

PIPERIDINE DERIVATIVES AS INHIBITORS OF NICOTINAMIDE N-METHYL TRANSFERASE

TECHNICAL FIELD

- 5 The technical field relates to certain piperidine derivatives of Formula **(I)**, to their use in the treatment of a nicotinamide N-methyl transferase related disease or condition, for example chronic kidney disease, acute kidney injury or heart failure.

BACKGROUND

- 10 Nicotinamide N-methyl transferase (NNMT) is a cytosolic methyl transferase expressed in many tissues with highest expression in liver, adipose tissue and blood vessels. In healthy kidney tissue, expression is very low, but increases markedly in chronic kidney disease (CKD).
- NNMT catalyzes the transfer of a methyl group from S-adenosyl L-methionine (SAM) to
15 nicotinamide producing 1-methyl nicotinamide (1-MNA) and S-adenosyl L-homocysteine (SAH) which can be further metabolized to homocysteine. Metabolism of nicotinamide to 1-MNA by NNMT and further to N-methyl-2-pyridone-5-carboxamide (N-Me-2Py) and N-methyl-4-pyridone-3-carboxamide (N-Me-4Py) via aldehyde oxidase leads to its excretion (*Trends Endocrinol Metab.*, **2017**, 28(5), 340-353). N-Me-2Py has been reported to be a
20 uremic toxin (*Toxins* **2016**, 8, 339). High NNMT-activity may affect cellular homeostasis of nicotinamide adenine dinucleotide (NAD^+) by preventing nicotinamide from entering NAD^+ salvage pathway (*Int J Mol Sci.*, **2023**, 24, 137).
- The heart and the kidneys are the most energy demanding organs in the body. Large amounts of ATP is required in kidney tubules to support solute transport. NAD^+ is required for the
25 metabolism of glucose, pyruvate and fatty acids to acetyl-CoA and for metabolism of the latter in the Krebs cycle. The NADH generated in these processes is then used for ATP production in the electron transport chain. NAD^+ is also an important co-factor for the NAD^+ -dependent enzymes: sirtuins, PARPs and CD38 (*Mol. Sci.*, **2023**, 24, 137).
- Increase in cellular NNMT activity may also shift the ratio of SAM/SAH and thereby affect
30 additional SAM-dependent methyl transferases, possibly leading to epigenetic changes. High NNMT activity will also lead to increased production of homocysteine (*Atherosclerosis*, **2009**, 204(2), 412-7).

Transcriptomic analysis has demonstrated that NNMT is highly increased in human CKD of different etiologies including diabetic kidney disease (DKD) and highest NNMT expression in the tubulointerstitial compartment, particularly in proximal tubule cells (*Int. J. Gen. Med.*, **2023**, 3331-3344). *Sci. Rep.*, **2022**, 12, 6398) also report that NNMT localizes to atrophic
5 tubular cells in fibrotic lesions in human CKD.

In serum from CKD patients, N-Me-2Py and N-Me-4Py increase and nicotinamide decrease with increasing CKD-stage (*Sci. Rep.*, **2022**, 12, 6398). Doke, T et al (*Nat. Metab.*, **2023**, Mar. 5, 414-430) report decreased nicotinamide and NAD⁺ levels in kidney biopsies from CKD-patients.

10 Current standard of care for chronic kidney disease, that is, inhibitors of the renin-angiotensin-aldosterone system (RAAS) such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and more recently, inhibitors of the sodium/glucose cotransporter 2 (SGLT2), slow down progression of CKD. Despite this treatment, many patients still continue to lose kidney function and progress towards end-stage kidney disease
15 (ESKD) requiring kidney-replacement therapy – dialysis or kidney transplantation (*N. Engl. J. Med.*, **2020**, 383, 1436; *Cardiovasc Diabetol.*, **2021**, 20, 36).

Pharmacological inhibition of NNMT activity could stop the progression of tubular and glomerular injury and thereby the decline in kidney function in different forms of CKD, including diabetic kidney disease, DKD (*Int. J. Gen. Med.*, **2023**, 16, 3331-3344).

20 Acute kidney injury (AKI) is associated with decreased kidney NAD⁺ levels. Different approaches aimed at increasing kidney NAD⁺ levels by supplementation with nicotinamide (NAM), nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN) have shown protective effect in preclinical models of AKI (*Clin Kidney J.*, **2021**, 14(12), 2453-2462). Since inhibition of NNMT is expected to increase NAD⁺, NNMT-inhibitors may also be beneficial in
25 AKI.

In heart failure with preserved ejection fraction (HFpEF), cardiac levels of NAD⁺ are decreased and in preclinical models of HFpEF, nicotinamide supplementation improved cardiac function, suggesting that NNMT-inhibition may also be beneficial in HFpEF (*Sci. Trans. Med.*, **2021**, 13, 580).

30 *Molecules* **2021**, 26, 991 disclose small molecule inhibitors of NNMT.

J. Med. Chem. **2022**, 65 (21), 14642 disclose azaindole carboxamide inhibitors of NNMT.

WO2021163583 and WO2023129513 disclose NNMT inhibitors and methods of inhibiting tumor growth.

J. Med. Chem. **2019**, 62 (21), 9837 disclose alkynyl inhibitors of NNMT.

WO2023129512 disclose NNMT inhibitors and methods of inhibiting tumor growth.

5 *Bioorg. Med. Chem. Lett.* **2018**, 28, 922 and WO2021025975 disclose nicotinamides that inhibits NNMT.

US 10,087,449 B2 discloses a therapeutic agent for treating chronic kidney disease comprising a substance which inhibits the enzymatic activity of NNMT.

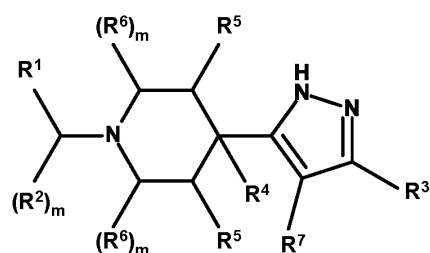
WO2018183668 disclose quinoline derived small molecule inhibitors of NNMT.

10 WO2012068463 discloses methods of inhibiting NNMT production or activity in a cell, and methods of treating or preventing obesity or a related metabolic condition, comprising administering a NNMT antagonist.

An object is to provide compounds that are inhibitors of nicotinamide N-methyl transferase (NNMT), their use as medicaments, pharmaceutical compositions containing them and
15 synthetic routes to their production.

SUMMARY

There is provided a compound of Formula (I)



(I)

20

wherein

R¹ is selected from a 8-, 9- or 10-membered heteroaryl substituted by **R⁸**, **R¹⁰** and 0, 1 or 2 substituents independently selected from **R⁹**;

R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from a 5- or 6-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³** or a 8-, 9- or 10-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³**;

R⁴ is selected from H, OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹² is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

m is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The compounds of Formula **(I)** are NNMT inhibitors. Thus, the compounds of Formula **(I)** may be used as a medicament, in particular for disorders, diseases or conditions responsive to inhibition of NNMT, and more specifically chronic kidney disease or kidney conditions or disorders in mammals including man. Further, the disclosed compounds are particularly indicated for use in the treatment of acute kidney injury (AKI), diabetic kidney disease (DKD), heart failure (HF), cardiorenal syndrome (CRS), metabolic dysfunction-associated steatohepatitis (MASH) and arrhythmia conditions or disorders in mammals including man. Conditions or disorders that may be specifically mentioned include diabetic kidney disease, hypertensive nephropathy, rapidly progressive glomerulonephritis, systemic lupus erythematosus, IgA nephropathy, focal segmental glomerulosclerosis and acute kidney injury, coronary artery disease, acute coronary syndrome, heart failure, heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, in which NNMT plays a role.

DETAILED DESCRIPTION

This detailed description and its specific examples, while indicating embodiments, are intended for purposes of illustration only. Therefore, there is no limitation to the illustrative embodiments described in this specification. In addition, it is to be appreciated that various

features that are, for clarity reasons, described in the context of separate embodiments, also may be combined to form a single embodiment. Conversely, various features that are, for brevity reasons, described in the context of a single embodiment, also may be combined to form sub-combinations thereof.

5 Listed below are definitions of various terms used in the specification and claims.

It is to be understood that where in this specification a group is qualified by “defined above” said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

It is to be understood that in this specification “C₁₋₃” means a carbon group having 1,
10 2 or 3 carbon atoms.

It is to be understood that in this specification “C₁₋₂” means a carbon group having 1 or 2 carbon atoms.

It is to be understood that in this specification “cyPr” means cyclopropyl.

It is to be understood that in this specification “cyBu” means cyclobutyl.

15 In this specification, unless stated otherwise, the term “alkyl” includes both straight and branched chain alkyl groups and may be, but is not limited to, methyl, ethyl, *n*-propyl or *i*-propyl.

It is to be understood that in this specification “8-, 9- or 10-membered heteroaryl” means a bicyclic aromatic or partially aromatic ring with 8, 9 or 10 atoms and
20 containing one or more heteroatoms independently selected from nitrogen, oxygen or sulphur.

It is to be understood that in this specification “5- or 6-membered heteroaryl” means an aromatic ring with 5 or 6 atoms and containing one or more heteroatoms independently selected from nitrogen, oxygen or sulphur.

It is to be understood that in this specification “6-membered heterocycloalkyl” means a partially or completely saturated ring system with 6 atoms and
25 wherein at least one of the ring carbon atoms is replaced with a heteroatom independently selected from nitrogen, oxygen or sulphur.

It is to be understood that in this specification a “heterocycloalkyl” substituent may be attached via a nitrogen atom having the appropriate valences, or via any
30 ring carbon atom.

In this specification, unless stated otherwise, the term “pharmaceutically acceptable” is used to characterize a moiety (e.g. a salt, dosage form, or excipient) as being appropriate for

use in accordance with sound medical judgment. In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

5

In one embodiment, there are provided compounds of Formula (I), or pharmaceutically acceptable salts thereof, wherein **R¹-R¹³** and **m** are as defined in Formula (I).

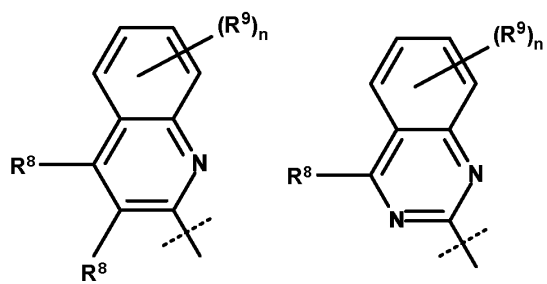
In one embodiment **R¹** is selected from a 8-, 9- or 10-membered heteroaryl substituted by **R⁸**, **R¹⁰** and 0, 1 or 2 substituents independently selected from **R⁹**.

10 **R⁸** is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl.

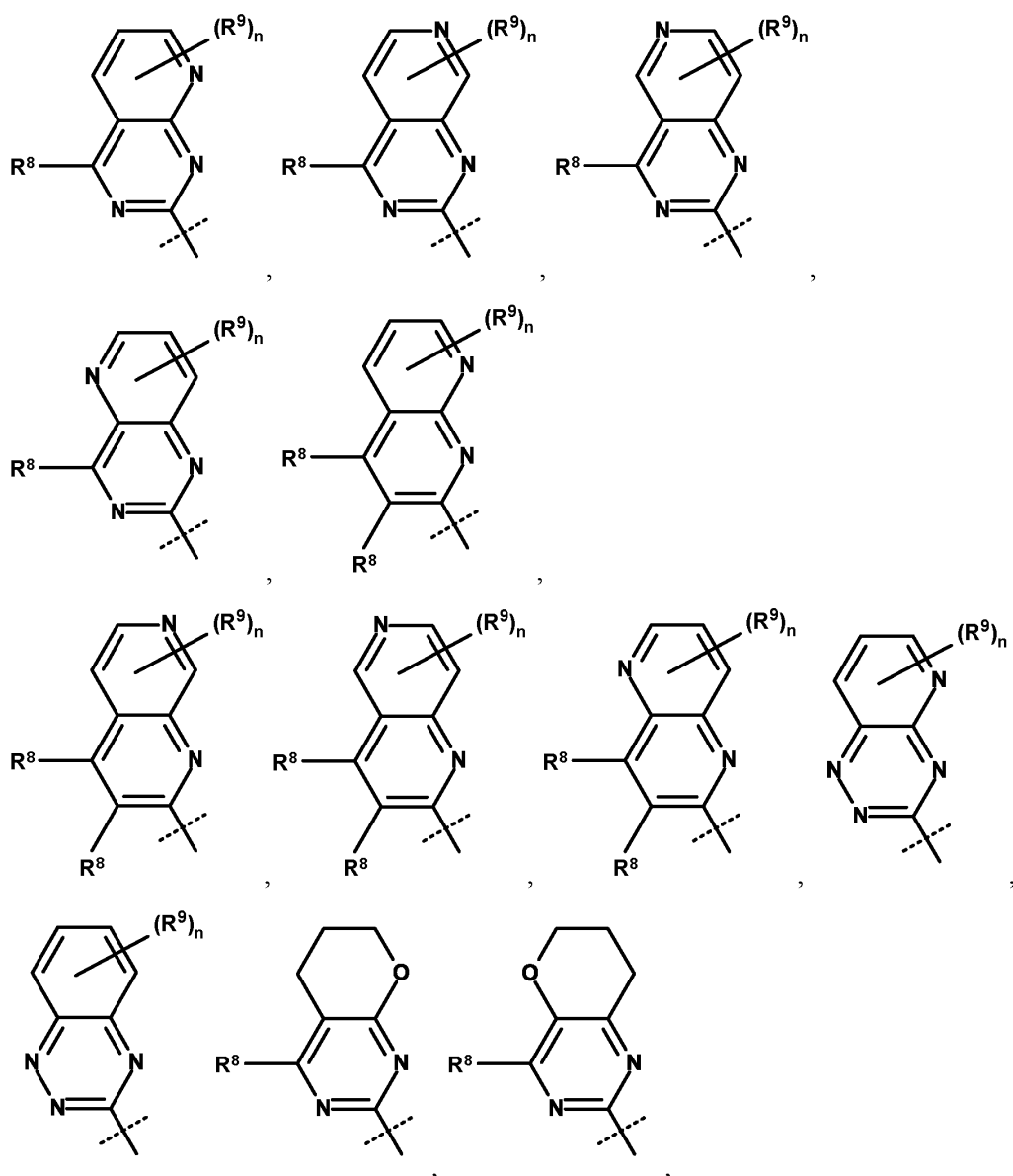
R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected
15 from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

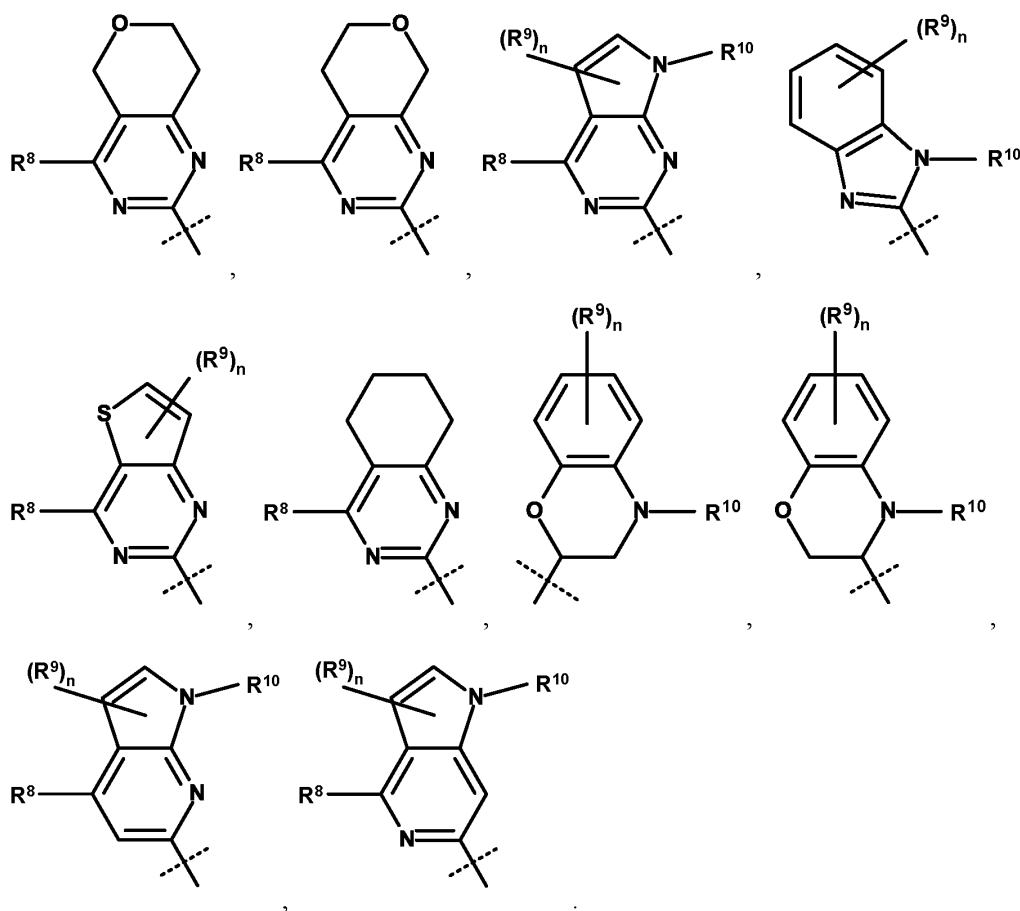
R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

20



In a further embodiment, R^1 is selected from



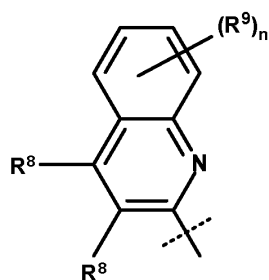


R^8 is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 5 OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl.

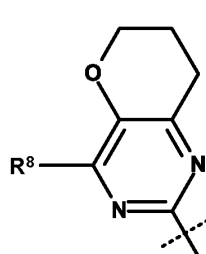
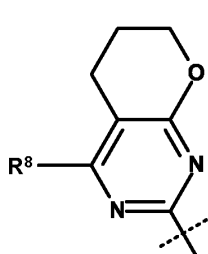
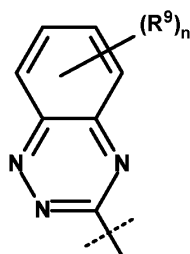
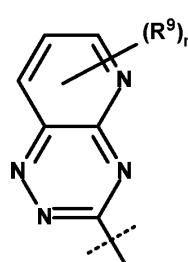
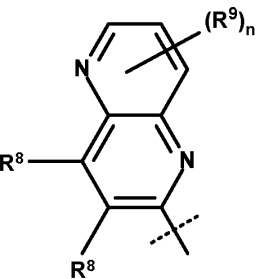
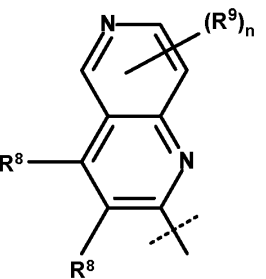
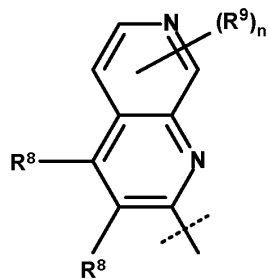
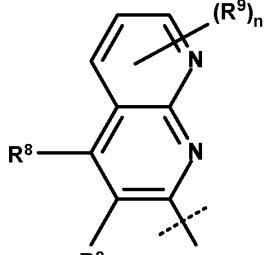
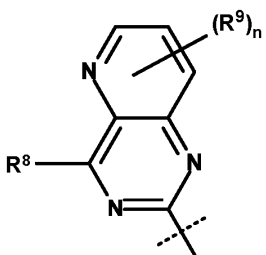
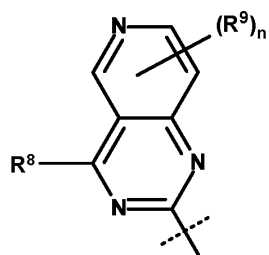
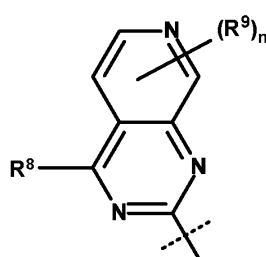
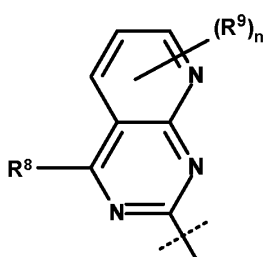
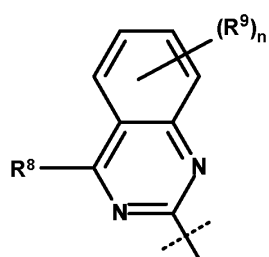
R^9 is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F,
 OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent
 selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected
 from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected
 10 from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

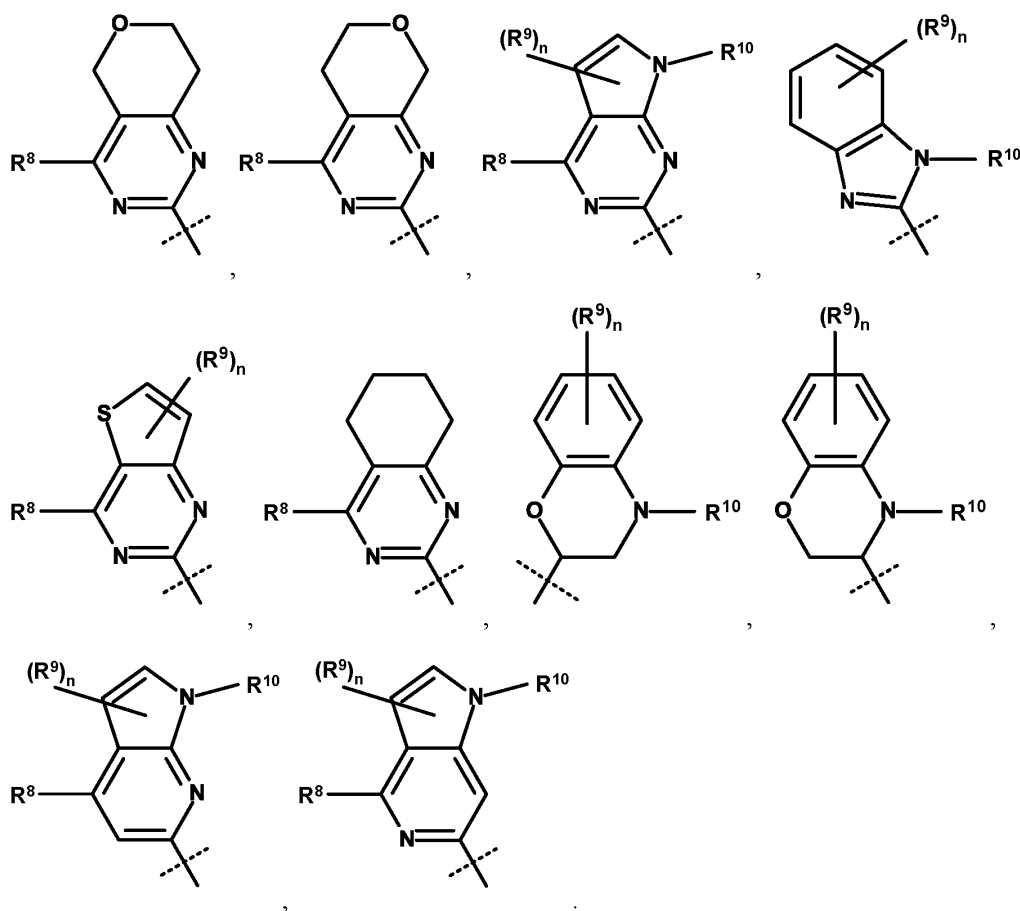
R^{10} is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or
 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1
 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

n is 0, 1 or 2.



In still a further embodiment, $\mathbf{R}^1$ is selected from



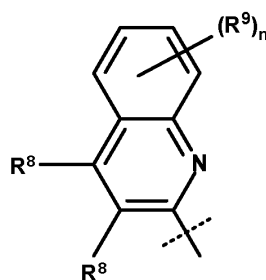


R^8 is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 5 OCH₂F, OCHF₂, OCF₃ or Cl.

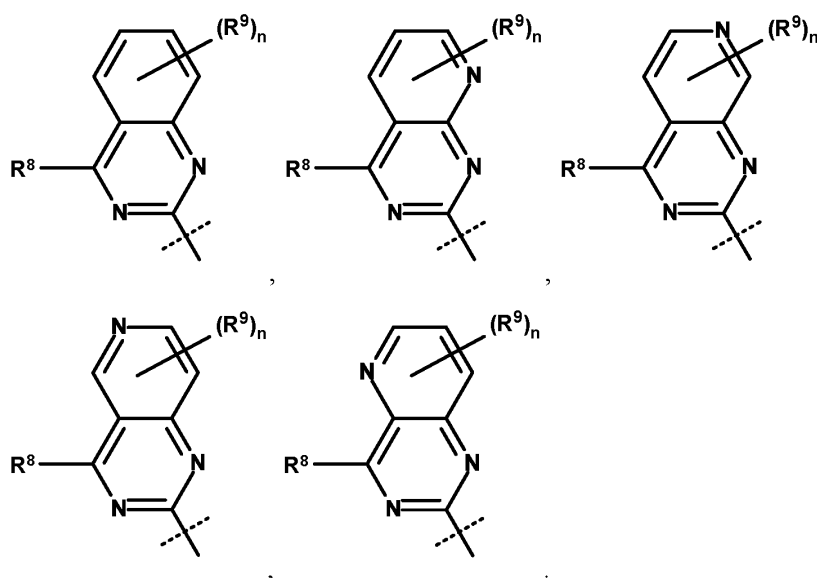
R^9 is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F,
 OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent
 selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected
 from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected
 10 from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

R^{10} is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃.

n is 0, 1 or 2.



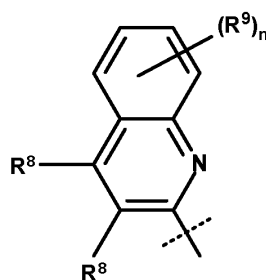
In still a further embodiment, **R¹** is selected from



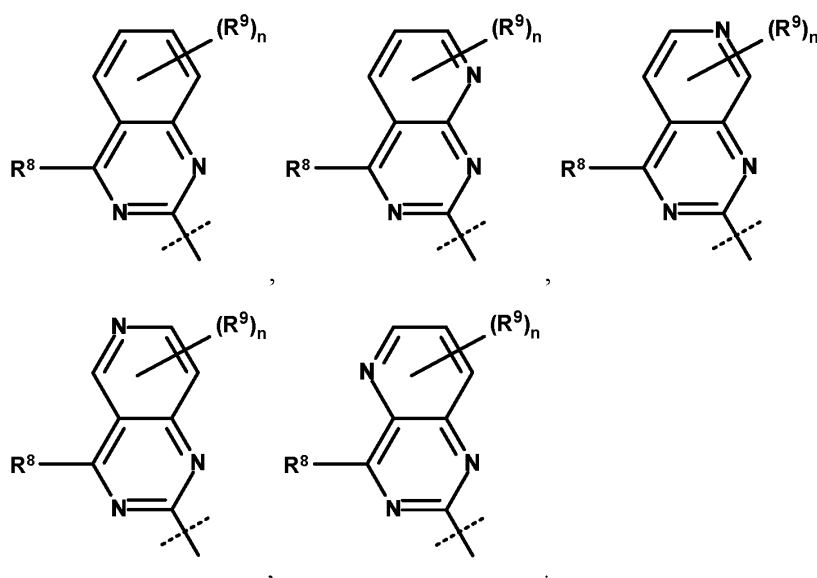
R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 5 OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl.

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F,
 OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent
 selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected
 from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected
 10 from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

n is 0, 1 or 2.



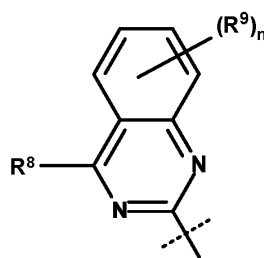
In still a further embodiment, **R¹** is selected from



R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 5 OCH₂F, OCHF₂, OCF₃ or Cl.

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F,
 OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent
 selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected
 from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected
 10 from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

n is 0, 1 or 2.

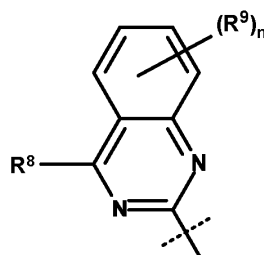


In still a further embodiment, **R¹** is selected from

R⁸ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl.

- R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

n is 0, 1 or 2.



- In still a further embodiment, **R¹** is selected from

R⁸ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or Cl.

- R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

n is 0, 1 or 2.

In one embodiment, **R²** is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃.

In a further embodiment, **R²** is independently selected from H and CH₃.

In still a further embodiment, **R²** is H.

In one embodiment, **R³** is selected from a 5- or 6-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³** or a 8-, 9- or 10-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³**.

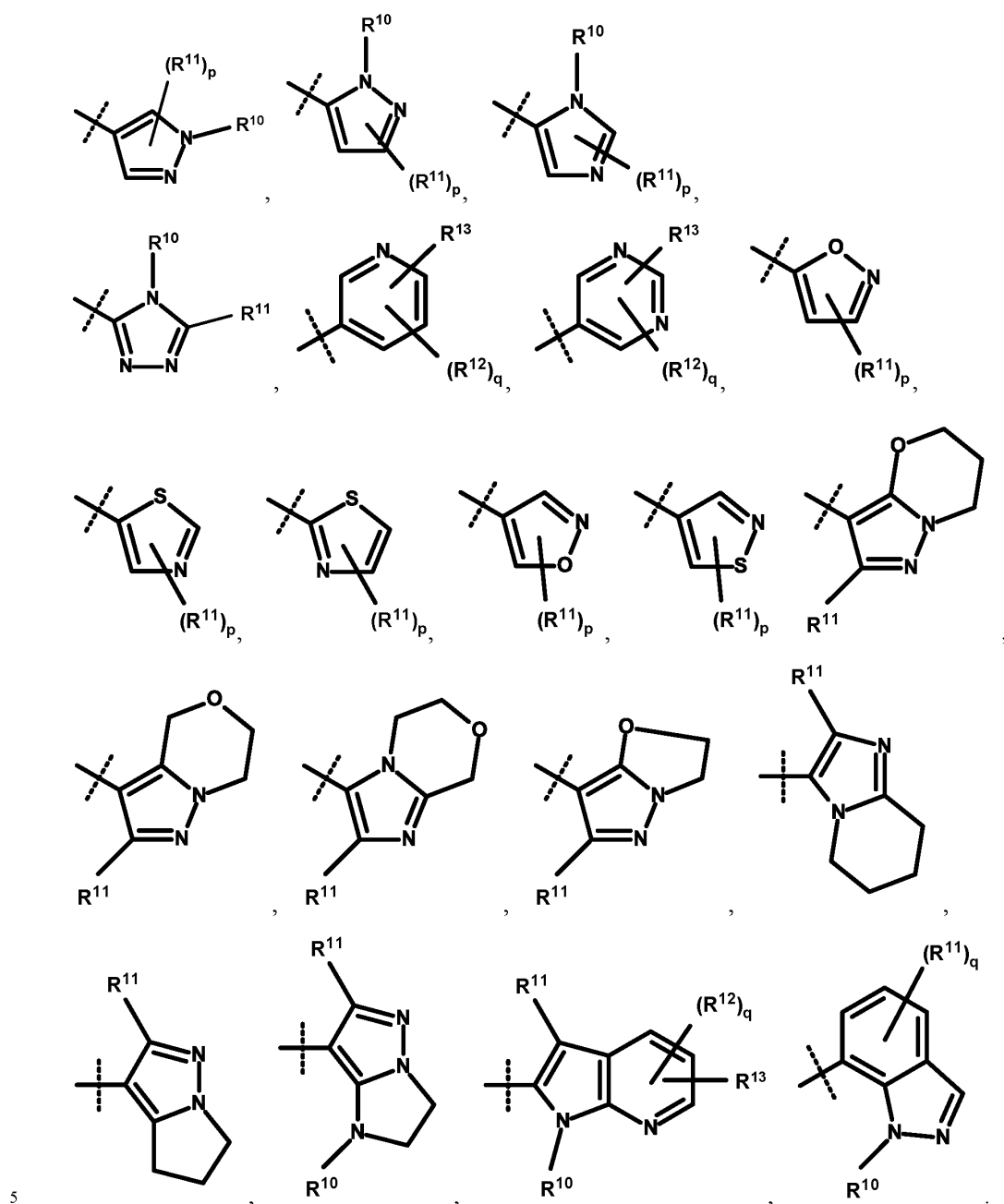
R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹² is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃.

In a further embodiment, **R³** is selected from



R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

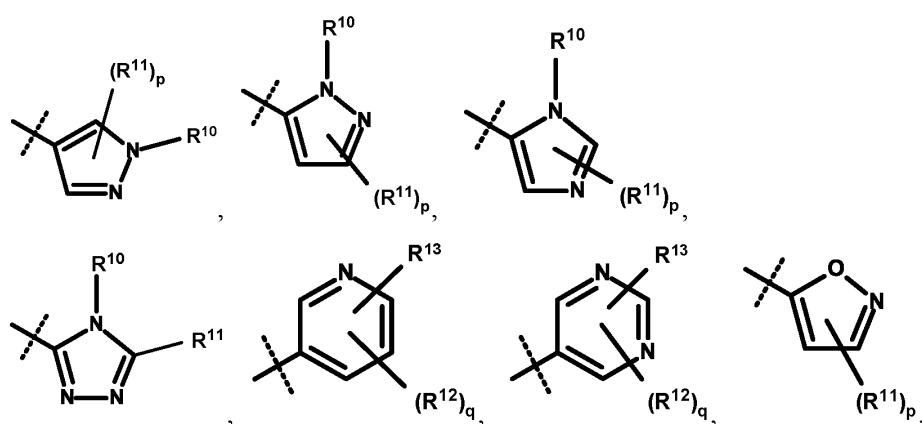
5 **R¹²** is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH.

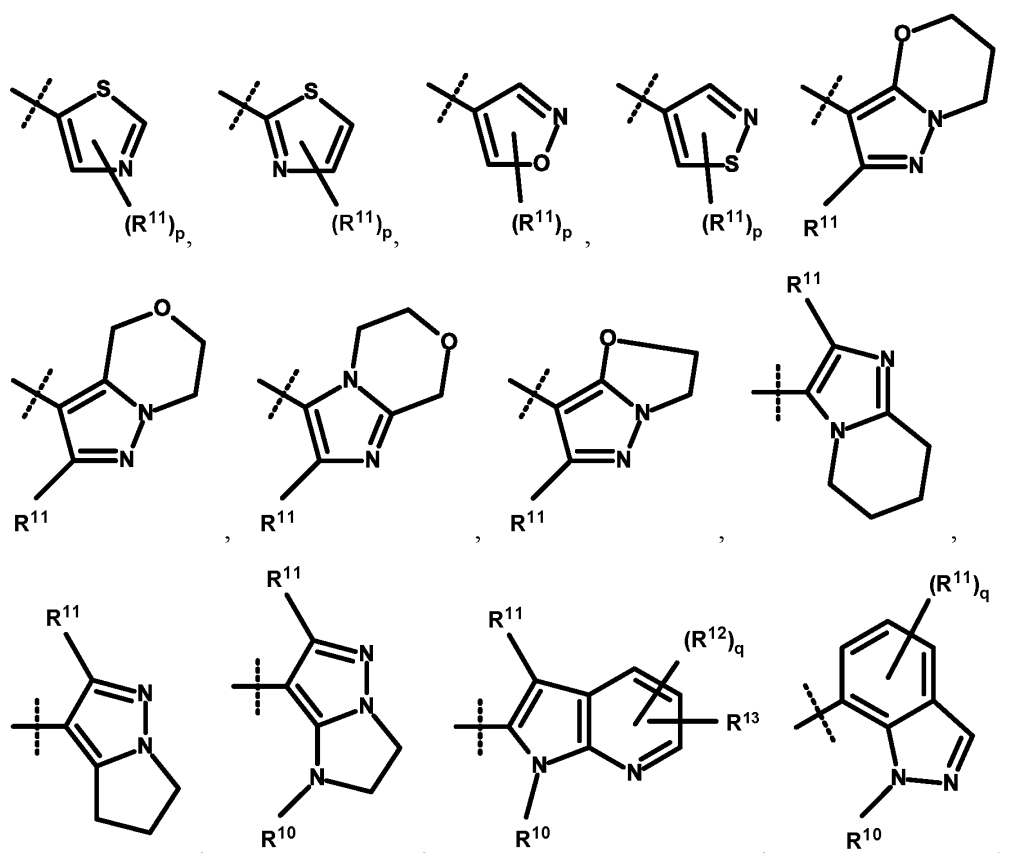
R¹³ is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃.

15 **p** is 0, 1 or 2.

q is 0, 1 or 2.

In still a further embodiment, **R³** is selected from



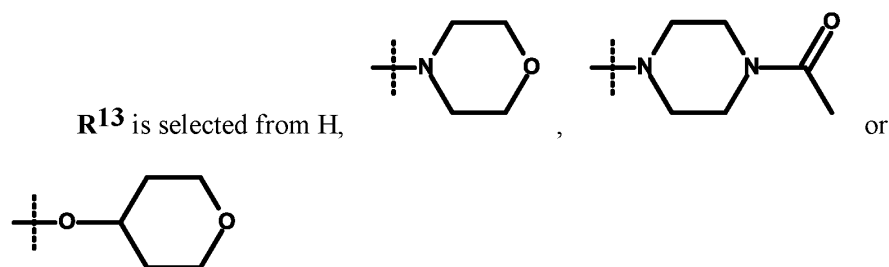


R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 5 OCH₂F, OCHF₂, OCF₃ or Cl.

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃.

R¹¹ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃,
 OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu.

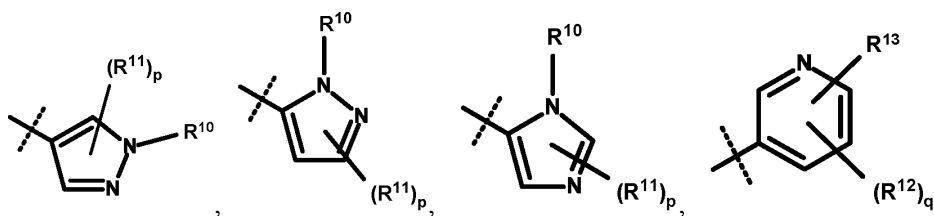
R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃,
 10 CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH.



p is 0, 1 or 2.

q is 0, 1 or 2.

- 5 In still a further embodiment, R^3 is selected from



R^{10} is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

- 10 R^{11} is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

- R^{12} is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH.

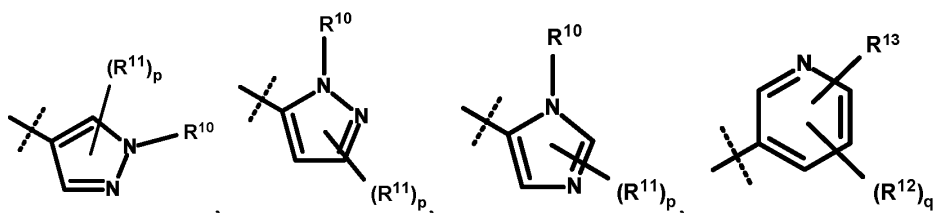
- R^{13} is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or

2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃.

p is 0, 1 or 2.

q is 0, 1 or 2.

5 In still a further embodiment, **R³** is selected from

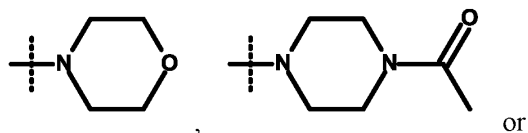


R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃.

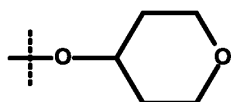
R¹¹ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu.

10 **R¹²** is independently selected from H, OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH.

R¹³ is selected from H,



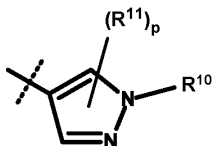
or



p is 0, 1 or 2.

15 **q** is 0, 1 or 2.

In still a further embodiment, **R³** is selected from

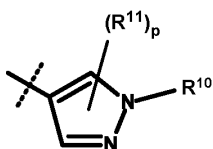


R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

R¹¹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

p is 0, 1 or 2.

In still a further embodiment, **R³** is selected from



10

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃.

R¹¹ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu.

p is 0, 1 or 2.

In one embodiment, **R⁴** is selected from H, OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl.

In a further embodiment, **R⁴** is selected from H, OH, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, CN, F.

In still a further embodiment, **R⁴** is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F.

In still a further embodiment, **R⁴** is OH.

In still a further embodiment, **R⁴** is OCH₃.

In one embodiment, **R⁵** is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃.

25

In a further embodiment, **R⁵** is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃.

In still a further embodiment, **R⁵** is independently selected from H, F, OH, OCH₃ or CH₃.

In still a further embodiment, **R⁵** is independently selected from H, F or OH.

5 In still a further embodiment, **R⁵** is independently selected from H or OH.

In one embodiment, **R⁶** is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F.

In a further embodiment, **R⁶** is independently selected from H, CH₃, CH₂F, CHF₂ or CF₃.

In still a further embodiment, **R⁶** is independently selected from H or CH₃.

10 In one embodiment, **R⁷** is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu.

In a further embodiment, **R⁷** is selected from H, F, Cl, CN or C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F.

15 In still a further embodiment, **R⁷** is selected from H, F, CH₃ or CN.

In still a further embodiment, **R⁷** is H.

In one embodiment, **R⁸** is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl.

In a further embodiment, **R⁸** is selected from H, CH₃, CH₂F, CHF₂, CF₃, OCH₃, OCH₂F,

20 OCHF₂, OCF₃ or Cl.

In still a further embodiment, **R⁸** is selected from H, CH₃ or OCH₃.

In still a further embodiment, **R⁸** is CH₃.

In one embodiment, **R⁹** is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0

25 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl.

In a further embodiment, **R⁹** is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, CN, F or Cl.

In still a further embodiment, **R⁹** is independently selected from H, CH₃, CH₂F, CHF₂, CF₃,
5 CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CN, F or Cl.

In still a further embodiment, **R⁹** is independently selected from H, CH₃, OCH₃, CN, F or Cl.

In one embodiment, **R¹⁰** is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃.

In a further embodiment, **R¹⁰** is selected from H or CH₃.

In one embodiment, **R¹¹** is independently selected from H, C₁₋₂alkyl optionally substituted
10 by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃,
CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃
or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃.

In a further embodiment, **R¹¹** is independently selected from H, CH₃, CH₂F, CHF₂, CF₃,
CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu.

15 In still a further embodiment, **R¹¹** is independently selected from H, CH₃, CH₂CH₃, OCH₃,
CH₂OCH₃, cyPr, CH₂cyPr or cyBu.

In still a further embodiment, **R¹¹** is independently selected from H, CH₃ or OCH₃.

In one embodiment, **R¹²** is independently selected from H, CH₃, OH, OCH₃, CH₂F, CHF₂,
CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH.

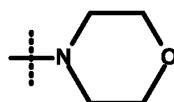
20 In a further embodiment, **R¹²** is independently selected from H, CH₃, OCH₃, CN, Cl or
CH₂OH.

In still a further embodiment, **R¹²** is independently selected from H, CH₃, OCH₃, CN or Cl.

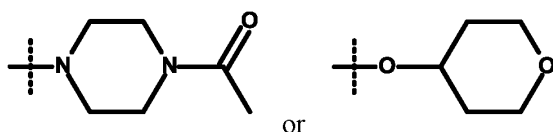
In one embodiment, **R¹³** is selected from H, a 6-membered heterocycloalkyl ring containing 1
or 2 heteroatoms independently selected from O, S or N wherein said 6-membered
25 heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected
from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or
(CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms

independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃.

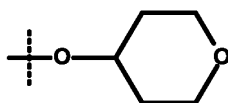
In a further embodiment, **R¹³** is selected from H,



5



or



10

In one embodiment, **m** is 0, 1 or 2.

In a further embodiment, **m** is 0 or 1.

In still a further embodiment, **m** is 2.

In still a further embodiment, **m** is 1.

In still a further embodiment, **m** is 0.

In one embodiment, **n** is 0, 1 or 2.

In a further embodiment, **n** is 0 or 1.

In still a further embodiment, **n** is 2.

In still a further embodiment, **n** is 1.

15

In still a further embodiment, **n** is 0.

In one embodiment, **p** is 0, 1 or 2.

In a further embodiment, **p** is 0 or 1.

In still a further embodiment, **p** is 2.

In still a further embodiment, **p** is 1.

20

In still a further embodiment, **p** is 0.

In one embodiment, **q** is 0, 1 or 2.

In a further embodiment, **q** is 0 or 1.

In still a further embodiment, **q** is 2.

In still a further embodiment, **q** is 1.

25

In still a further embodiment, **q** is 0.

In one embodiment, there are provided compounds of Formula (I) wherein

R¹ is selected from a 8-, 9- or 10-membered heteroaryl substituted by **R⁸**, **R¹⁰** and 0, 1 or 2 substituents independently selected from **R⁹**;

R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

- 5 **R³** is selected from a 5- or 6-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³** or a 8-, 9- or 10-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³**;

R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

- 15 **R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

- 20 **R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

- 25 **R¹⁰** is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

- 5 **R¹²** is independently selected from H, CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

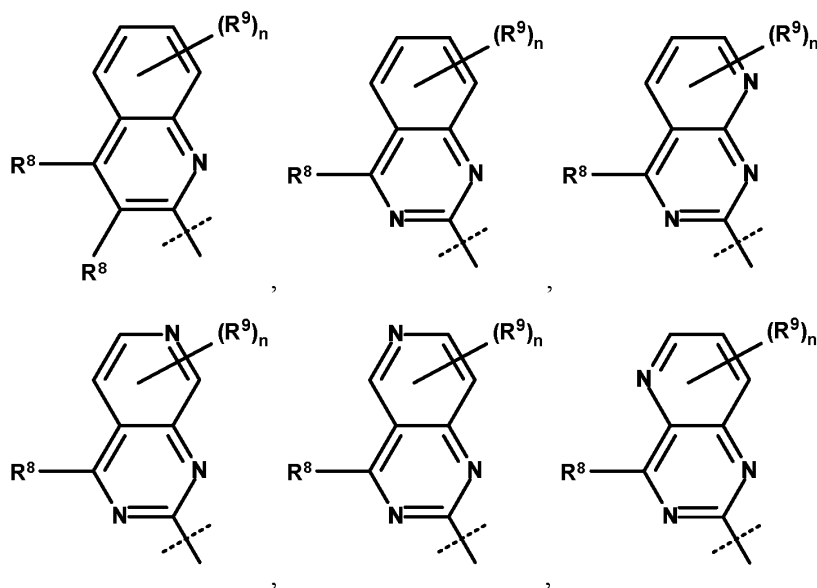
R¹³ is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃,

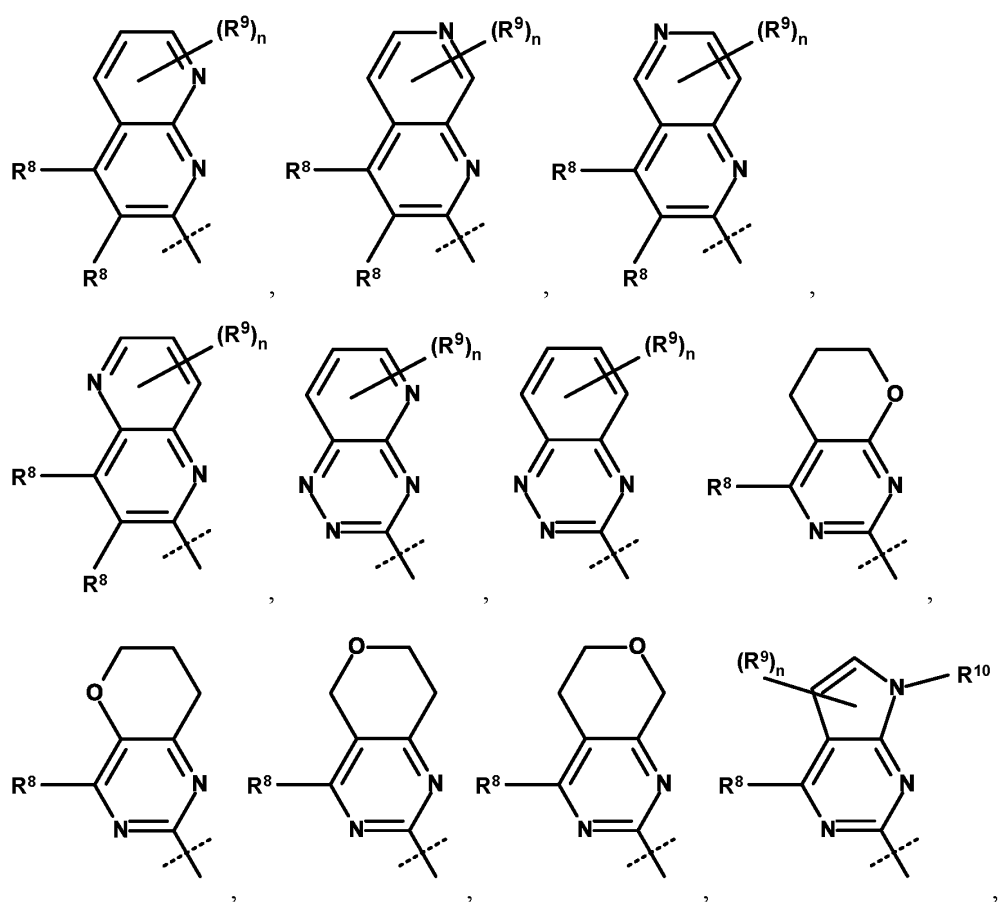
- 10 CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

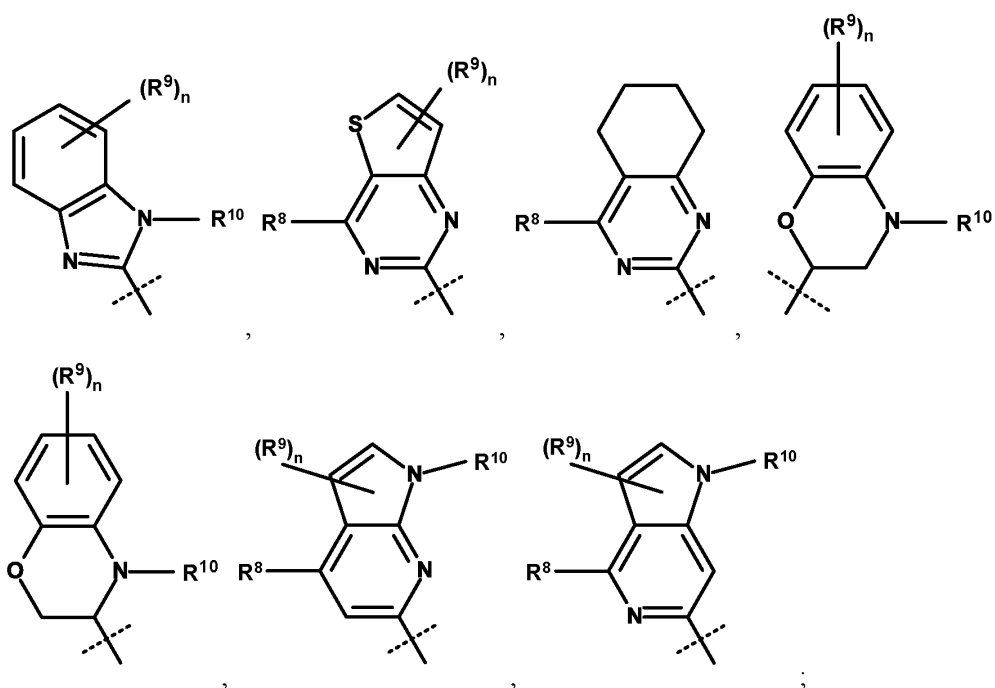
- 15 **m** is independently 0, 1 or 2;
or a pharmaceutically acceptable salt thereof.

In a further embodiment, there are provided compounds of Formula (I) wherein

R¹ is selected from

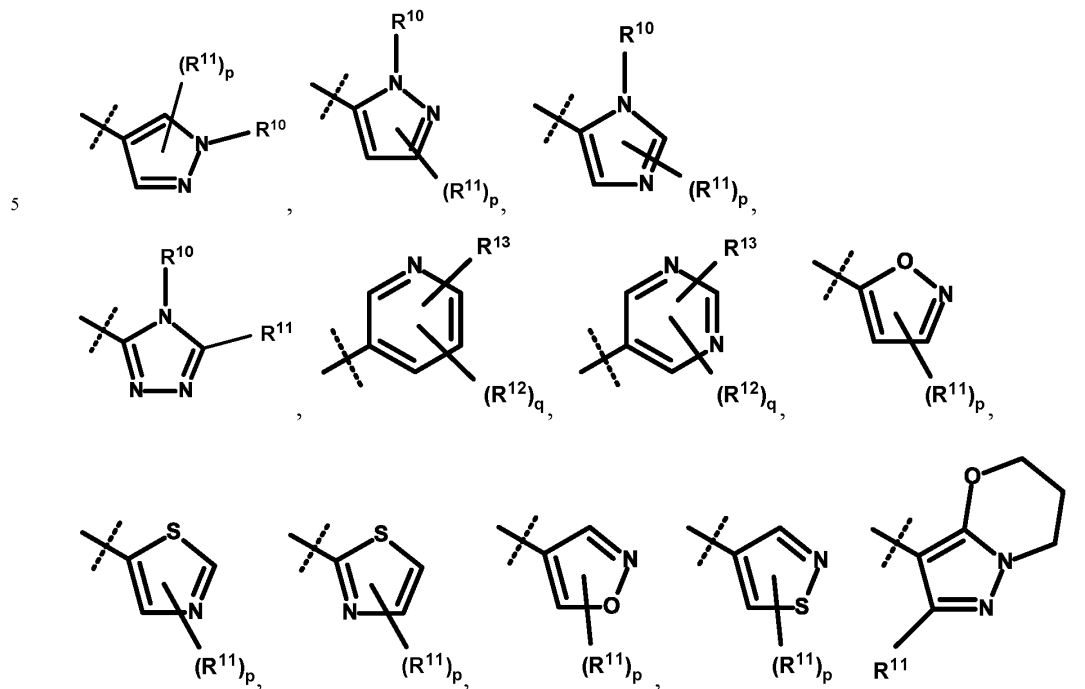


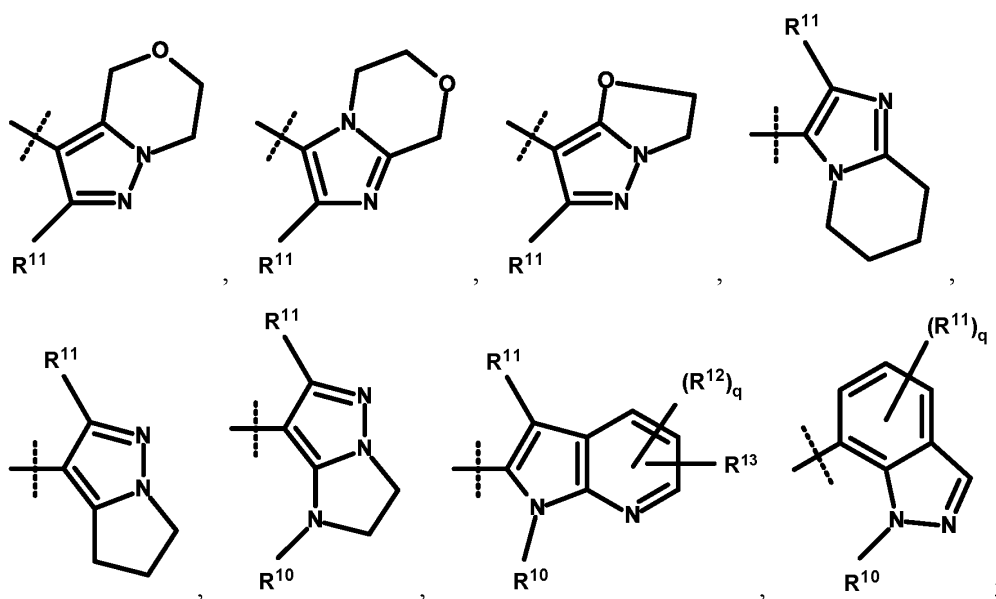




R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

$\mathbf{R}^3$ is selected from





R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

5 **R⁵** is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

10 **R⁸** is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

15

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹² is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

m is independently 0, 1 or 2;

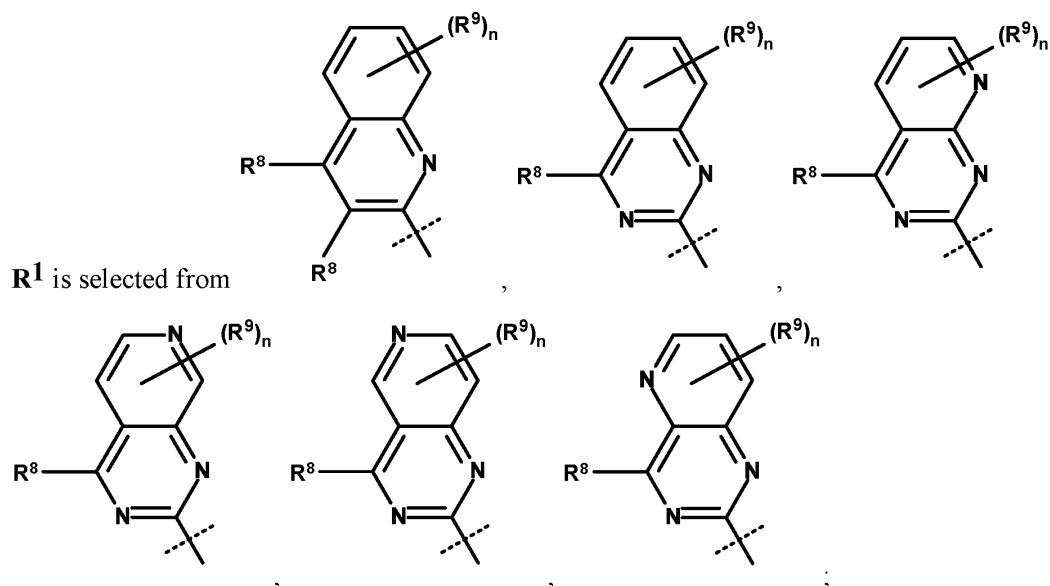
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

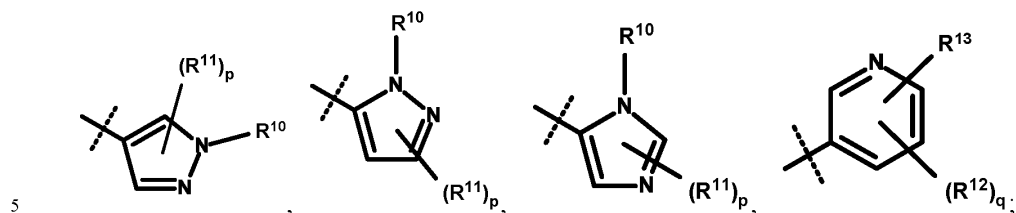
or a pharmaceutically acceptable salt thereof.

In a further embodiment, there are provided compounds of Formula **(I)** wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

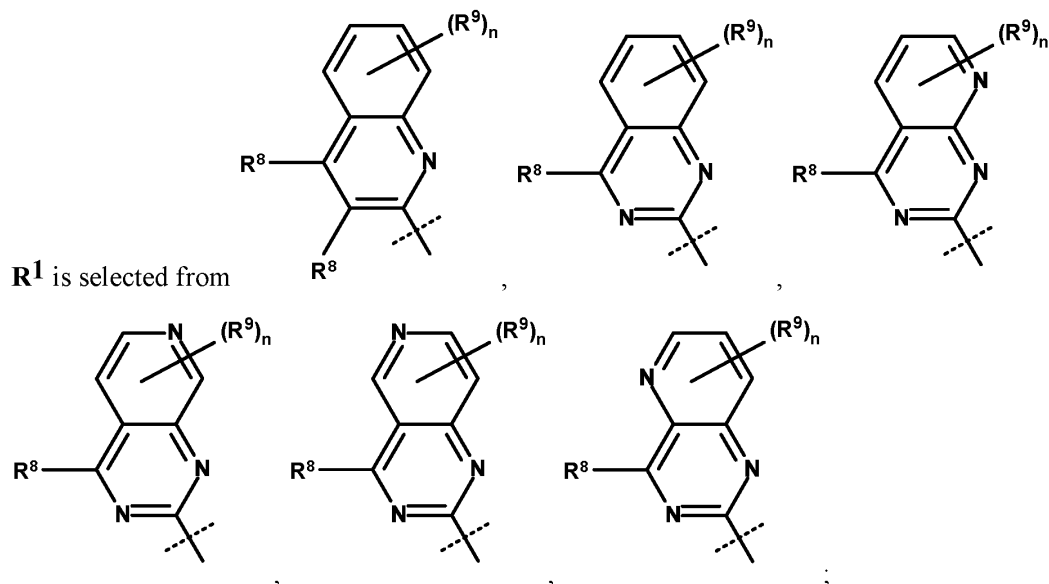
R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

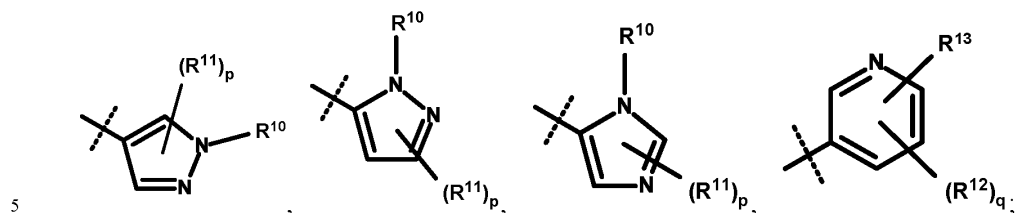
R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

- R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;
- R¹⁰** is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;
- R¹¹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;
- R¹²** is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;
- R¹³** is selected from a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;
- m** is independently 0, 1 or 2;
- n** is 0, 1 or 2;
- p** is 0, 1 or 2;
- q** is 0, 1 or 2;
- or a pharmaceutically acceptable salt thereof.
- In still a further embodiment, there are provided compounds of Formula (**I**) wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

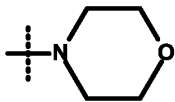
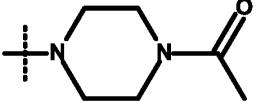
R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or Cl;

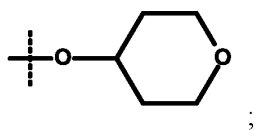
R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃;

R¹¹ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu;

R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH;

R¹³ is selected from H, ,  or



m is independently 0, 1 or 2;

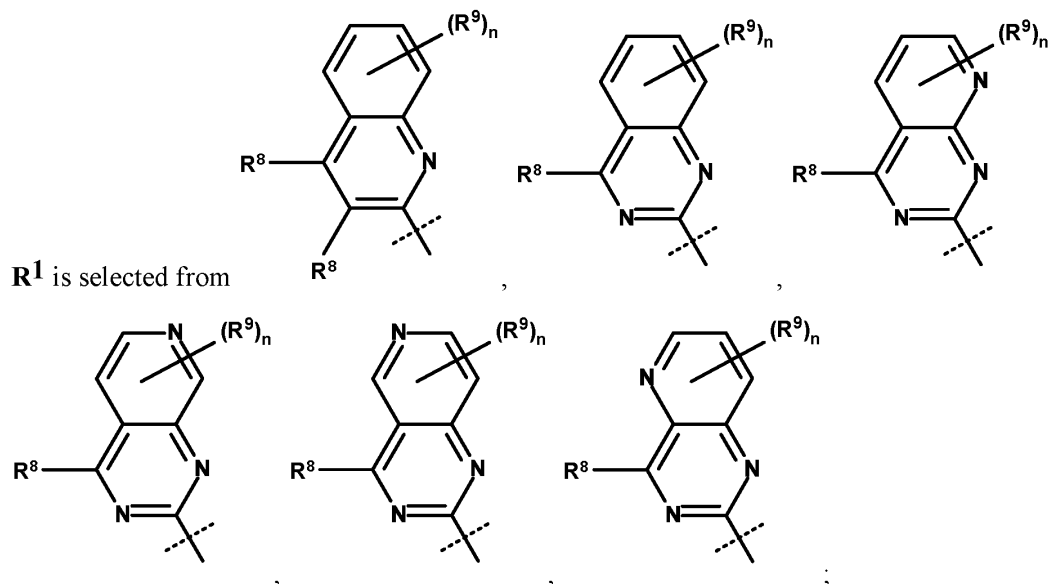
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

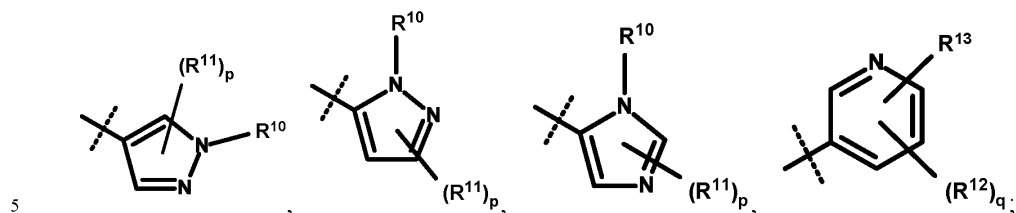
or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula **(I)** wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

10 **R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

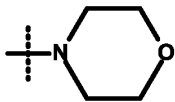
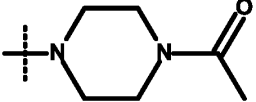
R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or Cl;

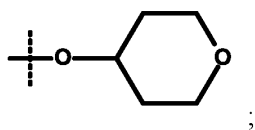
R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃;

R¹¹ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu;

R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH;

R¹³ is selected from H, ,  or



m is independently 0, 1 or 2;

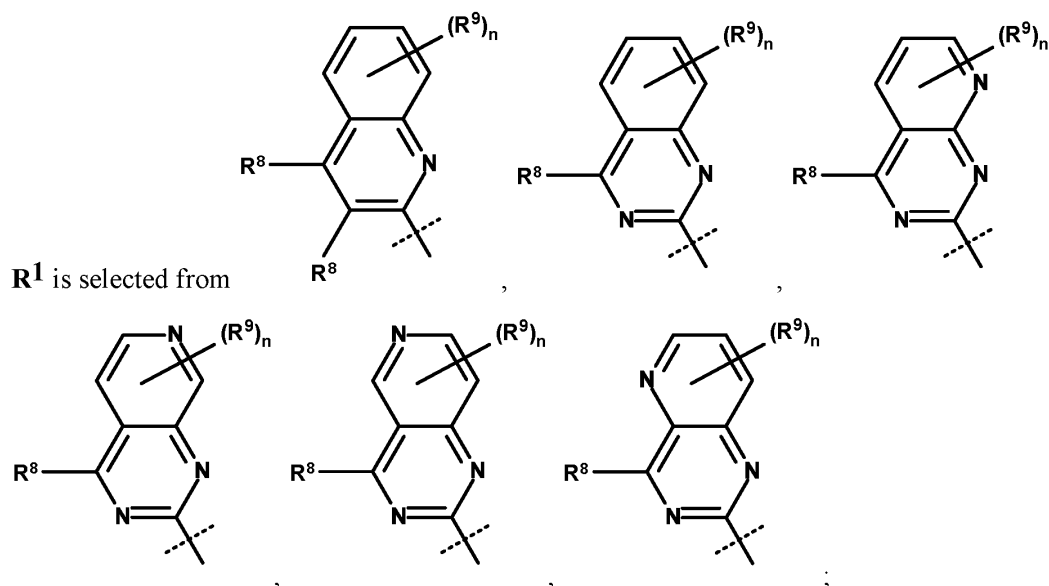
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

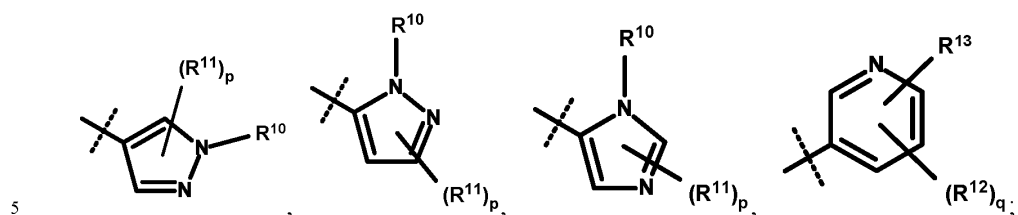
or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula **(I)** wherein



R² is H;

R³ is selected from



R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

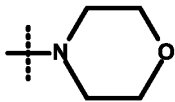
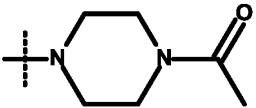
R⁸ is independently selected from H, CH₃ or OCH₃;

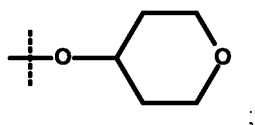
R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

R¹³ is selected from H, ,  or



m is independently 0, 1 or 2;

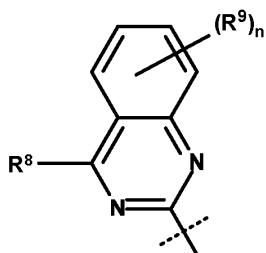
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

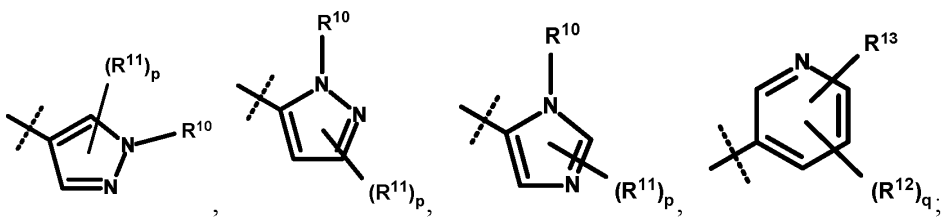
In still a further embodiment, there are provided compounds of Formula (**I**) wherein



R¹ is selected from

R² is H;

R³ is selected from



R⁴ is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl

optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

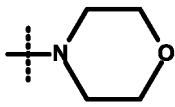
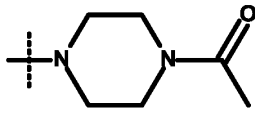
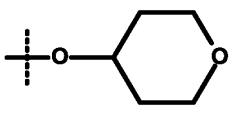
R⁸ is selected from H, CH₃ or OCH₃;

R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

5 **R¹⁰** is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

R¹³ is selected from H, , , or  ;

10 **m** is independently 0, 1 or 2;

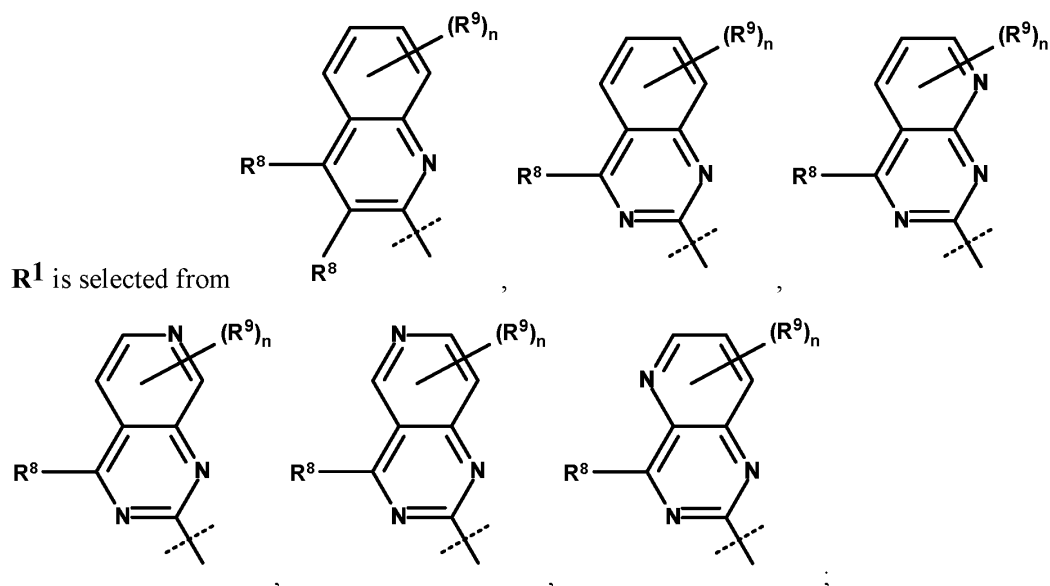
n is 0, 1 or 2;

p is 0, 1 or 2;

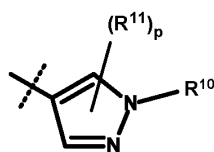
q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

15 In still a further embodiment, there are provided compounds of Formula **(I)** wherein



R² is H;



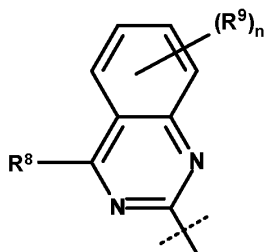
R³ is selected from

- 5 **R⁴** is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;
- R⁵** is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;
- R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;
- 10 **R⁷** is selected from H, F, CH₃ or CN;
- R⁸** is independently selected from H, CH₃ or OCH₃;
- R⁹** is independently selected from CH₃, OCH₃, CN, F or Cl;
- R¹⁰** is selected from H or CH₃;
- R¹¹** is independently selected from CH₃ or OCH₃;
- 15 **m** is independently 0, 1 or 2;
- n** is 0, 1 or 2;

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

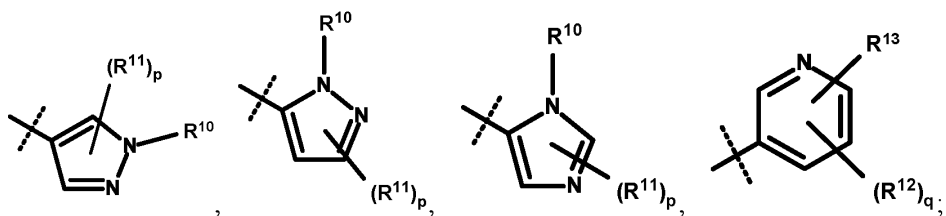
In still a further embodiment, there are provided compounds of Formula (**I**) wherein



R¹ is selected from

5 **R**² is H;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is independently selected from H, F or OH;

10 **R**⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

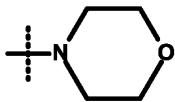
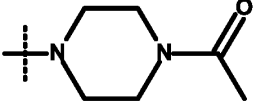
R⁸ is selected from H, CH₃ or OCH₃;

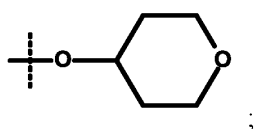
R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

15 **R**¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

R¹³ is selected from H, , , or



m is independently 0, 1 or 2;

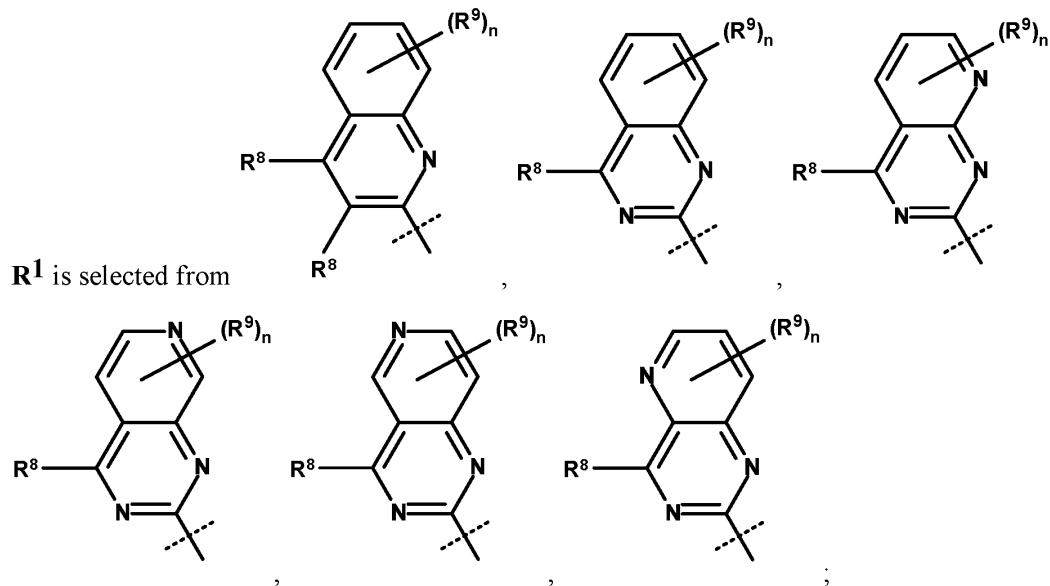
n is 0, 1 or 2;

5 **p** is 0, 1 or 2;

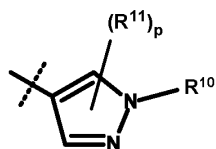
q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula (I) wherein



R² is H;



R³ is selected from

R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is independently selected from H, F or OH;

R^6 is independently selected from CH_3 , CH_2F , CHF_2 , CF_3 , CH_2CH_3 or F ;

R^7 is selected from H , F , CH_3 or CN ;

R^8 is independently selected from H , CH_3 or OCH_3 ;

R^9 is independently selected from CH_3 , OCH_3 , CN , F or Cl ;

5 R^{10} is selected from H or CH_3 ;

R^{11} is independently selected from CH_3 or OCH_3 ;

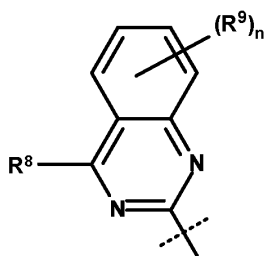
m is independently 0, 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

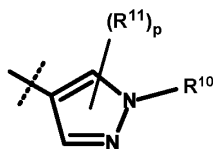
10 or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula (I) wherein



R^1 is selected from ;

R^2 is H ;



R^3 is selected from ;

15 R^4 is selected from OH , OCH_3 , OCH_2F , $OCHF_2$, OCF_3 , $-CH_2OH$, CN , F ;

R^5 is independently selected from H , F or OH ;

R^6 is independently selected from CH_3 , CH_2F , CHF_2 , CF_3 , CH_2CH_3 or F ;

R^7 is selected from H , F , CH_3 or CN ;

R^8 is selected from H , CH_3 or OCH_3 ;

20 R^9 is independently selected from CH_3 , OCH_3 , CN , F or Cl ;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

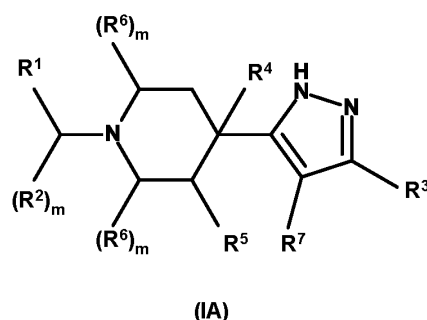
m is independently 0, 1 or 2;

n is 0, 1 or 2;

5 **p** is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment, there are provided compounds of Formula **(IA)**



wherein

10 **R¹** is selected from a 8-, 9- or 10-membered heteroaryl substituted by **R⁸**, **R¹⁰** and 0, 1 or 2 substituents independently selected from **R⁹**;

R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from a 5- or 6-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and

15 0 or 1 substituents independently selected from **R¹³** or a 8-, 9- or 10-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³**;

R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

20 **R⁵** is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent
5 selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1
10 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

15 **R¹²** is independently selected from H, CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃,

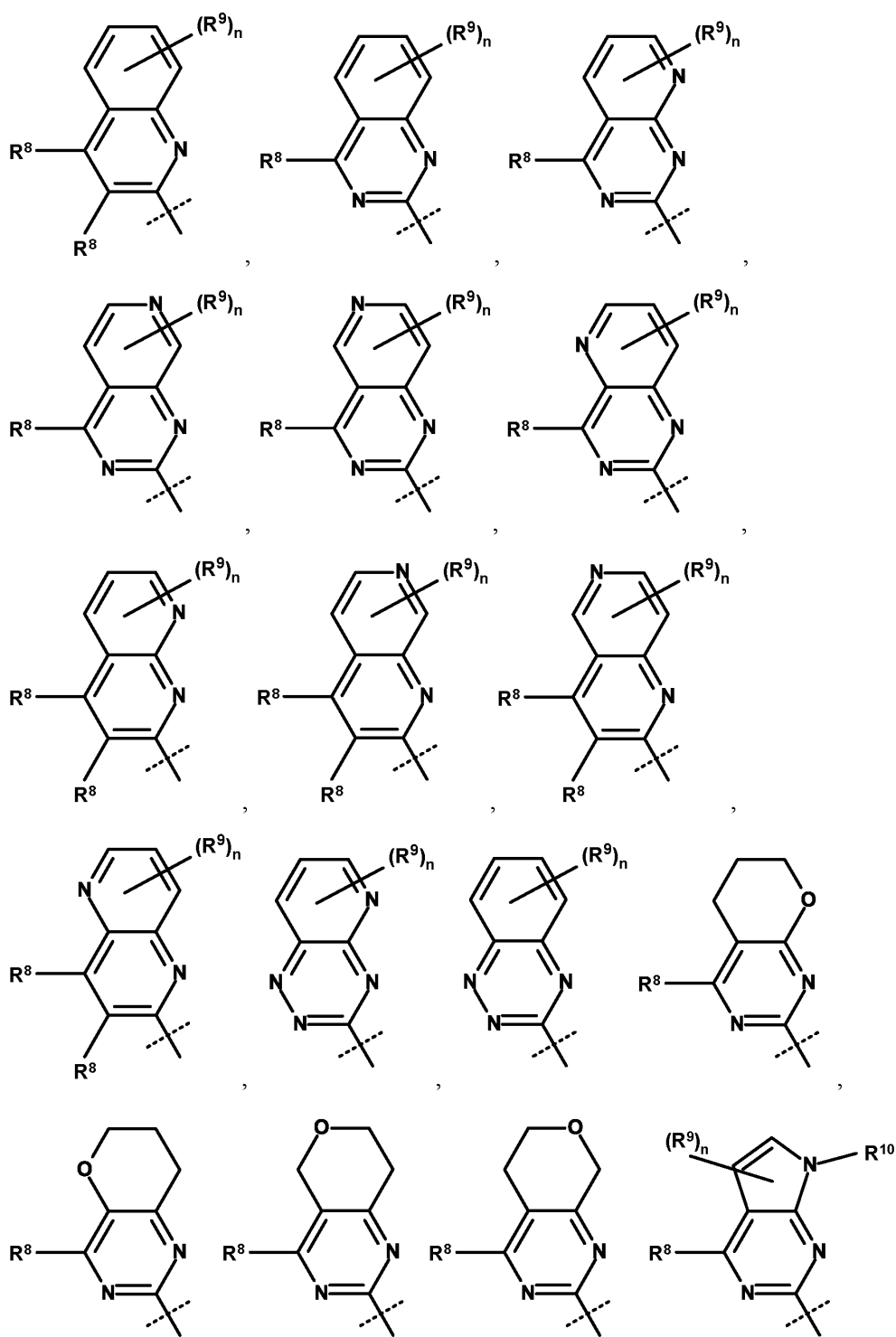
20 CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

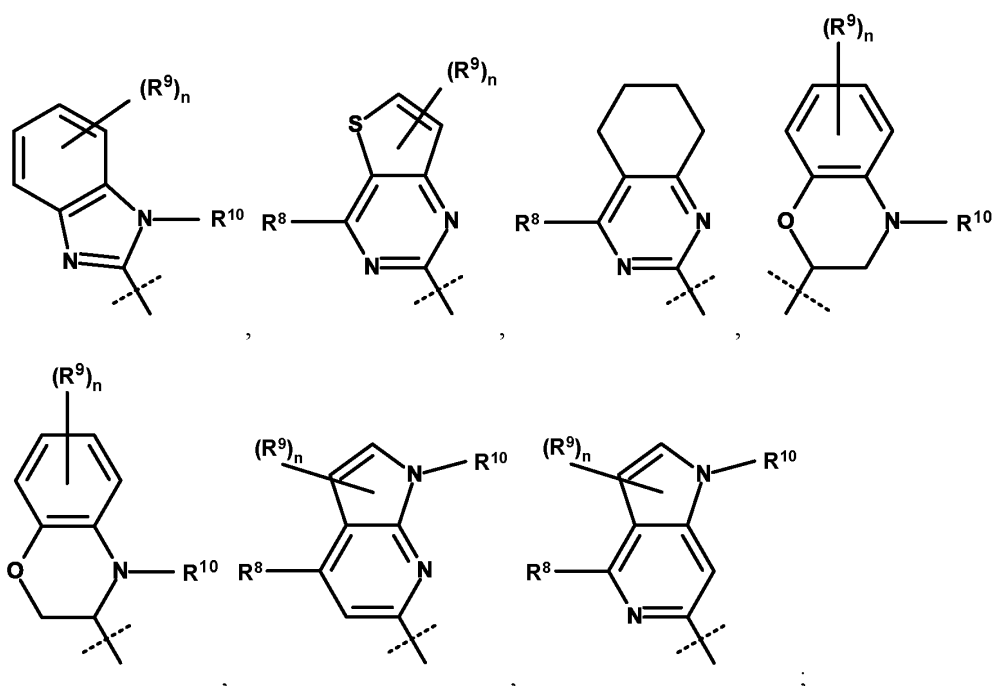
25 **m** is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In a further embodiment, there are provided compounds of Formula **(IA)** wherein

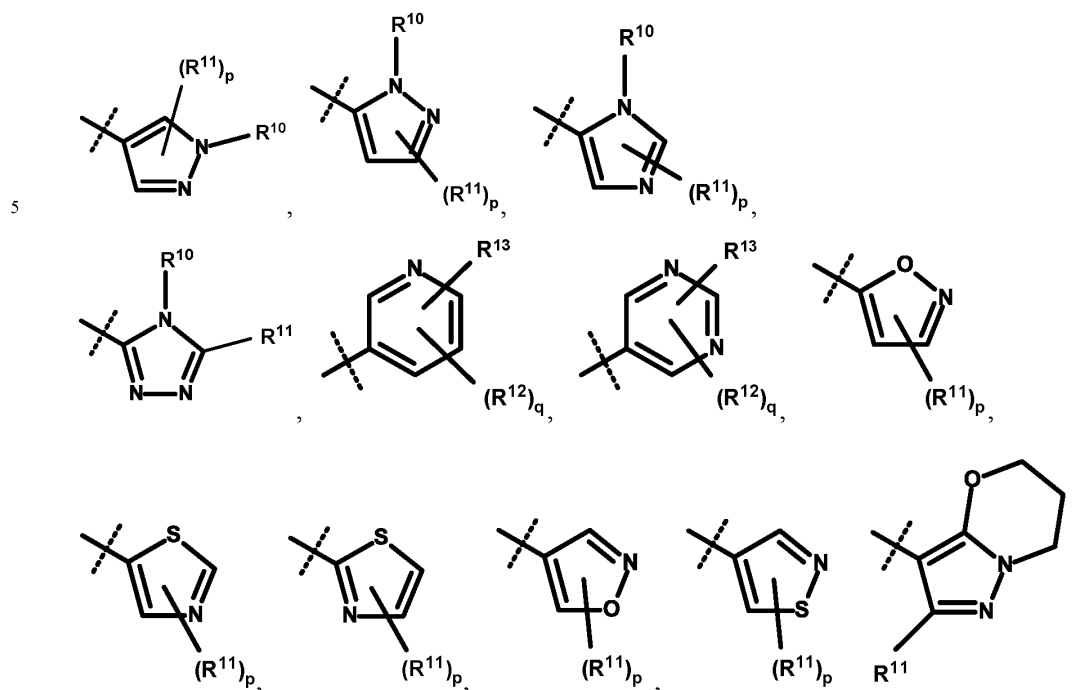
R¹ is selected from

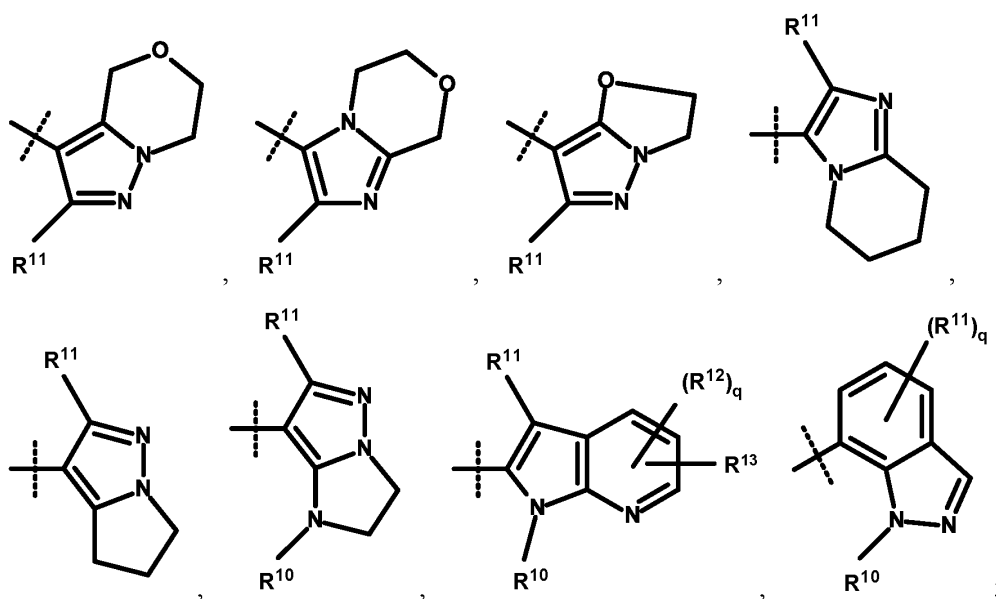




R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

$\mathbf{R}^3$ is selected from





R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

5 **R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

10 **R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

15 **R¹⁰** is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from H, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

- 5 **R¹²** is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from H, a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃,

- 10 CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

- 15 **m** is independently 0, 1 or 2;

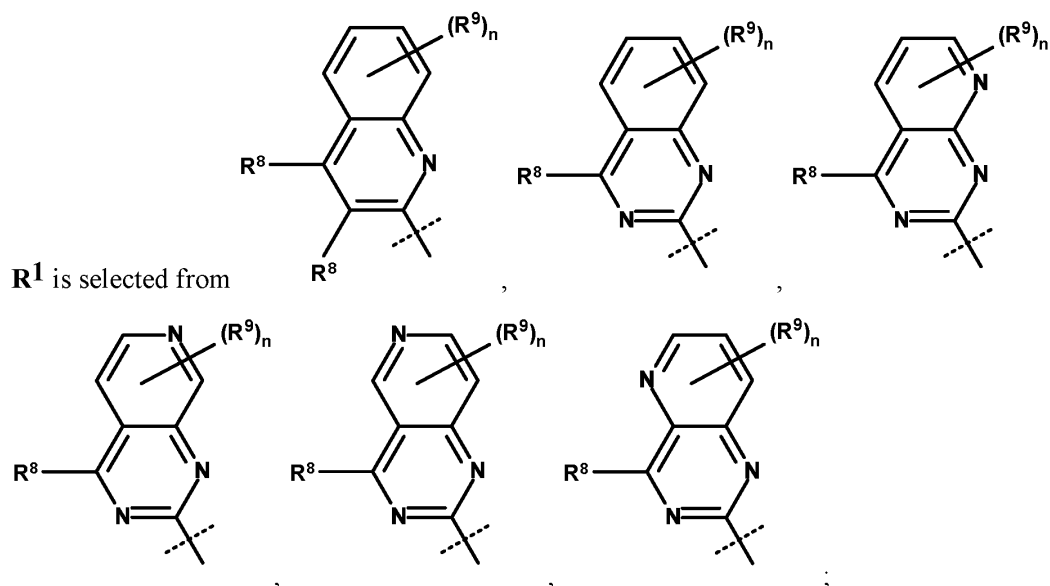
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

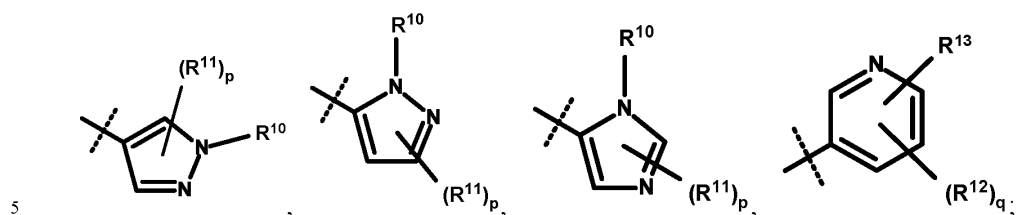
or a pharmaceutically acceptable salt thereof.

