 (1 H, m) 2.98 (1 H, dt, J=13.6, 6.7 Hz) 2.70 - 2.83 (1 H, m) 2.56 (3 H, s) 2.39 (1 H, br. s.) 1.85 - 2.04 (1 H, m) 1.49 - 1.71 (3 H, m) 1.10 (3 H, d, J=6.3 Hz), m/z (ESI, +ve) 362.1 (M+H)^+.

Example 124: (Acetyloxy)methyl (9S, HE, 13S)-13,16-dimethyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1.0^4,9.0^18,22]tetracosa-1(22),2(24),4,15,17,18,20,22-nonaene-7-carboxylate
Step 1: (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one

(S)-7-Allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (Example 33, Step 1; 0.964 g, 2.488 mmol) and DIEA (Aldrich; 0.433 ml, 2.488 mmol) were dissolved in DCM (250 mL) under N\textsubscript{2} and cooled in an ice bath. Chloromethyl chloroformate (Aldrich; 1.0 ml, 11.24 mmol) was added dropwise and the reaction stirred for 45 min then the solution was removed from the cold bath and stirred at RT After an additional 105 min the solution had turned dark red. The mixture was washed with water (200 mL) and the organic layer was dried with MgSO\textsubscript{4} before evaporating to dryness under reduced pressure. The crude was triturated with DCM and the solids were discarded. The filtrate was purified using silica chromatography (0-10% MeOH in DCM gradient) to give the desired (S)-7-allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (0.964 g, 2.488 mmol) as a yellow - brown solid: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) d ppm 12.28 (1 H, br. s.), 7.88 - 7.94 (1 H, m), 7.70 (1 H, dd, J=8.0, 1.2 Hz), 7.39 (1 H, t, J\textsubscript{=7.8 Hz}), 7.12 (1 H, d, J\textsubscript{/=2.2 Hz}), 6.11 (1 H, ddd, J=\textbackslash 1.2, 10.6, 3.9 Hz), 5.88 - 5.94 (2 H, m), 5.77 - 5.88 (1 H, m), 5.23 - 5.35 (2 H, m), 5.13 - 5.21 (2 H, m), 5.00 (1 H, d, J\textsubscript{/=6.7 Hz}), 4.65 - 4.75 (1 H, m), 4.32 (1 H, dd, J\textsubscript{/=13.1, 4.3 Hz}), 4.09 (1 H, dd, J\textsubscript{/=13.0, 4.2 Hz}), 3.71 - 3.77 (1 H, m), 3.04 (1 H, dq, J=8.9, 4.5 Hz), 2.62 (3 H, s), 2.37
A-1700-WO-PCT

- 2.56 (2 H, m), 1.82 - 1.89 (1 H, m), 1.55 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 479.9 (M+H)+.

Step 2: chloromethyl (9S, HE, 13S)-13,16-dimethyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4, 11, 15, 17, 18, 20, 22-nonaene-7-carboxylate

(S)-Chloromethyl 7-allyl-2-(3-((S)-but-3-en-2-ylamino)-2-methylquinoxalin-5-yl)-4-oxo-6,7-dihydro-lH-pyrrolo[3,2-c]pyridine-5(4H)-carboxylate (0.750 g, 1.563 mmol) was dissolved in CHCl₃ (100 ml) under N₂. Grubbs catalyst 2nd generation (Aldrich; 0.120 g, 0.141 mmol) was added and the reaction heated to reflux. After 10 min, the mixture was cooled and concentrated to ~20 mL under reduced pressure. Purification using silica chromatography (0-10% MeOH in DCM gradient) gave the macrocycle (0.619 g, 1.370 mmol, 88% yield) as a yellow-orange solid, m/z (ESI, +ve) 452.0 (M+H)+.

Step 3: (acetyloxy)methyl (9S, HE, 13S)-13,16-dimethyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4, 11, 15, 17, 18, 20, 22-nonaene-7-carboxylate from Step 2 (0.053 g, 0.117 mmol) and tetrabutylammonium acetate (Aldrich; 0.070 g, 0.232 mmol) were suspended in dry ACN (5 mL) under N₂ and heated in a 75 °C oil bath. After stirring for 40 minutes the mixture was cooled and evaporated to dryness under reduced pressure. Purification using silica chromatography (DCM to EtOAc gradient) gave the desired macrocycle contaminated with some tetrabutylammonium salts. The material was dissolved in DCM (10 mL) and washed with water (2 x 10 mL). The organic was dried with MgSO₄ and evaporated to dryness under reduced pressure to give (acetyloxy)methyl (9S, 1HE, 13S)-13,16-dimethyl-6-oxo-3,7,14,17,23-pentaazapentacyclo[13.6.2.1~2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4, ll, 15, 17, 18, 20, 22-nonaene-7-carboxylate (0.0468 g, 0.098 mmol, 84% yield): ³H NMR (400 MHz, CDCl₃) dppm 13.52 (1 H, br. s.), 7.86 - 7.93 (1 H, m), 7.64 (1 H, d, J=8.0 Hz), 7.37 (1 H, t, J=7.8 Hz), 7.04 (1 H, d, J=2.2 Hz), 5.93 (2 H, q, J=5.7 Hz), 5.78 - 5.84 (2 H, m), 4.72 (1 H, s), 4.51 (1 H, dd, J=12.3, 4.7 Hz), 4.20 (1 H, quin, J=6.2 Hz), 3.40 (1 H, t, J=12.5 Hz), 3.22 -

- 237 -
3.32 (1 H, m), 2.50 - 2.63 (4 H, m), 2.06 - 2.19 (4 H, m), 1.51 (3 H, d, J=6.8 Hz), m/z (ESI, +ve) 476.0 (M+H)+.

