

INHIBITORY COMPOUNDS

FIELD OF THE INVENTION

[0001] The present invention relates to certain compounds that function as inhibitors of METTL3 (N6-adenosine-methyltransferase 70 kDa subunit) activity. The present invention
5 also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their use in the treatment of proliferative disorders, such as cancer, autoimmune, neurological, infectious and inflammatory diseases, as well as other diseases or conditions in which METTL3 activity is implicated.

BACKGROUND OF THE INVENTION

10 [0002] N6-methyladenosine (m6A) is the most common and abundant covalent modification of messenger RNA, modulated by 'writers', 'erasers' and 'readers' of this mark (Meyer & Jaffrey 2014, Niu Y et al, 2013, Yue et al 2015). Approximately 0.1 to 0.5% of all mRNA adenosines are m6A modified (Li Y et al 2015). *In vitro* data have shown that m6A influences
15 fundamental aspects of mRNA biology, mainly mRNA expression, splicing, stability, localisation and translation (Meyer et al, 2015; Sledz & Jinek 2016). M6A modifications are tissue specific and there is significant variability in their occurrence profiles in non-diseased tissues (eg brain, heart, kidney) and diseased tissues and cells (lung, renal, breast, and
leukemic cancer cells) (Meyer et al 2012).

[0003] The m6A modifications and its erasers and writers such as FTO, ALKBH5,
20 methyltransferase like 3 (METTL3) and METTL14 are associated with major diseases such as solid organ cancers, leukaemia, type 2 diabetes, neuropsychiatric behavioural and depressive disorders (Chandola et al 2015; Koranda et al 2018).

[0004] The RNA methyltransferase, METTL3, is the major, but not the sole enzyme, that catalyses m6A modification of RNA. It exists as a hetero-trimeric complex with METTL14 (Liu
25 et al 2014, Wang et al 2016) and Wilm's Tumour Associated Protein (WTAP) (Ping et al 2014). Catalytic activity resides in METTL3, which transfers a methyl group from the co-factor S-adenosyl methionine to the substrate RNA and METTL14 facilitates substrate RNA binding. WTAP localises the complex in specific nuclear regions and also localises RNA substrates to the complex (Wang X et al 2016).

30 [0005] METTL3 has been reported to play a role in many aspects of the development of cancer (Fry et al 2018). Genetic knockdown of METTL3 in lung cancer cell lines (A549, H1299 and H1792) and HeLa cells leads to decreased growth, survival and invasion of human lung cancer cells (Lin S et al 2016). METTL3 is significantly up-regulated in human bladder cancer (Cheng et al 2019). Knockdown of METTL3 drastically reduced bladder cancer cell
35 proliferation, invasion, and survival in vitro and tumorigenicity in vivo. AF4/FMR2 family

member 4 (AFF4), two key regulators of NF- κ B pathway (IKBKB and RELA) and MYC were further identified as direct targets of METTL3-mediated m6A modification. In renal carcinoma cell lines (CAK-1, CAK-2 and ACHN), genetic knockdown reduced cell proliferation via the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signalling pathway (Li X et al 2017).

[0006] Recently Barbieri et al (2017), defined a set of RNA-modifying enzymes that are necessary for acute myeloid leukaemia (AML) and identified a key leukaemic pathway for the METTL3 RNA methyltransferase. In this pathway, METTL3 is stably recruited by the CCAAT-box binding transcription factor CEBPZ to promoters of a specific set of active genes, resulting in m6A methylation of the respective mRNAs and increased translation. One important target is *SP1*, an oncogene in several cancers, which regulates *c-MYC* expression. Consistent with these findings, it has been reported that METTL3 can methylate its targets co-transcriptionally.

[0007] The pathway described by Barbieri et al., is critical for AML leukaemia, as three of its components are required for AML cell growth: (i) the m6A RNA methyltransferase METTL3; (ii) the transcription factor CEBPZ, which targets this enzyme to promoters; and (iii) *SP1*, whose translation is dependent upon the m6A modification by METTL3. Together, the observations of Barbieri et al define METTL3 enzymatic activity as a new candidate target for the treatment of AML.

[0008] In separate, independent studies it has been reported that METTL3 plays an essential role in controlling myeloid differentiation of mammalian normal hematopoietic and leukemic cells (Vu et al 2017). Forced expression of wild type METTL3, but not a mutant METTL3 (with defect in catalytic activity), significantly promotes cell proliferation and inhibits cell differentiation of human cord blood-derived CD34+ haematopoietic stem/progenitor cells (HSPCs). Genetic knockdown of METTL3 has the opposite effects. METTL3 is highly expressed in AML compared to normal HSPCs or other types of cancers. Knockdown of METTL3 in human AML cell lines significantly induces cell differentiation and apoptosis and inhibits leukaemia progression in mice xeno-transplanted with MOLM-13 AML cells. The biological function of METTL3 is likely attributed to the promotion of translation of its mRNA targets such as MYC, BCL-2, and PTEN in an m6A-dependent manner.