- 20 In a further embodiment, there are provided compounds of Formula **(IA)** wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

10 **R⁷** is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

15 **R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected

from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹² is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

m is independently 0, 1 or 2;

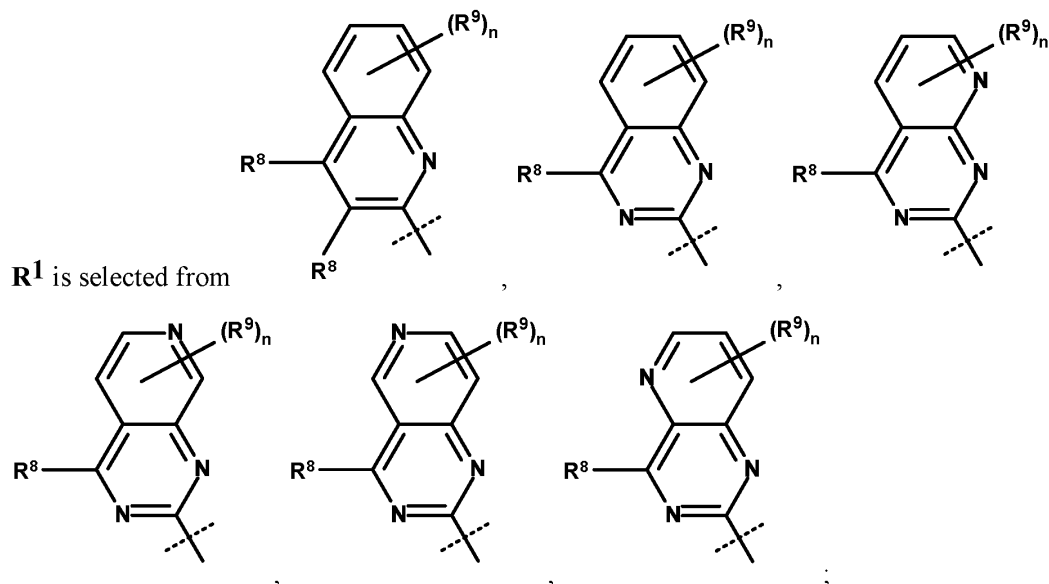
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

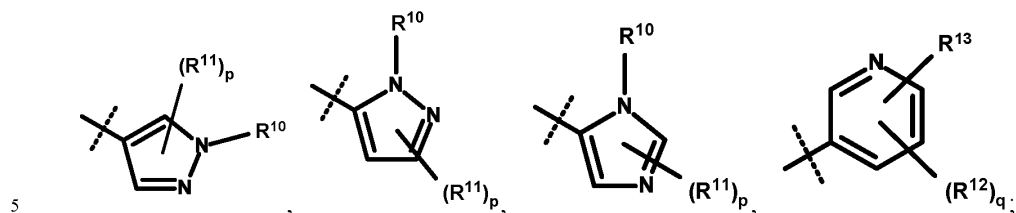
or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

10 **R⁷** is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or Cl;

15 **R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected

from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃;

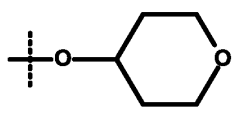
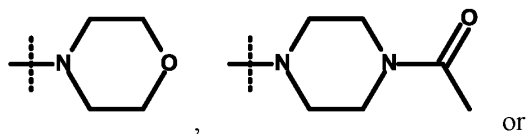
R¹¹ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F,

5 OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu;

R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃,

CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH;

R¹³ is selected from H,



10 **m** is independently 0, 1 or 2;

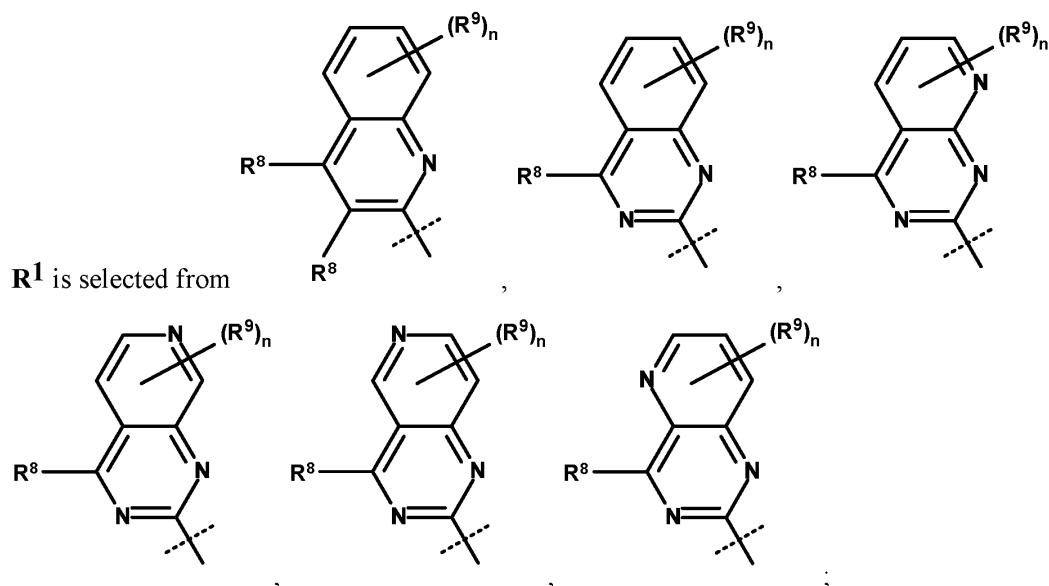
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

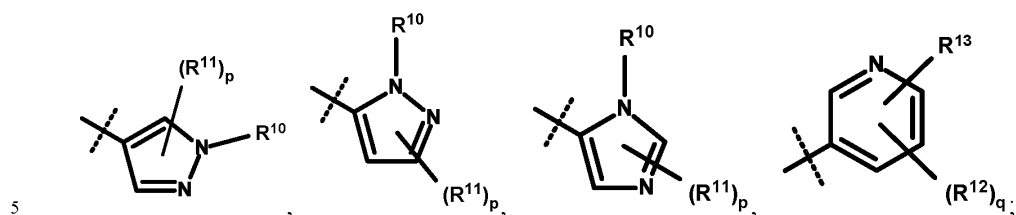
or a pharmaceutically acceptable salt thereof.

15 In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

10 **R⁷** is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or Cl;

15 **R⁹** is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected

from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃;

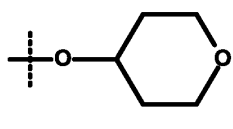
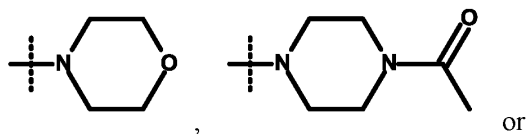
R¹¹ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F,

5 OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu;

R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃,

CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH;

R¹³ is selected from H,



10 **m** is independently 0, 1 or 2;

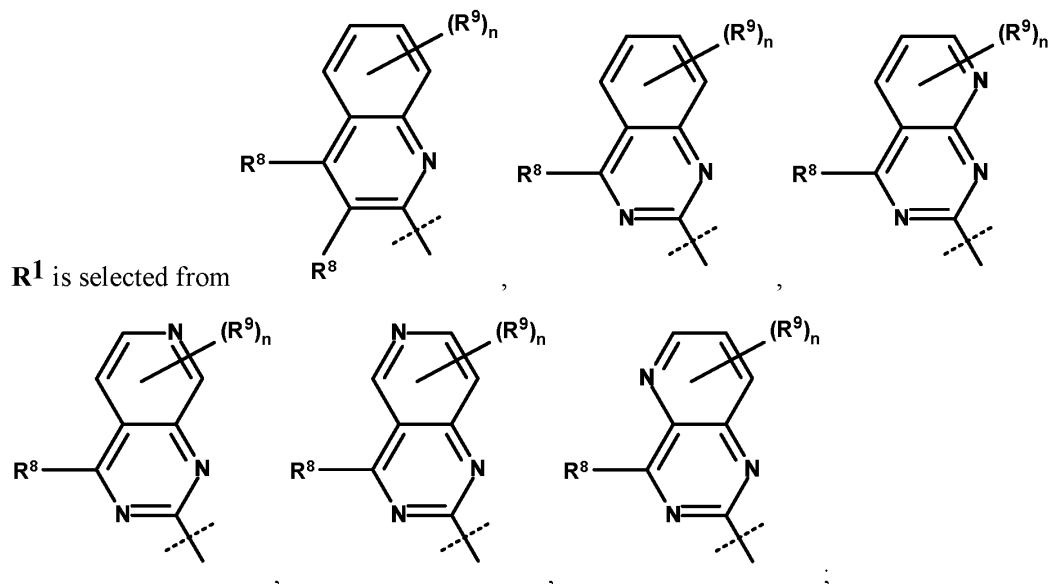
n is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

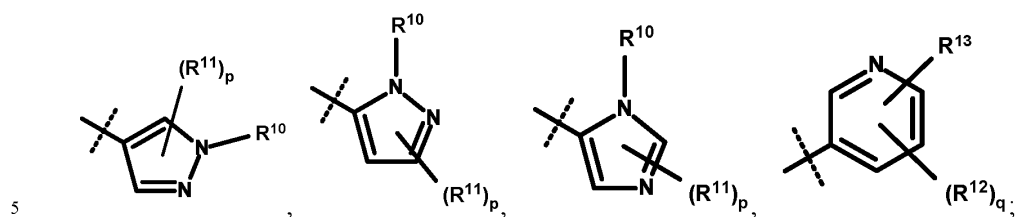
or a pharmaceutically acceptable salt thereof.

15 In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



R² is H;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

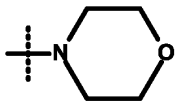
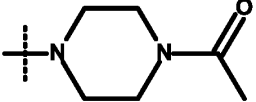
10 **R⁸** is independently selected from H, CH₃ or OCH₃;

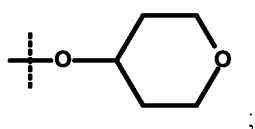
R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

R¹³ is selected from H, , , or



m is independently 0, 1 or 2;

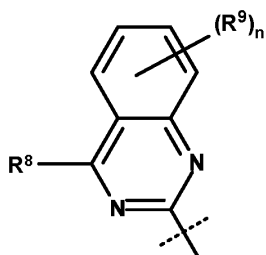
n is 0, 1 or 2;

5 **p** is 0, 1 or 2;

q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

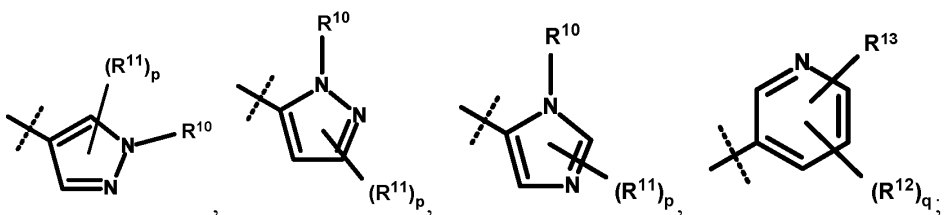
In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



R¹ is selected from

10 **R²** is H;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

15 **R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

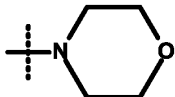
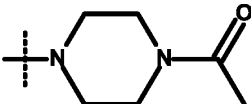
R⁸ is selected from H, CH₃ or OCH₃;

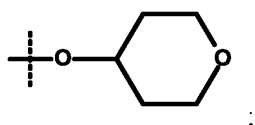
R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

R¹³ is selected from H, ,  or



m is independently 0, 1 or 2;

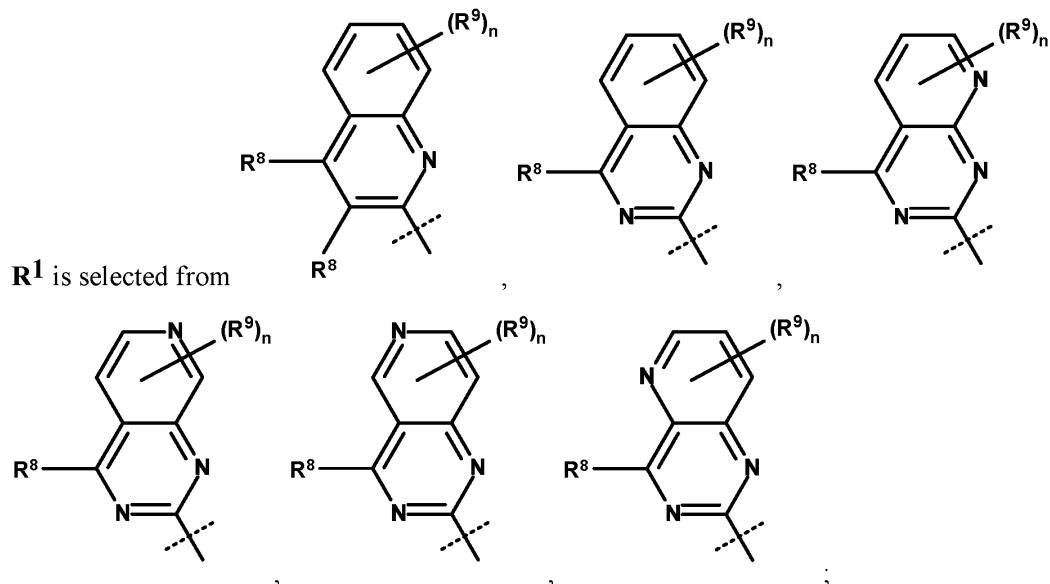
n is 0, 1 or 2;

p is 0, 1 or 2;

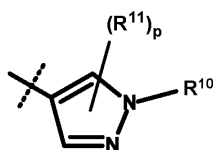
q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula (IA) wherein



R² is H;



R³ is selected from ;

R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

5 **R⁷** is selected from H, F, CH₃ or CN;

R⁸ is independently selected from H, CH₃ or OCH₃;

R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

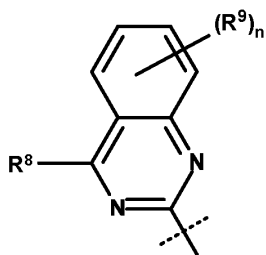
10 **m** is independently 0, 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

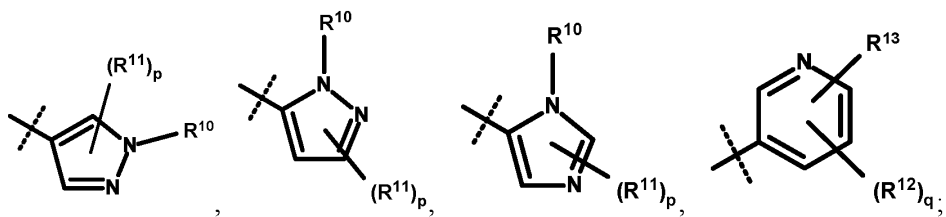
In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



15 **R¹** is selected from ;

R² is H;

R³ is selected from



R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

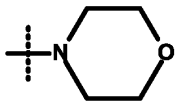
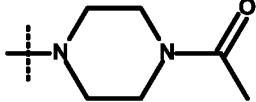
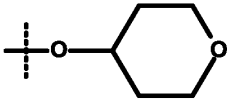
5 **R⁸** is selected from H, CH₃ or OCH₃;

R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

R¹² is independently selected from CH₃, OCH₃, CN or Cl;

10 **R¹³** is selected from H, , , or  ;

m is independently 0, 1 or 2;

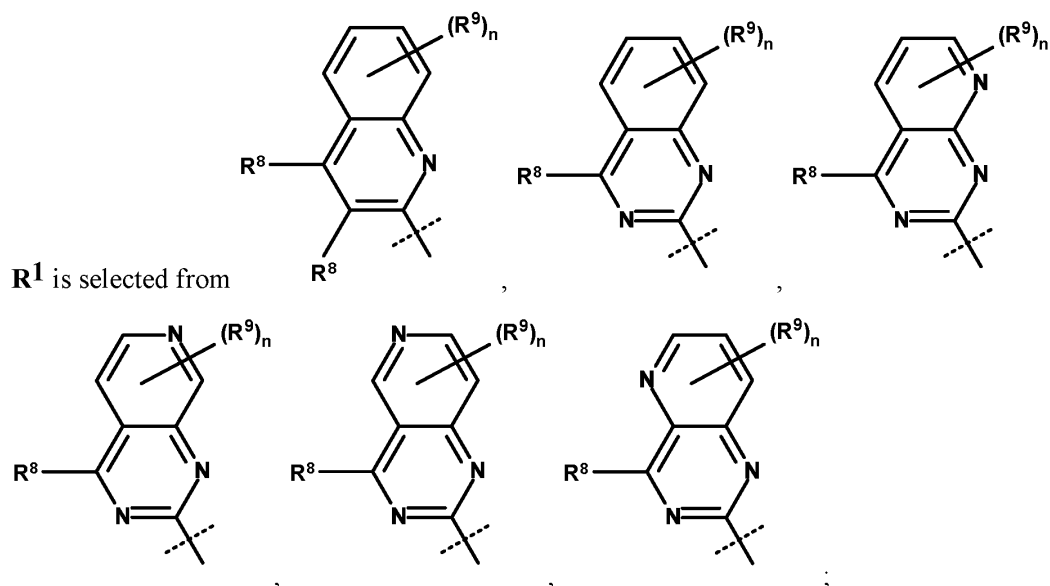
n is 0, 1 or 2;

p is 0, 1 or 2;

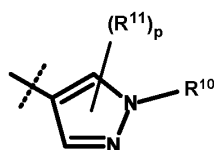
15 **q** is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula **(IA)** wherein



R² is H;



R³ is selected from

R⁴ is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

R⁸ is independently selected from H, CH₃ or OCH₃;

R⁹ is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

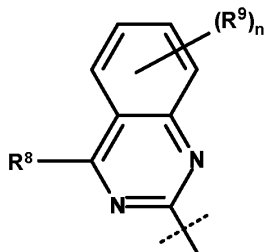
m is independently 0, 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

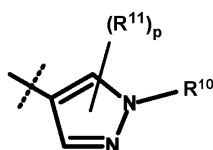
or a pharmaceutically acceptable salt thereof.

In still a further embodiment, there are provided compounds of Formula (IA) wherein



R¹ is selected from ;

R² is H;



R³ is selected from ;

5 **R⁴** is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F;

R⁵ is selected from F or OH;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, CH₃ or CN;

R⁸ is selected from H, CH₃ or OCH₃;

10 **R⁹** is independently selected from CH₃, OCH₃, CN, F or Cl;

R¹⁰ is selected from H or CH₃;

R¹¹ is independently selected from CH₃ or OCH₃;

m is independently 0, 1 or 2;

n is 0, 1 or 2;

15 **p** is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment the compound of Formula (I) is selected from:

2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinoline,

20 2-((4-(5-(4-isopropylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,

- 2-((4-(5-(4,6-dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine,
6-chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
8-fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
5 8-fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
6-methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine,
10 2-((4-(5-(4-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,
4-methyl-2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine,
4-methyl-2-((4-(5-(5-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine,
15 4-methyl-2-((4-(5-(2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine,
(3-(3-(1-((4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridin-4-yl)methanol,
20 2-((4-(5-(2-ethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,
2-((4-(5-(2,4-diethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,
3-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-8-methylbenzo[*e*][1,2,4]triazine,
25 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,
2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine,
30 2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine,

- 5-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1,8-naphthyridine,
4,7-dimethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine,
5 6-chloro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
5-chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4,6-dimethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
10 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline-6-carbonitrile,
6-methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,4-*d*]pyrimidine,
8-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
15 6-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
5-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
20 7-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
6-methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidine,
2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine,
25 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine,
4-(methoxy-*d*3)-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidine,
30 4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine,

- 6-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine,
1-ethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1*H*-benzo[*d*]imidazole,
5 *rac*-(*R*)-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine,
4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine,
2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
10 4-chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine,
4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine,
15 *rac*-4-methyl-2-(((2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
4-ethyl-2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6*H*-pyrano[3,4-*d*]pyrimidine,
20 4-ethyl-2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
2-((4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
25 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
30 2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,

- 4-ethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-ethyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
5 4-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine,
4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-
10 4-ol,
(3*R*,4*R*)-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-ol,
15 (3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
2-((4-fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-4-carbonitrile,
20 2-((4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
2-((4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
25 *rac*-4-methyl-2-(((2*R*,4*S*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
(1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-yl)methanol,
1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol,
30 (3*R*,4*R*)-4-(5-(1-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,

- (3*R*,4*R*)-4-(5'-Methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*R*)-4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
5 (3*S*,4*S*)-4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidin-1-yl)methyl)-4-methylquinazoline,
2-((4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-
10 4-methylquinazoline,
(3*R*,4*S*)-4-methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*S*)-4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
15 (3*R*,4*S*)-4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*S*)-4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*S*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
20 (3*R*,4*S*)-4-methoxy-4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*S*)-1-((5-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
25 (3*R*,4*S*)-1-((5-chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
(3*R*,4*S*)-1-((6-chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
(3*R*,4*S*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-
30 bipyrazol]-5-yl)piperidin-3-ol,
(3*S*,4*R*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,

- (3*R*,4*S*)-4-methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
(3*R*,4*S*)-4-(3',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol,
5 (3*R*,4*S*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol,
(3*R*,4*S*)-1-((8-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
(3*R*,4*S*)-1-((8-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
10 1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
rac-(3*R*,4*S*)-3-fluoro-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol,
rac-(3*R*,4*R*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol,
15 4-methyl-2-((4-(1',3',4,5'-tetramethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
1',3',5'-trimethyl-5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*,2*H*-[3,4'-bipyrazole]-4-carbonitrile,
N-methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridin-3-amine,
20 4-methyl-2-((4-(5-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(1-methyl-1*H*-indazol-7-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
25 4-methyl-2-((4-(5-(5-((tetrahydro-2*H*-pyran-4-yl)oxy)pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
1-(4-(5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridin-3-yl)piperazin-1-yl)ethan-1-one,
30 4-methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)nicotinonitrile,

- 4-(5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridin-3-yl)morpholine,
2-((4-(5-(5-methoxypyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
5 2-((4-(5-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
4-methyl-2-((4-(5-(5-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(5-(2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
10 4-methyl-2-((4-(5-(2-(trifluoromethyl)pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline.
2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
2-((4-(5-(4-(methoxymethyl)-2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-
15 4-methylquinazoline,
2-({4-[3-(4-ethyl-2-methylpyridin-3-yl)-1*H*-pyrazol-5-yl]piperidin-1-yl}methyl)-4-methylquinazoline,
2-((4-(5-(4,6-dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
20 2-((4-(5-(1,4-dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
4-methyl-2-((4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-5,6-dihydro-8*H*-
25 imidazo[2,1-*c*][1,4]oxazine,
3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine,
2-((4-(5-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
30 3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine,

- 7-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-2,3-dihydropyrazolo[5,1-*b*]oxazole,
3,5-dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)isoxazole,
5 4-methyl-2-((4-(5-(1,2,4-trimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline,
2-((4-(5-(1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
2,4-dimethyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)thiazole,
10 5-methyl-2-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-4-(trifluoromethyl)thiazole,
3,5-dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)isothiazole,
15 2-((4-(5-(4-ethyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
3,4-dimethyl-5-(5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-3-yl)isoxazole,
2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
20 methylquinazoline,
2-((4-(3',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
4-methyl-2-((4-(1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-
25 yl)methyl)quinazoline,
2-((4-(5'-cyclobutyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
2-((4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
30 4-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,

- 2-((4-(5'-(methoxymethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 2-((4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 5 2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 4-methyl-2-((4-(2',4',5'-trimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
- 2-((4-(4',5'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
- 10 methylquinazoline,
- 2-((4-(1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 15 2-((4-(5'-ethyl-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- 2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline,
- rac*-(3*R*,4*S*)-4-Ethyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-
- 20 bipyrazol]-5-yl)piperidin-3-ol,
- rac*-(3*R*,4*S*)-4-Methyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol and
- pharmaceutically acceptable salts thereof.

- 25 It shall be noted that any one of these specific compounds may be disclaimed from any of the herein mentioned embodiments.

In one embodiment there is provided a process for the preparation of compounds of Formula **(I)** or pharmaceutically acceptable salts of compounds of Formula **(I)**, and the intermediates used in the preparation thereof.

- 30 Another embodiment is a product obtainable by any of the processes or examples disclosed herein.

MEDICAL AND PHARMACEUTICAL USE

The compounds of Formula **(I)** and their pharmaceutically acceptable salts are useful because they possess pharmacological activity as inhibitors of the enzyme NNMT.

The compounds of Formula **(I)** and their pharmaceutically acceptable salts are indicated for
5 use in the treatment or prophylaxis of diseases or conditions in which modulation of the activity of the enzyme nicotinamide N-methyl transferase (NNMT) is desirable. In particular, linkage of NNMT activity to disease has been implicated in chronic kidney disease. Therefore the disclosed compounds are particularly indicated for use in the treatment of chronic kidney disease or kidney conditions or disorders in mammals including man. Further, the disclosed
10 compounds are particularly indicated for use in the treatment of acute kidney injury (AKI), diabetic kidney disease (DKD), heart failure (HF), cardiorenal syndrome (CRS), metabolic dysfunction-associated steatohepatitis (MASH) and arrhythmia conditions or disorders in mammals including man.

Conditions or disorders that may be specifically mentioned include diabetic kidney disease,
15 hypertensive nephropathy, rapidly progressive glomerulonephritis, systemic lupus erythematosus, IgA nephropathy, focal segmental glomerulosclerosis and acute kidney injury, coronary artery disease, acute coronary syndrome, heart failure, heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have
20 suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening or identified through specific biomarker pattern to be particularly susceptible to developing the disease or condition.

25 For the above-mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. The compounds of Formula **(I)**, and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent
30 or carrier. Thus, another aspect concerns a pharmaceutical composition comprising a novel compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not

limited to, enteral (including oral, sublingual or rectal), intranasal, inhalation, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, *Pharmaceuticals - The Science of Dosage Form Designs*, M. E. Aulton, Churchill Livingstone, 2nd Ed. 2002. The
5 pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention
10 or treatment of chronic kidney disease or kidney conditions or disorders in a mammal, particularly a human.

In a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of a condition where inhibition of NNMT would be beneficial.

15 In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of chronic kidney disease in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially
20 in the prevention or treatment of acute kidney injury in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of diabetic kidney disease in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a
25 pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of cardiorenal syndrome in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of heart failure in a mammal, particularly a human.

30 In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially

in the prevention or treatment of heart failure with reduced ejection fraction in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially
5 in the prevention or treatment of heart failure with preserved ejection fraction in a mammal, particularly a human.

In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of MASH in a mammal, particularly a human.

10 In still a further embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), for use in therapy, especially in the prevention or treatment of arrhythmia in a mammal, particularly a human.

In one embodiment there is provided a method of treating, or reducing the risk of, diseases or
15 conditions in which inhibition of the enzyme NNMT is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a further embodiment there is provided a method of treating, or reducing the risk of,
20 chronic kidney disease or kidney conditions or disorders, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of,
25 chronic kidney disease, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, acute kidney injury, in a person suffering from or at risk of, said disease or condition, wherein
30 the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, diabetic kidney disease, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

5 In still a further embodiment there is provided a method of treating, or reducing the risk of, cardiorenal syndrome, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of,
10 heart failure, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, heart failure with reduced ejection fraction, in a person suffering from or at risk of, said
15 disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, heart failure with preserved ejection fraction, in a person suffering from or at risk of, said
20 disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, MASH, in a person suffering from or at risk of, said disease or condition, wherein the method
25 comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further embodiment there is provided a method of treating, or reducing the risk of, arrhythmia, in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a
30 compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a pharmaceutical formulation comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically

acceptable salt of a compound of Formula (I), and a pharmaceutically acceptable diluent, excipient and/or inert carrier.

In a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
5 therapy, especially in the prevention or treatment of a condition where inhibition of NNMT would be beneficial.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
10 therapy, especially in the prevention or treatment of chronic kidney disease in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
15 therapy, especially in the prevention or treatment of acute kidney injury in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
20 therapy, especially in the prevention or treatment of diabetic kidney disease in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
25 therapy, especially in the prevention or treatment of heart failure in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in
30 therapy, especially in the prevention or treatment of heart failure with reduced ejection fraction in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in therapy, especially in the prevention or treatment of heart failure with preserved ejection fraction in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in therapy, especially in the prevention or treatment of MASH in a mammal, particularly a human.

In still a further embodiment there is provided a pharmaceutical formulation comprising a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in therapy, especially in the prevention or treatment of arrhythmia in a mammal, particularly a human.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

The compounds of Formula (I) herein exemplified, when tested in an NNMT cellular assay, for example Test A described below, preferably with an IC₅₀ less than 50 μ M. The compounds of Formula (I) also display a promising pharmacological profiles by separating desired and undesired effects *in vivo*.

These and other embodiments are described in greater detail herein below, where further aspects will be apparent to one skilled in the art from reading this specification.

PHARMACOLOGICAL PROPERTIES

The compounds of Formula (I) or pharmaceutically acceptable salts thereof are believed to be useful in the prevention or treatment of chronic kidney disease or kidney conditions or disorders, acute kidney injury, heart failure, heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, cardiorenal syndrome, metabolic dysfunction-associated steatohepatitis and arrhythmia conditions or disorders in a mammal, particularly a human.

For the avoidance of doubt, as used herein, the term “treatment” includes therapeutic and/or prophylactic treatment.

When a compound or salt described herein is administered as therapy for treating a disorder, a “therapeutically effective amount” is an amount sufficient to reduce or completely alleviate
5 symptoms or other detrimental effects of the disorder, cure the disorder, reverse, completely stop, or slow the progress of the disorder or reduce the risk of the disorder getting worse.

The compounds described herein are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions.

The compounds described herein have the advantage that they may be more efficacious, be
10 less toxic, be more selective, be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than compounds known in the prior art.

COMBINATION THERAPY

15 The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, may also be administered in conjunction with other compounds used for the treatment of the above conditions.

In another embodiment, there is a combination therapy wherein a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a second active ingredient are administered
20 concurrently, sequentially or in admixture, for the treatment of one or more of the conditions listed above. Such a combination may be used in combination with one or more further active ingredients.

Compounds described herein may be of use in treating cardiovascular, metabolic and renal disease in combination with agents that are angiotensin converting enzyme inhibitors,
25 angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, glucagon-like peptide-1 modulators or endothelin receptor antagonists.

When used in a combination therapy, it is contemplated that the compounds of Formula (I) or pharmaceutically acceptable salts thereof and the other active ingredients may be
30 administered in a single composition, completely separate compositions, or a combination thereof. It also is contemplated that the active ingredients may be administered concurrently, simultaneously, sequentially, or separately. The particular composition(s) and dosing

frequency(ies) of the combination therapy will depend on a variety of factors, including, for example, the route of administration, the condition being treated, the species of the patient, any potential interactions between the active ingredients when combined into a single composition, any interactions between the active ingredients when they are administered to
5 the animal patient, and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

PHARMACEUTICAL COMPOSITIONS

There is provided a method of treatment of a condition where inhibition of NNMT is required,
10 which method comprises administration of a therapeutically effective amount of a compound of Formula (I) to a person suffering from, or susceptible to, such a condition.

The compounds of Formula (I) will normally be administered via the oral, topical, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical
15 preparations comprising the active ingredient or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, *Pharmaceuticals - The Science of Dosage Form*
20 *Designs*, M. E. Aulton, Churchill Livingstone, 2nd Ed. 2002.

Suitable daily doses of the compounds of Formula (I) in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight.

Oral formulations are preferred, particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the
25 range of 0.007 mg to 700 mg.

The optimum dosage and frequency of administration will depend on the particular condition being treated and its severity; the species of the patient; the age, sex, size and weight, diet, and general physical condition of the particular patient; brain/body weight ratio; other medication the patient may be taking; the route of administration; the formulation; and various other
30 factors known to physicians and others skilled in the art.

According to a further aspect there is thus provided a pharmaceutical formulation comprising a compound of Formula (I), or pharmaceutically acceptable derivatives thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

The compounds of Formula (I) may be present in the pharmaceutical formulation in a
5 concentration from 0.1 to 99.5%, such as from 0.5 to 95%, by weight of the total formulation.

PREPARATION OF THE COMPOUNDS

It will be appreciated by those skilled in the art that in the processes certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting
10 groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in *Protective Groups in Organic Synthesis*, 4th Ed, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (2006) and *Protecting Groups*, 3rd Ed, P.J. Kocienski, Georg Thieme Verlag (2005).

15 The skilled person will recognize that at any stage of the preparation of the compounds of Formula (I), mixtures of isomers (e.g. racemates) of compounds may be utilized. At any stage of the preparation, a single stereoisomer may be obtained by isolating it from a mixture of isomers (e.g., a racemate) using, for example, chiral chromatographic separation.

A further embodiment encompasses pharmaceutically acceptable salts of the compounds of
20 Formula (I).

A salt of a compound of Formula (I) may be advantageous due to one or more of its chemical or physical properties, such as stability in differing temperatures and humidities, or a desirable solubility in H₂O, oil, or other solvent. In some instances, a salt may be used to aid in the isolation or purification of the compound. In some embodiments (particularly where the salt is
25 intended for administration to an animal, e.g. a human, or is a reagent for use in making a compound or salt intended for administration to an animal), the salt is pharmaceutically acceptable.

The term "pharmaceutically acceptable" is used to characterize a moiety (e.g. a salt, dosage form, or excipient) as being appropriate for use in accordance with sound medical judgment.

30 In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any

deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

Where the compound is sufficiently basic, pharmaceutically acceptable salts include, but are not limited to, inorganic or organic acid addition salts.

- 5 For reviews on suitable salts, see Berge *et al.*, *J. Pharm. Sci.*, **1977**, *66*, 1-19 or *Handbook of Pharmaceutical Salts: Properties, selection and use*, P.H. Stahl, P.G. Vermuth, IUPAC, Wiley-VCH, **2002**.

Where an acid co-former is a solid at r.t. and there is no or only partial proton transfer between the compound of Formula **(I)** and such an acid co-former, a co-crystal of the co-
10 former and compound of Formula **(I)** may result rather than a salt. All such co-crystal forms of the compound of Formula **(I)** are encompassed herein.

It is also to be understood that certain compounds of Formula **(I)** may exist in solvated form, e.g. hydrates, including solvates of a pharmaceutically acceptable salt of a compound of Formula **(I)**.

- 15 In a further embodiment, certain compounds of Formula **(I)** may exist as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. Certain compounds of Formula **(I)** may also contain linkages (e.g. carbon-carbon bonds, carbon-nitrogen bonds such as amide bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring bond or double bond.

- 20 Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallization, or the stereoisomers may be made by stereoselective synthesis.

In a further embodiment, the compounds of Formula **(I)** encompass any isotopically-labelled (or "radio-labelled") derivatives of a compound of Formula **(I)**. Such a derivative is a derivative of a compound of Formula **(I)** wherein one or more atoms are replaced by an atom
25 having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that may be incorporated include ²H (also written as "D" for deuterium).

In a further embodiment, the compounds of Formula **(I)** may also contain various tautomeric forms. It is to be understood that all such tautomeric forms are encompassed.

- 30 In a further embodiment, the compounds of Formula **(I)** may be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the Formula **(I)**.

Various forms of prodrugs are known in the art. For examples of prodrug derivatives, see: *Nature Reviews Drug Discovery* **2008**, 7, 255 and references cited therein.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

5 PHARMACOLOGICAL ACTIVITY

The pharmacological activity of compounds disclosed herein was tested in the following screen (Test A).

Test A - Cellular assay of human NNMT in RPTEC/TERT1 cells

Cryopreserved RPTEC/TERT1 cells (CRL-4031 from ATCC) endogenously expressing
10 human NNMT were thawed, centrifuged and diluted into cell media (DMEM/F-12 + GlutaMAX-I (Gibco 31331-028), containing 0.1 mg/ml Genectin (Gibco, 10131027)). The cell suspension was dispensed to 384-well microplates (Corning 3764) containing compounds dissolved in DMSO, using a Multidrop Combi (ThermoFisher; 8000 cells per well, final assay volume 30 μ l, 0.3% final DMSO). The microplates were incubated in a cell incubator (37 °C
15 in humidified 5% CO₂/air atmosphere). After 24 h the cell media was removed and cells were washed with PBS using a BlueWasher (BlueCatBio GmbH, Germany), followed by addition of 20 μ l water (Multidrop Combi) and freezing on dry ice. Plates were stored at -20 °C until sample preparation for the LC-MS analysis. Cellular NNMT activity was determined measuring 1-MNA (1-methylnicotinamide) levels using a LC-MS detection system. Frozen
20 cell lysates were thawed and diluted into methanol/acetonitrile (50/50) containing 1-MNA-D3 (M323237, TRC, Toronto, Canada) and centrifuged at 2600 g for 30 minutes prior to sampling in the API 5000 LC/MS/MS system with Qjet (Applied biosystems; sample volume of 10 μ l, Phase A: 5mM acetic acid / 0.2% formic acid, Phase B: acetonitrile; Column: Xbridge amide 3.5 mm 2.1 x 50 mm column, Waters / Bridge 186004859). 1-MNA levels
25 were quantified as the area under the curve of the 1-MNA peak and normalized using 1-MNA-D3. Data processing, assay quality control and concentration response curve fitting was analyzed using Genedata Screener (Basel, Switzerland). Compound potencies were determined from 10-point concentration response curves using 3-fold dilution steps, with a final assay concentration ranging from 30 mM down to 15 nM. The Z'-factor was between
30 0.5-0.8.

The IC₅₀ values (NNMT) for the Example compounds are set forth in **Table 1** herein below.

Table 1

Ex. No.	NNMT Cell IC ₅₀ (μM)	Ex. No.	NNMT Cell IC ₅₀ (μM)
1		73	0.007
2	0.106	74	0.006
3	0.274	75	0.007
4	0.269	76	0.005
5	0.053	77	0.005
6	0.016	78	0.012
7	0.023	79	0.010
8	0.295	80	0.005
9	0.011	81	0.006
10	0.016	82	0.007
11	0.343	83	0.009
12	0.094	84	0.696
13	0.328	85	
14	0.339	86	0.085
15		87	0.056
16	0.016	88	0.015
17	0.038	89	0.009
18	0.088	90	0.684
19	0.073	91	0.062
20	0.055	92	0.051
21	0.064	93	0.021
22	0.007	94	0.276
23	0.293	95	0.692
24	0.009	96	0.188
25	0.006	97	0.210
26	0.256	98	0.031

27	0.009	99	0.582
28	0.004	100	0.158
29	0.005	101	0.090
30	0.011	102	0.206
31	0.008	103	0.136
32	0.061	104	0.071
33	0.035	105	0.010
34	0.150	106	0.070
35	0.316	107	0.039
36	0.038	108	
37	0.126	109	0.016
38	0.050	110	0.062
39	0.198	111	0.031
40	0.156	112	0.035
41	0.047	113	0.188
42	0.078	114	0.010
43	0.036	115	0.015
44	0.282	116	0.101
45	0.022	117	0.059
46	0.406	118	0.113
47	0.019	119	0.159
48	0.023	120	0.188
49	0.080	121	0.075
50	0.039	122	0.015
51	0.064	123	0.048
52	0.024	124	0.529
53	0.049	125	0.011
54	0.076	126	0.745
55	0.011	127	0.136
56	0.043	128	0.006
57	0.063	129	0.189

58	0.089	130	0.294
59	0.074	131	0.011
60	0.100	132	0.011
61	0.074	133	0.012
62	0.044	134	0.011
63	0.009	135	0.017
64	0.005	136	0.008
65	0.006	137	0.007
66	0.632	138	0.007
67	0.073	139	0.040
68	0.063	140	0.110
69	0.022	141	0.019
70	0.028	142	0.009
71	0.818	143	0.008
72	0.009	144	0.021
		145	0.016

EXAMPLES

The following examples are non-limiting examples.

5

GENERAL CONDITIONS

- (i) operations were carried out at room temperature (rt), *i.e.* in the range 17 to 25 °C and under an atmosphere of an inert gas such as N₂(g) unless otherwise stated; optionally reactions were carried out using a MBRAUN UNILab Plus ECO or a MBRAUN UNILab SP Eco glovebox workstation or a KitAlysis™ Benchtop Inertion Box from Sigma-Aldrich, in which case it is indicated;
- (ii) where reactions refer to being degassed or purged, this can be performed for example by purging the reaction solvent with a constant flow of nitrogen for a suitable period of time (for example 5 to 10 min) or by repeatedly evacuating the vessel and backfill with appropriate inert atmosphere (for example nitrogen (g) or argon (g));
- 10
- 15

- (iii) where reactions refer to the use of a microwave reactor, one of the following microwave reactors were used: Biotage Initiator, Personal Chemistry Emrys Optimizer, Personal Chemistry Smith Creator or CEM Explorer;
- (iv) where reactions refer to the use of irradiation with LED a commercial, standardized
- 5 EvoluChem™ PhotoRedOx Box Photoreactor from HepatoChem equipped with a Kessil H150 blue LED (456 nm, 34W) or a commercial standardized Photoreactor m2 from Penn Photon Devices equipped with a LED module (365 nm) were used, photochemistry
- (v) where reactions refer to the use of flow chemistry it was performed by administering the components using syringe pumps into a 6.8 mL PFA coil reactor (o.d. 3.2 mm) at rt, unless
- 10 otherwise stated, and at a flow rate of the components as indicated in the description
- (vi) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high performance liquid chromatography (HPLC or UPLC) which was usually coupled to a mass spectrometer (LCMS).
- (vii) when necessary, organic solutions were dried over anhydrous MgSO_4 or Na_2SO_4 , or by
- 15 using ISOLUTE® Phase Separator, and work-up procedures were carried out using traditional phase separating techniques. When a drying agent such as e.g. MgSO_4 or Na_2SO_4 is used for drying an organic layer, it is understood that said organic layer is filtered before concentration of said layer.
- (viii) It is understood that washing solutions used in the work-up procedures or reagent used
- 20 for acidifying such as e.g. Brine, NaHCO_3 , NH_4Cl , HCl , NaH_2PO_4 are presumed to be aqueous solutions unless otherwise stated
- (ix), evaporations were carried out either by rotary evaporation *in vacuo* or in a Genevac HT-4 / EZ-2 or Biotage V10;
- (x) unless otherwise stated, flash column chromatography was performed on straight phase
- 25 silica, using either Merck Silica Gel (Art. 9385) or prep-packed cartridges such as Biotage® SNAP cartridges (40–63 μm silica, 4–330 g), Biotage® Sfär Silica HC D cartridges (20 μm , 10–100 g), Interchim puriFlash™ cartridges (25 μm , 4–120 g), Interchim puriFlash™ cartridges (50 μm , 25–330 g), Grace™ GraceResolv™ Silica Flash Cartridges (4–120 g) or Agela Flash Colum Silica-CS cartridges (80–330 g), or on reversed phase silica using Agela
- 30 Technologies C-18, spherical cartridges (20–35 μm , 100A, 80–330g), manually or automated using a Grace Reveleris® X2 Flash system or similar system;

(xi) preparative reverse phase HPLC and preparative reverse phase SFC were performed using standard HPLC and SFC instruments, respectively, equipped with either a MS and/or UV triggered fraction collecting instrument, using either isocratic or a gradient of the mobile phase as described in the experimental section, and one of the following methods as described below; **PrepMethod A**; The compound was purified by preparative HPLC on a Kromasil C8 column (10 μ m, 250 $\times$ 20 mm ID) using a gradient of MeCN in H₂O/MeCN/FA (95/5/0.2) as mobile phase; **PrepMethod B**; The compound was purified by preparative HPLC-MS on a XBridge™ C18 ODB column (5 μ m, 100 $\times$ 10 mm ID) using a gradient of MeCN in NH₃/H₂O (0.2%, pH10) as mobile phase; **PrepMethod C**; The compound was purified by preparative SFC on a Waters™ BEH, (5 μ m, 250 $\times$ 30 mm ID) using MeOH/H₂O (NH₃ 50 mM) (97/3) in CO₂ as mobile phase; **PrepMethod D**; The compound was purified by preparative HPLC on a XBridge™ C18 column (10 μ m, 250 $\times$ 19 mm ID) using a gradient of MeCN in H₂O/MeCN/NH₃ (95/5/0.2) as mobile phase; **PrepMethod E**; The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 μ m, 150 $\times$ 30 mm ID) using a gradient of MeCN in H₂O/ /NH₄HCO₃ (10 mM) as mobile phase; **PrepMethod F**; The compound was purified by preparative HPLC on a XBridge™ C18 column (10 μ m, 250 $\times$ 50 mm ID) using a gradient of MeCN in H₂O/MeCN/NH₃ (95/5/0.2) as mobile phase; **PrepMethod G**; The compound was purified by preparative HPLC on a Kromasil C8 column (10 μ m, 250 $\times$ 50 mm ID) using a gradient of MeCN in H₂O/MeCN/FA (95/5/0.2) as mobile phase; **PrepMethod H**; The compound was purified by preparative HPLC on a Waters™ Sunfire™ C18 OBD column (5 μ m, 150 $\times$ 30 mm ID) using a gradient of MeCN in H₂O/FA (0.1%) as mobile phase; **PrepMethod I**; The compound was purified by preparative HPLC on a Xbridge™ C18 ODB column (5 μ m, 150 $\times$ 19 mm ID) using a gradient of MeCN in a H₂O/NH₃ (0.2%, pH 10) buffer system as mobile phase; **PrepMethod J**; The compound was purified by preparative HPLC on a Waters™ Sunfire™ C18 OBD column (5 μ m, 150 $\times$ 30 mm ID) using a gradient of MeCN in H₂O/FA (0.1 M) as mobile phase; **PrepMethod K**; The compound was purified by preparative HPLC on a Waters™ Sunfire™ C18 OBD column (5 μ m, 150 $\times$ 19 mm ID) using a gradient of MeCN in H₂O/FA (0.1 M) as mobile phase; **PrepMethod L**; The compound was purified by preparative SFC on a Phenomenex Luna® HILIC column (5 μ m, 250 $\times$ 30 mm ID) using MeOH/NH₃ (20 mM) in CO₂ as mobile phase; **PrepMethod N**; The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 μ m, 150 $\times$ 30 mm ID) using a gradient of MeCN in a H₂O/NH₄HCO₃ (10 mM)/NH₃ (0.1%, aq)

buffer system as mobile phase; **PrepMethod O**; The compound was purified by preparative SFC on a Waters™ BEH 2-EP, (5 µm, 250×30 mm ID) using MeOH/NH₃ (20 mM) in CO₂ as mobile phase; **PrepMethod P**; The compound was purified by preparative HPLC on a XBridge™ Shield C18 column (5 µm, 150×30 mm ID) using a gradient of MeCN in a

5 H₂O/NH₄CO₃ (10 mM)/NH₃ (0.1%, aq) buffer system as mobile phase; **PrepMethod Q**; The compound was purified by preparative HPLC on a YMC-Actus Triart C18 ExRS column (5 µm, 150×30 mm ID) using a gradient of MeCN in H₂O/NH₄HCO₃ (10 mM) as mobile phase; **PrepMethod R**; The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 150×19 mm ID) using a gradient of MeCN in H₂O/NH₄HCO₃ (0.1 M) as

10 mobile phase; **PrepMethod T**; The compound was purified by preparative HPLC on a XBridge™ C18 column (5 µm, 150×25 mm ID) using a gradient of MeCN in H₂O/NH₄HCO₃ (0.01 M) as mobile phase; **PrepMethod U**; The compound was purified by preparative SFC on a Waters™ Acquity UPC2 BEH, (3.5 µm, 100×3 mm ID) using MeOH/H₂O/NH₃ 97/3/50 mM in CO₂ as mobile phase; **PrepMethod V**; The compound was purified by preparative SFC

15 on a SuperSep 1, Viridis 2-EP column (5 µm, 250×30) using MeOH/NH₃ (100/20 mM) in CO₂ as mobile phase; **PrepMethod W**; The compound was purified by preparative HPLC on a Water Atlantis T3 C18 OBD column (5 µm, 150×19 mm ID) using a gradient of MeCN in H₂O/FA (0.1 M) as mobile phase; **PrepMethod X**; The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 150×19 mm ID) using a gradient

20 of MeCN in a H₂O/NH₄HCO₃ (0.01 M) buffer system as mobile phase; **PrepMethod Y**; The compound was purified by preparative SFC on a Waters™ BEH, (5 µm, 250×30 mm ID) using MeOH/NH₃ (20 mM) in CO₂ as mobile phase; **PrepMethod Z**; The compound was purified by preparative SFC on a Kromasil DIOL, (5 µm, 50 x 30 mm ID) using EtOH/NH₃ (100/20 mM) in CO₂ as mobile phase; **PrepMethod CC**; The compound was purified by

25 preparative HPLC on a XBridge™ C18 column (10 µm, 250×19 mm ID) using a gradient of MeCN in a H₂O/MeCN/NH₄HCO₃ (95/5/10 mM) buffer system as mobile phase.

PrepMethod DD; The compound was purified by preparative SFC on a Kromasil CN, (5 µm, 250 x 30 mm ID) using EtOH/DEA (100/20 mM) in CO₂ as mobile phase. **PrepMethod EE**; The compound was purified by preparative HPLC on a Waters Atlantis T3 C18 OBD column

30 (5 µm, 150×19 mm ID) using a gradient of MeCN in H₂O/TFA (0.15 M) as mobile phase.

PrepMethod FF; The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 150×19 mm ID) using a gradient of MeCN in a H₂O/MeCN/TFA

(95/5/150 mM) buffer system as mobile phase. **PrepMethod GG;** The compound was purified by preparative HPLC on a Waters XSelect CSH Fluoro Phenyl OBD column (5 μ m, 150 $\times$ 19 mm ID) using a gradient of MeCN in H₂O/TFA (0.15 M) as mobile phase;

PrepMethod HH; The compound was purified by preparative HPLC on a XBridge™ C18

5 OBD column (5 μ m, 150 $\times$ 19 mm ID) using a gradient of MeCN in a H₂O/NH₄HCO₃ (10 mM)/NH₃ (0.1%, aq) buffer system as mobile phase. **PrepMethod II;** The compound was purified by preparative HPLC on a YMC-Actus Triart C18 ExRS column (5 μ m, 150 $\times$ 30 mm ID) using a gradient of MeCN in a H₂O/NH₄HCO₃ (10 mM)/NH₃ (0.1%, aq) buffer system as mobile phase. **PrepMethod JJ;** The compound was purified by preparative HPLC on a

10 XBridge™ C18 column (10 μ m, 250 $\times$ 50 mm ID) using a gradient of MeCN in H₂O/MeCN/NH₄HCO₃ (95/5/10 mM) as mobile phase; **PrepMethod NN;** The compound was purified by preparative SFC on a Kromasil XT, (10 μ m, 250 x 50 mm ID) using MeOH/NH₃ (100/20 mM) in CO₂ as mobile phase. **PrepMethod OO;** The compound was purified by preparative HPLC on a Kromasil C8 column (10 μ m, 250 $\times$ 50 mm ID) using a
15 gradient of MeCN in a H₂O/MeCN/AcOH (95/5/0.2) buffer buffer system as mobile phase.

PrepMethod PP; The compound was purified by preparative HPLC on a Kromasil C8 column (10 μ m, 250 $\times$ 20 mm ID) using a gradient of MeCN in a H₂O/MeCN/AcOH (95/5/0.2) buffer system as mobile phase.

PrepMethod QQ; The compound was purified by preparative HPLC on a Xbridge BEH C18
20 column (5 μ m, 100 $\times$ 10 mm ID) using a gradient of MeCN in a H₂O as mobile phase.

Relevant fractions were collected, combined and freeze-dried to give the purified compound or relevant fractions were collected, combined and concentrated at reduced pressure, extracted with DCM or EtOAc, and the organic phase was dried either over Na₂SO₄ or by using a phase-separator, and then concentrated at reduced pressure to give the purified compound.

25 (xii) chiral preparative chromatography was carried out using HPLC or SFC on a standard HPLC or SFC instruments, respectively, and using either isocratic or gradient run with mobile phase as described in the experimental section;

(xiii) yields, where present, are not necessarily the maximum attainable, and when necessary, reactions were repeated if a larger amount of the reaction product was required;

30 (xiv) where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the

number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(xv) in general, the structures of the end-products of the Formula **(I)** were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; proton NMR chemical shift values were measured on the delta scale using Bruker Avance III 300, 400, 500 and 600 spectrometers, operating at ¹H frequencies of 300, 400, 500 and 600 MHz, respectively. The experiments were typically recorded at 25 °C. Chemical shifts are given in ppm with the solvent as internal standard. Protons on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therefore be missing. In certain instances, protons can be masked or partially masked by solvent peaks and will therefore either be missing and not reported or reported as multiplets overlapping with solvent. The following abbreviations have been used (and derivatives thereof, e.g. dd, doublet of doublets, ddd, doublet of doublet of doublets, dt, doublet of triplets, dq, doublet of quartet etc.): s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; qn, quintet; p, pentet; h, heptet. It is understood, where the NMR spectra contains residual impurities and/or residual solvent(s), this is not reported unless it coincides or partially coincides with peaks of Intermediates and/or structures of Formula **(I)**, in which case they are reported as multiplets, partially overlapping with said solvent or impurity and the integral is omitted. In some cases, the structures of the end-products of the Formula **(I)** might appear as rotamers in the NMR-spectrum, in which instances only peaks of the major rotamer are reported. In some cases, the structures of the end-products of Formula **(I)** might appear as rotamers in more equal portions, in such instances the peaks of such rotamers are either reported as multiplets, if the signals of said rotamers are partially overlapping, or as individual peaks, if the signals of said rotamers are well separated. Electrospray mass spectral data were obtained using a Waters Acquity UPLC coupled to a Waters single quadrupole mass spectrometer or similar equipment, acquiring both positive and negative ion data, and generally, only ions relating to the parent structure are reported; high resolution electrospray mass spectral data were obtained using a Waters XEVO qToF mass spectrometer or similar equipment, coupled to a Waters Acquity UPLC, acquiring either positive and negative ion data, and generally, only ions relating to the parent structure are reported

(xvi) intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC/UPLC, and/or NMR analysis and/or mass spectrometry;

(xvii) unless stated otherwise compounds containing an asymmetric carbon and/or sulfur atom were not resolved;

(xviii) in general Examples and Intermediate compounds are named using ChemDraw Professional version 22.2.0 from PerkinElmer. ChemDraw Professional version 22.2.0

- 5 generates the names of chemical structures using the Cahn-Ingold-Prelog (CIP) rules for stereochemistry and follows IUPAC rules as closely as possible when generating chemical names. Stereoisomers are differentiated from each other by stereodescriptors cited in names and assigned in accordance with the CIP rules.

ChemDraw is optionally using labels in the graphical representation of stereocenters such as
10 '**&**' and '**or**' to describe the configuration of the stereochemical centers present in the structure.

A number following the '**&**' and '**or**' flag is assigned to each stereocenter present in the structure. The numbers are incremented automatically to indicate that stereocenters may vary independently to each other.

- 15 In general, for chemical structures of Examples and Intermediates where more than one stereocenter is present and said stereocenters have a fixed relative configuration, the same number is used after the label '**&**' and '**or**' to indicate that said stereocenters forms a group. A third stereocenter present in the same chemical structure, that varies independently to the former stereocenters, is designated with a unique new number following the label '**&**' and '**or**'.
- 20 In general, chemical structures of Examples and Intermediates containing the label '**&**' at a stereocenter, means the configuration of such Example or Intermediate at that stereocenter is a mixture of both (**R**) and (**S**); and a label '**or**' means the configuration of such Example or Intermediate at that stereocenter is either (**S**) or (**R**). Absolute, unspecified, '**&**', and '**or**' stereocenters can all be present in a single structure.
- 25 In general, for structures of Examples and Intermediates, where all of the stereocenters are designated as '**&**', the structure is named with a "rac-" prefix. For structures of Examples and Intermediates, where all of the stereocenters are designated as '**or**', the structure is named with a "**rel-**" prefix.
- In general Examples and Intermediate compounds are named using the descriptors (**RS**) and
30 (**SR**) to denote general '**&**' centers for chemical structures with multiple chiral centers where only some are designated as '**&**'. The descriptors (**R***) and (**S***) are used to denote the general

'or' centers for chemical structures with multiple chiral centers where only some are designated as 'or'.

In general Examples and Intermediate compounds containing stereocenters having a relationship that is either cis or trans, are named using the descriptors (*RS*, *SR*) or (*RS*, *RS*),
 5 to denote chemical structures with multiple chiral centers where only some are designated as '&'.

In general, for structures of Examples and Intermediates where all stereocenters present are racemic, no flag is designated to the stereocenter(s) and the structure is drawn with straight bond(s) at each stereocenter.

10 In general, for structures of Examples and Intermediates where two or more stereocenters are present in a ring and fixed to each other and do not vary independently of each other, e.g. are cis or trans to each other, said stereocenters are drawn with stereobonds representing their internal relationship. Said stereocenters are labelled with an "&1" flag representing a mixture of cis-configuration or a mixture of trans-configuration, or an "or1" flag representing a single
 15 cis-isomer or a single trans-isomer with unknown absolute stereochemistry. In general, should the structure of said Example or Intermediate further contain one or more stereocenters that are racemic and not fixed in relation to the former stereocenters, said stereocenter(s) is drawn with straight bond(s) at said stereocenters.

In general the descriptors (*r*) and (*s*) are used to describe the absolute configuration of any
 20 pseudoasymmetric centers in the structures of Examples and Intermediates.

In general the label "Isomer 1" corresponds to the first eluted isomer, and "Isomer 2" corresponds to the second eluted isomer, on a given chiral HPLC column and eluent, and are used to distinguish two isomers containing one or more stereocenters with absolute unknown configuration;

25 (xix) in addition to the ones mentioned above, the following abbreviations and units have been used:

1 <i>R</i> -(-)-CSA	(1 <i>R</i>)-(-)-camphor-10-sulfonic acid	LC	liquid chromatography
4-CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene	LCMS	liquid chromatography Mass spectrometry
Abs	absolute	LED	light emitting diode
Ac	acetyl	mCPBA	3-chloroperbenzoic acid

AcOH	acetic acid	Me	CH ₃
Ac ₂ O	acetic anhydride	MeCN	acetonitrile
AlMe ₃	aluminum trimethanide	MeOH	methanol
A-Phos	(4-(<i>N,N</i> -dimethylamino)phenyl) di- <i>tert</i> -butyl phosphine	MS	mass spectrometry
Aq	aqueous	MsCl	mesyl chloride
BF ₃ •OEt ₂	boron trifluoride diethyl etherate	MTBE	methyl <i>tert</i> -butyl ether
BMS	borane dimethyl sulfide complex	m/z	mass spectrometry peak(s)
Boc	<i>tert</i> -butoxycarbonyl	NaHMDS	sodium bis(trimethylsilyl)amide
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate	NaOMe	sodium methoxide
Brine	sat aq NaCl solution	NBS	<i>N</i> -bromosuccinimide
<i>t</i> Bu	<i>tert</i> -butyl	NCS	<i>N</i> -chlorosuccinimide
<i>n</i> -BuLi	1-butyllithium	NaH	sodium hydride
Calcd	calculated	NH ₄ OAc	ammonium acetate
CDI	1,1'-carbonyldiimidazole	NIS	1-iodopyrrolidine-2,5-dione
CSA	(1 <i>S</i>)-(+)-camphorsulfonic acid	NMM	4-methylmorpholine
d	day	NMR	nuclear magnetic resonance
DAST	<i>N,N</i> -diethyl-1,1,1-trifluoro- <i>l</i> ⁴ -sulfanamine	OTf	triflate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Oxone	potassium peroxydisulfate
DCM	dichloromethane	Pd ₂ dba ₃	tris(dibenzylideneacetone)dipalladium(0)
DEA	diethylamine	Pd(dtbpf)Cl ₂	[1,1'-bis(di- <i>tert</i> -butylphosphino)ferrocene]dichloropalladium(II)
D-Epoxy	2,2,5',5'-tetramethyl-tetrahydro-2 <i>H</i> -spiro[[1,3]dioxolo[4,5- <i>c</i>]pyran-6,2'-[1,4]dioxolan]-7-one	Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

DIAD	diisopropyl azodicarboxylate	Pd(OAc) ₂	palladium(II) acetate
DIBAL	diisobutylaluminium hydride	Pd(PPh ₃) ₄	Palladium-tetrakis(triphenylphosphine)
DIC	diisopropylmethanediimine	Pd(PPh ₃) ₂ Cl ₂	bis(triphenylphosphine)palladium chloride
DIPE	diisopropyl ether	PE	petroleum ether
DIPEA	<i>N</i> -ethyl- <i>N</i> -isopropylpropan-2-amine	Ph	phenyl
DMA	<i>N,N</i> -dimethylacetamide	PPh ₃	triphenylphosphine
DMAP	<i>N,N</i> -dimethylpyridin-4-amine	Rochelle salt	potassium sodium tartrate
DMC	2-chloro-1,3-dimethylimidazolinium chloride	rt	room temperature
DME	dimethoxyethane	(s)	solid
DMF	<i>N,N</i> -dimethylformamide	sat	saturated
DMSO	dimethyl sulfoxide	SELECTFLUOR	(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
EDTA-Na ₂	ethylenediaminetetraacetic acid disodium salt	SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
eq	equivalent	SFC	supercritical fluid chromatography
ESI	electrospray ionization	SILIAMETS Imidazole	CAS no 2785331-52-2
Et ₂ O	diethyl ether	S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
EtOAc	ethyl acetate	TBDMSCl	<i>tert</i> -butylchlorodimethylsilane
EtOH	ethanol	TBDPSCl	<i>tert</i> -butyldiphenylchlorosilane
FA	formic acid	tBuXPhos Pd G3	(2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate, CAS No. 1447963-75-8
(g)	gas	TEA	triethylamine
G3	generation 3	TFA	trifluoroacetic acid
HPLC	high performance liquid chromatography	THF	tetrahydrofuran

ID	inner diameter	TMEDA	<i>N</i> ¹ , <i>N</i> ¹ , <i>N</i> ² , <i>N</i> ² -tetramethylethane-1,2-diamine
IPA	2-propyl alcohol	TLC	thin layer chromatography
iPr	isopropyl	TMS	trimethylsilyl
IPrOAc	isopropyl acetate	TsCl	<i>p</i> -toluenesulfonyl chloride
HOAc	acetic acid	TsOH	4-methylbenzenesulfonic acid
HRMS	high resolution mass spectrometry	UPLC	ultra performance liquid chromatography
KHMD S	potassium bis(trimethylsilyl)amide	UV	ultraviolet
LDA	lithium diisopropylamide	X-Phos Pd G3	(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate, CAS Number: 1445085-55-1
LiHMD S	lithium bis(trimethylsilyl)amide	Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, (9,9-dimethyl-9 <i>H</i> -xanthene-4,5-diyl)bis(diphenylphosphine)

Intermediate 1

Piperidine-4-carboxylic acid

TFA (6 mL) was added to a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid in
 5 DCM (20 mL) and stirred at rt for 30 min. The reaction mixture was concentrated to dryness to grant the TFA salt of the title compound (2.69 g, 100%).

Intermediate 2

1-(1-(Quinazolin-2-ylmethyl)piperidin-4-yl)ethan-1-one

10 Piperidine-4-carboxylic acid, TFA **Intermediate 1** (2.69 g, 11.15 mmol) and sodium triacetoxyhydroborate (4.73 g, 22.3 mmol) were added to a solution of quinoline-2-carbaldehyde (2.63 g, 16.73 mmol) in DCM (30 mL) and the resulting mixture was stirred at rt for 42 h. 8% NaHCO₃ (aq) was added and the stirring continued for 20 min. The phases
 were separated using a phase separator and the organic layer was concentrated. The crude
 15 product was purified by straight phase flash chromatography on silica (gradient 0-100% EtOAc in heptane (1% TEA)) to grant the title compound (2.25 g, 75%) as a brown oil. MS (ESI) *m/z* [M+H]⁺ 269.3.

Intermediate 31-(4-Methylpyridin-3-yl)-3-(1-(quinolin-2-ylmethyl)piperidin-4-yl)propane-1,3-dione

A solution containing 4-methylnicotinic acid (73 mg, 0.53 mmol) and CDI (86 mg, 0.53 mmol) in THF (1.5 mL) was stirred at rt for 1 h. 1 M LiHMDS in THF (0.533 mL, 0.53 mmol) was added to a stirred solution of 1-(1-(quinazolin-2-ylmethyl)piperidin-4-yl)ethan-1-one, TFA **Intermediate 2** (110 mg, 0.41 mmol) in THF (1.5 mL) at -78 °C, under an atmosphere of N₂ (g), and the reaction mixture was stirred for 30 min. The CDI-activated acid solution was added dropwise, and the reaction mixture was stirred at -78 °C for 30 min, and then allowed to warm to rt over 18 h. The mixture was diluted with EtOAc, washed with sat NaHCO₃ (aq), brine and concentrated. The residue was purified by preparative HPLC, PrepMethod D, (gradient: 10–55%) to yield the title compound (5 mg, 3%) as an off white solid. MS (ESI) *m/z* [M+H]⁺ 388.3.

Intermediate 4*tert*-Butyl 4-(5-(pyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

4-Methylbenzenesulfonohydrazide (1.72 g, 9.24 mmol) was added to a solution of pyrimidine-5-carbaldehyde (1 g, 9.25 mmol) in toluene (10 mL) and the reaction mixture was stirred at 20 °C for 3 h under an atmosphere of N₂ (g). The mixture was allowed to cool to 0 °C and 5 M NaOH (aq, 1.85 mL, 9.25 mmol) was added to the suspension and stirred at 0 °C for 20 min. *tert*-Butyl 4-ethynylpiperidine-1-carboxylate (5.81 g, 27.75 mmol) was added and the reaction mixture was stirred at 50 °C for 48 h. The mixture was poured into brine and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–100% MeCN in water) to grant the title compound (1.5 g, 49%) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 330.1.

Intermediate 5*tert*-Butyl 4-(5-(4-isopropylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

2-Hydroxyisoindoline-1,3-dione (44.6 mg, 0.27 mmol) and DMAP (1.11 mg, 9.10 μmol) were added to isobutyric acid (29.9 μL, 0.33 mmol) in a microwave vial. DMSO (0.86 mL) was added, followed by DIC (42.3 μL, 0.27 mmol) and the reaction mixture was stirred at rt

for 24 h. A solution of *tert*-butyl 4-(5-(pyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 4** (60.0 mg, 0.18 mmol) in DMSO (0.75 mL) and TFA (27.9 μ L, 0.36 mmol) in DMSO (0.5 mL) was added to the reaction, followed by 4-CzIPN (1.437 mg, 1.82 μ mol). The mixture was evacuated and filled with N₂(g) three times and then degassed
5 vigorously for 10 min. The vial was irradiated with a 34 W LED (λ_{max} 456 nm) for 3 h. The solution was filtered and the filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 20–65%), to grant the title compound (27 mg, 40%) as a white solid. MS (ESI) m/z [M+H]⁺ 372.3.

10 **Intermediate 6**

2-((3-Acetylpyridin-2-yl)amino)-2-oxoethyl acetate

TEA (0.77 mL, 5.52 mmol) was added to a solution of 1-(2-aminopyridin-3-yl)ethan-1-one (500 mg, 3.67 mmol) in DCM (17.2 mL) followed by 2-chloro-2-oxoethyl acetate (0.40 mL, 3.67 mmol) and the reaction mixture was stirred at rt for 5 h. Additional 2-chloro-2-oxoethyl
15 acetate (0.08 mL, 0.734 mmol) was added and the reaction mixture was stirred for a further 1 h. The reaction was quenched with sat NaHCO₃ (aq) and stirred overnight. The mixture was passed through a phase separator and concentrated. The crude product was purified by straight phase flash chromatography on silica (gradient: 50-100% EtOAc in heptane) to grant the title compound (720 mg, 83%) as a white solid. MS (ESI) m/z [M+H]⁺ 237.1.

20

Intermediate 7

(4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl acetate

NH₄OAc (34.3 g, 444.49 mmol) was added in small portions to a solution of 2-((3-acetylpyridin-2-yl)amino)-2-oxoethyl acetate **Intermediate 6** (21 g, 88.90 mmol) in AcOH
25 (200 mL). The reaction mixture was equally separated into 7 batches and each batch was stirred at 130 °C in a microwave reactor for 1 h. The batches were combined and concentrated. The concentrate was diluted with EtOAc and washed three times with sat NaHCO₃ (aq) solution. The combined organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified by straight phase flash chromatography on
30 silica, (gradient: 0–15% MeOH in DCM), to grant the title compound (14.0 g, 73%) as an orange solid. MS (ESI) m/z [M+H]⁺ 218.3.

Intermediate 8(4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methanol

NaOMe in MeOH (3.94 g, 21.88 mmol) was added slowly to a solution of (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl acetate **Intermediate 7** (12 g, 55.24 mmol) in MeOH (120 mL) under an atmosphere of N₂ (g). The reaction mixture was stirred at 25 °C for 45 min. The mixture was poured into brine and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by straight phase flash chromatography on silica (gradient: 0–100% EtOH in DCM), to grant the title compound (8.70 g, 90%) as a pale-yellow solid. MS (ESI) *m/z* [M+H]⁺ 176.3.

10

Intermediate 9(4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate

DIPEA (418 μL, 2.40 mmol) was added to a suspension of (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methanol **Intermediate 8** (210 mg, 1.20 mmol) in DCM (5.58 mL) followed by MsCl (313 mg, 1.80 mmol). The reaction mixture was stirred for 1 h and then concentrated. The crude product was purified by straight phase flash chromatography on silica (isocratic EtOAc) to grant the title compound (0.28 g, 91%) as a slightly yellow oil. MS (ESI) *m/z* [M+H]⁺ 254.1.