BIOLGICAL ACTIVITY

5 **Pim-1 and Pim-2**

**Cloning and Expression:**

Full-length human cDNAs encoding Pim-1 (MGC ID 3913552) or Pim-2 (IMAGE ID 5092935) were purchased from Invitrogen, Carlsbad, CA. These cDNAs were used as templates in PCR reactions to produce full-length DNA clones of the PIMs. Oligonucleotide PCR primers for Pim-1 were 5’-tggtctgatacttcttcttcatcaatgctcttgtccaaaatc-3’ and 5’-attagatattatttgtgacatggcc-3’. Oligonucleotide PCR primers for Pim-2 were 5’-tgcaagatccatgtgacacagtct-3’ and 5’-acgtgaattctctctctgacatg-3’. PCR products were digested with Bell and EcoRI and ligated into a modified baculovirus transfer vector (pFastBacI) cleaved with BamHI and EcoRI. For bacterial expression, the same cleaved PCR products encoding Pim-1 or Pim-2 were ligated into a modified E. coli expression vector pET28(a) cleaved with BamHI and EcoRI. Amino-terminal hexahistidine tags followed by a thrombin cleavage site were previously added to the vectors using standard methods of molecular biology.

Recombinant baculoviruses expressing Pim-1 or Pim-2 were made using standard methods (Fastbac manual, Invitrogen, Carlsbad, CA). Infection of Sf9 cells was done at an m.o.i. of greater than 5 for 24-48 h. Cells were harvested by centrifugation and frozen at -80°C. For E. coli expression, cells carrying pET28-His6-Th-Pim-1 or pET28-His6-Th-Pim-2 were picked from a single colony and grown o/n in LB media. The o/n culture was used to inoculate a 2 liter flask with 500 mL media. This was grown o/n and used to inoculate 15-20 liters of Terrific Broth in a New Brunswick Scientific fermentor. The E. coli were grown at 37°C to and OD600 > 1.6. The temperature was dropped to 18°C and o/n expression was induced with 0.5 mM IPTG. Cells were harvested by centrifugation and frozen at -80°C.

30 **PURIFICATION**

The frozen cell pellets were thawed by stirring in chilled lysis buffer (0.05 M HEPES, pH 8.0, 0.25 M NaCl, 0.01 M 2-mercaptoethanol, 10 % (v/v) glycerol, 0.5 % (v/v) protease inhibitor cocktail (Sigma P-8340) at a ratio of IL/200g cells until
homogeneous. The thawed suspension was applied to a microfluidizer at 10,000 PSI to disrupt the cells and the whole lysates were clarified by centrifugation at 50,000 x g for 90 min, 4 °C. Imidazole was added to the clarified lysate to a final concentration of 2.5 mM and the lysate was mixed with 10 mL of Talon resin (Clontech) and the slurry rocked gently overnight at 4 °C. The slurry was centrifuged at 1,000 x g for 5 min, the supernatant decanted, and the resin suspended in 40 mL of lysis wash buffer (lysis buffer at 0.75 M NaCl). This step was repeated 3X and the resin was transferred to a 2.5 cm glass column. Ten column volumes of wash buffer (0.05 M HEPES, pH 8.0, 0.1 M NaCl, 0.01 M 2-mercaptoethanol, 10 % (w/v) glycerol) were applied to the resin followed by 10 column volumes of elution buffer (0.05 M HEPES, pH 8.0, 0.25 M NaCl, 0.01 M 2-mercaptoethanol, 10 % (w/v) glycerol, 0.1 M imidazole). Fractions were analyzed by SDS-PAGE and those containing the protein of interest were pooled and concentrated. The concentrated protein was applied to an Amersham Superdex 75 (XK 26/60) column equilibrated in 0.025 M Tris-HCl, pH 7.5, 0.1 M NaCl, 0.01 M 2-mercaptoethanol, 10 % (w/v) glycerol. The protein eluted at a retention time indicative of it being monomeric and fractions were analyzed by SDS-PAGE. Fractions containing the monomeric protein of interest were pooled, concentrated to ~2 mg/mL, and stored at -80 °C.