[0009] Recently, METTL3 mediated m6A modification has been demonstrated to play an important role in T cell homeostasis and signal dependent induction of mRNA degradation in CD4 positive T cell lineages (Li et al 2017). Deletion of METTL3 in mouse T cells disrupts T cell homeostasis and differentiation. In a lymphopenic mouse adoptive transfer model, naive *Mettl3*-deficient T cells failed to undergo homeostatic expansion and remained in the naive state for up to 12 weeks, thereby preventing colitis. Consistent with these observations, the mRNAs of SOCS family genes encoding the STAT signalling inhibitory proteins SOCS1, SOCS3 and CISH were marked by m6A, exhibited slower mRNA decay and showed increased

mRNAs and levels of protein expression in *Mettl3*-deficient naive T cells. This increased SOCS family activity consequently inhibited IL-7-mediated STAT5 activation and T cell homeostatic proliferation and differentiation. Thus METTL3 mediated m6A methylation has important roles for inducible degradation of Socs mRNAs in response to IL-7 signalling in order to reprogram naive T cells for proliferation and differentiation, pointing to a role in auto-immunity.

[0010] Recent studies have revealed that depletion of METTL3 leads to alterations in the propagation of diverse viruses (Winkler et al). Following viral infection or stimulation of cells with an inactivated virus, deletion of the m6A 'writer' METTL3 led to an increase in the induction of interferon-stimulated genes. Consequently, propagation of different viruses was suppressed in an interferon-signaling-dependent manner. Significantly, the mRNA of IFNB, was m6A modified and was stabilized following repression of METTL3. m6A serves as a negative regulator of interferon response by dictating the fast turnover of interferon mRNAs and consequently facilitating viral propagation.

[0011] METTL3 activity and deposition of the m6A modification have been linked to a number of brain cancers including Glioblastoma Multiforme (GBM) where it has been shown that silencing of METTL3 expression inhibits the transformation of astrocytes and also the growth of GBM cells in an orthotopic brain tumour model (Visvanathan et al, 2018). METTL3 activity has also been linked to chemoresistance in GBM where METTL3 was shown to promote temozolomide resistance by increasing expression of DNA damage repair genes such as MGMT which mediates O6-meG repair (Jia Shi et al, 2021) providing an additional therapeutic context in which METTL3 inhibition to overcome chemoresistance.

[0012] METTL3 inhibitors could therefore be of utility in a range of brain neoplasms including but not limited to Glioma, Glioblastoma Multiforme, Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas or other brain neoplasms as classified by the WHO ICD-11 classification.

[0013] In addition, treatment with a METTL3 inhibitor may also prove to be of utility in treating secondary tumours of cancer that have metastasized to the brain.

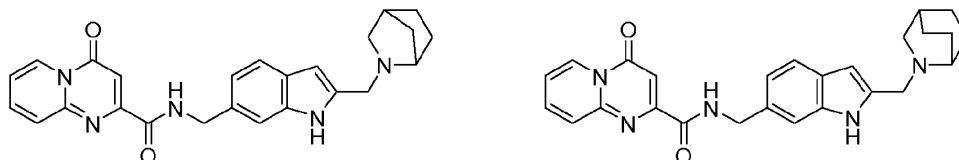
[0014] Inhibition of METTL3 may also be of utility in diseases of the central nervous system (CNS).

[0015] METTL3 inhibitors are potentially useful therapeutics agents for treating diseases related to the re-activation of the silenced X-chromosome (Patil et al, Nature, 2016 Sep 15;537(7620):369-373). As such they are potentially effective therapeutic agents for the treatment of RETT syndrome.

[0016] METTL3 inhibitors have shown the ability to re-activate expression of genes from the silenced X-chromosome (WO2022086935A1, which is incorporated herein by reference)

which suggests that inhibition of METTL3 activity could be useful for a wide range of diseases where X-chromosome inactivation is involved.

[0017] WO202111124 describes METTL3 inhibitors having the following structural formulas:



- 5 **[0018]** METTL3 activity and m6A modification of RNA has also been reported to be involved in the regulation of Tau oligomers which are thought to play a role in tauopathy diseases including Alzheimer's (Lulu Jiang et al, 2021) and furthermore levels of m6A are elevated in the brains of Alzheimer's patients suggesting that inhibition of METTL3 activity could be a useful therapeutic approach in Alzheimer's. There are a range of tauopathy related
- 10 diseases (see Zhang et al, 2022 for review) and inhibition of METTL3 activity may therefore have therapeutic potential in treating a range of tauopathies.

[0019] METTL3-dependent m6A on HBV and HCV viral genome regulates recognition of the viral genome by RIG-I RNA sensor. Depletion of METTL3 enhances viral dsRNA recognition and induces an anti-viral immune response (Kim et al.).

- 15 **[0020]** Therefore, METTL3 inhibitors may provide a novel therapeutic approach to a range of infectious and inflammatory diseases. In particular, they provide a potential treatment for viral diseases (e.g. DNA and RNA viruses).

[0021] Furthermore, METTL3-dependent m6A on endogenous mRNAs regulates recognition of immunogenic RNA (such as, but not limited to dsRNA) by MAVS-dependent RNA sensors.