Intermediate 10*tert*-Butyl 4-(5-(4,6-dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

tert-Butyl 4-ethynylpiperidine-1-carboxylate (1.83 g, 9.83 mmol) was added to 4-methylpyrimidine-5-carbaldehyde (1.2 g, 9.83 mmol) in toluene (15 mL) and the reaction mixture was stirred for 3 h at 10 °C. 5 M NaOH (aq, 1.97 mL, 9.85 mmol) was added to the mixture and stirred at 0 °C for 30 min. 4-Methylbenzenesulfonohydrazide (6.17 g, 29.48 mmol) was added to the reaction mixture at 10 °C and then stirred at 50 °C for 50 h. The mixture was poured into brine and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by reversed phase flash chromatography on a C18 column, (gradient: 0–100% MeCN in water), to grant the title compound (1.00 g, 30%) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 344.4.

30

Intermediate 11

4,6-Dimethyl-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyrimidine

A microwave vial was charged with, *tert*-butyl 4-(5-(4,6-dimethylpyrimidin-5-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 10** (71.8 mg, 0.21 mmol) and (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (4.69 mg, 4.18 μmol). The vial was sealed, evacuated, and filled with N₂ (g). MeCN (0.95 mL) and TFA (0.95 mL) were added. The reaction mixture was cooled in an ice bath and degassed with N₂ (g) for 2 min, followed by addition of *tert*-butyl ethaneperoxoate (200 μL, 0.63 mmol). The mixture was degassed for an additional 5 min and then irradiated with a 34 W LED (λ_{max} 456 nm) for 1.5 h. The mixture was concentrated, and the residue was treated with water and MTBE. The layers were separated, and the MTBE layer was extracted with water. The combined aqueous layers were concentrated, and the resulting crude material was purified by preparative HPLC, PrepMethod D, (gradient–40%), to grant the title compound (11 mg, 21%) as a clear oil. MS (ESI) *m/z* [M+H]⁺ 258.2.

Intermediate 122-((3-Acetyl-6-methylpyridin-2-yl)amino)-2-oxoethyl acetate

TEA (19.31 mL, 138.5 mmol) was added to 1-(2-amino-6-methylpyridin-3-yl)ethan-1-one (10.4 g, 69.25 mmol) and 2-chloro-2-oxoethyl acetate (9.45 g, 69.25 mmol) in DCM (200 mL) at 0 °C over a period of 5 min. The reaction mixture was stirred at 15 °C for 16 h. The solvent was removed under reduced pressure. The crude solid was triturated with 20% EtOAc in petroleum ether and filtered. The precipitate was washed with 20% EtOAc in petroleum ether and dried under vacuum to grant the title compound (17.2 g, 99%) as a brown solid. MS (ESI) *m/z* [M+H]⁺ 372.3.

Intermediate 13(4,7-Dimethylpyrido[2,3-d]pyrimidin-2-yl)methyl acetate

A solution of 2-((3-acetyl-6-methylpyridin-2-yl)amino)-2-oxoethyl acetate **Intermediate 12** (247 mg, 0.99 mmol) and NH₄OAc (380 mg, 4.93 mmol) in AcOH (2.47 mL) was heated in a microwave reactor at 130 °C for 40 min. The solution was concentrated and the residue was purified using straight phase flash chromatography on silica (gradient: 50–100% EtOAc in heptane) to grant the title compound (89 mg, 39%) as a yellow oil. MS (ESI) *m/z* [M+H]⁺ 232.2.

Intermediate 14(4,7-Dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methanol

NaOMe (30 wt.% in MeOH, 397 μ L, 2.14 mmol) was added to a solution of (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl acetate **Intermediate 13** (495 mg, 2.14 mmol) in MeOH (6.62 mL). The reaction mixture was stirred at rt for 10 min followed by addition of AcOH (123 μ L, 2.14 mmol) and then concentrated. The residue was dissolved in DCM (and a drop of MeOH), filtered using a syringe filter and purified by straight phase chromatography on silica (gradient: 0–20% MeOH in EtOAc) to grant the title compound (306 mg, 75%) as a slightly yellow solid. MS (ESI) m/z $[M+H]^+$ 190.2.

10

Intermediate 15(4,7-Dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate

A solution of methanesulfonic anhydride (337 mg, 1.93 mmol) in DCM (2 mL) was added to a solution of (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methanol **Intermediate 14** (305 mg, 1.61 mmol) and DIPEA (421 μ L, 2.42 mmol) in DCM (6 mL) at 0 °C. The reaction mixture was stirred for 15 min and then quenched with sat NaHCO₃ (aq) and diluted with DCM. The aqueous layer was extracted with DCM and the combined organic layer was washed once with water and once with brine before drying over MgSO₄. The organic layer was filtered and concentrated to afford the title compound (424 mg, 98%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 268.1.

20

Intermediate 16*tert*-Butyl 4-(3-oxo-3-(pyridin-3-yl)propanoyl)piperidine-1-carboxylate

CDI (3.89 g, 24.0 mmol) was added to 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (5.00 g, 21.8 mmol) in THF (42 mL) and the mixture was stirred at rt for 1 h. In a separate flask, 1 M LiHMDS in toluene (43.6 mL, 43.6 mmol) was added dropwise to a solution of 3-acetylpyridine (4.79 mL, 43.6 mmol) in THF (42 mL) at -78 °C and stirred for 30 min. The solution containing CDI-activated carboxylic acid was added dropwise to the acetylpyridine solution and the reaction mixture was allowed to warm to rt. The reaction mixture was diluted with EtOAc and washed sequentially with 10% citric acid (aq), NaHCO₃ (aq) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 35–65% EtOAc in

30

heptane) to give the title compound (5.91 g). The product contained 3-acetylpyridine. MS (ESI) m/z $[M+H]^+$ 333.3.

Intermediate 17

5 *tert*-Butyl 4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate
35% Hydrazine hydrate (aq, 2.63 mL, 29.0 mmol) was added to a solution of *tert*-butyl 4-(3-oxo-3-(pyridin-3-yl)propanoyl)piperidine-1-carboxylate **Intermediate 16** (8.12 g, 22.0 mmol) in EtOH (85 mL). The reaction mixture was stirred at rt for 3 h. The mixture was diluted with EtOAc and water. The organic layer was separated and washed with brine, dried over Na₂SO₄
10 , filtered and concentrated. 1.2 g of the crude product was purified by preparative HPLC, PrepMethod F, (gradient:25–85%), and the remainder of the crude material was purified by washing with EtOAc. The two batches were combined to grant the title compound (5.4 g, 70%) as a white solid. MS (ESI) m/z $[M+H]^+$ 329.3.

15 Intermediate 18

3-(3-(Piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine
TFA (5 mL, 64.9 mmol) was added to a solution of *tert*-butyl 4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 17** (1g, 3.04 mmol) in DCM (30 mL) and the reaction mixture was stirred at 20 °C for 2 h. The solvent was removed under reduced
20 pressure. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 9–90% MeCN in water), to give the TFA salt of the title compound (0.70 g) as a pale yellow oil. MS (ESI) m/z $[M+H]^+$ 229.1.

Intermediate 19

25 2-((4-Chloro-2-formylphenyl)amino)-2-oxoethyl acetate
2-Chloro-2-oxoethyl acetate (1.54 mL, 14.32 mmol) was added to a solution of 2-amino-5-chlorobenzaldehyde (2.13 g, 13.69 mmol) and TEA (2.86 mL, 20.49 mmol) in DCM (63.9 mL) at rt. The reaction mixture was stirred at rt for 1.5 h and then additional 2-chloro-2-oxoethyl acetate was added (0.5 mL, 3.59 mmol). The reaction mixture was stirred for an
30 additional 1.5 h and then diluted with water (50 mL). The layers were separated, and the organic layer was passed through a phase separator and concentrated. The residue was washed with EtOAc and the product was collected as a white solid by filtration. The mother liquor

was concentrated and purified by straight phase flash chromatography on silica (gradient: EtOAc in heptane). The product containing fractions were collected, evaporated and combined with the precipitate to grant the title compound (2.25 g, 64%) as a white solid. MS (ESI) m/z $[M+H]^+$ 254.1 and 256.1.

5

Intermediate 20(6-Chloroquinazolin-2-yl)methyl acetate

AcOH (16.7 mL) was added to a mixture of 2-((4-chloro-2-formylphenyl)amino)-2-oxoethyl acetate **Intermediate 19** (1.71 g, 6.69 mmol) and NH_4OAc (1.55 g, 20.01 mmol) in a
10 microwave vial. The vial was sealed, heated to 130 °C and stirred for 5 min. The mixture was concentrated, redissolved in DCM, and treated with sat NaHCO_3 (aq). The aqueous layer was extracted and the combined organic layers were concentrated to afford the crude title compound (2.03 g). MS (ESI) m/z $[M+H]^+$ 237.2 and 239.2.

15 **Intermediate 21**(6-Chloroquinazolin-2-yl)methanol

1 M LiOH (aq, 12.87 mL, 12.87 mmol) was added to a solution of (6-chloroquinazolin-2-yl)methyl acetate **Intermediate 20** (2.03 g, 8.58 mmol) in THF (40 mL) and MeOH (20 mL) and the reaction mixture was stirred at rt for 30 min. The mixture was diluted with DCM and
20 sat NaHCO_3 (aq), then passed through a phase separator. The filtrate was concentrated to grant the title compound (1.595 g, 96%). MS (ESI) m/z $[M+H]^+$ 195.1 and 197.1.

Intermediate 22(6-Chloroquinazolin-2-yl)methyl methanesulfonate

DCM (35 mL) was added to a mixture of methanesulfonic anhydride (1.948 g, 11.18 mmol) and (6-chloroquinazolin-2-yl)methanol **Intermediate 21**. TEA (2.08 mL, 14.92 mmol) was added and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with water, extracted with EtOAc and concentrated. The crude residue was purified by straight phase chromatography on silica (gradient: 20–50% EtOAc in heptane) to grant the title compound
30 (1.2 g, 59%) as a light-yellow solid. MS (ESI) m/z $[M+H]^+$ 273.2 and 275.2.

Intermediate 23

2-((2-Acetyl-6-fluorophenyl)amino)-2-oxoethyl acetate

1-(2-Amino-3-fluorophenyl)ethan-1-one (0.936 g, 5.81 mmol) was dissolved in DCM (20 mL) and cooled in an ice-bath. 4-Methylmorpholine (1.28 mL, 11.64 mmol) was added followed by a dropwise addition of 2-chloro-2-oxoethyl acetate (0.77 mL, 7.16 mmol). After 5 15 min the cooling bath was removed, and the reaction mixture was stirred at rt overnight. The solution was diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ (aq), brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to grant the crude title compound as a brown oil (1.714 g). MS (ESI) *m/z* [M+H]⁺ 254.0.

Intermediate 24(8-Fluoro-4-methylquinazolin-2-yl)methanol

A solution containing 2-((2-acetyl-6-fluorophenyl)amino)-2-oxoethyl acetate **Intermediate 23** (1.47 g, 5.81 mmol) in 4 M NH₃ in MeOH (15.96 mL, 63.86 mmol) was heated under microwave irradiation at 80 °C and stirred for 2 h. The solution was concentrated under 15 reduced pressure and the crude residue was redissolved in EtOAc, washed with NaHCO₃ and the organic layer was concentrated to afford the title compound (1.047 g, 94%). MS (ESI) *m/z* [M+H]⁺ 193.0.

Intermediate 252-(Chloromethyl)-6-methoxy-4-methylquinazoline

1-(2-Amino-5-methoxyphenyl)ethan-1-one (190 mg, 1.15 mmol) was dissolved in dioxane (0.5 mL) and cooled to 0 °C. 4 M HCl in dioxane (1.73 mL, 6.90 mmol) was added dropwise and the reaction mixture was stirred to rt overnight. The mixture was cooled to 0 °C and a solution of 2-chloroacetonitrile (109 µL, 1.73 mmol) in dioxane (0.1 mL) was added dropwise 25 and the reaction mixture was stirred at rt over the weekend. 2-Chloroacetonitrile (109 µL, 1.73 mmol) was added and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was added dropwise to 2 M NaOH (aq, 6.90 mL, 13.80 mmol) at rt, stirred for 15 min, and then extracted with DCM. The organic layers were filtered through a phase separator and concentrated. The residue was purified by straight phase flash chromatography on silica 30 (gradient: 10–50% EtOAc in heptane) to grant the title compound (33 mg, 13%) as a tan solid. MS (ESI) *m/z* [M+H]⁺ 222.9 and 224.8.

Intermediate 26

tert-Butyl 4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)propanoyl)piperidine-1-carboxylate
1-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethan-1-one (21.6 g, 0.14 mol) was dissolved in THF (600 mL) under an atmosphere of Ar (g). The turbid solution was cooled in an ice bath to 3 °C. 1 M KHMDS in THF (250 mL, 0.25 mol) and 1 M NaHMDS in THF (34 mL, 0.03 mol) were added dropwise, within 15 min, maintaining the temperature below 5 °C. The reaction mixture was stirred for 30 min and then 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (69.1 g, 0.28 mol) was added in 5 portions over 10 min. The reaction mixture was heated to 60 °C for 16 h. The mixture was cooled to rt and brine (200 mL) was added. The organic solvent was removed in vacuo and the residue was extracted with EtOAc (4×150 mL). The combined organic layers were dried over Na₂SO₄, filtered and then concentrated in vacuo. The crude residue was dissolved in MeOH (200 mL). A solution of LiOH hydrate (6.30 g, 0.15 mol) in water (200 mL) was added, and the reaction mixture was rapidly stirred for 2 h at rt. The formed precipitate was isolated by filtration. The filtrate was concentrated under reduced pressure to approximately half volume, and a second crop of precipitate was isolated by filtration after standing for 2 h. The solids were combined, washed with a small amount of water, and dried in vacuo to afford (39.02 g, 76%) of colorless solid. MS (ESI) *m/z* [M+H]⁺ 364.4.

Intermediate 27

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
tert-Butyl 4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)propanoyl)piperidine-1-carboxylate
Intermediate 26 (39.0 g, 107.30 mmol) was suspended in 99.5% EtOH (350 mL) and 64% hydrazine hydrate (aq, 16.31 mL, 215 mmol) was added. The reaction mixture was stirred at rt for 16 h followed by heating to 70 °C for 20 h. The mixture was concentrated in vacuo followed by the addition of DMF (100 mL). More 64% hydrazine hydrate (aq, 8.15 mL, 168.01 mmol) was added and the mixture was heated for 18 h to 70 °C. H₃PO₄ (2.372 mL, 36 mmol) was added and stirring was continued at 70 °C for 16 h. The mixture was concentrated in vacuo. The residue was taken up in EtOAc (350 mL), filtered, and the filtrate was washed with brine (×4), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was stirred for 12 h in a mixture of EtOAc (40mL) and heptane (160 mL). The solid was isolated by filtration and dried in vacuo to yield the title compound (30.26 g, 78%) as a colorless solid.

¹H NMR (500 MHz, DMSO-*d*₆) 1.38 – 1.42 (9H, m), 1.49 (2H, qd), 1.86 – 1.92 (2H, m), 2.15 – 2.2 (3H, m), 2.30 (3H, s), 2.81 (3H, bs), 3.66 (3H, s), 4.00 (2H, d), 6.06 (1H, s), 12.2 – 12.49 (1H, m). MS (ESI) *m/z* [M+H]⁺ 360.4.

5 **Intermediate 28**

1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 27 (30.25 g, 84.15 mmol) was dissolved in a mixture of water (50 mL) and 37% HCl (aq, 50 mL) and the reaction mixture was stirred for 20 min. The mixture was concentrated in vacuo and dried overnight under vacuum. IPA (120 mL) was added to the solids and the mixture was stirred for 6 h. Solid precipitate formed was isolated by filtration and washed with small amounts of IPA, IPA/MTBE (1:1) and MTBE. The precipitate was dried under vacuum to give the HCl-salt of the title compound (26.733 g, 96%) as colourless solid. ¹H NMR (500 MHz, D₂O, 25°C) δ 1.88–2.00 (2H, m), 2.24–2.30 (2H, m), 2.35 (6H, d), 3.11–3.26 (3H, m), 3.52 (2H, dt), 3.88 (3H, s), 6.49–6.53 (1H, m). MS (ESI) *m/z* [M+H]⁺ 260.4.

Intermediate 29

tert-Butyl 4-(5-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-

20 yl)piperidine-1-carboxylate and *tert*-butyl 4-(3-(pyridin-3-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidine-1-carboxylate (1:1 mixture)

NaH (60 wt.% in mineral oil) (102 mg, 2.55 mmol) was added to a mixture of *tert*-butyl 4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 17** (558 mg, 1.70 mmol) and SEM-Cl (331 μL, 1.87 mmol) in THF (8.16 mL) at 0 °C. The reaction mixture was stirred for 1 h and then quenched by addition of sat NaHCO₃ (aq). The mixture was diluted with DCM, filtered through a phase separator, and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient: EtOAc in heptane 33-66%) to grant the title compounds (0.486 g, 62%) as a yellow oil. The two regioisomers were formed in a 1:1 ratio. MS (ESI) *m/z* [M+H]⁺ 459.5.

30

Intermediate 30

(3-(3-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate and (3-(5-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (1:1 mixture)

1 M Methanesulfonic anhydride in DCM (598 μ L, 0.60 mmol) was added dropwise to a solution of *tert*-butyl 4-(5-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate and *tert*-butyl 4-(3-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidine-1-carboxylate (1:1 mixture)

Intermediate 29 (218 mg, 0.66 mmol) in DCM (5.30 mL) at -46 °C. The reaction mixture was stirred for 2 h and then cooled to -78 °C, and DBU (89 μ L, 0.60 mmol) was added. The mixture was warmed to rt and stirred for 30 min, then diluted with DCM and washed with water. The organic layer was passed through a phase separator and concentrated to grant the title compound (542.8 mg, 97%) as a (1:1) mixture of regioisomers. MS (ESI) m/z [M+H]⁺ 788.7.

Intermediate 31

4-Chloro-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine

A vial containing (3-(3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate and (3-(5-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (1:1 mixture) **Intermediate 30** (0.563 g, 0.6 mmol) was transferred into a glovebox. Anhydrous LiCl (0.102 g, 2.40 mmol) was added followed by dioxane (3 mL). The vial was removed from the glove box, heated to 80 °C and stirred over the weekend. The mixture was cooled to rt and concentrated. The crude residue was dissolved in DCM (4 mL) and treated with TFA (4 mL, 0.60 mmol). The reaction mixture was stirred overnight and concentrated. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (33 mg, 21%) as a colourless film. MS (ESI) m/z [M+H]⁺ 263.1 and 265.1.

Intermediate 32

tert-Butyl 4-(3-(4-methylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate

The reaction to synthesise this intermediate was conducted in a flow reactor. 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (10.08 g, 43.95 mmol) was added to CDI (6.80 g, 41.95 mmol) in THF (400 mL) at 25°C and stirred for 1 h. 1-(4-Methylpyridin-3-yl)ethan-
5 1-one (5.40 g, 39.95 mmol) was added to the mixture. A second solution containing 1 M LiHMDS in THF was prepared and the two solutions were mixed in flow reactor so that the pumping of 1 mL/min 1 M LiHMDS in THF was mixed with 2 mL/min of the CDI activated acid solution. The eluted solution was stirred under an atmosphere of N₂ (g) for 10 min and then concentrated. The concentrate was diluted with EtOAc and washed sequentially with 0.5
10 M citric acid (aq), water and brine. The organic layers were dried over Na₂SO₄, filtered and concentrated to afford the title compound (12.8 g, 92%) as a yellow oil. MS (ESI) *m/z* [M+H]⁺ 347.1.

Intermediate 33*tert*-Butyl 4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine monohydrate (5.06 g, 101.03 mmol) was added dropwise to *tert*-butyl 4-(3-(4-methylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 32** (7.00 g, 20.21 mmol) in EtOH (150 mL) and the reaction mixture was stirred at 20 °C for 1 h. The mixture was concentrated, and the crude residue was purified by reverse phase flash chromatography
20 on a C18 column (gradient: 5–40% MeCN in water) to give the title compound (4.90 g, 71%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 343.1.

Intermediate 344-Methyl-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine

TFA (3 mL, 3.02 mmol) was added to a solution of *tert*-butyl 4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 33** (1.03 g, 3.01 mmol) in DCM (9 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was concentrated and redissolved in MeOH (10 mL). Et₂O (50 mL) was added, and the solution was stirred, white precipitate formed which was filtered off and washed with MTBE. The precipitate was dried
30 under vacuum to grant the TFA salt of the title compound (1.33 g, 93%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 243.2.

Intermediate 35*tert*-Butyl 4-(3-(5-chloropyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate

CDI (2.78 g, 17.15 mmol) was added to a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (3.98 g, 17.36 mmol) in THF (31.2 mL) and stirred at rt for 1 h. In a separate
5 flask, 1 M LiHMDS (18.01 mL, 18.01 mmol) was added dropwise to a solution of 1-(5-chloropyridin-3-yl)ethan-1-one (2.67g, 17.15 mmol) in THF (36.5 mL) at -78 °C and stirred for 30 min. The solution containing CDI-activated carboxylic acid was added dropwise and the reaction mixture was warmed to rt. The reaction mixture was diluted with EtOAc and washed sequentially with 10% citric acid (aq), sat NaHCO₃ (aq) and brine. The organic layers
10 were dried over Na₂SO₄ and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 20–35% EtOAc in heptane) and then further purified by preparative HPLC, PrepMethod G, (gradient 20–80%), to grant the title compound (2.88g, 46%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 365.2.

Intermediate 36*tert*-Butyl 4-(5-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 0.796 mL, 16.36 mmol) was added to a solution of *tert*-butyl 4-(3-(5-chloropyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 35** (3.0 g, 8.18 mmol) in EtOH (26.5 mL). The reaction mixture was heated to 50 °C and stirred overnight.
20 The solvent was concentrated, and the residue was purified by straight phase flash chromatography on silica (gradient; 5–50% EtOAc in heptane) to give the title compound as a white solid. MS (ESI) *m/z* [M+H]⁺ 363.3.

Intermediate 373-Chloro-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine

TFA (8 mL) was added to a suspension of *tert*-butyl 4-(5-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 36** (2.86 g, 7.88 mmol) in DCM (30 mL). The reaction mixture was stirred for 1 h at rt and then concentrated to afford a yellow oil which was treated with Et₂O. The product precipitated and was collected by filtration and washed
30 with additional Et₂O to afford the TFA salt of the title compound as an off white solid (3.72 g, 96%). MS (ESI) *m/z* [M+H]⁺ 263.3.

Intermediate 38

2-((4-(5-(5-Chloropyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine

(4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (71.4 mg, 0.28 mmol) and DIPEA (196 μ l, 1.13 mmol) was added to a solution of 3-chloro-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine, 2 TFA **Intermediate 37** (160 mg, 0.33 mmol) in DMSO (1 mL). The reaction mixture was stirred at rt for 3 h, and then filtered using a syringe filter. The resulting solution was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (0.067 g, 57%) as a slightly yellow solid. MS (ESI) m/z [M+H]⁺ 220.3.

Intermediate 39

tert-Butyl 4-(3-(2-methylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate

The reaction to synthesise this intermediate was conducted in a flow reactor. 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (10.08 g, 43.95 mmol) was added to CDI (6.80 g, 41.95 mmol) in THF (400 mL) and stirred at 20 °C for 1 h. 1-(2-Methylpyridin-3-yl)ethan-1-one (5.40 g, 39.95 mmol) was added to the solution. A second solution containing 1 M LiHMDS in THF was prepared and the two solutions were mixed in flow so that the pumping of 1 mL/min 1 M LiHMDS in THF was mixed with 2 mL/min of the solution of CDI activated acid with no cooling. The eluted solution was stirred under an atmosphere of N₂ (g) for 10 min before concentrating under vacuum. The concentrate was diluted with EtOAc and washed sequentially with 0.5 M citric acid (aq), water, and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford the title compound (12.1 g, 87%) as a yellow oil. MS (ESI) m/z [M+H]⁺ 347.1.

Intermediate 40

tert-Butyl 4-(5-(2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine monohydrate (4.34 g, 86.60 mmol) was added dropwise to a solution containing *tert*-butyl 4-(3-(2-methylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 39** (6.00 g, 17.32 mmol) in EtOH (150 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h and then concentrated under reduced pressure. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 5–40% MeCN

in water) to give the title compound (4.30 g, 73%) as a white solid. MS (ESI) m/z $[M+H]^+$ 343.2.

Intermediate 41

5 2-Methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine

TFA (3 mL, 3.12 mmol) was added to a solution of 2-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 40** (1.07 g, 3.12 mmol) in DCM (9 mL) and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated and redissolved in MeOH (10 mL). Et₂O (50 mL) was added, and the solution was stirred. The precipitate formed was
10 collected by filtration, washed with MTBE and dried under vacuum to grant the TFA salt of the title compound (1.376 g, 94%) as a white solid. MS (ESI) m/z $[M+H]^+$ 243.2.

Intermediate 42

15 3-(3-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-5-yl)-4-(hydroxymethyl)pyridine 1-oxide

70% mCPBA (aq, 91 mg, 0.37 mmol) was added to a solution of *tert*-butyl 4-(5-(4-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 33** (106 mg, 0.31 mmol) in DCM (1.55 mL) and stirred at rt for 1 h. The mixture was purified by straight phase flash chromatography on silica (gradient: 0–20% MeOH in EtOAc) to grant the title
20 compound (96 mg, 87%) as a white solid. MS (ESI) m/z $[M+H]^+$ 359.3.

Intermediate 43

tert-Butyl 4-(5-(4-(hydroxymethyl)pyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate
A solution of 3-(3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1H-pyrazol-5-yl)-4-(hydroxymethyl)pyridine 1-oxide **Intermediate 41** (42.0 mg, 0.12 mmol) in Ac₂O (0.7 mL, 0.12 mmol) was heated to 80 °C and stirred for 6 h. The solvent was concentrated and MeOH (1 mL) was added. 2 M NaOH (aq, 0.293 mL, 0.59 mmol) was added and the mixture was stirred at rt for 1 h and then concentrated. The residue was treated with DMSO and filtered using a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D,
30 (gradient: 15–55%), to grant the title compound (20 mg, 48%) as a clear oil. MS (ESI) m/z $[M+H]^+$ 359.3.

Intermediate 44*tert*-Butyl 4-(5-(2-ethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Propionic acid (68.1 μ L, 0.91 mmol) and DIC (106 μ L, 0.69 mmol) were added to a solution of 2-hydroxyisoindoline-1,3-dione (149 mg, 0.91 mmol) and DMAP (5.58 mg, 0.05 mmol) in DMSO (2.197 mL). The reaction mixture was stirred at rt for 24 h. A solution of *tert*-butyl 4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 17** (150 mg, 0.46 mmol) and (1*R*)-(-)-CSA (212 mg, 0.91 mmol) in DMSO (2.2 mL) was added to the reaction mixture, followed by 4-CzIPN (3.60 mg, 4.57 μ mol). The reaction mixture was evacuated and filled with N₂ (g) three times and then degassed with N₂ (g) vigorously for 10 min. The vial was irradiated with a 34 W LED (λ_{max} 456 nm) for 24 h and then purified by preparative HPLC, PrepMethod OO, (gradient: 30–70%), to grant the title compound (10.0 mg, 6%). MS (ESI) m/z [M+H]⁺ 287.4.

Intermediate 45*tert*-Butyl 4-(5-(2,4-diethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylateStep a) 1,3-Dioxoisindolin-2-yl propionate

DIC (0.313 mL, 2.00 mmol) was added to a solution of propionic acid (148 mg, 2 mmol), DMAP (12 mg, 0.10 mmol) and 2-hydroxyisoindoline-1,3-dione (0.326 g, 2.00 mmol) in anhydrous DMSO (5.67 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was filtered to grant a 0.3 M solution of the title compound. The solution was used in the next step.

Step b) *tert*-Butyl 4-(5-(2,4-diethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

A microwave vial was charged with *tert*-butyl 4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 33** (66 mg, 0.20 mmol), 4CzIPN (3.17 mg, 4.02 μ mol) and CSA (93 mg, 0.40 mmol) followed by DMSO (1.1 mL) and 1,3-dioxoisindolin-2-yl propionate **Intermediate 45 Step a)** (0.3 M in DMSO, 1.34 mL, 0.40 mmol). The vial was sealed, evacuated and refilled with N₂ (g) three times. The reaction mixture was irradiated with a 34 W LED (λ_{max} 456 nm) for 2.5 h. The mixture was filtered and purified by preparative HPLC, PrepMethod D, (gradient: 25–75%), to grant the title compound (4.6 mg, 6%). MS (ESI) m/z [M+H]⁺ 385.5.

Intermediate 46

tert-Butyl 4-(3-(2,4-dimethylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate

The reaction to synthesise this intermediate was conducted in a flow reactor. 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (3.38 g, 14.75 mmol) was added to CDI (2.28 g, 14.08 mmol) in THF (400 mL) at 20 °C. The resulting solution was stirred at 55 °C for 1 h. 1-(2,4-Dimethylpyridin-3-yl)ethan-1-one (2.00 g, 13.41 mmol) was added to the solution. A second solution containing 1 M LiHMDS in THF was prepared and the two solutions were mixed in flow so that the pumping of 1 mL/min 1 M LiHMDS in THF was mixed with 2 mL/min of the CDI activated acid solution. The eluted solution was stirred under an atmosphere of N₂ (g) for 10 min before quenching with brine. The mixture was extracted with EtOAc and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–100% MeCN in water) to grant the title compound (2.00 g, 41%) as a brown oil. MS (ESI) *m/z* [M+H]⁺ 361.1.

Intermediate 47

tert-Butyl 4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 3.12 g, 62.42 mmol) was added to *tert*-butyl 4-(3-(2,4-dimethylpyridin-3-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 46** (4.5 g, 12.48 mmol) in EtOH (50 mL) at 20 °C under an atmosphere of N₂ (g) and stirred at 80 °C for 3 h. The solvent was removed under reduced pressure. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–100% MeCN in water) to grant the title compound (3.75 g, 84%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 357.2.

Intermediate 48

Ethyl (Z)-2-chloro-2-(2-(2-methyl-6-nitrophenyl)hydrazineylidene)acetate

12.5 M HCl (aq, 5.26 mL, 65.72 mmol) was added to 2-methyl-6-nitroaniline (2 g, 13.14 mmol) in MeOH (12.6 mL) at 0 °C and the reaction mixture was stirred for 15 min under an atmosphere of N₂ (g). A solution of NaNO₂ (0.998 g, 14.46 mmol) in water (2.40 mL) was added and the reaction mixture was stirred at 0 °C for 2 h. The mixture was filtered through a pad of CELITE and ethyl 2-chloro-3-oxobutanoate (2.81 g, 17.09 mmol) was added to the filtrate. The reaction mixture was stirred at 20 °C for 2 h. The precipitate formed was

collected by filtration, washed with water, and dried under vacuum to afford the title compound (3.50 g, 93%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 286.0.

Intermediate 49

5 Ethyl 8-methylbenzo[*e*][1,2,4]triazine-3-carboxylate

Under an atmosphere of N₂ (g), 12.5 M HCl (aq, 1.80 mL, 22.53 mmol) was added to ethyl (Z)-2-chloro-2-(2-(2-methyl-6-nitrophenyl)hydrazineylidene)acetate **Intermediate 48** (3 g, 11.27 mmol) in AcOH (17.8 mL) at 20 °C. The solution was added dropwise to a solution of Fe(s) (3.15 g, 56.34 mmol) in water (4.3 mL) and the reaction mixture was stirred for 16 h.

10 The mixture was poured into brine and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–50% EtOAc in heptane) to grant the title compound (2 g, 82%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 218.1.

15 **Intermediate 50**

(8-Methylbenzo[*e*][1,2,4]triazin-3-yl)methanol

Under an atmosphere of N₂ (g), 2 M LiAlH₄ in THF (9.21 mL, 18.41 mmol) was added dropwise over 30 min to ethyl 8-methylbenzo[*e*][1,2,4]triazine-3-carboxylate **Intermediate 49** (2 g, 9.21 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h
20 and then the reaction was quenched by the addition of 2 M NaOH (aq). The mixture was filtered through CELITE and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod N, (gradient: 5–30%), to grant the title compound (1 g, 62%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 176.1.

25 **Intermediate 51**

(8-Methylbenzo[*e*][1,2,4]triazin-3-yl)methyl methanesulfonate

DIPEA (253 µL, 1.45 mmol) was added to a solution of (8-methylbenzo[*e*][1,2,4]triazin-3-yl)methanol **Intermediate 50** (212 mg, 1.21 mmol) in DCM (6 mL) and the mixture was cooled to 0 °C. A solution of methanesulfonic anhydride (232 mg, 1.33 mmol) in DCM (1
30 mL) was added and the reaction mixture was stirred for 1 h at rt. Further methanesulfonic anhydride (200 mg, 1.96 mmol) was added, and the reaction mixture was stirred for 5 min. The mixture was concentrated and purified by straight phase flash chromatography on silica

(gradient: 25–50% EtOAc in heptane) to grant the title compound (0.266 g, 87%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 254.2.

Intermediate 52

5 2,4-Dimethyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine

4 M HCl in dioxane (3.51 mL, 14.03 mmol) was added to *tert*-butyl 4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 47** (500 mg, 1.40 mmol) in dioxane (5 mL) under an atmosphere of N₂ (g). The reaction mixture was stirred at 20 °C for 1 h. The solvent was removed under reduced pressure, to afford the TFA salt of the title compound (500 mg) as a yellow solid. ¹H NMR (300 MHz, DMSO) δ 8.67 (1H, d), 7.89 (1H, d), 6.36 (1H, s), 3.37 – 3.25 (2H, m), 3.13 – 2.93 (3H, m), 2.59 (s, 3H), 2.42 (s, 3H), 2.17 (2H, m), 1.88 (2H, m).

Intermediate 53

15 5-Methoxy-1-methyl-1H-pyrazole-4-carbonyl chloride

5-Methoxy-1-methyl-1H-pyrazole-4-carboxylic acid (0.131 g, 0.8 mmol) was suspended in DCM (2.2 mL). Oxalyl chloride (0.143 mL, 1.60 mmol) was added, and the mixture was cooled in an ice-bath. DMF (6.19 μ L, 0.08 mmol) was added and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure and co-evaporated with DCM to afford the title compound (0.137 g, 98%). ¹H NMR (500 MHz, DMSO-*d*₆) 3.60 (3H, s), 4.06 (3H, s), 7.63 (1H, s).

Intermediate 54

25 *tert*-Butyl 4-(3-(5-methoxy-1-methyl-1H-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

Pd(PPh₃)₂Cl₂ (0.017 g, 0.02 mmol) was added to a solution of *tert*-butyl 4-ethynylpiperidine-1-carboxylate (0.103 g, 0.493 mmol), 5-methoxy-1-methyl-1H-pyrazole-4-carbonyl chloride **Intermediate 53** (0.129 g, 0.74 mmol), CuI (4.7 mg, 0.02 mmol) and TEA (0.412 mL, 2.96 mmol) in THF (0.85 mL) and toluene (0.85 mL). The reaction mixture was stirred under an atmosphere of N₂ (g) at rt for 3 h. DCM (7 mL) and sat NaHCO₃ (aq, 7 mL) were added. The mixture was stirred, filtered through a phase separator, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica

(gradient 0–40% (EtOAc/4M NH₃ in MeOH (9/1)) in DCM) to give the title compound (0.038 g, 22%). MS (ESI) m/z [(M-Boc)+H]⁺ 248.1. ¹H NMR (500 MHz, CDCl₃) 1.46 (9H, s), 1.64 – 1.75 (2H, m), 1.86 – 1.94 (2H, m), 2.76 – 2.87 (1H, m), 3.22 (2H, ddd), 3.67 (3H, s), 3.70 – 3.80 (2H, m), 4.21 (3H, s), 7.86 (1H, s).

5

Intermediate 55

tert-Butyl 4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(3-(5-methoxy-1-methyl-1H-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 54** (0.037 g, 0.11 mmol) was dissolved in 99.5% EtOH (0.7 mL).

64% Hydrazine hydrate (aq, 0.026 mL, 0.53 mmol) was added, and the reaction mixture was stirred at rt overnight. DCM and NaHCO₃ (aq) were added, the mixture was stirred, filtered through a phase separator, and concentrated to yield the title compound (0.039 g). Used as such in the next step.

MS (ESI) m/z [M+H]⁺ 362.3.

15

Intermediate 56

5'-Methoxy-1'-methyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

TFA (15.77 mg, 0.14 mmol) was added to a solution of *tert*-butyl 4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 55** (50 mg, 0.14 mmol)

in DCM (1 mL) at 10 °C and the reaction mixture was stirred for 2 h. The mixture was concentrated to grant the TFA salt of the title compound (40 mg). MS (ESI) m/z [M+H]⁺ 262.1.

Intermediate 57

5-Methyl-1,8-naphthyridine-2-carboxylic acid

Under an atmosphere of N₂ (g), NaOH (1.175 g, 29.38 mmol) was added to 2-amino-4-methylnicotinaldehyde (1 g, 7.34 mmol) and methyl 2-oxopropanoate (1.5 g, 14.69 mmol) in IPA (50 mL) and water (50 mL). The reaction mixture was stirred at 20 °C for 16 h. The mixture was filtered and the solvent was removed under reduced pressure to grant the title compound (1.3 g, 94%) as a yellow solid. MS (ESI) m/z [M+H]⁺ 188.8.

30

Intermediate 58

Methyl 5-methyl-1,8-naphthyridine-2-carboxylate

SOCl₂ (0.465 mL, 6.38 mmol) was added to 5-methyl-1,8-naphthyridine-2-carboxylic acid **Intermediate 57** (1.2 g, 6.38 mmol) in MeOH (10 mL) at 0 °C. The reaction mixture was stirred at 60 °C for 2 h. The solvent was removed under reduced pressure to afford crude product which was purified by straight phase flash chromatography on silica (gradient: 30–50% EtOAc in petroleum ether) to grant the title compound 0.750 g, 58%) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 203.2.

Intermediate 59(5-Methyl-1,8-naphthyridin-2-yl)methanol

NaBH₄ (374 mg, 9.89 mmol) was added to methyl 5-methyl-1,8-naphthyridine-2-carboxylate **Intermediate 58** (500 mg, 2.47 mmol) in MeOH (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with ice water and extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude product was purified by preparative HPLC, PrepMethod Q, (gradient: 10–25%), to grant the title compound (265 mg, 62%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 175.3.

Intermediate 602-((2-Acetyl-4-chlorophenyl)amino)-2-oxoethyl acetate

2-Chloro-2-oxoethyl acetate (310 μL, 2.79 mmol) was added dropwise to a solution of 1-(2-amino-5-chlorophenyl)ethan-1-one (395 mg, 2.33 mmol) and NMM (512 μL, 4.66 mmol) in DCM (9 mL) at 0 °C and stirred for 15 min. The cooling bath was removed and the reaction mixture was stirred at rt overnight. The solution was diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ (aq) and brine. The organic layers were dried over Na₂SO₄, filtered and concentrated to grant the title compound (769 mg) as a brown oil. MS (ESI) *m/z* [M+H]⁺ 270.2.

Intermediate 61(6-Chloro-4-methylquinazolin-2-yl)methanol

2-((2-Acetyl-4-chlorophenyl)amino)-2-oxoethyl acetate **Intermediate 60** (628 mg, 2.33 mmol) was dissolved in 4 M NH₃ in MeOH (6.4 mL, 25.6 mmol) and stirred at 85 °C for 10 h

in a microwave reactor. The mixture was concentrated, redissolved in EtOAc and washed with sat NaHCO₃ (aq). The organic layers were concentrated to afford the title compound (449 mg, 92%) as a beige solid. MS (ESI) m/z [M+H]⁺ 209.1.

5 **Intermediate 62**

6-Chloro-2-(chloromethyl)-4-methylquinazoline

NCS (316 mg, 2.37 mmol) was added to a solution of (6-chloro-4-methylquinazolin-2-yl)methanol **Intermediate 61** (449 mg, 2.15 mmol) and PPh₃ (621 mg, 2.37 mmol) in DCM (7 mL) at 0 °C and stirred for 3 h. The reaction mixture was concentrated and purified by
10 straight phase flash chromatography on silica (gradient: 5–40%), to grant the title compound (217 mg, 44%) as a white solid. ¹H NMR (500 MHz, CDCl₃, 25°C) δ 2.95 (3H, s), 4.84 (2H, s), 7.83 (1H, m), 7.98 (1H, m), 8.07 (1H, m).

Intermediate 63

15 2-((3-Chloro-2-formylphenyl)amino)-2-oxoethyl acetate

2-Chloro-2-oxoethyl acetate (3.7 mL, 34.4 mmol) was added dropwise to a solution of 2-amino-6-chlorobenzaldehyde (4.46 g, 28.67 mmol) and DIPEA (7.49 mL, 43.0 mmol) in DCM (60 mL) at 0 °C and stirred for 2 h. Further 2-chloro-2-oxoethyl acetate (0.616 mL, 5.73 mmol) was added and the reaction mixture was stirred for 45 min. The mixture was diluted
20 with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to grant the title compound (6.46 g, 88%) as a brown solid. MS (ESI) m/z [M-H]⁻ 253.9.

Intermediate 64

25 (5-Chloroquinazolin-2-yl)methyl acetate

2-((3-Chloro-2-formylphenyl)amino)-2-oxoethyl acetate **Intermediate 63** (6.97 g, 27.26 mmol) and NH₄OAc (6.30 g, 81.79 mmol) were suspended in AcOH (91 mL). The mixture was divided into 7 microwave vials and each of the vials were stirred at 130 °C for 3 min under microwave irradiation and then all the mixtures were combined, and solvent was
30 removed under reduced pressure. The residue was diluted with toluene and washed with water, sat NaHCO₃ (aq) and brine. The combined organic layers were dried over Na₂SO₄,

filtered and concentrated to grant the title compound (5.46 g, 85%) as a brown solid. MS (ESI) m/z $[M+H]^+$ 209.1.

Intermediate 65

5 (5-Chloroquinazolin-2-yl)methanol

LiOH (0.112 g, 4.67 mmol) was added to a solution of (5-chloroquinazolin-2-yl)methyl acetate **Intermediate 64** (0.85 g, 3.59 mmol) in THF (9 mL), MeOH (6 mL) and water (5 mL) and stirred at rt for 0.5 h. The mixture was diluted water and extracted with DCM. The combined organic layers were passed through a phase separator and concentrated to afford the
10 title compound (0.640 g, 92%) as a yellow solid.

Intermediate 66

(5-Chloroquinazolin-2-yl)methyl methanesulfonate

Methanesulfonyl chloride (258 μ L, 3.33 mmol) was added to a solution of (5-chloroquinazolin-2-yl)methanol **Intermediate 65** (499 mg, 2.56 mmol) and DIPEA (672 μ L, 3.85 mmol) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 90 min and then diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to grant the title compound (689.6 mg, 99%) as a brown oil. MS (ESI) m/z $[M+H]^+$ 273.0.
20

Intermediate 67

2-((2-Acetyl-4-bromophenyl)amino)-2-oxoethyl acetate

2-Chloro-2-oxoethyl acetate (0.616 mL, 5.56 mmol) was added dropwise to a solution of 1-(2-amino-5-bromophenyl)ethan-1-one (0.992 g, 4.63 mmol) and NMM (1.019 mL, 9.27 mmol) in DCM (16 mL) at 0 °C. The reaction mixture was stirred for 15 min and then the cooling bath was removed and the reaction mixture was allowed to warm to rt overnight. The mixture was diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ (aq) and brine. The organic layers were dried over Na₂SO₄, filtered and concentrated to grant the title compound (1.623 g) as a brown solid. MS (ESI) m/z $[M-H]^-$ 312.0 and 314.0.
25
30

Intermediate 68

(6-Bromo-4-methylquinazolin-2-yl)methanol

2-((2-Acetyl-4-bromophenyl)amino)-2-oxoethyl acetate **Intermediate 67** (1.456 g, 4.63 mmol) was dissolved in 4 M NH₃ in MeOH (12.75 mL, 50.98 mmol) and heated in a microwave reactor for 8 h at 85 °C. The solution was concentrated in vacuo, redissolved in EtOAc and washed with sat NaHCO₃ (aq). The organic layers were concentrated to afford the
5 title compound (1.112 g, 95%) as a beige solid. MS (ESI) *m/z* [M+H]⁺ 252.9 and 254.9.

Intermediate 69

6-Bromo-2-(chloromethyl)-4-methylquinazoline

PPh₃ (1.268 g, 4.83 mmol) was added to a solution of (6-bromo-4-methylquinazolin-2-yl)methanol **Intermediate 68** (1.112 g, 4.39 mmol) in DCM (15 mL). The mixture was
10 cooled to 0 °C and NCS (0.645 g, 4.83 mmol) was added and the reaction mixture was stirred for 3 h. The mixture was concentrated and purified by straight phase flash chromatography on silica (gradient: 10–40% EtOAc in heptane), to grant the title compound (0.581 g, 49%) as white solid. MS (ESI) *m/z* [M-H]⁻ 269.0 and 271.0.

15

Intermediate 70

6-Bromo-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinoline

A solution of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2'*H*-3,4'-bipyrazole, HCl **Intermediate 28** (156 mg, 0.60 mmol), 6-bromo-2-(chloromethyl)-4-methylquinazoline **Intermediate 69**
20 (158 mg, 0.58 mmol) and K₂CO₃ (663 mg, 4.80 mmol) in MeCN (9 mL) was stirred at 42 °C overnight. After cooling to rt, precipitated solids were filtered off and washed with MeCN. The filtrate was concentrated and purified by reversed phase flash chromatography on a C18 column (gradient: 5–95% MeCN in 0.1% NH₄OH (aq)) to grant the title compound (217 mg,
25 73%) as a beige solid. MS (ESI) *m/z* [M+H]⁺ 494.2 and 496.1.

Intermediate 71

tert-Butyl (4-acetyl-6-methoxypyridin-2-yl)carbamate

A solution of *tert*-butyl (4-acetyl-6-methoxypyridin-2-yl)carbamate (5.25 g, 23.41 mmol) and
30 TMEDA (10.9 mL, 23.41 mmol) in dry Et₂O (100 mL) was cooled under an atmosphere of Ar (g) to -70 °C, and 1.6 M *n*BuLi in heptane (43.9 mL, 70.24 mmol) was added slowly. After complete addition the reaction mixture was stirred for 2 h at -15 °C. The mixture was cooled

to -70 °C, and *N*-methoxy-*N*-methylacetamide (5 mL, 52.37 mmol) was added dropwise over 10 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt overnight. The mixture was poured into a solution of NH₄Cl (aq) and ice. The layers were separated, the aqueous layer was extracted with MTBE, and the combined organic layers were washed with 5% citric acid (aq) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (15% EtOAc in heptane) to give 1.48 g of the title compound as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 267.1.

Intermediate 72

1-(5-Amino-2-methoxypyridin-4-yl)ethan-1-one

TFA (5.79 mL, 75.10 mmol) was added to a solution of *tert*-butyl (4-acetyl-6-methoxypyridin-3-yl)carbamate **Intermediate 71** (1 g, 3.76 mmol) in DCM (12.4 mL) and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The organic layers were combined, filtered through a hydrophobic frit and concentrated to grant the title compound (0.616 g, 99%) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 167.1.

Intermediate 73

2-((4-Acetyl-6-methoxypyridin-3-yl)amino)-2-oxoethyl acetate

2-Chloro-2-oxoethyl acetate (0.427 mL, 3.97 mmol) was added to a solution containing TEA (2.52 mL, 18.05 mmol) and 1-(5-amino-2-methoxypyridin-4-yl)ethan-1-one **Intermediate 72** (600 mg, 3.61 mmol) in DCM (20 mL) at 0 °C and stirred for 3 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude residue was purified by straight phase flash chromatography on silica (0–50% EtOAc in heptane) to grant the title compound (869 mg, 90%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃, 25°C) δ 2.18 (3H, s), 2.55 (3H, s), 3.88 (4H, s), 4.64 (2H, s), 7.23 (1H, ds), 8.62 (1H, s).

Intermediate 74

(6-Methoxy-4-methylpyrido[3,4-*d*]pyrimidin-2-yl)methanol

2-((4-Acetyl-6-methoxypyridin-3-yl)amino)-2-oxoethyl acetate **Intermediate 73** (869 mg, 3.26 mmol) in 4 M NH₃ in MeOH (10 mL) was heated under microwave irradiation at 80 °C for 4 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, filtered through a hydrophobic frit and concentrated. The residue was redissolved in 4 M NH₃ in MeOH (10 mL) and heated under microwave irradiation at 80 °C for 3 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, filtered through a hydrophobic frit and concentrated to grant the title compound (547 mg, 82%). MS (ESI) *m/z* [M+H]⁺ 206.0.

Intermediate 75

2-(Chloromethyl)-8-fluoro-4-methylquinazoline

(8-Fluoro-4-methylquinazolin-2-yl)methanol **Intermediate 24** (111 mg, 0.58 mmol) was dissolved in DCM (2 mL) and PPh₃ (166 mg, 0.63 mmol) was added. The reaction mixture was cooled in an ice-bath and NCS (85 mg, 0.63 mmol) was added. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 25–50% EtOAc in heptane) to give the title compound (0.093 g, 77%) as white solid. MS (ESI) *m/z* [M+H]⁺ 211.0. ¹H NMR (500 MHz, CDCl₃) 3.00 (3H, s), 4.89 (2H, s), 7.57 – 7.64 (2H, m), 7.87 – 7.94 (1H, m).

Intermediate 76

2-((2-Acetyl-4-fluorophenyl)amino)-2-oxoethyl acetate

1-(2-Amino-5-fluorophenyl)ethan-1-one (4.95 g, 31.35 mmol) was dissolved in DCM (90 mL) and cooled in an ice-bath. NMM (6.89 mL, 62.70 mmol) was added followed by a dropwise addition of acetoxyacetyl chloride (4.17 mL, 37.62 mmol). After 15 min the cooling bath was removed, and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with DCM, washed with 10% citric acid (aq), sat NaHCO₃ (aq) and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the title compound (8.72 g) as brown oil. MS (ESI) *m/z* [M+H]⁺ 254.0. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 2.36 (3H, s), 2.65 (3H, s), 4.72 (2H, s), 7.29 (1H, ddd), 7.58 (1H, dd), 8.80 (1H, dd), 12.10 (1H, s). ¹⁹F NMR (471 MHz, CDCl₃) δ -117.68.

Intermediate 77(6-Fluoro-4-methylquinazolin-2-yl)methanol

2-((2-Acetyl-4-fluorophenyl)amino)-2-oxoethyl acetate **Intermediate 76** (1.498 g, 5.92 mmol) was suspended in 4 M NH₃ in MeOH (16.27 mL, 65.07 mmol) and heated in a
5 microwave reactor for 8 h at 85 °C. The mixture was concentrated in vacuo, redissolved in EtOAc and washed with sat NaHCO₃ (aq). The organic layers were dried over Na₂SO₄, filtered and concentrated to afford the title compound (1.00 g, 88%) as a beige solid. MS (ESI) *m/z* [M+H]⁺ 193.0. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 2.92 (3H, s), 3.90 – 4.00 (1H, m), 4.91–4.96 (2H, m), 7.62 - 7.73 (2H, m), 8.00 – 8.04 (1H, m). ¹⁹F NMR (471 MHz,
10 CDCl₃) δ -110.22.

Intermediate 782-(Chloromethyl)-6-fluoro-4-methylquinazoline

(6-Fluoro-4-methylquinazolin-2-yl)methanol **Intermediate 77** (0.111 g, 0.58 mmol) was
15 dissolved in DCM (2 mL) and PPh₃ (0.167 g, 0.64 mmol) was added. The reaction mixture was cooled in an ice-bath and NCS (0.085 g, 0.64 mmol) was added. The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 15–50% EtOAc in heptane) to give the title compound (0.085 g, 70%) as white solid. ¹H NMR (500 MHz,
20 CDCl₃, 25 °C) δ 2.94 (3H, s), 4.85 (2H, s), 7.64–7.72 (2H, m), 8.03 – 8.09 (1H, m). ¹⁹F NMR (470 MHz, CDCl₃) δ -109.02.

Intermediate 792-((2-Acetyl-3-fluorophenyl)amino)-2-oxoethyl acetate

1-(2-Amino-6-fluorophenyl)ethan-1-one (0.998 g, 6.52 mmol) was dissolved in DCM (21 mL) and cooled in an ice-bath. NMM (1.433 mL, 13.03 mmol) was added followed by a dropwise addition of acetoxyacetyl chloride (0.867 mL, 7.82 mmol). After 15 min the cooling bath was removed, and the reaction mixture was stirred at rt overnight. The mixture was diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ (aq), and brine.
30 The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound (1.895 g) as brown oil. MS (ESI) *m/z* [M+H]⁺ 254.1 ¹H NMR (500

MHz, CDCl₃, 25 °C) δ 2.36 (3H, s), 2.67 (3H, d), 4.71 (2H, s), 6.90 (1H, ddd), 7.49 (1H, td), 8.47 – 8.52 (1H, m), 11.86 (1H, s). ¹⁹F NMR (471 MHz, CDCl₃) δ -103.84.

Intermediate 80

5 (5-Fluoro-4-methylquinazolin-2-yl)methanol

2-((2-Acetyl-3-fluorophenyl)amino)-2-oxoethyl acetate **Intermediate 79** (1.650 g, 6.52 mmol) was suspended in 4 M NH₃ in MeOH (17.92 mL, 71.67 mmol) and heated in a microwave reactor at 85 °C for 8 h. The mixture was concentrated in vacuo. The residue was redissolved in EtOAc and washed with sat NaHCO₃ (aq). The organic layer was dried over
10 Na₂SO₄, filtered and concentrated to afford the title compound (1.164 g, 93%) as brown solid. MS (ESI) *m/z* [M+H]⁺ 193.0. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 3.08 (3H, d), 3.86–4.21 (1H, m), 4.95 (2H, s), 7.78–7.86 (2H, m). ¹⁹F NMR (471 MHz, CDCl₃) δ -107.38.

Intermediate 81

15 2-(Chloromethyl)-5-fluoro-4-methylquinazoline

(5-Fluoro-4-methylquinazolin-2-yl)methanol **Intermediate 80** (0.222 g, 1.16 mmol) was dissolved in DCM (4 mL) and PPh₃ (0.333 g, 1.27 mmol) was added. The mixture was cooled in an ice-bath and NCS (0.170 g, 1.27 mmol) was added. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The crude residue was purified by straight
20 phase flash chromatography on silica (gradient 15–45% EtOAc in heptane) to give the title compound (0.106 g, 44%) as beige-white solid. MS (ESI) *m/z* [M+H]⁺ 211.0. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 3.09 (3H, d), 4.84 (2H, s), 7.30 (1H, ddd), 7.79–7.89 (2H, m). ¹⁹F NMR (471 MHz, CDCl₃) δ -107.43.

25 **Intermediate 82**

2-((2-Acetyl-5-fluorophenyl)amino)-2-oxoethyl acetate

1-(2-Amino-4-fluorophenyl)ethan-1-one (1.041 g, 6.80 mmol) was dissolved in DCM (21 mL) and cooled in an ice-bath. NMM (1.495 mL, 13.59 mmol) was added followed by a dropwise addition of acetoxyacetyl chloride (0.904 mL, 8.16 mmol). After 15 min the
30 cooling bath was removed, and the reaction mixture was stirred at rt over the weekend. The mixture was diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ (aq), and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced

pressure to afford the title compound (1.940 g) as a brown solid. ^1H NMR (500 MHz, CDCl_3 , 25 °C) δ 2.37 (3H, s), 2.65 (3H, s), 4.73 (2H, s), 6.85 (1H, ddd), 7.93 (1H, dd), 8.59 (1H, dd), 12.50 (1H, s).

5 **Intermediate 83**

(7-Fluoro-4-methylquinazolin-2-yl)methanol

2-((2-Acetyl-5-fluorophenyl)amino)-2-oxoethyl acetate **Intermediate 82** (1.719 g, 6.79 mmol) was suspended in 4 M NH_3 in MeOH (18.67 mL, 74.67 mmol) and heated in a microwave reactor at 85 °C for 9 h. The mixture was concentrated in vacuo, redissolved in EtOAc and washed with sat NaHCO_3 (aq). The organic layer was dried over Na_2SO_4 , filtered and concentrated to afford the title compound (1.218 g, 93%) as a light brown solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ 193.0. ^1H NMR (500 MHz, CDCl_3 , 25 °C) δ 2.93 (3H, s), 3.93–4.11 (1H, m), 4.91 (2H, s), 7.38 (1H, ddd), 7.60 (1H, dd), 8.12 (1H, dd). ^{19}F NMR (470 MHz, CDCl_3) δ -101.96.

15

Intermediate 84

2-(Chloromethyl)-7-fluoro-4-methylquinazoline

(7-Fluoro-4-methylquinazolin-2-yl)methanol **Intermediate 83** (0.266 g, 1.38 mmol) was dissolved in DCM (4.7 mL) and PPh_3 (0.399 g, 1.52 mmol) was added. The mixture was cooled in an ice-bath and NCS (0.203 g, 1.52 mmol) was added. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 15–50% EtOAc in heptane) to give the title compound (0.178 g, 61%) as a light-yellow solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ 210.9. ^1H NMR (500 MHz, CDCl_3 , 25 °C) δ 2.97 (3H, s), 4.83 (2H, s), 7.42 (1H, ddd), 7.65 (1H, ddd), 8.14 (1H, ddd). ^{19}F NMR (471 MHz, CDCl_3) δ -101.90.

25

Intermediate 85

2-(Chloromethyl)-6-methoxypyrido[3,2-*d*]pyrimidin-4(3*H*)-one

Methyl 3-amino-6-methoxypicolinate (0.225 g, 1.2 mmol) and 2-chloroacetonitrile (0.379 mL, 6.00 mmol) were dissolved in 4 M HCl in 1,4-dioxane (4.50 mL, 18.00 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was cooled to rt and Et_2O was added. The mixture was stirred, and the formed precipitate was collected by filtration, washed

30

with Et₂O, and dried under vacuum to yield the title compound (0.322 g) as HCl-salt. MS (ESI) m/z [M+H]⁺ 226.1. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 3.96 (3H, s), 4.55 (2H, s), 7.29 (1H, d), 8.01 (1H, d).

5 **Intermediate 86**

6-Methoxy-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidin-4-ol

1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt **Intermediate 28** (0.164 g, 0.63 mmol), 2-(chloromethyl)-6-methoxypyrido[3,2-*d*]pyrimidin-4(3*H*)-one, HCl-salt

10 **Intermediate 85** (0.191 g, 0.64 mmol) and DIPEA (0.884 mL, 5.06 mmol) were mixed in DMSO (4.0 mL) and stirred at rt overnight. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous phase was sublimated. EtOAc was added to the freeze-dried material and the solid material was filtered off to afford the title compound (0.226 g, 80%). MS (ESI) m/z [M+H]⁺ 449.2.

15

Intermediate 87

4-Chloro-6-methoxy-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidine

A suspension of 6-methoxy-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidin-4-ol **Intermediate 86** (0.226 g, 0.50 mmol) and DIPEA (0.176 mL, 1.01 mmol) in POCl₃ (0.892 mL, 9.57 mmol) was heated at 100 °C for 3 h. The mixture was concentrated under reduced pressure, and EtOAc was added followed by ice-water. The organic layer was separated and washed with sat NaHCO₃ (aq), filtered through a phase separator, and concentrated to yield the title compound (0.095 g, 40%). MS (ESI) m/z

25 [M+H]⁺ 467.2

Intermediate 88

tert-Butyl 4-(3-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate

Step a) 1,4-Dimethyl-1*H*-pyrazole-5-carbonyl chloride

30 1,4-Dimethyl-1*H*-pyrazole-5-carboxylic acid, HCl-salt (200 mg, 1.13 mmol) was treated with 1 M NaOH (aq, 1.132 mL, 1.13 mmol) and MeOH (a few mL) and stirred until everything had dissolved, and then concentrated under reduced pressure. The residue was treated with

THF/MeOH (1:1) and filtered using a syringe filter. The resulting solution was concentrated and then treated with SOCl₂ (3 mL, 1.13 mmol) and stirred at 70 °C for 2 h and then concentrated under reduced pressure to give the sub-title compound.

Step b) *tert*-Butyl 4-(3-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate

tert-Butyl 4-acetylpiperidine-1-carboxylate (309 mg, 1.36 mmol) was dissolved in THF (8 mL) and cooled to -78 °C. A solution of 2 M LDA in THF/heptane/ethylbenzene (0.736 mL, 1.47 mmol) was added dropwise. The mixture was stirred for 1 h followed by dropwise addition of 1,4-dimethyl-1*H*-pyrazole-5-carbonyl chloride **Intermediate 88 Step a)** dissolved in THF (3 mL). The cooling bath was removed, and the reaction mixture warmed to rt and the reaction was quenched with water and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 20–35% EtOAc in heptane) to give the title compound (0.052 g, 13%) as a clear oil. MS (ESI) *m/z* [M-H]⁻ 348.5. ¹H NMR (500 MHz, CDCl₃) δ 7.28 (s, 1H), 5.80 (s, 1H), 4.12 – 4.26 (m, 2H), 4.07 (s, 3H), 2.71 – 2.82 (m, 2H), 2.41 (tt, 1H), 2.22 (s, 3H), 1.84 – 1.90 (m, 2H), 1.60 (qd, 2H), 1.45 (s, 9H).

Intermediate 89

tert-Butyl 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(3-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 88** (52 mg, 0.15 mmol) was dissolved in EtOH (2 mL) and 64% hydrazine hydrate (aq, 100 μL, 2.20 mmol) was added at rt. The reaction mixture was heated to 65 °C and stirred for 1 h and then cooled to rt and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 30–100% EtOAc in heptane) to give the title compound (0.038 g, 74%) as white solid. MS (ESI) *m/z* [M+H]⁺ 346.4. ¹H NMR (500 MHz, CDCl₃) δ 7.32 (s, 1H), 6.16 (s, 1H), 4.00 – 4.29 (m, 2H), 3.89 (s, 3H), 2.64 – 2.88 (m, 3H), 2.07 (s, 3H), 1.95 – 1.85 (m, 2H), 1.59 (qd, 2H), 1.45 (s, 9H).

Intermediate 90

2,4-Dimethyl-5'-(piperidin-4-yl)-2*H*,2'*H*-3,3'-bipyrazole

tert-Butyl 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 89 (37.9 mg, 0.11 mmol) was dissolved in DCM (1 mL) and TFA (0.5 mL, 0.11 mmol) was added. The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure to afford the TFA salt of the title compound (40 mg). MS (ESI) *m/z* [M+H]⁺ 246.3. ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.41 (s, 1H), 6.41 (s, 1H), 3.88 (s, 3H), 3.54 – 3.47 (m, 2H), 3.23 - 3.10 (m, 3H), 2.36 - 2.24 (m, 2H), 2.09 (s, 3H), 2.02 - 1.91 (m, 2H).

Intermediate 91

2-((4-(5-(Pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

DIPEA (695 μL, 3.99 mmol) was added to a solution of 3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine, TFA **Intermediate 18** (500 mg, 1.10 mmol) and 2-(chloromethyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (200 mg, 1.00 mmol) in DMSO (4.29 mL) and the reaction mixture was stirred at rt overnight. The mixture was filtered and the filtrate purified by preparative HPLC, PrepMethod D, (gradient: 10–55%), to grant the title compound as a white solid. MS (ESI) *m/z* [M+H]⁺ 393.4.

Intermediate 92

4-Chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidine

A suspension of 2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one **Intermediate 91** (26.0 mg, 0.07 mmol) in POCl₃ (0.5 mL, 0.07 mmol) was heated to 100 °C for 1 h. The reaction mixture was cooled to rt and poured into a stirred solution of sat NaHCO₃ (aq). The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (25 mg, 87%) as a yellow residue. MS (ESI) *m/z* [M+H]⁺ 411.4.

Intermediate 93

2-(Chloromethyl)-4-methyl-5,6,7,8-tetrahydroquinazoline

MeCN (6 mL) and 2-acetylcyclohexan-1-one (879 μL, 6.74 mmol) were added to a vial charged with 2-chloroacetimidamide, HCl (956 mg, 7.41 mmol). The reaction mixture was

heated to 140 °C in a microwave reactor for 4 h. The solvent was evaporated, and the residue was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude material was purified by straight phase flash chromatography on silica (gradient: 18–25% EtOAc in heptane) to afford the title compound (0.192 g, 15%) as a pale-yellow oil. MS (ESI) m/z [M+H]⁺ 197.2.

Intermediate 94

N-(4-Cyano-1-methyl-1*H*-pyrrol-3-yl)-2-(4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)acetamide

Step a) 2,4-Dimethyl-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine

TFA (2 mL, 1.25 mmol) was added to a solution of *tert*-butyl 4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 47** (447 mg, 1.25 mmol) in DCM (5 mL). The reaction mixture was stirred at rt for 2 h and then concentrated to dryness and redissolved in DMSO (5 mL).

Step b) 2-Chloroacetyl chloride (0.110 mL, 1.38 mmol) was added to a solution of 2-amino-1-methyl-1*H*-pyrrole-3-carbonitrile (152 mg, 1.25 mmol) in dioxane (5 mL) and stirred at rt for 6 h. The DMSO solution of **Intermediate 94 Step a**) was added followed by DIPEA (2.7 mL, 15.50 mmol) and the reaction mixture was stirred for 2 d. The mixture was concentrated to remove the dioxane and the resulting dark solution was purified by preparative HPLC, PrepMethod F, (gradient: 10–55%) to grant the title compound (0.137 g, 26%) as a red-brown solid. MS (ESI) m/z [M+H]⁺ 417.0.

Intermediate 95

2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-7-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one

12 M HCl (aq, 1 mL, 0.27 mmol) was added to a stirred solution of *N*-(4-cyano-1-methyl-1*H*-pyrrol-3-yl)-2-(4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)acetamide **Intermediate 94** (113 mg, 0.27 mmol) in AcOH (3 mL) and heated to 80 °C for 1 h. The mixture was concentrated to dryness and redissolved in 2 M NaOH (aq, 2 mL, 4.00 mmol) and MeOH (4 mL) and stirred at 65 °C for 2 h. The mixture was concentrated and the residue was diluted with water and DCM. The layers were separated, and the aqueous layer was

extracted with DCM. The combined organic layers were dried over MgSO₄, filtered and concentrated to afford the title compound (57 mg, 50%) as a pink-purple film. MS (ESI) m/z [M+H]⁺ 418.4.

5 **Intermediate 96**

4-Chloro-2-((4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidine

A suspension of 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-7-methyl-3,7-dihydro-4H-pyrrolo[2,3-*d*]pyrimidin-4-one **Intermediate 95** (57.0 mg, 0.14 mmol) in POCl₃ (2 mL, 0.14 mmol) was heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to rt and added dropwise to a stirred solution of sat NaHCO₃ (aq). The mixture was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to afford the title compound (50 mg, 84%) as a clear film. MS (ESI) m/z [M+H]⁺ 436.4 and 438.2.

15

Intermediate 97

rac-(3,4-Dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methanol

rac-(3,4-Dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methanol, HCl (1 g, 4.96 mmol) was dissolved in MeOH (10 mL). Carbonate on solid support (3.5 mmol/g, 2 g, 16.79 mmol) was added and the reaction mixture was stirred at rt for 1h. The polymer was filtered off and the filtrate was concentrated to grant the title compound (0.65 g, 79%) as a dark oil. MS (ESI) m/z [M+H]⁺ 166.0.

Intermediate 98

25 *rac-tert* Butyl 2-(hydroxymethyl)-2,3-dihydro-4H-benzo[*b*][1,4]oxazine-4-carboxylate
rac-(3,4-Dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methanol **Intermediate 97** (0.65 g, 3.93 mmol) was dissolved in THF (12 mL) in a microwave vial and flushed with N₂ (g). A solution of Boc₂O (3.65 mL, 15.74 mmol) in THF (3 mL) was added dropwise, and the vial was sealed and stirred at 60 °C for 19 h. The solvent was removed in vacuo, and the remaining mixture was diluted with DCM. The organic layers were washed with water, filtered through a phase
30 separator and concentrated. The crude residue was purified by straight phase flash

chromatography on silica, (gradient: 0–50% EtOAc in heptane) to grant the title compound (250 mg, 24%) as a tan semi-solid. MS (ESI) m/z $[M-H]^-$ 264.1.

Intermediate 99

5 *rac-tert*-Butyl 2-((tosyloxy)methyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate
TsCl (287 mg, 1.51 mmol) was added to a mixture of *rac-tert*-butyl 2-(hydroxymethyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate **Intermediate 98** (250 mg, 0.94 mmol) in pyridine (5 mL) and stirred at rt overnight. DCM and 10% citric acid (aq) were added, and the mixture was stirred, filtered through a phase separator and concentrated. The crude residue
10 was purified by straight phase flash chromatography on silica (gradient: 0–25% EtOAc in heptane) to grant the title compound (320 mg, 81%) as a tan foam. 1H NMR (500 MHz, $CDCl_3$) 1.52 (9H, s), 2.45 (3H, s), 3.49 (1H, d), 4.03 – 4.14 (1H, m), 4.14 – 4.23 (2H, m), 4.35 (1H, m), 6.77 (1H, m), 6.87 (1H, m), 6.95 (1H, m), 7.35 (2H, d), 7.69 (1H, s), 7.76 – 7.85 (2H, m).

Intermediate 100

rac-(3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate
6 M HCl in IPA (0.397 mL, 2.38 mmol) was added to a solution of *rac-tert*-butyl 2-((tosyloxy)methyl)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate **Intermediate 99**
20 (200 mg, 0.48 mmol) in DCM (4 mL) and the reaction mixture was stirred at rt overnight. 6 M HCl in IPA (0.397 mL, 2.38 mmol) was added and the reaction mixture was stirred at 30 °C overnight. The mixture was concentrated and redissolved in MeOH (5 mL). Carbonate on solid support (3.5 mmol/g, 1 g, 8.39 mmol) was added and the mixture was stirred at rt for 2 h. The solids were filtered off and the filtrate concentrated to grant the title compound (144
25 mg, 95%) as a tan oil. MS (ESI) m/z $[M+H]^+$ 320.0.

Intermediate 101

rac-(4-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate
In a microwave vial, a solution of *rac*-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate **Intermediate 100** (145 mg, 0.45 mmol) and K_2CO_3 (75 mg, 0.54
30 mmol) in DMF (2.5 mL) was stirred at rt for 20 min. The mixture was cooled to 0°C and MeI (0.043 mL, 0.68 mmol) was added. The vial was sealed and stirred at 50°C for 3 h. MeI

(0.043 mL, 0.68 mmol) was added and the reaction mixture was stirred at 50 °C overnight. The mixture was diluted with sat NaHCO₃ (aq) and DCM and stirred, filtered through a phase separator and concentrated. Another batch was prepared as described above starting with *rac*-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate **Intermediate**
5 **100** (55 mg, 0.17 mmol). The batches were combined after the workup stage and purified by straight phase flash column chromatography (gradient: 0–40% EtOAc in heptane) to grant the title compound (73 mg, 35%) as a colourless oil. MS (ESI) *m/z* [M+H]⁺ 334.1.

Intermediate 102

10 2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-3,5,7,8-tetrahydro-4*H*-pyrano[4,3-*d*]pyrimidin-4-one

2-(Chloromethyl)-3,5,7,8-tetrahydro-4*H*-pyrano[4,3-*d*]pyrimidin-4-one (87 mg, 0.43 mmol) was added to a mixture of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt **Intermediate 28** (109 mg, 0.42 mmol) and DIPEA (0.732 mL, 4.20 mmol) in DMF
15 (1.368 mL) and the reaction mixture was stirred at rt for 3 h and then at 70 °C for 8 h. The mixture was cooled to rt and water was added, and the mixture was extracted with EtOAc (×2). The aqueous layer was concentrated, and the residue was purified by preparative HPLC, PrepMethod D, (gradient: 0–30%), to yield the title compound (0.106 g, 60%) as beige solid. MS (ESI) *m/z* [M+H]⁺ 424.2. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.69 (2H, qd), 1.84–
20 1.92 (2H, m), 2.1–2.38 (8H, m), 2.55–2.66 (3H, m), 2.85–2.93 (2H, m), 3.37 (2H, s), 3.66 (3H, s), 3.84 (2H, t), 4.33–4.38 (2H, m), 6.04 (1H, s), 11.74–12.53 (2H, m).

Intermediate 103

25 4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine

2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-3,5,7,8-tetrahydro-4*H*-pyrano[4,3-*d*]pyrimidin-4-one **Intermediate 102** (105.9 mg, 0.25 mmol) was dissolved in POCl₃ (4 mL, 42.92 mmol) and stirred at 110 °C for 2 h. The mixture was cooled to rt and 10% NaHCO₃ (aq) solution was added. The mixture was basified with 1N NaOH
30 (aq) solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound (0.096 g, 87%) as brown solid. MS (ESI) *m/z* [M+H]⁺ 442.3.

Intermediate 1043-Acetyltetrahydro-2H-pyran-2-one

Tetrahydro-2H-pyran-2-one (1.446 g, 14.44 mmol) was dissolved in THF (37 mL) and cooled
5 to -78 °C. 1 M LiHMDS in THF (28.9 mL, 28.88 mmol) was added and the reaction mixture
was stirred for 10 min and then Ac₂O (1.362 mL, 14.44 mmol) was added. The reaction
mixture was stirred for 10 min and then warmed to rt and stirred for 1 h. HOAc (6 mL) was
added followed by MTBE (40 mL). The precipitate was filtered off and washed with MTBE.
The filtrate was concentrated under reduced pressure. The crude residue was purified by
10 straight phase flash chromatography on silica (gradient 0–30% EtOAc in heptane) to give the
title compound (0.886 g, 43%). ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.89–1.95 (2H, m), 2.01
(3H, s), 2.41 (2H, t), 4.26–4.32 (2H, m), 13.70 (1H, s).

Intermediate 1052-(Chloromethyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol

3-Acetyltetrahydro-2H-pyran-2-one **Intermediate 104** (97 mg, 0.68 mmol) was dissolved in
and MeOH (1 mL) in a microwave vial. 2-Chloroacetimidamide, HCl-salt (152 mg, 1.18
mmol) and K₂CO₃ (229 mg, 1.66 mmol) were added. The vial was sealed and heated to 50 °C
for 30 min. The suspension was filtered using a syringe filter and concentrated under reduced
20 pressure. The crude residue was purified by straight phase flash chromatography on silica
(gradient: 0–20% MeOH in EtOAc) to give the title compound (0.065 g, 44%) as an orange
solid. MS (ESI) *m/z* [M+H]⁺ 217.1. ¹H NMR (500 MHz, Methanol-d₄, 25 °C) δ 1.67–1.74
(2H, m), 2.34 (3H, s), 2.55–2.62 (2H, m), 3.57 (2H, t), 4.41 (2H, s).

Intermediate 1062-((4-Ethynylpiperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol

4-Ethynylpiperidine, TFA-salt (670 mg, 3.00 mmol), 2-(chloromethyl)-5-(3-hydroxypropyl)-
6-methylpyrimidin-4-ol **Intermediate 5** (650 mg, 3.00 mmol) and DIPEA (2.62 mL, 15.00
mmol) were stirred in DMSO (6 mL) at rt overnight. The material was purified by preparative
30 HPLC, PrepMethod D, (gradient: 10–50%), to give the title compound (622 mg, 72%) as tan
solid. MS (ESI) *m/z* [M+H]⁺ 290.4. ¹H NMR (500 MHz, Methanol-d₄, 25 °C) δ 1.64–1.76

(4H, m), 1.84–1.93 (2H, m), 2.29–2.37 (5H, m), 2.38 (1H, d), 2.4–2.5 (1H, m), 2.55–2.61 (2H, m), 2.72–2.81 (2H, m), 3.42 (2H, s), 3.57 (2H, t).

Intermediate 107

5 2-((4-Ethynylpiperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine
2-((4-Ethynylpiperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol

Intermediate 1 (460 mg, 1.59 mmol) and PPh₃ (625 mg, 2.38 mmol) were dissolved in THF (25 mL) and cooled in an ice-bath. DIAD (0.469 mL, 2.38 mmol) was added dropwise. The reaction mixture was stirred for 10 min and then warmed to rt and stirred for 1 h. The mixture
10 was concentrated under reduced pressure and the crude product was purified by straight phase flash chromatography on silica (gradient: 0–10% MeOH (2 M NH₃) in DCM) and then by preparative HPLC, PrepMethod G, (gradient: 5–50%), to give the formate-salt of the title compound (327 mg, 76%) as tan solid. Part of the salt (264 mg, 0.83 mmol) was dissolved in DCM (5 mL) and sat (aq) NaHCO₃ (3 mL). The mixture was stirred for 5 min, then filtered
15 through a phase separator and concentrated under reduced pressure to give the free base of the title compound (223 mg, 99%) of as tan solid. ¹H NMR (500 MHz, Methanol-*d*₄, 25 °C) δ 1.61–1.71 (2H, m), 1.82–1.89 (2H, m), 2.01–2.1 (2H, m), 2.27–2.4 (3H, m), 2.41 (3H, s), 2.74 (2H, t), 2.77–2.85 (2H, m), 3.53 (2H, s), 4.36–4.41 (2H, m), 5.49 (1H, s).

20 Intermediate 108

1-(1,4-Dimethyl-1H-pyrazol-5-yl)-3-(1-((4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidin-
2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine

Intermediate 107 (70 mg, 0.26 mmol) was dissolved in THF (0.5 mL) and toluene (0.5 mL).
25 1,4-Dimethyl-1H-pyrazole-5-carbonyl chloride (61.4 mg, 0.39 mmol), CuI (2.5 mg, 0.01 mmol) and TEA (0.216 mL, 1.55 mmol) were added followed by Pd(PPh₃)₂Cl₂ (9.1 mg, 0.01 mmol) and the reaction mixture was stirred under an atmosphere of N₂ (g) at rt for 2.5 h. DCM (5 mL) and sat NaHCO₃ (aq, 5 mL) were added. The mixture was stirred, filtered through a phase separator and concentrated under reduced pressure. The crude residue was
30 purified by straight phase flash chromatography on silica (gradient 1–10% MeOH (2M NH₃)) in DCM) to give the title compound (80 mg, 79%). MS (ESI) *m/z* [M+H]⁺ 394.6. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.66–1.76 (1H, m), 1.79–1.88 (2H, m), 1.89–2.09 (4H, m), 2.24–

2.32 (2H, m), 2.33–2.4 (5H, m), 2.61–2.68 (2H, m), 2.78–3.00 (2H, m), 3.58 (2H, d), 4.07 (3H, d), 4.27–4.35 (2H, m), 7.24–7.28 (1H, m).

Intermediate 109

5 2-(Chloromethyl)-7,8-dihydro-6H-pyrano[3,2-*d*]pyrimidin-4-ol

Ethyl 3-oxotetrahydro-2H-pyran-2-carboxylate (0.740 g, 4.30 mmol) was dissolved in MeOH (6 mL) under an atmosphere of N₂ (g). 2-Chloroacetimidamide, HCl-salt (0.642 g, 4.73 mmol) was added followed by a dropwise addition of 30% NaOMe in MeOH (0.959 mL, 5.16 mmol) over a few min. The reaction mixture was stirred at rt overnight. The mixture was
10 filtered and concentrated under reduced pressure to yield the title compound (1.140 g). MS (ESI) *m/z* [M+H]⁺ 201.1.

Intermediate 110

15 2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6H-pyrano[3,2-*d*]pyrimidin-4-ol

A mixture of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt

Intermediate 28 (0.197 g, 0.53 mmol), 2-(chloromethyl)-7,8-dihydro-6H-pyrano[3,2-*d*]pyrimidin-4-ol **Intermediate 109** (0.107 g, 0.53 mmol) and DIPEA (0.553 mL, 3.17 mmol) in DMSO (4.0 mL) was stirred at rt overnight. The mixture was diluted with EtOAc and
20 water. The aqueous layer was sublimated, EtOAc was added and the solids were filtered off to afford the title compound (0.206 g, 92%). MS (ESI) *m/z* [M+H]⁺ 424.2.

Intermediate 111

25 *rac-tert*-Butyl (2*R*,4*R*)-2-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)propanoyl)piperidine-1-carboxylate

A mixture of *rac*-(2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-2-methylpiperidine-4-carboxylic acid (823 mg, 3.38 mmol) and CDI (680 mg, 4.19 mmol) in THF (14 mL) was stirred at rt for 2 h. A solution of 1-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethan-1-one (669 mg, 4.40 mmol) in THF (14 mL) was prepared in a separate flask, cooled to -78 °C and 1 M LiHMDS in THF (4.57 mL,
30 4.57 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h and then the CDI-activated carboxylic acid was added. The cooling bath was removed after 10 min and the reaction mixture was allowed to reach rt and stirred for 1 h. The reaction was quenched with

sat NaHCO₃ (aq) and the mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title compound (1.276 g). MS (ESI) m/z [M+H]⁺ 378.2.