**Pim Enzyme Assays**

The assay for the determination of Pim activity is based on the formation of phosphorylated biotinylated-BAD peptide at the Serine 112 residue (SI 12) and employs HTRF® (homogeneous time resolved fluorescence) technology to detect the product in a 96-well plate format. The phosphorylation of biotinylated-BAD (SI 12) peptide by full length recombinant Pim-1, Pim-2, or Pim-3 protein was detected with streptavidin:Allophycocyanin (APC) conjugate and a europium (Eu) labeled antibody directed against phosphorylated-BAD (SI 12). Excitation of Eu by a high energy laser light (337 nm) leads to a transfer of energy to the APC molecule, and results in an emission at 665 nm. The fluorescence is directly proportional to the amount of phosphorylated BAD peptide present in the reaction. Compounds were prepared in DMSO by conducting 3-fold serial dilutions to give a 10-point dosing curve having a high dose of 1 uM. A reference compound was included on each assay plate in order to validate that plate; on one plate of every assay run, two additional reference compounds were included. The final buffer conditions were as follows: 60 mM Hepes, pH 7.0, 0.05% BSA, 2 mM DTT. Incubations were carried out at RT (22°C) for 2 h for Pim-1, 1 hour...
and 30 min for Pim-3, and 45 min for Pim-2. The reaction was stopped by the addition of 3 mM EDTA, and fluorescence was measured by an HTRF® Rubystar microplate reader. For each plate, percent of control (POC) values were calculated for each well. Values for the IC50 IP were estimated using a standard 4-parameter logistic model. The results are provided in Tables 1-2.

**Pim-1/Mn Enzyme Assays.**

The assay for the determination of Pim activity is based on the formation of phosphorylated biotinylated-BAD peptide at the Serine 112 residue (SI 12) and employs HTRF® (homogeneous time resolved fluorescence) technology to detect the product in a 384-well plate format. The phosphorylation of biotinylated-BAD (SI 12) peptide by full length recombinant Pim-1, Pim-2, or Pim-3 protein was detected with streptavidin:Allophycocyanin (APC) conjugate and a europium (Eu) labeled antibody directed against phosphorylated-BAD (SI 12). Excitation of Eu by a high energy laser light (337 nm) leads to a transfer of energy to the APC molecule, and results in an emission at 665 nm. The fluorescence is directly proportional to the amount of phosphorylated BAD peptide present in the reaction. Compounds were prepared in DMSO by conducting 3-fold serial dilutions to give a 22-point dosing curve having a high dose of 1 µM. A reference compound was included on each assay plate [Costar 3658] in order to validate that plate; on one plate of every assay run, two additional reference compounds were included. The Reaction Buffer consisted of 45mM Hepes, pH 7.0 , 15 mM NaCl , and 1 mM MgCl. The quench/detection buffer consisted of 50 mM Tris, 100 mM NaCl, 0.05% BSA, 0.1% Tween and 3 mM EDTA. Biotinylated BAD peptide (Biopeptide), 10 mM ATP (Sigma), Labeled p-BAD (SI 12) mAb (Cell Signalling and Perkin Elmer) [with 0.05% BSA and 2 mM DTT added] streptavidin:Allophycocyanin [Perkin Elmer]. Final concentrations - either Pim-1 enzyme [5 pM], or Pim-2 enzyme [0.5 pM], DMSO [1%], BLC BAD (SI12) [0.5 µM], ATP [1.5 µM], streptavidin:Allophycocyanin [0.002 mg/mL] and biotinylated-BAD (SI 12) mAb [100 pM]. Initial incubations were carried out at RT (22°C) for 30 min for both Pim-1 and for Pim-2. Pim enzyme is added to compound in buffer, and plates are incubated of 30 min. Biotinylated BAD and ATP are added and plates are incubated for 1h. A mixture of labeled p-BAD (SI 12) mAb and quench/detection buffer are added and incubated for 2h. Fluorescence was measured by an HTRF® Envision microplate reader. For each plate, percent of control (POC) values were calculated for each well. Values for the ICS0 IP
were estimated using a standard 3 or 4-parameter logistic model. The results are provided in Tables 1-2.

**Pirn Cell Assay**

### KMS-12-BM

The cellular phosphorylation assay for activity of Pirn inhibitors in the KMS-12-BM myeloma cells measures cellular levels of phospho-BAD and total BAD. It was conducted as follows:

The suspension cells were plated out onto 96-well, V-bottom plates at an initial density of 80,000 cells/well in 100 uL of complete growth medium (RPMI Medium 1640-Invitrogen #11875, 10% Heat inactivated FBS-Hyclone #30070.03HI, 1x L-glutamine-Invitrogen #25030). The cells were then incubated overnight at 37°C, 5% CO₂. Compounds were initially diluted in DMSO by conducting 3-fold serial dilutions to give a 10-point dosing curve having a high dose of 31.6 uM. In addition to the 10-point dosing curve of the test compound, DMSO alone was run as the high control and 7.9 uM 25 I0883 as the low control. This dilution in DMSO was then diluted again into cell growth medium. Aliquots (11.1 uL) of the compound diluted in growth medium were then transferred to the appropriate wells of the 96-well plates containing cells to yield a final DMSO concentration of 0.3%. The cell plates were then incubated with compound for 2 hours at 37°C, 5% CO₂. After a two h incubation, the compound-containing medium was removed. The cell plates were placed on ice and given 50 uL of ice-cold complete lysis buffer (MSD kit components, Protease Inhibitor Cocktail Tablets-Roche # 04 693 116 001). The cell plates containing lysis buffer were then immediately stored at -70°C. These prepared lysates were then assayed for phospho and total BAD according to the manufacturer's protocols (Meso Scale Diagnostics, Cat#K15103C-3 & #K15103D-3). The plates were read on the MSD Sector Imager 6000, and results were calculated according to the assay protocols ((%Phosphoprotein = ((2 x Phospho signal) / (Phospho signal + Total signal)) x 100)). The results are provided in Tables 1-2.