- 20 Depletion of METTL3 enhances endogenous dsRNA recognition and induces an auto-immune response (Gao et al.). This implies that an anti-tumour immune response might be enhanced by METTL3 inhibition.

[0022] Thus, METTL3 inhibitors may also provide a novel therapeutic approach to enhance an anti-tumour immune response.

- 25 **[0023]** Multidrug resistance in cancer chemotherapy remains a significant barrier to successful treatment and increased expression of human ABC efflux transporters, such as ABCB1 (MDR1-P-gp), is a recognized mechanism by which cancer cells can develop resistance to treatment (Szakács et al.). There is a need to provide METTL3 inhibitors which exhibit potent cellular antiproliferative effects, increased cellular permeability and reduced
- 30 human P-glycoprotein (P-gp) efflux liability.

[0024] METTL3 has been demonstrated to be related to the pathogenesis of Amyotrophic Lateral Sclerosis (ALS), a constellation of neurodegenerative conditions that includes, but is

not limited to, Lou Gehrig's disease, frontotemporal dementia and Motor Neuron Disease. Disrupting RNA metabolism by removing METTL3, and by extension METTL3-dependent m6A, led to amelioration of the functional deficits in an ALS model (McMillan et al.). This same report (McMillan et al) also measured an increase in m6A in ALS patient spinal cord tissue, suggesting that you could use m6A to diagnostically understand the clinical stages of ALS. Similar results have been obtained using other genetic models of ALS (Timoteo et al.) suggesting that a therapeutic utility of METTL3 inhibition could apply generally to ALS, and also to other conditions that are associated with aberrant formation of stress granules (Ries et al., Fu and Zhuang).

10 **[0025]** METTL3 has been linked to the pathogenesis of Alzheimer's Disease, a disease characterised at the molecular level by the aggregation of amyloid and tau. A link to tau pathology has been noted above. This link to tauopathy could be linked to other named tauopathies including, but not limited to, Pick's Disease, Frontotemporal Dementia, Corticobasal Degeneration, Progressive Supranuclear Palsy, Primary Age-related Tauopathy
15 (PART) and Agryophilic Grain Disease (AGD) (Oakley et al.) - METTL3 inhibition could be helpful in all of these cases.

[0026] METTL3 has been linked to Huntington's Disease (HD), which is caused by the expansion of the CAG repeat in the huntingtin (HTT) gene. CAG expansion is thought to impair the interaction between HTT and RNA-binding proteins and contribute to pathogenesis of HD
20 (Schilling et al.). Aberrant HTT transcripts were found to be m6A hypermethylated in the striatum of an HD mouse model, HD cell lines and human HD samples. METTL3 has been specifically implicated in HD as pharmacological inhibition of METTL3 reduced the m6A methylation and expression of aberrant HTT transcripts, but not full length HTT (Pupak et al.).

[0027] METTL3 has been linked to the APOE4 variant of apolipoprotein E, which is the strongest genetic risk factor for AD (Yamazaki et al.) and leads to vascular dysfunction, neurodegeneration and dementia (Montagne et al.). METTL3 expression was demonstrated to be higher in APOE4-positive AD brain samples compared to APOE4-negative samples (Du et al.). METTL3 inhibition elicits alterations in viral mimicry pathways and innate immune signalling (Guirguis et al.), and there is emerging evidence that links sporadic AD to viral
30 infection, and subsequent dysfunction in host antiviral pathways (De Vlieger et al.). By inference, this links inhibition of METTL3 to potential therapeutic utility in all forms of Alzheimer's Disease, whether sporadic or familial in aetiology.

[0028] Cerebral vascular dysfunction contributes to early cognitive impairment and AD (Wardlaw et al. and Montagne et al.). M6A methylation and METTL3 have both been linked to
35 vascular diseases. Expression of the m6A reader protein, HNRNPA2B1, was shown to be elevated in AD and vascular dementia brain samples (Du et al.). Expression of METTL3 and ferroptosis markers were increased in vitro and in mouse models of intracranial hemorrhage,

whereas silencing of METTL3 suppressed ferroptosis in vitro through downregulation of m6A, as well as led to reduced lesion size and neurological deficit following cerebral ischemic stroke in vivo (Zhang et al. and Wu et al.). These findings suggest that METTL3 inhibition could have therapeutic utility in all classes of dementia, including, but not limited to, vascular dementia and all forms of Alzheimer's Disease.

[0029] Decreased m6A levels and increased FTO expression in the striatum are linked to dopaminergic neuron degeneration in Parkinson's Disease (PD), highlighting the role of m6A methylation, and thus METTL3, in PD pathogenesis (Chen et al., 2019). These findings suggest that METTL3 inhibition could have utility in this context, especially if the reduced m6A is part of a natural mechanism to reduce the severity of the symptoms of PD.

[0030] The deletion of METTL14 and overexpression of FTO in multiple sclerosis contribute to impaired oligodendrocyte maturation and myelination, emphasizing the role of m6A methylation in Multiple Sclerosis pathology, and indicating that targeting METTL3 activity might impact treatment outcomes. (Xu et al., 2020).

[0031] Altered m6A methylation by FTO and ALKBH5 is linked to epilepsy, with treatments targeting these pathways showing potential antiepileptic effects, thereby implicating METTL3 as a potential target for therapeutic intervention. (Wu et al., 2019).