5

Intermediate 112

rac-tert-Butyl (2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

rac-tert-Butyl (2*R*,4*R*)-2-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-

10 yl)propanoyl)piperidine-1-carboxylate **Intermediate 111** (1.276 g, 3.38 mmol) was dissolved in EtOH (2 mL) and 64%hydrazine hydrate (aq, 200 μ L, 4.11 mmol) was added. The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 25–65%), to give the title compound (90 mg, 7%) as a white solid. MS (ESI) m/z [M+H]⁺ 374.2. ¹H NMR (500
15 MHz, CDCl₃, 25 °C) δ 1.06 (3H, d), 1.44 (9H, s), 1.67–1.77 (1H, m), 1.8–1.9 (1H, m), 2.01–2.14 (2H, m), 2.23 (6H, s), 2.88–3.00 (1H, m), 3.14–3.26 (1H, m), 3.70 (3H, s), 3.80 (1H, ddd), 3.97–4.09 (1H, m), 6.02 (1H, s).

Intermediate 113

20 *rac*-5-(3-Hydroxypropyl)-6-methyl-2-(((2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol

rac-tert-Butyl (2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 112** (90 mg, 0.24 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). The reaction mixture was stirred for 1 h and then concentrated
25 under reduced pressure. The residue was dissolved in DMSO (2 mL) and 2-(chloromethyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 5** (59 mg, 0.27 mmol) and K₂CO₃ (165 mg, 1.19 mmol) were added. The reaction mixture was stirred at rt overnight, filtered using a syringe filter and purified by preparative HPLC, PrepMethod D, (gradient: 10–50%), to give the title compound (78 mg, 71%) as a white solid. MS (ESI) m/z [M+H]⁺ 454.4.

30

Intermediate 114

3-Propionyltetrahydro-2*H*-pyran-2-one

Tetrahydro-2*H*-pyran-2-one (2.54 g, 25.37 mmol) was dissolved in THF (51 mL) and cooled at -78 °C. 1 M LiHMDS in THF (50.7 mL, 50.74 mmol) was added and the reaction mixture was stirred for 10 min. Propionic anhydride (3.25 mL, 25.37 mmol) was added and the reaction mixture was stirred for 10 min and then allowed to warm to rt and stirred for 1 h.
5 HOAc (8 mL) was added followed by MTBE. The precipitate formed was filtered off and washed with MTBE. The filtrate was concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–30% EtOAc in heptane) to give the title compound (1.458 g, 37%). MS (ESI) m/z [M+H]⁺ 157.1.

10 Intermediate 115

2-(Chloromethyl)-6-ethyl-5-(3-hydroxypropyl)pyrimidin-4-ol

3-Propionyltetrahydro-2*H*-pyran-2-one **Intermediate 114** (1.455 g, 9.32 mmol) was dissolved in MeOH (10 mL) under an atmosphere of N₂ (g). 2-Chloroacetimidamide, HCl-salt (1.391 g, 10.25 mmol) was added followed by a dropwise addition of 30% NaOMe in MeOH
15 (2.080 mL, 11.18 mmol) over a few min. The reaction mixture was stirred at rt overnight, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–50% (EtOAc/MeOH (4/1)) in heptane) to give the title compound (0.649 g, 30%) as solid. MS (ESI) m/z [M+H]⁺ 231.1. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.24 (3H, t), 1.73–1.82 (2H, m), 2.65 (2H, q), 2.72 (2H, t), 3.56 (2H,
20 t), 4.53 (2H, s).

Intermediate 116

6-Ethyl-5-(3-hydroxypropyl)-2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol

25 A mixture of 5'-methoxy-1'-methyl-5-(piperidin-4-yl)-1*H*,1'*H*-3,4'-bipyrazole, TFA-salt **Intermediate 56** (0.041 g, 0.11 mmol), 2-(chloromethyl)-6-ethyl-5-(3-hydroxypropyl)pyrimidin-4-ol **Intermediate 115** (0.024 g, 0.105 mmol) and DIPEA (0.110 mL, 0.63 mmol) in DMSO (1 mL) was stirred at rt overnight. The product was purified by preparative HPLC, PrepMethod CC, (gradient: 15–45%), to yield the title compound (0.030 g,
30 63%). MS (ESI) m/z [M+H]⁺ 456.4. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.12 (3H, t), 1.50–1.58 (2H, m), 1.67 (2H, qd), 1.83–1.89 (2H, m), 2.15–2.25 (2H, m), 2.38–2.45 (2H, m),

2.85–2.92 (2H, m), 3.31 (1H, s), 3.34 (2H, s), 3.37–3.41 (2H, m), 3.64 (3H, s), 3.89 (3H, s), 4.47 (1H, t), 6.14 (1H, s), 7.54 (1H, s), 11.86 (1H, s), 12.41 (1H, s).

Intermediate 117

5 2-(Chloromethyl)-5,8-dihydro-6H-pyrano[3,4-*d*]pyrimidin-4-ol

Ethyl 5-hydroxy-3,6-dihydro-2H-pyran-4-carboxylate (0.917 g, 5.33 mmol) was dissolved in MeOH (7 mL) under an atmosphere of N₂ (g). 2-Chloroacetimidamide, HCl-salt (0.795 g, 5.86 mmol) was added followed by a dropwise addition of 30% NaOMe in MeOH (1.189 mL, 6.39 mmol) over a few min. The reaction mixture was stirred at rt overnight, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethodG, (gradient: 0–30%), to yield the title compound (0.431 g, 40%) as solid. MS (ESI) *m/z* [M-H]⁻ 199.1. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 2.37–2.44 (2H, m), 3.81 (2H, t), 4.31–4.36 (2H, m), 4.43 (2H, s), 12.74 (1H, s)

15 **Intermediate 118**

2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6H-pyrano[3,4-*d*]pyrimidin-4-ol

A mixture of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt

Intermediate 28 (0.093 g, 0.25 mmol), 2-(chloromethyl)-5,8-dihydro-6H-pyrano[3,4-*d*]pyrimidin-4-ol **Intermediate 117** (0.048 g, 0.238 mmol) and DIPEA (0.249 mL, 1.43 mmol) in DMSO (1.5 mL) was stirred at rt overnight. The product was purified by preparative HPLC, PrepMethod CC, (gradient: 15–55%), to yield the title compound (0.057 g, 57%) as beige solid. MS (ESI) *m/z* [M+H]⁺ 424.2. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.68 (2H, qd), 1.82–1.91 (2H, m), 2.12–2.24 (5H, m), 2.30 (3H, s), 2.37–2.42 (2H, m), 2.55–2.65 (1H, m), 2.85–2.92 (2H, m), 3.33 (2H, s), 3.66 (3H, s), 3.81 (2H, t), 4.3–4.38 (2H, m), 6.04 (1H, s), 12.07 (1H, s), 12.40 (1H, s).

Intermediate 119

30 4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6H-pyrano[3,4-*d*]pyrimidine

2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6H-pyrano[3,4-*d*]pyrimidin-4-ol **Intermediate 118** (0.055 g, 0.13 mmol)) was suspended in

POCl₃ (1.440 mL, 15.45 mmol) and heated to 106 °C for 90 min. The reaction mixture was cooled and concentrated in vacuo. The residue was mixed with toluene (10 mL) and concentrated again. The remaining oil was partitioned between DCM and sat NaHCO₃ (aq). The aqueous layer was extracted with DCM, and the combined organic layers were washed
5 with brine, filtered through a phase separator and concentrated under reduced pressure. The crude residue was purified by preparative HPLC, PrepMethod CC, (gradient: 30–70%), to yield the title compound (0.034 g, 59%). MS (ESI) *m/z* [M+H]⁺ 442.2. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.59–1.71 (2H, m), 1.82–1.9 (2H, m), 2.12–2.24 (5H, m), 2.30 (3H, s), 2.55–2.63 (1H, m), 2.77 (2H, t), 2.87–2.98 (2H, m), 3.61–3.68 (5H, m), 3.97 (2H, t), 4.66
10 (2H, s), 6.04 (1H, s), 12.34 (1H, s).

Intermediate 120

tert-Butyl 4-(3-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate

CDI (0.175 g, 1.08 mmol) was added to a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (0.243 g, 1.06 mmol) in THF (3 mL) and the reaction mixture was stirred at rt for 2 h. In a separated flask, a solution of 1-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)ethan-1-one (0.173 g, 1.03 mmol) in THF (6 mL) was cooled to -78 °C. 1 M LiHMDS in THF (2.57 mL, 2.57 mmol) was added and the reaction mixture was stirred for 30 min at -78 °C followed
20 by a dropwise addition over 10 min of the CDI-activated acid. The cold bath was removed, and the reaction mixture was stirred at rt overnight. 10% citric acid (aq, 3 mL) was added, and the mixture extracted with EtOAc. The organic layer was washed with brine, filtered through a phase separator, and concentrated under reduced pressure to afford the title compound. (0.430 g). MS (ESI) *m/z* [M+H]⁺ 380.3.

25

Intermediate 121

tert-Butyl 4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(3-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 120** (0.390 g, 1.03 mmol) was dissolved in 99.5% EtOH (3.5 mL) and 64% hydrazine hydrate (aq, 0.150 mL, 3.08 mmol) was added. The reaction mixture was
30 stirred at rt overnight and then co-evaporated with toluene under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 10–100%

(EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.242 g, 63%) as yellow solid.
MS (ESI) m/z $[M+H]^+$ 376.1.

Intermediate 122

- 5 5'-Methoxy-1',3'-dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole
tert-Butyl 4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
Intermediate 121 (0.242 g, 0.64 mmol) was dissolved in DCM (4.5 mL) and TFA (0.745
mL, 9.67 mmol) was added. The reaction mixture was stirred at rt for 1 h and then
concentrated under reduced pressure to yield TFA-salt of the title compound (0.250 g, 100%).
10 MS (ESI) m/z $[M+H]^+$ 276.2.

Intermediate 123

- 6-Ethyl-5-(3-hydroxypropyl)-2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-
yl)piperidin-1-yl)methyl)pyrimidin-4-ol
15 A mixture of 5'-methoxy-1',3'-dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, TFA-salt
Intermediate 122 (0.250 g, 0.64 mmol), 2-(chloromethyl)-6-ethyl-5-(3-
hydroxypropyl)pyrimidin-4-ol **Intermediate 115** (0.148 g, 0.64 mmol) and DIPEA (0.672
mL, 3.85 mmol) in DMSO (5.5 mL) was stirred at rt overnight. The product was purified by
preparative HPLC, PrepMethod CC, (gradient: 15–40%), to yield the title compound (0.544
20 g). MS (ESI) m/z $[M+H]^+$ 470.2.

Intermediate 124

- tert*-Butyl 4-(3-(5-cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-
carboxylate
25 5-Cyclopropyl-1-methyl-1*H*-pyrazole-4-carboxylic acid (0.133 g, 0.80 mmol) was suspended
in THF (2.5 mL) and CDI (0.131 g, 0.81 mmol) was added. The suspension was stirred at rt
for 4 h. In a separate flask, a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (0.175 g,
0.77 mmol) in THF (5 mL) was cooled to -78 °C and 1 M LiHMDS in THF (1.925 mL, 1.93
mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, followed by a
30 dropwise addition of the solution of the CDI-activated acid. The reaction mixture was stirred
at -78 °C for 5 min then at rt overnight. The reaction was quenched by addition of sat
NaHCO₃ (aq) and diluted with EtOAc. The layers were separated and the aqueous layer was

extracted with EtOAc. The combined organic layers were filtered through a phase separator and concentrated under reduced pressure to afford the title compound (0.323 g). MS (ESI) m/z $[M+H]^+$ 376.3.

5 **Intermediate 125**

tert-Butyl 4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
tert-Butyl 4-(3-(5-cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-
carboxylate **Intermediate 124** (0.289 g, 0.77 mmol) was dissolved in 99.5% EtOH (7.5 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.056 mL, 1.16 mmol) was added,
10 followed by HOAc (0.075 mL), and the reaction mixture was stirred at rt overnight. The mixture was poured into water (5mL) and sat NaHCO₃ (aq, 0.5 mL) and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 10–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.156 g,
15 55%). MS (ESI) m/z $[M+H]^+$ 372.2. ¹H NMR (500 MHz, DMSO, 25 °C) δ 0.53 (2H, s), 1.01 (2H, d), 1.41 (9H, s), 1.43–1.52 (2H, m), 1.8–1.93 (3H, m), 2.74–2.93 (3H, m), 3.83 (3H, s), 3.93–4.02 (2H, m), 6.19 (1H, s), 7.54 (1H, s), 12.42 (1H, s).

Intermediate 126

20 5'-Cyclopropyl-1'-methyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole
tert-Butyl 4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
Intermediate 125 (0.154 g, 0.41 mmol) was dissolved in DCM (4 mL) and cooled in an ice-bath. TFA (0.592 mL, 7.69 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced
25 pressure. The residue was triturated with Et₂O (5 mL). The solvent was decanted, and the resulting precipitate was dried under vacuum to yield the TFA-salt of the title compound (0.160 g, 100%) as. MS (ESI) m/z $[M+H]^+$ 272.1.

Intermediate 127

30 2-((4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol

A mixture of 5'-cyclopropyl-1'-methyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, TFA-salt **Intermediate 126** (0.160 g, 0.42 mmol), 2-(chloromethyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 5** (0.090 g, 0.415 mmol) and DIPEA (0.435 mL, 2.49 mmol) in DMSO (4 mL) was stirred at rt overnight. EtOAc and sat NaHCO₃ (aq) were added
5 and the mixture was filtered through a phase separator and concentrated under reduced pressure to afford the title compound (0.162 g, 86%). MS (ESI) *m/z* [M+H]⁺ 452.5.

Intermediate 128

Ethyl 3-(2-amino-4-hydroxy-6-methylpyrimidin-5-yl)propanoate

10 Diethyl 2-acetylpentanedioate (13.51 g, 58.67 mmol) was dissolved in 99.5% EtOH (dried over 3 Å molecular sieves, 100 mL). Guanidinium carbonate (12.1 g, 67.16 mmol) was added and the reaction mixture was heated to reflux for 12 h. The mixture was concentrated in vacuo. Water (40 mL) and concentrated HCl (aq, 5.8 mL) were added, and the mixture was shaken. The precipitate formed was collected by filtration, washed with water, and dried in
15 vacuo to give (12.6 g) of a colorless solid. The product was resolidified from 95% EtOH (approx. 150 mL) to give the title compound (7.396 g, 49%) as colorless solid. MS (ESI) *m/z* [M+H]⁺ 226.3. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.16 (3H, t), 2.05 (3H, s), 2.32–2.38 (2H, m), 2.48–2.54 (zm), 4.03 (2H, q), 6.30 (2H, s), 10.80 (1H, s).

Intermediate 129

Ethyl 3-(2,4-dihydroxy-6-methylpyrimidin-5-yl)propanoate

A concentrated solution of NaNO₂ (3.38 g, 48.99 mmol) in water (4.5 mL) was added dropwise to a mixture of ethyl 3-(2-amino-4-hydroxy-6-methylpyrimidin-5-yl)propanoate **Intermediate 128** (7.37 g, 32.72 mmol) in HOAc (60 mL) and water (20 mL). The reaction
25 mixture was stirred at rt for 2 h and then slowly heated to 60 °C and stirred for 2 h. The mixture was concentrated in vacuo to half the volume and acidified to pH3 by addition of HCl. The precipitate formed was collected by filtration, washed with water, and dried in vacuo to yield the title compound (2.45 g, 33%). MS (ESI) *m/z* [M+H]⁺ 227.3. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.16 (3H, t), 2.06 (3H, s), 2.31–2.48 (4H, m), 4.03 (2H, q), 10.67
30 (1H, s), 10.96 (1H, s).

Intermediate 130

Ethyl 3-(2,4-dichloro-6-methylpyrimidin-5-yl)propanoate

POCl₃ (20 mL) was added to ethyl 3-(2,4-dihydroxy-6-methylpyrimidin-5-yl)propanoate **Intermediate 129** (2.45 g, 10.83 mmol), followed by of *N,N*-dimethylaniline (20 drops, 10.83 mmol) and the reaction mixture was heated to approximately 100 °C for 2 h. The mixture was cooled and concentrated in vacuo. The residue was mixed with toluene and concentrated again. The residue was partitioned between ice water and EtOAc. The organic layer was washed with water (×2) and brine. The organic layer was dried over NaSO₄, and filtered through silica. The filtrate was concentrated in vacuo to yield the title compound (2.48 g, 87%) as orange oil. ¹H NMR (500 MHz, CDCl₃) 1.26 (3H, t), 2.56 – 2.6 (2H, m), 2.61 (3H, s), 3.05 – 3.09 (2H, m), 4.16 (2H, q). ¹³C NMR (126 MHz, CDCl₃) δ 171.67, 170.54, 163.31, 157.86, 131.70, 55.02, 32.66, 25.54, 22.53, 15.63.

Intermediate 1313-(2,4-Dichloro-6-methylpyrimidin-5-yl)propan-1-ol

Ethyl 3-(2,4-dichloro-6-methylpyrimidin-5-yl)propanoate **Intermediate 130** (2.48 g, 9.43 mmol) was dissolved in THF (85 mL) and cooled to -78 °C. 1 M DIBAL-H in heptane (28.4 mL, 28.40 mmol) was added dropwise over 30 min. After complete addition and additional stirring for 30 min the cooling bath was removed and stirring was continued at rt for 19 h. The reaction mixture was poured into a solution of Rochelle salt (52 g) in water (200 mL). After the gas evolution had ceased the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over NaSO₄, filtered and concentrated in vacuo to yield the title compound (2.010 g, 96%) as dark orange oil. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.62 (1H, s), 1.77–1.85 (2H, m), 2.59 (3H, s), 2.83–2.91 (2H, m), 3.74 (2H, t). ¹³C NMR (126 MHz, CDCl₃) δ 170.38, 161.95, 156.96, 130.56, 61.84, 30.61, 25.21, 22.42.

Intermediate 1322-Chloro-4-methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine

NaH (60 wt% in mineral oil, 0.367 g, 9.17 mmol) was washed oil free with heptane and suspended in THF (15 mL). 3-(2,4-Dichloro-6-methylpyrimidin-5-yl)propan-1-ol

Intermediate 131 (2.01 g, 8.73 mmol) was dissolved in THF (30 mL) and added dropwise under an atmosphere of Ar (g) over 20 min to the NaH suspension. The reaction mixture was stirred at rt overnight, filtered through CELITE and the filtrate was concentrated in vacuo to

give the title compound (1.601 g, 99%) as pale-yellow solid. MS (ESI) m/z $[M+H]^+$ 185.2. 1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 2.04–2.11 (2H, m), 2.40 (3H, s), 2.68 (2H, t), 4.35–4.41 (2H, m).

5 **Intermediate 133**

4-Methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine-2-carbonitrile

3-Quinoclidinol (0.13 g, 1.02 mmol) was added to a mixture of 2-chloro-4-methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine **Intermediate 132** (1.599 g, 8.66 mmol) and KCN (0.80 g, 12.29 mmol) in DMSO (15 mL) and water (0.2 mL), and the reaction mixture stirred at 60
10 °C for 24 h. The mixture was cooled to rt and partitioned between iPrOAc and water. The aqueous layer was extracted with iPrOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (1.402 g, 92%) as red solid. 1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 2.07–2.16 (2H, m), 2.45 (3H, s), 2.76 (2H, t), 4.39–4.45 (2H, m). ^{13}C NMR (126 MHz,
15 $CDCl_3$) δ 167.65, 167.08, 141.83, 116.75, 115.64, 67.95, 21.52, 21.09, 20.82.

Intermediate 134

Methyl 4-methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine-2-carboxylate

4-Methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine-2-carbonitrile **Intermediate 133** (1.398 g,
20 7.98 mmol) was dissolved in MeOH (80 mL). 4.37 M NaOMe in MeOH (5.3 mL, 23.16 mmol) was added and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was poured into water (80 mL) containing H_3PO_4 (2.5 mL) and the mixture was stirred for 1 h. The MeOH was removed by concentration in vacuo. The remaining liquid was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4
25 and filtered, and concentrated in vacuo to yield the title compound (1.486 g, 89%) as pale orange solid. MS (ESI) m/z $[M+H]^+$ 209.3. 1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 2.07–2.15 (2H, m), 2.51 (3H, s), 2.76 (2H, t), 3.99 (3H, s), 4.37–4.42 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.35, 167.20, 163.92, 153.72, 115.63, 67.60, 53.35, 21.56, 21.31, 21.06.

30 **Intermediate 135**

(4-Methyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidin-2-yl)methanol

Methyl 4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine-2-carboxylate **Intermediate 134** (104 mg, 0.50 mmol) was dissolved in MeOH (5 mL) and cooled in an ice-bath. NaBH₄ (56.7 mg, 1.5 mmol) was added, and the reaction mixture was stirred for 2 h. Additional NaBH₄ (28 mg, 0.75 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. Sat NH₄Cl (aq, 5 mL) was added, and the mixture was stirred for 10 min at rt and then concentrated in vacuo. The residue was extracted with EtOAc, and the organic layer was concentrated in vacuo to afford the title compound (85 mg, 94%) as light-yellow solid. MS (ESI) *m/z* [M+H]⁺ 181.2. ¹³C NMR (126 MHz, Methanol-*d*₄) δ 167.17, 166.49, 165.62, 111.69, 67.63, 63.74, 20.97, 20.51, 19.27.

Intermediate 136

1-(5-Methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

Intermediate 107 (45 mg, 0.17 mmol) was dissolved in THF (0.4 mL) and toluene (0.4 mL). 5-Methoxy-1-methyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 53** (43.4 mg, 0.25 mmol), CuI (3.2 mg, 0.02 mmol) and TEA (0.139 mL, 0.99 mmol) were added followed by Pd(PPh₃)₂Cl₂ (11.6 mg, 0.02 mmol) and the reaction mixture was stirred under an atmosphere of N₂ (g) at rt for 2 h. DCM (5 mL) and sat NaHCO₃ (aq, 5 mL) were added, and the mixture was stirred, filtered through a phase separator, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–10% MeOH in DCM) to give the title compound (36 mg, 53%). MS (ESI) *m/z* [M+H]⁺ 410.4.

Intermediate 137

1-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

Intermediate 107 (60 mg, 0.22 mmol) was dissolved in THF (0.4 mL) and toluene (0.4 mL).

1,5-Dimethyl-1*H*-pyrazole-4-carbonyl chloride (52.6 mg, 0.33 mmol), CuI (2.1 mg, 0.01

mmol) and TEA (0.185 mL, 1.33 mmol), were added followed by Pd(PPh₃)₂Cl₂ (7.8 mg, 0.01 mmol) and the reaction mixture was stirred under an atmosphere of N₂ (g) at rt overnight.

DCM (5 mL) and sat NaHCO₃ (aq, 5 mL) were added, and the mixture was stirred, filtered

through a phase separator, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 1–10% MeOH (2 M NH₃) in DCM) to give the title compound (47 mg, 54%). MS (ESI) m/z [M+H]⁺ 394.5. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.8–1.9 (2H, m), 1.92–2.01 (2H, m), 2.01–2.07 (2H, m), 2.31–2.44 (5H, m), 2.54 (3H, s), 2.59–2.7 (3H, m), 2.82–2.95 (2H, m), 3.63 (2H, s), 3.77 (3H, s), 4.29–4.34 (2H, m), 7.85 (1H, s).

Intermediate 138

5-Methoxy-1,3-dimethyl-1H-pyrazole-4-carbonyl chloride

5-Methoxy-1,3-dimethyl-1H-pyrazole-4-carboxylic acid (0.324 g, 1.90 mmol) was suspended in DCM (6.7 mL) and oxalyl chloride (0.340 mL, 3.81 mmol) was added. The reaction mixture was cooled to 0 °C and DMF (0.015 mL, 0.19 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was concentrated twice more from DCM to afford the title compound (0.359 g, 100%). ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 2.44 (3H, s), 3.68 (3H, s), 4.07 (3H, s).

Intermediate 139

1-(5-Methoxy-1,3-dimethyl-1H-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine **Intermediate 107** (60 mg, 0.22 mmol) was dissolved in THF (0.4 mL) and toluene (0.4 mL). 5-Methoxy-1,3-dimethyl-1H-pyrazole-4-carbonyl chloride **Intermediate 138** (63 mg, 0.33 mmol), CuI (2.1 mg, 0.01 mmol) and TEA (0.185 mL, 1.33 mmol), were added to the mixture, followed by Pd(PPh₃)₂Cl₂ (7.8 mg, 0.01 mmol). The reaction mixture was stirred under an atmosphere of N₂ (g) at rt for 3 h. DCM (5 mL) and sat NaHCO₃ (aq, 5 mL) were added, and the mixture was stirred, filtered through a phase separator, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 1–10% MeOH (2% NH₃) in DCM) to give the title compound (37 mg, 40%). MS (ESI) m/z [M+H]⁺ 424.3.

Intermediate 140

6-Ethyl-5-(3-hydroxypropyl)-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol

A mixture of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt

Intermediate 28 (0.093 g, 0.25 mmol), 2-(chloromethyl)-6-ethyl-5-(3-

- 5 hydroxypropyl)pyrimidin-4-ol **Intermediate 115** (0.055 g, 0.238 mmol) and DIPEA (0.249 mL, 1.43 mmol) in DMSO (1.5 mL) was stirred at rt overnight. The crude product was purified by preparative HPLC, PrepMethod CC, (gradient: of 20–55%), to yield the title compound (0.125 g). MS (ESI) *m/z* [M+H]⁺ 454.4.

10 **Intermediate 141**

tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

TEA (11.92 mL, 87.44 mmol) followed by Pd(PPh₃)₂Cl₂ (0.614 g, 0.87 mmol) was added to a mixture of *tert*-butyl 4-ethynylpiperidine-1-carboxylate (3.66 g, 17.49 mmol), 1,5-dimethyl-

1*H*-pyrazole-4-carbonyl chloride (3.17 g, 20 mmol) and CuI (0.167 g, 0.87 mmol) in THF

- 15 (37.8 mL) and toluene (37.8 mL). The flask was evacuated and filled with N₂ (g) and then stirred at rt overnight. EtOAc was added and the mixture was washed with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 30–50% EtOAc in heptane) to give the title compound (4.38 g, 76%) as orange oil. MS (ESI)
- 20 *m/z* [(M-Boc)+H]⁺ 232.1 ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.45 (9H, s), 1.66–1.75 (2H, m), 1.84–1.95 (2H, m), 2.57 (3H, s), 2.79–2.85 (1H, m), 3.21 (2H, ddd), 3.71–3.79 (2H, m), 3.80 (3H, s), 7.89 (1H, s).

Intermediate 142

25 *tert*-Butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

Intermediate 141 (4.38 g, 13.22 mmol) was dissolved in EtOH (41 mL) and 64% hydrazine hydrate (aq, 3 mL, 61.66 mmol) was added. The reaction mixture was stirred at rt overnight, and then concentrated under reduced pressure and dissolved in hot EtOAc and filtered

- 30 immediately and cooled to afford the title compound (2.480 g, 54%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 346.4. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.47 (9H, s), 1.65 (2H, qd),

1.91–2.01 (2H, m), 2.43 (3H, s), 2.78–2.9 (3H, m), 3.83 (3H, s), 4.08–4.29 (2H, m), 6.11 (1H, s), 7.59 (1H, s).

Intermediate 143

5 2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6-ethyl-5-(3-hydroxypropyl)pyrimidin-4-ol

TFA (1 mL, 0.30 mmol) was added to a solution of *tert*-butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 142** (113 mg, 0.33 mmol) in DCM (2 mL). The reaction mixture was stirred at rt for 1 h and then concentrated under reduced
10 pressure. The residue was dissolved in DMSO (2 mL), K₂CO₃ (210 mg, 1.52 mmol) and 2-(chloromethyl)-6-ethyl-5-(3-hydroxypropyl)pyrimidin-4-ol **Intermediate 115** (70 mg, 0.30 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and purified by preparative HPLC, PrepMethod D, (gradient: 10–55%), to yield the title compound (96 mg, 72%) as white solid. MS (ESI) *m/z* [M+H]⁺
15 440.3. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.14 (3H, t), 1.71 (2H, p), 1.75–1.87 (2H, m), 1.88–1.95 (2H, m), 2.21–2.31 (2H, m), 2.35 (3H, s), 2.53 (2H, q), 2.58–2.71 (3H, m), 2.8–2.89 (2H, m), 3.43 (2H, s), 3.55 (2H, t), 3.75 (3H, s), 6.05 (1H, s), 7.59 (1H, s).

Intermediate 144

20 *tert*-Butyl 4-(3-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate

CDI (0.131 g, 0.81 mmol) was added to a suspension of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (0.158 g, 0.80 mmol) in THF (2.5 mL) and the mixture was stirred at rt for 4 h. In a separate flask, 1 M LiHMDS in THF (1.925 mL, 1.93 mmol) was added
25 dropwise to a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (0.175 g, 0.77 mmol) in THF (5 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. The solution of the CDI-activated acid was added dropwise and the reaction mixture was stirred at -78 °C for 5 min and then at rt overnight. The reaction was quenched by addition of sat NaHCO₃ (aq) and the mixture was diluted with EtOAc. The layers were separated and the aqueous layer
30 was extracted using EtOAc (×3). The combined organic layers were filtered through a phase separator and concentrated under reduced pressure to afford the title compound (0.311 g, 100%). MS (ESI) *m/z* [M-H]⁻ 402.0

Intermediate 145

tert-Butyl 4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

- 5 *tert*-Butyl 4-(3-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 144** (0.311 g, 0.77 mmol) was dissolved in 99.5% EtOH (7.5 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.056 mL, 1.16 mmol) was added, followed by HOAc (0.075 mL) and the reaction mixture was stirred at rt overnight. Water (5 mL) and sat NaHCO₃ (aq 0.5 mL) was added to the mixture and the layers were separated.
- 10 The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient: 10–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.197 g, 64%). MS (ESI) *m/z* [M+H]⁺ 400.3. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.40 (9H, d), 1.42–1.52 (2H, m), 1.83–1.92 (2H, m), 2.7–2.94
- 15 (3H, m), 3.85–4.13 (5H, m), 6.18 (1H, s), 7.76 (1H, s), 12.75 (1H, s). ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -56.02.

Intermediate 146

1'-Methyl-5-(piperidin-4-yl)-5'-(trifluoromethyl)-1'*H*,2*H*-3,4'-bipyrazole

- 20 *tert*-Butyl 4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 145** (0.197 g, 0.49 mmol) was dissolved in DCM (4 mL) and cooled in an ice-bath. TFA (0.704 mL, 9.14 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to afford the TFA salt of the title compound (0.203 g, 100%). MS (ESI) *m/z* [M+H]⁺ 300.1.

25

Intermediate 147

5-(3-Hydroxypropyl)-6-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol

- A mixture of 1'-methyl-5-(piperidin-4-yl)-5'-(trifluoromethyl)-1'*H*,2*H*-3,4'-bipyrazole, TFA-salt **Intermediate 146** (0.203 g, 0.49 mmol), 2-(chloromethyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 5** (0.106 g, 0.49 mmol) and DIPEA (0.513 mL, 2.94
- 30 mmol) in DMSO (4.5 mL) was stirred at rt overnight. The reaction mixture was diluted with

EtOAc and washed with sat NaHCO₃ (aq). The organic layer was filtered through a phase separator and concentrated under reduced pressure to yield the crude title compound (0.260 g). MS (ESI) m/z [M+H]⁺ 480.4.

5 **Intermediate 148**

2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol

TFA (0.5 mL, 0.23 mmol) was added to a solution of *tert*-butyl 4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 47** (83 mg, 0.23 mmol) in DCM
10 (1 mL) and the reaction mixture was stirred for 1 h. The mixture was concentrated under reduced pressure and the residue was dissolved in DMSO (1.5 mL). DIPEA (250 μ L, 1.44 mmol) and 2-(chloromethyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 5** (65.0 mg, 0.30 mmol) was added and the reaction mixture was stirred at rt for 24 h. The mixture was filtered using a syringe filter and the residue was purified by preparative HPLC,
15 PrepMethod D, (gradient: 10–50%), to give the title compound (0.078 g, 77%) as white solid. MS (ESI) m/z [M+H]⁺ 437.4. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.62–1.71 (2H, m), 1.72–1.85 (2H, m), 1.88–1.97 (5H, m), 2.19–2.31 (8H, m), 2.55–2.60 (2H, m), 2.61–2.7 (1H, m), 2.77–2.87 (2H, m), 3.40 (2H, d), 3.44–3.52 (2H, m), 5.93 (1H, d), 6.93 (1H, d), 8.22 (1H, d).

20 **Intermediate 149**

Isopropyl 5-(2,4-dimethylpyridin-3-yl)-3-(1-((4-methyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidin-2-yl)methyl)piperidin-4-yl)-1H-pyrazole-1-carboxylate

2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 148** (78 mg, 0.18 mmol) and PPh₃
25 (70.3 mg, 0.27 mmol) were dissolved in THF (2 mL) and cooled in an ice-bath. DIAD (52.8 μ L, 0.27 mmol) was added and the reaction mixture was stirred for 10 min and then warmed to rt and stirred for 1 h. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (0.056 g, 62%) as a clear oil. MS (ESI) m/z [M+H]⁺ 505.6. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.42 (6H, d), 1.75–1.88 (2H, m), 1.99–
30 2.06 (4H, m), 2.11 (3H, s), 2.25–2.34 (5H, m), 2.38 (3H, s), 2.65 (2H, t), 3.08–3.18 (2H, m), 3.37 (1H, tt), 3.66 (2H, s), 4.29–4.34 (2H, m), 5.19–5.29 (1H, m), 6.13 (1H, s), 6.96 (1H, d), 8.29 (1H, d).

Intermediate 150

tert-Butyl 4-(3-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-oxoprop-1-yn-1-yl)-4-hydroxypiperidine-1-carboxylate

- 5 Pd(PPh₃)₂Cl₂ (0.021 g, 0.03 mmol) was added to a solution of TEA (0.247 ml, 1.77 mmol), *tert*-butyl 4-ethynyl-4-hydroxypiperidine-1-carboxylate (0.133 g, 0.59 mmol), 1,4-dimethyl-1*H*-pyrazole-5-carbonyl chloride (0.103 g, 0.65 mmol) and CuI (5.63 mg, 0.03 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 2.5 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were filtered through a
10 phase separator and concentrated. The crude material was purified by straight phase flash chromatography on silica (10–100% EtOAc in heptane) to grant the title compound as a yellow oil (98 mg, 48%). ¹H NMR (500 MHz, CDCl₃) 1.46 (9H, s), 1.82 – 1.89 (2H, m), 1.95 – 2.03 (2H, m), 2.41 (3H, s), 3.48 (2H, m), 3.64 (2H, m), 4.12 (3H, s), 7.32 (1H, m).

Intermediate 151

tert-Butyl 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)-4-hydroxypiperidine-1-carboxylate

Hydrazine hydrate (aq, 28.0 μL, 0.58 mmol) was added to a solution of *tert*-butyl 4-(3-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-oxoprop-1-yn-1-yl)-4-hydroxypiperidine-1-carboxylate

- Intermediate 150** (100 mg, 0.29 mmol) in EtOH (1.1 mL) and the reaction mixture was
20 stirred at rt for 1 h. The mixture was concentrated to grant the title compound as a white foam. MS (ESI) *m/z* [M+H]⁺ 362.1.

Intermediate 152

4-(2',4'-Dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-4-ol

- 25 TFA (320 μL, 4.15 mmol) was added to a solution of *tert*-butyl 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)-4-hydroxypiperidine-1-carboxylate **Intermediate 151** (100 mg, 0.28 mmol) in DCM (1 mL) and stirred at rt for 30 min. The mixture was concentrated to give the TFA salt of the title compound (assuming quantitative yield) as a tan foam. MS (ESI) *m/z* [M+H]⁺ 262.0.

30

Intermediate 153

tert-Butyl 4-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate

Ethynyltrimethylsilane (5.94 mL, 42.05 mmol) was dissolved in THF (118 mL) and cooled to -78 °C. 2.5 M *n*BuLi in hexane (16.82 mL, 42.05 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 40 min and then allowed to reach rt. After 70 min, the reaction mixture was cooled to -78 °C and a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (7.12 g, 35.04 mmol) in THF (72 mL) was added dropwise. The mixture was warmed to rt and stirred for 3 h. The reaction was quenched with sat NH₄Cl (aq) followed by addition of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Heptane was added to the residue and the mixture was heated to 45 °C and sonicated. White solid precipitated after cooling to rt. The solids were filtered off and washed with cold heptane. The mother liquor was concentrated and purified by straight phase flash chromatography on silica (gradient: 2–32% EtOAc in heptane) and the product containing fractions were collected and combined with the precipitate to give the title compound (9.444g, 91%). ¹H NMR (500 MHz, CDCl₃, 18 °C) δ 0.17 (9H, s), 1.45 (9H, s), 1.67 (2H, ddd), 1.83 – 2.10 (3H, m), 3.20 (2H, ddd), 3.76 - 3.84 (2H, m).

Intermediate 154

tert-Butyl 4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

tert-Butyl 4-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate **Intermediate 153** (12.775 g, 42.95 mmol) was dissolved in DCM (120 mL) and cooled in an ice-bath. DMAP (5.77 g, 47.24 mmol) was added, followed by TEA (17.96 mL, 128.84 mmol) and a dropwise addition of methanesulfonyl chloride (10.04 mL, 128.84 mmol). The reaction mixture was allowed to warm to rt and stirred for 18 h. The mixture was poured into water. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with 1M HCl and sat NaHCO₃ (aq), and then dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was dissolved in heptane and filtered. The solids filtered off were washed with heptane. The combined filtrate was concentrated to afford the title compound (12.18 g). ¹H NMR (500 MHz, CDCl₃, 18 °C) δ 0.17 (9H, s), 1.45 (9H, s), 2.19 - 2.28 (2H, m), 3.47 (2H, t), 3.92 - 3.97 (2H, m), 6.06 (1H, s).

Intermediate 155

tert-Butyl 4-ethynyl-3,6-dihydropyridine-1(2*H*)-carboxylate

tert-Butyl 4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 154** (7.31 g, 26.16 mmol) was dissolved in MeOH (132 mL). K₂CO₃ (7.23 g, 52.32 mmol) was added, and the reaction mixture was stirred at rt overnight. The mixture was filtered and concentrated under reduced pressure. EtOAc and water were added, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was dissolved in heptane and filtered to afford the title compound (5.27 g, 97%) as a yellow brown oil. ¹H NMR (500 MHz, CDCl₃, 19 °C) δ 1.46 (9H, s), 2.25 (2H, s), 2.89 (1H, s), 3.45 – 3.54 (2H, m), 3.96 (2H, s), 6.10 (1H, s).

Intermediate 156

tert-Butyl 4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

tert-Butyl 4-ethynyl-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 155** (3.35 g, 16.16 mmol) was dissolved in toluene (76 mL). CuI (0.154 g, 0.81 mmol), 1,3,5-trimethyl-1*H*-pyrazole-4-carbonyl chloride (3.36 g, 19.46 mmol), and TEA (4.73 mL, 33.94 mmol) were added followed by Pd(PPh₃)₂Cl₂ (0.567 g, 0.81 mmol). The reaction mixture was stirred under an atmosphere of N₂ (g) at rt for 3 h and then diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried using MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 50–80% EtOAc in heptane) to give the title compound (3.47 g, 63%) as orange solid. MS (ESI) *m/z* [M+H]⁺ 344.3. ¹H NMR (500 MHz, CDCl₃) 1.47 (9H, s), 2.30 – 2.39 (2H, m), 2.52 (3H, s), 2.57 (3H, s), 3.54 (2H, t), 3.75 (3H, s), 4.01 – 4.09 (2H, m), 6.36 (1H, s).

Intermediate 157

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

64% Hydrazine hydrate (aq, 0.983 mL, 20.21 mmol) was added to a solution of *tert*-butyl 4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 156** (3.47 g, 10.10 mmol) in EtOH (32.7 mL) and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure. The

crude residue was purified by straight phase flash chromatography on silica (isocratic EtOAc) to give the title compound (2.64 g, 73%) as white solid. MS (ESI) m/z $[M+H]^+$ 358.5. 1H NMR (500 MHz, $CDCl_3$, 25°C) δ 1.47 (9H, s), 2.25 (6H, d), 2.49–2.59 (2H, m), 3.59 (2H, t), 3.72 (3H, s), 4.00–4.08 (2H, m), 6.16 (1H, s), 6.25 (1H, s), 10.93 (1H, s).

5

Intermediate 158

tert-Butyl 4-(1',3',5'-trimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and

10 *tert*-butyl 4-(1',3',5'-trimethyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 157** (5.38 g, 15.04 mmol) was dissolved in THF (72.3 mL) and NaH (60% wt% in mineral oil, 0.902 g, 22.56 mmol) was added. The reaction mixture was stirred for 10 min at rt and then cooled in an ice-bath. SEM-Cl (2.86 mL, 15.79 mmol) was added, and the reaction mixture was stirred for 30 min and then warmed to rt and stirred for 2 h. The reaction mixture was cooled in an ice-bath and the reaction was quenched with sat NaHCO₃ (aq). The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried using MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–50% EtOAc in heptane) to afford a regio isomer mixture of the title compounds (5.83 g, 79%) as brown gum. MS (ESI) m/z $[M+H]^+$ 488.4.

Intermediate 159

25 *rac-tert*-Butyl (3*R*,4*R*)-3-hydroxy-4-(1',3',5'-trimethyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

BH₃·S(CH₃)₂ (0.401 mL, 4.22 mmol) was added to a solution of *tert*-butyl 4-(1',3',5'-trimethyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-Butyl 4-(1',3',5'-trimethyl-1-((2-

30 (trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 158** (1.03 g, 2.11 mmol) in THF (5.64 mL) and stirred at rt overnight. The reaction was quenched by the addition of water (1 mL) and EtOH (1 mL) and

stirred for 1 h. 10% NaOH (aq, 4 mL, 2.11 mmol) and H₂O₂ (0.518 mL, 16.89 mmol) were added and the reaction mixture was stirred at rt overnight and then heated to 50 °C for 4 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was purified by preparative HPLC, PrepMethod F, (gradient: 30–70%), to grant the title compound (0.457 g, 43%) as a yellow oil. MS (ESI) *m/z* [M+H]⁺ 506.3. ¹H NMR (500 MHz, CDCl₃) -0.14 (9H, s), 0.69 – 0.76 (2H, m), 1.36 (9H, s), 1.59 (1H, m), 1.91 – 1.97 (1H, m), 1.98 (3H, s), 2.02 (3H, s), 2.55 – 2.77 (3H, m), 3.39 – 3.48 (2H, m), 3.54 – 3.61 (1H, m), 3.66 (3H, s), 3.95 – 4.37 (2H, m), 5.06 (2H, s), 5.94 (1H, s).

Intermediate 160

rac-(3*R*,4*R*)-1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

TFA (1 mL, 0.15 mmol) was added to a solution of *tert*-butyl (3*R*,4*R*)-3-hydroxy-4-(1',3',5'-trimethyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 159** (50.2 mg, 0.10 mmol) in DCM (0.5 mL). The reaction mixture was stirred at rt overnight, concentrated and redissolved in DMSO (1 mL). 2-(Chloromethyl)-4-methylquinazoline (31.2 mg, 0.16 mmol) and DIPEA (0.128 mL, 0.74 mmol) were added and the reaction mixture stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod A, (gradient: 5–45%) to grant the product. The product was further purified by preparative HPLC, PrepMethod D, (gradient: 15–55%) to grant the title compound (24 mg, 56%) as a white solid. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2498.

Intermediate 161

tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

Pd(PPh₃)₂Cl₂ (0.254 g, 0.36 mmol) was added to a mixture of *tert*-butyl 4-ethynyl-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 155** (1.5 g, 7.24 mmol), 1,5-dimethyl-1*H*-pyrazole-4-carbonyl chloride (1.721 g, 10.86 mmol), CuI (0.069 g, 0.36 mmol) and TEA (5.04 mL, 36.18 mmol) in toluene (31.1 mL) under an atmosphere of N₂ (g), and the reaction mixture was stirred at rt overnight. The mixture was diluted with water and DCM, filtered

through a phase separator and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% EtOAc in heptane) to give the title compound (945 mg). MS (ESI) m/z $[M+H]^+$ 330.2

5 **Intermediate 162**

tert-Butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 161** (940 mg, 2.85 mmol) was dissolved in EtOH (13.7 mL) and 64% hydrazine hydrate (aq, 0.555 mL, 11.41 mmol) was added. The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (468 mg, 48%). MS (ESI) m/z $[M+H]^+$ 344.4. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.47–1.5 (9H, m), 2.42 (3H, d), 2.51–2.61 (2H, m), 3.58–3.67 (2H, m), 3.83 (3H, d), 4.03–4.11 (2H, m), 6.16 (1H, s), 6.31 (1H, d), 7.59 (1H, s).

Intermediate 163

rac-tert-Butyl (3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3-hydroxypiperidine-1-carboxylate and

tert-butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-hydroxypiperidine-1-carboxylate BMS (0.388 mL, 4.09 mmol) was added to a solution of *tert*-butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 169** (468 mg, 1.36 mmol) in THF (6.6 mL) at 0 °C. The reaction mixture was warmed to 50 °C and stirred for 2 h. The mixture was cooled to 0 °C and the reaction was quenched with water (2 mL) and EtOH (2 mL), and then stirred for a further 10 min. 10% NaOH (aq, 1.5 mL, 1.36 mmol) and 30% H₂O₂ (aq, 0.557 mL, 5.45 mmol) were added and the reaction mixture was heated to 50 °C and stirred overnight. The mixture was cooled to rt and diluted with brine and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was purified by preparative HPLC, PrepMethod F, (gradient: 15–55%), to grant the title compounds (195 mg, 40%) as an inseparable mixture of regio-isomers. MS (ESI) m/z $[M+H]^+$ 362.4.

Intermediate 164

rac-(3*R*,4*R*)-4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol and 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol

TFA (1 mL, 0.54 mmol) was added to a solution containing the regio-isomer mixture of *rac*-
5 *tert*-butyl (3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3-hydroxypiperidine-1-
carboxylate and *tert*-butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-
hydroxypiperidine-1-carboxylate **Intermediate 163** (195 mg, 0.54 mmol) in DCM (2 mL)
and the reaction mixture was stirred at rt for 30 min. The mixture was concentrated to grant
the TFA salt of the title compounds as a regio-isomer mixture (141 mg). MS (ESI) *m/z*
10 $[M+H]^+$ 262.2.

Intermediate 165

tert-Butyl 4-hydroxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

1,3,5-Trimethyl-1*H*-pyrazole-4-carboxylic acid (1.65 g, 10.70 mmol) was suspended in DCM
15 (45 mL) and oxalyl chloride (3.8 mL, 44.91 mmol) was added. DMF (10 μ L) was added, and
the reaction mixture was stirred at rt for 5 h. The reaction mixture was concentrated in vacuo.
The residue was dissolved in THF (45 mL), and *tert*-butyl 4-ethynyl-4-hydroxypiperidine-1-
carboxylate (2.253 g, 10 mmol), CuI (0.10 g, 0.53 mmol), Pd(PPh₃)₂Cl₂ (0.3 g, 0.43 mmol),
20 and TEA (3.9 mL, 27.90 mmol) were added under an atmosphere of Ar (g). The reaction
mixture was stirred at rt overnight. Solid material formed were filtered off and set aside. The
filtrate was collected and filtered through silica gel. The second filtrate was collected and
combined with the solid material and concentrated to dryness to give the title compound (3.75
g) as yellow oil. MS (ESI) *m/z* $[M+H]^+$ 362.4.

25

Intermediate 166

tert-Butyl 4-hydroxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

64% Hydrazine hydrate (aq, 1 mL, 14.02 mmol) was added to a solution of crude *tert*-butyl 4-
30 hydroxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-
carboxylate **Intermediate 165** (3.61 g, 10 mmol) in 99.5% EtOH (50 mL) and the reaction
mixture was stirred at rt for 20 h. Insoluble material was removed by filtration, and the filtrate

was concentrated in vacuo. The crude material was dissolved in DMSO (20 mL) and filtered through CELITE. The residue was purified by preparative HPLC, PrepMethod G, (gradient: 15–55%) and the product containing fractions were neutralised by addition of NaHCO₃ (s). MeCN was removed under reduced pressure and the remaining solution was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (2.76 g, 74%). MS (ESI) m/z [M+H]⁺ 376.4. ¹H NMR (500 MHz, DMSO, 25°C) δ 1.40 (9H, s), 1.71–1.79 (2H, m), 1.80–1.88 (2H, m), 2.18 (3H, s), 2.30 (3H, s), 3.10–3.28 (2H, m), 3.64–3.74 (5H, m), 5.17 (1H, s), 6.17 (1H, s), 12.45 (1H, s).

Intermediate 167

tert-Butyl 4-fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
tert-Butyl 4-hydroxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 166** (188 mg, 0.5 mmol) was dissolved in DCM (9 mL) under an atmosphere of Ar (g) and cooled to -78 °C. DAST (100 µL, 0.76 mmol) was added and the reaction mixture was stirred at -78 °C for 20 min, and then warmed to rt. After 2 h at rt the reaction mixture was cooled to -78 °C and additional DAST (100 µL, 0.76 mmol) was added. The reaction mixture was stirred at -78 °C for 20 min, and then warmed to rt. After 2 h at rt the mixture was washed with sat NaHCO₃ (aq). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to yield the title compound (161 mg, 85%). MS (ESI) m/z [M+H]⁺ 378.5. ¹H NMR (500 MHz, CDCl₃) 1.46 (9H, s), 2.05 – 2.22 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 3.19 – 3.35 (2H, m), 3.75 (3H, s), 3.88 – 4.07 (2H, m), 6.22 – 6.25 (1H, m). ¹⁹F NMR (471 MHz, CDCl₃) -152.41.

Intermediate 168

5-(4-Fluoropiperidin-4-yl)-1',3',5'-trimethyl-1'*H*,2*H*-3,4'-bipyrazole
tert-Butyl 4-fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 167** (213 mg, 0.56 mmol) was dissolved in DCM (1 mL) and TFA (1.00 mL) was added. The reaction mixture was stirred at rt for 30 min and then concentrated in vacuo to afford the TFA-salt of the title compound (374 mg) as. ¹⁹F NMR (471 MHz, D₂O) δ -75.72 (s, 9H), -150.87 (s, 1H). ¹H NMR (500 MHz, D₂O) δ 2.35 (s, 6H), 2.37 – 2.58 (m, 4H), 3.39 – 3.50 (m, 4H), 3.90 (s, 3H), 6.61 (d, 1H).

MS (ESI) m/z $[M+H]^+$ 278.4.

Intermediate 169

tert-Butyl 4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

25% NaOMe in MeOH (0.4 mL, 1.6 mmol) was added to *tert*-butyl 4-fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 167** (151 mg, 0.40 mmol) and the reaction mixture was stirred at rt for 10 min. Sat NH₄Cl (aq) was added and the mixture was extracted with DCM. The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (140 mg, 90%) as a yellow oil. MS (ESI) m/z $[M+H]^+$ 390.5. ¹H NMR (500 MHz, CDCl₃) δ 1.45 (s, 9H), 1.94 - 2.12 (m, 4H), 2.29 (s, 3H), 2.31 (s, 3H), 3.10 (s, 3H), 3.25 - 3.34 (m, 2H), 3.70 - 3.84 (m, 5H), 6.18 (s, 1H).

Intermediate 170

5-(4-Methoxypiperidin-4-yl)-1',3',5'-trimethyl-1'*H*,2*H*-3,4'-bipyrazole

TFA (0.5 mL) was added to a solution of *tert*-butyl 4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 169** (137 mg, 0.35 mmol) in DCM (0.5 mL) and the reaction mixture was stirred at rt for 20 min. The mixture was concentrated in vacuo to afford the TFA-salt of the title compound (220 mg, 99%). MS (ESI) m/z $[M+H]^+$ 290.4.

Intermediate 171

tert-Butyl 4-ethynyl-4-methoxypiperidine-1-carboxylate

tert-Butyl 4-ethynyl-4-hydroxypiperidine-1-carboxylate (8.9 g, 37.53 mmol) was dissolved in anhydrous DMF (100 mL) and NaH (60% wt% in mineral oil, 1.876 g, 46.91 mmol) was added in portions over 5 min at rt under an atmosphere of N₂ (g). The reaction mixture was stirred at rt for 25 min, then MeI (2.92 mL, 46.91 mmol) was added dropwise over 10 min under an atmosphere of N₂ (g). The reaction mixture was stirred at rt for 1 h. The mixture was poured onto ice-water and when reached rt extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 5–40% EtOAc in heptane)

to give the title compound (6.6 g, 74%) as colorless oil. ¹H NMR (500 MHz, CDCl₃) 1.45 (9H, s), 1.66 - 1.74 (2H, m), 1.85 - 1.95 (2H, m), 2.52 (1H, s), 3.24 - 3.33 (2H, m), 3.38 (3H, s), 3.64 - 3.76 (2H, m).

5 **Intermediate 172**

tert-Butyl 4-methoxy-4-(3-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

tert-Butyl 4-ethynyl-4-methoxypiperidine-1-carboxylate **Intermediate 171** (0.123 g, 0.515 mmol), 5-methoxy-1,3-dimethyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 138** (0.146 g, 0.77 mmol), CuI (4.9 mg, 0.03 mmol) and TEA (0.431 mL, 3.09 mmol) were mixed in THF (0.9 mL) and toluene (0.9 mL). Pd(PPh₃)₂Cl₂ (0.018 g, 0.03 mmol) was added and the reaction mixture was stirred under an atmosphere of N₂ (g) at rt overnight. DCM and sat NaHCO₃ (aq) were added, the mixture was stirred, filtered through a phase separator, and concentrated under reduced pressure to afford the title compound (0.240 g). MS (ESI) *m/z* [M+H]⁺ 392.3.

Intermediate 173

tert-Butyl 4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

20 *tert*-Butyl 4-methoxy-4-(3-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 172** (0.202 g, 0.52 mmol) was dissolved in 99.5% EtOH (3.8 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.126 mL, 2.58 mmol) was added and the reaction mixture was stirred at rt for 1h. The mixture was poured into water (7mL) and sat NaHCO₃ (aq) and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.083 g, 40%). MS (ESI) *m/z* [M+H]⁺ 406.3. ¹H NMR (500 MHz, DMSO-*d*₆) 1.40 (9H, s), 1.80 - 1.92 (2H, m), 1.96 - 2.05 (2H, m), 2.16 (3H, s), 2.95 (3H, s), 3.13 - 3.28 (2H, m), 3.51 - 3.63 (5H, m), 3.78 (3H, s), 6.25 (1H, s), 12.58f (1H, s).

Intermediate 174

5'-Methoxy-5-(4-methoxypiperidin-4-yl)-1',3'-dimethyl-1'H,2H-3,4'-bipyrazole
tert-Butyl 4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 173** (0.083 g, 0.20 mmol) was dissolved in DCM (3 mL) and cooled in an ice-bath. TFA (0.292 mL, 3.79 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was triturated with Et₂O (5 mL). The solvent was decanted, and the resulting precipitate was dried under vacuum to yield the TFA-salt of the title compound (0.086 g, 100%). MS (ESI) *m/z* [M+H]⁺ 306.3.

Intermediate 175

rac-tert-Butyl (2*R*,4*S*)-2-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate
rac-tert-Butyl (2*R*,4*S*)-4-ethynyl-2-methylpiperidine-1-carboxylate (0.198 g, 0.89 mmol) was dissolved in THF (3.2 mL) and added to a solution of 1,3,5-trimethyl-1*H*-pyrazole-4-carbonyl chloride (0.230 g, 1.33 mmol) in THF (1.6 mL). CuI (0.034 g, 0.18 mmol) and Pd(PPh₃)₂Cl₂ (0.064 g, 0.09 mmol) were added followed by TEA (0.865 mL, 6.21 mmol). The reaction mixture was evacuated and refilled with N₂ (g) (×3). The reaction mixture was stirred under an atmosphere of N₂ (g) at rt overnight. DCM and sat NaHCO₃ (aq) were added and the layers were separated. The organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound (0.319 g, 100%). MS (ESI) *m/z* [M+H]⁺ 360.4.

Intermediate 176

rac-tert-Butyl (2*R*,4*S*)-2-methyl-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

rac-tert-Butyl (2*R*,4*S*)-2-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 175** (0.319 g, 0.89 mmol) was dissolved in EtOH (4.2 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.215 mL, 4.44 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was poured into water and sat NaHCO₃ (aq) and the mixture was extracted with EtOAc (3×). The organic layers were combined and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% (EtOAc/MeOH (9/1)) in heptane). The obtained product was dissolved in

EtOAc and treated with SILIAMETS Imidazole for 1 h. The solution was filtered and the solids were washed with EtOAc. The combined filtrate was concentrated to afford the title compound (0.200 g, 60%). MS (ESI) m/z $[M+H]^+$ 374.2.

5 **Intermediate 177**

rac-1',3',5'-trimethyl-5-((2*R*,4*S*)-2-methylpiperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

rac-*tert*-Butyl (2*R*,4*S*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 176** (0.195 g, 0.52 mmol) was dissolved in EtOAc (2.6 mL). 6 M HCl in IPA (0.870 mL, 5.22 mmol) was added dropwise and the reaction mixture was stirred
10 at 40 °C for 2 h. The mixture was concentrated under reduced pressure to give the HCl salt of the title compound (0.224 g). MS (ESI) m/z $[M+H]^+$ 274.2.

Intermediate 178

1-(*tert*-Butoxycarbonyl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-4-carboxylic acid

1-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)piperidine-4-carboxylic acid (0.662 g, 2.55 mmol)
15 and imidazole (0.521 g, 7.66 mmol) were mixed in DCM (15 mL). TBDMS-Cl (0.770 g, 5.11 mmol) was added, and the reaction mixture was stirred at rt overnight. 5% Citric acid (aq, 18 mL) was added and the mixture was stirred for 1 h. The mixture was filtered through a phase separator and concentrated under reduced pressure. The residue was purified by straight phase
20 flash chromatography on silica (isocratic DCM (1% HOAc)). 0.1 M HCl (aq) was added to the crude product, and the mixture was stirred and then extracted with EtOAc. The organic layer was concentrated and the crude product was purified by straight phase flash chromatography on silica (isocratic DCM with 1% HOAc) to give the title compound (0.510 g, 54%). ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.03 (6H, s), 0.87 (9H, s), 1.37–1.48 (11H, m),
25 2.01–2.1 (2H, m), 2.96–3.06 (2H, m), 3.62 (2H, s), 3.83–3.92 (2H, m).

Intermediate 179

tert-Butyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)propanoyl)piperidine-1-carboxylate

1-(*tert*-Butoxycarbonyl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-4-carboxylic acid
30 **Intermediate 178** (0.490 g, 1.31 mmol) was dissolved in THF (4.5 mL) and CDI (0.223 g, 1.38 mmol) was added. The reaction mixture was stirred at rt for 2 h. In a separate flask a

solution of 1-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethan-1-one (0.200 g, 1.31 mmol) in THF (8.7 mL) was cooled to -78 °C, and 1 M LiHMDS in THF (3.28 mL, 3.28 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min. The CDI-activated acid was added dropwise to the mixture over 10 min at -78 °C. The cold bath was removed, and the reaction mixture was stirred at rt overnight. 10% Citric acid (aq, 6 mL) was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, filtered through a phase separator, and concentrated under reduced pressure to afford the title compound (0.666 g, 100%). MS (ESI) *m/z* [M-H]⁻ 506.2

Intermediate 180

tert-Butyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)propanoyl)piperidine-1-carboxylate **Intermediate 179** (0.666 g, 1.31 mmol) was dissolved in EtOH (6 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.318 mL, 6.56 mmol) was added, and the reaction mixture was stirred at rt overnight. The mixture was poured into water and sat NaHCO₃ (aq) and the mixture was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.271 g, 41%). MS (ESI) *m/z* [M+H]⁺ 504.4.

Intermediate 181

(4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-yl)methanol

tert-Butyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 180** (0.270 g, 0.54 mmol) was dissolved in EtOAc (3.3 mL). 6 M HCl in IPA (1.072 mL, 6.43 mmol) was added dropwise and the reaction mixture was stirred at 40 °C for 2 h. The mixture was concentrated under reduced pressure to give the HCl salt of the title compound (0.235 g)- MS (ESI) *m/z* [M+H]⁺ 290.1. ¹H NMR (500 MHz, DMSO, 25 °C) δ 1.96–2.06 (2H, m), 2.15–2.39 (9H, m), 2.71–2.83 (2H, m), 3.20 (2H, d), 3.40 (1H, s), 3.74 (3H, s), 6.39 (1H, s), 8.82 (1H, s), 9.06 (1H, s).

Intermediate 182*rac-tert*-Butyl (3*R*,4*R*)-3-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate

Ethynyltrimethylsilane (4.17 mL, 30.11 mmol) was dissolved in Et₂O (189 mL) and cooled in an ice-bath. 2.5 M *n*-BuLi in hexane (12.05 mL, 30.11 mmol) and 2 M AlMe₃ in toluene (13.80 mL, 27.60 mmol) were added and the reaction mixture was allowed to warm to rt. A solution of *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (5.00 g, 25.09 mmol) in Et₂O (25.3 mL) was added. The reaction mixture was cooled to -78 °C and BF₃•OEt₂ (6.19 mL, 50.19 mmol) was added. The reaction mixture was stirred at -78 °C for 2 h and then the reaction was quenched with anhydrous MeOH (20 mL) and stirred for 15 min. Sat NH₄Cl (aq) (13 mL) was added. The mixture was allowed to warm to rt and diluted with MTBE and water. The layers were separated and the aqueous layer was extracted with MTBE. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 20–30% EtOAc in heptane) to give the title compound (6.34 g, 85%) as colorless oil. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.16 (9H, s), 1.22–1.34 (2H, m), 1.46 (9H, s), 1.9–2 (1H, m), 2.21 (1H, d), 2.39–2.54 (1H, m), 2.9–3.03 (1H, m), 3.59 (1H, s), 3.66–3.92 (1H, m), 4.00 (1H, dd).

Intermediate 1831-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonyl chloride

Oxalyl chloride (0.092 mL, 1.08 mmol) was added to a suspension of 1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxylic acid (70.0 mg, 0.42 mmol) in DCM (1.3 mL) followed by DMF (4.17 μL, 0.05 mmol). The reaction mixture was stirred at rt for 6 h and then concentrating to grant the title compound as a white solid.

Intermediate 184*rac-tert*-Butyl (3*R*,4*R*)-4-ethynyl-3-hydroxypiperidine-1-carboxylate*rac-tert*-Butyl (3*R*,4*R*)-3-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate

Intermediate 182 (6.34 g, 21.31 mmol) was dissolved in MeOH (107 mL) and K₂CO₃ (5.89 g, 42.62 mmol) was added. The reaction mixture was stirred at rt for 1.5 h and then concentrated under reduced pressure. EtOAc and water were added to the residue, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined

organic layers were dried over MgSO₄, filtered and concentrated to yield the title compound (4.52 g, 94%) as clear oil. ¹H NMR (500 MHz, CDCl₃, 25°C) δ 1.46 (9H, s), 1.52–1.61 (1H, m), 1.95–2.02 (1H, m), 2.19 (1H, d), 2.29 (1H, s), 2.42–2.51 (1H, m), 2.83–3.11 (2H, m), 3.62 (1H, s), 3.69–3.93 (1H, m), 4.01 (1H, dd).

5

Intermediate 185

rac-(3*R*,4*R*)-4-Ethynyl-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

rac-tert-Butyl (3*R*,4*R*)-4-ethynyl-3-hydroxypiperidine-1-carboxylate **Intermediate 191** (4.52 g, 20.05 mmol) was dissolved in DCM (65 mL) and TFA (30 mL, 20.05 mmol) was added.

10 The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was dissolved in MeCN (65 mL) and 2-(chloromethyl)-4-methylquinazoline (5.02 g, 26.07 mmol) and K₂CO₃ (16.63 g, 120.33 mmol) was added to the solution. The reaction mixture was stirred at rt for 21 h and then concentrated. The reaction mixture was diluted with DCM and water and the layers were separated. The aqueous layer was extracted
15 with DCM. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford the title compound (5.64 g) as a yellow oil. MS (ESI) *m/z* [M+H]⁺ 282.1. ¹H NMR (500 MHz, CDCl₃, 25°C) δ 1.7–1.78 (1H, m), 2.07–2.18 (2H, m), 2.4–2.6 (3H, m), 2.81–2.89 (1H, m), 2.95 (3H, s), 3.04 (1H, d), 3.78–3.85 (1H, m), 3.91–4 (2H, m), 7.58–7.65 (1H, m), 7.86 (1H, ddd), 7.98–8.02 (1H, m), 8.06–8.1 (1H, m)

20

Intermediate 186

rac-2-(((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline

rac-(3*R*,4*R*)-4-Ethynyl-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 185**

25 (439 mg, 1.56 mmol) was dissolved in DCM (3.9 mL). Imidazole (234 mg, 3.43 mmol), DMAP (19.06 mg, 0.16 mmol) and TBDMSCl (259 mg, 1.72 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water and the mixture was diluted with DCM. The aqueous layer was extracted with DCM and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue
30 was purified by preparative HPLC, PrepMethod D, (gradient: 50–100%), to give the title compound (471 mg, 76%) as yellow oil. MS (ESI) *m/z* [M+H]⁺ 396.6. ¹H NMR (500 MHz, CDCl₃, 25°C) δ -0.01–0.11 (6H, m), 0.82 (9H, s), 1.75–1.86 (1H, m), 1.88–1.95 (1H, m),

1.95–2.04 (2H, m), 2.05–2.14 (1H, m), 2.20 (1H, dddd), 2.88–2.98 (4H, m), 3.18–3.29 (1H, m), 3.80 (1H, td), 3.88–3.98 (2H, m), 7.57 (1H, ddd), 7.82 (1H, ddd), 7.96–8.01 (1H, m), 8.02–8.06 (1H, m).

5 **Intermediate 187**

rac-3-(((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)prop-2-yn-1-one

A solution of *rac*-2-(((3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 186** (237 mg, 0.60 mmol) in toluene (2.4 mL) and THF (1.2 mL) was added to a mixture of 1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonyl chloride **Intermediate 183** (111 mg, 0.60 mmol), Pd(PPh₃)₂Cl₂ (21.06 mg, 0.03 mmol) and CuI (5.71 mg, 0.03 mmol) under an atmosphere of N₂ (g). TEA (409 µL, 3.00 mmol) was added and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 45–95%), to give the title compound (93 mg, 29%). MS (ESI) *m/z* [M+H]⁺ 545.4. ¹H NMR (500 MHz, CDCl₃, 25°C) δ -0.05–0.14 (6H, m), 0.77 (9H, d), 1.82–2.03 (3H, m), 2.12 (1H, t), 2.35–2.46 (1H, m), 2.88 (3H, d), 2.96 (1H, d), 3.22 (4H, d), 3.74–3.82 (2H, m), 3.83–3.96 (3H, m), 4.03–4.13 (2H, m), 7.49–7.57 (1H, m), 7.68 (1H, d), 7.75–7.82 (1H, m), 7.92–7.97 (1H, m), 7.98–8.05 (1H, m).

Intermediate 188

rac-(3*R*,4*R*)-4-(5-(1-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

rac-3-(((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)prop-2-yn-1-one **Intermediate 187** (93 mg, 0.17 mmol) was dissolved in EtOH (1 mL) and 64% hydrazine hydrate (aq, 0.025 mL, 0.51 mmol) was added. The reaction mixture was stirred at rt for 6 h and then concentrated under reduced pressure. The residue was dissolved in TFA (0.9 mL) and water (0.1 mL) and heated at 60 °C for 4 h. The mixture was concentrated under reduced pressure and the crude residue was purified by preparative HPLC, PrepMethod D,

(gradient: 15–55%), to give the title compound (52 mg, 68%) as white solid. MS (ESI) m/z [M+H]⁺ 445.4. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.9–1.99 (2H, m), 2.17 (1H, t), 2.26 (1H, td), 2.54–2.6 (1H, m), 2.91 (6H, d), 3.05–3.13 (1H, m), 3.24–3.32 (1H, m), 3.65–3.76 (2H, m), 3.88 (1H, td), 3.92–4.01 (2H, m), 4.07–4.13 (2H, m), 6.05 (1H, s), 7.44 (1H, s),
5 7.55–7.6 (1H, m), 7.78–7.87 (1H, m), 7.99 (1H, d), 8.02–8.08 (1H, m).

Intermediate 189

rac-3-((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)prop-2-yn-1-one

10 TEA (505 μL, 3.70 mmol) and Pd(PPh₃)₂Cl₂ (26.0 mg, 0.04 mmol) were added to a mixture of *rac*-2-(((3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 186** (293 mg, 0.74 mmol), 5-methoxy-1,3-dimethyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 138** (140 mg, 0.74 mmol) and CuI (7.1 mg, 0.04 mmol) in THF (1.6 mL) and toluene (1.6 mL). The reaction mixture was evacuated and filled
15 with N₂ (g) (×3) and then stirred at rt overnight. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 50–100%), to give the title compound (193 mg, 48%) as yellow oil. MS (ESI) m/z [M+H]⁺ 548.4. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.01–0.1 (6H, m), 0.80
20 (9H, s), 1.86–2.08 (m), 2.16 (1H, td), 2.41–2.52 (4H, m), 2.93 (3H, s), 2.97–3.04 (1H, m), 3.26–3.34 (1H, m), 3.59 (3H, s), 3.91 (1H, td), 3.95 (2H, s), 4.03 (3H, s), 7.56–7.61 (1H, m), 7.84 (1H, ddd), 7.98–8.01 (1H, m), 8.03–8.08 (1H, m).

Intermediate 190

25 *rac*-(3*R*,4*R*)-4-(5'-Methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol
rac-3-((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)prop-2-yn-1-one
Intermediate 189 (192 mg, 0.35 mmol) was dissolved in EtOH (2 mL) and 64% hydrazine hydrate (aq, 0.1 mL, 2.06 mmol) was added. The reaction mixture was stirred at rt for 4 d and
30 then concentrated under reduced pressure. The resulting residue was dissolved in TFA (1.8 mL) and water (0.2 mL) and stirred at 50 °C for 5 h and then cooled to rt and stirred

overnight. The mixture was concentrated and the crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (138 mg, 88%) as yellow solid. MS (ESI) m/z $[M+H]^+$ 448.4. 1H NMR (500 MHz, $CDCl_3$, 25°C) δ 1.93–2 (2H, m), 2.1–2.27 (5H, m), 2.56–2.65 (1H, m), 2.87 (3H, s), 3.01–3.09 (1H, m), 3.22–3.31 (1H, m), 3.56 (3H, s), 3.71 (3H, s), 3.86–3.98 (3H, m), 6.02 (1H, s), 7.51–7.56 (1H, m), 7.76–7.81 (1H, m), 7.94 (1H, d), 7.98–8.02 (1H, m).

Intermediate 191

5-Cyclopropyl-1-methyl-1H-pyrazole-4-carbonyl chloride

5-Cyclopropyl-1-methyl-1H-pyrazole-4-carboxylic acid (0.083 g, 0.50 mmol) was dissolved in DCM (1 mL) and oxalyl chloride (50 μ L, 0.58 mmol) was added. The reaction mixture was cooled in an ice-bath and DMF (1.936 μ L, 0.03 mmol) was added. The reaction mixture was warmed to rt and stirred overnight. The mixture was concentrated under reduced pressure to yield the title compound (0.092 g). 1H NMR (500 MHz, DMSO) 0.82 – 0.90 (2H, m), 0.96 – 1.05 (2H, m), 1.81 – 1.91 (1H, m), 3.83 (3H, s), 7.66 (1H, s).

Intermediate 192

rac-3-((3R,4R)-3-((tert-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-cyclopropyl-1-methyl-1H-pyrazol-4-yl)prop-2-yn-1-one

rac-2-(((3R,4R)-3-((tert-Butyldimethylsilyl)oxy)-4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 186** (316 mg, 0.80 mmol), 5-cyclopropyl-1-methyl-1H-pyrazole-4-carbonyl chloride **Intermediate 191** (148 mg, 0.8 mmol) and CuI (7.62 mg, 0.04 mmol) were mixed in THF (1.73 mL) and toluene (1.73 mL). TEA (546 μ L, 4.00 mmol) and $Pd(PPh_3)_2Cl_2$ (28.1 mg, 0.04 mmol) were added. The reaction mixture was evacuated and filled with N_2 (g) ($\times 3$) and then stirred at rt for 4 d. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried using $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 50–100%), to give the title compound (215 mg, 49%) as yellow oil. MS (ESI) m/z $[M+H]^+$ 544.4. 1H NMR (500 MHz, $CDCl_3$, 25°C) δ 0.00 (3H, s), 0.05 (3H, s), 0.74–0.84 (11H, m), 1.04–1.12 (2H, m), 1.71–1.79 (1H, m), 1.83–1.93 (1H, m), 1.94–2.07 (2H, m), 2.14 (1H, td), 2.44 (1H, ddd), 2.90 (3H, s), 2.93–2.99 (1H, m), 3.22–3.29 (1H, m), 3.83–3.93 (6H, m), 7.55 (1H, ddd), 7.81 (1H, ddd), 7.87 (1H, s), 7.96 (1H, dt), 8.03 (1H, ddd).

Intermediate 193

rac-(3*R*,4*R*)-4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

5 *rac*-3-((3*R*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)prop-2-yn-1-one

Intermediate 192 (215 mg, 0.40 mmol) was dissolved in EtOH (2 mL) and 64% hydrazine hydrate (aq, 0.1 mL, 2.06 mmol) was added. The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure. The resulting residue was dissolved in TFA
10 (1.8 mL) and water (0.2 mL) and heated at 60 °C for 5 h and then concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (152 mg, 87%) as yellow solid. MS (ESI) *m/z* [M+H]⁺ 444.5. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.41–0.51 (2H, m), 0.87–0.96 (2H, m), 1.63 (1H, tt), 1.89–1.96 (2H, m), 2.08–2.22 (2H, m), 2.59 (1H, q), 2.86 (3H, s), 2.97–3.06 (1H, m), 3.22–3.29 (1H, m), 3.79
15 (3H, s), 3.83–3.95 (3H, m), 6.14 (1H, s), 7.48 (1H, s), 7.5–7.55 (1H, m), 7.74–7.79 (1H, m), 7.92–7.96 (1H, m), 7.97–8 (1H, m).

Intermediate 194

tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-4-methoxypiperidine-1-carboxylate

20 *tert*-Butyl 4-ethynyl-4-methoxypiperidine-1-carboxylate **Intermediate 171** (6.6 g, 27.58 mmol), 1,5-dimethyl-1*H*-pyrazole-4-carbonyl chloride (6.56 g, 41.37 mmol), CuI (0.263 g, 1.38 mmol) and TEA (23.06 mL, 165.47 mmol) were mixed in THF (50 mL) and toluene (50 mL). Pd(PPh₃)₂Cl₂ (0.988 g, 1.38 mmol) was added and the reaction mixture was stirred
25 under an atmosphere of N₂ (g) at rt for 2 d. DCM (250 mL) and sat NaHCO₃ (aq) (250 mL) were added and the mixture was stirred, filtered through a phase separator, and concentrated to give the crude title compound (15 g). MS (ESI) *m/z* [(M-Boc)+H]⁺ 262.1.

Intermediate 195

30 *tert*-Butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidine-1-carboxylate
tert-Butyl 4-(3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-4-methoxypiperidine-1-carboxylate **Intermediate 194** (9.76 g, 27 mmol) was suspended in 99.5% EtOH (200 mL).

The mixture was cooled in an ice-bath and 64% hydrazine hydrate (aq, 6.57 mL, 135.00 mmol) was added. The reaction mixture was stirred at rt for 2 h. The mixture was poured into water (200 mL) and sat NaHCO₃ (aq) (40 mL). The mixture was concentrated and the remaining aqueous layer was extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% (EtOAc/MeOH (9/1)) to give the title compound (6.3 g, 62%). MS (ESI) *m/z* [M+H]⁺ 376.4. ¹H NMR (500 MHz, DMSO-*d*₆) 1.40 (9H, s), 1.77 – 2.06 (4H, m), 2.30 – 2.47 (3H, m), 2.95 (3H, s), 3.10 – 3.31 (2H, m), 3.42 – 3.66 (2H, m), 3.76 (3H, s), 6.30 (1H, s), 7.61 (1H, s), 12.68 (1H, s).

Intermediate 196

5-(4-Methoxypiperidin-4-yl)-1',5'-dimethyl-1'*H*,2*H*-3,4'-bipyrazole

tert-Butyl 4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidine-1-carboxylate

Intermediate 195 (5.8 g, 15.45 mmol) was dissolved in EtOAc (50 mL). 6 M HCl in IPA (25.7 mL, 154.47 mmol) was added dropwise, and the reaction mixture was stirred at 50 °C for 3 h. The mixture was concentrated under reduced pressure to yield the HCl-salt of the title compound (6.06 g). MS (ESI) *m/z* [M+H]⁺ 276.2. ¹H NMR (500 MHz, DMSO-*d*₆) 2.15 – 2.33 (4H, m), 2.41 (3H, s), 2.96 (3H, s), 3.00 – 3.13 (4H, m), 3.78 (3H, s), 6.41 – 6.48 (1H, m), 7.73 – 7.83 (1H, m), 9.33 (2H, s).

Intermediate 197

tert-Butyl 4-methoxy-4-(3-(5-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

tert-Butyl 4-ethynyl-4-methoxypiperidine-1-carboxylate **Intermediate 171** (0.123 g, 0.515 mmol), 5-methoxy-1-methyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 53** (0.135 g, 0.77 mmol), CuI (4.9 mg, 0.03 mmol) and TEA (0.431 mL, 3.09 mmol) were mixed in THF (0.9 mL) and toluene (0.9 mL). Pd(PPh₃)₂Cl₂ (0.018 g, 0.03 mmol) was added and the reaction mixture was stirred under an atmosphere of N₂ (g) at rt overnight. DCM and sat NaHCO₃ (aq) were added, and the mixture was stirred, filtered through a phase separator, and concentrated under reduced pressure to afford the title compound (0.194 g, 100%). MS (ESI) *m/z* [(M-Boc)+H]⁺ 278.1.

Intermediate 198

tert-Butyl 4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-methoxy-4-(3-(5-methoxy-1-methyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 197** (0.194 g, 0.51 mmol) was dissolved in 99.5% EtOH (3.8 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.125 mL, 2.57 mmol) was added, and the reaction mixture was stirred at rt overnight. The mixture was poured into water (7 mL) and sat NaHCO₃ (aq) (0.7 mL) and the mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–100% (EtOAc/MeOH (9/1) in heptane) to give the title compound (0.032 g, 16%). MS (ESI) *m/z* [M+H]⁺ 392.3.

Intermediate 199

5'-Methoxy-5-(4-methoxypiperidin-4-yl)-1'-methyl-1'*H*,2*H*-3,4'-bipyrazole
tert-Butyl 4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 198** (0.030 g, 0.08 mmol) was dissolved in DCM (2 mL) and cooled in an ice-bath. TFA (0.109 mL, 1.42 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure. The residue was triturated with Et₂O (5 mL). The solvent was decanted, and the resulting precipitate was dried under vacuum to yield the TFA-salt of the title compound (0.031 g, 100%). MS (ESI) *m/z* [M+H]⁺ 292.3.

Intermediate 200

rac-tert-Butyl (1*R*,6*R*)-6-((trimethylsilyl)ethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate
tert-Butyl 4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 154** (8.035 g, 28.75 mmol) was dissolved in DCM (170 mL) and the flask was kept in the dark and cooled in an ice-bath. *m*CPBA (19.33 g, 86.26 mmol) was dissolved in DCM (100 mL) and added dropwise via a dropping funnel. The reaction mixture was stirred at rt overnight. The mixture was diluted with DCM and water and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with

water and brine, filtered through a phase separator, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 3–12% EtOAc in heptane) to give the title compound (4.30 g, 51%) as white solid. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.17 (9H, s), 1.44 (9H, s), 2.05–2.26 (2H, m), 2.97–3.08 (1H, m),
5 3.35–3.46 (1H, m), 3.46–3.68 (2H, m), 3.84–4.06 (1H, m).

Intermediate 201

rac-tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate
10 *rac-tert*-Butyl (1*R*,6*R*)-6-((trimethylsilyl)ethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate **Intermediate 200** (4.297 g, 14.54 mmol) was dissolved in MeOH (135 mL) and TsOH (5.53 g, 29.09 mmol) was added at rt. The reaction mixture was stirred for 1 h. The reaction was quenched with sat NaHCO₃ (aq) and diluted with EtOAc and water. The layers were separated, and the aqueous layer extracted with EtOAc, dried over MgSO₄, filtered, and
15 concentrated under reduced pressure to afford the title compound (3.73 g, 78%) as yellow oil. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.20 (9H, s), 1.44–1.58 (11H, m), 2.08 (1H, ddd), 3.04–3.16 (2H, m), 3.41 (3H, s), 3.53 (1H, dd), 3.79–3.87 (1H, m), 3.96 (1H, ddd).

Intermediate 202

20 *rac*-(3*R*,4*S*)-4-Methoxy-4-((trimethylsilyl)ethynyl)piperidin-3-ol carboxylate
TFA (12.53 mL, 162.60 mmol) was added to an ice-cold solution of *rac-tert*-butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate **Intermediate 201** (4.841 g, 14.78 mmol) in DCM (140 mL). The reaction mixture was stirred at rt for 1 h and then concentrated to grant the TFA salt of the title compound (6.14 g). ¹H NMR (500 MHz, CDCl₃, 25°C) δ 0.21 (9H, m), 1.46 (1H, s), 2.04–2.12 (1H, m), 2.29–2.37 (1H, m), 3.1–3.32
25 (2H, m), 3.39–3.42 (3H, m), 3.9–3.96 (1H, m), 6.39 (3H, s), 7.64 (1H, s), 8.98 (1H, s).