### KMS12 #2

The flow cytometry assay for determination of the Pirn activity in the engineered KMS-12-BM cell lines (DSMZ cat# ACC 551) measures levels of phospho-BAD normalized against total BAD protein levels. It was conducted as follows:
Protocol:

Compounds are initially diluted in DMSO by conducting 2-fold serial dilutions to give a 22-point dosing curve having a high dose of 30 μM. Exponentially growing KMS-12-BM cells (50 μL, between 0.5 and 1.5x10^6/ml, DSMZ) in Assay Media (RPMI/20% heat inactivated FBS/1X NaPyruvate/1X NEAA/1X PSG (pen/strep glutamine)) are added to a 384-well plate containing 200 nL of compound. The cell plates are then incubated with compound for 110 min at 37°C, 5% CO₂. BD Phosflow Lyse/Fix (BD Biosciences) is diluted to 2X with Assay Media. 50 μL of the diluted BD Phosflow Lyse/Fix is added to each well. The cell plates are incubated for 15 min at RT. The plates are spun for 15 sec at 2K RPM then aspirated. Staining Media (IxPBS with 0.5% FBS) is added (80 μL). The plates again are spun for 15 sec at 2K RPM then aspirated. BD Perm/Wash Buffer (1X, 50 μL, BD Biosciences) is added. The cell plates are then incubated for >30 min at RT in the dark. The plates are spun for 15 sec at 2K RPM then aspirated. Staining Media (IxPBS with 0.5% FBS) is added (80 μL). The plates are spun for 15 sec at 2K RPM then aspirated and additional Staining Media (IxPBS with 0.5% FBS) is added (80 μL). The plates are spun for 15 sec at 2K RPM then aspirated. Rabbit anti-human pBAD Ser126 Ab (Cell Signaling) is diluted in Staining Media (1:120). The diluted pBAD Ab (10 μL) is added to each well. The cell plates are incubated for >1hr at RT. The plates are spun for 15 sec at 2K RPM then aspirated. Staining Media (IxPBS with 0.5% FBS) is added (80 μL). Goat Anti Rabbit Alexa-647 (Invitrogen) is diluted in Staining Media (1:4000). The diluted Goat Anti Rabbit Alexa-647 (70 μL) is added to each well. The cell plates are then incubated for >30 min at RT in the dark. The plates are spun for 15 sec at 2K RPM then aspirated. Staining Media (IxPBS with 0.5% FBS) is added (80 μL). The plates are spun for 15 sec at 2K RPM then aspirated and additional Staining Media (IxPBS with 0.5% FBS) is added (80 μL). The plates are spun for 15 sec at 2K RPM then aspirated. Staining Media (IxPBS with 0.5% FBS) is added (30 μL). The plates are read on a BD LSRII, and results were calculated according to the assay protocols ((%Phosphoprotein = ((2 x Phospho signal) / (Phospho signal + Total signal)) x 100)). The results are provided in Tables 1-2.
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The compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment.

The dosage regimen for using these compounds diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this
invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

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

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols.
that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (e.g., solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills,
the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Likewise, the compounds of this invention may exist as enantiomers, that is compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate that it is possible to prepare compounds of this invention in which these substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of
the compounds of this invention are to be construed as encompassed within the scope of the present invention.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts include, but are not limited to, the following:

acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate,
butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate,
dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate,
heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-
hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-
naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 2-phenylpropionate,
picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and
undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such
agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides
and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long
chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides,
aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or
dispersible products are thereby obtained.

Examples of acids that may be employed to from pharmaceutically acceptable
acid addition salts include such inorganic acids as HCl acid, sulfuric acid and phosphoric
acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Other examples include salts with alkali metals or alkaline earth metals, such as sodium,
potassium, calcium or magnesium or with organic bases.

Also encompassed in the scope of the present invention are pharmaceutically
acceptable esters of a carboxylic acid or hydroxyl containing group, including a
metabolically labile ester or a prodrug form of a compound of this invention. A
metabolically labile ester is one which may produce, for example, an increase in blood
levels and prolong the efficacy of the corresponding non-esterified form of the compound.
A prodrug form is one which is not in an active form of the molecule as administered but
which becomes therapeutically active after some in vivo activity or biotransformation,
such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general
discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism
masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl,
ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-
methoxybenzyl), and alkylcarbonyloxalkyl (for example, pivaloyloxymethyl). Amines
have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by
esterases in vivo releasing the free drug and formaldehyde (Bunagard J. Med. Chem.
2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide,
indole and the like, have been masked with N-acyloxymethyl groups (Bunagard Design
of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers.
EP 039,051 (Sloan and Little, 4/1 1/81) discloses Mannich-base hydroxamic acid
prodrugs, their preparation and use. Esters of a compound of this invention may include,
for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters
formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile
esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, a
methoxymethyl, groups such as a-((Ci-C4)alkyloxy)ethyl, for example, methoxymethyl,
ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups,
such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, etc.; Ci-C3 alkylthiomethyl groups, for
example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acylloxymethyl
groups, for example, pivaloyloxymethyl, a-acetoxyethyl, etc.; ethoxycarbonyl-1-
methyl; or α-acyloxy-a-substituted methyl groups, for example a-acetoxyethyl.