[0032] The present invention was devised with the foregoing in mind.

References

- Barbieri I, Tzelepis K, Pandolfini L, Shi J, Millán-Zambrano G, Robson SC, Aspris D, Migliori V, Bannister AJ, Han N, De Braekeleer E, Ponstingl H, Hendrick A, Vakoc CR, Vassiliou GS, Kouzarides T. *Nature*. 2017 Dec 7;552(7683):126-131.
- Chandola U, Das R, Panda B. *Brief Funct Genomics*. 2015 May;14(3):169-79.
- Cheng M, Gao Q, Wu M, Liang Y, Zhu F, Zhang Y, Zhang X, Li Y, Sheng L, Zhang H, Xiong Q, Yuan Q, *Oncogene* (2019; e-publication ahead of print).
- Fry NJ, Law BA, Ilkayeva OR, Carraway KR, Holley CL, Mansfield KD. *Oncotarget*. 2018 Jul 27;9(58):31231-31243.
- Koranda JL, Dore L, Shi H, Patel MJ, Vaasjo LO, Rao MN, Chen K, Lu Z, Yi Y, Chi W, He C, Zhuang X. *Neuron*. 2018 July 25; 99(2): 283-292.
- Li HB, Tong J, Zhu S, Batista PJ, Duffy EE, Zhao J, Bailis W, Cao G, Kroehling L, Chen Y, Wang G, Broughton JP, Chen YG, Kluger Y, Simon MD, Chang HY, Yin Z, Flavell RA. *Nature*. 2017 Aug 17;548 (7667):338-342

- Li X, Tang J, Huang W, Wang F, Li P, Qin C, Qin Z, Zou Q, Wei J, Hua L, Yang H, Wang Z. *Oncotarget*. 2017 Oct 10;8(56):96103-96116.
- Li Y, Wang Y, Zhang Z, Zamudio AV, Zhao JC. *RNA*. 2015 Aug;21(8):1511-8.
- Lin S, Choe J, Du P, Triboulet R, Gregory RI. *Mol Cell*. 2016 May 5;62(3):335-345.
- 5 • Liu J, Yue Y, Han D, Wang X, Fu Y, Zhang L, Jia G, Yu M, Lu Z, Deng X, Dai Q, Chen W, He C. *Nat Chem Biol*. 2014 Feb;10(2):93-5.
- Meyer KD, Patil DP, Zhou J, Zinoviev A, Skabkin MA, Elemento O, Pestova TA, Qian SB, Jaffrey SR. *Cell*. 2015 Nov 5; 163(4): 999-1010.
- Meyer KD, Jaffrey SR. *Nat Rev Mol Cell Biol*. 2014 May;15(5):313-26.
- 10 • Meyer KD, Saletore Y, Zumbo P, Elemento O, Mason CE, Jaffrey SR. *Cell*. 2012 Jun 22;149(7):1635-46.
- Niu Y, Zhao X, Wu YS, Li MM, Wang XJ, Yang YG. *Genomics Proteomics Bioinformatics*. 2013 Feb;11(1):8-17.
- Ping XL, Sun BF, Wang L, Xiao W, Yang X, Wang WJ, Adhikari S, Shi Y, Lv Y, Chen YS, Zhao X, Li A, Yang Y, Dahal U, Lou XM, Liu X, Huang J, Yuan WP, Zhu XF, Cheng T, Zhao YL, Wang X, Rendtlew Danielsen JM, Liu F, Yang YG. *Cell Res*. 2014 Feb;24(2):177-89.
- 15 • Śledź P, Jinek M. *Elife*. 2016 Sep 14;5.
- Vu LP, Pickering BF, Cheng Y, Zaccara S, Nguyen D, Minuesa G, Chou T, Chow A, Saletore Y, MacKay M, Schulman J, Famulare C, Patel M, Klimek VM, Garrett-Bakelman FE, Melnick A, Carroll M, Mason CE, Jaffrey SR, Kharas MG. *Nat Med*. 2017 Nov;23(11):1369-1376.
- 20 • Wang X, Feng J, Xue Y, Guan Z, Zhang D, Liu Z, Gong Z, Wang Q, Huang J, Tang C, Zou T, Yin P. *Nature*. 2016 Jun 23;534(7608):575-8
- 25 • Wang P, Doxtader KA, Nam Y. *Mol Cell*. 2016 Jul 21;63(2):306-317.
- Winkler R, Gillis E, Lasman L, Safra M, Geula S, Soyris C, Nachshon A, Tai-Schmiedel J, Friedman N, Le-Trilling Vu T K, Trilling M, Mandelboim M, Hanna, J H, Schwartz S, Stern-Ginossar N. *Nature Immunology* (2018, e-publication ahead of print).
- 30 • Visvanathan A, Patil V, Arora A, Hegde AS, Arivazhagan A, Santosh V, Somasundaram K. *Oncogene*. 2018 Jan 25;37(4):522-533. Epub 2017 Oct 9. PMID: 28991227.