Intermediate 203

rac-(3*R*,4*S*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-((trimethylsilyl)ethynyl)piperidin-3-ol
30 A solution of *rac*-(3*R*,4*S*)-4-methoxy-4-((trimethylsilyl)ethynyl)piperidin-3-ol **Intermediate 202** (5.025 g, 14.72 mmol), 2-(chloromethyl)-4-methylquinazoline (2.95 g, 15.16 mmol) and

DIPEA (15.42 mL, 88.31 mmol) in DMSO (50 mL) was stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with sat NaHCO₃ (aq). The organic layers were filtered through a phase separator and concentrated to grant the title compound (5.65 g, 100%). MS (ESI) m/z [M+H]⁺ 384.4.

5

Intermediate 204*rac*-(3*R*,4*S*)-4-Ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

A solution of *rac*-(3*R*,4*S*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-((trimethylsilyl)ethynyl)piperidin-3-ol **Intermediate 203** (5.65 g, 14.73 mmol) in MeOH (67 mL) was treated with K₂CO₃ (4.07 g, 29.46 mmol) and stirred at rt overnight. The mixture was filtered and concentrated. The residue was diluted with EtOAc, and washed with sat NaHCO₃ (aq), filtered through a phase separator and concentrated. The crude product was purified by preparative HPLC, PrepMethod F, (gradient 20–50%), to grant the title compound (2.273 g, 50%) as a solid. MS (ESI) m/z [M+H]⁺ 312.2.

15

Intermediate 205(3*S*,4*R*)-4-Ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol**Intermediate 206**(3*R*,4*S*)-4-Ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

rac-(3*R*,4*S*)-4-Ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 204** was separated into its respective enantiomers by chiral SFC on a YMC SZ (imob C2) column (5 μm, 250×30 mm ID), eluted with 15% EtOH/DEA (100/20 mM) in CO₂, 120 bar, at a flow rate of 140 mL/min and detected at 280 nm. The first eluted compound was collected to give the title compound **Intermediate 206** (100 mg, 36%, 99.9% ee). MS (ESI) m/z [M+H]⁺ 312.2, [α]_D²⁰ -2.3 (c 1, MeCN). The second eluted compound was collected to give the **Intermediate 205** (95 mg, 34%, 99.9% ee). MS (ESI) m/z [M+H]⁺ 312.2. [α]_D²⁰ +1.5 (c 1, MeCN).

30

Intermediate 2071-Methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride

Oxalyl chloride (89 μL, 1.00 mmol) followed by DMF (3.87 μL, 0.05 mmol) were added to a suspension of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (97 mg, 0.5 mmol)

in DCM (2.68 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated to afford the crude title compound.

Intermediate 208

5 5-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carbonyl chloride

Oxalyl chloride (0.223 mL, 2.50 mmol) followed by DMF (9.68 µL, 0.13 mmol) were added to a suspension of 5-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (0.220 g, 1.25 mmol) in DCM (6.71 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated to afford the crude title compound. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 4.11 (3H, t), 6.92–7.55 (m, overlapping with residual solvent), 8.02 (1H, m).

Intermediate 209

3-((3R,4S)-3-Hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1,3-dimethyl-1H-pyrazol-4-yl)prop-2-yn-1-one

15 A solution of (3R,4S)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (209 mg, 0.67 mmol) in THF (4.10 mL) was added to a solution of 5-methoxy-1,3-dimethyl-1H-pyrazole-4-carbonyl chloride **Intermediate 138** (190 mg, 1.01 mmol) and CuI (25.6 mg, 134 µmol) in THF (2.05 mL). Pd(PPh₃)₂Cl₂ (48.1 mg, 68.5 µmol) was added followed by TEA (0.561 mL, 4.03 mmol) and the reaction mixture vessel was evacuated and refilled with N₂ (g) three times. The reaction mixture was heated to 55 °C for 3 h and then allowed to cool to rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to grant the crude title compound as brown oil. MS (ESI) *m/z* [M+H]⁺ 464.5.

Intermediate 210

3-((3R,4S)-3-Hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1-methyl-1H-pyrazol-4-yl)prop-2-yn-1-one

30 A solution of (3R,4S)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (100 mg, 0.32 mmol) in THF (2.56 mL) was added to a solution of 5-methoxy-1-methyl-1H-pyrazole-4-carbonyl chloride **Intermediate 53** (84 mg, 0.48 mmol) and CuI (12.23 mg, 64.2 µmol) in THF (1.26 mL). Pd(PPh₃)₂Cl₂ (23.0 mg, 32.7 µmol) was

added followed by TEA (0.269 mL, 1.93 mmol) and the reaction mixture vessel was evacuated and refilled with N₂ (g) three times. The reaction mixture was heated to 55 °C for 3 h and then allowed to cool to rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over
5 MgSO₄, filtered and concentrated to grant the crude title compound as brown solid. MS (ESI) m/z [M+H]⁺ 450.5.

Intermediate 211

1,5-Dimethyl-1H-pyrazole-4-carbonyl chloride

10 Oxalyl chloride (50 µL, 0.58 mmol) was added to a suspension of 1,5-dimethyl-1H-pyrazole-4-carboxylic acid (70.1 mg, 0.5 mmol) in DCM (1 mL). The solution was cooled to 0 °C and DMF (1.936 µL, 0.03 mmol) was added. The reaction was warmed to rt, stirred overnight and then concentrated to afford the crude title compound. NMR (500 MHz, DMSO, 25°C) δ 2.46 (3H, s), 3.74 (3H, s), 7.68 (1H, s).

15

Intermediate 212

1-(1,5-Dimethyl-1H-pyrazol-4-yl)-3-((3R,4S)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

A solution of (3R,4S)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (100 mg, 0.32 mmol) in THF (2.56 mL) was added to a solution of 1,5-dimethyl-1H-pyrazole-4-carbonyl chloride **Intermediate 211** (76 mg, 0.48 mmol) and CuI (12.23 mg, 64.2 µmol) in THF (1.26 mL). Pd(PPh₃)₂Cl₂ (23.0 mg, 32.7 µmol) was added followed by TEA (0.269 mL, 1.93 mmol) and the reaction mixture vessel was evacuated and refilled with N₂ (g) three times. The reaction mixture was heated to 55 °C for 3 h and then
25 allowed to cool to rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to grant the crude title compound as brown solid. MS (ESI) m/z [M+H]⁺ 434.3.

Intermediate 213

3-((3R,4S)-3-Hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-7-yl)prop-2-yn-1-one

A solution of (3*R*,4*S*)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (100 mg, 0.32 mmol) in THF (1.48 mL) was added to a solution of 1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonyl chloride **Intermediate 183** (89 mg, 0.48 mmol) and CuI (12.23 mg, 64.2 μ mol) in THF (0.74 mL). Pd(PPh₃)₂Cl₂ (23.0 mg, 32.7 μ mol) was added followed by TEA (0.269 mL, 1.93 mmol) and the reaction mixture vessel was evacuated and refilled with N₂ (g) three times. The reaction mixture was heated to 55 °C for 3 h and then allowed to cool to rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to grant the crude title compound as brown solid.

MS (ESI) *m/z* [M+H]⁺ 461.4.

Intermediate 214

rac-tert-Butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate

rac-tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate **Intermediate 201** (3.726 g, 11.38 mmol) was dissolved in MeOH (52 mL) and K₂CO₃ (3.14 g, 22.75 mmol) was added. The reaction mixture was stirred at rt overnight, filtered and the filtrate was concentrated under reduced pressure. The crude residue was dissolved in EtOAc and washed with sat NaHCO₃ (aq). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 3–60% EtOAc in heptane) to give the title compound (2.279 g, 78%) as colorless oil. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.45 (9H, s), 1.57 (1H, ddd), 2.11 (1H, ddd), 2.63 (1H, s), 3.06–3.2 (2H, m), 3.42 (3H, s), 3.52–3.62 (1H, m), 3.72–3.92 (1H, m), 3.97 (1H, ddd).

Intermediate 215

rac-tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

rac-tert-Butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate

Intermediate 214 (1.475 g, 5.78 mmol) was dissolved in THF (18 mL). CuI (0.055 g, 0.29 mmol), a solution of 1,3,5-trimethyl-1*H*-pyrazole-4-carbonyl chloride (1.496 g, 8.67 mmol) in THF (9 mL) and Pd(PPh₃)₂Cl₂ (0.207 g, 0.29 mmol) were added followed by TEA (4.83 mL, 34.66 mmol). The reaction mixture vessel was evacuated and refilled with N₂ (g) ($\times$ 3). The

reaction mixture was stirred at rt overnight. DCM and NaHCO₃ (aq) were added, the layers were separated, and the DCM layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (2.262 g, 100%). MS (ESI) *m/z* [M+H]⁺ 392.3.

5 **Intermediate 216**

rac-tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

rac-tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 215** (2.262 g, 5.78 mmol) was
10 dissolved in EtOH (42 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 1.401 mL, 28.89 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The mixture was poured into water (50 mL) and NaHCO₃ (aq, 5 mL) and extracted with EtOAc (3×). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica
15 (gradient 40–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (1.700 g, 73%). MS (ESI) *m/z* [M+H]⁺ 406.3. ¹H NMR (500 MHz, DMSO-*d*₆, 25 °C) δ 1.35–1.45 (9H, m), 1.92–2.01 (1H, m), 2.09–2.41 (7H, m), 2.82–3.32 (5H, m), 3.62–3.86 (6H, m), 4.67–5.09 (1H, m), 6.18 (1H, s), 12.50 (1H, s).

20 **Intermediate 217**

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 218

25 *tert*-Butyl (3*S*,4*R*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

The enantiomers of *rac-tert*-butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1*H*,1'*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 216** (6.15 g, 15.17 mmol) were separated by chiral preparative SFC on a Chiralpak IA column (5 μm, 250×50 mm ID), using
30 EtOH/DEA (100/20 mM) in CO₂ as mobile phase (isocratic: 25%). The first eluted compound was collected to yield the title compound **Intermediate 217** (2.8 g, 46%, 99.6 ee). MS (ESI) *m/z* [M+H]⁺ 406.5. [α]_D²⁰ -16.8 (c 1.1, MeCN). The second eluted compound was collected to

yield the title compound **Intermediate 218** (2.8 g, 46%, 95.8 ee). MS (ESI) m/z $[M+H]^+$ 406.3. $[\alpha]_D^{20} +14.9$ (c 1.1, MeCN).

Intermediate 219

5 (3*R*,4*S*)-4-Methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol
tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-
yl)piperidine-1-carboxylate **Intermediate 217** (2.8 g, 6.91 mmol) was dissolved in EtOAc (25
mL). 6 M HCl in IPA (11.51 mL, 69.05 mmol) was added dropwise, and the reaction mixture
was stirred at 50 °C for 3 h. The mixture was concentrated under reduced pressure to give the
10 HCl-salt of the title compound (2.483 g, 95%). MS (ESI) m/z $[M+H]^+$ 306.4. ^1H NMR (500
MHz, DMSO- d_6 , 25 °C) δ 2.2–2.31 (4H, m), 2.32–2.42 (4H, m), 2.87–2.99 (4H, m), 3.02–
3.14 (2H, m), 3.2–3.29 (1H, m), 3.73 (3H, s), 4.05 (1H, s), 6.31 (1H, s), 8.40 (1H, d), 9.44
(1H, d).

Intermediate 220

15 2-((2-Acetyl-3-chlorophenyl)amino)-2-oxoethyl acetate
1-(2-Amino-6-chlorophenyl)ethan-1-one (241 mg, 1.42 mmol) was dissolved in DCM (6.62
mL) and cooled in an ice-bath. NMM (0.312 mL, 2.84 mmol) was added followed by
dropwise addition of 2-chloro-2-oxoethyl acetate (0.173 mL, 1.56 mmol). After 15 min the
20 cooling bath was removed and the mixture was stirred at rt overnight. The solution was
diluted with DCM and washed with 10% citric acid (aq), sat NaHCO₃ solution, brine and
dried over Na₂SO₄. The solvent was removed under reduced pressure to grant the title
compound (393 mg) as a brown oil. MS (ESI) m/z $[M+H]^+$ 270.1.

Intermediate 221

25 (5-Chloro-4-methylquinazolin-2-yl)methanol
A solution containing 2-((2-acetyl-3-chlorophenyl)amino)-2-oxoethyl acetate **Intermediate**
220 (393 mg, 1.46 mmol) in 4 M NH₃ in MeOH (7.3 mL) was heated to 80 °C in a sealed
microwave vial for 11 hours. The reaction mixture was diluted with sat NaHCO₃ (aq) and
30 extracted with DCM. The combined organic layers were washed with brine, dried over
MgSO₄, filtered and concentrated. The crude residue was purified by straight phase flash
chromatography on silica (gradient: 0–50% EtOAc in heptane) to grant the title compound

(132 mg, 43%) as a white solid. ^1H NMR (500 MHz, DMSO, 25°C) δ 3.18 (3H, s), 4.71 (2H, d), 5.39 (1H, t), 7.82 (1H, m), 7.90 (1H, m), 7.95 (1H, m).

Intermediate 222

5 5-Chloro-2-(chloromethyl)-4-methylquinazoline

NCS (92 mg, 0.69 mmol) was added to a solution containing 5-chloro-2-(chloromethyl)-4-methylquinazoline **Intermediate 221** (130 mg, 0.62 mmol) and PPh_3 (180 mg, 0.69 mmol) in DCM at 0 °C and stirred for 3 h. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–20% EtOAc in heptane) to grant the title compound
10 (101 mg, 72%) as a white solid. ^1H NMR (500 MHz, DMSO, 25°C) δ 3.20 (3H, s), 4.90 (2H, s), 7.86–7.9 (1H, m), 7.91–7.96 (1H, m), 7.96–7.99 (1H, m).

Intermediate 223

(3*S*,4*R*)-4-Methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol
15 *tert*-Butyl (3*S*,4*R*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 218** (2.8 g, 6.91 mmol) was dissolved in EtOAc (25 mL). 6 M HCl in IPA (11.51 mL, 69.05 mmol) was added dropwise, and the reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give the HCl-salt of the title compound (2.60 g, 100%). MS (ESI) m/z $[\text{M}+\text{H}]^+$ 306.2. ^1H
20 NMR (500 MHz, DMSO- d_6 , 25 °C) δ 2.22–2.31 (4H, m), 2.33–2.43 (4H, m), 2.87–3 (4H, m), 3.02–3.14 (2H, m), 3.18–3.29 (1H, m), 3.74 (3H, s), 4.05 (1H, s), 6.33 (1H, s), 8.36–8.47 (1H, m), 9.50 (1H, d).

Intermediate 224

25 *tert*-Butyl (1*R*,6*R*)-6-((trimethylsilyl)ethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate
tert-Butyl 4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 154** (1.8 g, 6.44 mmol), D-Epozone (0.832 g, 3.22 mmol) and tetrabutylammonium hydrogensulfate (0.087 g, 0.26 mmol) were stirred in a mixture of buffer solution (aq, 65 mL,
30 0.4 mM EDTA Na_2 and 0.05 M sodium tetraborate decahydrate) and MeCN (98 mL) at 0 °C. A solution of 0.89 M K_2CO_3 (aq, 42 mL) and a solution of OXONE (42.3 mL, 0.21 M in aq, 0.4 mM EDTA Na_2) were added dropwise simultaneously at the same rate (0.16 mL/min).

Upon complete addition the reaction was diluted with water and extracted with heptane. The combined organic layers were dried over MgSO₄ and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 0–10% EtOAc in heptane) to give the title compound (3.05 g, 59%) as a pale-yellow oil. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 0.17 (9H, s), 1.44 (9H, s), 2.03–2.27 (2H, m), 3.03 (1H, s), 3.32–3.71 (3H, m), 3.8–4.1 (1H, m).

Intermediate 225

tert-Butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate

tert-Butyl (1*R*,6*R*)-6-((trimethylsilyl)ethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate **Intermediate 224** (3 g, 10.15 mmol) was dissolved in MeOH (75 mL) and TsOH (0.386 g, 2.03 mmol) was added at rt. The reaction mixture was stirred for 1 h and then K₂CO₃ (3.09 g, 22.34 mmol) was added. The reaction mixture was stirred at rt over night. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and water. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound (2.0 g, 77%) as a pale-yellow oil. $[\alpha]_D^{25} +7.6$ (c 1.0, MeCN). ¹H NMR (500 MHz, MeOH-*d*₄) 1.46 (9H, s), 1.57 (1H, ddd), 2.09 (1H, ddd), 3.05 (1H, s), 3.17 – 3.29 (2H, m), 3.43 (3H, s), 3.50 (1H, dd), 3.67 (1H, d), 3.76 (1H, dd).

Intermediate 226

4-Methylnicotinoyl chloride

Oxalyl chloride (128 μL, 1.46 mmol) was added to a suspension of 4-methylnicotinic acid (100 mg, 0.73 mmol) in DCM (2.30 mL) at 0 °C followed by DMF (5.65 μL, 0.07 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated to afford the crude title compound. ¹H NMR (500 MHz, DMSO, 25 °C) δ 2.77 (3H, m), 7.97 (1H, m), 8.88 (1H, m), 9.10 (1H, s).

Intermediate 227

(3*R*,4*S*)-4-Methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol

Step a) *tert*-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-(4-methylpyridin-3-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate and (3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-methoxy-4-(3-(4-methylpyridin-3-yl)-3-oxoprop-1-yn-1-yl)piperidin-3-yl 4-methylnicotinate

A solution of *tert*-butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate

5 **Intermediate 225** (100 mg, 0.39 mmol) in THF (1.23 mL) was added to a solution of 4-methylnicotinoyl chloride **Intermediate 226** (91 mg, 0.59 mmol) and CuI (7.46 mg, 0.04 mmol) in THF (0.616 mL). Pd(PPh₃)₂Cl₂ (14.03 mg, 0.02 mmol) was added followed by TEA (0.328 mL, 2.35 mmol) and the reaction mixture vessel was evacuated and refilled with N₂ (g) three times. The reaction mixture was stirred at rt overnight. The mixture was diluted with sat
10 NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to grant a mixture of the title compounds as a brown oil. MS (ESI) *m/z* [M+H]⁺ 494.2 and 375.1.

Step b) (3*R*,4*S*)-4-Methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol

6 M HCl in IPA (0.107 mL, 0.64 mmol) was added to a solution of (3*R*,4*S*)-1-(*tert*-

15 *butoxycarbonyl*)-4-methoxy-4-(3-(4-methylpyridin-3-yl)-3-oxoprop-1-yn-1-yl)piperidin-3-yl 4-methylnicotinate and (3*R*,4*S*)-4-methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol (25 mg, 0.06 mmol) **Intermediate 227 Step a)** in EtOAc (0.536 mL) and stirred at rt for 5 h. The reaction mixture was concentrated to dryness to grant the HCl salt of the title compound (24 mg). MS (ESI) *m/z* [M+H]⁺ 289.1.

Intermediate 228

Ethyl 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate

NaH (60% wt in mineral oil, 66.6 mg, 1.66 mmol) was added to a solution of ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate (200 mg, 1.19 mmol) in THF (2.1 mL) at 0 °C and

25 stirred for 30 min. SEM-Cl (232 μL, 1.31 mmol) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to grant the title compound (346 mg, 97%) as a colourless oil. MS (ESI) *m/z* [M+H]⁺ 299.4.

Intermediate 229

3,5-Dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylic acid

LiOH (97 mg, 4.06 mmol) was added to a solution of ethyl 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate **Intermediate 228** (346 mg, 1.16 mmol) in water (3.8 mL) and THF (1 mL) and the reaction mixture was stirred at rt overnight. KOH (65 mg, 1.16 mmol) was added and EtOH (1 mL) and the reaction mixture was heated to 45 °C for 4 h. The mixture was diluted with water, acidified to pH 5 with 1 M HCl (aq) and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated to grant the title compound (285 mg, 91%) as a white solid. MS (ESI) *m/z* [M+H]⁺ 271.3.

Intermediate 230

3,5-Dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonyl chloride

Oxalyl chloride (48.6 µL, 0.55 mmol) was added to a suspension of 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylic acid **Intermediate 229** (75 mg, 0.28 mmol) in DCM (1.3 mL) at 0 °C followed by DMF (2.15 µL, 0.03 mmol). The reaction mixture was stirred at rt for 2 h at rt and then concentrated to afford the title compound (82 mg) as a yellow oil.

Intermediate 231

tert-Butyl (3*R*,4*S*)-4-((3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)ethynyl)-3-hydroxy-4-methoxypiperidine-1-carboxylate

A solution containing *tert*-butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate **Intermediate 225** (50 mg, 0.2 mmol), 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonyl chloride **Intermediate 230** (73.5 mg, 0.25 mmol), CuI (3.7 mg, 0.02 mmol) and Pd(PPh₃)₂Cl₂ (7.0 mg, 9.8 µmol) in THF (0.9 mL) was degassed with N₂ (g) for 5 min. TEA (164 µL, 1.18 mmol) was added and the reaction mixture was stirred at rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, filtered through a hydrophobic frit and concentrated to grant the title compound as a brown oil. (ESI) *m/z* [M+H]⁺ 508.6.

Intermediate 232

tert-Butyl (3*R*,4*S*)-4-(3',5'-dimethyl-1'-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3-hydroxy-4-methoxypiperidine-1-carboxylate

Hydrazine hydrate (aq, 48 μ L, 1.0 mmol) was added to a solution of *tert*-butyl (3*R*,4*S*)-4-((3,5-dimethyl-1'-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*-pyrazol-4-yl)ethynyl)-3-hydroxy-4-methoxypiperidine-1-carboxylate **Intermediate 231** (163 mg, 0.45 mmol) in EtOH (8.9 mL) and stirred at rt for 3 h. The reaction mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0-5% MeOH in EtOAc) to grant the title compound (138 mg, 82%) as a yellow foam. MS (ESI) m/z [M+H]⁺ 376.4.

Intermediate 233

(3*R*,4*S*)-4-(3',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidin-3-ol

TFA (452 mg, 3.97 mmol) was added to a solution of *tert*-butyl (3*R*,4*S*)-4-(3',5'-dimethyl-1'-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3-hydroxy-4-methoxypiperidine-1-carboxylate **Intermediate 232** (69 mg, 0.13 mmol) and stirred at rt overnight. The reaction mixture was concentrated to grant the TFA salt of the title compound (81 mg) as a red oil. MS (ESI) m/z [M+H]⁺ 292.4.

Intermediate 234

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(pyridin-3-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

tert-Butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate **Intermediate 225** (0.248 g, 0.97 mmol) was dissolved in THF (3.2 mL) and CuI (0.037 g, 0.19 mmol) was added followed by a solution of nicotinoyl chloride (0.201 g, 1.42 mmol) in THF (1.6 mL). Pd(PPh₃)₂Cl₂ (0.070 g, 0.10 mmol) was added followed by TEA (0.948 mL, 6.80 mmol). The reaction mixture vessel was evacuated and refilled with N₂ (g) ($\times$ 3). The reaction mixture was stirred at rt overnight. DCM and NaHCO₃ (aq) were added, and the layers were separated. The DCM layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (0.350 g). Used as such in the next step. MS (ESI) m/z [M+H]⁺ 361.3.

Intermediate 235

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(pyridin-3-yl)prop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 234** (0.350 g, 0.97 mmol) was dissolved in EtOH (4.5 mL) and cooled in an ice-bath. 64%Hydrazine hydrate (aq, 0.235 mL, 4.85 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was poured into water and sat NaHCO₃ (aq). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% (EtOAc/MeOH (9/1)) in heptane). The product was dissolved in EtOAc and treated with SILIAMETS Imidazole for 2 h. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was concentrated to afford the title compound (0.082 g, 23%). MS (ESI) *m/z* [M+H]⁺ 375.2. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.46 (11H, s), 1.95–2.03 (1H, m), 2.33–2.44 (1H, m), 3.12 (3H, s), 3.25–3.33 (1H, m), 3.57 (1H, s), 3.77–3.85 (1H, m), 4.1–4.17 (1H, m), 6.72 (1H, s), 7.84 (1H, s), 8.62 (2H, s), 9.17 (1H, s).

Intermediate 236

(3*R*,4*S*)-4-Methoxy-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 235** (0.079 g, 0.21 mmol) was dissolved in EtOAc (1 mL). 6 M HCl in IPA (0.352 mL, 2.11 mmol) was added dropwise and the reaction mixture was stirred at 40 °C for 2 h. The mixture was concentrated under reduced pressure to give the HCl-salt of the title compound (0.074 g). MS (ESI) *m/z* [M+H]⁺ 275.1.

Intermediate 237

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

tert-Butyl (3*R*,4*S*)-4-ethynyl-3-hydroxy-4-methoxypiperidine-1-carboxylate **Intermediate 225** (0.234 g, 0.92 mmol) was dissolved in THF (3.2 mL). CuI (0.035 g, 0.18 mmol) and a solution of 1,3,5-trimethyl-1*H*-pyrazole-4-carbonyl chloride (0.231 g, 1.34 mmol) in THF (1.6 mL) were added. Pd(PPh₃)₂Cl₂ (0.066 g, 0.09 mmol) and TEA (0.894 mL, 6.42 mmol)

were added and the reaction mixture vessel was evacuated and refilled with N₂ (g) (×3). The reaction mixture was stirred at rt overnight. DCM and NaHCO₃ (aq) were added, the layers were separated, and the DCM layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (0.359 g, 100%). MS (ESI) *m/z* [M+H]⁺ 392.3.

5

Intermediate 238

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 237** (0.359 g, 0.92 mmol) was dissolved in EtOH (4.5 mL) and cooled in an ice-bath. 64% Hydrazine hydrate (aq, 0.222 mL, 4.59 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was poured into water and NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 40–100% (EtOAc/MeOH (9/1)) in heptane). The product was dissolved in EtOAc and the mixture was treated with SILIAMETS Imidazole for 2 h, filtered and the cake was washed with EtOAc. The filtrate was concentrated to afford the title compound (0.204 g, 55%). MS (ESI) *m/z* [M+H]⁺ 406.2. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.46 (9H, s), 1.88–1.94 (1H, m), 2.3–2.39 (7H, m), 3.15 (3H, s), 3.35 (1H, ddd), 3.51–3.64 (1H, m), 3.68–3.79 (5H, m), 3.9–4.09 (1H, m), 6.26 (1H, s).

20

Intermediate 239

(3*R*,4*S*)-4-Methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

tert-Butyl (3*R*,4*S*)-3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 238** (74 mg, 0.18 mmol) was dissolved in EtOAc (1 mL). 6 M HCl in IPA (0.304 mL, 1.82 mmol) was added dropwise, and the reaction mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated under reduced pressure and co-evaporated from EtOH (×2) to give the HCl-salt of the title compound (56 mg, 100%). MS (ESI) *m/z* [M+H]⁺ 306.

30

Intermediate 240

rac-(3*R*,4*S*)-3-Fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol
tert-Butyl 4-(1',3',5'-trimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,1'*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(1',3',5'-trimethyl-2-((2-(trimethylsilyl)ethoxy)methyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 158** (168 mg, 0.34 mmol) was dissolved in MeCN (3.3 mL) and water (1 mL). SELECTFLUOR (160 mg, 0.45 mmol) was added, and the reaction mixture was stirred at rt overnight. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in DCM (2 mL) and treated with TFA (1 mL, 0.34 mmol). The reaction mixture was stirred at rt overnight and concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient of 0–30%), to give the title compound (8 mg, 8%). MS (ESI) *m/z* [M+H]⁺ 294.2. ¹H NMR (500 MHz, CDCl₃, 25 °C) δ 1.74–1.82 (1H, m), 2.17–2.35 (7H, m), 2.87–2.97 (1H, m), 3.04–3.18 (2H, m), 3.23–3.37 (1H, m), 3.73 (3H, s), 4.23–4.56 (2H, m), 6.22 (1H, d).

Intermediate 241

tert-Butyl 3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,1'*H*-[3,4'-bipyrazol]-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **Intermediate 157** (156 mg, 0.44 mmol) was dissolved in MeOH (5 mL) at rt. *m*CPBA (293 mg, 1.31 mmol) was added and the reaction mixture was stirred for 2.5 d. The mixture was diluted with EtOAc and washed with Na₂S₂O₃ (aq) and sat NaHCO₃ (aq), and finally brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod D, (gradient of 15–55%), to give the title compound (67 mg, 38%) as white solid. MS (ESI) *m/z* [M+H]⁺ 406.4.

Intermediate 242

tert-Butyl 4-(4-bromo-1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 27** (1.366 g, 3.80 mmol) was dissolved in EtOAc (13.2 mL) and NBS (1.015 g,

5.70 mmol) was added. The reaction mixture was stirred at rt for 20 min and then washed with a solution of Na₂S₂O₃ (aq) until colorless. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (isocratic EtOAc) to give the title compound (1.584 g, 95%) as white solid. MS (ESI) *m/z* [M-H]⁻ 436.2. ¹H NMR (500 MHz, CDCl₃) 1.47 (9H, s), 1.75 (2H, qd), 1.90 – 1.98 (2H, m), 2.13 – 2.19 (6H, m), 2.77 – 2.94 (3H, m), 3.75 (3H, s), 4.12 – 4.31 (2H, m).

Intermediate 243

tert-Butyl 4-(1',3',4,5'-tetramethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
1,4-Dioxane (2 mL) was added to a mixture of *tert*-butyl 4-(4-bromo-1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 242** (96 mg, 0.22 mmol), XPhos Pd G3 (9.27 mg, 10.95 μmol) and K₂CO₃ (91 mg, 0.66 mmol) under an atmosphere of N₂ (g), and the mixture was purged with N₂ (g) for 2 min. Trimethylboroxine (0.064 mL, 0.44 mmol) was added and the reaction mixture was heated to 100 °C and stirred for 1 h. The mixture was cooled to rt and diluted with EtOAc and water. The layers were separated, and the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod D, (gradient of 25–65%), to give the title compound (49.0 mg, 60%) as white solid. MS (ESI) *m/z* [M+H]⁺ 374.3. ¹H NMR (500 MHz, CDCl₃) 1.43 (9H, s), 1.62 – 1.75 (2H, m), 1.78 – 1.89 (5H, m), 2.04 (6H, d), 2.63 – 2.90 (3H, m), 3.70 (3H, s), 4.03 – 4.31 (2H, m).

Intermediate 244

tert-Butyl 4-(4-cyano-1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
A mixture of *tert*-butyl 4-(4-bromo-1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 242** (349 mg, 0.80 mmol), tBuXPhos Pd G3 (51.0 mg, 0.06 mmol) and Zn(CN)₂ (61.7 mg, 0.53 mmol) in THF/H₂O (1:5, 4 mL) was evacuated and filled with N₂ (g). The reaction mixture was heated to 40 °C and stirred vigorously for 16 h. Diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod D, (gradient of 25–60%), to give the title compound (22 mg, 7%) as a white solid. MS (ESI) *m/z*

$[M+H]^+$ 385.5. 1H NMR (500 MHz, $CDCl_3$) 1.44 (9H, s), 1.80 (2H, qd), 1.94 – 2.05 (2H, m), 2.20 (3H, s), 2.25 (3H, s), 2.72 – 2.93 (2H, m), 2.99 (1H, tt), 3.74 (3H, s), 4.06 – 4.29 (2H, m).

5 **Intermediate 245**

tert-Butyl 4-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine monohydrate in water (52.3 g, 835.1 mmol) was added to *tert*-butyl 4-(3-ethoxy-3-oxopropanoyl)piperidine-1-carboxylate (50.0 g, 167.0 mmol) in EtOH (200 mL) at 10 °C and the reaction mixture was stirred at 10 °C for 16 h. The mixture was evaporated to yield the
10 titled compound (50.0 g, 112%); MS (ESI) m/z $[M-tBu]^+$ 212.0.

Intermediate 246

tert-Butyl 4-(5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

1,1,1-Trifluoro-*N*-phenyl-*N*-(((trifluoromethyl)sulfonyl)methanesulfonamide (85.0 g, 238.3
15 mmol) was added to *tert*-butyl 4-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 245** (49.0 g, 183.3 mmol) and TEA (55.6 g, 549.9 mmol) in DCM (250 mL) at 10 °C. The reaction mixture was stirred at 10 °C for 3 h. The solvent was evaporated and the crude product was purified by straight phase flash chromatography on silica (gradient: 0–50% EtOAc in petroleum ether) to afford the titled compound (50.0 g,
20 68.3%) as a colourless solid; MS (ESI) m/z $[M-H]^-$ 398.0, $[2M-H]^-$ 797.1

Intermediate 247

3-(Piperidin-4-yl)-1*H*-pyrazol-5-yl trifluoromethanesulfonate

tert-Butyl 4-(5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

25 **Intermediate 246** (4.0 g, 10.0 mmol) was added to 4 M HCl in 1,4-dioxane (5 mL, 20 mmol) at 10 °C. The reaction mixture was stirred at 10 °C for 3 h. The mixture was evaporated, quenched with sat $NaHCO_3$ (aq, 200 mL) and extracted with EtOAc (5×100 mL). The combined organic layer was dried over Na_2SO_4 , filtered and evaporated to afford the titled compound (2.0 g, 67%) as a colourless solid. 1H NMR (300 MHz, $DMSO-d_6$) δ 1.70 – 1.85
30 (2H, m), 2.04 – 2.15 (2H, m), 2.89 – 3.06 (3H, m), 3.22 – 3.34 (2H, m), 3.38 (br s, partial overlap with solvent), 6.22 (1H, s), 13.15 (1H, br s).

Intermediate 248

3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl trifluoromethanesulfonate

2-(Chloromethyl)-4-methylquinazoline (0.721 g, 3.74 mmol) was added to 3-(piperidin-4-yl)-
5 1H-pyrazol-5-yl trifluoromethanesulfonate **Intermediate 247** (1.40 g, 4.68 mmol) in DMF
(15 mL) at 10 °C. The reaction mixture was stirred at 10 °C for 16 h. The mixture was filtered
through CELITE and washed with MeOH. The crude product was purified by reversed phase
flash chromatography on C18-column (gradient: 0–100% MeCN in water) to afford the title
compound (1.20 g, 56%) as a yellow solid; MS (ESI) m/z $[M+H]^+$ 456.05.

10

Intermediate 249

tert-Butyl 4-(5-bromo-1H-pyrazol-3-yl)piperidine-1-carboxylate

tert-Butyl nitrite (3.64 mL, 30.62 mmol) was added to a suspension of CuBr (3.94 g, 27.5
mmol) and LiBr (1.99 g, 22.92 mmol) in MeCN (137 mL). After 10 min of stirring, the
15 mixture was added to a solution of tert-butyl 4-(5-amino-1H-pyrazol-3-yl)piperidine-1-
carboxylate (4.88 g, 18.33 mmol) in MeCN (45 mL). The reaction mixture was stirred at rt for
1 h and then heated to 50 °C and stirred for 3 h. The mixture was diluted with water and
extracted with EtOAc. The combined organic layers were washed with brine, dried over
MgSO₄, filtered and concentrated. The crude residue was purified by straight phase flash
20 chromatography on silica (gradient: 10–50% EtOAc in heptane) to give the title compound
(1.84 g, 30%) as a grey solid. MS (ESI) m/z $[M+H]^+$ 328.3 and 330.3.

Intermediate 250

tert-Butyl 4-(5-(2-(trifluoromethyl)pyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate

25 A solution of tert-butyl 4-(5-bromo-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate**
249 (67.0 mg, 0.20 mmol) and (2 (2-(trifluoromethyl)phenyl)boronic acid (47.6 mg, 0.25
mmol) in DME (1 mL) was degassed with N₂ (g) for 10 min. A degassed solution of
Pd(OAc)₂ (2.4 mg, 10.69 μmol) and A-Phos (6.84 mg, 0.03 mmol) in DME (0.500 mL) was
added followed by a degassed solution of K₂CO₃ (84 mg, 0.61 mmol) in water (0.50 mL). The
30 reaction mixture was heated to 80 °C and stirred for 24 h. The mixture was allowed to cool to
rt and stirred for 3 d The mixture was diluted with DCM, passed through a phase separator,
and concentrated. The crude residue was purified by preparative HPLC, PrepMethod D,

(gradient: 10–50%), to grant the title compound (2.60 mg, 3%) as a white solid. MS (ESI) m/z [M-H]⁻ 395.4

Intermediate 251

5 3-(3-(Piperidin-4-yl)-1H-pyrazol-5-yl)-2-(trifluoromethyl)pyridine
TFA (0.1 mL, 6.56 μmol) was added to a solution of *tert*-butyl 4-(5-(2-(trifluoromethyl)pyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 250** (2.60 mg, 6.56 μmol) in DCM (0.1 mL) and stirred at rt for 2 h. The reaction mixture was concentrated to give the TFA salt of the title product (1.94 mg, 100%). MS (ESI) m/z [M+H]⁺ 297.3.

Intermediate 252

tert-Butyl 4-(5-(4-(methoxymethyl)-2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate
15 2-Hydroxyisoindoline-1,3-dione (61 mg, 0.37 mmol) and DMAP (2 mg, 0.02 mmol) were added to 2-methoxyacetic acid (33.8 mg, 0.375 mmol) in a microwave vial. DMSO (1.25 mL) was added, followed by DIC (60 μL, 0.39 mmol). The reaction mixture was stirred at rt for 24 h. A solution of *tert*-butyl 4-(5-(2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 40** (90 mg, 0.26 mmol) in DMSO (0.75 mL), a solution of 1*R*-(-)-CSA (122 mg, 0.53 mmol) in DMSO (0.5 mL) and 4-CzIPN (2 mg, 2.54 μmol) were added.
20 The mixture was evacuated and filled with N₂ (g) three times and then degassed vigorously for 10 min. The reaction mixture was irradiated with a 34 W LED (λ_{max} 456 nm) for 24 h at rt. The solution was concentrated, redissolved in DMSO (1.5 mL) and filtered. The filtrate was purified by preparative HPLC, PrepMethod I, (gradient 5–95%), to grant the title compound
25 (6.8 mg, 7%). MS (ESI) m/z [M+H]⁺ 387.2.

Intermediate 253

4-(Methoxymethyl)-2-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine
tert-Butyl 4-(5-(4-(methoxymethyl)-2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 252** (6.68 mg, 17 μmol) was dissolved in DCM (1 mL) and treated
30 with TFA (1 mL). The mixture was stirred at rt for 2 h and then concentrated to afford the TFA salt of the title compound as a colourless film. MS (ESI) m/z [M+H]⁺ 287.4.

Intermediate 254

tert-Butyl 4-(5-(4-ethyl-2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

2-Hydroxyisoindoline-1,3-dione (61 mg, 0.375 mmol) and DMAP (1.53 mg, 12.5 μ mol) were added to propionic acid (27.8 mg, 0.375 mmol) in a microwave vial. DMSO (1.25 mL) was added, followed by DIC (47.3 mg, 0.375 mmol). The reaction mixture was stirred at rt for 24 h. A solution of *tert*-butyl 4-(5-(2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 40** (90 mg, 0.26 mmol) in DMSO (0.75 mL), a solution of 1*R*(-)-CSA (122 mg, 0.53 mmol) in DMSO (0.5 mL) and 4-CzIPN (2.07 mg, 2.63 μ mol) were added. The mixture was evacuated and filled with N₂ (g) three times and then degassed vigorously for 10 min. The reaction mixture was irradiated with a 34 W LED (λ_{max} 456 nm) for 24 h at rt. The solution was concentrated, redissolved in DMSO (1.5 mL) and filtered. The crude filtrate was purified by preparative HPLC, PrepMethod I, (gradient 5–95%), to grant the title compound (15.9 mg, 16%) MS (ESI) m/z [M+H]⁺ 371.2.

Intermediate 255

4-Ethyl-2-methyl-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine

tert-Butyl 4-(5-(4-ethyl-2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Intermediate 254 (15.9 mg, 0.04 mmol) was dissolved in DCM (0.5 mL) and treated with TFA (0.5 mL) at rt. The reaction mixture was stirred for 70 min and then concentrated to give the TFA salt of the title compound. MS (ESI) m/z [M+H]⁺ 271.3.

Intermediate 256

1,4-Dimethyl-1*H*-imidazole-5-carbonyl chloride

A solution of 1,4-dimethyl-1*H*-imidazole-5-carboxylic acid (140 mg, 1.00 mmol) in DCM (1 mL) was cooled to 0°C and DMF (3.87 μ L, 0.05 mmol) was added. Oxalyl chloride (0.094 mL, 1.10 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 2 h and then concentrated to give the title compound. ¹H NMR (500 MHz, DMSO, 25°C) δ 3.95 (3H, d), 9.15 (1H, s).

Intermediate 257

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methylquinazoline

tert-Butyl 4-ethynylpiperidine-1-carboxylate (3.06 g, 14.62 mmol) was dissolved in DCM (20 mL) and treated with TFA (1.667 g, 14.62 mmol). The reaction mixture was stirred for 15 min and then concentrated under reduced pressure. The residue was redissolved in MeCN (50 mL) and 2-(chloromethyl)-4-methylquinazoline (4.22 g, 21.93 mmol) and K₂CO₃ (6.06 g, 43.86 mmol) were added. The reaction mixture was stirred at rt for 3 d and then concentrated. EtOAc and water were added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and then reduced to half volume. The EtOAc solution was extracted using 1 M HCl (15 mL) and water (10 mL). The combined aqueous layers were treated with 2 M NaOH (10 mL) and the formed precipitate was collected by filtration and washed with additional water and dried under vacuum to yield the title compound (3.10 g, 80%). MS (ESI) *m/z* [M+H]⁺ 266.2. ¹H NMR (500 MHz, CDCl₃) 1.75 - 1.84 (2H, m), 1.87 - 1.94 (2H, m), 2.06 (1H, d), 2.28 - 2.49 (3H, m), 2.86 - 2.98 (5H, m), 3.91 (2H, s), 7.55 - 7.63 (1H, m), 7.85 (1H, ddd), 8.01 - 8.05 (1H, m), 8.05 - 8.11 (1H, m).

Intermediate 258

1-(1-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Toluene (1.67 mL) and THF (0.83 mL) were added to a mixture of CuI (4.0 mg, 0.02 mmol), Pd(PPh₃)₂Cl₂ (14.74 mg, 0.02 mmol), 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (111 mg, 0.42 mmol) and 1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonyl chloride **Intermediate 183** (78 mg, 0.42 mmol) under an atmosphere of N₂ (g). TEA (286 μL, 2.10 mmol) was added and the reaction mixture was stirred for 6 h at rt and then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by preparative HPLC, PrepMethod A, (gradient: 10–50%), to grant the title compound (108 mg, 56%) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ 415.3.

Intermediate 259

5,6-Dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazine-3-carbonyl chloride

Oxalyl chloride (92 μ L, 1.08 mmol) was added to a suspension of 5,6-dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazine-3-carboxylic acid (91 mg, 0.54 mmol) in DCM (2.6 mL) at 0 °C followed by DMF (4.17 μ L, 0.05 mmol). The reaction mixture was warmed to rt and stirred for 2 h and then concentrated to grant the title compound (101 mg, 100%) as a white solid.

5

Intermediate 260

1-(5,6-Dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Toluene (1.2 mL) and THF (1.2 mL) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.143 g, 0.54 mmol), 5,6-dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazine-3-carbonyl chloride **Intermediate 2** (0.101 g, 0.54 mmol) and CuI (5.14 mg, 0.03 mmol) under an atmosphere of N₂ (g). TEA (0.376 mL, 2.70 mmol) and Pd(PPh₃)₂Cl₂ (19 mg, 0.03 mmol) were added. The reaction mixture was degassed with N₂ (g) for 20 s and then stirred at rt overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give the title compound. MS (ESI) *m/z* [M+H]⁺ 416.4.

15

Intermediate 261

6,7-Dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine-3-carbonyl chloride

Oxalyl chloride (0.049 mL, 0.63 mmol) was added to a suspension of 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine-3-carboxylic acid (84.1 mg, 0.5 mmol) in DCM (1 mL) followed by DMF (1.936 μ L, 0.03 mmol). The reaction mixture was stirred at rt overnight and then concentrated to afford the title compound. ¹H NMR (500 MHz, DMSO, 25°C) δ 4.05 (2H, t), 4.14 (2H, t), 4.93 (2H, s), 7.80 (1H, s).

20

Intermediate 262

1-(6,7-Dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (12 mg, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (88 mg, 0.333 mmol), 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine-3-carbonyl chloride **Intermediate 261** (93.3 mg, 0.50 mmol) and CuI (3.17 mg, 0.02 mmol) in

25

30

toluene (1.5 mL) and THF (0.5 mL). The reaction mixture was purged with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (60.8 mg, 44%). MS (ESI) *m/z* [M+H]⁺ 416.5.

Intermediate 263

5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-3-carbonyl chloride

Oxalyl chloride (49 μL, 0.63 mmol) was added to a suspension of 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-3-carboxylic acid (76.08 mg, 0.5 mmol) in DCM (1 mL) followed by DMF (1.936 μL, 0.03 mmol). The reaction mixture was stirred at rt overnight and then concentrated to afford the title compound. ¹H NMR (500 MHz, DMSO, 25°C) δ 2.57 (m, overlapping with solvent), 2.96 (2H, t), 4.09 (2H, t), 7.76 (1H, s).

Intermediate 264

1-(5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazol-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (12 mg, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (88 mg, 0.333 mmol), 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-3-carbonyl chloride **Intermediate 263** (85.3 mg, 0.50 mmol) and CuI (3.17 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.5 mL). The reaction mixture was degassed with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with water and EtOAc and the layers were separated- The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (41.1 mg, 31%). MS (ESI) *m/z* [M+H]⁺ 400.2

Intermediate 265

6,7-Dihydro-5H-pyrazolo[5,1-*b*][1,3]oxazine-3-carbonyl chloride

Oxalyl chloride (50 μL, 0.58 mmol) was added to a suspension of 6,7-dihydro-5H-pyrazolo[5,1-*b*][1,3]oxazine-3-carboxylic acid (84 mg, 0.50 mmol) in DCM (1 mL). The

solution was cooled to 0 °C followed by addition of DMF (1.936 µL, 0.03 mmol). The reaction mixture was warmed to rt, stirred overnight and then concentrated to afford the title compound. ¹H NMR (500 MHz, DMSO) 2.18 (2H, m), 4.07 (2H, m), 4.33 – 4.52 (2H, m), 7.57 (1H, s).

5

Intermediate 266

1-(6,7-Dihydro-5H-pyrazolo[5,1-*b*][1,3]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Toluene (1.2 mL) and THF (0.5 mL) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (88 mg, 0.333 mmol), 6,7-dihydro-5H-pyrazolo[5,1-*b*][1,3]oxazine-3-carbonyl chloride **Intermediate 265** (62 mg, 0.33 mmol), Pd(PPh₃)₂Cl₂ (12 mg, 0.02 mmol) and CuI (3.17 mg, 0.02 mmol). TEA (0.271 mL, 2.00 mmol) was added and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude product was stirred with 200 mg SILAMETS Imidazole in EtOAc overnight and then filtered and concentrated. The residue was purified by preparative HPLC, PrepMethod A, (gradient: 5–50%), to grant the title compound (64 mg, 46%) as a red solid. MS (ESI) *m/z* [M+H]⁺ 416.5.

20 **Intermediate 267**

tert-Butyl 4-(5-(2,3-dihydropyrazolo[5,1-*b*]oxazol-7-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate

CDI (176 mg, 1.08 mmol) was added to a suspension of 2,3-dihydropyrazolo[5,1-*b*]oxazole-7-carboxylic acid (159 mg, 1.03 mmol) in THF (7 mL) and stirred at rt for 4 h. In a separate flask a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (469 mg, 2.06 mmol) in THF (7.00 mL) was cooled to -78 °C and 2 M LDA in THF (1.057 mL, 2.11 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h followed by dropwise addition of the CDI-activated acid solution. The reaction mixture was stirred for 5 min at -78 °C and was then allowed to warm to rt and stirred for a further 15 min. The reaction was quenched with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was dissolved in EtOH (3 mL), treated with hydrazine hydrate (aq, 0.251 mL, 5.16 mmol) and stirred for 2 h at rt. The mixture was

30

concentrated, redissolved in DMSO and purified by preparative HPLC, PrepMethod F, (gradient: 15–55%), to grant the title compound (53 mg, 14%) as clear film. MS (ESI) m/z $[M+H]^+$ 360.4

5 **Intermediate 268**

3,5-Dimethylisoxazole-4-carbonyl chloride

Oxalyl chloride (50 μ L, 0.58 mmol) was added to a suspension of 6,7-dihydro-5H-pyrazolo[5,1-*b*][1,3]oxazine-3-carboxylic acid (79.78 mg, 0.5 mmol) in DCM (1 mL). The solution was cooled to 0 °C followed by addition of DMF (1.936 μ L, 0.03 mmol). The
10 reaction mixture was warmed to rt, stirred overnight and then concentrated to afford the title compound. ^1H NMR (500 MHz, DMSO, 25°C) δ 2.32 (2H, s), 2.59 (2H, s).

Intermediate 269

1-(3,5-Dimethylisoxazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (12 mg, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (88 mg, 0.333 mmol), 3,5-dimethylisoxazole-4-carbonyl chloride **Intermediate 268** (79.79 mg, 0.50 mmol) and CuI (3.17 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.5 mL). The reaction mixture
20 was degassed with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (70.2 mg, 54%). MS (ESI) m/z $[M+H]^+$ 389.3.

25

Intermediate 270

1,2,4-Trimethyl-1H-imidazole-5-carbonyl chloride

Oxalyl chloride (143 μ L, 1.66 mmol) was added to a suspension of 1,2,4-trimethyl-1H-imidazole-5-carboxylic acid (128 mg, 0.83 mmol) in DCM (3.17 mL) at 0 °C followed by
30 DMF (6.43 μ L, 0.08 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated to afford the title compound. ^1H NMR (500 MHz, DMSO) 2.48 (3H, s), 2.59 (3H, s), 3.83 (3H, s).

Intermediate 271

3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1,2,4-trimethyl-1H-imidazol-5-yl)prop-2-yn-1-one

5 THF (1.78 mL) and toluene (1.78 mL) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (220 mg, 0.83 mmol), 1,2,4-trimethyl-1H-imidazole-5-carbonyl chloride **Intermediate 270** (143 mg, 0.83 mmol) and CuI (12.23 mg, 64.2 μ mol) under an atmosphere of N₂ (g). Pd(PPh₃)₂Cl₂ (23.0 mg, 32.7 μ mol) and TEA (0.269 mL, 1.93 mmol) were added and the reaction mixture was degassed with N₂ (g) for 20
10 s. The reaction mixture was stirred at rt overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude material was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (157 mg, 47%) as a white solid. MS (ESI) m/z [M+H]⁺ 402.2.

15

Intermediate 272

1,2-Dimethyl-1H-imidazole-5-carbonyl chloride

Oxalyl chloride (120 μ L, 1.41 mmol) was added to a suspension of 1,2-dimethyl-1H-imidazole-5-carboxylic acid (99 mg, 0.70 mmol) in DCM (3.40 mL) at 0 °C followed by
20 DMF (5.43 μ L, 0.07 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated to afford the title compound as a white solid. ¹H NMR (500 MHz, DMSO) 2.63 (3H, s), 3.89 (3H, s), 8.27 (1H, s).

Intermediate 273

25 1-(1,2-Dimethyl-1H-imidazol-5-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

THF (1.51 mL) and toluene (1.151 mL) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.186 g, 0.70 mmol), 1,2-dimethyl-1H-imidazole-5-carbonyl chloride **Intermediate 272** (0.111 g, 0.7 mmol) and CuI (6.67 mg, 0.04
30 mmol) under an atmosphere of N₂ (g). Pd(PPh₃)₂Cl₂ (0.025 g, 0.04 mmol) and TEA (0.488 mL, 3.50 mmol) were added and the reaction mixture was degassed with N₂ (g) for 20 s. The reaction mixture was stirred at rt overnight. The mixture was diluted with water and extracted

with EtOAc. The combined organic layers were dried over MgSO_4 , filtered and concentrated to give the title compound. MS (ESI) m/z $[\text{M}+\text{H}]^+$ 388.4.

Intermediate 274

5 *tert*-Butyl 4-(3-(2,4-dimethylthiazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate
CDI (149 mg, 0.92 mmol) was added to a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (200 mg, 0.87 mmol) in THF (3.3 mL) at rt and the reaction mixture was stirred at rt for 2 h. A solution containing (1-(2,4-dimethylthiazol-5-yl)ethan-1-one (149 mg, 0.87 mmol) in THF (3.3 mL) was cooled to -78°C . 1 M LiHMDS in THF (2.181 mL, 2.18
10 mmol) was added and the mixture was stirred for 30 min. The reaction mixture containing the CDI activated acid was added dropwise over 5 min at -78°C and the reaction mixture was allowed to warm to rt overnight. The mixture was diluted with sat NaHCO_3 (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to grant the title compound (320 mg, 100%) as an orange oil. MS (ESI) m/z
15 $[\text{M}+\text{H}]^+$ 367.2.

Intermediate 275

tert-Butyl 4-(5-(2,4-dimethylthiazol-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate
Hydrazine hydrate (aq, 0.213 mL, 4.35 mmol) was added to a solution of *tert*-butyl 4-(3-(2,4-dimethylthiazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 274** (319 mg, 0.87 mmol) in EtOH (17.187 mL) and stirred at rt for 3 h. The mixture was diluted with sat NaHCO_3 (aq) and extracted with DCM. The organic layers were combined and washed with brine, filtered through a hydrophobic frit and concentrated. The crude residue was purified by straight phase flash column chromatography on silica (gradient: 0–80% EtOAc in heptane) to
20 grant the title compound (140 mg, 44%) as a yellow foam. MS (ESI) m/z $[\text{M}+\text{H}]^+$ 363.3.

Intermediate 276

2,4-Dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)thiazole
6 M HCl in IPA (0.828 mL, 4.97 mmol) was added to a solution of *tert*-butyl 4-(5-(2,4-dimethylthiazol-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 275** (180 mg, 0.50 mmol) in EtOAc (5 mL) and stirred at 45°C for 3 h. The reaction mixture was
30

concentrated to dryness to grant the HCl salt of the title compound (137 mg) as a yellow foam. MS (ESI) m/z $[M+H]^+$ 263.3

Intermediate 277

5 *tert*-Butyl 4-(3-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

A solution containing *tert*-butyl 4-ethynylpiperidine-1-carboxylate (100 mg, 0.48 mmol), 2-methyl-4-(trifluoromethyl)thiazole-5-carbonyl chloride (132 mg, 0.57 mmol), CuI (9.1 mg, 0.05 mmol) and Pd(PPh₃)₂Cl₂ (17.1 mg, 0.02 mmol) in THF (4.2 mL) was degassed with N₂ (g) for 5 min and then TEA (0.40 mL, 2.87 mmol) was added. The reaction mixture was stirred at rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, filtered through a hydrophobic frit and concentrated to grant the title compound as a brown oil. MS (ESI) m/z $[M-H]^-$ 400.9.

15 Intermediate 278

tert-Butyl 4-(5-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 0.118 mL, 2.40 mmol) was added to a solution of *tert*-butyl 4-(3-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

20 **Intermediate 277** (193 mg, 0.48 mmol) in EtOH (8.9 mL) and stirred at rt for 3 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient: 5–50% EtOAc in heptane) to grant the title compound (51 mg, 26%) as an orange solid. MS (ESI) m/z $[M+H]^+$ 417.4.

Intermediate 279

5-Methyl-2-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)-4-(trifluoromethyl)thiazole

6 M HCl in IPA (204 μ L, 1.22 mmol) was added to a solution of *tert*-butyl 4-(5-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 278** (51 mg, 0.12 mmol) in EtOAc (1.2 mL) and stirred at 45 °C for 3 h. The mixture was

concentrated to dryness to grant the HCl salt of the title compound (43.7 mg) as a yellow foam. MS (ESI) m/z $[M+H]^+$ 316.5.

Intermediate 280

5 3,5-Dimethylisothiazole-4-carbonyl chloride

Oxalyl chloride (0.114 mL, 1.30 mmol) was added to a suspension of 3,5-dimethylisothiazole-4-carboxylic acid (102 mg, 0.65 mmol) in DCM (3 mL) at 0 °C followed by DMF (5.03 μ L, 0.07 mmol). The reaction mixture was stirred at rt for 2 h at rt and then concentrated to afford the title compound as a brown oil. ^1H NMR (500 MHz, DMSO, 25°C)
10 δ 2.52 (3H, s), 2.67 (3H, s).

Intermediate 281

tert-Butyl 4-(3-(3,5-dimethylisothiazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate

A solution of *tert*-butyl 4-ethynylpiperidine-1-carboxylate (100 mg, 0.48 mmol), 3,5-dimethylisothiazole-4-carbonyl chloride **Intermediate 280** (101 mg, 0.57 mmol), CuI (9.1
15 mg, 0.05 mmol) and Pd(PPh₃)₂Cl₂ (17.1 mg, 0.02 mmol) in THF (4.2 mL) was degassed with N₂ (g) for 5 min. TEA (0.40 mL, 2.87 mmol) was added and the reaction mixture was stirred at rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, filtered through a hydrophobic frit and
20 concentrated to grant the title compound as a brown oil.

Intermediate 282

tert-Butyl 4-(5-(3,5-dimethylisothiazol-4-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 0.118 mL, 2.40 mmol) was added to a solution of *tert*-butyl 4-(3-(3,5-dimethylisothiazol-4-yl)-3-oxoprop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 281**
25 (167 mg, 0.48 mmol) in EtOH (8.9 mL) and stirred at rt for 3 h. The reaction mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient: 0–80% EtOAc in heptane)
30 to grant the title compound (28 mg, 16%) as an orange foam. MS (ESI) m/z $[M+H]^+$ 363.3.

Intermediate 283

3,5-Dimethyl-4-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)isothiazole

6 M HCl in IPA (129 μ L, 0.77 mmol) was added to a solution of *tert*-butyl 4-(5-(3,5-dimethylisothiazol-4-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 282** (28 mg, 0.08 mmol) in EtOAc (1.4 mL) and stirred at 45 °C for 3 h. The mixture was concentrated to dryness to grant the HCl salt of the title compound (29.6 mg) as a yellow foam. MS (ESI) m/z [M+H]⁺ 263.1.

Intermediate 284*tert*-Butyl 4-(5-methoxy-3,5-dioxopentanoyl)piperidine-1-carboxylate

NaH (60% mineral oil, 0.166 g, 4.15 mmol) was added to a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (0.555 g, 2.44 mmol) in THF (12 mL) and stirred for 15 min at rt. Dimethyl oxalate (432 mg, 3.66 mmol) was added and the reaction mixture was refluxed for 10 h under at atmosphere of N₂ (g). The mixture was poured into ice water and 0.1 M HCl (aq) was added until the pH reached pH 2. The mixture was extracted with EtOAc and the combined organic layers were filtered through a phase separator and concentrated to grant the title compound (0.765 g, 100%). MS (ESI) m/z [M-H]⁻ 312.1.

Intermediate 285*tert*-Butyl 4-(5-(methoxycarbonyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 0.141 mL, 2.91 mmol) was added to a solution of *tert*-butyl 4-(5-methoxy-3,5-dioxopentanoyl)piperidine-1-carboxylate **Intermediate 284** (0.607 g, 1.94 mmol) in EtOH (10 mL) and AcOH (0.1 mL) at 0 °C and the reaction mixture was stirred at rt overnight. The mixture was diluted with water and sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–100% (10% MeOH in EtOAc) in heptane) to grant the title compound (0.412 g, 69%). MS (ESI) m/z [M-H]⁻ 308.2.

Intermediate 2863-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-5-carboxylic acid

NaOH (3.88 mL, 3.88 mmol) was added to a suspension of *tert*-butyl 4-(5-(methoxycarbonyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 285** (500 mg,

1.62 mmol) in THF (7.5 mL) and MeOH (7.5 mL) and stirred at 50 °C for 2h. The reaction mixture was stirred at rt overnight. The mixture was concentrated, diluted with water and washed with EtOAc. The pH of the aqueous layer was adjusted to pH 2 with 3.8 M HCl (aq) and extracted with EtOAc. The combined organic layers were filtered through a hydrophobic
5 frit and concentrated to grant the title compound (464 mg, 97%). MS (ESI) m/z [M-H]⁻ 294.0.

Intermediate 287

tert-Butyl 4-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate
Acetohydrazine (72 mg, 0.97 mmol), DMC (0.623 g, 3.68 mmol) and DIPEA (1.287 mL, 7.37
10 mmol) were added to a solution of 3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-5-carboxylic acid **Intermediate 286** (0.272 g, 0.92 mmol) in DCM (9.5 mL) and stirred at 80 °C overnight. The mixture was diluted with water and the layers were separated. The organic layers were washed with water, filtered through a phase separator and concentrated. The crude residue was purified by straight phase flash chromatography on silica (gradient 0-100% (10%
15 MeOH in EtOAc) in heptane) to grant the title compound. MS (ESI) m/z [M+H]⁺ 334.1.

Intermediate 288

2-Methyl-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)-1,3,4-oxadiazole
TFA (1.598 mL, 20.74 mmol) was added to a solution of *tert*-butyl 4-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 287** (373 mg, 1.12
20 mmol) in DCM at 0 °C. The reaction mixture was stirred at rt for 1 h. The mixture was concentrated to grant the TFA salt of the title compound (180 mg, 43%). MS (ESI) m/z [M+H]⁺ 234.2.

Intermediate 289

2-Methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)-1,3,4-oxadiazole
DIPEA (0.534 mL, 3.11 mmol) was added to a solution of 2-methyl-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)-1,3,4-oxadiazole, TFA **Intermediate 288** (180 mg, 0.52 mmol) and 2-
30 (chloromethyl)-4-methylquinazoline 101 mg, 52 mmol) in DMSO (4 mL) and the reaction mixture was stirred at rt overnight. The mixture was diluted with EtOAc and washed with sat

NaHCO₃ (aq). The organic layers were filtered through a phase separator and concentrated to grant the title compound (180 mg, 89%). MS (ESI) m/z [M+H]⁺ 390.1.

Intermediate 290

5 *tert*-Butyl 4-(3-(3,4-dimethylisoxazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate
CDI (0.175 g, 1.08 mmol) was added to a suspension of 3,4-dimethylisoxazole-5-carboxylic acid (0.151 g, 1.07 mmol) in THF (3 mL) and the suspension was stirred at rt for 4 h. In a separate flask a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (0.234 g, 1.03 mmol) in THF (7 mL) was cooled to -78 °C and 1 M LiHMDS in THF (2.58 mL, 2.58 mmol) was
10 added dropwise. The reaction mixture was stirred at -78 °C for 1 h and then the solution of the CDI-activated acid was added dropwise. The reaction mixture was stirred for 5 min and then allowed to warm to rt and stirred overnight. The reaction was quenched by addition of NaHCO₃ (aq) and diluted with EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were filtered through a phase separator and concentrated under
15 reduced pressure to yield the title compound (0.372 g). MS (ESI) m/z [M-H]⁻ 349.3.

Intermediate 291

tert-Butyl 4-(5-(3,4-dimethylisoxazol-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate
tert-Butyl 4-(3-(3,4-dimethylisoxazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate
20 **Intermediate 290** (0.361 g, 1.03 mmol) was dissolved in 99.5% EtOH (3.5 mL) and 64% hydrazine hydrate (aq, 0.150 mL, 3.09 mmol) was added. The reaction mixture was stirred at rt over the weekend. Toluene was added and the mixture was concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.084 g,
25 24%). MS (ESI) m/z [M-H]⁻ 345.3. ¹H NMR (500 MHz, DMSO-*d*₆) 1.41 (9H, s), 1.50 (2H, qd), 1.85 – 1.94 (2H, m), 2.34 (3H, s), 2.67 – 2.99 (3H, m), 3.88 – 4.09 (2H, m), 6.28 (1H, s), 12.77 (1H, s).

Intermediate 292

30 3,4-Dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)isoxazole
tert-Butyl 4-(5-(3,4-dimethylisoxazol-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate
Intermediate 291 (0.084 g, 0.24 mmol) was dissolved in DCM (3 mL), cooled in an ice-bath

and TFA (0.346 mL, 4.50 mmol) was added. The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was triturated with Et₂O (5 mL). The solvent was decanted, and the resulting precipitate was dried under high vacuum to yield the TFA salt of title compound (0.087 g, 100%). MS (ESI) *m/z* [M+H]⁺ 247.0.

5

Intermediate 293

1-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Toluene (1.5 mL) and THF (0.5 mL) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (88 mg, 0.333 mmol), 1,5-dimethyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 211** (79.0 mg, 0.50 mmol) and CuI (3.17 mg, 0.02 mmol) under an atmosphere of N₂ (g). TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (12 mg, 0.02 mmol) were added. The reaction mixture was degassed with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude material was purified by preparative HPLC, PrepMethod A, (gradient: 10-50%), to grant the title compound 78 mg, 60%) as a red solid. MS (ESI) *m/z* [M+H]⁺ 388.2.

15

Intermediate 294

tert-Butyl 4-(3-(1-methyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate

A solution of 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate (15.44 g, 60 mmol) and 1-(1-methyl-1*H*-pyrazol-4-yl)ethan-1-one (7.45 g, 60.00 mmol) in THF (90 mL) was distributed evenly into 8 microwave vials. 1 M LiHMDS in THF (7.5 mL, 7.5 mmol) was added to each of the vials and the reaction mixtures were heated in a microwave reactor for 30 min at 100 °C. The mixtures were combined and filtered through CELITE. The filtrate was concentrated to a residue which was dissolved in EtOAc (80 mL). The precipitate formed was filtered off and the filtrate was concentrated and purified by straight phase flash chromatography on silica, (isocratic: EtOAc), to grant the title compound (4.09 g, 20%) as a colourless solid. MS (ESI) *m/z* [M-*t*Bu+H]⁺ 280.2.

25

Intermediate 295

tert-Butyl 4-(1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

30

Hydrazine hydrate (aq, 2 mL, 40.00 mmol) was added to a solution of *tert*-butyl 4-(3-(1-methyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 294** (4.09 g, 12.19 mmol) in EtOH (30 mL). The reaction mixture was stirred at 40 °C for 1 h and then concentrated. The residue was dissolved in MTBE (12 mL) and stirred for 4 h. DIPE (4 mL)
5 was added dropwise and the mixture was stirred for 1 h. The precipitate formed was isolated by filtration, washed with DIPE and dried to grant the title compound (3.77 g, 93%). MS (ESI) *m/z* [M+H]⁺ 332.3.

Intermediate 296

10 1'-Methyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole
tert-Butyl 4-(1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 295** (3.77 g, 11.38 mmol) was suspended in 1.25 M HCl in MeOH (10 mL, 12.50 mmol). 4 M HCl in dioxane (20 mL, 80.0 mmol) was added and the reaction mixture was stirred at rt for 30 min. Further 4 M HCl in dioxane (10 mL, 12.5 mmol) was added and the reaction mixture
15 was stirred for 30 min. The mixture was diluted with Et₂O and precipitate formed. The precipitate was isolated by filtration, washed with Et₂O and dried in vacuo to grant the HCl salt of the title compound (4.01 g) as a colourless powder. MS (ESI) *m/z* [M+H]⁺ 232.2.

Intermediate 297

20 5-Cyclobutyl-1-methyl-1*H*-pyrazole-4-carbonyl chloride
5-Cyclobutyl-1-methyl-1*H*-pyrazole-4-carboxylic acid (0.090g, 0.5 mmol) was suspended in DCM (1 mL) and oxalyl chloride (0.049 mL, 0.63 mmol) was added followed by DMF (1.94 mL, 0.03 mmol). The reaction mixture was stirred at rt overnight and then concentrated to afford the title compound (0.099g, 100%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.67 (s, 1H),
25 4.06 – 3.96 (m, 1H), 3.84 (s, 3H), 2.61 – 2.53 (m, 2H), 2.29 – 2.21 (m, 2H), 2.03 – 1.92 (m, 1H), 1.89 – 1.80 (m, 1H).

Intermediate 298

30 1-(5-Cyclobutyl-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one
TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g,

0.333 mmol), 5-cyclobutyl-1-methyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 297** (0.099g, 0.50 mmol) and CuI (3.2 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.500 mL). The reaction mixture was purged with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer
5 was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to give the title compound (0.111g, 78%). MS (ESI) *m/z* [M+H]⁺ 428.3.

Intermediate 299

10 1-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g, 0.333 mmol), 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonyl chloride (0.097g, 0.50
15 mmol) and CuI (3.17 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.5 mL). The reaction mixture was purged with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod D,
20 (gradient of 15–55%), to give the title compound (0.039g, 27%). MS (ESI) *m/z* [M+H]⁺ 424.2.

Intermediate 300

25 1-(1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g, 0.333 mmol), 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride (0.106 g, 0.50
30 mmol) and CuI (3.2 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.500 mL). The reaction mixture was purged with N₂ (g) for 5 min and then stirred at rt overnight. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated.

The crude was purified by preparative HPLC, PrepMethod D, (gradient of 15–55%), to give the title compound (0.066g, 45%). MS (ESI) m/z $[M+H]^+$ 442.4.

Intermediate 301

5 5-(Methoxymethyl)-1-methyl-1H-pyrazole-4-carbonyl chloride

5-(Methoxymethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (85mg, 0.5 mmol) was suspended in DCM (1 mL). Oxalyl chloride (0.049 mL, 0.63 mmol) was added followed by DMF (1.936 μ L, 0.03 mmol). The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure to afford the title compound (0.094g, 100%). 1H NMR (500 MHz, DMSO- d_6) δ 7.76 (s, 1H), 4.77 (s, 2H), 3.83 (s, 3H), 3.26 (s, 3H).

Intermediate 302

1-(5-(Methoxymethyl)-1-methyl-1H-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

TEA (0.271 mL, 2.00 mmol) and Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) were added to a mixture of 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g, 0.333 mmol), 5-(methoxymethyl)-1-methyl-1H-pyrazole-4-carbonyl chloride **Intermediate 301** (0.094g, 0.50 mmol) and CuI (3.2 mg, 0.02 mmol) in toluene (1.5 mL) and THF (0.5 mL). The reaction mixture was purged with N₂ (g) for 5 min and stirred at rt overnight. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod D, (gradient of 15–55%), to give the title compound (0.064g, 46%). MS (ESI) m/z $[M+H]^+$ 418.2.

Intermediate 303

1-(5-Cyclopropyl-1-methyl-1H-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g, 0.333 mmol) was dissolved in toluene (1.3 mL) and THF (0.5 mL) under an atmosphere of N₂ (g). 5-Cyclopropyl-1-methyl-1H-pyrazole-4-carbonyl chloride **Intermediate 191** (0.092 g, 0.5 mmol), CuI (3.2 mg, 0.02 mmol), Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) and TEA (0.272 mL,

2.00 mmol) were added and the reaction mixture was stirred overnight. The mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc and SILAMETS Imidazole (200 mg) was added, and the mixture was stirred overnight and then filtered and concentrated. The crude product was purified by preparative HPLC, PrepMethod A, (gradient of 5–50%), to give the title compound (0.133 g, 97%) as red solid. MS (ESI) m/z [M+H]⁺ 414.4. ¹H NMR (500 MHz, CDCl₃) 0.83 – 0.90 (2H, m), 1.09 – 1.16 (2H, m), 1.74 – 1.84 (1H, m), 1.87 – 2.00 (2H, m), 2.03 – 2.16 (2H, m), 2.64 – 2.84 (3H, m), 2.94 (3H, s), 3.05 – 3.17 (2H, m), 3.90 (3H, s), 4.08 (2H, s), 7.58 – 7.65 (1H, m), 7.79 – 7.91 (2H, m), 8.01 (1H, d), 8.05 – 8.11 (1H, m).

Intermediate 304

1-(5-Methoxy-1,3-dimethyl-1H-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (0.088 g, 0.333 mmol) was dissolved in toluene (1.3 mL) and THF (0.5 mL) under an atmosphere of N₂ (g). 5-Methoxy-1,3-dimethyl-1H-pyrazole-4-carbonyl chloride **Intermediate 138** (0.094 g, 0.5 mmol), CuI (3.2 mg, 0.02 mmol), Pd(PPh₃)₂Cl₂ (0.012 g, 0.02 mmol) and TEA (0.272 mL, 2.00 mmol) were added and the mixture was stirred for 3 h. The mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc and SILAMETS Imidazole (200 mg) was added, and the mixture was stirred overnight and then filtered and concentrated. The crude product was purified by preparative HPLC, PrepMethod A, (gradient of 10–50%), to give the title compound (0.098 g, 71%) as red solid. MS (ESI) m/z [M+H]⁺ 418.3. ¹H NMR (500 MHz, CDCl₃) 1.91 – 2.03 (2H, m), 2.07 – 2.17 (2H, m), 2.45 (3H, s), 2.64 – 2.83 (3H, m), 2.94 (3H, s), 3.15 – 3.24 (2H, m), 3.61 (3H, s), 4.04 (3H, s), 4.11 (2H, s), 7.59 – 7.66 (1H, m), 7.82 – 7.90 (1H, m), 8.01 (1H, d), 8.05 – 8.11 (1H, m).

Intermediate 305

3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1,3,4-trimethyl-1H-pyrazol-5-yl)prop-2-yn-1-one

2-((4-Ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (159 mg, 0.60 mmol) was dissolved in toluene/THF (1:1, 2.6 mL) under an atmosphere of N₂ (g). CuI (5.7 mg, 0.03 mmol), 1,3,4-trimethyl-1*H*-pyrazole-5-carbonyl chloride (104 mg, 0.6 mmol), Pd(PPh₃)₂Cl₂ (21.1 mg, 0.03 mmol) and TEA (418 µL, 3.00 mmol) were added. The reaction mixture was degassed with N₂ (g) for 20 sec and then stirred at rt overnight. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried using MgSO₄, filtered and concentrated under reduced pressure. The compound was purified by preparative HPLC, PrepMethod F, (gradient of 30–70%), to give the title compound (167 mg, 69%) as an orange oil. MS (ESI) *m/z* [M+H]⁺ 402.5.

Intermediate 306

tert-Butyl 4-(3-(3,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate

Step a) Ethyl 3,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate NaH (60% wt% in mineral oil, 346 mg, 8.66 mmol) was added to a solution of ethyl 3,4-dimethyl-1*H*-pyrazole-5-carboxylate (971 mg, 5.77 mmol) in THF (29 mL) at 0°C and the reaction mixture was stirred for 30 min. SEM-Cl (1.124 mL, 6.35 mmol) was added and the reaction mixture was stirred for 15 h at rt. The reaction was quenched by the addition of water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated to give a mixture of regio-isomers in a 3:1 ratio. The isomers were separated by straight phase flash chromatography on silica (gradient: 0–50% EtOAc in heptane) to yield the title compound (1.05 g, 61%). MS (ESI) *m/z* [M+H]⁺ 299.42.

Step b) 3,4-Dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylic acid
Ethyl 3,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylate

Intermediate 306 step a (1.050 g, 3.52 mmol) was dissolved in MeOH/THF (2:1, 15 mL). 1 M LiOH (7.04 mL, 7.04 mmol) was added, and the reaction mixture was stirred at rt for 20 h. The mixture was concentrated under reduced pressure. 1 M HCl (aq, 7mL) was added followed by EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to yield the title compound (0.924 g, 97%) as white solid. MS (ESI) *m/z* [M+H]⁺ 271.2.

Step c) *tert*-Butyl 4-(3-(3,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate

3,4-Dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-carboxylic acid

Intermediate 306 step b (0.289 g, 1.07 mmol) was suspended in THF (3 mL) and CDI (0.175

5 g, 1.08 mmol) was added. The suspension was stirred at rt for 4 h. In a separate flask a solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (0.234 g, 1.03 mmol) in THF (7 mL) was cooled to -78 °C and a solution of 1 M LiHMDS in THF (2.58 mL, 2.58 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, followed by a dropwise addition of the solution of the CDI-activated acid. The mixture was stirred for 5 min at 0 °C and then at rt overnight. The reaction was quenched by addition of NaHCO₃ (aq) and then diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were filtered through a phase separator and concentrated under reduced pressure to afford the title compound (0.494 g, 100%). MS (ESI) *m/z* [M-H]⁻ 478.2

Intermediate 307

tert-Butyl 4-(4',5'-dimethyl-2'-((2-(trimethylsilyl)ethoxy)methyl)-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidine-1-carboxylate

64% Hydrazine hydrate (aq, 0.150 mL, 3.09 mmol) was added to a solution of *tert*-butyl 4-(3-(3,4-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 306** (0.494 g, 1.03 mmol) in 99.5% EtOH (3.5 mL) and the reaction mixture was stirred at rt overnight. Toluene was added and the mixture was concentrated under reduced pressure. The crude residue was purified by straight phase flash chromatography on silica (gradient 10–100% (EtOAc/MeOH (9/1)) in heptane) to give the title compound (0.300 g, 61%). MS (ESI) *m/z* [M+H]⁺ 476.3.

Intermediate 308

4,5-Dimethyl-5'-(piperidin-4-yl)-2*H*,2'*H*-3,3'-bipyrazole

tert-Butyl 4-(4',5'-dimethyl-2'-((2-(trimethylsilyl)ethoxy)methyl)-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 307** (0.297 g, 0.62 mmol) was dissolved in DCM (4.5 mL) and TFA (0.722 mL, 9.36 mmol) was added. The reaction mixture was stirred at rt

for 1 h. Toluene was added and the reaction mixture was concentrated under reduced pressure to yield the TFA-salt of the title compound (0.224 g). MS (ESI) m/z $[M+H]^+$ 246.1.

Intermediate 309

tert-Butyl 4-(3-(1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate

1-(1,3-Dimethyl-1*H*-pyrazol-4-yl)ethan-1-one (300 mg, 2.17 mmol) was dissolved in THF (6 mL) and cooled in an ice-bath. 1 M KHMDS in THF (4.342 mL, 4.34 mmol) was added slowly and the reaction mixture was stirred for 30 min at 0 °C. 1-(*tert*-Butyl) 4-methyl piperidine-1,4-dicarboxylate (1057 mg, 4.34 mmol) was added and the reaction mixture was stirred at 60 °C for 2 h. The mixture was poured into water, and extracted with EtOAc. The organic layers were combined and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (EtOAc/petroleum ether, 2:1) to afford the title compound (0.690 g, 91%) as pale-yellow oil. MS (ESI) m/z $[M+H]^+$ 350.2.

Intermediate 310

tert-Butyl 4-(1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Hydrazine hydrate (aq, 240 mg, 3.83 mmol) was added to *tert*-butyl 4-(3-(1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 309** (670 mg, 1.92 mmol) in EtOH (6 mL) and the reaction mixture was stirred at rt for 5 h. The solvent was removed under reduced pressure to afford the title compound (0.630 g, 95%) as a white gum. MS (ESI) m/z $[M+H]^+$ 346.3. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.78 (s, 1H), 6.10 (s, 1H), 4.09 - 3.94 (d, 2H), 3.74 (s, 3H), 2.90 - 2.68 (m, 3H), 2.26 (s, 3H), 1.92 - 1.83 (m, 2H), 1.54 - 1.43 (m, 2H), 1.39 (s, 9H).

Intermediate 311

1',3'-Dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

4 M HCl in 1,4-dioxane (883 μL, 3.53 mmol) was added to *tert*-butyl 4-(1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 310** (610 mg, 1.77 mmol). The reaction mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure to afford the HCl-salt of the title compound (0.400 g, 80%). MS (ESI) m/z $[M+H]^+$ 246.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.26 (s, 1H), 6.59 (s, 1H), 3.83 (s, 3H), 3.35 - 3.25

(m, 2H), 3.15 - 3.09 (m, 1H), 3.05 - 2.95 (m, 2H), 2.35 (s, 3H), 2.24 - 2.15 (m, 2H), 2.03 - 1.87 (m, 2H).

Intermediate 312

5 1-(5-Ethyl-1,3-dimethyl-1H-pyrazol-4-yl)ethan-1-one

Step a) 5-Ethyl-1,3-dimethyl-1H-pyrazole and 3-Ethyl-1,5-dimethyl-1H-pyrazole

Methylhydrazine sulfate (5.05 g, 35.04 mmol) were added to hexane-2,4-dione (2 g, 17.52 mmol) and DIPEA (6.79 g, 52.57 mmol) in EtOH (20 mL) at 20°C. The reaction mixture was stirred at 20 °C for 2 hours. The mixture was poured into brine (750 mL), extracted with
10 DCM (3×300 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford the title compounds as a regio-isomer mixture (2.0 g, 92%).

Step b) 1-(5-Ethyl-1,3-dimethyl-1H-pyrazol-4-yl)ethan-1-one

AlCl₃ (2.255 g, 16.91 mmol) was dissolved in DCM (15 mL) and cooled in an ice-bath. 5-Ethyl-1,3-dimethyl-1H-pyrazole (1.4 g, 5.64 mmol) was added, and the reaction mixture was
15 stirred at 0 °C for 30 min. AcCl (1.327 g, 16.91 mmol) was added dropwise over 5 min to the reaction mixture at 0 °C, and the reaction mixture was kept stirring at 0 °C for 3 h. The mixture was poured into brine and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (EtOAc/PE, 1:1) and the regio-isomers were separated by chiral preparative
20 SFC on a GreenSep Basic column (3 μM, 150×50 mm ID) using 8% of IPA:hexane, 1:1 (0.1% 2 M NH₃-MeOH) in CO₂ as mobile phase. The second eluted compound was collected to give the title compound (0.100 g, 11%) as colorless oil. ¹H NMR (300 MHz, Methanol-*d*₄) δ 1.11 - 1.24 (3 H, m), 2.44 (3 H, s), 2.51 (3 H, s), 2.82 (2 H, q), 3.75 (3 H, s).