Further, the compounds of the invention may exist as crystalline solids which can
be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water,
or the like. Thus, crystalline forms of the compounds of the invention may exist as
polymorphs, solvates and/or hydrates of the parent compounds or their pharmaceutically
acceptable salts. All of such forms likewise are to be construed as falling within the
scope of the invention.

While the compounds of the invention can be administered as the sole active
pharmaceutical agent, they can also be used in combination with one or more compounds
of the invention or other agents. When administered as a combination, the therapeutic
agents can be formulated as separate compositions that are given at the same time or
different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit
the invention to the disclosed compounds. Variations and changes which are obvious to
one skilled in the art are intended to be within the scope and nature of the invention which
are defined in the appended claims.
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
What is claimed:

1. A compound of Formula 1'

wherein

- ring a is a ring that together with the 2 carbon atoms to which it attaches, forms a phenyl ring or a 5-6 membered heterocyclic ring;
- X is N or CH;
- Z is O, S, NR³, C=0 or C(R²)₂;
- Q is a linker saturated or unsaturated chain;
- q is N, NH, CH or CH₂;
- r is CH, NH, CH₂ or N;
- s is N or CH;
- w is CH, CH₂, N or NH;
- ring b is unsaturated, or partially saturated;
- ring c is saturated, or partially saturated;
- R¹ is H, or halo;
- R² is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;
- R³ is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonylaminoalkyl, alkylcarbonylaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl; and
- R⁴ is H, -PO(Oalkyl)₂, alkylcarbonyl, alkylcarbonyloxyalkoxycarbonyl, alkoxy carbonyl, aminoalkylcarbonyloxyalkoxycarbonyl or hydroxyalkyl;
and a pharmaceutically acceptable salt thereof.

2. Compound of Claim 1 wherein ring $\text{a}$ is

\[
\begin{align*}
&\text{R}_1, \quad \text{N}, \quad \text{C}=0, \quad \text{C}(\text{R}^1)_2, \\
&\text{or} \quad \text{H}, \quad \text{halo}; \quad \text{and}
\end{align*}
\]

wherein $\text{R}^1$ is H, or halo; and a pharmaceutically acceptable salt thereof.

3. Compound of Claim 1 comprising

\[
\begin{align*}
&\text{X} \quad \text{is} \quad \text{N} \quad \text{or} \quad \text{CH}; \\
&\text{Z} \quad \text{is} \quad \text{O}, \quad \text{N}, \quad \text{NNR}^1; \quad \text{C}=0, \quad \text{or} \quad \text{C}(\text{R}^1)_2; \\
&\text{wherein} \quad \text{Q} \quad \text{is} \quad \text{a} \quad 3-8 \text{ membered linker that attaches with Z};
\end{align*}
\]
A-1700-WO-PCT

\[
\text{ring a is } \ \ \ \ \ \ ;
\]

\( R^1 \) is \( H \), or halo;
\( R^2 \) is \( H \), \( \text{Ci-6} \) haloalkyl, \( \text{C}_4 \)-hydroxyalkyl, \( \text{C}_{1-6} \) alkyl, \( \text{Cl}_{1-6} \) alkoxy, \( \text{H} \text{C}(=\text{O})_- \), carboxy, \( \text{C}_{1-6} \) alkoxy carbonyl, \( \text{C}_{3-6} \) cycloalkyl, or substituted or unsubstituted heterocycle;
\( R^b \) is \( H \), \( \text{Ci-6} \) alkyl, \( \text{Cl}_{1-6} \) haloalkyl, \( \text{Cl}_{1-6} \) hydroxyalkyl, \( \text{Cl}_{1-6} \) alkylsulfonfyl-\( \text{Cl}_{1-6} \) alkyl, BOC-\( \text{amino} \)-\( \text{Cl}_{1-6} \) alkyl, amino-\( \text{Cl}_{1-6} \) alkyl, cyano-\( \text{Cl}_{1-6} \)-alkyl, \( \text{Cl}_{1-6} \)-alkoxy-\( \text{Cl}_{1-6} \)-alkyl, \( \text{Cl}_{1-6} \)-alkylsulfonfyl -\( \text{Cl}_{1-6} \)-alkylamino-\( \text{Cl}_{1-6} \)-alkyl, \( \text{Cu}6 \) alkylsulfonfylaminino -\( \text{Cl}_{1-6} \)-alkyl, \( \text{Cu}6 \) alkyloxy carbonylamino -\( \text{Cl}_{1-6} \)-alkyl, unsubstituted or substituted \( \text{C}_{3-6} \)-cycloalkyl, unsubstituted or substituted ary1, unsubstituted or substituted ary1-\( \text{Cl}_{1-6} \) or unsubstituted or substituted heterocyclyl;

wherein \( R^6 \) is \( H \); and

wherein \( R^7 \) is \( H \) or \( \text{C}_{1-3} \) alkyl; and a pharmaceutically acceptable salt thereof.