- Shi J, Chen G, Dong X, Li H, Li S, Cheng S, Li Y, Wang L, Yuan J, Qian Z, Dong J. *Front Oncol.* 2021 Jul 15;11:702983. PMID: 34336690.
- Patil et al, *Nature*, 2016 Sep 15;537(7620):369-373
- Jiang L, Lin W, Zhang C, Ash PEA, Verma M, Kwan J, van Vliet E, Yang Z, Cruz AL,
5 Boudeau S, Maziuk BF, Lei S, Song J, Alvarez VE, Hovde S, Abisambra JF, Kuo
MH, Kanaan N, Murray ME, Crary JF, Zhao J, Cheng JX, Petrucelli L, Li H, Emili A,
Wolozin B. *Mol Cell.* 2021 Oct 21;81(20):4209-4227.e12. doi:
10.1016/j.molcel.2021.07.038. Epub 2021 Aug 27. PMID: 34453888; PMCID:
PMC8541906.
- Zhang Y, Wu KM, Yang L, Dong Q, Yu JT. *Tauopathies: new perspectives and
10 challenges.* *Mol Neurodegener.* 2022 Apr 7;17(1):28. doi: 10.1186/s13024-022-
00533-z. PMID: 35392986; PMCID: PMC8991707.
- Yue Y, Liu J, He C. *Genes Dev.* 2015 Jul 1;29(13):1343-55.
- Geon-Woo Kim, Hasan Imam, Mohsin Khan, Aleem Siddiqui, *J Biol Chem*, (27 Jul
15 2020; online publication ahead of print).
- Yimeng Gao, Radovan Vasic, Yuanbin Song, Rhea Teng, Chengyang Liu , Rana
Gbyli, Giulia Biancon, Raman Nelakanti, Kirsten Lobben, Eriko Kudo, Wei Liu,
Anastasia Ardasheva, Xiaoying Fu, Xiaman Wang, Poorval Joshi, Veronica Lee,
Burak Dura, Gabriella Viero, Akiko Iwasaki, Rong Fan, Andrew Xiao, Richard A
20 Flavell, Hua-Bing Li, Toma Tebaldi, Stephanie Halene; *Immunity* (16 June 2020;
Volume 52; 6; p887-1132).
- Rosa M Rubio, Daniel P Depledge, Christopher Bianco, Letitia Thompson, Ian Mohr;
Genes Dev. 2018 Dec 1;32(23-24):1472-1484.
- Szakács G, Annereau J-P, Lababidi S, Shankavaram U, Arciello A, Bussey KJ,
25 Reinhold W, Guo Y, Kruh GD, Reimers M, Weinstein JN, and Gottesman MM.
Cancer Cell 6, no. 2 (1 August 2004): 129–37
- McMillan, Michael, et al. "RNA methylation influences TDP43 binding and disease
pathogenesis in models of amyotrophic lateral sclerosis and frontotemporal
dementia." *Molecular cell* 83.2 (2023): 219-236
- Di Timoteo, Gaia, et al. "m6A reduction relieves FUS-associated ALS
30 granules." *Nature Communications* 15.1 (2024): 5033
- Ries, Ryan J., et al. "m6A governs length-dependent enrichment of mRNAs in stress
granules." *Nature Structural & Molecular Biology* 30.10 (2023): 1525-1535
- Fu, Ye, and Xiaowei Zhuang. "m6A-binding YTHDF proteins promote stress granule
35 formation." *Nature chemical biology* 16.9 (2020): 955-963Oakley, Sebastian S., et al.

"Tau filament self-assembly and structure: tau as a therapeutic target." *Frontiers in Neurology* 11 (2020): 590754

- 5 » Schilling, J., N. Griesche, and S. Krauß. "Mechanisms of RNA-induced toxicity in diseases characterised by CAG repeat expansions, eLS John Wiley & Sons." Ltd, Chichester (2016).
- » Pupak, Anika, et al. "m6A RNA modification of mHtt intron 1 regulates the generation of Htt1a in Huntington's Disease." *bioRxiv* (2023): 2023-11.
- Yamazaki, Yu, et al. "Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies." *Nature Reviews Neurology* 15.9 (2019): 501-518.
- 10 • Montagne, Axel, et al. "APOE4 accelerates advanced-stage vascular and neurodegenerative disorder in old Alzheimer's mice via cyclophilin A independently of amyloid- β ." *Nature Aging* 1.6 (2021): 506-520.
- Du, Bingying, et al. "N6-methyladenosine (m6A) modification and its clinical relevance in cognitive dysfunctions." *Aging (Albany NY)* 13.16 (2021): 20716.
- 15 • Guirguis, Andrew A., et al. "Inhibition of METTL3 results in a cell-intrinsic interferon response that enhances antitumor immunity." *Cancer Discovery* 13.10 (2023): 2228-2247.
- De Vlieger, Lize, Roosmarijn E. Vandenbroucke, and Lien Van Hoecke. "Recent insights into viral infections as a trigger and accelerator in alzheimer's disease." *Drug*
- 20 *Discovery Today* 27.11 (2022): 103340.
- Montagne, Axel, et al. "APOE4 accelerates advanced-stage vascular and neurodegenerative disorder in old Alzheimer's mice via cyclophilin A independently of amyloid- β ." *Nature Aging* 1.6 (2021): 506-520.
- Wardlaw, Joanna M., et al. "Neuroimaging standards for research into small vessel
- 25 disease and its contribution to ageing and neurodegeneration." *The Lancet Neurology* 12.8 (2013): 822-838.
- Du, Bingying, et al. "N6-methyladenosine (m6A) modification and its clinical relevance in cognitive dysfunctions." *Aging (Albany NY)* 13.16 (2021): 20716.
- 30 • Zhang, Liu, et al. "Methyltransferase-like 3 silenced inhibited the ferroptosis development via regulating the glutathione peroxidase 4 levels in the intracerebral hemorrhage progression." *Bioengineered* 13.6 (2022): 14215-14226.
- Wu, Xun, et al. "The m6A methyltransferase METTL3 drives neuroinflammation and neurotoxicity through stabilizing BATF mRNA in microglia." *Cell Death & Differentiation* (2024): 1-18.
- 35 • Chen, Xuechai, et al. "Down-regulation of m6A mRNA methylation is involved in dopaminergic neuronal death." *ACS chemical neuroscience* 10.5 (2019): 2355-2363.