25 Intermediate 313

tert-Butyl 4-(3-(5-ethyl-1,3-dimethyl-1H-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate

1 M KHMDS in THF (2.346 mL, 2.35 mmol) was added to 1-(5-ethyl-1,3-dimethyl-1H-pyrazol-4-yl)ethan-1-one **Intermediate 312** (0.13 g, 0.78 mmol) and 1-(*tert*-butyl) 4-methyl
30 piperidine-1,4-dicarboxylate (0.571 g, 2.35 mmol) in THF (2 mL) at rt under an atmosphere of N₂ (g). The reaction mixture was stirred at 70 °C for 3 h. The mixture was poured into brine, extracted with EtOAc, and the organic layer was dried over Na₂SO₄, filtered, and

concentrated to afford the title compound (0.1 g, 34%) as a brown oil. MS (ESI) m/z $[M+H]^+$ 378.2

Intermediate 314

5 *tert*-Butyl 4-(5'-ethyl-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate
Hydrazine hydrate (aq, 0.106 g, 2.65 mmol) was added to *tert*-butyl 4-(3-(5-ethyl-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-oxopropanoyl)piperidine-1-carboxylate **Intermediate 313** (0.1 g, 0.26 mmol) in EtOH (2 mL) at rt under an atmosphere of N₂ (g). The reaction mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure. The crude product was
10 purified by reversed phase flash chromatography on a C18 column (gradient of 0–100% MeCN in water), to give the title compound (0.040 g, 40%) as a white solid. MS (ESI) m/z $[M+H]^+$ 374.3. ¹H NMR δ (400 MHz, CDCl₃) 1.18 (3 H, t), 1.50 (9 H, s), 1.59 – 1.74 (3 H, m), 1.86 – 1.93 (1 H, m), 1.99 – 2.05 (2 H, m), 2.30 (3 H, s), 2.43 – 2.51 (1 H, m), 2.72 (2 H, q), 2.81 – 2.93 (2 H, m), 3.80 (3 H, s), 6.07 (1 H, s).

15

Intermediate 315

5'-Ethyl-1',3'-dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole
2 M HCl in 1,4-dioxane (1.339 mL, 2.68 mmol) was added to *tert*-butyl 4-(5'-ethyl-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 314** (0.1 g, 0.27 mmol) in MeOH (1 mL) at rt under an atmosphere of N₂ (g). The reaction mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure to afford the HCl-salt of the title compound (0.100 g) as a pale-yellow solid of the. MS (ESI) m/z $[M+H]^+$ 274.2.

20

Intermediate 316

25 1-(*tert*-Butyl) 4-ethyl 4-ethyl-3-oxopiperidine-1,4-dicarboxylate
Iodoethane (115.03 g, 58.99 mL 737.64 mmol) was added to a stirred suspension of 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (100.0 g, 368.82 mmol) and K₂CO₃ (152.59 g, 1.11 mol) in dry acetone (1 L) at 58°C under an atmosphere of Ar(g). The reaction mixture was stirred at 58°C for 48 h, and then cooled to rt and filtered. The filtrate was concentrated
30 under reduced pressure. The residue was diluted with EtOAc (150 mL), and the organic layer was washed with water (100 mL) and brine (50 mL), dried over dry Na₂SO₄, filtered and

concentrated under reduced pressure to give the title compound (108.0 g, 83%). MS (ESI) m/z $[M+H]^+$ 300.0.

Intermediate 317

5 *rac*-1-(*tert*-Butyl) 4-ethyl (3*R*,4*R*)-4-ethyl-3-hydroxypiperidine-1,4-dicarboxylate
NaBH₄ (13.73 g, 360.99 mmol) was added to a solution of 1-(*tert*-butyl) 4-ethyl 4-ethyl-3-oxopiperidine-1,4-dicarboxylate **Intermediate 316** (108.0 g, 360.99 mmol) in MeOH (1.05 L) at 0°C and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated under vacuum and the obtained residue was dissolved in mixture of DCM (100 mL) and sat
10 NH₄Cl (aq, 100 mL). The aqueous layer was extracted twice with DCM (50 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (70.0 g, 61%). MS (ESI) m/z $[M+H]^+$ 302.2.

Intermediate 318

15 *rac*-1-(*tert*-Butyl) 4-ethyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethylpiperidine-1,4-dicarboxylate
2,6-Dimethylpyridine (29.84 g, 278.72 mmol) was added to the solution of *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*R*)-4-ethyl-3-hydroxypiperidine-1,4-dicarboxylate **Intermediate 317** (70.0 g, 232.27 mmol) in DCE (700 mL). TBDMS triflate (73.59 g, 278.72 mmol, 63.94 mL) was
20 added in five portions and the reaction mixture was stirred at 80°C for 16 h. The mixture was cooled to rt and washed once with 1 M HCl (aq, 1 L), sat NaHCO₃ (aq, 1.5 L), and brine (1 L). The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by normal phase column chromatography on silica (hexane:MTBE, 75:25) to give the title compound (37.8 g, 35%). MS (ESI) m/z $[M+H]^+$
25 416.0.

Intermediate 319

rac-tert-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-(hydroxymethyl)piperidine-1-carboxylate
30 Neat DIBAL (25.85 g, 181.89 mL, 181.89 mmol) was cannulated to a solution of *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethylpiperidine-1,4-dicarboxylate **Intermediate 318** (37.8 g, 90.94 mmol) in DCM (250 mL) at -78°C, and the reaction mixture

was stirred at -78°C for 1 h. A solution of NH₄Cl (14.46 g, 272.83 mmol) in water (100 mL) was added, and the aqueous layer was extracted with DCM (3×100 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by normal phase flash chromatography on silica (MTBE:hexane, 50:50) to give the title compound (6.0 g, 18%). MS (ESI) *m/z* [M+H]⁺ 374.2.

Intermediate 320

rac-tert-Butyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-formylpiperidine-1-carboxylate

IBX (13.49 g, 48.18 mmol) was added to a solution of *rac-tert*-butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-(hydroxymethyl)piperidine-1-carboxylate **Intermediate 319** (6.0 g, 16.06 mmol) in MeCN (60 mL) and the reaction mixture was refluxed for 1.5 h. The mixture was cooled to 0°C and then filtered. The filtrate was concentrated under reduced pressure to give the title compound, which was used in the next step without additional purification (5.8 g, 88%). MS (ESI) *m/z* [M+H]⁺ 371.2.

Intermediate 321

rac-tert-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-ethynylpiperidine-1-carboxylate

K₂CO₃ (8.61 g, 62.44 mmol) was added to a solution of *rac-tert*-butyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-formylpiperidine-1-carboxylate **Intermediate 320** (5.8 g, 15.61 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (3.9 g, 20.29 mmol) in MeOH (100 mL) at 0°C and the reaction mixture was stirred at 0°C for 2 h and then at rt for 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by normal phase flash chromatography on silica (hexane: MTBE, 70:30) to give the title compound (3.65 g, 57%). MS (ESI) *m/z* [M+H]⁺ 368.0.

Intermediate 322

rac-tert-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Step a) *rac-tert-Butyl (3R,4S)-3-((tert-butyldimethylsilyl)oxy)-4-ethyl-4-(3-oxo-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate*

Pd(PPh₃)₂Cl₂ (695.23 mg, 993.15 μmol), CuI (188.53 mg, 993.15 μmol), TEA (6.03 g, 59.59 mmol, 8.3 mL) and then 1,3,5-trimethyl-1H-pyrazole-4-carbonyl chloride (2.05 g, 11.92 mmol) were added to a solution of *rac-tert-butyl (3R,4S)-3-((tert-butyldimethylsilyl)oxy)-4-ethyl-4-ethynylpiperidine-1-carboxylate* **Intermediate 321** (3.65 g, 9.93 mmol) in THF (73 mL). The reaction mixture was stirred under an atmosphere of Ar(g) at rt for 16 h. The mixture was diluted with sat NaHCO₃ (aq, 100 mL) and the aqueous layer was extracted with EtOAc (2×70 mL). The combined organic layer was washed with NaHCO₃ (aq, 100 mL), dried over Na₂SO₄, filtered and concentrated to give the crude title compound which was used immediately in the next step (5.6 g, 56%, 50.0% purity). MS (ESI) *m/z* [M+H]⁺ 504.2.

Step b) *rac-tert-Butyl (3R,4S)-3-((tert-butyldimethylsilyl)oxy)-4-ethyl-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate*

Hydrazine hydrate (1.11 g, 22.23 mmol, 1.11 mL) was added to *rac-tert-butyl (3R,4S)-3-((tert-butyldimethylsilyl)oxy)-4-ethyl-4-(3-oxo-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate* **Intermediate 322 Step a)** (5.6 g) in EtOH (60 mL) and the reaction mixture was heated at 80°C for 16 h. The mixture was concentrated under reduced pressure, and the residue was poured into water. The aqueous layer was extracted with EtOAc (3×30 mL), and the combined organic layer was washed with water (2×50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (4.3 g, 60%). MS (ESI) *m/z* [M+H]⁺ 518.2.

Intermediate 323

rac-5-((3R,4R)-4-Ethyl-3-methylpiperidin-4-yl)-1',3',5'-trimethyl-1'H,2H-3,4'-bipyrazole
HCl (4 M in dioxane, 22 mL) followed by water (1.5 mL) were added dropwise to a solution of *rac-tert-butyl (3R,4S)-3-((tert-butyldimethylsilyl)oxy)-4-ethyl-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate* **Intermediate 322** (4.3 g, 8.3 mmol) in DCM (22 mL) at 0°C and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated at reduced pressure. The residue was purified by trituration in EtOAc to give the hydrochloride of the title compound (2.0 g, 53%). MS (ESI) *m/z* [M+H]⁺ 304.2.

Intermediate 3241-(*tert*-Butyl) 4-ethyl 4-methyl-3-oxopiperidine-1,4-dicarboxylate

Iodomethane (104.69 g, 737.62 mmol, 45.92 mL) was added to a stirred suspension of 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (100.0 g, 368.81 mmol) and K₂CO₃ (152.59 g, 1.11 mol) in dry acetone (1 L) at 58°C under an atmosphere of Ar(g). The reaction mixture was stirred at 58°C for 16 h, and then cooled to rt and filtered. The filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (200 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (104.0 g, 94%). MS (ESI) *m/z* [M+H]⁺ 286.0.

Intermediate 325*rac*-1-(*tert*-Butyl) 4-ethyl (3*R*,4*R*)-3-hydroxy-4-methylpiperidine-1,4-dicarboxylate

NaBH₄ (13.87 g, 364.71 mmol) was added to a solution of 1-(*tert*-butyl) 4-ethyl 4-methyl-3-oxopiperidine-1,4-dicarboxylate **Intermediate 324** (104.0 g, 364.71 mmol) in MeOH (1.05 L) at 0°C and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated under vacuum and the obtained residue was dissolved in DCM (150 mL) and NH₄Cl (aq, 150 mL). The aqueous layer was extracted with DCM (2×70 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by normal phase flash chromatography on silica (hexane: MTBE, 50:50) to give the title compound (50.0 g, 48%). MS (ESI) *m/z* [M+H]⁺ 288.0.

Intermediate 326*rac*-1-(*tert*-Butyl) 4-ethyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methylpiperidine-1,4-dicarboxylate

2,6-Dimethylpyridine (21.39 g, 199.73 mmol) was added to a solution of *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*R*)-3-hydroxy-4-methylpiperidine-1,4-dicarboxylate **Intermediate 325** (47.83 g, 166.44 mmol) in DCE (100 mL). TBDMS triflate (52.74 g, 199.73 mmol, 45.82 mL) was added in portions and the reaction mixture was stirred at 80°C for 16 h. The reaction mixture was cooled to rt and washed once with 1 M HCl (aq, 100 mL), sat NaHCO₃ (aq, 200 mL), and brine (100 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by normal phase flash chromatography on

silica (hexane: MTBE, 60:40) to give the title compound (44.0 g, 66%). MS (ESI) m/z $[M+H]^+$ 403.0.

Intermediate 327

5 *rac-tert*-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate

Neat DIBAL (24.07 g, 169.32 mmol, 169.32 mL) was cannulated to a solution of *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methylpiperidine-1,4-dicarboxylate

Intermediate 326 (34.0 g, 84.66 mmol) in DCM (200 mL) at -78°C. The reaction mixture
10 was stirred at -78°C for 1 h. A solution of NH₄Cl (13.46 g, 253.97 mmol) in water (100 mL) was added. The aqueous layer was extracted with DCM (3×100), and the combined organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by normal phase flash chromatography on silica (hexane: MTBE: 50:50) to give the title compound (15.4 g, 46%). MS (ESI) m/z $[M+H]^+$
15 360.2.

Intermediate 328

rac-tert-Butyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-formyl-4-methylpiperidine-1-carboxylate

20 IBX (36.0 g, 128.6 mmol) was added to a solution of *rac-tert*-butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate **Intermediate 327** (15.4 g, 42.87 mmol) in MeCN (190 mL) and the reaction mixture was refluxed for 1.5 h. The mixture was cooled to 0°C and filtered. The filtrate was concentrated under reduced pressure to give the title compound (13.3 g, 78%), which was used in the next step without
25 additional purification. MS (ESI) m/z $[M+H]^+$ 358.2.

Intermediate 329

rac-tert-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-methylpiperidine-1-carboxylate

30 K₂CO₃ (24.99 g, 181.22 mmol) was added to a solution of *rac-tert*-butyl (3*R*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-formyl-4-methylpiperidine-1-carboxylate **Intermediate 328** (16.2 g, 45.31 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (11.31 g, 58.9 mmol) in

MeOH (160 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 h and then at rt for 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by normal phase flash chromatography on silica (hexane: MTBE, 60: 40) to give the title compound (11.5 g, 65%). MS (ESI) m/z $[M+H]^+$ 354.0.

5

Intermediate 330

rac-tert-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

Pd(PPh₃)₂Cl₂ (1.39 g, 1.98 mmol), CuI (375.81 mg, 1.98 mmol), TEA (12.01 g, 118.78 mmol, 10 16.54 mL) and then 1,3,5-trimethyl-1*H*-pyrazole-4-carbonyl chloride (4.09 g, 23.76 mmol) were added to a solution of *rac-tert*-butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-methylpiperidine-1-carboxylate **Intermediate 329** (7.0 g, 19.8 mmol) in THF (140 mL) and the reaction mixture was stirred at rt under an atmosphere of Ar(g) for 16 h. The mixture was diluted with sat NaHCO₃ (aq, 40 mL) and the aqueous layer was extracted with EtOAc (2×30 15 mL). The combined organic layer was washed with NaHCO₃ (aq, 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (11.8 g, 60.0% purity, 73%). MS (ESI) m/z $[M+H]^+$ 490.2.

Intermediate 331

20 *rac-tert*-Butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Hydrazine hydrate (2.41 g, 48.15 mmol, 2.41 mL) was added to a solution of *rac-tert*-butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-(3-oxo-3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)prop-1-yn-1-yl)piperidine-1-carboxylate **Intermediate 330** (11.79 g, 24.08 mmol) in EtOH 25 (120 mL) and the reaction mixture was heated at 80°C for 16 h. The mixture was concentrated under reduced pressure and the residue was diluted with water and then extracted with EtOAc (3×30 mL). The combined organic layer was washed with water (2×50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (8.1 g, 57%). MS (ESI) m/z $[M+H]^+$ 504.4.

30

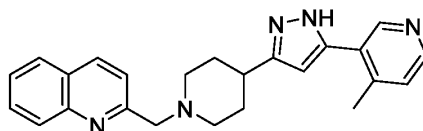
Intermediate 332

rac-(3*R*,4*S*)-4-Methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

HCl (4 M in dioxane, 40 mL), then water (3 mL) were added dropwise to a solution of *rac*-*tert*-butyl (3*R*,4*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 331** (8.1 g, 16.08 mmol) in DCM (40 mL) at 0°C and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated under reduced pressure. The residue was triturated in DCM to give the hydrochloride of the title compound (5.2 g, 71%). MS (ESI) *m/z* [M+H]⁺ 290.0.

Example 1

2-((4-(5-(4-Methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinoline



10

Hydrazine hydrate (aq, 0.031 mL, 0.65 mmol) was added to a stirred solution of 1-(4-methylpyridin-3-yl)-3-(1-(quinolin-2-ylmethyl)piperidin-4-yl)propane-1,3-dione

Intermediate 3 (5 mg, 0.01 mmol) in EtOH (1 mL) and heated at 60 °C for 1 h. The mixture was diluted with toluene and concentrated. The crude residue was purified by preparative

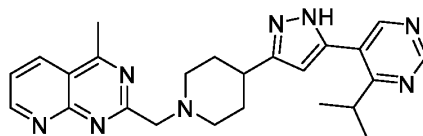
HPLC, PrepMethod D, (gradient: 10–65%), to grant the title compound (2 mg, 40%) as an off white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.83 – 2.09 (m, overlapping with solvent), 2.34 (t, 2H), 2.48 (s, 3H), 2.79 (m, 1H), 3.07 (d, 2H), 3.91 (s, 2H), 6.30 (s, 1H), 7.18 (d, 1H), 7.54 (t, 1H), 7.64 7.76 (m, 2H), 7.82 (d, 1H), 8.10 (d, 1H), 8.16 (d, 1H), 8.43 (d, 1H), 8.69 (s, 1H).

HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₆N₅: 384.2182, found: 384.2194.

20

Example 2

2-((4-(5-(4-Isopropylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine



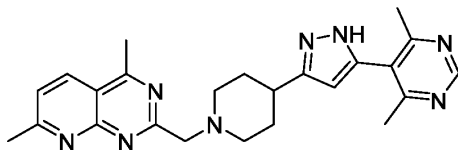
TFA (0.5 mL, 0.07 mmol) was added to a solution of *tert*-butyl 4-(5-(4-isopropylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 5** (27.5 mg, 74 μmol) in DCM (1 mL) and stirred at rt for 30 min and then concentrated. The residue was dissolved in DMSO

25

(1.0 mL) followed by addition of DIPEA (0.064 mL, 0.37 mmol) and (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (18.8 mg, 74 μ mol). The reaction mixture was stirred at rt for 24 h and the filtered using a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (16.8 mg, 53%) as a white solid. ¹H NMR (500 MHz, MeOH-*d*₄) δ 9.23 (m, 1H), 9.05 (s, 1H), 8.80 (m, 1H), 8.70 (s, 1H), 7.78 (m, 1H), 6.38 (s, 1H), 4.02 (s, 2H), 3.54 – 3.7 (m, 1H), 3.23 (d, 2H), 3.05 (s, 3H), 2.79 – 2.89 (m, 1H), 2.47 (m, 2H), 2.05 (m, 2H), 1.87 – 1.99 (m, 2H), 1.26 (d, 6H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₉N₈: 429.2510, found: 429.2516.

Example 3

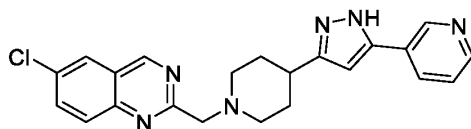
2-((4-(5-(4,6-Dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine



DIPEA (23.02 μ L, 0.13 mmol) was added to a solution of 4,6-dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrimidine **Intermediate 11** (11.4 mg, 0.04 mmol) and (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 15** (11.8 mg, 0.04 mmol) in DMSO (0.5 mL). The reaction mixture was stirred at 20 °C for 4 h and then filtered using a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 10–55%), to grant the title compound (14.6 mg, 77%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 8.34 (d, 1H), 7.47 (d, 1H), 6.07 (s, 1H), 4.10 (s, 2H), 3.28 (m, 2H), 2.97 (s, 3H), 2.78 – 2.9 (m, 4H), 2.47 – 2.59 (m, 2H), 2.35 (s, 6H), 2 – 2.13 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₉N₈: 429.2510, found: 429.2492.

Example 4

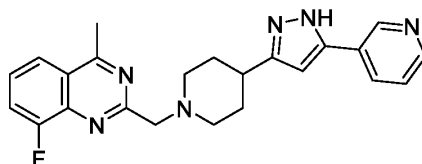
6-Chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



DMSO (2.079 mL) was added to a mixture of 3-(5-(piperidin-4-yl)-1*H*-pyrazol-3-yl)pyridine **Intermediate 18** (106 mg, 0.23 mmol), (6-chloroquinazolin-2-yl)methyl methanesulfonate **Intermediate 22** (56.7 mg, 0.21 mmol) and K₂CO₃ (101 mg, 0.73 mmol). The reaction mixture was stirred at rt over the weekend and then filtered through a syringe filter. The resulting solution was purified by preparative HPLC, PrepMethod PP, (gradient: 5–45%), to grant the title compound (49.4 mg, 59%). ¹H NMR (500 MHz, CDCl₃) δ 9.31 (s, 1H), 8.97 (s, 1H), 8.46 – 8.5 (m, 1H), 8.00 (d, 1H), 7.95 (d, 1H), 7.87 (s, 1H), 7.77 – 7.81 (m, 1H), 7.23 – 7.27 (m, 1H), 6.36 (s, 1H), 3.96 (s, 2H), 3.07 (m, 2H), 2.71 (m, 1H), 2.18 – 2.28 (m, 2H), 1.88 – 1.98 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₂ClN₆: 405.1588, found: 405.1582.

Example 5

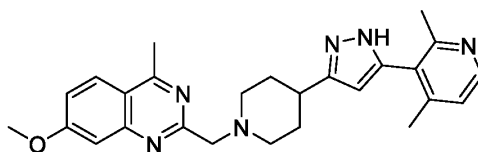
8-Fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



NCS (37 mg, 0.275 mmol) was added to an ice-cold stirring solution of (8-fluoro-4-methylquinazolin-2-yl)methanol **Intermediate 24** (48 mg, 0.25 mmol) and PPh₃ (72 mg, 0.275 mmol) in DCM (1 mL). After 1 h the solvent was removed under reduced pressure at rt. 3-(5-(Piperidin-4-yl)-1*H*-pyrazol-3-yl)pyridine **Intermediate 18** (91 mg, 0.2 mmol), K₂CO₃ (138 mg, 1 mmol) and DMSO (1.8 mL) were added, and the suspension was stirred for 1 d at rt. Precipitated materials were removed by filtration through CELITE, and the filtrate was purified by preparative HPLC, PrepMethod K, (gradient: 5–95%), to grant the title compound (23.4 mg, 26%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.47 (m, 1H), 8.17 (m, 2H), 8.08 – 8.12 (m, 2H), 7.8 – 7.85 (m, 1H), 7.68 – 7.72 (m, 1H), 7.39 – 7.43 (m, 1H), 6.62 (s, 1H), 3.95 (s, 2H), 3.09 – 3.13 (m, 2H), 2.95 (s, 3H), 2.70 (m, 1H), 2.39 – 2.45 (overlapping with solvent), 1.91 – 1.96 (m, 2H), 1.71 – 1.79 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₄FN₆: 403.2040, found: 403.2034.

Example 6

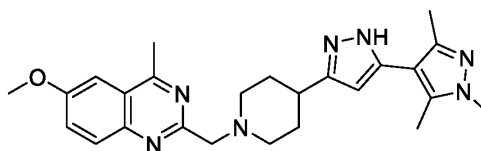
8-Fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



4,6-Dimethyl-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyrimidine **Intermediate 11** (45.6 mg, 0.18 mmol), 2-(chloromethyl)-6-methoxy-4-methylquinazoline **Intermediate 25** (33 mg, 0.15 mmol) and DIPEA (207 μ L, 1.19 mmol) were mixed in DMSO (1 mL). The reaction mixture was stirred at rt over the weekend. The reaction mixture was diluted with DMSO (1 mL) and filtered. The filtrate was purified by preparative SFC, PrepMethod L, (gradient: 15–20%) to grant the title compound. (31.1 mg, 47%). ^1H NMR (600 MHz, DMSO- d_6) 1.69 (2H, m), 1.89 (2H, m), 2.08 (3H, s), 2.21 – 2.29 (5H, m), 2.62 (m, overlapping with solvent), 2.88 (3H, s), 2.95 – 3.03 (2H, m), 3.76 (2H, s), 3.95 (3H, s), 6.06 (1H, m), 7.10 (1H, m), 7.47 (1H, m), 7.59 (1H, m), 7.88 (1H, d), 8.25 (1H, m). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{31}\text{N}_6\text{O}$: 443.2554, found: 443.2554.

Example 7

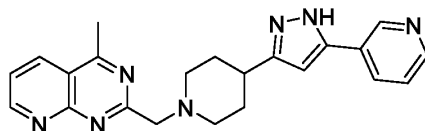
6-Methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole, HCl **Intermediate 28** (30.7 mg, 0.12 mmol), 2-(chloromethyl)-6-methoxy-4-methylquinazoline **Intermediate 25** (22 mg, 0.10 mmol) and DIPEA (138 μ L, 0.79 mmol) were mixed in DMSO (0.5 mL). The reaction mixture was stirred at rt overnight and then at 50 $^{\circ}\text{C}$ for 1 h. The reaction mixture was diluted with DMSO, filtered, and the filtrate was purified by preparative SFC, PrepMethod C, (gradient: 25–30%) to grant the title compound (20 mg, 45%). ^1H NMR (600 MHz, DMSO- d_6) 1.63 – 1.72 (2H, m), 1.83 – 1.9 (2H, m), 2.18 (3H, s), 2.24 (overlapping with solvent, m), 2.30 (3H, s), 2.89 (3H, s), 2.96 – 3.03 (2H, m), 3.66 (3H, s), 3.76 (2H, s), 3.96 (3H, s), 6.04 (1H, s), 7.48 (1H, m), 7.60 (1H, m), 7.89 (1H, d). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{32}\text{N}_7\text{O}$: 446.2662, found: 446.2660.

Example 8

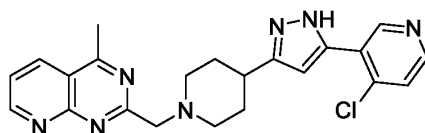
4-Methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine



- 5 DMSO (2.0 mL) was added to a mixture of 3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine **Intermediate 18** (94 mg, 0.21 mmol), (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (40.0 mg, 0.16 mmol) and K₂CO₃ (87 mg, 0.63 mmol). The reaction mixture was stirred at rt for 1 h and then filtered through a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title
- 10 compound (44.8 mg, 74%) as a white solid. ¹H NMR (500 MHz, MeOH-*d*₄) δ 9.23 (m, 1H), 8.96 (s, 1H), 8.81 (m, 1H), 8.48 (m, 1H), 8.20 (m, 1H), 7.78 (m, 1H), 7.49 (m, 1H), 6.62 (s, 1H), 4.02 (s, 2H), 3.23 (m, 2H), 3.06 (s, 3H), 2.82 (m, 1H), 2.47 (m, 2H), 2.04 (m, 2H), 1.87 – 1.97 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₄N₇: 386.2088, found: 386.2098.

Example 9

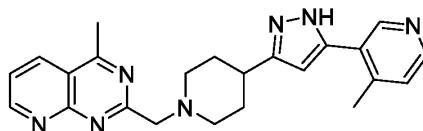
2-((4-(5-(4-Chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine



- (4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (18.99 mg, 0.07 mmol) was added to a solution of 4-chloro-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine **Intermediate 31** (19.7 mg, 0.07 mmol) and DIPEA (26.1 μL, 0.15 mmol) in DMSO (0.5 mL). The reaction mixture was stirred at rt overnight and then filtered using a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (14.2 mg, 45%) as a white solid. ¹H NMR (500 MHz,
- 25 CDCl₃) δ 9.25 (m, 1H), 8.96 (s, 1H), 8.48 (m, 1H), 8.41 (m, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 6.58 (s, 1H), 4.05 (s, 2H), 3.21 (d, 2H), 3.01 (s, 3H), 2.83 (m, 1H), 2.39 (m, 2H), 1.95 – 2.06 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₃ClN₇: 420.1698, found: 420.1686.

Example 10

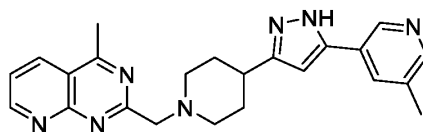
4-Methyl-2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine



DIPEA (3.729 mL, 21.35 mmol) was added to a solution of (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (284 mg, 1.12 mmol) and 4-methyl-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine **Intermediate 34** (500 mg, 1.07 mmol) in DCM (6 mL) and MeCN (1.5 mL). The reaction mixture was stirred at rt for 16 h. It was taken up in DCM and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by straight phase flash chromatography on silica, (isocratic: 10% MeOH in DCM), to elute the product. The product was further purified by resolidified in MeOH, the precipitate was filtered off and washed with MTBE to afford the title compound (253.3 mg, 59%) as a pale-yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.82 (s, 1H), 9.22 (m, 1H), 8.75 (m, 1H), 8.68 (s, 1H), 8.32 (m, 1H), 7.73 (m, 1H), 7.25 (m, 1H), 6.43 (s, 1H), 3.87 (s, 2H), 3.03 – 3.09 (m, 2H), 2.95 (s, 3H), 2.65 – 2.74 (m, 1H), 2.47 (s, 3H), 2.27 – 2.35 (m, 2H), 1.88 – 1.94 (m, 2H), 1.67 – 1.77 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₆N₇: 400.2244, found: 400.2236.

Example 11

4-Methyl-2-((4-(5-(5-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine

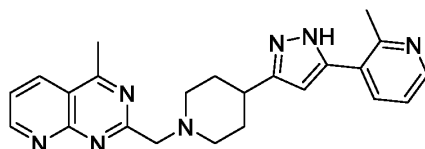


A vial was charged with a 2-((4-(5-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine **Intermediate 38** (37.4 mg, 0.09 mmol), S-Phos (12.4 mg, 0.03 mmol) and Pd(OAc)₂ (4.9 mg, 0.02 mmol) and transferred into a glove box. Cs₂CO₃ (87 mg, 0.27 mmol) was added followed by 1,4-dioxane (0.471 mL) and trimethylboroxine (12.45 μL, 0.09 mmol). The vial was removed from the glove box. Degassed water (0.120 mL) was added, and the reaction mixture was stirred and heated to 100

°C for 18 h. The reaction mixture was cooled to rt, diluted with DCM, passed through a phase separator and concentrated. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 15-55%), to grant the title compound (14.5 mg, 41%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 9.25 (m, 1H), 8.81 (m, 1H), 8.48 (m, 1H), 8.36 (m, 1H), 7.89 (s, 1H), 7.59 (m, 1H), 6.40 (s, 1H), 4.05 (s, 2H), 3.21 (m, 2H), 3.00 (s, 3H), 2.81 (m, 1H), 2.34 – 2.41 (m, 5H), 1.91 – 2.03 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₆N₇: 400.2244, found: 400.2254.

Example 12

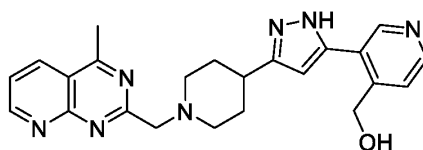
4-Methyl-2-((4-(5-(2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine



(4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (38.2 mg, 0.15 mmol) and DIPEA (131 μL, 0.75 mmol) were added to a solution of 2-methyl-3-(piperidin-4-yl)-1H-pyrazol-5-ylpyridine **Intermediate 41** (71.0 mg, 0.15 mmol) in DMSO (1 mL). The reaction mixture was stirred at rt for 2 h and then filtered using a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the product (45.7 mg, 76%) as a white solid. The product (40.1 mg, 0.10 mmol) was dissolved in MeOH (10 mL) and 4 M HCl in dioxane (25 μL, 0.10 mmol) was added. The reaction mixture was stirred for 1 min and then concentrated to dryness to afford the HCl salt of the title compound (43.1 mg, 98%) as a white solid. ¹H NMR (500 MHz, MeOH-*d*₄) δ 2.12–2.3 (2H, m), 2.3–2.42 (2H, m), 2.55–2.69 (3H, m), 3.07 (3H, s), 3.12–3.22 (1H, m), 3.66–4.05 (2H, m), 4.64–4.81 (1H, m), 6.48 (1H, m), 7.28–7.41 (1H, m), 7.8–7.97 (2H, m), 8.39–8.5 (1H, m), 8.88 (1H, m), 9.29 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₆N₇: 400.2244, found: 400.2260.

Example 13

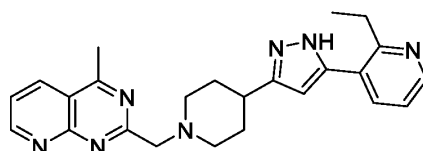
3-(3-(1-((4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-4-yl)methanol



TFA (200 μ L, 2.60 mmol) was added to a solution of *tert*-butyl 4-(5-(4-(hydroxymethyl)pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 43** (20.0 mg, 0.06 mmol) in DCM (500 μ L). The reaction mixture was stirred for 30 min, concentrated and redissolved in DMSO (0.5 mL). (4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (14.1 mg, 0.06 mmol) and DIPEA (48.6 μ L, 0.28 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod I, (gradient: 5–95%), to grant the title compound (4.9 mg, 21%). ^1H NMR (600 MHz, DMSO-*d*₆) δ 12.89 (br s, 1H), 9.23 (m, 1H), 8.71 – 8.79 (m, 2H), 8.48 (m, 1H), 7.74 (m, 1H), 7.59 (m, 1H), 6.51 (s, 1H), 5.48 (m, 1H), 4.73 (s, 2H), 3.90 (s, 2H), 3.09 (m, 2H), 2.96 (s, 3H), 2.31 – 2.38 (m, 2H), 1.93 (m, 2H), 1.71 – 1.76 (m, 2H). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₃H₂₆N₇O: 416.2194, found: 416.2192.

Example 14

2-((4-(5-(2-Ethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine

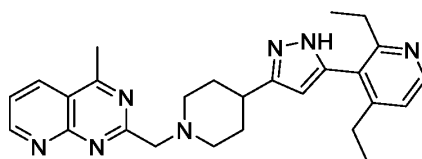


TFA (200 μ L, 2.60 mmol) was added to a solution of *tert*-butyl 4-(5-(2-ethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 44** (14.0 mg, 0.04 mmol) in DCM (500 μ L). The mixture was stirred for 2 h, concentrated and redissolved in DMSO (0.2 mL). (4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (10.0 mg, 0.04 mmol) and DIPEA (34.2 μ L, 0.20 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (7.6 mg, 47%) as a white solid. ^1H NMR (500 MHz, CDCl₃) δ 9.26 (s, 1H), 8.53 (m, 1H), 8.50 (m, 1H), 7.76 (m, 1H), 7.61 (m, 1H), 7.16 (m, 1H), 6.25 (s, 1H), 4.11 (s, 2H), 3.28 (d, 2H), 3.02

(s, 3H), 2.99 (q, 2H), 2.82 (m, 1H), 2.48 (s, 2H), 1.98 – 2.07 (m, 4H), 1.28 (t, 3H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{28}N_7$: 414.2400, found: 414.2412.

Example 15

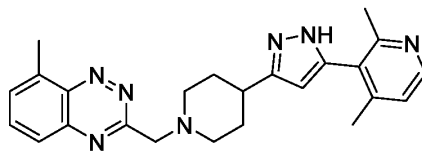
5 2-((4-(5-(2,4-Diethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine



TFA (200 μ L, 2.60 mmol) was added to a solution of *tert*-butyl 4-(5-(2,4-diethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 45** (1.7 mg, 4.42 μ mol) in DCM (500 μ L). The reaction mixture was stirred for 2 h, concentrated and redissolved in DMSO (0.2 mL). (4-Methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (1.1 mg, 4.34 μ mol) and DIPEA (3.85 μ L, 0.02 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (1.1 mg, 56%). 1H NMR (500 MHz, $CDCl_3$) δ 9.27 (m, 1H), 8.48 – 8.54 (m, 2H), 7.63 (m, 1H), 7.08 (d, 1H), 6.10 (s, 1H), 4.07 – 4.34 (m, 2H), 3.3 – 3.47 (m, 2H), 3.04 (s, 3H), 2.81 – 2.96 (m, 1H), 2.61 (q, 2H), 2.43 (q, 2H), 2.08 – 2.19 (m, 4H), 1.17 (t, 3H), 1.10 (t, 3H). MS (ESI) m/z $[M+H]^+$ 442.4.

Example 16

20 3-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-8-methylbenzo[e][1,2,4]triazine

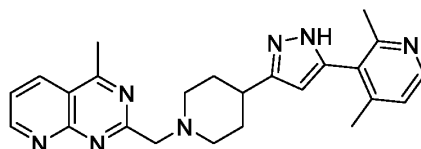


TFA (13.1 μ L, 4.42 μ mol) was added to a solution of *tert*-butyl 4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 47** (62.0 mg, 0.17 mmol) in DCM (0.7 mL). The reaction mixture was stirred for 2 h at rt, concentrated and redissolved in DMSO (0.8 mL). (8-Methylbenzo[e][1,2,4]triazin-3-yl)methyl methanesulfonate

Intermediate 51 (44.1 mg, 0.17 mmol) and DIPEA (242 μ L, 1.39 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod C, (gradient: 22–27%), to grant the title compound (25.3 mg, 35%). ^1H NMR (600 MHz, DMSO- d_6) δ 8.28 (m, 1H), 8.06 (m, 1H), 7.97 (d, 1H), 7.85 (d, 1H), 7.13 (d, 1H), 6.10 (s, 1H), 4.36 (s, 2H), 3.12 – 3.19 (m, 5 overlapping with solvent), 2.97 (s, 3H), 2.75 (m, 1H), 2.26 (s, 3H), 2.09 (s, 3H), 1.99 (m, 2H), 1.78 (m, 2H). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{N}_7$: 414.2400, found: 414.2412.

Example 17

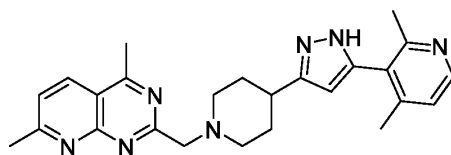
2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine



K_2CO_3 (323 mg, 2.34 mmol) was added to 2,4-dimethyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine TFA **Intermediate 52** (200 mg, 0.78 mmol) and (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (198 mg, 0.78 mmol) in MeOH (1 mL) at 20 °C under an atmosphere of N_2 (g). The reaction mixture was stirred at 60 °C for 1 h. The mixture was filtered through a CELITE pad, and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod N, (gradient: 15–35%), to grant the title compound (30 mg, 9%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.69 (s, 1H), 9.23 (m, 1H), 8.75 (m, 1H), 8.27 (s, 1H), 7.74 (m, 1H), 7.12 (s, 1H), 6.09 (s, 1H), 3.86 (s, 2H), 3.04 (m, 2H), 2.95 (s, 3H), 2.32 (m, 2H), 2.26 (s, 3H), 2.09 (s, 3H), 1.96 – 1.88 (m, 2H), 1.71 (m, 2H). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{N}_7$: 414.2400, found: 414.2410.

Example 18

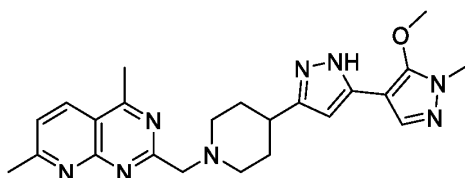
2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine



DIPEA (26.7 μ L, 0.15 mmol) was added to a solution of 2,4-dimethyl-3-((4-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine 2 TFA **Intermediate 52** (29.7 mg, 0.06 mmol) and (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 15** (8.2 mg, 0.03 mmol) in DMSO (0.3 mL) and the reaction mixture was stirred at rt overnight. The resulting solution was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (5.8 mg, 44%) as a white solid. ^1H NMR (500 MHz, MeOH-*d*₄) δ 8.66 (d, 1H), 8.28 (d, 1H), 7.67 (d, 1H), 7.21 (d, 1H), 6.18 (s, 1H), 4.07 (s, 2H), 3.28 (d, 2H), 3.01 (s, 3H), 2.84 – 2.91 (m, 1H), 2.82 (s, 3H), 2.56 (m, 2H), 2.33 (s, 3H), 2.18 (s, 3H), 2.09 (d, 2H), 1.95 (m, overlapping with solvent). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₅H₃₀N₇: 428.2558, found: 428.2568.

Example 19

2-(((4-(5'-Methoxy-1'-methyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine

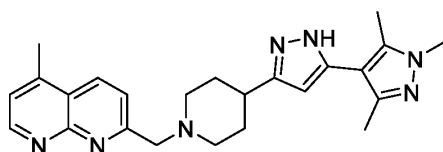


5'-Methoxy-1'-methyl-5-(piperidin-4-yl)-1*H*,2*H*-3,4'-bipyrazole, TFA **Intermediate 56** (400 mg, 1.11 mmol) was added to (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 15** (357 mg, 1.34 mmol) and K₂CO₃ (1.54 g, 11.14 mmol) in MeCN (8 mL) at 10 °C. The resulting solution was stirred at 60 °C for 16 h. The reaction mixture was poured into water and extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by preparative HPLC, PrepMethod P, (gradient: 10–38%), to grant the title compound (400 mg, 83%) as a yellow solid. ^1H NMR (300 MHz, DMSO-*d*₆) δ 12.41 (s, 1H), 8.59 (d, 1H), 7.59 (d, 1H), 7.52 (s, 1H), 6.12 (s, 1H), 3.88 (s, 3H), 3.80 (s, 2H), 3.62 (s, 3H), 3.02 (m, 2H), 2.88 (s, 3H), 2.71

(s, 3H), 2.59 (s, 1H), 2.26 (t, 2H), 1.85 (m, 2H), 1.65 (q, 2H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{29}N_8O$: 433.2458, found: 433.2480.

Example 20

5 5-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1,8-naphthyridine



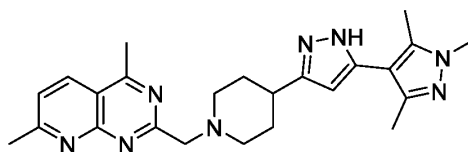
Vial 1): TFA (0.25 mL) was added to a solution of *tert*-butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 27** (57 mg, 0.16 mmol) in DCM
10 (0.5 mL) and stirred for 90 min at rt. The solvent was removed under reduced pressure to grant the HCl salt of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole. The crude residue was dissolved in DMSO (2 mL) and K_2CO_3 (138 mg, 1.00 mmol) was added.

Vial 2): NCS (30 mg, 0.22 mmol) was added to an ice-cold solution of (5-methyl-1,8-naphthyridin-2-yl)methanol **Intermediate 59** (35 mg, 0.20 mmol) and PPh_3 (58 mg, 0.22
15 mmol) in DCM (1 mL). The mixture was stirred for 90 min at 0 °C.

The contents of vial 2 were added to vial 1 and the DCM was removed under reduced pressure. The reaction mixture was stirred at rt for 1 d. The mixture was filtered through CELITE and purified by preparative SFC, PrepMethod O, (gradient:20–25%), to grant the title compound (18.1 mg, 28%). 1H NMR (600 MHz, $DMSO-d_6$) 1.68 – 1.76 (2H, m), 1.9 –
20 1.94 (2H, m), 2.18 – 2.24 (m, overlapping with byproduct peak), 2.31 (s, overlapping with byproduct peak), 2.71 (3H, s), 2.91 – 2.94 (2H, m), 3.67 (s, overlapping with byproduct peak), 3.83 (2H, s), 6.07 (1H, s), 7.44 (1H, m), 7.77 (1H, d), 8.56 (1H, d), 8.90 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{30}N_7$: 416.2558, found: 416.2566.

25 Example 21

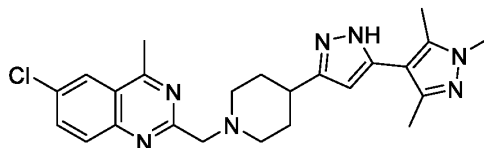
4,7-Dimethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine



MsCl (72.6 mg, 0.63 mmol) was added slowly to a mixture of (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methanol **Intermediate 14** (100 mg, 0.53 mmol) and TEA (107 mg, 1.06 mmol) in DCM (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The solvent
 5 was removed under reduced pressure. The residue was dissolved in MeCN (3 mL) and 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (137 mg, 0.53 mmol) and K₂CO₃ (146 mg, 1.06 mmol) were added at 10 °C. The resulting solution was stirred at 60 °C for 3 d. The reaction mixture was poured into water and extracted with DCM. The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude
 10 product was purified by preparative HPLC, PrepMethod N, (gradient: 34–59%), to grant the title compound (30 mg, 13%) as a red solid. ¹H NMR (300 MHz, DMSO-*d*₆) 1.70 (2H, m), 1.88 (2H, m), 2.19 (3H, m), 2.29 (5H, m), 2.73 (4H, m), 2.91 (3H, s), 3.05 (2H, d), 3.66 (3H, s), 3.83 (2H, s), 6.05 (1H, s), 7.62 (1H, d), 8.61 (1H, d), 12.31 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₁N₈: 431.2666, found: 431.2674.

Example 22

6-Chloro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline

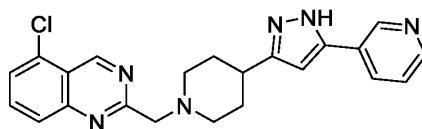


A mixture of 6-chloro-2-(chloromethyl)-4-methylquinazoline **Intermediate 62** (44 mg, 0.19 mmol), 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (52 mg, 0.20 mmol) and K₂CO₃ in MeCN (3.5 mL) were stirred at 42 °C overnight. The reaction mixture was cooled to rt and precipitated solids were filtered off and washed with MeCN. The filtrate was diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic
 25 layer was filtered through a phase separator and concentrated. The crude residue was purified by preparative SFC, PrepMethod Z, (gradient 22–27%), to grant the title compound (60 mg, 67%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.61–1.73 (2H, m), 1.82–1.9 (2H, m), 2.17 (3H, s),

2.21–2.35 (5H, m), 2.55–2.66 (1H, m), 2.91 (3H, s), 2.97–3.04 (2H, m), 3.65 (3H, s), 3.79 (2H, s), 6.04 (1H, s), 7.95–8.02 (2H, m), 8.35 (1H, m), 12.40 (1H, s). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}ClN_7$: 450.2168, found: 450.2154.

5 Example 23

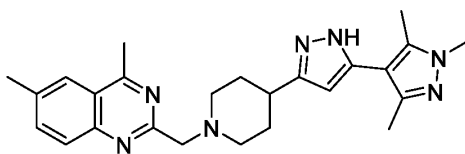
5-Chloro-2-((4-(5-(pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



DIPEA (3.20 mL, 18.33 mmol) was added to a solution of (5-chloroquinazolin-2-yl)methyl methanesulfonate **Intermediate 66** (0.25 g, 0.92 mmol), (3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 18** (469 mg, 1.03 mmol) in DCM (8 mL) and MeCN (2 mL) and the reaction mixture was stirred at rt overnight. The mixture was concentrated and DCM was added to the residue. The organic phase was washed with water, passed through a phase separator and concentrated to give the title compound (0.350 g, 94%) as an orange solid. 1H NMR (400 MHz, DMSO- d_6) δ 1.6 – 1.79 (m, 2H), 1.90 (m, 2H), 2.30 (t, 2H), 2.67 (s, 1H), 3.02 (d, 2H), 3.93 (s, 2H), 6.60 (s, 1H), 7.40 (m, 1H), 7.88 (m, 1H), 7.99 – 8.03 (m, 2H), 8.10 (m, 1H), 8.46 (s, 1H), 8.96 (s, 1H), 9.76 (s, 1H), 12.79 (s, 1H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{22}ClN_6$: 405.1588, found: 405.1560.

Example 24

4,6-Dimethyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline

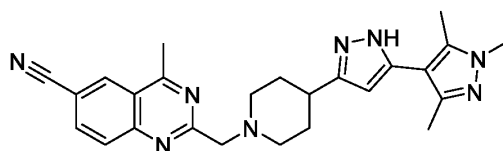


A vial was charged with 6-bromo-4-methyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinoline **Intermediate 70** (40 mg, 0.08 mmol), Pd(dtbpf)Cl₂ (5.74 mg, 8.8 μ mol), K₂CO₃ (45 mg, 0.33 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.162 mL, 0.57 mmol). 1,4-dioxane (0.7 mL) and water (0.15 mL) were added and the vial was purged with N₂ (g) and evacuated three times. The reaction mixture

was heated in a microwave reactor at 120 °C for 1 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layer was filtered through a phase separator and concentrated. The crude residue was purified by preparative HPLC, PrepMethod EE, (gradient: 5–95%), to grant the title compound (12.8 mg, 37%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.98–2.06 (4H, m), 2.16–2.24 (5H, m), 2.29 (3H, s), 2.58 (m, overlapping with solvent), 2.96 (3H, s), 3.27–3.35 (2H, m), 4.71 (2H, s), 6.11 (1H, s), 7.89–7.97 (2H, m), 8.14 (1H, s), 10.13 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇: 430.2714, found: 430.2712

Example 25

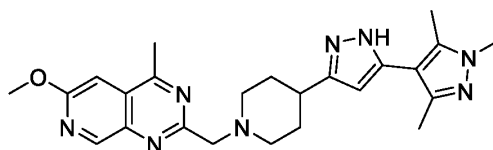
4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline-6-carbonitrile



6-Bromo-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinoline **Intermediate 70** (0.072 g, 0.146 mmol), Zn(CN)₂ (10.5 mg, 0.09 mmol), Xantphos (4.35 mg, 7.30 μmol) and Pd₂(dba)₃ (3.34 mg, 3.65 μmol) were added to a microwave vial. The vial was sealed, evacuated and backfilled with N(g) three times. DMF (0.8 mL) was added, and the reaction was heated at 110°C for 2 h. The reaction mixture was diluted with EtOAc, filtered through CELITE and washed with sat NaHCO₃ (aq). The organic phase was filtered through a phase separator and concentrated. The crude residue was purified by preparative SFC, PrepMethod O, (gradient: 22–27%), to grant the title compound (19.2 mg, 30%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.68 (2H, m), 1.83–1.89 (2H, m), 2.06 (1H, m), 2.16 (3H, s), 2.23–2.32 (5H, m), 2.95 (3H, s), 3.01 (2H, m), 3.64 (3H, s), 3.84 (2H, s), 6.03 (1H, s), 8.08 (1H, m), 8.23 (1H, m), 8.91 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₂₉N₈: 441.2510, found: 441.2516.

Example 26

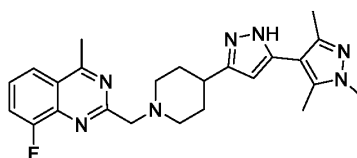
6-Methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,4-*d*]pyrimidine



NCS (30 mg, 0.22 mmol) was added at 0 °C to a solution of (6-methoxy-4-methylpyrido[3,4-*d*]pyrimidin-2-yl)methanol **Intermediate 74** (41.0 mg, 0.20 mmol) and PPh₃ (58 mg, 0.22 mmol) in DCM (1 mL). The mixture was stirred in an ice bath for 1.25 h. 1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (53.2 mg, 0.16 mmol), DMSO (2 mL) and K₂CO₃ (118 mg, 0.86 mmol) were added, and the DCM was removed under reduced pressure. The remaining suspension was stirred at rt for 2 h. The insolubles were removed by filtration and the filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (23 mg, 32%) as an orange solid. ¹H NMR (500 MHz, D₂O containing 1 μL of conc. HCl) δ 2.01 - 2.13 (m, 2), 2.16 (s, 3H), 2.22 (s, 3H), 2.25 - 2.32 (m, 2H), 2.88 (s, 3H), 3.07 - 3.18 (m, 1H), 3.29 - 3.45 (m, 2H), 3.69 (s, 3H), 3.83 (m, 2H), 3.99 (s, 3H), 4.65 (s, overlapping with solvent), 6.29 (s, 1H), 7.34 (s, 1H), 9.04 (s, 1H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₁N₈O: 447.2616, found: 447.2624.

Example 27

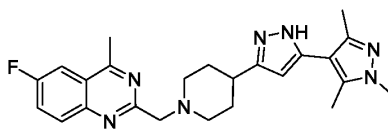
8-Fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (112 mg, 0.43 mmol) and 2-(chloromethyl)-8-fluoro-4-methylquinazoline **Intermediate 75** (91 mg, 0.43 mmol) were mixed in DMSO (2.5 mL) and DIPEA (150 μL, 0.87 mmol) was added. The reaction mixture was stirred at rt overnight, filtered using a syringe filter and purified by preparative HPLC, PrepMethod F, (gradient: 15%–55%), to give the title compound (0.180 g, 96%) as white solid after lyophilization. ¹H NMR (500 MHz, CDCl₃) 1.89 – 1.97 (4H, m), 2.23 – 2.33 (8H, m), 2.65 – 2.75 (1H, m), 2.95 (3H, s), 3.12 – 3.18 (2H, m), 3.70 (3H, s), 3.98 (2H, s), 6.03 (1H, s), 7.48 – 7.55 (2H, m), 7.82 – 7.87 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₉FN₇: 434.2462, found: 434.2482.

Example 28

6-Fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



5

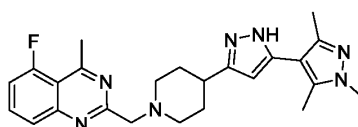
1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole, HCl **Intermediate 28** (0.105 g, 0.405 mmol), 2-(chloromethyl)-6-fluoro-4-methylquinazoline **Intermediate 78** (0.082 g, 0.39 mmol) and K₂CO₃ (0.448 g, 3.24 mmol) were mixed in MeCN (4 mL) and stirred at 42 °C overnight. After cooling to rt, the solids were filtered off and washed with MeCN (×3). The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod O, (gradient: 12–17%), to give the title compound (0.078 g, 44%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.67 (2H, qd), 1.82–1.89 (2H, m), 2.17 (3H, s), 2.23 (2H, td), 2.29 (3H, s), 2.56–2.64 (1H, m), 2.86 (3H, s), 2.95–3.03 (2H, m), 3.65 (3H, s), 3.78 (2H, s), 6.02 (1H, s), 7.81–7.87 (1zH, m), 7.96–8.05 (2H, m), 12.38 (1H, s).

HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₉FN₇: 434.2462, found: 434.2464.

15

Example 29

5-Fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



20

1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole, HCl **Intermediate 28** (0.105 g, 0.405 mmol), 2-(chloromethyl)-5-fluoro-4-methylquinazoline **Intermediate 81** (0.082 g, 0.39 mmol) and K₂CO₃ (0.448 g, 3.24 mmol) were mixed in MeCN (4 mL) and stirred at 42 °C overnight. After cooling to rt, the solids were filtered off, and washed with MeCN (×3). The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative HPLC PrepMethod GG, (gradient 15–30%), to give the title compound (0.046 g, 21%) as TFA-salt. ¹H NMR (600 MHz, DMSO-*d*₆) δ 2.01–2.12 (2H, m), 2.19 (3H, s), 2.20–2.26 (2H, m), 2.29 (3H, s), 2.94–3.38 (6H, m), 3.68 (3H, s), 3.71–3.81 (2H,

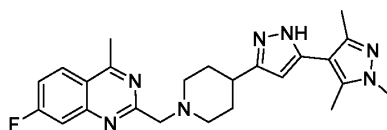
25

m), 4.76 (2H, s), 6.14 (1H, s), 7.60 (1H, dd), 7.90 (1H, d), 7.00 – 8.09 (1H, m), 10.34 (1H, s).

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}FN_7$: 434.2462, found: 434.2460

Example 30

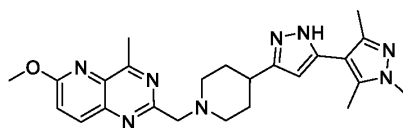
5 7-Fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2'*H*-3,4'-bipyrazole, HCl **Intermediate 28** (0.052 g, 0.20 mmol), 2-(chloromethyl)-7-fluoro-4-methylquinazoline **Intermediate 84** (0.040 g, 0.19 mmol) and K_2CO_3 (0.221 g, 1.60 mmol) were mixed in MeCN (2.8 mL) and stirred at 42 °C overnight. After cooling to rt, the solids were filtered off, washed with MeCN ($\times 3$). The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod C, (gradient 25–30%), to give the title compound (0.054 g, 62%). 1H NMR (600 MHz, DMSO- d_6) δ 1.68 (2H, qd), 1.83–1.89 (2H, m), 2.25 (2H, td), 2.57–2.63 (1H, m), 2.89 (3H, s), 2.96–3.04 (2H, m), 3.17–3.18 (6H, m), 3.65 (3H, s), 3.78 (2H, s), 6.03 (1H, s), 7.58 (1H, td), 7.69 (1H, dd), 8.34 (1H, dd), 12.41 (1H, s). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}FN_7$: 434.2462, found: 434.2458.

Example 31

20 6-Methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidine

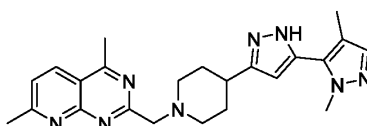


A mixture of 4-chloro-6-methoxy-2-((4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidine **Intermediate 87** (0.095 g, 0.20 mmol) and $Pd(PPh_3)_4$ (0.024 g, 0.02 mmol) in THF (3.5 mL) was degassed with N_2 (g) for 5 min at rt. 2 M $AlMe_3$ in toluene (0.389 mL, 0.78 mmol) was added dropwise. The reaction mixture was heated at 50 °C overnight. The mixture was cooled to rt and the reaction was quenched with sat $NaHCO_3$ (aq). The mixture was diluted with EtOAc and DCM, filtered through a phase

separator and concentrated under reduced pressure. The residue was redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod Y, (gradient 27–32%), to give the title compound (6 mg, 6%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.67 (2H, qd), 1.83–1.89 (2H, m), 2.17 (3H, s), 2.2–2.34 (5H, m), 2.87 (3H, s), 2.95–3.04 (2H, m), 3.65 (3H, s), 3.79 (2H, s),
 5 4.04 (3H, s), 4.13 (1H, q), 6.04 (1H, s), 7.45 (1H, d), 8.23 (1H, d), 12.39 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₁N₈O: 447.2616, found: 447.2620

Example 32

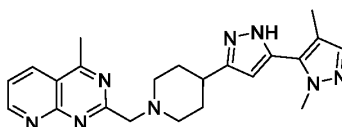
2-((4-(2',4'-Dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-
 10 dimethylpyrido[2,3-*d*]pyrimidine



2,4-Dimethyl-5'-(piperidin-4-yl)-2*H*,2'*H*-3,3'-bipyrazole, TFA **Intermediate 90** (0.020 g, 0.055 mmol) and (4,7-dimethylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 15** (0.016 g, 0.06 mmol) were mixed in DMSO (0.5 mL). DIPEA (50 μL, 0.29
 15 mmol) was added and the reaction mixture was stirred at rt for 5 h. The mixture was filtered using a syringe filter and purified by preparative HPLC, PrepMethod D, (gradient 15–55%), to yield the title product (15 mg). The product was dissolved in MeOH (1 mL) and 1 M HCl (36 μL) was added. The solution was stirred for 1 min and then concentrated under reduced pressure to afford the HCl-salt of the title compound (16 mg, 64%) as white solid. ¹H NMR
 20 (500 MHz, CDCl₃) δ 8.31 (d, 1H), 7.43 (d, 1H), 7.29 (s, 1H), 6.18 (s, 1H), 4.02 (s, 2H), 3.92 (s, 3H), 3.13–3.24 (m, 2H), 2.94 (s, 3H), 2.72–2.85 (s, 4H), 2.33–2.46 (m, 2H), 2.08 (s, 3H), 1.90–2.01 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₉N₈: 417.2510, found: 417.2506.

Example 33

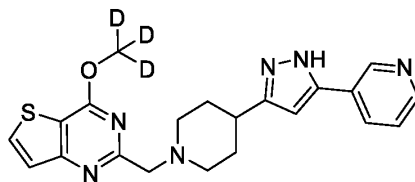
2-((4-(2',4'-Dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
 25 methylpyrido[2,3-*d*]pyrimidine



DIPEA (0.038 mL, 0.22 mmol) was added to a mixture of 2,4-dimethyl-5'-(piperidin-4-yl)-2*H*,2'*H*-3,3'-bipyrazole, TFA **Intermediate 90** (0.020 g, 0.055 mmol) and (4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl methanesulfonate **Intermediate 9** (0.015 g, 0.06 mmol) in DMSO (0.5 mL) and the reaction mixture was stirred at rt for 24 h. The mixture was
 5 filtered using a syringe filter and the residue was purified by preparative HPLC, PrepMethod D, (gradient 15–55%) to afford the title compound (0.019 g, 84%). ¹H NMR (500 MHz, CDCl₃) δ 9.22 (dd, 1H), 8.46 (dd, 1H), 7.57 (dd, 1H), 7.28 (s, 1H), 6.18 (s, 1H), 4.05 (s, 2H), 3.92 (s, 3H), 3.15–3.27 (m, 2H), 2.98 (s, 3H), 2.73–2.84 (m, 1H), 2.33–2.45 (m, 2H), 2.08 (s, 3H), 1.89 – 2.02 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 170.81, 166.53, 157.86, 157.62,
 10 149.76 (broad), 141.18 (broad), 138.86, 134.44, 133.44 (broad), 122.89, 117.53, 115.38, 102.55, 65.48, 53.84, 38.32, 33.50, 31.81, 21.51, 9.65. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₇N₈: 403.2354, found: 403.2366.

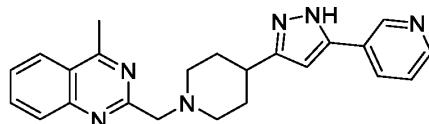
Example 34

15 4-(Methoxy-*d*3)-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidine

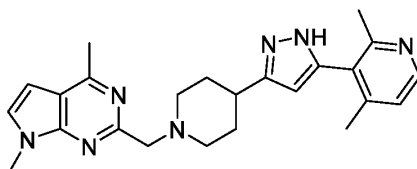


NaH (60% wt. in mineral oil, 12.2 mg, 0.30 mmol) was added portion wise to a solution of 4-chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidine
 20 **Intermediate 92** (25.0 mg, 0.06 mmol) in methan-*d*3-ol-*d* (300 μL, 0.06 mmol) and stirred at rt for 30 min. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was purified by preparative HPLC, PrepMethod A, (gradient: 15–55%) to grant the title compound (15.9 mg, 64%). ¹H NMR (500 MHz, CDCl₃) δ 9.02 (s, 1H), 8.54 (m, 1H), 8.07 (d, 1H), 7.85
 25 (d, 1H), 7.52 (d, 1H), 7.32 (m, 1H), 6.43 (s, 1H), 3.92 (s, 2H), 3.23 (d, 2H), 2.77 (m, 1H), 2.3 – 2.39 (m, 2H), 1.96 – 2.04 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₁H₂₃N₆OS: 410.1836, found: 410.1848.

Example 35

4-Methyl-2-((4-(5-(pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

DMSO (661 μ L) and DIPEA (92 μ L, 0.53 mmol) were added to a mixture of 3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 18** (82 mg, 0.18 mmol) and 2-(chloromethyl)-4-methyl-5,6,7,8-tetrahydroquinazoline **Intermediate 93** (29.6 mg, 0.15 mmol) and the reaction mixture was stirred at rt overnight. The mixture was filtered and the crude residue was purified by preparative SFC, PrepMethod C, (gradient: 27-32%), to grant the title compound (23.8 mg, 41%). ^1H NMR (500 MHz, CDCl_3) δ 1.85 (4H, m), 1.93–2.06 (4H, m), 2.3–2.38 (2H, m), 2.41 (3H, s), 2.57–2.67 (2H, m), 2.77 (1H, m), 2.84 (2H, m), 3.15 (2H, m), 3.79 (2H, s), 6.39 (1H, s), 7.29 (1H, m), 7.97–8.08 (1H, m), 8.51 (1H, m), 8.97 (1H, m). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{N}_6$: 389.2448, found: 389.2442.

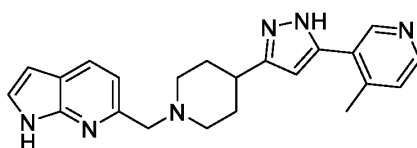
Example 362-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

A solution of 4-chloro-2-((4-(5-(2,4-dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidine **Intermediate 96** (68.5 mg, 0.16 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (19 mg, 0.02 mmol) was degassed at rt with N_2 (g) for 5 min followed by a dropwise addition of 2 M AlMe_3 in toluene (300 μ L, 0.60 mmol). The reaction mixture was heated to 50 $^\circ\text{C}$ and stirred for 6 h before being cooled to rt and quenched with sat NaHCO_3 (aq). The mixture was diluted with EtOAc and DCM and filtered through a phase separator. The filtrate was concentrated, and the crude product was purified by preparative HPLC, PrepMethod D, (gradient: 15-55%) to grant the title compound (34.9 mg, 54%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.28 (d, 1H), 7.08 (d, 1H), 6.95 (d, 1H), 6.50 (d, 1H), 6.00 (s, 1H), 3.91 (s, 2H), 3.83 (s, 3H), 3.17 (d, 2H), 2.66 – 2.74 (m, 4H), 2.24 – 2.35 (m,

5H), 2.08 (s, 3H), 1.91 – 2 (m, 4H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{30}N_7$: 416.2558, found: 416.2574.

Example 37

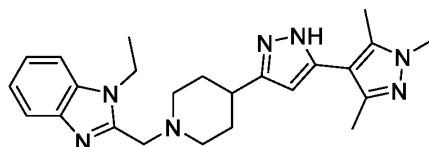
5 6-((4-(5-(4-Methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-1H-pyrrolo[2,3-
b]pyridine



A solution of 4-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 34** (72.0 mg, 0.15 mmol), 6-(chloromethyl)-1H-pyrrolo[2,3-b]pyridine (25.5 mg, 0.15 mmol) and
10 DIPEA (133 μ L, 0.77 mmol) in DMSO (1.397 mL) was stirred at rt over the weekend and then filtered using a syringe filter. The crude product was purified by preparative HPLC, PrepMethod I, (gradient: 5-95%), to grant the title compound (24.1 mg, 42%). 1H NMR (600 MHz, DMSO- d_6) δ 11.52 (s, 1H), 8.67 (s, 1H), 8.35 (m, 1H), 7.91 (d, 1H), 7.39 – 7.41 (m, 1H), 7.27 (m, 1H), 7.16 (d, 1H), 6.42 (s, 1H), 6.41 (m, 2H), 3.66 (s, 2H), 2.94 (d, 2H), 2.66 –
15 2.71 (m, overlapping with solvent), 2.46 (s, 3H), 2.11 – 2.18 (m, 2H), 1.91 (m, 2H), 1.71 (m, 2H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{25}N_6$: 373.2136, found: 373.2138.

Example 38

1-Ethyl-2-((4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1H-
20 benzo[d]imidazole

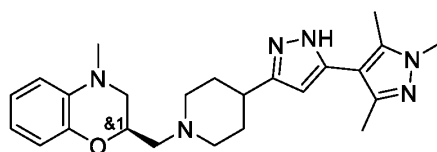


A solution of 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole, HCl **Intermediate 28** (41 mg, 0.11 mmol), 2-(chloromethyl)-1-ethyl-1H-benzo[d]imidazole, HCl (24 mg, 0.105 mmol) and DIPEA (0.128 mL, 0.74 mmol) in DMSO (0.75 mL) was stirred at rt overnight.
25 The crude product was purified by preparative HPLC, PrepMethod R, (gradient: 5-95%), to grant the title compound (18 mg, 41%). 1H NMR (600 MHz, DMSO- d_6) δ 12.31 (s, 1H), 7.54 (d, 1H), 7.50 (d, 1H), 7.18 (t, 1H), 7.13 (t, 1H), 5.99 (s, 1H), 4.30 (q, 2H), 3.74 (s, 2H), 3.61 (s,

3H), 2.86 (d, 2H), 2.58 (m, overlapping with solvent), 2.25 (s, 3H), 2.13 (s, 5H), 1.87 (d, 2H), 1.58 (m, 2H), 1.34 (t, 3H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{32}N_7$: 418.2714, found: 418.2728.

5 Example 39

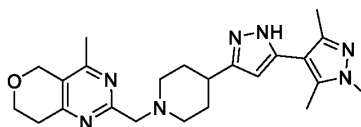
rac-(R)-4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine



In a microwave vial, *rac*-(R)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl 4-methylbenzenesulfonate **Intermediate 101** (73 mg, 0.41 mmol), 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (160 mg, 0.62 mmol) and DIPEA (0.216 mL, 1.24 mmol) were mixed in DMSO (2 mL). The vial was sealed and the reaction mixture was stirred at 80 °C overnight. The crude product was purified by preparative SFC, PrepMethod C, (gradient: 25-30%), to grant the title compound (78 mg, 45%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.63 (2H, m), 1.81 – 1.87 (2H, m), 2.08 (1H, m), 2.14 (4H, m), 2.26 (3H, s), 2.78 (3H, s), 2.86 – 3.01 (3H, m), 3.25 (1H, m), 3.62 (2H, s), 4.25 – 4.32 (1H, m), 6.01 (1H, s), 6.52 (1H, m), 6.61 – 6.66 (2H, m), 6.7 – 6.74 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{33}N_6O$: 421.2710, found: 421.2720.

20 Example 40

4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine

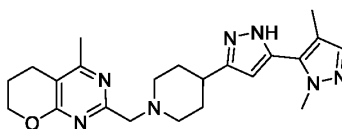


4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine **Intermediate 103** (96 mg, 0.22 mmol) and Pd(PPh₃)₄ (25.1 mg, 0.02 mmol) were mixed in THF (1.846 mL) in a sealed tube. The mixture was degassed with Ar (g) for 5 min followed by a dropwise addition of 2 M AlMe₃ in toluene (326

μL, 0.65 mmol). The reaction mixture was stirred at 50 °C for 16 h. The mixture was cooled down to rt, diluted with EtOAc/MeOH (9/1), washed with 10% NaHCO₃ (aq) and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod D, (gradient of 5–45%), to afford the title compound (0.031 g, 34%) as red solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 6.04 (s, 1H), 4.69 (s, 2H), 3.94 (t, 2H), 3.66 (s, 3H), 3.59 (s, 2H), 2.91-2.99 (m, 2H), 2.82 (t, 2H), 2.52 – 2.66 (m, 4H), 2.29 (s, 3H), 2.13-2.23 (s, 5H), 1.81-1.89 (m, 2H), 1.58 – 1.70 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₃₂N₇O: 422.2662, found: 422.2670

10 Example 41

2-((4-(2',4'-Dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

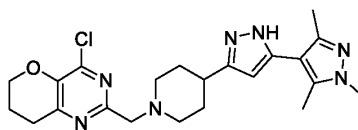


1-(1,4-Dimethyl-1*H*-pyrazol-5-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 108** (80 mg, 0.20 mmol) was dissolved in 99.5% EtOH (1 mL) and hydrazine hydrate (aq, 0.015 mL, 0.30 mmol) was added. The reaction mixture was stirred at rt overnight. DCM and sat NaHCO₃ (aq) were added, the mixture was stirred, filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative SFC, PrepMethod O, (gradient of 12–17%), to give the title compound (26 mg, 31%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.87 (s, 1H), 7.24 (s, 1H), 6.29 (s, 1H), 4.30 – 4.26 (m, 2H), 3.88 (s, 3H), 3.47 (s, 2H), 2.96 – 2.90 (m, 2H), 2.69 – 2.62 (m, 3H), 2.31 (s, 3H), 2.17 (td, 2H), 2.05 (s, 3H), 1.98 – 1.91 (m, 2H), 1.91 – 1.83 (m, 2H), 1.66 (qd, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₃₀N₇O: 408.2506, found: 408.2496

25

Example 42

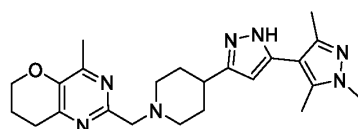
4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine



2-((4-(1',3',5'-Trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidin-4-ol **Intermediate 110** (344 mg, 0.81 mmol) was suspended in POCl₃ (9 mL) and heated to 110 °C for 90 min. The mixture was cooled to rt, toluene was added and the mixture was concentrated in vacuo. DCM and sat NaHCO₃ (aq) was added and the layers were separated. The aqueous layer was extracted with DCM, and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give crude title compound (319 mg). 22 mg of the crude title compound was dissolved in DMSO and purified by preparative HPLC, PrepMethod W, (gradient of 0–50%), to afford the formate-salt of the title compound (9 mg, 35%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.63-1.76 (2H, m), 1.86 – 1.93 (2H, m), 2.0-2.11 (2H, m), 2.17 (3H, s), 2.26 – 2.36 (5H, m), 2.89 (2H, t), 2.97 – 3.03 (2H, m), 3.66 (3H, s), 3.68 (2H, s), 4.31 – 4.35 (2H, m), 6.05 (1H, s), 8.14 (2H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₉ClN₇O: 442.2116, found: 442.2114.

15 **Example 43**

4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine



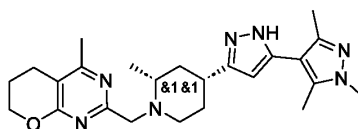
4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine, formate-salt **Example 42** (0.037 g, 0.08 mmol) was dissolved in THF (1.7 mL) and Pd(PPh₃)₄ (9.67 mg, 8.37 μmol) was added. The reaction mixture was degassed with N₂ (g) for 5 min followed by a dropwise addition of 2 M AlMe₃ in toluene (0.160 mL, 0.32 mmol) at rt. The reaction mixture was heated to 50 °C and stirred overnight. The mixture was cooled to rt and the reaction was quenched with sat NaHCO₃ (aq). The mixture was extracted with EtOAc and the organic layer was filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative SFC, PrepMethod O, (gradient of 12–17%), to give the title compound (7.8 mg,

22%). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 1.62 (2H, qd), 1.79 - 1.87 (2H, m), 2.04 (2H, m), 2.09–2.19 (5H, m), 2.28 (6H, s), 2.78 (2H, t), 2.86–2.93 (2H, m), 3.16 (2H, d), 3.64 (3H, s), 4.17–4.25 (3H, m), 6.03 (1H, s), 12.41 (1H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{32}\text{N}_7\text{O}$: 422.2662, found: 422.2654

5

Example 44

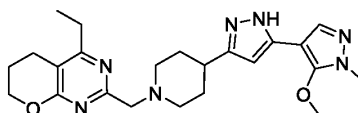
rac-4-Methyl-2-(((2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



10 *rac*-5-(3-Hydroxypropyl)-6-methyl-2-(((2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol **Intermediate 113** (78 mg, 0.17 mmol) and PPh_3 (135 mg, 0.52 mmol) were dissolved in THF (1.6 mL) and cooled in an ice-bath. DIAD (102 μL , 0.52 mmol) was added dropwise. The reaction mixture was stirred for 5 min and then quenched with water. The mixture was diluted with EtOAc and brine and the layers
15 were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod D, (gradient of 15–55%) and then by preparative HPLC, PrepMethod F, (gradient of 15–55%) to yield the title compound (44 mg, 59%) as white solid. ^1H NMR (500 MHz, CDCl_3) 1.21 (3H, d), 1.51 - 1.63 (1H, m), 1.76
20 (1H, qd), 1.81 - 1.90 (2H, m), 1.99 - 2.06 (2H, m), 2.23 (6H, d), 2.36 (3H, s), 2.39 - 2.51 (2H, m), 2.64 (2H, t), 2.70 (1H, tt), 3.06 (1H, dt), 3.63 (1H, d), 3.68 (3H, s), 4.00 (1H, d), 4.28 - 4.32 (2H, m), 5.98 (1H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{34}\text{N}_7\text{O}$: 436.2820, found: 436.2832

25 **Example 45**

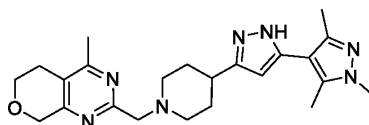
4-Ethyl-2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



6-Ethyl-5-(3-hydroxypropyl)-2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol **Intermediate 116** (0.030 g, 0.07 mmol) was dissolved in THF (1.5 mL) and PPh₃ (0.052 g, 0.20 mmol) was added and the reaction mixture was cooled in an ice-bath. DIAD (0.040 mL, 0.20 mmol) was added dropwise. The reaction mixture was stirred for 5 min and then quenched with water. The mixture was diluted with EtOAc and brine and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod CC, (gradient of 30–65%) and then by preparative HPLC, PrepMethod CC, (gradient of 20–60%) to afford the title compound (2 mg, 7%). ¹H NMR (500 MHz, Methanol-*d*₄) 1.26 (3H, t), 1.83 (2H, qd), 1.92 – 1.98 (2H, m), 2.03 – 2.12 (2H, m), 2.28 – 2.36 (2H, m), 2.71 – 2.84 (5H, m), 3.03 – 3.12 (2H, m), 3.63 (2H, s), 3.70 (3H, s), 3.90 (3H, s), 4.36 – 4.44 (2H, m), 6.24 (1H, s), 7.58 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₃₂N₇O₂: 438.2612, found: 438.2600

Example 46

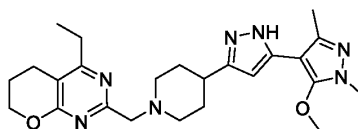
4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6*H*-pyrano[3,4-*d*]pyrimidine



4-Chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6*H*-pyrano[3,4-*d*]pyrimidine **Intermediate 119** (0.034 g, 0.08 mmol) and Pd(PPh₃)₄ (8.89 mg, 7.69 μmol) were dissolved in THF (1.5 mL) and degassed with N₂ (g) for 5 min. 2 M AlMe₃ in toluene (0.147 mL, 0.29 mmol) was added dropwise at rt. The reaction mixture was heated to 50 °C and stirred overnight. The mixture was cooled to rt and the reaction was quenched with sat NaHCO₃ (aq). The mixture was diluted with EtOAc and DCM, filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod CC, (gradient of 25–60%) to afford the title compound (0.021 g, 65%). ¹H NMR (500 MHz, DMSO-*d*₆) 1.56 – 1.70 (2H, m), 1.81 – 1.89 (2H, m), 2.10 – 2.23 (5H, m), 2.30 (3H, s), 2.38 (3H, s), 2.55 – 2.62 (1H, m), 2.72 (2H, t), 2.88 – 2.97 (2H, m), 3.57 (2H, s), 3.66 (3H, s), 3.94 (2H, t), 4.59 (2H, s), 6.04 (1H, s), 12.38 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₃₂N₇O: 422.2662, found: 422.2676

Example 47

4-Ethyl-2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



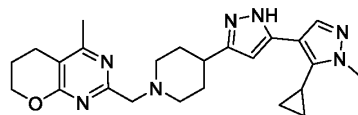
5

6-Ethyl-5-(3-hydroxypropyl)-2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol **Intermediate 123** (0.301 g, 0.64 mmol) was dissolved in THF (8 mL) and PPh_3 (0.504 g, 1.92 mmol) was added. The reaction mixture was cooled in an ice-bath and DIAD (0.374 mL, 1.92 mmol) was added dropwise. The reaction mixture was stirred for 5 min and then quenched with water. The mixture was diluted with EtOAc and sat NaHCO_3 (aq). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod JJ, (gradient of 15–55%) to afford the title compound (0.052 g, 18%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) 1.17 (3H, t), 1.63 (2H, qd), 1.80 – 1.88 (2H, m), 1.90 – 1.99 (2H, m), 2.14 – 2.23 (5H, m), 2.54 – 2.70 (5H, m), 2.90 – 2.98 (2H, m), 3.49 (2H, s), 3.56 (3H, s), 3.79 (3H, s), 4.25 – 4.32 (2H, m), 6.08 (1H, s), 12.35 (1H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{34}\text{N}_7\text{O}_2$: 452.2768, found: 452.2776

15

Example 48

2-((4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



20

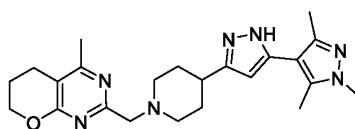
25

2-((4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5-(3-hydroxypropyl)-6-methylpyrimidin-4-ol **Intermediate 127** (0.162 g, 0.36 mmol) was dissolved in THF (3.5 mL). PPh_3 (0.282 g, 1.08 mmol) was added, and the reaction mixture was cooled in an ice-bath. DIAD (0.220 mL, 1.08 mmol) was added dropwise. The reaction mixture was stirred for 10 min and then quenched with water. The mixture was diluted with

EtOAc and sat NaHCO₃ (aq). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod GG, (gradient of 12–27%) to afford the title compound (6.2 mg, 4%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 0.49–0.54 (2H, m), 0.99–1.04 (2H, m), 1.83–1.88 (1H, m), 1.93–2.03 (4H, m), 2.13–2.19 (2H, m), 2.39 (3H, s), 2.70 (2H, t), 3.84 (3H, s), 4.34–4.37 (2H, m), 4.40 (2H, s), 6.23 (1H, s), 7.58 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₂N₇O: 434.2662, found: 434.2670

Example 49

4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



Step a): 1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

tert-Butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 27 (0.074 g, 0.205 mmol) was dissolved in DCM (0.6 mL) and TFA (0.3 mL) was added. The reaction mixture was stirred for 1 h at rt and then concentrated in vacuo to give the TFA salt of the title compound. The residue was dissolved in DMSO (1.8 mL).