4. Compound of Claim 1 comprising

\[
\text{1' b or 1' e ;}
\]

wherein
\( X \) is \( N \) or \( \text{CH} \);
\( Z \) is \( O \), \( S \), \( \text{NR}^b \), \( C=0 \), or \( C(R^b)_2 \);
\( Q \) is optionally substituted \( \text{C}_4 \)-\( \text{C}_6 \) alkenylenyl, optionally substituted \( \text{C}_4 \)-\( \text{C}_3 \) alkylidencylenyl, optionally substituted \( \text{C}_4 \)-\( \text{C}_5 \) alkynylene, optionally substituted cycloalkyl -\( \text{C}_3 \)-\( \text{C}_4 \) alkenylenyl, optionally substituted phenyl -\( \text{Cl}_{1-2} \) alkenylenyl, -(\( \text{CH}_2 \)\(_n\))-\( \text{O}-(\text{CH}_2 \)\(_m\)), or optionally substituted \( \text{Cl}_{1-2} \) alkenylenyl-aminocarbonyl -\( \text{Cl}_{1-2} \) alkenylenyl, when \( Q \) attaches to \( Z \); or wherein \( Q \) is optionally substituted 5-7 membered heterocyclyl-alkenyl, or optionally substituted 5-7 membered heterocyclyl-alkenyl, when \( Q \) incorporates \( Z \) into the heterocyclic ring;
A-1700-WO-PCT

\[ \begin{align*}
\text{ring a is} & ; \\
R^1 & \text{is H, or halo;} \\
R^2 & \text{is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, } \text{HC(=0)-, carboxy, } \\
& \text{alkoxycarbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;}
\end{align*} \]

\[ \begin{align*}
R^b & \text{ is H, C}_{1.4}\text{-alkyl, C}_{i.6}\text{-haloalkyl, C}_{i.4}\text{-hydroxyalkyl, C}_{i.4}\text{-alkylsulfonyl-C}_{i.4}\text{-alkyl, BOC-} \\
& \text{amino-C}_{i.4}\text{-alkyl, C}_{i.4}\text{-aminoalkyl, C}_{i.4}\text{-cyanoalkyl, C}_{i.4}\text{-alkoxy-C}_{i.4}\text{-alkyl, C}_{1.4}\text{-} \\
& \text{alkylsulfonyle-C}_{1.4}\text{-alkylamino-C}_{1.4}\text{-alkyl, C}_{1.4}\text{-} \\
& \text{alkylcarbonylamino-C}_{1.4}\text{-alkyl, unsubstituted or substituted C}_{1.6}\text{-cycloalkyl,} \\
& \text{unsubstituted or substituted phenyl, unsubstituted or substituted phenyl-C}_{i.2}\text{-alkyl or} \\
& \text{unsubstituted or substituted 4-6 membered heterocyclyl;} \\
\text{wherein} & \ R^6 \text{ is H; and} \\
\text{wherein} & \ R^7 \text{ is H;} \\
\text{and a pharmaceutically acceptable salt thereof.}
\end{align*} \]

5. Compound of Claim 1 wherein \( Z \) is \( O, S, NR^b, \text{ or } \text{CHR}^b \); wherein \( R^b \) is \( \text{H, C}_{1.2} \text{-alkyl, C}_{1.2} \text{-hydroxyalkyl, C}_{1.2} \text{-alkylsulfonyl-C}_{1.2} \text{-alkyl, BOC-} \text{amino-C}_{1.2} \text{-alkyl, amino-C}_{1.2} \text{-alkyl, C}_{1.2} \text{-alkylsulfonyl-C}_{1.2} \text{-alkylamino-C}_{1.2} \text{-alkyl, cyano-C}_{1.2} \text{-alkyl,} \)
\[ \begin{align*}
& \text{alkylsulfonyle-C}_{i.2}\text{-alkyl or C}_{i.2}\text{-alkylcarbonylamino-C}_{i.2}\text{-alkyl; and a} \\
& \text{ pharmaceutically acceptable salt thereof.}
\end{align*} \]

6. Compound of Claim 1 wherein \( R^1 \) is H or fluoro; and a pharmaceutically acceptable salt thereof.

7. Compound of Claim 1 wherein ring a is \( \begin{align*} \\
\end{align*} \); wherein \( R^1 \) is H or fluoro; and a pharmaceutically acceptable salt thereof.

8. Compound of Claim 1 wherein \( R^2 \) is H, methylcarbonyl, \( -\text{PO(0-methyl)}_2, -\text{PO(0-tert-butyl)}_2 \), methylcarbonyloxy \( -\text{methoxycarbonyl, tert-butylcarbonyloxy-methoxycarbonyl, isopropylcarbonyloxy-methoxycarbonyl, 1,5-diaminopentyl-carbonyloxy-methoxycarbonyl, butoxycarbonyl or hydroxymethyl;} \) and a pharmaceutically acceptable salt thereof.
9. Compound of Claim 1 wherein Q and Z together form
A-1700-WO-PCT
10. Compound of Claim 1 wherein R\textsubscript{2} is H, C\textsubscript{1-2} alkyl, HC(=0)- or C\textsubscript{1-2} hydroxyalkyl; and a pharmaceutically acceptable salt thereof.

11. Compound of Claim 1 wherein R\textsubscript{2} is H, methyl, HC(=0)- or hydroxymethyl; and a pharmaceutically acceptable salt thereof.
12. Compound of Claim 1 wherein R₂ is H; and a pharmaceutically acceptable salt thereof.

13. A compound of Formula 2

\[
\begin{array}{c}
\text{N} \\
Z \\
\text{H} \\
\text{Q} \\
\text{O}
\end{array}
\]

wherein Z is O or NH; and
wherein Q is optionally substituted C₄-C₅ alkenylenyl, or optionally substituted phenyl-C₁₂ alkylbnyl;
and a pharmaceutically acceptable salt thereof.