- Xu, Huan, et al. "m6A mRNA methylation is essential for oligodendrocyte maturation and CNS myelination." *Neuron* 105.2 (2020): 293-309.
- Wu, Rong, et al. "A novel m6A reader Prrc2a controls oligodendroglial specification and myelination." *Cell research* 29.1 (2019): 23-41.

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SUMMARY OF THE INVENTION

[0033] In one aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof.

10 [0034] In another aspect, the present invention provides a pharmaceutical composition as defined herein which comprises a compound as defined herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0035] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

15 [0036] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative condition.

20 [0037] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of cancer. In a particular embodiment, the cancer is a human cancer.

[0038] In particular embodiment, the cancer is a cancer of the CNS. Cancers of the CNS include but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

25 [0039] In another particular embodiment, the cancer is leukaemia (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia or chronic lymphocytic leukaemia (CLL)).

30 [0040] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the inhibition of METTL3 activity.

[0041] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of disorder of the CNS.

[0042] The disorder of the CNS may be a neurodegenerative disorder, for example a tauopathy, a motor neuron disease (including ALS), a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease), Parkinson's Disease or multiple sclerosis.

[0043] The disorder of the CNS may be epilepsy.

[0044] Tauopathies are progressive neurodegenerative disorders that are pathologically defined by tau-positive deposits in the brain. Tauopathies include but are not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglial pathology, primary age-related tauopathy and chronic traumatic encephalopathy.

[0045] Motor neuron diseases (MNDs) are a group of progressive neurological disorders that destroy motor neurons, the cells that control skeletal muscle activity such as walking, breathing, speaking, and swallowing. This group includes diseases such as amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. MNDs are also linked to frontotemporal dementia. The term "motor neuron disease" is often used interchangeably with amyotrophic lateral sclerosis because ALS is the most common adult-onset presentation of this disease.

[0046] Suitably, the motor neurone disease is selected from amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. In the context of the present invention, the treatment of a motor neurone disease also encompasses the treatment of frontotemporal dementia linked to motor neurone disease.

[0047] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a motor neuron disease (including ALS).

[0048] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a repeat expansion disease. Suitably, the repeat expansion disease is Huntington's Disease.

[0049] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of dementia. Suitably, the dementia is selected from frontotemporal

dementia (including MND related frontotemporal dementia), vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease,

[0050] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein,
5 for use in the treatment of Parkinson's Disease

[0051] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of multiple sclerosis.

[0052] In another aspect, the present invention provides a compound as defined herein, or a
10 pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of epilepsy.

[0053] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease related to the inactivation of the X-chromosome.
15 Suitably, the disease related to the inactivation of the X-chromosome is selected from Adrenal hypoplasia; siderius X-linked mental retardation syndrome; Agammaglobulinaemia, Bruton type; Choroidoretinal degeneration; Choroidaemia; Albinism, ocular; Dent's disease 2; fragile X syndrome; Rett/ Epileptic encephalopathy, early infantile, 2 (CDKL5 deficiency disorder); Albinism-deafness syndrome; paroxysmal nocturnal hemoglobinuria; Aldrich syndrome; Alport syndrome; Anaemia, hereditary hypochromic; Anemia, sideroblastic, with ataxia; Fabry
20 disease; Spinal muscular atrophy 2; Cataract, congenital; Charcot-Marie-Tooth, peroneal; Spastic paraplegia; Colour blindness; Diabetes insipidus, nephrogenic; DDX3X syndrome; Dyskeratosis congenita; Ectodermal dysplasia, anhidrotic; Faciogenital dysplasia (Aarskog syndrome); Glucose-6-phosphate dehydrogenase deficiency; Glycogen storage disease type
25 VIII; Gonadal dysgenesis (XY female type); Granulomatous disease (chronic); Haemophilia A; Haemophilia B; Hydrocephalus (aqueduct stenosis); Hypophosphataemic rickets; Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency); Incontinentia pigmenti; Kallmann syndrome; Keratosis follicularis spinulosa; Lowe (oculocerebrorenal) syndrome; Menkes syndrome; Renpenning Syndrome; Mental
30 retardation, with or without fragile site (numerous specific types); Coffin-Lowry syndrome; Microphthalmia with multiple anomalies (Lenz syndrome); Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types); Myotubular myopathy; Night blindness, congenital stationary; Norrie's disease (pseudoglioma); Nystagmus, oculomotor or 'jerky'; Orofaciodigital syndrome (type I); Ornithine transcarbamylase deficiency (type I hyperammonaemia);
35 Phosphoglycerate kinase deficiency; Phosphoribosylpyrophosphate synthetase deficiency;