Step b): 2-(Chloromethyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

(4-Methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methanol **Intermediate 135** (0.043 g, 0.24 mmol) and PPh₃ (0.071 g, 0.27 mmol) was dissolved in DCM (1 mL) and cooled in an ice-bath. NCS (0.036 g, 0.27 mmol) was added, and the reaction mixture was stirred at rt for 1 h and then concentrated in vacuo.

Step c): 4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-

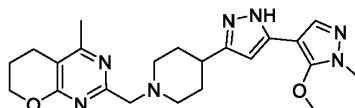
yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

The solution of **step a)** was poured onto the residue obtained in **step b)**. K₂CO₃ (0.166 g, 1.2 mmol) was added, and the suspension was stirred at rt for 18 h. The solids were removed by filtration through CELITE, and the filtrate was purified by preparative SFC, PrepMethod Y, (gradient of 25–30%), to give the title compound (21 mg, 25%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.63 (2H, qd), 1.81 – 1.87 (2H, m), 1.91 – 1.98 (2H, m), 2.12 – 2.21 (5H, m), 2.24 – 2.37

(6H, m), 2.64 (2H, t), 2.91 – 2.95 (2H, m), 3.47 (2H, s), 3.66 (3H, s), 4.29 (2H, s), 6.04 (1H, s), 12.41 (1H, s). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{32}N_7O$: 422.2662, found: 422.2742

Example 50

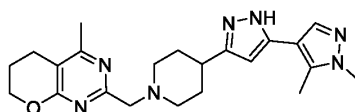
5 2-((4-(5'-Methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



Hydrazine hydrate (8.29 μ L, 0.17 mmol) was added to a solution of 1-(5-methoxy-1-methyl-1'*H*-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 136** (35 mg, 0.09 mmol) in 99.5% EtOH (0.5 mL), and the reaction was stirred at rt overnight. DCM and sat NaHCO_3 (aq) were added, and the mixture was filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative SFC, PrepMethod C, (gradient of 27–32%), to give the title compound (17.9 mg, 49%). ^1H NMR (600 MHz, $\text{DMSO-}d_6$) 1.61 (2H, qd), 1.78 – 1.87 (2H, m), 1.91 – 1.98 (2H, m), 2.12 – 2.19 (2H, td), 2.32 (3H, s), 2.64 (2H, t), 2.87 – 2.95 (2H, m), 3.46 (2H, s), 3.63 (3H, s), 3.89 (3H, s), 4.24 – 4.32 (2H, m), 6.13 (1H, s), 7.53 (1H, s), 12.42 (1H, s). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{30}N_7O_2$: 424.2456, found: 424.2468

Example 51

20 2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

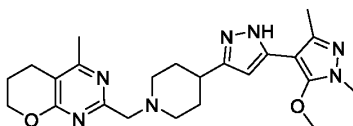


Hydrazine hydrate (0.012 mL, 0.24 mmol) was added to a solution of 1-(1,5-dimethyl-1'*H*-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 137** (47 mg, 0.12 mmol) in 99.5% EtOH (0.6 mL) and the reaction mixture was stirred at rt overnight. DCM and sat NaHCO_3 (aq) were added, the mixture was stirred, filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative SFC, PrepMethod C, (gradient of

27–32%), to give the title compound (28.1 mg, 58%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.62 (2H, qd), 1.81 – 1.87 (2H, m), 1.91 – 1.98 (2H, m), 2.16 (2H, td), 2.32 (3H, s), 2.40 (3H, s), 2.63 (3H, t), 2.89 – 2.95 (2H, m), 3.46 (2H, s), 3.73 (3H, s), 4.25 – 4.30 (2H, m), 6.12 (1H, s), 7.54 (1H, s), 12.31 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₃₀N₇O: 408.2506, found: 408.2530

Example 52

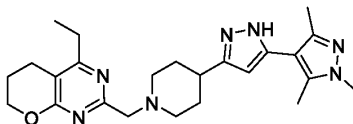
2-((4-(5'-Methoxy-1',3'-dimethyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine



1-(5-Methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 139** (37 mg, 0.09 mmol) was dissolved in 99.5% EtOH (0.6 mL) and hydrazine hydrate (aq, 8.48 μL, 0.17 mmol) was added. The reaction mixture was stirred at rt overnight. DCM and sat NaHCO₃ (aq) were added, the mixture was stirred, filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative SFC, PrepMethod C, (gradient of 25–30%), to give the title compound (16.8 mg, 44%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.64 (2H, qd), 1.82 – 1.88 (2H, m), 1.93 – 1.98 (2H, m), 2.18 (5H, d), 2.32 (3H, s), 2.65 (2H, t), 2.92 (2H, dt), 3.46 (2H, s), 3.57 (3H, s), 3.80 (3H, s), 4.26 – 4.31 (2H, m), 6.09 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₃₂N₇O₂: 438.2612, found: 438.2604

Example 53

4-Ethyl-2-((4-(1',3',5'-trimethyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

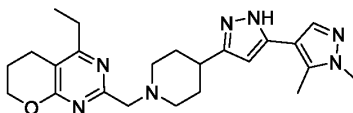


PPh₃ (0.094 g, 0.36 mmol) was dissolved in THF (1.5 mL) and cooled in an ice-bath. DIAD (0.073 mL, 0.36 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min, then added dropwise to a solution of 6-ethyl-5-(3-hydroxypropyl)-2-((4-(1',3',5'-

trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol **Intermediate 140** (0.108 g, 0.24 mmol) in THF (1.5 mL) at 0 °C. The reaction mixture was stirred for 10 min and then warmed to rt and stirred overnight. The reaction mixture was cooled in an ice-bath and more PPh₃ (0.094 g, 0.36 mmol) and DIAD (0.073 mL, 0.36 mmol) were added and
 5 the reaction mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and K₂CO₃ (0.066 g, 0.48 mmol) was added and the reaction mixture was stirred for a few min. The solvent was removed under reduced pressure and the crude compound was purified by preparative HPLC, PrepMethod CC, (gradient of 15–50%). The product was dissolved in MeOH (1 mL) and 1M HCl (36 µL)
 10 was added. The solution was stirred for 1 min and then concentrated to dryness to afford the HCl-salt of the title compound (16 mg, 64%) as white solid. ¹H NMR (500 MHz, DMSO-*d*₆) 1.19 (3H, t), 1.75 – 1.93 (2H, m), 1.93 – 2.00 (2H, m), 2.00 – 2.12 (2H, m), 2.17 (3H, s), 2.29 (3H, s), 2.59 – 2.99 (7H, m), 3.66 (3H, s), 3.75 – 4.29 (2H, m), 4.33 (2H, t), 6.07 (1H, s), 12.37 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₄N₇O: 436.2820, found: 436.2830

Example 54

2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-ethyl-6,7-dihydro-5H-pyrano[2,3-*d*]pyrimidine

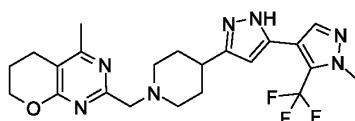


2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6-ethyl-5-(3-hydroxypropyl)pyrimidin-4-ol **Intermediate 143** (96 mg, 0.22 mmol) and PPh₃ (172 mg, 0.66 mmol) were dissolved in THF (3 mL) and cooled in an ice-bath. DIAD (0.129 mL, 0.66 mmol) was added dropwise, and the reaction mixture was stirred for 5 min. The reaction was quenched with water and diluted with EtOAc and brine. The layers were separated, and the
 25 aqueous layer was extracted with EtOAc. The combined organic layers were dried using MgSO₄, filtered and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod F, (gradient of 15–55%) to afford the title compound (74.9 mg, 81%) as white solid. ¹H NMR (500 MHz, CDCl₃) 1.13 – 1.19 (3H, m), 1.73 – 1.88 (4H, m), 1.95 – 2.03 (2H, m), 2.10 – 2.21 (2H, m), 2.30 – 2.37 (3H, m), 2.56 – 2.68 (5H, m), 2.97 –
 30 3.07 (2H, m), 3.59 – 3.63 (2H, m), 3.69 – 3.76 (3H, m), 4.23 – 4.31 (2H, m), 5.98 – 6.04 (1H,

m), 7.50 – 7.61 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{32}N_7O$: 422.2662, found: 422.2664

Example 55

5 4-Methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

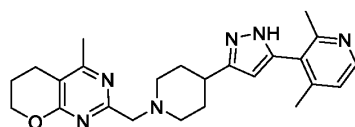


5-(3-Hydroxypropyl)-6-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrimidin-4-ol **Intermediate 147** (0.235 g, 0.49 mmol) and PPh_3 (0.386 g, 1.47 mmol) were dissolved in THF (4.6 mL) and cooled in an ice-bath. DIAD (0.301 mL, 1.47 mmol) was added dropwise, and the reaction mixture was stirred for 5 min. The reaction was quenched with water and diluted with EtOAc and sat $NaHCO_3$ (aq). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were filtered through a phase separator and concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod GG, (gradient of 15–30%) to afford the title compound (4.0 mg, 1%) as TFA-salt. 1H NMR (600 MHz, DMSO- d_6) δ 1.90 – 2.02 (4H, m), 2.11–2.20 (2H, m), 2.39 (3H, s), 2.70 (2H, t), 2.87–3.05 (3H, m), 3.18–3.27 (2H, m), 4.00 – 4.03 (3H, m), 4.33–4.37 (2H, m), 4.40 (2H, s), 6.23 (1H, s), 7.79 (1H, s). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{27}F_3N_7O$: 462.2224, found: 462.2226

20

Example 56

2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine

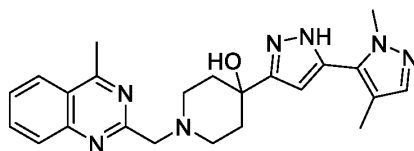


25 A mixture of isopropyl 5-(2,4-dimethylpyridin-3-yl)-3-(1-((4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazole-1-carboxylate **Intermediate 149** (56.0 mg, 0.11 mmol) and K_2CO_3 (30.7 mg, 0.22 mmol) in MeOH (1 mL) was stirred at

rt for 1 h. The mixture was filtered using a syringe filter and the filtrate was diluted with EtOAc and filtered again through a syringe filter. The filtrate was concentrated under reduced pressure to afford the title compound (0.048 g) as a white solid. ¹H NMR (500 MHz, CDCl₃) 8.23 (1H, d), 6.90 (1H, d), 5.91 (1H, s), 4.25 – 4.31 (2H, m), 3.58 (2H, s), 2.96 – 3.04 (2H, m),
 5 2.56 – 2.65 (3H, m), 2.34 (3H, s), 2.25 (3H, s), 2.14 (2H, td), 1.96 – 2.06 (5H, m), 1.77 – 1.89 (4H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₁N₆O: 419.2554, found: 419.2560

Example 57

4-(2',4'-Dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-ol

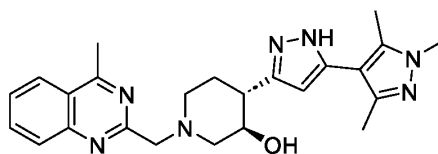


A solution of 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-4-ol **Intermediate 152** (71 mg, 0.27 mmol), 2-(chloromethyl)-4-methylquinazoline (57 mg, 0.30 mmol) and DIPEA (0.236 mL, 1.35 mmol) in DMSO (1 mL) were stirred at rt overnight. The reaction mixture
 15 was purified by preparative SFC, PrepMethod U, (gradient: 25-30%), to grant the title compound (31.3 mg, 28%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.81 (2H, m), 2.04 (5H, m), 2.62 – 2.76 (4H, m), 2.91 (3H, m), 3.86 (5H, m), 5.20 (1H, s), 6.38 (1H, s), 7.25 (1H, s), 7.64 – 7.74 (1H, m), 7.96 (2H, m), 8.2 – 8.28 (1H, m), 12.95 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇O: 418.2350, found: 418.2346.

20

Example 58

(3*R*,4*R*)-1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

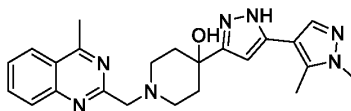


25 The isomers of *rac*-(3*R*,4*R*)-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol **Intermediate 160** (24 mg, 56 μmol) were separated by preparative chiral HPLC on a YMC SA (IA) column (3 μm, 150×4.6 mm) using 35%

EtOH/DEA (20 mM) system as a mobile phase, to give the first eluting compound as the title compound (9 mg, 21%). ¹H NMR (500 MHz, CDCl₃) 1.93 – 2.09 (2H, m), 2.16 – 2.34 (8H, m), 2.63 (1H, m), 2.93 (3H, s), 3.12 (1H, d), 3.27 – 3.38 (1H, m), 3.71 (3H, s), 3.89 – 4.05 (3H, m), 6.07 (1H, s), 7.59 (1H, m), 7.84 (1H, m), 8.00 (1H, m), 8.02 – 8.1 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2504.

Example 59

4-(1',5'-Dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-ol



10

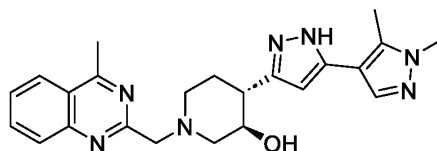
K₂CO₃ (448 mg, 3.24 mmol) was added to a suspension containing a crude mixture of regio-isomers *rac*-(3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol TFA and 4-(1',5'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol TFA **Intermediate 164** (141 mg) and 2-(chloromethyl)-4-methylquinazoline (109 mg, 0.57 mmol) in MeCN (2.7 mL) and the reaction mixture was stirred at rt overnight. The mixture was diluted with MeOH and DCM, filtered using a syringe filter and concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod F, (gradient of 15–55%), to give the title compound (102 mg, 45% over 2 steps) as white solid. ¹H NMR (500 MHz, CDCl₃) 1.85 – 1.93 (2H, m), 2.21 – 2.31 (2H, m), 2.35 (3H, s), 2.69 (2H, td), 2.85 – 2.91 (2H, m), 2.92 (3H, s), 3.75 (3H, s), 3.97 (2H, s), 5.59 – 5.82 (1H, m), 6.13 (1H, s), 7.53 – 7.61 (2H, m), 7.82 (1H, ddd), 7.98 – 8.03 (1H, m), 8.03 – 8.07 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇O: 418.2350, found: 418.2348

20

Example 60

(3*R*,4*R*)-4-(1',5'-Dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

25



Step a) *rac*-(3*R*,4*R*)-4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

The title compound was prepared and isolated as described for **Example 59** (61 mg, 27% over 2 steps) as a white solid. MS (ESI) m/z $[M+H]^+$ 418.4.

5

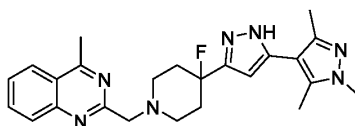
Step b) (3*R*,4*R*)-4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

The racemate *rac*-(3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol was separated into the respective enantiomers by
 10 chiral chromatography on a Chiralpak-IBN column (5 μ m, 250 $\times$ 30 mm), eluted with 30-35% MeOH-DEA (100/20 mM) in CO₂, 120 bar, at a flow rate of 100 mL/min and detected at 224 nm, to give the first eluting compound as the title compound (26 mg, 43%). ¹H NMR (500 MHz, CDCl₃) 1.87 – 1.98 (2H, m), 2.19 – 2.27 (2H, m), 2.28 (3H, s), 2.59 – 2.66 (1H, m), 2.88 (3H, d), 3.05 – 3.14 (1H, m), 3.28 – 3.35 (1H, m), 3.72 (3H, s), 3.92 (1H, td), 3.96 (2H,
 15 s), 6.03 (1H, s), 7.49 (1H, d), 7.56 (1H, ddd), 7.81 (1H, ddd), 7.97 (1H, d), 8.01 (1H, dd). HRMS (ESI) m/z $[M+H]^+$ calcd for C₂₃H₂₈N₇O: 418.2350, found: 418.2344.

Example 61

2-((4-Fluoro-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

20

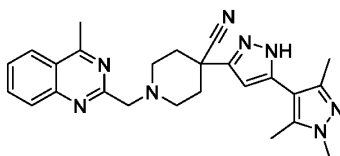


K₂CO₃ (0.33 g, 2.39 mmol) and 2-(chloromethyl)-4-methylquinazoline (0.115 g, 0.60 mmol) were added to a suspension of 5-(4-fluoropiperidin-4-yl)-1',3',5'-trimethyl-1'*H*,2*H*-3,4'-bipyrazole, TFA-salt **Intermediate 168** (0.37 g, 0.60 mmol) in DMSO (4 mL) and the
 25 reaction mixture was stirred at rt for 1 h. The mixture was filtered through CELITE. FA (14 μ L) was added to the filtrate and then purified by preparative HPLC, PrepMethod A, (gradient of 10–50%), to give the formate-salt of the title compound (134 mg, 47%) as a colourless solid. ¹H NMR (500 MHz, D₂O) 2.14 (3H, s), 2.20 (3H, s), 2.48 – 2.63 (4H, m), 2.94 (3H, s), 3.59 – 3.79 (7H, m), 4.68 (1H, s), 6.48 (1H, s), 7.76 (1H, t), 7.96 – 8.03 (2H, m), 8.27 (1H, d),
 30 8.40 (s). ¹³C NMR (500/126 MHz, D₂O) δ 8.24/126.08, 7.96/135.50, 7.94/127.26,

7.72/128.83, 6.46/102.16, 4.65/60.59 (CH₂), 3.63/49.02 (CH₂), 3.63/35.09, 2.90/20.78, 2.56/31.96 (CH₂), 2.17/9.21, 2.11/11.17. HRMS (ESI) m/z [M+H]⁺ calcd for C₂₄H₂₉FN₇: 434.2462, found: 434.2466

5 Example 62

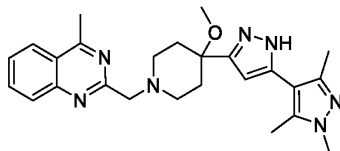
1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-4-carbonitrile



2-((4-Fluoro-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline **Example 61** (31 mg, 0.06 mmol) was dissolved in DMSO (1 mL) and KCN (50 mg, 0.89 mmol) was added. The reaction mixture was stirred at rt for 5 h, and at 50 °C for 15 h. The mixture was filtered and 2 drops of water was added. The filtrate was purified by preparative HPLC, PrepMethod A, (gradient of 10–50%), to give formate-salt of the title compound (13 mg, 44%) as colourless solid as the. ¹H NMR (500 MHz, D₂O containing a drop of DCl) 2.33 – 2.38 (6H, m), 2.56 – 2.83 (5H, m), 3.00 (3H, s), 3.74 (2H, t), 3.83 – 4.02 (5H, br. m), 6.67 (1H, s), 7.82 (1H, ddd), 8.01 – 8.05 (1H, m), 8.05 – 8.10 (1H, m), 8.19 (s), 8.32 – 8.35 (1H, m). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₅H₂₉N₈: 441.2510, found: 441.2518.

20 Example 63

2-((4-Methoxy-4-(1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



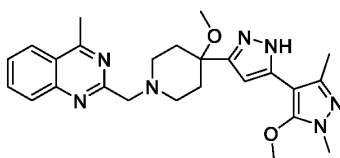
5-(4-Methoxypiperidin-4-yl)-1',3',5'-trimethyl-1'H,2H-3,4'-bipyrazole, TFA-salt

25 **Intermediate 170** (0.216 g, 0.34 mmol), K₂CO₃ (0.19 g, 1.37 mmol) and 2-(chloromethyl)-4-methylquinazoline (0.066 g, 0.34 mmol) was suspended in DMSO (2.5 mL) and the reaction mixture was stirred at rt for 1 h. The mixture was filtered through CELITE and washed with

DMSO (1.5 mL). The crude compound was purified by preparative HPLC, PrepMethod R, (gradient of 0–50%) to afford the title compound (42 mg, 28%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 2.01 (bs, 3H), 2.12 - 2.36 (m, 6H), 2.56 - 2.61 (m, 2H), 2.61 - 2.69 (m, 2H), 2.89 (s, 3H), 2.94 (s, 3H), 3.66 (s, 3H), 3.77 (s, 2H), 6.17 (s, 1H), 7.65 - 7.71 (m, 1H), 7.91 - 7.97 (m, 2H),
 5 8.20 - 8.25 (m, 1H), 12.23 - 12.82 (m, 1H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O: 446.2662, found: 446.2656.

Example 64

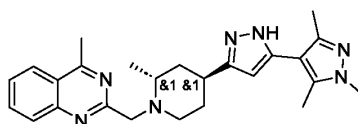
2-((4-Methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



A mixture of 5'-methoxy-5-(4-methoxypiperidin-4-yl)-1',3'-dimethyl-1'*H*,2*H*-3,4'-bipyrazole, TFA-salt **Intermediate 174** (0.086 g, 0.21 mmol), 2-(chloromethyl)-4-methylquinazoline (0.040 g, 0.21 mmol) and DIPEA (0.215 mL, 1.23 mmol) in DMSO (2.0 mL) was stirred at rt
 15 overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃ (aq). The mixture was filtered through a phase separator and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod J, (gradient of 0–50%), to give the formate-salt of the title compound (0.018 g, 17%) as the. ¹H NMR (600 MHz, DMSO-*d*₆) 2.06 – 2.10 (4H, m), 2.16 (3H, s), 2.72 – 2.87 (4H, m), 2.91 (3H, s), 2.94 (3H, s), 3.57 (3H, s),
 20 3.77 (3H, s), 3.99 (2H, s), 6.24 (1H, s), 7.71 (1H, ddd), 7.93 – 8.00 (2H, m), 8.18 (2H, s), 8.23 – 8.28 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O₂: 462.2612, found: 462.2626

Example 65

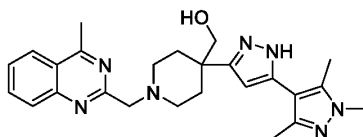
rac-4-Methyl-2-(((2*R*,4*S*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



rac-1',3',5'-Trimethyl-5-((2*R*,4*S*)-2-methylpiperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt **Intermediate 177** (0.143 g, 0.52 mmol), 2-(chloromethyl)-4-methylquinazoline (0.097 g, 0.50 mmol) and K₂CO₃ (0.578 g, 4.18 mmol) were mixed in MeCN (5.1 mL) and stirred at 42 °C overnight. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod C, (gradient of 27–32%), to give the title compound (0.122 g, 54%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.12 (3H, d), 1.63–1.75 (2H, m), 1.77–1.84 (1H, m), 1.87–1.97 (1H, m), 2.15 (3H, s), 2.27 (3H, s), 2.63–2.75 (2H, m), 2.87 (3H, s), 2.92–3.01 (1H, m), 3.05–3.15 (1H, m), 3.64 (3H, s), 3.8–3.9 (2H, m), 6.02 (1H, s), 7.62–7.68 (1H, m), 7.87–7.95 (2H, m), 8.17–8.22 (1H, m), 12.36 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇: 430.2714, found: 430.2716.

Example 66

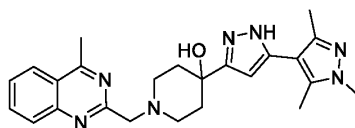
1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-yl)methanol



A mixture of 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-yl)methanol, HCl-salt **Intermediate 181** (0.194 g, 0.49 mmol), 2-(chloromethyl)-4-methylquinazoline (0.094 g, 0.49 mmol) and K₂CO₃ (0.538 g, 3.89 mmol) in MeOH (0.8 mL) and MeCN (5.8 mL) was stirred at 42 °C overnight. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod C, (gradient of 30–35%), to give the title compound (0.044 g, 20%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.75–1.83 (2H, m), 1.92–2.02 (2H, m), 2.17 (3H, s), 2.24–2.32 (5H, m), 2.69–2.77 (2H, m), 2.85 (3H, s), 3.36 (2H, d), 3.66 (5H, d), 4.74 (1H, s), 6.05 (1H, s), 7.65 (1H, ddd), 7.86–7.94 (2H, m), 8.16–8.20 (1H, m), 12.31 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O: 446.2662, found: 446.2666.

Example 67

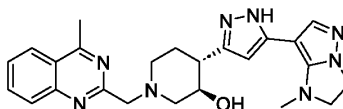
1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol



TFA (1 mL, 0.69 mmol) was added to a solution of *tert*-butyl 4-hydroxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 166** (260 mg, 0.69 mmol) in DCM (3 mL). The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was dissolved in MeCN (3 mL) and then K₂CO₃ (479 mg, 3.46 mmol) and 2-(chloromethyl)-4-methylquinazoline (133 mg, 0.69 mmol) was added. The reaction mixture was stirred at rt overnight and then heated to 50 °C and stirred for additional 4 h. The mixture was cooled to rt, filtered using a syringe filter and concentrated. The crude compound was purified by preparative HPLC, PrepMethod F, (gradient of 15–55%) to afford the title compound (119 mg, 40%) as white solid. ¹H NMR (500 MHz, CDCl₃) 1.91 – 2.01 (2H, m), 2.27 (3H, s), 2.30 (3H, s), 2.37 – 2.49 (2H, m), 2.80 – 3.01 (5H, m), 3.05 – 3.23 (3H, m), 3.73 (3H, s), 4.04 – 4.25 (2H, m), 6.14 – 6.18 (1H, m), 7.58 – 7.66 (1H, m), 7.83 – 7.91 (1H, m), 8.04 (1H, d), 8.09 (1H, d). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2506.

Example 68

(3*R*,4*R*)-4-(5-(1-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

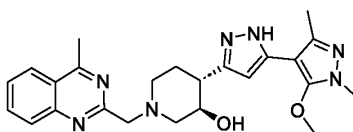


The enantiomers of *rac*-(3*R*,4*R*)-4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 188** (51 mg, 0.11 mmol) were separated by chiral preparative SFC on a Whelk-O1 column (10 μm, 250×50 mm ID), using EtOH/DEA (100/20 mM) in CO₂ (isocratic 40%) as mobile phase. The first eluted compound was collected to yield the title compound (21 mg, 41%, ee 99.2) as white solid. ¹H NMR (500 MHz, CDCl₃) 1.88 – 2.05 (2H, m), 2.16 (1H, t), 2.23 (1H, td), 2.52 – 2.62 (1H, m), 2.90 (6H, s), 3.04 – 3.12 (1H, m), 3.23 – 3.30 (1H, m), 3.64 – 3.74 (2H, m), 3.82 – 4.01 (3H, m), 4.02 – 4.12 (2H, m), 6.03 (1H, s), 7.43 (1H, s), 7.58 (1H, ddd), 7.82 (1H,

ddd), 7.96 – 8.01 (1H, m), 8.01 - 8.06 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}N_8O$: 445.2458, found: 445.2470.

Example 69

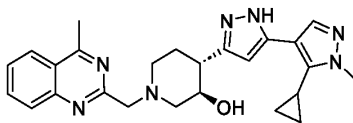
5 (3*R*,4*R*)-4-(5'-Methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



The enantiomers of *rac*-(3*R*,4*R*)-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 190** were separated
 10 by chiral preparative SFC on a YMC SZ (imob C2) column (3 μ m, 250 $\times$ 30) using EtOH/DEA (100/20 mM) in CO₂ (isocratic 25%) as mobile phase. The first eluted compound was collected to yield the title compound (44 mg, 32%, 99.9% ee) as a white solid. $[\alpha]_D^{20} +21.6$ (c 1, MeCN). ¹H NMR (500 MHz, CDCl₃) 1.96 – 2.04 (2H, m), 2.15 – 2.23 (4H, m), 2.27 (1H, td), 2.58 - 2.67 (1H, m), 2.90 (3H, s), 3.05 - 3.12 (1H, m), 3.25 – 3.34 (1H, m), 3.60 (3H, s),
 15 3.75 (3H, s), 3.88 – 4.02 (3H, m), 6.13 (1H, s), 7.53 – 7.60 (1H, m), 7.78 - 7.86 (1H, m), 7.97 (1H, d), 8.00 – 8.06 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{30}N_7O_2$: 448.2456, found: 448.2470

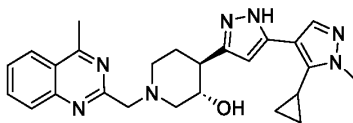
Example 70

20 3*R*,4*R*)-4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



Example 71

25 (3*S*,4*S*)-4-(5'-Cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

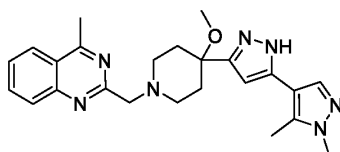


The enantiomers of *rac*-(3*R*,4*R*)-4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 193** (152 mg, 0.34 mmol) were separated by chiral preparative SFC on a CelluCoat column (5 μ m, 250 $\times$ 30 mm ID), using EtOH/MeOH/DEA (50/50/20 mM) in CO₂ (gradient of 27–30%) as mobile phase. The first eluted compound was collected to yield the title compound **Example 70** (56 mg, 37%, 99.9% ee) as white solid. $[\alpha]_D^{20} +26.4$ (*c* 1, MeCN). ¹H NMR (500 MHz, CDCl₃) 0.42 – 0.58 (2H, m), 0.86 – 1.04 (2H, m), 1.61 – 1.70 (1H, m), 1.88 – 1.98 (2H, m), 2.12 – 2.26 (2H, m), 2.61 (1H, q), 2.89 (3H, s), 3.00 – 3.09 (1H, m), 3.22 – 3.35 (1H, m), 3.80 – 3.90 (4H, m), 3.94 (2H, s), 6.14 (1H, s), 7.49 (1H, s), 7.52 – 7.57 (1H, m), 7.77 – 7.82 (1H, m), 7.98 (1H, d), 7.99 – 8.06 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₀N₇O: 444.2506, found: 444.2504.

The second eluted compound was collected to yield the title compound **Example 71** (52 mg, 34%, 95.1% ee) as white solid. $[\alpha]_D^{20} -26$ (*c* 1, MeCN). ¹H NMR (500 MHz, CDCl₃) δ 0.47–0.58 (2H, m), 0.93–1.03 (2H, m), 1.63–1.74 (1H, m), 1.89–2.01 (2H, m), 2.18 (1H, t), 2.25 (1H, td), 2.56–2.67 (1H, m), 2.91 (3H, s), 3.04–3.12 (1H, m), 3.26–3.35 (1H, m), 3.84–3.92 (4H, m), 3.93–4.01 (2H, m), 6.17 (1H, s), 7.51 (1H, s), 7.54–7.59 (1H, m), 7.78–7.85 (1H, m), 7.97–8.01 (1H, m), 8.02–8.06 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₀N₇O: 444.2506, found: 444.2528.

20 **Example 72**

2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidin-1-yl)methyl)-4-methylquinazoline



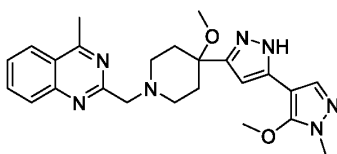
A mixture of 5-(4-methoxypiperidin-4-yl)-1',5'-dimethyl-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt **Intermediate 196** (5.36 g, 15.4 mmol), 2-(chloromethyl)-4-methylquinazoline (2.82 g, 14.63 mmol) and K₂CO₃ (17.03 g, 123.20 mmol) in MeCN (100 mL) and stirred at 60 °C for 24 h. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative SFC, PrepMethod NN, (isocratic 25%), to give the title compound (2.6 g, 39%) as tan solid.

¹H NMR (500 MHz, Methanol-*d*₄) 2.12 – 2.24 (4H, m), 2.43 (3H, s), 2.67 – 2.86 (4H, m), 2.98 (3H, s), 3.06 (3H, s), 3.82 (3H, s), 3.91 (2H, s), 6.33 (1H, s), 7.64 (1H, s), 7.72 (1H, ddd), 7.94 – 8.01 (2H, m), 8.23 – 8.29 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2508.

5

Example 73

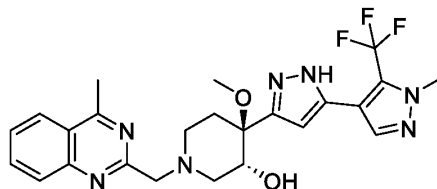
2-((4-Methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



- 10 A mixture of 5'-methoxy-5-(4-methoxypiperidin-4-yl)-1'-methyl-1'*H*,2'*H*-3,4'-bipyrazole, TFA-salt **Intermediate 199** (0.031 g, 0.08 mmol), 2-(chloromethyl)-4-methylquinazoline (0.015 g, 0.08 mmol) and DIPEA (0.080 mL, 0.46 mmol) in DMSO (1 mL) was stirred at rt overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃ (aq) and filtered through a phase separator and concentrated under reduced pressure. The crude
- 15 compound was purified by preparative HPLC, PrepMethod FF, (gradient of 15–30%) to afford the TFA-salt of the title compound (0.013 g, 30%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 2.07 (3H, s), 2.25-2.32 (1H, m), 2.43-2.47 (1H, m), 2.91-3.04 (6H, m), 3.39–3.46 (1H, m), 3.60–3.70 (5H, m), 3.89 (3H, s), 4.82 (2H, s), 6.35 (1H, s), 7.64 (1H, s), 7.82 (1H, t), 7.96–8.14 (2H, m), 8.37 (1H, d), 10.17 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O₂:
- 20 448.2456, found: 448.2454

Example 74

(3*R*,4*S*)-4-Methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



25

Step a) (3*R*,4*S*)-4-Methoxy-4-(3-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and

3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)prop-2-yn-1-one

A solution of (3*R*,4*S*)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (100 mg, 0.32 mmol) in THF (2.526 mL) was added to a solution of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride **Intermediate 207** (102 mg, 0.48 mmol) and CuI (12.2 mg, 64.1 μ mol) in THF (1.263 mL). Pd(PPh₃)₂Cl₂ (23.0 mg, 32.8 μ mol) was added followed by TEA (0.269 mL, 1.93 mmol) and the mixture was evacuated and refilled with N₂ (g) three times. The reaction mixture was stirred at rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to grant a mixture of the title compounds as brown solid. MS (ESI) *m/z* [M+H]⁺ 664.7 and 488.5.

Step b) (3*R*,4*S*)-4-Methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and

(3*R*,4*S*)-4-methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

Hydrazine hydrate (aq, 78 μ L, 1.60 mmol) was added to a solution containing a mixture of (3*R*,4*S*)-4-methoxy-4-(3-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and 3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)prop-2-yn-1-one

Example 74 Step a) (0.156 g, 0.32 mmol) in EtOH (2.38 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to grant a mixture of the title compounds. MS (ESI) *m/z* [M+H]⁺ 502.4 and 678.4.

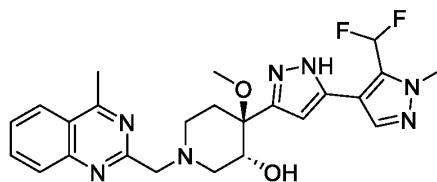
Step c) (3*R*,4*S*)-4-Methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

LiOH (30.7 mg, 1.28 mmol) was added to a solution containing a mixture of (3*R*,4*S*)-4-methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-

methylquinazolin-2-yl)methyl)piperidin-3-yl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and (3*R*,4*S*)-4-methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol (217 mg, 0.32 mmol) in THF (3 mL) and water (1 mL). The reaction was stirred at rt for 2 h and then heated to reflux for 1 h. The reaction mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were filtered through a phase separator and concentrated. The crude residue was purified by preparative HPLC, PrepMethod O, (gradient: 12-17%), to grant the title compound (22.3 mg, 14%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.94 (1H, m), 2.29 (1H, m), 2.81 (1H, m), 2.89 (3H, s), 2.92 (3H, s), 3.71–3.88 (3H, m), 4.00 (3H, m), 4.19 (2H, m), 4.85 (1H, m), 6.34 (1H, s), 7.70 (1H, m), 7.80 (1H, s), 7.91–7.98 (2H, m), 8.24 (1H, m), 12.78 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₇F₃N₇O₂: 502.2172, found: 502.2166.

Example 75

(3*R*,4*S*)-4-(5'-(Difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



Step a) (3*R*,4*S*)-4-(3-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate and 1-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

A solution of (3*R*,4*S*)-4-ethynyl-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol **Intermediate 206** (300 mg, 0.96 mmol) in THF (7.49 mL) was added to a solution of 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonyl chloride **Intermediate 208** (243 mg, 1.25 mmol) and CuI (36.7 mg, 0.19 mmol) in THF (3.75 mL). Pd(PPh₃)₂Cl₂ (69.0 mg, 0.10 mmol) was added followed by TEA (0.806 mL, 5.78 mmol) and the mixture was evacuated and refilled with N₂ (g) three times. The reaction mixture was heated to 55 °C for 3 h and allowed to cool to rt overnight. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄ and

concentrated to grant a mixture of the title compounds as a brown solid. MS (ESI) m/z $[M+H]^+$ 470.3 and 628.3.

Step b) (3*R*,4*S*)-4-(5'-(Difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate and

(3*R*,4*S*)-4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol.

1 M Hydrazine in THF (1.44 mL, 1.44 mmol) was added to a solution containing a mixture of (3*R*,4*S*)-4-(3-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-yn-1-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate and 1-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Example 75 Step a) (0.451 g, 0.96 mmol) in EtOH (8 mL) at 0 °C and the reaction mixture was stirred at rt for 2 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with

EtOAc. The combined organic layers were filtered through a hydrophobic frit and concentrated to grant a mixture of the title compounds. MS (ESI) m/z $[M+H]^+$ 484.4 and 642.5

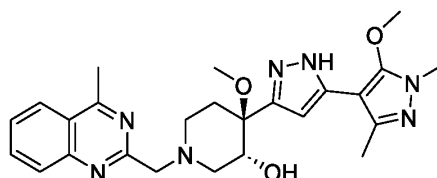
Step c) (3*R*,4*S*)-4-(5'-(Difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

LiOH (75 mg, 3.13 mmol) was added to a solution containing a mixture of (3*R*,4*S*)-4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-yl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate and (3*R*,4*S*)-4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

Example 75 Step b) (616 mg, 0.96 mmol) in THF (3.0 mL) and water (1.0 mL) and the reaction mixture was heated to reflux for 1 h. The mixture was diluted with sat NaHCO₃ (aq) and extracted with DCM. The combined organic layers were filtered through a phase separator and concentrated. The crude residue was purified by preparative HPLC, PrepMethod W, (gradient: 5-95%), to grant the title compound (17.0 mg, 4%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 2.01 (m, overlapping with solvent), 2.33 (1H, m), 2.64 (1H, m), 2.80 (1H, m), 2.87 (3H, s), 2.90 (3H, s), 2.94 (1H, m), 3.79 (m, overlapping with solvent), 3.9–4.04 (m, overlapping with solvent), 6.48 (1H, s), 7.46–7.61 (1H, m), 7.68 (1H, m), 7.79 (1H, s), 7.9–7.97 (2H, m), 8.12 (2H, s), 8.22 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for C₂₄ H₂₈ F₂ N₇ O₂: 484.2266, found: 484.2258.

Example 76

(3*R*,4*S*)-4-Methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

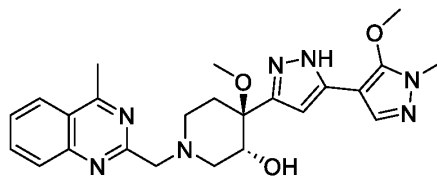


5

Hydrazine hydrate (aq, 163 μ L, 3.35 mmol) was added to a solution of 3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)prop-2-yn-1-one **Intermediate 209** (311 mg, 0.67 mmol) in EtOH (5 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was
 10 diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude residue was dissolved in DMSO and purified by preparative HPLC, PrepMethod R, (gradient: 5–95%), to grant the title compound (63 mg, 20%). $[\alpha]_D^{20}$ -27.6 (c 1, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.9–2 (1H, m), 2.13–2.19 (3H, m), 2.27–2.35 (1H, m), 2.64 (m, overlapping with solvent),
 15 2.82 (1H, m), 2.88 (3H, s), 2.92 (3H, s), 3.56 (overlapping with solvent, m), 3.72–3.9 (6H, m), 6.27 (1H, s), 7.68 (1H, m), 7.89–8.02 (2H, m), 8.22 (1H, m), 12.27–12.65 (1H, m). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₅H₃₂N₇O₃: 478.2562, found: 478.2568.

Example 77

20 (3*R*,4*S*)-4-Methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

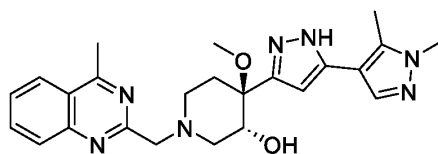


Hydrazine hydrate (aq, 78 μ L, 1.60 mmol) was added to a solution of 3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(5-methoxy-1-methyl-1*H*-
 25 pyrazol-4-yl)prop-2-yn-1-one **Intermediate 210** (144 mg, 0.32 mmol) in EtOH (2.38 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was

diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude residue was dissolved in DMSO and purified by preparative HPLC, PrepMethod T, (gradient: 5-95%), to grant the title compound (18.7 mg, 13%). $[\alpha]_D^{20}$ -25.2 (c 1, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.91–2 (1H, m), 2.26–2.37 (1H, m), 2.49–2.51 (m, overlapping with solvent), 2.65 (m, overlapping with solvent), 2.78–2.85 (1H, m), 2.89 (3H, s), 2.91 (3H, s), 3.64 (3H, s), 3.78 (2H, m), 3.82–3.91 (4H, m), 6.31 (1H, s), 7.58 (1H, s), 7.69 (1H, m), 7.9–7.98 (2H, m), 8.24 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O₃: 464.2404, found: 464.2410.

Example 78

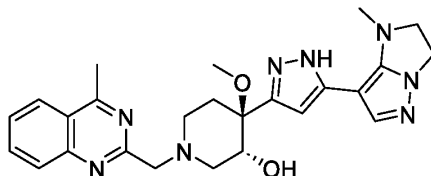
(3*R*,4*S*)-4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



Hydrazine hydrate (aq, 78 μL, 1.60 mmol) was added to a solution of 1-(1,5-dimethyl-1*H*-pyrazol-4-yl)-3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 212** (139 mg, 0.32 mmol) in EtOH (2.38 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, to grant the title compound (18.7 mg, 13%). $[\alpha]_D^{20}$ -20.8 (c 1, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.92–2.01 (1H, m), 2.18–2.37 (1H, m), 2.38–2.41 (overlapping with solvent, m), 2.66–2.72 (overlapping with solvent, m), 2.76–2.86 (1H, m), 2.90 (3H, s), 2.92 (3H, s), 3.74 (3H, s), 3.75–3.82 (2H, m), 3.85 (1H, m), 4.14–4.24 (1H, m), 6.31 (1H, s), 7.59 (1H, s), 7.70 (1H, m), 7.91–8 (2H, m), 8.24 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O₂: 448.2456, found: 448.2460.

Example 79

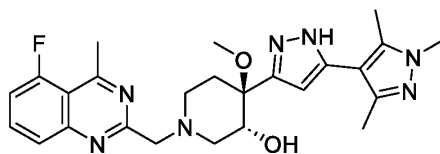
(3*R*,4*S*)-4-Methoxy-4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



Hydrazine hydrate (aq, 78 μ L, 1.60 mmol) was added to a solution of 3-((3*R*,4*S*)-3-hydroxy-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)prop-2-yn-1-one **Intermediate 213** (147 mg, 0.32 mmol) in EtOH (2.38 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was diluted with sat NaHCO₃ (aq) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient: 15–20%), to grant the title compound (26.7 mg, 18%). $[\alpha]_D^{20}$ -42.9 (c 1, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.84–1.94 (1H, m), 2.18–2.3 (1H, m), 2.61 (m, overlapping with solvent), 2.76 (1H, m), 2.86 (3H, s), 2.87 (3H, s), 2.97–3.07 (2H, m), 3.59–3.83 (5H, m), 4.01 (2H, m), 4.52–4.93 (1H, m), 5.95–6.41 (1H, m), 7.4–7.5 (1H, m), 7.66 (1H, m), 7.87–7.94 (2H, m), 8.20 (1H, m), 12.25 (1H, s). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₄H₃₀N₇O₂: 448.2456, found: 448.2460.

Example 80

(3*R*,4*S*)-1-((5-Fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

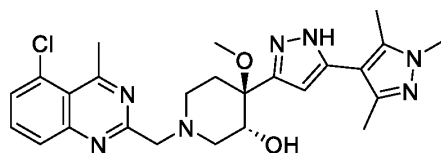


A mixture of 2-(chloromethyl)-5-fluoro-4-methylquinazoline **Intermediate 81** (98 mg, 0.47 mmol), (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl **Intermediate 239** (206 mg, 0.49 mmol) and K₂CO₃ (542 mg, 3.92 mmol) in MeCN (9.8 mL) was heated to 45 °C and stirred overnight. The mixture was filtered and washed with MeCN. The filtrate was concentrated and purified by preparative SFC, PrepMethod L,

(gradient: 20–25%), to grant the title compound (101.5 mg, 43%). $[\alpha]_D^{20}$ -24.2 (c 0.9, MeOH). ^1H NMR (600 MHz, DMSO- d_6) δ 1.83–1.97 (1H, m), 2.15 (3H, s), 2.26 (3H, s), 2.31 (1H, m), 2.62–2.68 (1H, m), 2.79 (1H, m), 2.89 (3H, d), 2.90 (3H, s), 3.14 (2H, s), 3.62 (3H, s), 3.76 (3H, m), 4.13 (1H, m), 6.18 (1H, s), 7.39 (1H, m), 7.71 (1H, m), 7.85 (1H, m), 12.42 (1H, s).
 5 HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{FN}_7\text{O}_2$: 480.2518, found: 480.2518.

Example 81

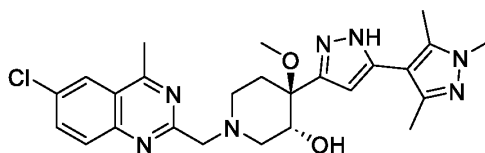
(3*R*,4*S*)-1-((5-Chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



TEA (72.8 μL , 0.52 mmol) was added to a solution of 5-chloro-2-(chloromethyl)-4-methylquinazoline **Intermediate 222** (43.5 mg, 0.19 mmol), (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl **Intermediate 239** (140 mg, 0.17 mmol) and K_2CO_3 (120 mg, 87 mmol) in MeCN (1.7 mL). The reaction mixture was stirred at
 15 rt for 3 h and then heated to 45 °C overnight. The mixture was diluted with MeCN and filtered. The filtrate was purified by preparative SFC, PrepMethod O, (gradient: 25–30%), to grant the title compound (52.1 mg, 60%). $[\alpha]_D^{20}$ -11 (c 1, MeCN). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{ClN}_7\text{O}_2$: 496.2222, found: 496.2226. ^1H NMR (600 MHz, DMSO- d_6) δ 1.86–2.01 (1H, m), 2.18 (3H, s), 2.30 (3H, s), 2.32–2.38 (1H, m), 2.61–2.72 (m, overlapping with
 20 solvent), 2.82 (1H, m), 2.94 (3H, s), 3.14 (3H, s), 3.66 (3H, s), 3.73–3.85 (4H, m), 6.21 (1H, s), 7.77 (1H, m), 7.84 (1H, t), 7.89 (1H, m).

Example 82

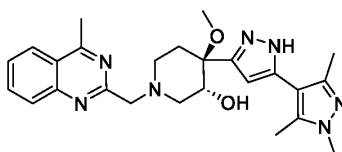
(3*R*,4*S*)-1-((6-Chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



TEA (72.8 μ L, 0.52 mmol) was added to a solution of 6-chloro-2-(chloromethyl)-4-methylquinazoline **Intermediate 62** (43.5 mg, 0.19 mmol), (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl **Intermediate 239** (140 mg, 0.17 mmol) and K₂CO₃ (120 mg, 87 mmol) in MeCN (1.7 mL). The reaction mixture was stirred at
 5 rt for 3 h and then heated to 45 °C overnight. The mixture was diluted with MeCN, filtered and concentrated. The crude residue was purified by preparative SFC, PrepMethod Y, (gradient 25–30%), to grant the title compound (36.8 mg, 45%). $[\alpha]_D^{20}$ -40 (c 1, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.85–1.98 (1H, m), 2.14 (3H, s), 2.26 (3H, s), 2.28–2.33 (1H, m), 2.62–2.67 (m, overlapping with solvent), 2.77 (1H, m), 2.85 (3H, s), 2.90 (3H, s), 3.63
 10 (3H, s), 3.69–3.82 (3H, m), 3.9–4.21 (2H, m), 6.17 (1H, s), 7.91 (2H, m), 8.28 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₁ClN₇O₂: 496.2222, found: 496.2222.

Example 83

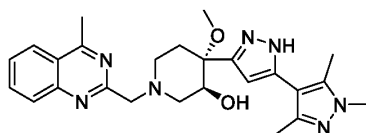
(3*R*,4*S*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol
 15



A mixture of (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl-salt **Intermediate 219** (2.483 g, 6.56 mmol), 2-(chloromethyl)-4-methylquinazoline (1.227 g, 6.30 mmol) and K₂CO₃ (7.26 g, 52.51 mmol) in MeCN (48 mL) were stirred at
 20 °C for 24 h. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure and the residue was purified by preparative SFC, PrepMethod DD, (isocratic 30%), to give the title compound (1.50 g, 50%, 97.8% ee) as white solid after lyophilization. $[\alpha]_D^{20}$ -17.6 (c 1.00, MeCN). ¹H NMR (500 MHz, Methanol-*d*₄) δ 2.05 – 2.37 (7H, m), 2.37 – 2.62 (2H, m), 2.64 – 2.94 (2H, m), 3.00 (3H, s), 3.01–3.11
 25 (4H, s), 3.75 (3H, s), 3.83 – 4.03 (3H, m), 6.30 (1H, s), 7.71 – 7.77 (1H, m), 7.97 – 8.02 (2H, m), 8.30 (1H, dt). ¹³C NMR (126 MHz, CDCl₃) δ 169.04, 161.61, 149.65, 145.46, 137.35, 134.01, 128.77, 127.61, 125.09, 123.08, 110.06, 103.31, 75.07, 70.39, 63.91, 55.06, 55.04, 50.45, 49.20, 36.00, 28.22, 21.74, 13.13, 10.77. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O₂: 462.2612, found: 462.2616

Example 84

(3*S*,4*R*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



5

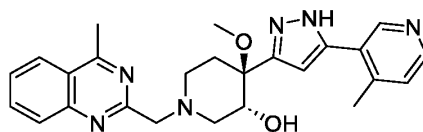
A mixture of (3*S*,4*R*)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl-salt **Intermediate 223** (2.6 g, 6.87 mmol), 2-(chloromethyl)-4-methylquinazoline (1.284 g, 6.60 mmol) and K₂CO₃ (7.60 g, 54.98 mmol) in MeCN (48 mL) was stirred at 60 °C for 24 h. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure to give (2.977 g, 94%) of the crude product. A portion (300 mg) of the crude product was purified by preparative SFC, PrepMethod Y, (gradient of 27–32%), to give the title compound (124.1 mg, 41%). $[\alpha]_D^{20} +58.9$ (c 0.9, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.92 (1H, d), 2.15 (3H, s), 2.26 (3H, s), 2.27–2.35 (1H, m), 2.58 – 2.66 (2H, m), 2.77 – 2.82 (1H, m), 2.83 (3H, s), 2.89 (3H, s), 3.14 (2H, s), 3.62 (3H, s), 3.69–3.89 (3H, m), 6.18 (1H, s), 7.58 – 7.64 (1H, m), 7.86–7.91 (2H, m), 8.12 – 8.16 (1H, m), 12.42 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O₂: 462.2612, found: 462.2642

15

Example 85

(3*R*,4*S*)-4-Methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol

20



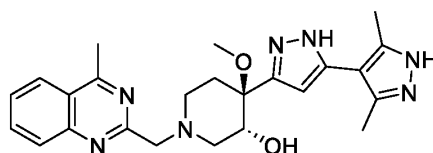
A mixture of 2-(chloromethyl)-4-methylquinazoline (9.1 mg, 0.05 mmol), (3*R*,4*S*)-4-methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol, HCl **Intermediate 227** (24 mg, 0.05 mmol), K₂CO₃ (55.2 mg, 0.40 mmol) and TEA (14 μL, 0.10 mmol) in MeCN (0.485 mL) was stirred at rt overnight. The mixture was filtered and washed with MeOH. The filtrate was concentrated and purified by preparative SFC, PrepMethod C, (gradient 25–30%), to grant the title compound (7.8 mg, 35%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.92–1.99 (1H, m), 2.25–2.34 (1H, m), 2.63–2.68 (1H, m), 2.77–2.82 (1H, m), 2.87 (3H, s), 2.92 (3H, s),

25

3.71–3.87 (3H, m), 4.74–4.94 (1H, m), 6.47–6.6 (1H, m), 7.19–7.37 (1H, m), 7.67 (1H, m), 7.85–7.97 (2H, m), 8.22 (1H, m), 8.26–8.43 (1H, m), 8.51–8.78 (1H, m), 12.71–13.05 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{29}N_6O_2$: 445.2346, found: 445.2348.

5 Example 86

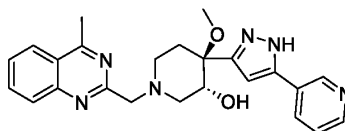
(3*R*,4*S*)-4-(3',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol



TEA (33 μ L, 0.24 mmol) was added to a solution containing K_2CO_3 (82 mg, 0.59 mmol),
 10 (3*R*,4*S*)-4-(3',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidin-3-ol, TFA
Intermediate 233 (80 mg, 0.12 mmol) and 2-(chloromethyl)-4-methylquinazoline (25.2 mg,
 0.13 mmol) in MeCN (1.2 mL) and MeOH (0.1 mL) and the reaction mixture was stirred at rt
 overnight. The mixture was filtered and the solids were washed with MeCN and the filtrate
 was concentrated and purified by preparative HPLC, PrepMethod X, (gradient 5–95%), to
 15 grant the title compound (7.7 mg, 14%). 1H NMR (600 MHz, $DMSO-d_6$) δ 1.89–1.97 (1H,
 m), 2.21 (5H, m), 2.75–2.81 (1H, m), 2.86 (3H, s), 2.87 (3H, s), 3.69–3.86 (m, overlapping
 with solvent), 6.17 (1H, s), 7.67 (1H, m), 7.86–7.96 (2H, m), 8.21 (1H, m). HRMS (ESI) m/z
 $[M+H]^+$ calcd for $C_{24}H_{30}N_7O_2$: 448.2456, found: 448.2458.

20 Example 87

(3*R*,4*S*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol

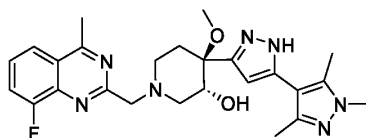


A mixture of (3*R*,4*S*)-4-methoxy-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-3-ol, HCl-salt
 25 **Intermediate 236** (0.074 g, 0.18 mmol), 2-(chloromethyl)-4-methylquinazoline (0.032 g,
 0.17 mmol) and K_2CO_3 (0.194 g, 1.40 mmol) in MeCN (2 mL) was stirred at 42 °C overnight.
 After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was

concentrated under reduced pressure and the residue was redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod C, (gradient of 25–30%), to give the title compound (0.029 g, 38%). $[\alpha]_{\text{D}}^{20}$ -48.8 (*c* 0.9, MeOH). ^1H NMR (600 MHz, DMSO- d_6) δ 1.95 – 2.03 (1H, m), 2.30 – 2.39 (1H, m), 2.66–2.74 (2H, m), 2.80 – 2.85 (1H, m), 2.90 (3H, s), 2.94 (3H, s), 3.13–3.20 (1H, m), 3.70–4.99 (4H, m), 6.79 (1H, s), 7.38–7.44 (1H, m), 7.69 (1H, ddd), 7.89–7.98 (2H, m), 8.13 (1H, dt), 8.21–8.27 (1H, m), 8.47 (1H, dd), 8.98 - 9.03 (1H, m), 12.90 (1H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{27}\text{N}_6\text{O}_2$: 431.2190, found: 431.2192.

Example 88

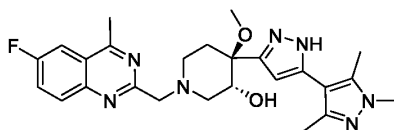
(3*R*,4*S*)-1-((8-Fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



A mixture of (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol, HCl-salt **Intermediate 239** (0.240 g, 0.51 mmol), 2-(chloromethyl)-8-fluoro-4-methylquinazoline **Intermediate 75** (0.103 g, 0.49 mmol) and K_2CO_3 (0.565 g, 4.09 mmol) in MeCN (4.2 mL) was stirred at 42 °C overnight. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure and redissolved in DMSO, filtered, and purified by preparative HPLC, PrepMethod K, (gradient of 0–50%), to give the formate-salt of the title compound (0.135 g, 55%). $[\alpha]_{\text{D}}^{20}$ -28 (*c* 0.9, MeOH). ^1H NMR (600 MHz, DMSO- d_6) δ 2.1 – 2.18 (4H, m), 2.27 (3H, s), 2.42 – 2.49 (1H, m), 2.83 – 2.9 (4H, m), 2.92–3.04 (5H, m), 3.11 – 3.16 (1H, m), 3.64 (3H, s), 3.93 (1H, s), 4.15 (2H, q), 6.22 (1H, s), 7.64 (1H, td), 7.72 – 7.78 (1H, m), 8.01 (1H, d), 8.23 (1H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{FN}_7\text{O}_2$: 480.2518, found: 480.2520.

Example 89

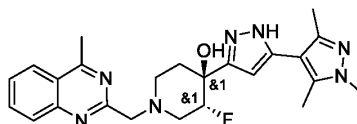
(3*R*,4*S*)-1-((6-Fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



A mixture of (3*R*,4*S*)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrzole]-5-yl)piperidin-3-ol, HCl-salt **Intermediate 239** (0.056 g, 0.18 mmol), 2-(chloromethyl)-6-fluoro-4-methylquinazoline **Intermediate 78** (0.037 g, 0.18 mmol) and K₂CO₃ (0.203 g, 1.47 mmol) in MeCN (2.8 mL) was stirred at 42 °C overnight. After cooling to rt, solids were filtered off and washed with MeCN. The filtrate was concentrated under reduced pressure, redissolved in DMSO, filtered, and purified by preparative SFC, PrepMethod L, (20–25%), to give the title compound (0.042 g, 48%). $[\alpha]_D^{20}$ -33.4 (c 0.9, MeOH). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.88 - 2.00 (1H, m), 2.18 (2H, s), 2.28 - 2.34 (2H, m), 2.79 - 2.84 (1H, m), 2.87 (3H, s), 2.93 (3H, s), 3.17 (6H, d), 3.66 (3H, s), 3.77 – 3.85 (2H, m), 4.14 (2H, q), 6.21 (1H, s), 7.87 (1H, td), 7.99–8.06 (2H, m), 12.43 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₁N₇O₂: 480.2518, found: 480.2518

Example 90

rac-(3*R*,4*S*)-3-Fluoro-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrzole]-5-yl)piperidin-4-ol

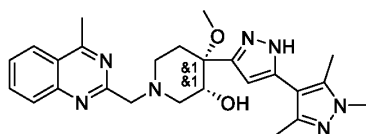


DIPEA (9.98 μL, 0.06 mmol) was added to a mixture of *rac*-(3*R*,4*S*)-3-fluoro-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrzole]-5-yl)piperidin-4-ol **Intermediate 240** (8.4 mg, 0.03 mmol) and 2-(chloromethyl)-4-methylquinazoline (7.3 mg, 0.04 mmol) in DMSO (0.276 mL) and the reaction mixture was stirred at rt for 5 h. The mixture was filtered using a syringe filter and purified by preparative HPLC, PrepMethod D, (gradient of 15–55%), to give the title compound (10 mg, 78%) as a white solid after lyophilization. ¹H NMR (500 MHz, CDCl₃) 1.88 – 1.95 (1H, m), 2.25 (3H, s), 2.27 (3H, s), 2.52 – 2.6 (1H, m), 2.83 – 2.92 (2H, m), 2.94 (3H, s), 2.99 - 3.13 (1H, m), 3.14 - 3.27 (1H, m), 3.71 (3H, s), 4.05 (2H, q), 4.59 (1H, d), 6.27 (1H, d), 7.56 - 7.64 (1H, m), 7.81 - 7.87 (1H, m), 8.01 (1H, d), 8.07 (1H, d). ¹³C NMR (126 MHz, CDCl₃) 168.63, 162.45, 152.95, 149.81, 145.42, 140.30, 137.51, 133.73, 129.02, 127.33, 125.04, 123.01, 109.19, 102.78, 91.81 (J = 181.3), 69.12 (J = 21.9), 64.69, 53.15 (J =

20.0), 48.67, 36.09, 33.97, 21.93, 13.00, 10.62. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}FN_7O$: 450.2412, found: 450.2430

Example 91

5 *rac*-(3*R*,4*R*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



Step a) 4-Methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

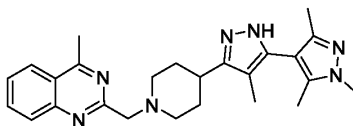
tert-Butyl 3-hydroxy-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 241** (67 mg, 0.17 mmol) was dissolved in DCM (3 mL) and TFA (1 mL, 0.17 mmol) was added. The reaction mixture was stirred at rt for 2 h, MeCN was added and the mixture was concentrated under reduced pressure to give the TFA salt of the title compound.

Step b) *rac*-(3*R*,4*R*)-4-Methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol

2-(Chloromethyl)-4-methylquinazoline (38.2 mg, 0.20 mmol) was added to crude 4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol TFA **Example 91 Step a)** followed by MeCN (1.6 mL) and K_2CO_3 (114 mg, 0.83 mmol). The reaction mixture was stirred at rt overnight and then heated to 50 °C for 6 h. The mixture was cooled to rt and concentrated under reduced pressure. EtOAc and water were added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude compound was purified by preparative HPLC, PrepMethod F, (gradient of 15–55%), to give the title compound (26 mg, 34%) as white solid. 1H NMR (500 MHz, $CDCl_3$) 2.14 – 2.23 (1H, m), 2.29 (3H, s), 2.31 – 2.39 (4H, m), 2.49 (1H, t), 2.59 (1H, t), 2.80 – 2.90 (1H, m), 2.93 (3H, s), 2.99 – 3.07 (1H, m), 3.11 (3H, s), 3.72 (3H, s), 3.99 (2H, s), 4.04 (1H, dd), 5.28 (1H, s), 6.21 (1H, s), 7.55 – 7.62 (1H, m), 7.81 – 7.87 (1H, m), 7.98 – 8.02 (1H, m), 8.03 – 8.09 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{32}N_7O_2$: 462.2612, found: 462.2636

30 Example 92

4-Methyl-2-((4-(1',3',4,5'-tetramethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



Step a) 1',3',4,5'-Tetramethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole

5 *tert*-Butyl 4-(1',3',4,5'-tetramethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 243 (49.0 mg, 0.13 mmol) was dissolved in DCM (1 mL) and TFA (1 mL, 0.13 mmol) was added. The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure to give the crude TFA salt of the title compound.

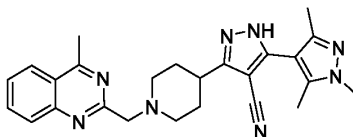
Step b) 4-Methyl-2-((4-(1',3',4,5'-tetramethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline

10 Crude 1',3',4,5'-tetramethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole **Example 92 Step a)** was redissolved in DMSO (1 mL) and 2-(chloromethyl)-4-methylquinazoline (27.8 mg, 0.14 mmol) and DIPEA (0.183 mL, 1.05 mmol) were added. The reaction mixture was stirred at rt overnight, filtered using a syringe filter and purified by preparative HPLC, PrepMethod D, 15 (gradient of 15–55%), to give the title compound (36 mg, 64%) as white solid. ¹H NMR (500 MHz, CDCl₃) 1.83 – 1.92 (5H, m), 1.97 – 2.13 (8H, s), 2.24 – 2.39 (2H, m), 2.64 – 2.74 (1H, m), 2.93 (3H, s), 3.14 – 3.25 (2H, m), 3.70 (3H, s), 3.97 (2H, s), 7.57 (1H, ddd), 7.82 (1H, ddd), 7.99 – 8.03 (1H, m), 8.03 – 8.07 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇: 430.2714, found: 430.2710.

20

Example 93

1',3',5'-Trimethyl-5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'H,2H-[3,4'-bipyrazole]-4-carbonitrile



25 **Step a)** 1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'H,2H-[3,4'-bipyrazole]-4-carbonitrile

tert-Butyl 4-(4-cyano-1',3',5'-trimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate

Intermediate 244 (22.0 mg, 0.06 mmol) was dissolved in DCM (2 mL) and TFA (200 μL,

0.06 mmol) was added. The reaction mixture was stirred at rt for 30 min and then concentrated under reduced pressure to give the TFA salt of the title compound.

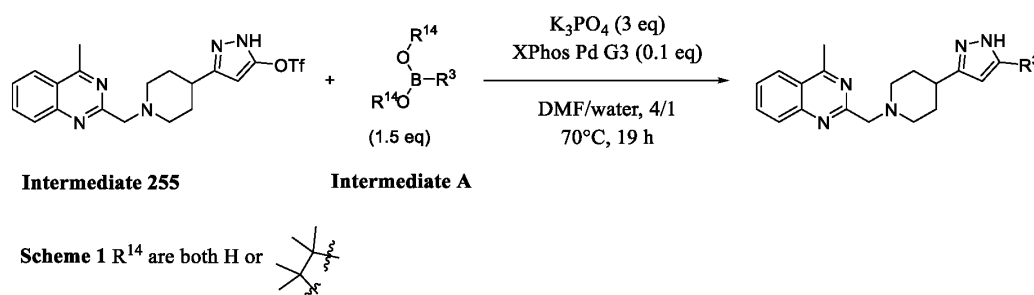
Step b) 1',3',5'-Trimethyl-5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'H,2H-[3,4'-bipyrazole]-4-carbonitrile

Crude 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'H,2H-[3,4'-bipyrazole]-4-carbonitrile **Example 93 Step a)** was redissolved in DMSO (1 mL) and 2-(chloromethyl)-4-methylquinazoline (19.50 mg, 0.10 mmol) was added followed by DIPEA (49.8 μ L, 0.29 mmol). The reaction mixture was stirred at rt overnight and then filtered using a syringe filter. The crude compound was purified by preparative HPLC, PrepMethod W, (gradient of 0–50%), to give the formate-salt of the title compound (16 mg, 51%). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) 1.81 – 1.95 (4H, m), 2.13 (3H, s), 2.22 (3H, s), 2.36 – 2.42 (2H, m), 2.76 – 2.88 (1H, m), 2.93 (3H, s), 3.09 – 3.17 (2H, m), 3.71 (3H, s), 3.92 (2H, s), 7.68 – 7.75 (1H, m), 7.97 – 8.00 (2H, m), 8.12 (2H, s), 8.27 (1H, d). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{29}\text{N}_8$: 441.2510, found: 441.2510.

Example 94-102

The following **Examples 94 to 102** were prepared as described in General Synthesis Scheme 1 and General Preparation Method A from **Intermediate 248** and appropriate boronic acid or boronic ester **Intermediate A** as described below. **Intermediate A** are commercially available if not otherwise stated.

General Synthesis Scheme 1



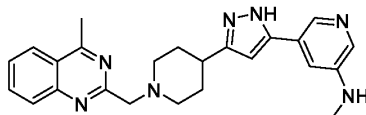
General Preparation Method A

A vial (4 mL) with 5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-3-yl trifluoromethanesulfonate **Intermediate 248** (13.7 mg, 30.0 μ mol), XPhos Pd G3 (2.54 mg,

3.00 μmol), K_3PO_4 (19.1 mg, 90.0 μmol) and appropriate boronic acid/ester (1.5 eq, 45.0 μmol) was placed in a Benchtop Inertion Box with Ar (g) atmosphere. Degassed solvents, DMF (1200 μL) and water (300 μL), were added to the reaction vial which was capped. Outside the benchtop box the reaction was shaken at 70 $^\circ\text{C}$ for 19 h. SILIAMET S THIOL (5 mg) was added and the vial was continued to be shaken at rt for 16 h. The reaction mixture was filtered, rinsed with DCM and solvents were evaporated. The crude product was dissolved in DMSO (300 μL) and purified by preparative HPLC to give the title compound.

Example 94

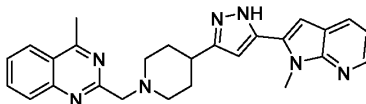
N-Methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-3-amine



Prepared according to **General Preparation Method A** using (5-(methylamino)pyridin-3-yl)boronic acid as **Intermediate A** (6.84 mg, 45.0 μmol) and purified by preparative HPLC, PrepMethod B (gradient 2-94%) to give the title compound (4.4 mg, 35%). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{N}_7$: 414.2400, found: 414.2390; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 1.64 – 1.74 (2H, m), 1.84 – 1.91 (2H, m), 2.23 – 2.31 (2H, m), 2.73 (3H, d), 2.92 (3H, s), 3.00 – 3.05 (2H, m), 3.81 (2H, s), 5.91 (1H, br s), 6.50 (1H, s), 7.18 (1H, s), 7.68 – 7.73 (1H, m), 7.84 (1H, d), 7.94 – 7.98 (2H, m), 8.15 (1H, d), 8.24 – 8.27 (1H, m).

Example 95

4-Methyl-2-((4-(5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



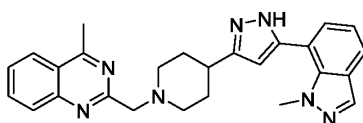
Prepared according to **General Preparation Method A** using (1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)boronic acid as **Intermediate A** (7.92 mg, 45.0 μmol) and purified by preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (5.2 mg, 40%). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{28}\text{N}_7$: 438.2400, found: 438.2396; ^1H NMR

(600 MHz, DMSO- d_6) δ 1.68 – 1.78 (2H, m), 1.88 – 1.94 (2H, m), 2.25 – 2.33 (2H, m), 2.92 (3H, s), 3.02 – 3.07 (2H, m), 3.82 (2H, s), 4.07 (2H, br s), 6.56 (1H, s), 6.73 (1H, s), 7.05 – 7.10 (1H, m), 7.71 (1H, ddd), 7.89 – 7.94 (1H, m), 7.95 – 7.99 (2H, m), 8.21 – 8.28 (2H, m), 12.89 (1H, s).

5

Example 96

4-Methyl-2-((4-(5-(1-methyl-1H-indazol-7-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

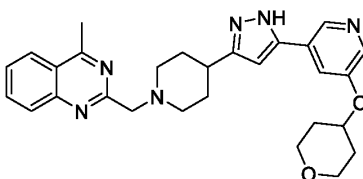


- 10 Prepared according to **General Preparation Method A** using (1-methyl-1H-indazol-7-yl)boronic acid as **Intermediate A** (7.92 mg, 45.0 μ mol) and purified by preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (3.0 mg, 23%). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₆H₂₈N₇: 438.2400, found: 438.2396; ¹H NMR (600 MHz, DMSO- d_6) δ 1.68 – 1.78 (2H, m), 1.93 (2H, d), 2.26 – 2.33 (2H, m), 2.92 (3H, s), 3.03 (2H, d), 3.73 – 3.84 (4H, m), 6.33 (1H, s), 7.15 (1H, dd), 7.31 (1H, dd), 7.71 (1H, ddd), 7.74 – 7.80 (1H, m), 7.94 – 7.98 (2H, m), 8.10 (1H, s), 8.24 – 8.28 (1H, m), 12.81 (1H, br s).
- 15

Example 97

4-Methyl-2-((4-(5-(5-((tetrahydro-2H-pyran-4-yl)oxy)pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

20

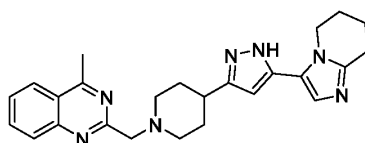


- Prepared according to **General Preparation Method A** (5-((tetrahydro-2H-pyran-4-yl)oxy)pyridin-3-yl)boronic acid as **Intermediate A** (10.04 mg, 45.0 μ mol) and purified by preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (4.8 mg, 33%). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₈H₃₃N₆O₂: 485.2660, found: 485.2658; ¹H NMR (600 MHz, DMSO- d_6) δ 1.56 – 1.65 (2H, m), 1.66 – 1.74 (2H, m), 1.88 (2H, d), 1.99 (2H, d), 2.24 – 2.32 (2H, m), 2.92 (3H, s), 3.03 (2H, d), 3.46 – 3.53 (2H, m), 3.82 (2H, s), 3.83 – 3.89
- 25

(2H, m), 4.69 – 4.75 (1H, m), 6.64 (1H, s), 7.66 – 7.74 (2H, m), 7.94 – 7.98 (2H, m), 8.20 (1H, d), 8.24 – 8.28 (1H, m), 8.56 (1H, s), 12.77 (1H, br s).

Example 98

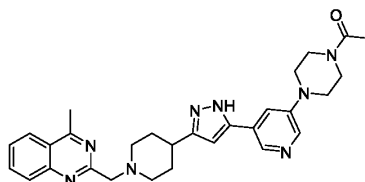
5 4-Methyl-2-((4-(5-(5,6,7,8-tetrahydroimidazo[1,2- α]pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



Prepared according to **General Preparation Method A** using (5,6,7,8-tetrahydroimidazo[1,2- α]pyridin-3-yl)boronic acid as **Intermediate A** (7.47 mg, 45.0 μ mol) and purified by
10 preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (1.4 mg, 11%). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{30}N_7$: 428.2558, found: 428.2566

Example 99

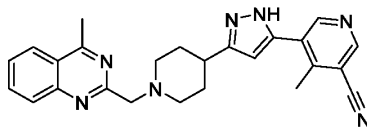
15 1-(4-(5-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-3-yl)piperazin-1-yl)ethan-1-one



Prepared according to **General Preparation Method A** using (5-(4-acetylpiperazin-1-yl)pyridin-3-yl)boronic acid as **Intermediate A** (11.21 mg, 45 μ mol) and purified by
preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (1.2 mg, 8%).
20 HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{29}H_{35}N_8O$: 511.2928, found: 511.2936

Example 100

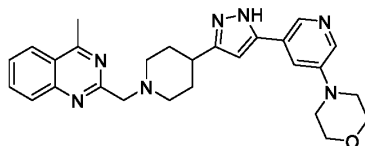
4-Methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)nicotinonitrile



Prepared according to **General Preparation Method A** using 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile as **Intermediate A** (10.98 mg, 45 μ mol) and purified by preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (1.7 mg, 13%). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{26}N_7$: 424.2244, found: 424.2238

Example 101

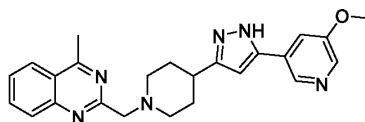
4-(5-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)pyridin-3-yl)morpholine



Prepared according to **General Preparation Method A** using (5-morpholinopyridin-3-yl)boronic acid as **Intermediate A** (9.36 mg, 45.0 μ mol) and purified by preparative HPLC, PrepMethod B, (gradient 2-94%) to give the title compound (7.7 mg, 53%). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{32}N_7O$: 470.2662, found: 470.2662; 1H NMR (600 MHz, $DMSO-d_6$) δ 1.64 – 1.74 (2H, m), 1.89 (2H, d), 2.25 – 2.31 (m, partial overlap with solvent), 2.92 (3H, s), 3.02 (2H, d), 3.18 – 3.23 (4H, m), 3.74 – 3.78 (4H, m), 3.81 (2H, s), 6.62 (1H, s), 7.60 (1H, dd), 7.68 – 7.73 (1H, m), 7.95 – 7.98 (2H, m), 8.20 (1H, d), 8.24 – 8.28 (1H, m), 8.31 (1H, br s), 8.42 (1H, d).

Example 102

2-((4-(5-(5-Methoxypyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

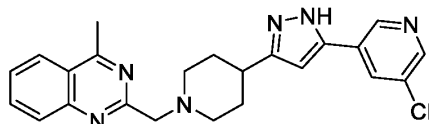


Prepared according to **General Preparation Method A** using (5-methoxypyridin-3-yl)boronic acid as **Intermediate A** (6.88 mg, 45.0 μ mol) and purified by preparative HPLC,

PrepMethod B, (gradient 2-94%) to give the title compound (0.3 mg, 2.4%). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}N_6O$: 415.2240, found: 415.2252

Example 103

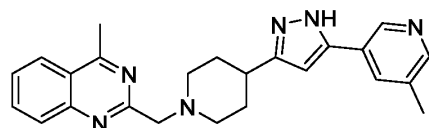
5 2-((4-(5-(5-Chloropyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline



2-(Chloromethyl)-4-methylquinazoline (0.436 g, 2.26 mmol) was added to mixture of 3-chloro-5-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 37** (1.11 g, 2.26 mmol) and K_2CO_3 (1.25 g, 9.05 mmol) in DMSO (9 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was filtered, and the filtrate purified by preparative HPLC, PrepMethod D, (gradient 15–60%), to grant the title compound (230.8 mg, 24%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.34 (s, 1H), 7.95 – 7.98 (m, 2H), 7.91 (d, 1H), 7.75 (m, 1H), 7.50 (m, 1H), 6.30 (s, 1H), 3.88 (s, 2H), 3.06 (d, 2H), 2.84 (s, 3H), 2.68 (m, 1H), 2.14 – 2.21 (m, 2H), 1.85 – 1.91 (m, 4H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{24}ClN_6$: 419.1746, found: 419.1740.

Example 104

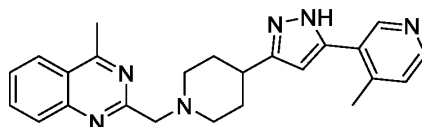
4-Methyl-2-((4-(5-(5-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



20 A vial was charged with 2-((4-(5-(5-chloropyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline **Example 103** (38.1 mg, 0.09 mmol), S-Phos (12.4 mg, 0.03 mmol) and $Pd(OAc)_2$ (3.6 mg, 0.02 mmol) and transferred into a glovebox. Cs_2CO_3 (89.0 mg, 0.27 mmol) was added followed by 1,4-dioxane (0.48 mL) and trimethylboroxine (12.7 μ L, 0.09 mmol). The vial was removed from the glove box. Degassed water (0.120 mL) was added, and the reaction mixture was stirred and heated to 100 $^{\circ}C$ for 18 h. The mixture was cooled to rt, diluted with DCM, passed through a phase separator and concentrated. The resulting residue was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (20.9 mg, 58%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ 8.81

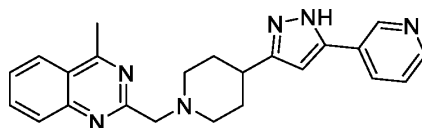
(s, 1H), 8.36 (s, 1H), 8.07 – 8.1 (m, 1H), 8.03 (m, 1H), 7.84 – 7.9 (m, 2H), 7.61 (m, 1H), 6.40 (s, 1H), 3.97 (s, 2H), 3.17 (d, 2H), 2.96 (s, 3H), 2.77 (m, 1H), 2.34 (s, 3H), 2.26 – 2.33 (m, 2H), 1.95 – 2.01 (m, 4H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}N_6$: 399.2292, found: 399.2284.

5

Example 1054-Methyl-2-((4-(5-(4-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

DIPEA (150 μ L, 0.86 mmol) was added to a solution containing 4-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 34** (77.0 mg, 0.16 mmol) and 2-(chloromethyl)-4-methylquinazoline (59.0 mg, 0.31 mmol) in DMSO (1 mL). The reaction mixture was stirred at rt for 2 h and then filtered with a syringe filter. The filtrate was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (46.3 mg, 71%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.32 (d, 1H), 8.03 (d, 1H), 7.98 (d, 1H), 7.80 (m, 1H), 7.55 (m, 1H), 7.06 (m, 1H), 6.20 (s, 1H), 3.94 (s, 2H), 3.13 (m, 2H), 2.90 (s, 3H), 2.65 – 2.76 (m, 1H), 2.39 (s, 3H), 2.21 – 2.28 (m, 2H), 1.88 – 2.01 (m, 4H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}N_6$: 399.2292, found: 399.2284

15

Example 1064-Methyl-2-((4-(5-(pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

25

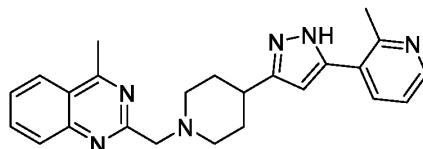
K_2CO_3 (363 mg, 2.63 mmol), KI (36.4 mg, 0.22 mmol) and 2-(chloromethyl)-4-methylquinazoline (422 mg, 2.19 mmol) were added to a solution of 3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine **Intermediate 18** (500 mg, 2.19 mmol) in DMSO (15 mL) and the reaction mixture was stirred at rt for 16 h. The crude product was purified by preparative HPLC, PrepMethod E, (gradient 22–35%), to grant the title compound (693 mg, 82%) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 1.71 (2H, m), 1.90 (2H, m), 2.29 (2H, t), 2.68 (1H, m), 2.93 (3H, s), 3.04 (2H, m), 3.82 (2H, s), 6.61 (1H, s), 7.41 (1H, m), 7.72 (1H, m),

7.94 – 8.00 (2H, m), 8.11 (1H, m), 8.27 (1H, m), 8.47 (1H, m), 8.98 (1H, m), 12.79 (1H, s).

HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{25}N_6$: 385.2136, found: 385.2146.