14. Compound of Claim 13 wherein Z is O; and a pharmaceutically acceptable salt thereof.

15. Compound of Claim 13 wherein Z is NH; and a pharmaceutically acceptable salt thereof.

16. Compound of Claim 13 wherein Q is but-2-enylenyl, 4-methylbut-2-enylenyl, 3-methylbut-2-enylenyl, 2-methylbut-2-enylenyl or phenylmethylenyl; and a pharmaceutically acceptable salt thereof.

17. Compound of Claim 1 selected from

(9S, 11Z, 13R)-1 3,1 6-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5~.0-
4,9~.0~.0~.0-1 8,22~.tetracosa-1 (22),2(24),4,1 1,15,1 7,1 8,20,22-nonaen-6-one;
(9S, 1,1E)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5~.0-
4,9~.0~.0-1 8,22~.tetracosa- 1(21),2(24),4,1 1,15,17,19,22-octaen-6-one;
(9S, 11Z)-12,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[1 3.6.2.1-2,5~.0-
4,9~.0~.0-1 8,22~.tetracosa-1 (22),2(24),4,1 1,15,1 7,1 8,20,22-nonaen-6-one;
A-1700-WO-PCT

(9S, 13S)-13,16-dimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,15,17,18,20,22-octaen-6-one; and

(9S, HZ)-12,14,16-trimethyl-3,7,14,17,23-pentaazapentacyclo[13.6.2.1-2,5~.0~4,9~.0~18,22~]tetracosa-l(22),2(24),4,11,15,17,18,20,22-nonaen-6-one.

18. A compound of Formula 3'

\[
\begin{align*}
&\text{R}^1 \text{R}^2 \\
&\text{N} \text{N} \\
&\text{H} \text{N} \\
&\text{O} \text{R}^6 \\
&\text{Q} \\
\end{align*}
\]

wherein \( \text{R}^1 \) is H or fluoro;
wherein \( \text{R}^2 \) is H, HC(=O)-, \text{Ci}_2 \text{ alkyl} or \text{C}_1 \text{ hydroxyalkyl};
wherein \( Z \) is O, S or NR\(^3\);
wherein \( R^3 \) is H, \text{Ci}_2 \text{ alkyl}, \text{Ci}_2 \text{ hydroxyalkyl}, \text{Ci}_2 \text{ alkylsulfonyl-Cu-alkyl}, \text{BOC-amino-Ci}_2 \text{ alkyl}, \text{amino-Ci}_2 \text{ alkyl}, \text{C}_2 \text{ alkylsulfonylamino-Ci}_2 \text{ alkyl}, \text{cyano-Ci}_4 \text{ alkyl or C}_i \text{ alkylcarbonylamino-Ci}_2 \text{ alkyl};
\( R^5 \) is H, -PO(0-Ci\(_2\)-alkyl), \text{Ci}_4 \text{ alkylcarbonyl}, \text{C}_1 \text{ alkoxy carbonyl, Ci}_4 \text{ alkoxy carbonyl, amino-Ci}_6 \text{ alkoxy carbonyl, Ci}_2 \text{ alkoxy carbonyl or C}_1 \text{ hydroxyalkyl};
wherein \( Q \) is optionally substituted \text{C}_4-C_5 \text{ alkylenyl, optionally substituted C}_4-C_6 \text{ alkenylenyl, optionally substituted C}_4-C_7 \text{ alkynyl, optionally substituted phenyl-Ci}_2 \text{ alkylenyl, optionally substituted cycloalkyl-C}_2\text{C}_4 \text{ alkenylenyl, or -(CH}_2)_n\text{0-(CH}_2)_m \text{ ;}
\text{wherein n is 1-2; and}
\text{wherein m is 1-2; provided n+m = 3 or 4;}
and a pharmaceutically acceptable salt thereof.

19. Compound of Claim 18 wherein \( \text{R}^1 \) is H; and a pharmaceutically acceptable salt thereof.
20. Compound of Claim 18 wherein $R^2$ is H, HC(=0)-, methyl or hydroxymethyl; and a pharmaceutically acceptable salt thereof.

21. Compound of Claim 18 wherein $R^2$ is H or methyl; and a pharmaceutically acceptable salt thereof.

22. Compound of Claim 18 wherein Z is O or S; and a pharmaceutically acceptable salt thereof.

23. Compound of Claim 18 wherein Z is HN, methylamino, hydroxyethylamino, BOC-aminoethylamino, aminoethylamino, cyanopropylamino, methylsulfonyl ethylaminoethylamino, methylsulfonylpropylamino, methylcarbonylvalinoethylamino or methylsulfonylpropylammonio; and a pharmaceutically acceptable salt thereof.