Retinitis pigmentosa; Retinoschisis; Rett syndrome; Muscular atrophy /Dihydrotestosterone receptor deficiency; Spinal muscular atrophy; Spondyloepiphyseal dysplasia tarda; Thrombocytopenia, hereditary; Thyroxine-binding globulin, absence; or McLeod syndrome. More suitably, the disease related to the inactivation of the X-chromosome is RETT syndrome.

5 **[0054]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in reactivating expression of a silenced X-chromosome.

10 **[0055]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of RETT syndrome.

[0056] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in promoting an immune response (e.g. anti-viral or anti-tumour immune response).

15 **[0057]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in increasing an innate immune response in a subject.

20 **[0058]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in increasing or enhancing an anti-tumour immune response during immune-oncology therapy.

[0059] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of an autoimmune disease.

25 **[0060]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a neurological disease.

[0061] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of an infectious disease.

30 **[0062]** In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a viral infection. Suitably, the viral infection is a RNA viral infection. Suitably, the viral infection is human papillomavirus (HPV) or hepatitis.

[0063] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of an inflammatory disease.

5 [0064] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a proliferative condition.

[0065] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer. In a particular embodiment, the medicament is for use in the treatment of human cancers. The cancer may be any of the cancers described herein.

[0066] In a particular embodiment, the medicament is for use in the treatment of a cancer of the CNS. Cancers of the CNS include but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

15 [0067] In a particular embodiment, the medicament is for use in the treatment of a cancer of the CNS. leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL))

[0068] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the inhibition of METTL3 activity.

20 [0069] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a neurodegenerative disorder, for example a tauopathy. The tauopathy may be selected from Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglialopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy.

30 [0070] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a motor neuron disease. Suitably, the motor neurone disease is selected from amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. More suitably, the motor neuron disease is ALS.

[0071] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a repeat expansion disease (such as Huntington's Disease).

5 [0072] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease),

[0073] In another aspect, the present invention provides a compound as defined herein, 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of Alzheimer's Disease.

[0074] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of Parkinson's Disease

15 [0075] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of multiple sclerosis.

[0076] In another aspect, the present invention provides a compound as defined herein, 20 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of epilepsy.

[0077] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disease related to the inactivation of the X-chromosome.

[0078] In another aspect, the present invention provides the use of a compound as defined 25 herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in reactivating expression of a silenced X-chromosome.

[0079] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of RETT syndrome.

30 [0080] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for promoting an immune response (e.g. anti-viral or anti-tumour immune response).

[0081] In another aspect, the present invention provides the use of a compound as defined 35 herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in increasing an innate immune response in a subject.

[0082] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in increasing or enhancing an anti-tumour immune response during immune-oncology therapy.

- 5 [0083] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an autoimmune disease.

- [0084] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for
10 use in the treatment of a disorder of the central nervous system.

[0085] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a neurological disease.

- [0086] In another aspect, the present invention provides the use of a compound as defined
15 herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an infectious disease.

- [0087] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a viral infection. Suitably, the viral infection is a RNA viral infection.
20 Suitably, the viral infection is human papillomavirus (HPV) or hepatitis.

[0088] In another aspect, the present invention provides the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an inflammatory disease.

- [0089] In another aspect, the present invention provides a method of inhibiting METTL3
25 activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

- [0090] In another aspect, the present invention provides a method of inhibiting cell proliferation *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount
30 of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0091] In another aspect, the present invention provides a method of inhibiting metastasis *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound

as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0092] In another aspect, the present invention provides a method of promoting an immune response (e.g. anti-viral or anti-tumour immune response) in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0093] In another aspect, the present invention provides a method of increasing an innate immune response in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0094] In another aspect, the present invention provides a method of increasing or enhancing an anti-tumour immune response during immune-oncology therapy, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0095] In another aspect, the present invention provides a method of treating a proliferative disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0096] In another aspect, the present invention provides a method of treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein. The cancer may be a human cancer. The cancer may be a cancer of the CNS. Cancers of the CNS include but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

[0097] In another aspect, the present invention provides a method of treating an autoimmune disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0098] In another aspect, the present invention provides a method of treating a disorder of the central nervous system, said method comprising administering to a subject in need thereof a

therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[0099] In another aspect, the present invention provides a method of treating a neurological disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[00100] In another aspect, the present invention provides a method of treating an infectious disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[00101] In another aspect, the present invention provides a method of treating a viral infection, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein. Suitably, the viral infection is a RNA viral infection. Suitably, the viral infection is human papillomavirus (HPV) or hepatitis.