Example 107

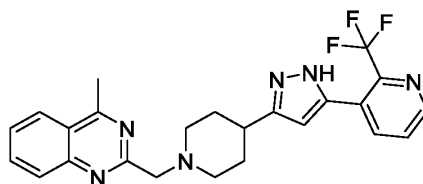
5 4-Methyl-2-((4-(5-(2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



K_2CO_3 (52.5 mg, 0.38 mmol), KI (0.631 mg, 3.80 μ mol) and 2-(chloromethyl)-4-methylquinazoline (8.1 mg, 0.04 mmol) were added to a solution of 2-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine, TFA **Intermediate 41** (9.2 mg, 42 μ mol) in DMSO (1 mL) and the reaction mixture was stirred at rt overnight. The crude product was purified by preparative HPLC, PrepMethod D, (gradient 15–55%), to grant the title compound (10.7 mg, 71%) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.5 (m, 1H), 8.1 (d, 1H), 8.0 (d, 1H), 7.9 (m, 1H), 7.8 (m, 1H), 7.6 (m, 1H), 7.1 (m, 1H), 6.3 (s, 1H), 4.0 (s, 2H), 3.2 (m, 2H), 3.0 (s, 3H), 2.8 (m, 1H), 2.7 (s, 3H), 2.3 – 2.4 (m, 2H), 1.9 – 2 (m, 4H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}N_6$: 399.2292, found: 399.2302.

Example 108

4-Methyl-2-((4-(5-(2-(trifluoromethyl)pyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline

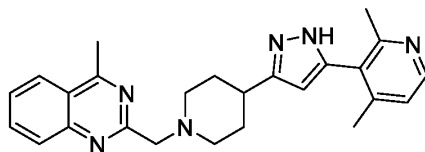


20 K_2CO_3 (4.5 mg, 32.6 μ mol), KI (1.1 mg, 6.63 μ mol) and 2-(chloromethyl)-4-methylquinazoline (1.4 mg, 7.28 μ mol) were added to a solution of 3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)-2-(trifluoromethyl)pyridine, TFA **Intermediate 251** (1.8 mg, 6.56 μ mol) in DMSO (0.4 mL) and the reaction mixture was stirred at rt overnight. The crude product was purified by preparative HPLC, PrepMethod D, (gradient 20–30%), to grant the title compound (0.9 mg, 30%). 1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, 1H), 8.13 (d, 1H), 8 – 8.08 (m, 2H),

7.93 (t, 1H), 7.69 (t, 1H), 7.53 (m, 1H), 6.36 (s, 1H), 4.46 (s, 2H), 3.67 – 3.8 (m, 2H), 3.01 – 3.16 (m, 3H), 2.97 (s, 3H), 2.45 – 2.58 (m, 2H), 2.14 – 2.27 (m, 2H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{24}F_3N_6$: 453.2008, found: 453.2018.

5 Example 109

2-((4-(5-(2,4-Dimethylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

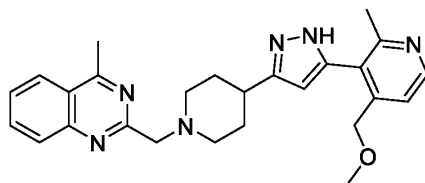


K_2CO_3 (108 mg, 0.78 mmol) was added to 2,4-dimethyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine, TFA **Intermediate 52** (200 mg, 0.78 mmol) and 2-(chloromethyl)-4-methylquinazoline (150 mg, 0.78 mmol) in MeOH (4 mL) at 20 °C under an atmosphere of N_2 (g) and the reaction mixture was stirred at 60 °C for 1 h. The mixture was filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC, PrepMethod H, (gradient: 1–12%) to afford the title compound (80 mg, 25%) as a tan solid.

1H NMR (400 MHz, Methanol- d_4) δ 8.40 – 8.34 (m, 3H), 8.11 – 8.02 (m, 2H), 7.81 (m, 1H), 7.25 (m, 1H), 6.29 (s, 1H), 4.63 (m, 2H), 3.78 (m, 2H), 3.28 (m, 2H), 3.22 – 3.11 (m, 1H), 3.05 (s, 3H), 2.35 (m, 5H), 2.20 (m, 5H). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{29}N_6$: 413.2448, found: 413.2432.

20 Example 110

2-((4-(5-(4-(Methoxymethyl)-2-methylpyridin-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

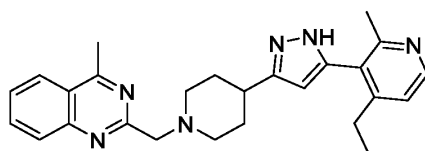


2-(Chloromethyl)-4-methylquinazoline (3.6 mg, 18.70 μ mol), K_2CO_3 (4.7 mg, 34.0 μ mol) and KI (0.3 mg, 1.81 μ mol) were added to a solution of 4-(methoxymethyl)-2-methyl-3-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyridine, TFA **Intermediate 253** (4.9 mg, 17.1 μ mol) in

DMSO (0.5 mL) and the reaction mixture was stirred at rt for 6 h. The mixture was filtered, and the crude filtrate was purified by preparative HPLC, PrepMethod J, (gradient 5–95%), to grant the title compound (5.6 mg, 74%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.71–1.89 (2H, m), 1.91–2.07 (2H, m), δ 2.30 (3H, s), 2.7–2.85 (1H, m), 2.94 (3H, s), 3.24 (3H, s), 4.22 (2H, s), 6.16 (1H, s), 7.30 (1H, d), 7.63–7.8 (1H, m), 7.99 (2H, q), 8.29 (1H, d), 8.38–8.47 (1H, m).
 5 HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₆H₃₁N₆O: 443.2554, found: 443.2572

Example 111

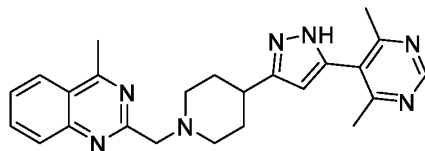
2-({4-[3-(4-Ethyl-2-methylpyridin-3-yl)-1*H*-pyrazol-5-yl]piperidin-1-yl}methyl)-4-
 10 methylquinazoline



K₂CO₃ (17.0 mg, 0.12 mmol), KI (0.7 mg, 4.22 μmol) and 2-(chloromethyl)-4-methylquinazoline (8.5 mg, 44.1 μmol) were added to a solution of 4-ethyl-2-methyl-3-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridine, TFA **Intermediate 255** (15.4 mg, 40.1 μmol) in
 15 DMSO (0.7 mL) and the reaction mixture was stirred at rt for 6 h and then filtered. The crude product was purified by preparative HPLC, PrepMethod J, (gradient 20–30%), to grant the title compound (17.9 mg). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.01 (3H, t), 1.71–1.87 (2H, m), 1.92–2.03 (2H, m), 2.22 (3H, s), 2.38 (2H, q), 2.69–2.82 (1H, m), 2.93 (3H, s), 6.06–6.19 (1H, m), 7.04–7.24 (1H, m), 7.65–7.8 (1H, m), 7.93–8.03 (2H, m), 8.29 (1H, d), 8.32–8.38
 20 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₆H₃₁N₆: 427.2604, found: 427.2596.

Example 112

2-((4-(5-(4,6-Dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-
methylquinazoline

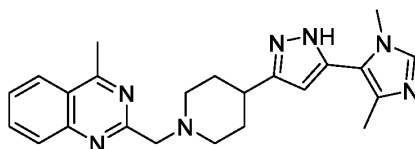


25 DIPEA (26.1 μL, 0.15 mmol) was added to a mixture of 4,6-dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrimidine **Intermediate 11** (12.9 mg, 0.05 mmol) and 2-(chloromethyl)-4-

methylquinazoline (12 mg, 0.06 mmol) in DMSO (0.5 mL) and the reaction mixture was stirred at 20 °C for 4 h. The mixture was filtered using a syringe filter and then purified by preparative HPLC, PrepMethod D, (gradient 15–55%), to grant the title compound (22.6 mg) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 8.08 (m, 1H), 8.02 (m, 1H), 7.86 (m, 1H), 7.61 (m, 1H), 6.07 (s, 1H), 4.00 (s, 2H), 3.13 – 3.32 (m, 2H), 2.96 (s, 3H), 2.79 (p, 1H), 2.29 – 2.41 (m, 8H), 2.01 (m, 4H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₈N₇: 414.2400, found: 414.2408.

Example 113

2-((4-(5-(1,4-Dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline



Step a) 1-(1,4-Dimethyl-1*H*-imidazol-5-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Toluene (1.2 mL) and THF (0.5 mL) were added to a mixture of CuI (6.9 mg, 0.04 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.02 mmol), 2-((4-ethynylpiperidin-1-yl)methyl)-4-methylquinazoline **Intermediate 257** (107 mg, 0.40 mmol) and 1,4-dimethyl-1*H*-imidazole-5-carbonyl chloride **Intermediate 256** (159 mg, 1 mmol) under an atmosphere of N₂ (g). TEA (330 μL, 2.42 mmol) was added and the reaction mixture was stirred for 3 h at rt and then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated to give the crude title compound.

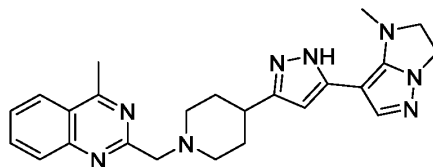
Step b) 2-((4-(5-(1,4-Dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

Crude 1-(1,4-dimethyl-1*H*-imidazol-5-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Example 113 Step a)** was dissolved in EtOH (2 mL) and treated with hydrazine hydrate (aq, 250 μL, 5.14 mmol). The reaction mixture was stirred at rt overnight and then concentrated. The crude residue was purified by preparative HPLC, PrepMethod D, (gradient: 15–55%), to grant the title compound (4.8 mg, 3%) as a clear film. ¹H NMR (500 MHz, CDCl₃) 1.98 – 2.06 (4H, m), 2.30 (3H, s), 2.36 – 2.45 (2H, m), 2.76 – 2.84 (1H, m),

2.97 (3H, s), 3.24 (2H, m), 3.70 (3H, s), 4.02 (2H, s), 6.17 (1H, s), 7.43 (1H, s), 7.62 (1H, m), 7.87 (1H, m), 8.04 (1H, m), 8.09 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{28}N_7$: 402.2400, found: 402.2392.

5 Example 114

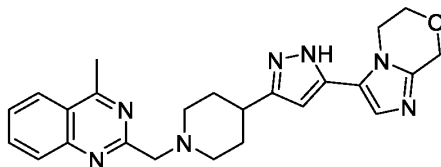
4-Methyl-2-((4-(5-(1-methyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-7-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



Hydrazine hydrate (aq, 50.7 μ L, 0.52 mmol) was added to a solution of 1-(1-methyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-7-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 258** (108 mg, 0.26 mmol) in EtOH (2.55 mL) and the reaction mixture was stirred at rt for 6 h. The mixture was concentrated and purified by preparative HPLC, PrepMethod F, (gradient: 15–55%), to grant the title compound (69.4 mg, 62%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) 1.91 – 2.01 (4H, m), 2.26 – 2.4 (2H, m), 2.72 (1H, m), 2.95 (3H, s), 2.98 (3H, s), 3.18 (2H, m), 3.73 (2H, m), 3.98 (2H, s), 4.12 (2H, m), 6.06 (1H, s), 7.49 (1H, s), 7.59 (1H, m), 7.85 (1H, m), 8.01 – 8.04 (1H, m), 8.07 (1H, m). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{29}N_8$: 429.2510, found: 429.2496.

Example 115

3-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine

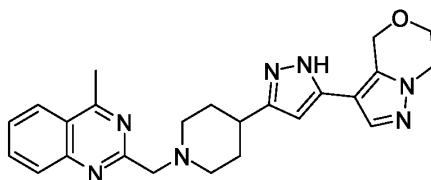


Hydrazine hydrate (aq, 100 μ L, 2.06 mmol) was added to a solution of 1-(5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 260** (291 mg, 0.7 mmol) in EtOH (2.23 mL). The reaction mixture was stirred at rt overnight and then concentrated. The crude compound was purified by

preparative HPLC, PrepMethod F, (gradient: 15–55%), to grant the title compound (20.5 mg, 7%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) 1.92 – 1.98 (4H, m), 2.29 (2H, m), 2.75 (1H, m), 2.95 (3H, s), 3.16 (2H, m), 3.96 (2H, s), 4.02 (2H, t), 4.28 (2H, t), 4.87 (2H, s), 6.19 (1H, s), 7.22 (1H, s), 7.59 (1H, m), 7.85 (1H, m), 8.02 (1H, d), 8.07 (1H, d). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₈N₇O: 430.2350, found: 430.2374.

Example 116

3-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine



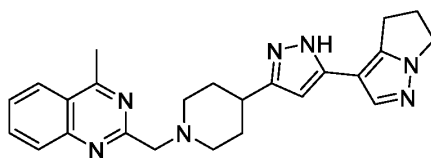
10

Hydrazine hydrate (aq, 20 μL, 0.41 mmol) was added to a solution of 1-(6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 262** (60.8 mg, 0.15 mmol) in EtOH (1 mL). The reaction mixture was stirred at rt for 1.5 h and then concentrated. The residue was dissolved in DMSO and filtered. The crude filtrate was purified by preparative HPLC, PrepMethod F, (gradient: 15–55%), to grant the title compound (34.7 mg, 55%) as a white solid. ¹H NMR (500 MHz, CDCl₃) 1.93 – 2.09 (4H, m), 2.38 – 2.5 (2H, m), 2.77 (1H, m), 2.96 (3H, s), 3.26 (2H, m), 4.05 (2H, s), 4.10 (2H, t), 4.21 (2H, t), 5.02 (2H, s), 6.07 (1H, s), 7.61 (1H, m), 7.72 (1H, s), 7.86 (1H, m), 8.03 (1H, m), 8.08 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₈N₇O: 430.2350, found: 430.2336.

20

Example 117

2-((4-(5-(5,6-Dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

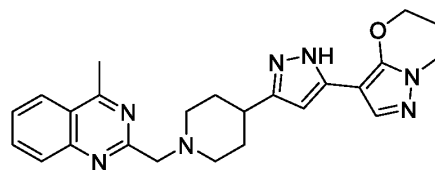


25

Hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added to a solution of 1-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 264** (41.1 mg, 0.10 mmol) in EtOH (1 mL). The reaction mixture was stirred at rt for 3 h and then concentrated. The residue was dissolved in DCM and washed with 1 M NaOH (aq). The organic layer was passed through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod L, (gradient: 20–25%), to grant the title compound (13.3 mg, 31%). ¹H NMR (500 MHz, CDCl₃) 1.91 – 1.99 (4H, m), 2.25 – 2.37 (2H, m), 2.63 – 2.69 (2H, m), 2.72 (1H, m), 2.96 (3H, s), 3 – 3.05 (2H, m), 3.14 – 3.22 (2H, m), 3.97 (2H, s), 4.11 – 4.19 (2H, m), 6.09 (1H, s), 7.60 (1H, m), 7.76 (1H, s), 7.85 (1H, m), 8.01 – 8.06 (1H, m), 8.08 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₈N₇: 414.2400, found: 414.2388.

Example 118

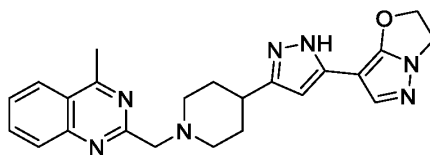
3-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine



Hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added to a solution of 1-(6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazin-3-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 266** (64.0 mg, 0.15 mmol) in EtOH (1 mL). The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was dissolved in DCM and washed with 1 M NaOH (aq). The organic layer was passed through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod C, (gradient: 30–35%), to grant the title compound (29.8 mg, 45%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.61 (2H, m), 1.77 – 1.85 (2H, m), 2.14 – 2.2 (2H, m), 2.23 (2H, m), 2.89 (3H, s), 2.97 (2H, m), 3.77 (2H, s), 4.07 (2H, m), 4.26 – 4.45 (2H, m), 6.02 (1H, s), 7.54 (1H, s), 7.69 (1H, m), 7.95 (2H, s), 8.23 (1H, d), 12.32 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₈N₇O: 430.2350, found: 430.2362.

Example 119

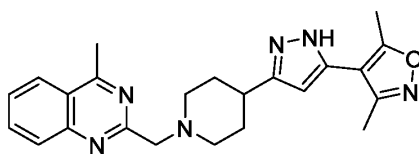
7-(3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)-2,3-dihydropyrazolo[5,1-*b*]oxazole



TFA (1 mL, 0.15 mmol) was added to a solution of *tert*-butyl 4-(5-(2,3-dihydropyrazolo[5,1-*b*]oxazol-7-yl)-1H-pyrazol-3-yl)piperidine-1-carboxylate **Intermediate 267** (53.0 mg, 0.15 mmol) in DCM (3 mL). The mixture was stirred for 30 min at rt, concentrated and redissolved in DMSO (1 mL). 2-(Chloromethyl)-4-methylquinazoline (31.2 mg, 0.16 mmol) and DIPEA (0.128 mL, 0.74 mmol) were added and the reaction mixture was stirred at rt overnight. The mixture was filtered using a syringe filter and the filtrate was purified by preparative HPLC, PrepMethod A, (gradient: 5–45%) and then by preparative HPLC, PrepMethod D, (gradient: 15–55%) to grant the title compound (32.2 mg, 53%) as a white solid. ¹H NMR (500 MHz, CDCl₃) 1.83 – 2 (4H, m), 2.29 (2H, s), 2.64 – 2.74 (1H, m), 2.92 (3H, s), 3.09 – 3.18 (2H, m), 3.95 (2H, s), 4.27 (2H, m), 5.09 (2H, m), 6.07 (1H, s), 7.56 (1H, m), 7.62 (1H, s), 7.82 (1H, m), 7.99 (1H, m), 8.01 – 8.06 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₆N₇O: 416.2194, found: 416.2184.

Example 120

3,5-Dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)isoxazole



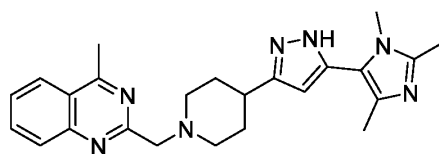
Hydrazine hydrate (aq, 20 μL, 0.41 mmol) was added to a solution of 1-(3,5-dimethylisoxazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 269** (70.2 mg, 0.18 mmol) in EtOH (1 mL). The reaction mixture was stirred at rt for 2 h and then concentrated. The residue was dissolved in DCM and washed with 1 M NaOH (aq). The organic layer was passed through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient: 12–17%), to grant the title compound (35.2 mg, 48%). ¹H NMR

(500 MHz, CDCl₃) 1.94 – 2.01 (4H, m), 2.27 – 2.34 (2H, m), 2.39 (3H, s), 2.52 (3H, s), 2.73 – 2.82 (1H, m), 2.97 (3H, s), 3.19 (2H, m), 3.98 (2H, s), 6.13 (1H, s), 7.61 (1H, m), 7.86 (1H, m), 8.05 (1H, m), 8.09 (1H, m). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₃H₂₇N₆O: 403.2240, found: 403.2246.

5

Example 121

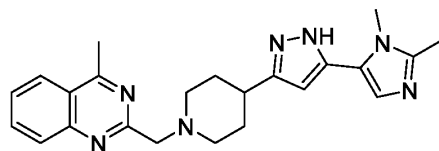
4-Methyl-2-((4-(5-(1,2,4-trimethyl-1H-imidazol-5-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline



- 10 Hydrazine hydrate (aq, 100 μ L, 2.06 mmol) was added to a solution of 3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1,2,4-trimethyl-1H-imidazol-5-yl)prop-2-yn-1-one **Intermediate 271** (157 mg, 0.39 mmol) in EtOH (1.2 mL) and stirred at rt overnight. The reaction mixture was concentrated, the residue was dissolved in DMSO and purified by preparative HPLC, PrepMethod F, (gradient: 15–55%) to grant the title compound (105 mg, 65%) as a white solid. ¹H NMR (500 MHz, CDCl₃) 1.91 – 1.98 (4H, m), 2.19 (3H, s), 2.22 – 2.31 (2H, m), 2.33 (3H, s), 2.68 – 2.78 (1H, m), 2.94 (3H, s), 3.13 (2H, m), 3.49 (3H, s), 3.93 (2H, s), 6.08 (1H, s), 7.59 (1H, m), 7.84 (1H, m), 8.01 (1H, m), 8.06 (1H, m). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₄H₃₀N₇: 416.2558, found: 416.2580.
- 15

20 **Example 122**

2-((4-(5-(1,2-Dimethyl-1H-imidazol-5-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline

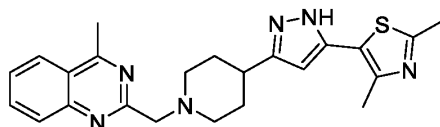


- Hydrazine hydrate (aq, 100 μ L, 2.06 mmol) was added to a solution of 1-(1,2-dimethyl-1H-imidazol-5-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 273** (271 mg, 0.7 mmol) in EtOH (2.23 mL) and the reaction mixture was stirred at rt overnight. The mixture was concentrated, the residue was dissolved in DMSO and
- 25

purified by preparative HPLC, PrepMethod F, (gradient: 15–55%) to grant the title compound (13.4 mg, 5%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.49 (2H, m), 1.68 (2H, m), 2.10 (3H, s), 2.12 – 2.18 (2H, m), 2.43 – 2.49 (1H, m), 2.70 (3H, s), 2.87 (2H, m), 3.48 (3H, s), 3.68 (2H, s), 6.03 (1H, s), 6.78 (1H, s), 7.49 (1H, m), 7.72 – 7.76 (2H, m), 8.04 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇: 402.2400, found: 402.2428.

Example 123

2,4-Dimethyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)thiazole



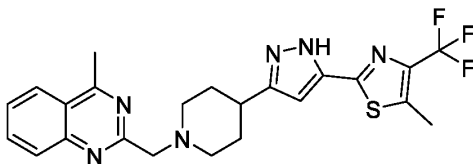
10

TEA (0.138 mL, 0.99 mmol) was added to a solution of K₂CO₃ (227 mg, 1.64 mmol), 2,4-dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)thiazole, HCl **Intermediate 276** and 2-(chloromethyl)-4-methylquinazoline (66.5 mg, 0.35 mmol) in MeCN (4.7 mL) and MeOH (0.5 mL) and the reaction mixture was heated to 45 °C for 18 h. The mixture was diluted with CHCl₃ and MeOH and filtered. The filtrate was concentrated and purified by preparative SFC, PrepMethod U, (gradient: 25–30%), to grant the title compound (2.8 mg, 2%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 2.41 (3H, s), 2.91 (3H, s), 6.19–6.35 (1H, m), 7.72 (1H, m), 7.9–8.03 (2H, m), 8.22–8.33 (1H, m), 12.7–12.84 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₇N₆S: 419.2012, found: 419.2012.

20

Example 124

5-Methyl-2-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-4-(trifluoromethyl)thiazole

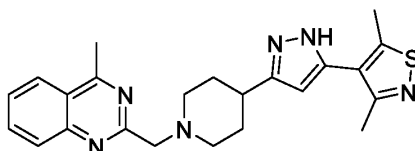


TEA (40.0 μL, 0.29 mmol) was added to a solution of K₂CO₃ (49.5 mg, 0.36 mmol), 5-methyl-2-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)-4-(trifluoromethyl)thiazole, HCl **Intermediate 279** (42 mg, 0.07 mmol) and 2-(chloromethyl)-4-methylquinazoline (16.6 mg, 0.09 mmol) in

MeCN (1.2 mL) and MeOH (127 μ L) and the reaction mixture was heated to 45 $^{\circ}$ C for 18 h. The mixture was filtered and the solids was washed with MeCN. The filtrate was concentrated and purified by preparative HPLC, PrepMethod X, (gradient: 5-95%), to grant the title compound (13.8 mg, 41%). ^1H NMR (600 MHz, DMSO- d_6) δ 1.63 (2H, m), 1.77–1.85 (2H, m), 2.22 (2H, m), 2.88 (3H, s), 2.97 (2H, m), 3.76 (2H, s), 6.26 (1H, s), 7.61–7.74 (1H, m), 7.92 (2H, m), 8.17–8.27 (1H, m), 12.91–13.14 (1H, m). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{F}_3\text{N}_6\text{S}$: 473.1730, found: 473.1746.

Example 125

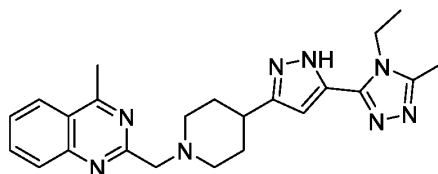
3,5-Dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1H-pyrazol-5-yl)isothiazole



TEA (28.3 μ L, 0.20 mmol) was added to a solution of K_2CO_3 (35.1 mg, 0.25 mmol), 3,5-dimethyl-4-(3-(piperidin-4-yl)-1H-pyrazol-5-yl)isothiazole, HCl **Intermediate 283** (29.6 mg, 0.05 mmol) and 2-(chloromethyl)-4-methylquinazoline (11.7 mg, 0.06 mmol) in MeCN (0.9 mL) and MeOH (0.1 mL) and the reaction mixture was heated to 45 $^{\circ}$ C for 18 h. The mixture was diluted with MeCN and filtered. The filtrate was concentrated and purified by preparative HPLC, PrepMethod X, (gradient: 5–95%), to grant the title compound (8.1 mg, 38%). ^1H NMR (600 MHz, DMSO- d_6) δ 1.66 (2H, m), 1.8–1.93 (2H, m), 2.23 (2H, m), 2.88 (3H, s), 2.98 (2H, m), 3.77 (2H, s), 6.22 (1H, s), 7.67 (1H, m), 7.92 (2H, m), 8.22 (1H, m), 12.61–12.84 (1H, m). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{N}_6\text{S}$: 419.2012, found: 419.1988.

Example 126

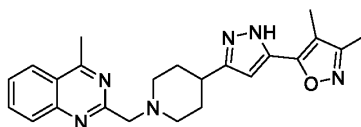
2-((4-(5-(4-Ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-1H-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline



2-Methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole **Intermediate 289** (12 mg, 0.032 mmol) was dissolved in AcOH (0.8 mL) and cooled in an ice-bath. Ethanamine (0.160 mL, 0.32 mmol) was added and the reaction mixture was heated in a microwave reactor to 110°C for 20 min and then to 150°C for 30 min. The solvent was removed under reduced pressure, diluted with EtOAc and washed with sat NaHCO₃ (aq). The organic layers were filtered through and phase separator and concentrated. Two more batches of crude product were prepared as described above. The crude products from the three batches were combined and purified by preparative SFC, PrepMethod U, (gradient: 30–35%), to grant the title compound (4.4 mg, 10%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 1.26 (3H, m), 1.65–1.73 (2H, m), 1.89 (2H, m), 2.28 (2H, m), 2.40 (3H, s), 2.92 (3H, s), 3.03 (2H, m), 3.81 (2H, s), 4.11 (2H, m), 4.31 (2H, m), 6.51 (1H, s), 7.69–7.73 (1H, m), 7.94–7.99 (2H, m), 8.26 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₉N₈: 417.2510, found: 417.2524.

Example 127

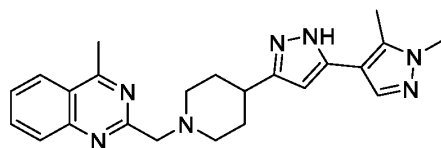
3,4-Dimethyl-5-(5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-3-yl)isoxazole



A mixture of 3,4-dimethyl-5-(3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)isoxazole, TFA-salt **Intermediate 292** (0.087 g, 0.24 mmol), 2-(chloromethyl)-4-methylquinazoline (0.047 g, 0.24 mmol) and DIPEA (0.337 mL, 1.93 mmol) in DMSO (2.2 mL) was stirred at rt overnight. The crude compound was purified by preparative HPLC, PrepMethod FF, (gradient of 15–30%), to give the TFA-salt of the title compound (0.036 g, 29%). ¹H NMR (600 MHz, DMSO-*d*₆) 2.00 – 2.28 (4H, m), 2.34 (3H, s), 2.51 (3H, s), 2.94 – 3.84 (8H, m), 4.76 (2H, s), 6.31 (1H, s), 7.78 – 7.85 (1H, m), 7.98 – 8.10 (2H, m), 8.34 – 8.38 (1H, m), 10.25 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₇N₆O: 403.2240, found: 403.2246

Example 128

2-((4-(1',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

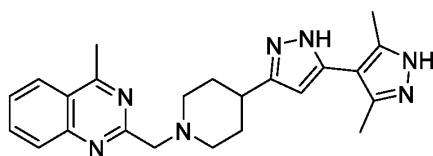


Hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added to a solution of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one

Intermediate 293 (77.8 mg, 0.20 mmol) in EtOH (1 mL). The reaction mixture was stirred at
 5 rt for 2 h and then concentrated. The residue was dissolved in DCM and washed with 1 M NaOH (aq). The solution was passed through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient: 12–17%), to grant the title compound (35.2 mg, 44%), ^1H NMR (500 MHz, CDCl_3) 1.92 – 2 (4H, m), 2.25 – 2.33 (2H, m), 2.43 (3H, m), 2.68 – 2.78 (1H, m), 2.96 (3H, s), 3.14 – 3.2 (2H,
 10 m), 3.81 (3H, s), 3.96 (2H, s), 6.12 (1H, s), 7.57 – 7.62 (2H, m), 7.85 (1H, m), 8.04 (1H, m), 8.08 (1H, m). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_7$: 402.2400, found: 402.2406.

Example 129

2-((4-(3',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
 15 methylquinazoline



Step a) 3',5'-Dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole

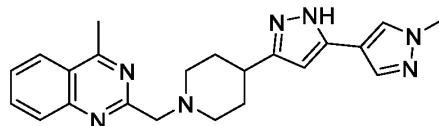
In a sealed reactor, a mixture of *tert*-butyl 4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 27** (48 mg, 0.13 mmol) and pyridine hydrochloride
 20 (154 mg, 1.34 mmol) were heated to 200 $^{\circ}\text{C}$ for 1.5 h. The mixture was cooled to rt and diluted with MeOH. The solution was decanted off and concentrated under reduced pressure to grant the HCl salt of the title compound containing 1',3',5'-trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28**. The crude product was used directly in the following step. MS (ESI) m/z $[\text{M}+\text{H}]^+$ 246.2.

Step b) 2-((4-(3',5'-Dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
 25 **methylquinazoline**

A mixture of 3',5'-dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Example 129** **Step a)** (32 mg, 0.13 mmol), 2-(chloromethyl)-4-methylquinazoline (30 mg, 0.16 mmol) and DIPEA (68 μ L, 0.39 mmol) in DMSO (1.23 mL) was stirred at rt for 3 h. The crude product was purified by preparative SFC, PrepMethod C, (gradient: 27–32%), to grant the title compound (2.9 mg, 6%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.26 (m, 1H), 7.95 – 7.99 (m, 2H), 7.71 (m, 1H), 6.06 (s, 1H), 3.80 (s, 2H), 2.99 – 3.05 (m, 2H), 2.92 (s, 3H), 2.6 – 2.64 (m, overlapping with solvent), 2.22 – 2.31 (m, 8H), 1.84 – 1.91 (m, 2H), 1.61 – 1.75 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇: 402.2400, found: 402.2402.

Example 130

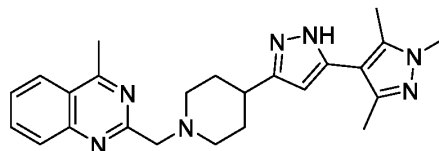
4-Methyl-2-((4-(1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



K₂CO₃ (6.90 g, 50 mmol) was added to a solution of 1'-methyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 296** (4.01 g, 14.91 mmol) and 2-(chloromethyl)-4-methylquinazoline (3.15 g, 16.33 mmol) in DMSO (48 mL) and the reaction mixture was stirred at rt for 18 h. K₂CO₃ (4.6 g, 33.3 mmol) was added and stirring was continued for a further 26 h. The insolubles were removed by filtration and the filtrate was purified by preparative HPLC, PrepMethod A, (gradient: 5–50%), to grant the title compound (3.03 g, 46%) as a colourless powder. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.64 – 12.25 (m, 1H), 8.26 (m, 1H), 7.99 – 7.89 (m, 3H), 7.74 – 7.64 (m, 2H), 6.15 (s, 1H), 3.84 (s, 3H), 3.80 (s, 2H), 3.01 (m, 2H), 2.92 (s, 3H), 2.66 – 2.54 (m, overlapping solvent), 2.26 (t, 2H), 1.85 (m, 2H), 1.65 (m, 2H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₆N₇: 388.2244, found: 388.2244.

Example 131

4-Methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline

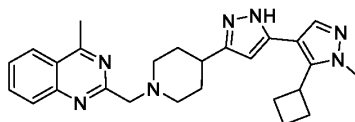


1',3',5'-Trimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl **Intermediate 28** (26.73 g, 80.44 mmol) was added to a turbid solution of 2-(chloromethyl)-4-methylquinazoline (13.887 g, 72.09 mmol) in MeCN (500 mL), followed by addition of K₂CO₃ (44.5 g, 321.7 mmol) and the reaction mixture was heated to 60 °C for 1 d. Further K₂CO₃ (16 g, 116 mmol) was added, and heating was continued for 20 h. Precipitated solids were removed by filtration and set aside. The filtrate was concentrated in vacuo to give a crude foam. The precipitated solids were diluted with water (300 mL) and extracted with DCM (×2). The combined organic layers were washed with a solution of K₂CO₃ (0.5 g, 2.61 mmol) in brine, dried over Na₂SO₄ and concentrated to give a crude foam. The two crude batches were combined and purified by preparative SFC, PrepMethod V, (isocratic: 7%), to grant the title compound (21 g, 70%) as a tan foam. ¹H NMR (500 MHz, DMSO-*d*₆) 1.63 – 1.73 (2H, m), 1.84 – 1.9 (2H, m), 2.18 (3H, s), 2.23 – 2.38 (5H, m), 2.57 – 2.67 (1H, m), 2.93 (3H, s), 3 – 3.05 (2H, m), 3.66 (3H, s), 3.80 (2H, s), 6.05 (1H, s), 7.68 – 7.75 (1H, m), 7.96 – 7.98 (2H, m), 8.25 – 8.29 (1H, m), 12.13 – 12.51 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇: 416.2558, found: 416.2572.

15

Example 132

2-((4-(5'-Cyclobutyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

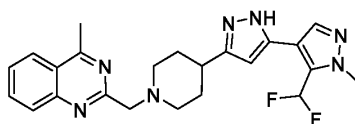


1-(5-Cyclobutyl-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 298** (110.8 mg, 0.26 mmol) was dissolved in EtOH (1 mL) and 64% hydrazine hydrate (aq, 20 μL, 0.41 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1 M NaOH. The organic layer was filtered through a phase separator and concentrated. The residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient of 12–17%), to give the title compound (46 mg, 40%). ¹H NMR (500 MHz, CDCl₃) 1.69 – 1.8 (1H, m), 1.88 – 2.02 (5H, m), 2.15 – 2.34 (6H, m), 2.67 – 2.76 (1H, m), 2.96 (3H, s), 3.12 – 3.20 (2H, m), 3.75 (1H, p), 3.82 (3H, s), 3.96 (2H, s), 6.05 (1H, s), 7.43 (1H, s), 7.59 (1H, ddd), 7.85 (1H, ddd), 8.03 (1H, d), 8.06 – 8.09 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₆H₃₂N₇: 442.2714, found: 442.2726

30

Example 133

2-((4-(5'-(Difluoromethyl)-1'-methyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



5

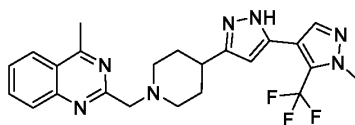
1-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 299** (38.7 mg, 0.09 mmol) was dissolved in EtOH (1 mL) and hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1 M NaOH. The organic layer was filtered through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient of 12–17%), to give the title compound (15 mg, 38%). ¹H NMR (500 MHz, CDCl₃) 1.92 – 2.05 (4H, m), 2.28 – 2.39 (2H, m), 2.70 – 2.80 (1H, m), 2.96 (3H, s), 3.15 – 3.24 (2H, m), 3.99 (2H, s), 4.06 (3H, s), 6.18 (1H, d), 7.44 (1H, t), 7.58 – 7.64 (2H, m), 7.86 (1H, ddd), 8.03 – 8.07 (1H, m), 8.07 – 8.10 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₆F₂N₇: 438.2212, found: 438.2210

15

Example 134

4-Methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline

20



25

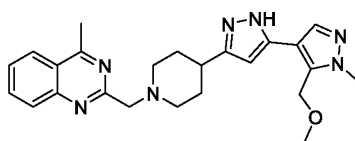
1-(1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 300** (65.7 mg, 0.15 mmol) was dissolved in EtOH (1 mL) and hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1 M NaOH. The solution was filtered through a phase separator and concentrated under reduced pressure. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient of 10–15%), to give the

title compound (30 mg, 45%). ¹H NMR (500 MHz, CDCl₃) 1.91 – 2.02 (4H, m), 2.24 – 2.35 (2H, m), 2.69 – 2.79 (1H, m), 2.96 (3H, s), 3.15 – 3.21 (2H, m), 3.97 (2H, s), 4.01 – 4.08 (3H, m), 6.20 (1H, s), 7.60 (1H, ddd), 7.70 (1H, s), 7.86 (1H, ddd), 8.02 – 8.06 (1H, m), 8.06 – 8.10 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₅F₃N₇: 456.2118, found: 456.2102.

5

Example 135

2-((4-(5'-(Methoxymethyl)-1'-methyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

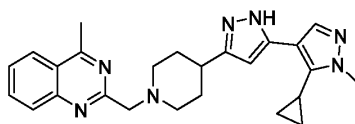


10 1-(5-(Methoxymethyl)-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 302** (63.8 mg, 0.15 mmol) was dissolved in EtOH (1 mL) and hydrazine hydrate (aq, 20 μL, 0.41 mmol) was added. The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1M NaOH. The organic layer was filtered
 15 through a phase separator and concentrated under reduced pressure. The crude product was dissolved in DMSO and purified by preparative SFC, PrepMethod O, (gradient of 12–17%), to give the title compound (21 mg, 32%). ¹H NMR (500 MHz, CDCl₃) 1.9 – 2.02 (4H, m), 2.28 – 2.35 (2H, m), 2.69 – 2.79 (1H, m), 2.97 (3H, s), 3.15 – 3.22 (2H, m), 3.39 (3H, s), 3.93 (3H, s), 3.98 (2H, s), 4.66 (2H, s), 6.18 (1H, s), 7.60 (1H, ddd), 7.65 (1H, s), 7.86 (1H, ddd),
 20 8.03 – 8.07 (1H, m), 8.07 – 8.10 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2508

Example 136

2-((4-(5'-Cyclopropyl-1'-methyl-1*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

25

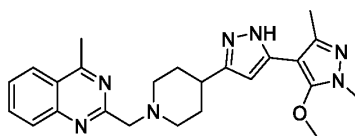


1-(5-Cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 303** (133 mg, 0.32 mmol) was

dissolved in EtOH (1 mL) and hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1M NaOH. The organic layer was filtered through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod C, (gradient of 27–32%), to give the title compound (50 mg, 36%). ¹H NMR (600 MHz, DMSO-*d*₆) 0.50 (2H, s), 0.94 – 1.02 (2H, m), 1.66 (2H, qd), 1.77 – 1.87 (3H, m), 2.18 – 2.29 (2H, m), 2.89 (3H, s), 2.94 – 3.02 (2H, m), 3.77 (2H, s), 3.81 (3H, s), 6.16 (1H, s), 7.53 (1H, s), 7.64 – 7.71 (1H, m), 7.91 – 7.96 (2H, m), 8.19 – 8.24 (1H, dd), 12.41 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₀N₇: 428.2558, found: 428.2574

Example 137

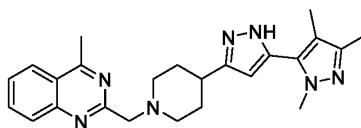
2-((4-(5'-Methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



15 1-(5-Methoxy-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)prop-2-yn-1-one **Intermediate 308** (98 mg, 0.23 mmol) was dissolved in EtOH (1 mL) and hydrazine hydrate (aq, 20 μ L, 0.41 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1 M NaOH. The organic layer was filtered through a phase separator and concentrated. The crude residue was dissolved in DMSO and purified by preparative SFC, PrepMethod C, (gradient of 25–30%), to give the title compound (32 mg, 31%). ¹H NMR (600 MHz, DMSO-*d*₆) 1.66 (2H, qd), 1.79 – 1.91 (2H, m), 2.16 (3H, s), 2.24 (2H, td), 2.89 (3H, s), 3.02 – 2.95 (2H, m), 3.54 (3H, s), 3.69 – 3.87 (5H, m), 6.08 (1H, s), 7.60 – 7.74 (1H, m), 7.87 – 8.03 (2H, m), 8.18 – 8.26 (1H, m), 12.43 (1H, s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₃₀N₇O: 432.2506, found: 432.2512

Example 138

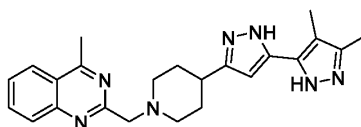
4-Methyl-2-((4-(2',4',5'-trimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline



3-(1-((4-Methylquinazolin-2-yl)methyl)piperidin-4-yl)-1-(1,3,4-trimethyl-1H-pyrazol-5-yl)prop-2-yn-1-one **Intermediate 309** (167 mg, 0.42 mmol) was dissolved in EtOH (1.29 mL) and hydrazine hydrate (aq, 100 μ L, 2.06 mmol) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The crude compound was purified by preparative HPLC, PrepMethod F, (gradient of 15–55%), to give the title compound (100 mg, 58%) as light-yellow solid. ^1H NMR (500 MHz, CDCl_3) 1.80 – 1.96 (7H, m), 2.09 – 2.19 (5H, m), 2.53 – 2.64 (1H, m), 2.88 (3H, s), 3.02 – 3.12 (2H, m), 3.77 (3H, s), 3.89 (2H, s), 6.10 (1H, s), 7.49 – 7.55 (1H, m), 7.7 – 7.81 (1H, m), 7.96 (1H, d), 8.00 (1H, d). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{N}_7$: 416.2558, found: 416.2564

Example 139

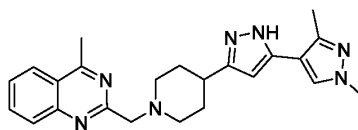
2-((4-(4',5'-Dimethyl-2H,2'H-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



A mixture of 4,5-dimethyl-5'-(piperidin-4-yl)-2H,2'H-3,3'-bipyrazole, TFA-salt **Intermediate 308** (0.224 g, 0.62 mmol), 2-(chloromethyl)-4-methylquinazoline (0.121 g, 0.63 mmol) and DIPEA (0.653 mL, 3.74 mmol) in DMSO (5.5 mL) was stirred at rt overnight. The crude compound was purified by preparative HPLC, PrepMethod C, (gradient: 25–30%), to give the title compound (0.027 g, 11%). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) 1.66 (2H, qd), 1.82 – 1.90 (2H, m), 2.02 – 2.15 (6H, m), 2.20 – 2.29 (2H, m), 2.58 – 2.65 (1H, m), 2.90 (3H, s), 2.95 – 3.03 (2H, m), 3.79 (2H, s), 6.26 (1H, s), 7.66 – 7.72 (1H, m), 7.92 – 7.97 (2H, m), 8.20 – 8.26 (1H, m), 12.46 (2H, s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_7$: 402.2400, found: 402.2414

Example 140

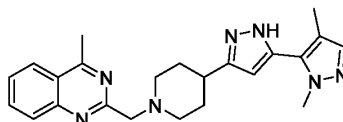
2-((4-(1',3'-Dimethyl-1'H,2H-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



1,3'-Dimethyl-5-(piperidin-4-yl)-1'H,2H-3,4'-bipyrazole, HCl-salt **Intermediate 311** (200 mg, 0.71 mmol) was dissolved in MeOH (8 mL) and 2-(chloromethyl)-4-methylquinazoline (273 mg, 1.42 mmol) and K₂CO₃ (196 mg, 1.42 mmol) were added. The reaction mixture was stirred at 60 °C for 2 h. After cooling to rt, solids were filtered off and washed with MeCN (3x). The filtrate was concentrated under reduced pressure, redissolved in DMSO and purified by preparative HPLC, PrepMethod Q, (gradient of 29–39%), to afford the title compound (0.120 g, 42%) as a white solid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.34 (1H, s), 8.23-8.29 (1H, m), 7.94 – 7.99 (2H, m), 7.74-7.67 (1H, m), 6.09 (1H, s), 3.80 (2H, s), 3.75 (3H, s), 2.97-3.06 (2H, m), 2.86-2.95 (3H, m), 2.55-2.64 (1H, m), 2.16-2.35 (5H, m), 1.80-1.89 (2H, m), 1.66 (2H, qd). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇: 402.2400, found: 402.2376

Example 141

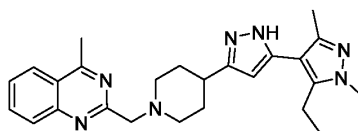
2-((4-(2',4'-Dimethyl-2H,2'H-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



2,4-Dimethyl-5'-(piperidin-4-yl)-2H,2'H-3,3'-bipyrazole, TFA-salt **Intermediate 90** (0.2 g, 0.71 mmol) was dissolved in MeOH (2 mL) and 2-(chloromethyl)-4-methylquinazoline (0.273 g, 1.42 mmol) and K₂CO₃ (0.294 g, 2.13 mmol) were added under an atmosphere of N₂ (g). The reaction mixture was stirred at 60 °C for 1 h. The mixture was poured into brine and extracted with DCM (3×). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod HH, (gradient of 30–100%), to afford the title compound (0.025 g, 9%) as white solid. ¹H NMR (300 MHz, Methanol-*d*₄) δ ppm 1.88 - 2.07 (m, 4 H), 2.09 (s, 3 H), 2.38 - 2.48 (m, 2 H), 2.75 - 2.93 (m, 1 H), 3.02 (s, 3 H), 3.15 - 3.22 (m, 2 H), 3.31 - 3.34 (m, 6 H), 3.88 (s, 3 H), 3.96 (s, 2 H), 6.33 (s, 1 H), 7.33 (s, 1 H), 7.75 (ddd, 1 H), 7.91 - 8.08 (m, 1 H), 7.92 - 8.07 (m, 1 H), 7.97 - 8.05 (m, 1 H), 8.30 (dt, 1 H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇: 402.2400, found: 402.2400

Example 142

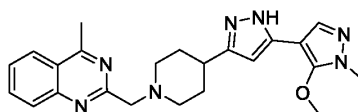
2-((4-(5'-Ethyl-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline



5'-Ethyl-1',3'-dimethyl-5-(piperidin-4-yl)-1'*H*,2*H*-3,4'-bipyrazole, HCl-salt **Intermediate 315** (0.1 g, 0.37 mmol) was dissolved in MeOH (2 mL). 2-(Chloromethyl)-4-methylquinazoline (0.141 g, 0.73 mmol) and K₂CO₃ (0.152 g, 1.10 mmol) were added under an atmosphere of N₂ (g) and the reaction mixture was stirred at 60 °C for 1 h. The mixture was poured into water and extracted with DCM (3×). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod N, (gradient of 25–100%), to afford the title compound (5.00 mg, 3%) as white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.09 (t, 3H), 1.72 (dq, 2H), 1.83 - 1.92 (m, 2H), 2.17 (s, 3H), 2.22 - 2.33 (m, 2H), 2.57 - 2.68 (m, 1H), 2.70 - 2.80 (m, 2H), 2.92 (s, 3H), 2.98 - 3.08 (m, 3H), 3.69 (s, 3H), 3.81 (s, 2H), 6.04 (s, 1H), 7.68 - 7.75 (m, 1H), 7.95 - 7.99 (m, 2H), 8.27 (dt, 1 H), 12.29 (s, 1H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇: 430.2714, found: 430.2710

Example 143

2-((4-(5'-Methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline

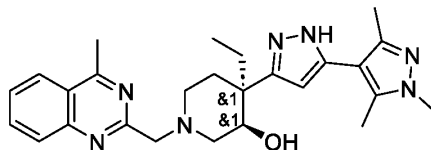


tert-Butyl 4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidine-1-carboxylate **Intermediate 55** (15 mg, 0.04 mmol) was dissolved in MeOH (1 mL) and 4 M HCl in dioxane (104 μL, 0.41 mmol) was added under an atmosphere of N₂ (g). The reaction mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (1 mL) and K₂CO₃ (17.21 mg, 0.12 mmol) and 2-(chloromethyl)-4-methylquinazoline (15.99 mg, 0.08 mmol) were added under an atmosphere of N₂ (g). The

reaction mixture was stirred at 60 °C for 1 h. The mixture was poured into brine and extracted with DCM (3×). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod II, (gradient of 14–100%), to afford the title compound (3 mg, 20%) as white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.67 (dq, 2H), 1.81 - 1.90 (m, 2H), 2.21 - 2.31 (m, 2H), 2.57 - 2.66 (m, 1H), 2.92 (s, 3H), 2.97 - 3.05 (m, 2H), 3.64 (s, 3H) 3.80 (s, 2H), 3.90 (br s, 3 H), 6.14 (s, 1H), 7.53 (br s, 1H) 7.68 - 7.75 (m, 1H), 7.95 - 7.98 (m, 2H), 8.27 (dt, 1H), 12.43 (br s, 1H). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₈N₇O: 418.2350, found: 418.2322.

Example 144

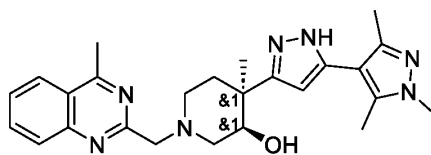
rac-(3*R*,4*S*)-4-Ethyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



DIPEA (1.25 g, 9.69 mmol, 1.69 mL) and 2-(chloromethyl)-4-methylquinazoline (316 mg, 1.65 mmol) were added to *rac*-5-((3*R*,4*R*)-4-ethyl-3-methylpiperidin-4-yl)-1',3',5'-trimethyl-1'*H*,2*H*-3,4'-bipyrazole hydrochloride **Intermediate 323** (800 mg, 1.94 mmol) in DMF (5 mL) and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated, and the residue was purified by preparative HPLC, PrepMethod QQ, (gradient: 13–70%) to give the title compound (178 mg, 20%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 0.63 (3H, s), 1.46 (2H, s), 1.88 (1H, s), 2–2.11 (2H, m), 2.12–2.24 (4H, m), 2.33 (3H, d), 2.73 (2H, s), 2.85 (3H, s), 3.51–3.76 (5H, m), 5.11–5.35 (1H, m), 6.14 (1H, s), 7.67 (1H, ddd), 7.86–7.95 (2H, m), 8.22 (1H, d), 11.74–12.42 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₆H₃₄N₇O: 460.2820, found: 460.2814.

Example 145

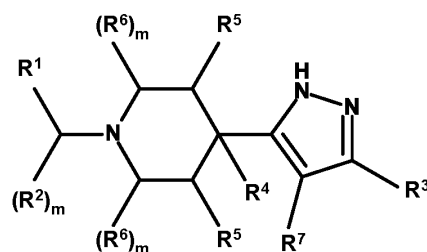
rac-(3*R*,4*S*)-4-Methyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol



DIPEA (1.27 g, 9.82 mmol, 1.71 mL) and 2-(chloromethyl)-4-methylquinazoline (330 mg, 1.72 mmol) were added to *rac*-(3*R*,4*S*)-4-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrzole]-5-yl)piperidin-3-ol hydrochloride **Intermediate 332** (798 mg, 2.46 mmol) in DMF (5 mL) and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated, and the residue was purified by preparative HPLC, PrepMethod QQ, (gradient: 13–70%) to give the title compound (283 mg, 26%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.25 (3H, s), 1.56 (1H, s), 2.03–2.42 (8H, m), 2.59–2.72 (1H, m), 2.76 (1H, s), 2.86 (3H, s), 3.29 (s, partly overlapping with solvent), 3.52 (1H, s), 3.65 (3H, s), 3.73 (2H, d), 4.93–5.24 (1H, m), 6.14 (1H, s), 7.68 (1H, dd), 7.85–8 (2H, m), 8.22 (1H, d), 11.78–12.46 (1H, m). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₅H₃₂N₇O: 446.2662, found: 446.2658.

CLAIMS

1. A compound of Formula (I)



(I)

wherein

5 **R¹** is selected from a 8-, 9- or 10-membered heteroaryl substituted by **R⁸**, **R¹⁰** and 0, 1 or 2 substituents independently selected from **R⁹**;

R² is independently selected from H, CH₃, CH₂F, CHF₂ and CF₃;

R³ is selected from a 5- or 6-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and
 10 0 or 1 substituents independently selected from **R¹³** or a 8-, 9- or 10-membered heteroaryl substituted by **R¹⁰**, 0, 1 or 2 substituents independently selected from **R¹¹**, 0, 1 or 2 substituents independently selected from **R¹²** and 0 or 1 substituents independently selected from **R¹³**,

R⁴ is selected from H, OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl
 15 optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;

R⁵ is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;

R⁶ is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;

R⁷ is selected from H, F, Cl, CN, C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH(CH₃)₂, oxetane, cyPr or cyBu;
 20

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH(CH₃)₂, cyPr, cyBu, CN, F or Cl;

R⁹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -O(oxetane) substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃, -CH(CH₃)₂, CN, F or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹¹ is independently selected from C₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₂alkyl optionally substituted by 1, 2, 3, 4 or 5 F, CH₂OCH₃, CH₂cyPr, cyPr substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃ or cyBu substituted by 0 or 1 substituent selected from F, CH₃, CH₂F, CHF₂ or CF₃;

R¹² is independently selected from CH₃, OH, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃ or CH₂OH;

R¹³ is selected from a 6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃, or -O(6-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently selected from O, S or N) wherein said 6-membered heterocycloalkyl ring is optionally substituted by 0, 1 or 2 substituents independently selected from F, OH, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F, OCHF₂, OCF₃ or (CO)CH₃;

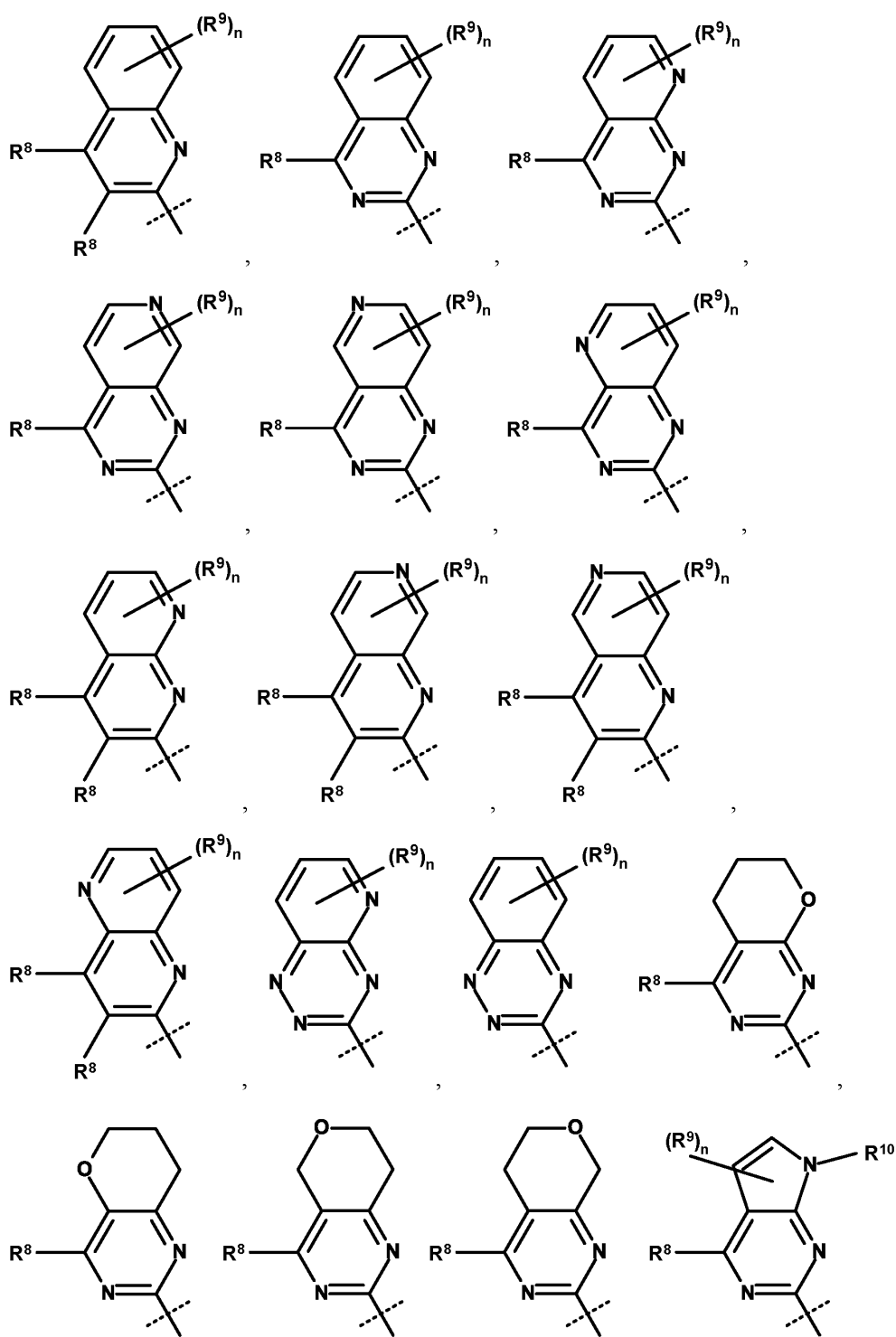
m is independently 0, 1 or 2;

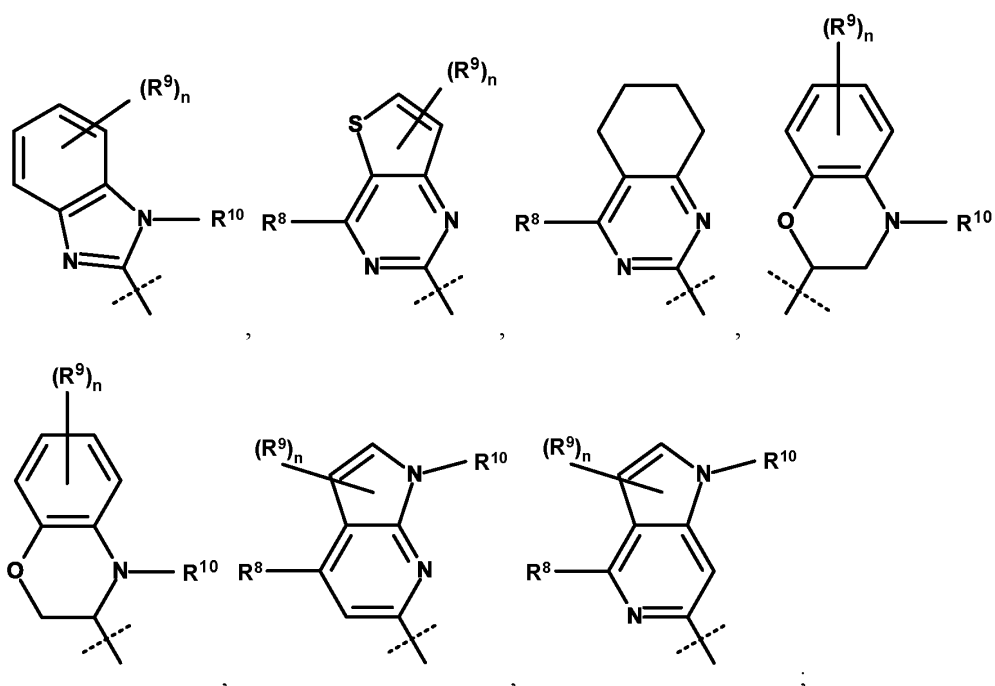
or a pharmaceutically acceptable salt thereof.

25

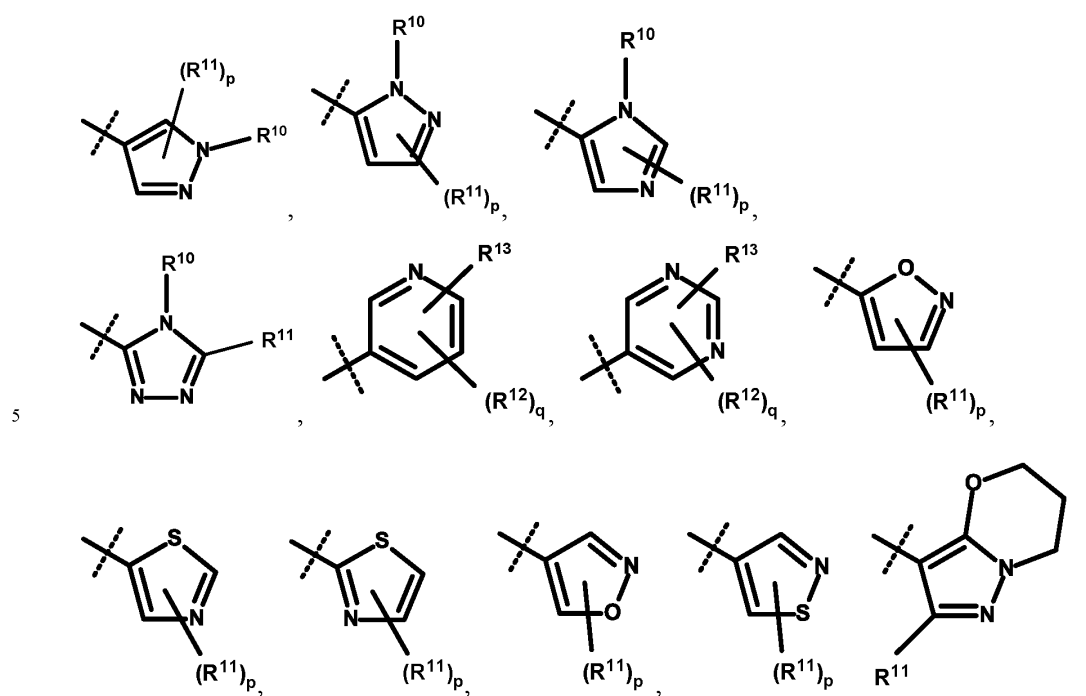
2. A compound according to claim 1 wherein

R¹ is selected from

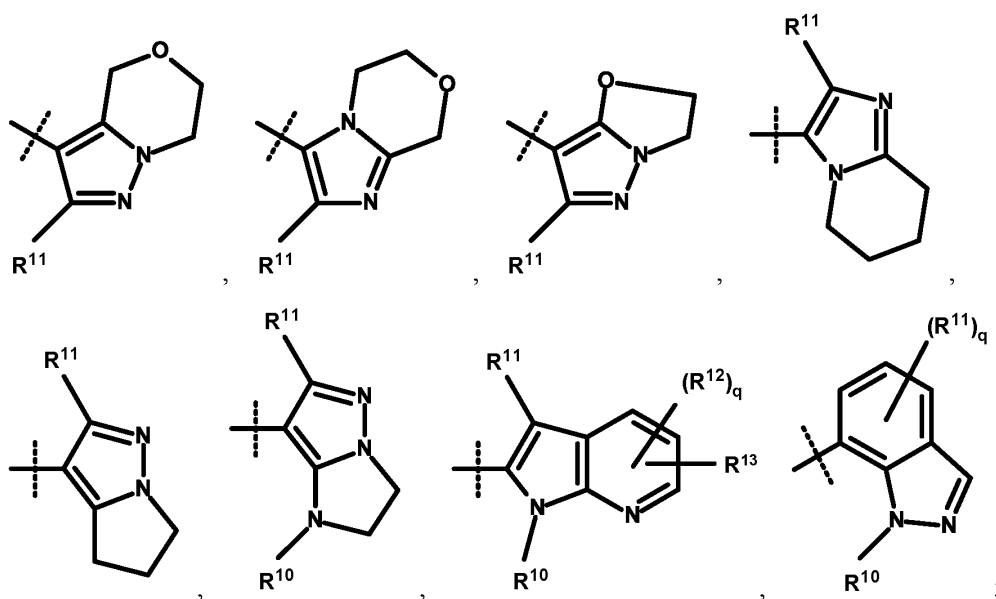




$\mathbf{R}^3$ is selected from



310



n is 0, 1 or 2;

p is 0, 1 or 2;

5 **q** is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 wherein

R⁸ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F,

10 OCHF₂, OCF₃ or Cl;

R¹⁰ is selected from H, CH₃, CH₂F, CHF₂, CF₃ or CH₂CH₃;

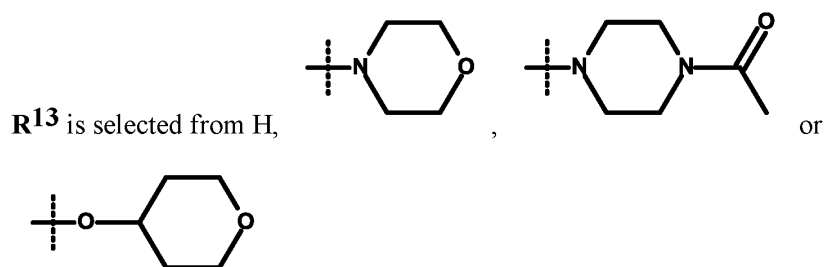
R¹¹ is independently selected from H, CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃, OCH₃, OCH₂F,

OCHF₂, OCF₃, CH₂OCH₃, cyPr, CH₂cyPr or cyBu;

R¹² is independently selected from OH, CH₃, OCH₃, CH₂F, CHF₂, CF₃, CH₂CH₃,

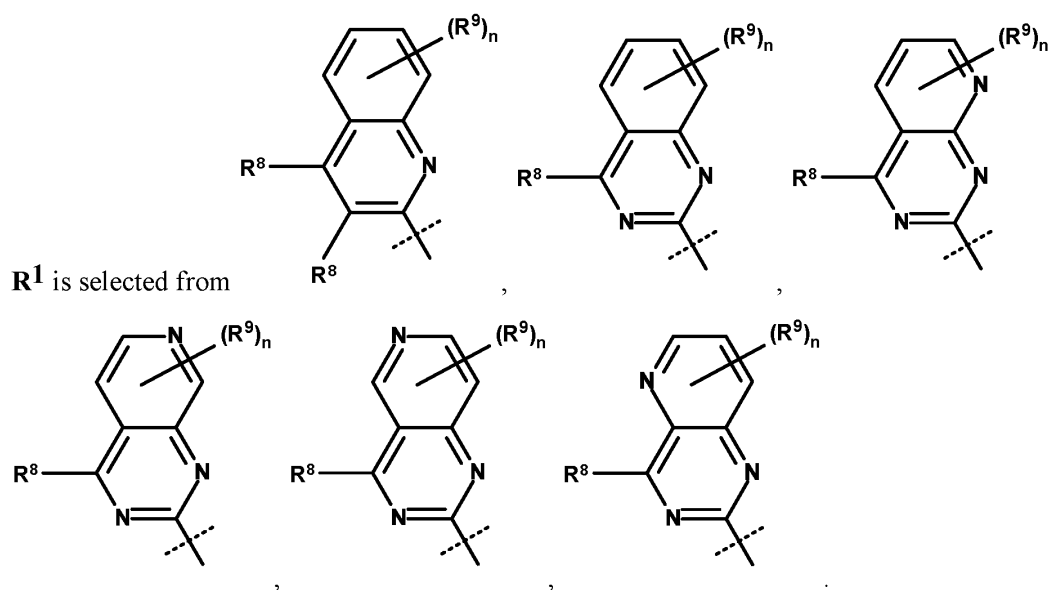
15 CH₂OCH₃, -CH(CH₃)₂, CN, Cl, NHCH₃, CH₂OH;

311



4. A compound according to any one of claims 1 to 3 wherein
5. **R⁴** is selected from OH, OCH₃, OCH₂F, OCHF₂, OCF₃, -CH₂OH, CN, F.

5. A compound according to claim 4 wherein

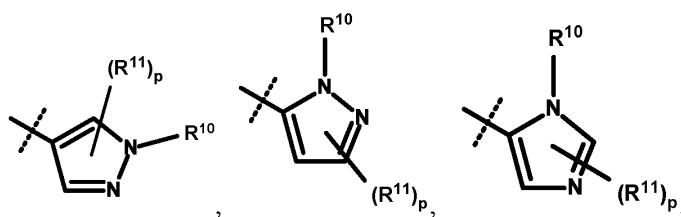
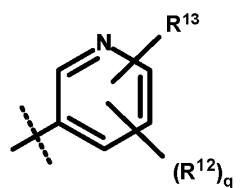


10

6. A compound according to claim 4 wherein

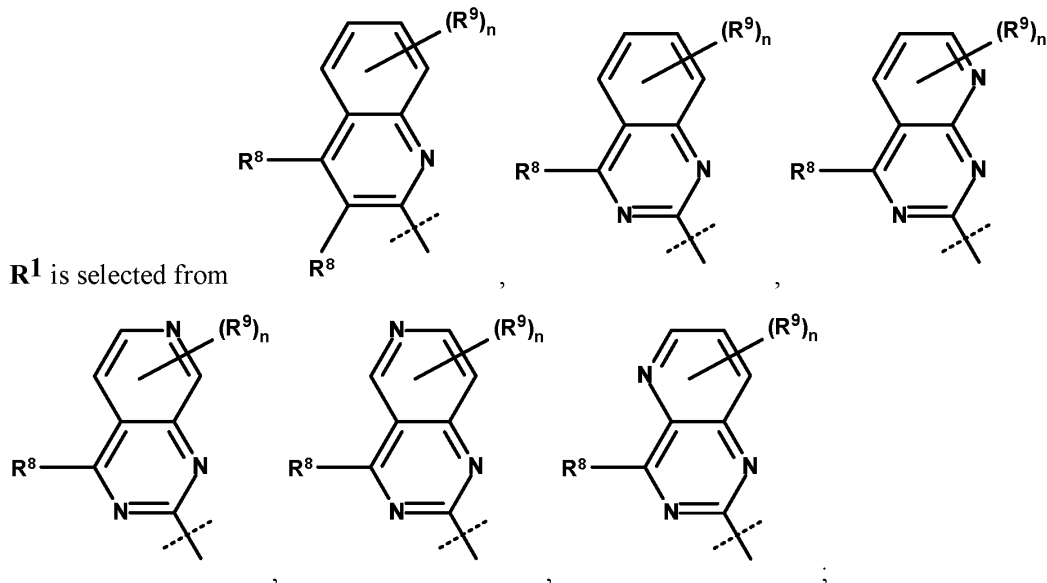
312

R³ is selected from



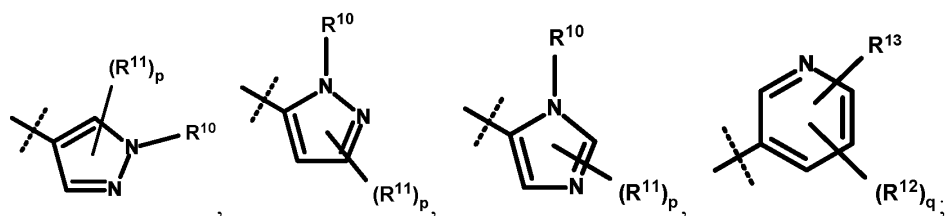
7. A compound according to claim 1 wherein

R¹ is selected from



R² is H;

R³ is selected from



- R⁴** is selected from OH, C₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, OC₁₋₃alkyl optionally substituted by 1, 2, 3, 4 or 5 F, -CH₂OH, -CH₂OCH₃, CN, F, Cl;
- R⁵** is independently selected from H, F, OH, OCH₃, OCH₂F, OCHF₂, OCF₃, CH₃, CH₂F, CHF₂ or CF₃;
- 5 **R⁶** is independently selected from CH₃, CH₂F, CHF₂, CF₃, CH₂CH₃ or F;
- R⁷** is selected from H, F, CH₃ or CN;
- R⁸** is independently selected from H, CH₃ or OCH₃;
- R⁹** is independently selected from CH₃, OCH₃, CN, F or Cl;
- R¹⁰** is selected from H or CH₃;
- 10 **R¹¹** is independently selected from CH₃ or OCH₃;
- R¹²** is independently selected from CH₃, OCH₃, CN or Cl;
- m** is independently 0, 1 or 2;
- n** is 0, 1 or 2;
- p** is 0, 1 or 2;
- 15 **q** is 0, 1 or 2.
8. A compound according to claim 1 selected from
- 2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinoline;
- 2-((4-(5-(4-isopropylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-
- 20 methylpyrido[2,3-*d*]pyrimidine;
- 2-((4-(5-(4,6-dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-
- dimethylpyrido[2,3-*d*]pyrimidine;
- 6-chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
- 8-fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
- 25 8-fluoro-4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
- 6-Methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-
- yl)methyl)quinazoline;
- 4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-
- d*]pyrimidine;

- 2-((4-(5-(4-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine;
- 4-methyl-2-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine;
- 5 4-methyl-2-((4-(5-(5-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine;
- 4-methyl-2-((4-(5-(2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine;
- (3-(3-(1-((4-methylpyrido[2,3-*d*]pyrimidin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyridin-4-yl)methanol;
- 10 2-((4-(5-(2-ethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine;
- 2-((4-(5-(2,4-diethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine;
- 15 3-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-8-methylbenzo[*e*][1,2,4]triazine;
- 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine;
- 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine,
- 20 2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine;
- 5-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1,8-naphthyridine;
- 25 4,7-dimethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[2,3-*d*]pyrimidine;
- 6-chloro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 5-chloro-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
- 30 4,6-dimethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;

- 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline-6-carbonitrile;
- 6-methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,4-*d*]pyrimidine;
- 5 8-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 6-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 5-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 10 7-fluoro-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 6-methoxy-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)pyrido[3,2-*d*]pyrimidine;
- 15 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4,7-dimethylpyrido[2,3-*d*]pyrimidine;
- 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylpyrido[2,3-*d*]pyrimidine;
- 4-(methoxy-*d*3)-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)thieno[3,2-*d*]pyrimidine;
- 20 4-methyl-2-((4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
- 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4,7-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine;
- 6-((4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine;
- 25 1-ethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-1*H*-benzo[*d*]imidazole;
- rac*-(*R*)-4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine;
- 30 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine;

- 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 4-chloro-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine;
- 5 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine;
- rac*-4-methyl-2-(((2*R*,4*R*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 4-ethyl-2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 10 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-5,8-dihydro-6*H*-pyrano[3,4-*d*]pyrimidine;
- 4-ethyl-2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 15 2-((4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 2-((4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 20 2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 25 4-ethyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-ethyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 4-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;
- 30 2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine;

- 4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-ol;
- (3*R*,4*R*)-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- 5 4-(1',5'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-4-ol;
- (3*R*,4*R*)-4-(1',5'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 2-((4-fluoro-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 10 1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidine-4-carbonitrile;
- 2-((4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 15 2-((4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- rac*-4-methyl-2-(((2*R*,4*S*)-2-methyl-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- (1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-yl)metanol;
- 20 1-((4-Methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol;
- (3*R*,4*R*)-4-(5-(1-Methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 25 (3*R*,4*R*)-4-(5'-Methoxy-1',3'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 3*R*,4*R*)-4-(5'-cyclopropyl-1'-methyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*S*,4*S*)-4-(5'-cyclopropyl-1'-methyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 30 2-((4-(1',5'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)-4-methoxypiperidin-1-yl)methyl)-4-methylquinazoline;

- 2-((4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- (3*R*,4*S*)-4-methoxy-4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 5 (3*R*,4*S*)-4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-methoxy-4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-methoxy-4-(5'-methoxy-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-1-((4-
- 10 methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-methoxy-4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- 15 (3*R*,4*S*)-1-((5-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- (3*R*,4*S*)-1-((5-chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- (3*R*,4*S*)-1-((6-chloro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-
- 20 1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- (3*R*,4*S*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- (3*S*,4*R*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- 25 (3*R*,4*S*)-4-methoxy-4-(5-(4-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-(3',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)piperidin-3-ol;
- (3*R*,4*S*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(5-(pyridin-3-yl)-1*H*-pyrazol-3-
- 30 yl)piperidin-3-ol;
- (3*R*,4*S*)-1-((8-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;

- (3*R*,4*S*)-1-((6-fluoro-4-methylquinazolin-2-yl)methyl)-4-methoxy-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
rac-(3*R*,4*S*)-3-fluoro-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-4-ol;
5 *rac*-(3*R*,4*R*)-4-methoxy-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
4-methyl-2-((4-(1',3',4,5'-tetramethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
1',3',5'-trimethyl-5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*,2'*H*-[3,4'-
10 bipyrazole]-4-carbonitrile;
N-methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*-pyrazol-5-yl)pyridin-3-amine;
4-methyl-2-((4-(5-(1-methyl-1'*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
15 4-methyl-2-((4-(5-(1-methyl-1'*H*-indazol-7-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
4-methyl-2-((4-(5-(5-((tetrahydro-2'*H*-pyran-4-yl)oxy)pyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
4-methyl-2-((4-(5-(5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-
20 1-yl)methyl)quinazoline;
1-(4-(5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*-pyrazol-5-yl)pyridin-3-yl)piperazin-1-yl)ethan-1-one;
4-methyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*-pyrazol-5-yl)nicotinonitrile;
25 4-(5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1'*H*-pyrazol-5-yl)pyridin-3-yl)morpholine;
2-((4-(5-(5-methoxypyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
2-((4-(5-(5-chloropyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
30 4-methyl-2-((4-(5-(5-methylpyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
4-methyl-2-((4-(5-(4-methylpyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
4-methyl-2-((4-(5-(pyridin-3-yl)-1'*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;

- 4-methyl-2-((4-(5-(2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
4-methyl-2-((4-(5-(2-(trifluoromethyl)pyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
2-((4-(5-(2,4-dimethylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
5 2-((4-(5-(4-(methoxymethyl)-2-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
2-({4-[3-(4-ethyl-2-methylpyridin-3-yl)-1*H*-pyrazol-5-yl]piperidin-1-yl}methyl)-4-methylquinazoline;
10 2-((4-(5-(4,6-dimethylpyrimidin-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
2-((4-(5-(1,4-dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
4-methyl-2-((4-(5-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
15 3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-5,6-dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazine;
3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine;
20 2-((4-(5-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
3-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine;
7-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-2,3-dihydropyrazolo[5,1-*b*]oxazole;
25 3,5-dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)isoxazole;
4-methyl-2-((4-(5-(1,2,4-trimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)quinazoline;
30 2-((4-(5-(1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;

- 2,4-dimethyl-5-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)thiazole;
- 5-methyl-2-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)-4-(trifluoromethyl)thiazole;
- 5 3,5-dimethyl-4-(3-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)isothiazole;
- 2-((4-(5-(4-ethyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-1*H*-pyrazol-3-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 3,4-dimethyl-5-(5-(1-((4-methylquinazolin-2-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-3-yl)isoxazole;
- 10 2-((4-(1',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 2-((4-(3',5'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 15 4-methyl-2-((4-(1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline,
- 4-methyl-2-((4-(1',3',5'-trimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 2-((4-(5'-cyclobutyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 20 2-((4-(5'-(difluoromethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 4-methyl-2-((4-(1'-methyl-5'-(trifluoromethyl)-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;
- 2-((4-(5'-(methoxymethyl)-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
- 25 methylquinazoline;
- 2-((4-(5'-cyclopropyl-1'-methyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 2-((4-(5'-methoxy-1',3'-dimethyl-1'*H*,2*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 30 4-methyl-2-((4-(2',4',5'-trimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)quinazoline;

- 2-((4-(4',5'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 2-((4-(1',3'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 5 2-((4-(2',4'-dimethyl-2*H*,2'*H*-[3,3'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 2-((4-(5'-ethyl-1',3'-dimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-methylquinazoline;
- 2-((4-(5'-methoxy-1'-methyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-1-yl)methyl)-4-
- 10 methylquinazoline;
- rac*-(3*R*,4*S*)-4-ethyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- rac*-(3*R*,4*S*)-4-methyl-1-((4-methylquinazolin-2-yl)methyl)-4-(1',3',5'-trimethyl-1'*H*,2'*H*-[3,4'-bipyrazol]-5-yl)piperidin-3-ol;
- 15 or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use as a medicament.
- 20 10. A pharmaceutical composition comprising a compound according to any one claims 1 to 8, or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
11. A method of treating, or reducing the risk of, diseases or conditions in which inhibition of the enzyme NNMT is beneficial which comprises administering to a person suffering from or
- 25 at risk of, said disease or condition, a therapeutically effective amount of a compound according to any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof.
12. The method according to claim 11, wherein said disease or condition is chronic kidney
- 30 disease (CKD).

13. The method according to claim 11, wherein said disease or condition is acute kidney injury (AKI).
14. The method according to claim 11, wherein said disease or condition is diabetic kidney
5 disease (DKD).
15. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use as a medicament.
- 10 16. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic kidney disease (CKD).
17. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute kidney injury (AKI).
- 15 18. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the treatment of diabetic kidney disease (DKD).
19. The use of a compound according to any one of claims 1 to 8, or a pharmaceutically
20 acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of the enzyme NNMT is beneficial.
20. The use according to claim 19, wherein said disease or condition is chronic kidney disease (CKD).
- 25 21. The use according to claim 19, wherein said disease or condition is acute kidney injury (AKI).
22. The use according to claim 19, wherein said disease or condition is diabetic kidney
30 disease (DKD).