24. Compound of Claim 18 wherein Q is butylenyl, 2-methylbutylenyl, 3-methylbutylenyl, 4-methylbutylenyl, 4-hydroxymethylbutylenyl, 2,3-dihydroxy-4-methylbutylenyl, but-2-enylenyl, 4-hydroxymethylbut-2-enylenyl, 4-hydroxyethylbut-2-enylenyl, 4-methoxybut-2-enylenyl, 2-methylbut-2-enylenyl, 3-methylbut-2-enylenyl, 4-methylbut-2-enylenyl, 4,4-dimethylbut-2-enylenyl, 4-trifluoromethylbut-2-enylenyl, 4-(methylsulfonyl)but-2-enylenyl, 3-methylbut-2-enylenyl, 2-methylbut-2-enylenyl, but-2-ynylenyl, 4-methylbut-2-ynylenyl, pentylenyl, pent-2-enylenyl, 2-methylpent-2-enylenyl, -(CH$_2$)$_2$-0-(CH$_2$)$_2$- , 3-(eth-2-enylenyl)cyclobutyl or phenylmethyleneyl; and a pharmaceutically acceptable salt thereof.

25. Compound of Claim 18 wherein $R^+$ is H; and a pharmaceutically acceptable salt thereof.

26. A compound of Formula 4
A-1700-WO-PCT

wherein $R_i$ is $H$;
wherein $R_2$ is $C_{i-2}$ alkyl;
wherein $Z$ is $CH_2$ or NH; and
wherein $Q$ is optionally substituted $C_4-C_5$ alkenylenyl, or optionally substituted $C_{i-2}$
alkylenyl-aminocarbonyl- $C_{1-2}$ alkylenylenyl,
and a pharmaceutically acceptable salt thereof.

27. Compound of Claim 26 wherein $R_2$ is methyl; and a pharmaceutically
acceptable salt thereof.

28. Compound of Claim 26 wherein $Z$ is NH; and a pharmaceutically acceptable
salt thereof.

29. Compound of Claim 26 wherein $Q$ is 3-methylbut-2-enylenyl,
ethylenylaminocarbonylmethylenyl, (2-methylglyoxyl)aminocarbonylmethylenyl, or
methylaminocarbonylmethylenyl; and a pharmaceutically acceptable salt thereof.

30. A compound of Formula 5

wherein ring $d$ forms a 4-7 membered nitrogen containing heterocyclyl;
wherein $R_1$ is $H$;
wherein $R_2$ is $H$ or $C_{1-2}$ alkyl; and
wherein Q is optionally substituted C_3-C_4 alkenylenyl; and a pharmaceutically acceptable salt thereof.

31. Compound of Claim 30 wherein R^2 is methyl; and a pharmaceutically acceptable salt thereof.

32. Compound of Claim 30 wherein ring d is morpholinyl or 2-oxo-oxazolidinyl; and a pharmaceutically acceptable salt thereof.

33. Compound of Claim 30 wherein ring d is \( \text{morpholinyl or 2-oxo-oxazolidinyl} \); and a pharmaceutically acceptable salt thereof.

34. Compound of Claim 30 wherein Q is 2-propenylenyl, or 3-propenylenyl; and a pharmaceutically acceptable salt thereof.

35. A compound of Formula 1

wherein

ring a is a ring that together with the 2 carbon atoms to which it attaches, forms a phenyl ring or a 5-6 membered heterocyclic ring;
X is N or CH;
Z is O, S, NR^b, C=O, CHR^b or C(R^b)_2;
Q is a linker saturated or unsaturated chain;
q is NH or CH;
r is CH₂ or N;
s is N or C;
w is CH or N;
ring b is unsaturated, or partially saturated;
ring c is saturated, or partially saturated;
R¹ is H, or halo;
R² is H, haloalkyl, hydroxyalkyl, alkyl, alkoxy, HC(=0)-, carboxy, alkoxy carbonyl, cycloalkyl, or substituted or unsubstituted heterocyclyl;
R³ is H, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonylalkyl, BOC-aminoalkyl, aminoalkyl, cyanoalkyl, alkoxyalkyl, alkylsulfonylalkylaminoalkyl, alkylsulfonlaminoalkyl, alkylcarbonylaminoalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl or unsubstituted or substituted heterocyclyl; and
R⁴ is H, -PO(OCH₃)₂, alkylcarbonyl or hydroxyalkyl;
and a pharmaceutically acceptable salt thereof.

36. A method for treating a condition by modulation of PIM kinase activity comprising administering to a patient in need of such treatment an effective amount of a compound of any one of Claims 1-35.

37. A composition comprising a therapeutically effective amount of compound of any one of Claims 1 through 35 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

38. A method for inhibiting PIM kinase activity in a patient, comprising administering to the patient a composition comprising a pharmacologically effective amount of a compound of any one of Claims 1 through 35.

39. A method for treating a cancer disorder in a patient, comprising administering to the patient a composition comprising an amount of a compound of any one of Claims 1 through 38.

40. A compound of any one of Claims 1 through 35 for use as a therapeutic agent.
41. A compound of any one of Claims 1 through 35 for use in manufacture of a medicament for the treatment of cancer.

42. The method of Claim 39 wherein the cancer disorder is head and neck cancer or prostate cancer.

43. The method of Claim 39 wherein the cancer disorder is a hematological malignancy.

44. The method of Claim 39 wherein the cancer disorder is multiple myeloma or Non Hodgkins Lymphoma, or AML.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/22 C07D498/22 A61K31/4725 A61K31/498 A61P35/00
ADD.

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
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Further documents are listed in the continuation of Box C. x See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search: 11 October 2013
Date of mailing of the international search report: 18/10/2013

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

Authorized officer: Cortes, Jose

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