[00102] In another aspect, the present invention provides a method of treating an inflammatory disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[00103] In another aspect, the present invention provides a method of treating a neurodegenerative disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt, or a pharmaceutical composition as defined herein.

[00104] The neurodegenerative disorder may be selected from a tauopathy such as Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy; a motor neuron disease (including ALS); a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease); multiple sclerosis; or Parkinson's Disease.

[00105] Suitably, the neurodegenerative disorder may be a tauopathy, for example Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias or chronic traumatic encephalopathy.

[00106] In another aspect, the present invention provides a method for treating a motor neuron disease (including ALS), said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein. Suitably, the motor neurone
5 disease is selected from amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. More suitably, the motor neuron disease is ALS.

In another aspect, the present invention provides a method for treating a repeat expansion disease (such as Huntington's Disease), said method comprising administering to a subject in
10 need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00107] In another aspect, the present invention provides a method for treating dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease), said method comprising administering to a subject
15 in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00108] In another aspect, the present invention provides a method for treating Alzheimer's Disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof,
20 or a pharmaceutical composition as defined herein.

[00109] In another aspect, the present invention provides a method for treating Parkinson's Disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof,
or a pharmaceutical composition as defined herein.

25 [00110] In another aspect, the present invention provides a method for treating multiple sclerosis, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00111] In another aspect, the present invention provides a method for treating epilepsy
30 said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00112] In another aspect, the present invention provides a method for treating a disease related to the inactivation of the X-chromosome, said method comprising

administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

5 [00113] In another aspect, the present invention provides a method for reactivating expression of a silenced X-chromosome said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

10 [00114] In another aspect, the present invention provides a method of treating RETT syndrome, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00115] In one aspect, the present invention provides a combination comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents.

15 [00116] The present invention further provides a method of synthesising a compound, or a pharmaceutically acceptable salt, as defined herein.

[00117] In another aspect, the present invention provides a compound as defined herein, or a pharmaceutically acceptable salt, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

20 [00118] In another aspect, the present invention provides novel intermediates as defined herein which are suitable for use in any one of the synthetic methods as set out herein.

[00119] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

DETAILED DESCRIPTION OF THE INVENTION

25 **Definitions**

[00120] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

30 [00121] It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2)

inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[00122] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[00123] In this specification the term "alkyl" includes both straight and branched chain alkyl groups. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. For example, "C₁₋₆alkyl" includes C₁₋₄alkyl, C₁₋₃alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example "phenyl(C₁₋₆alkyl)" includes phenyl(C₁₋₄alkyl), benzyl, 1-phenylethyl and 2-phenylethyl.

[00124] The term "(m-nC)" or "C_{m-n}", or "(m-nC) group" or "C_{m-n}" used alone or as a prefix, refers to any group having m to n carbon atoms.

[00125] The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

[00126] The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

[00127] An “alkylene” group is an alkyl group that is positioned between and serves to connect two other chemical groups. Thus, “(1-3C)alkylene” means a linear saturated divalent hydrocarbon radical of one to three carbon atoms or a branched saturated divalent hydrocarbon radical of three atoms, for example, methylene, ethylene, propylene, and the like.

5 [00128] The term “(m-nC)cycloalkyl” means a hydrocarbon ring containing from m to n carbon atoms, for example “(3-6C)cycloalkyl” means a hydrocarbon ring containing from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. The term “(m-nC)cycloalkyl” also encompasses non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic carbocyclic ring system(s), or polycyclic ring systems. The
10 term “(m-nC)cycloalkyl” includes both monovalent species and divalent species. Monocyclic “(m-nC)cycloalkyl” rings contain from about 3 to 12 (suitably from 3 to 8, most suitably from 5 to 6) ring carbon atoms. Bicyclic “(m-nC)cycloalkyl” contain from 7 to 17 ring carbon atoms, suitably 7 to 12 ring carbon atoms. Bicyclic “(m-nC)cycloalkyl” rings may be fused, spiro (e.g. spiro[3,3]heptane), or bridged ring systems (e.g. bicyclo[2.2.1]hept-2-ene and
15 bicyclo[1.1.1]pentanyl).

[00129] The term “halo” or “halogeno” refers to fluoro, chloro, bromo and iodo.

[00130] The term “heterocyclyl”, “heterocyclic” or “heterocycle” means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic, or polycyclic heterocyclic ring system(s). The term heterocyclyl includes both monovalent species and
20 divalent species. Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7, most suitably from 5 to 6) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocycles contain from about 7 to about 17 ring atoms, suitably from 7 to 12 ring atoms. Bicyclic heterocyclic(s) rings
25 may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidiny, pyrrolidiny, piperidiny, piperaziny, tetrahydrotriaziny, tetrahydropyrazoly, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and
30 hexahydrothiepine. Other heterocycles include dihydro-oxathiolyl, tetrahydro-oxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydro-oxathiazolyl, hexahydrotriaziny, tetrahydro-oxaziny, morpholiny, thiomorpholiny, tetrahydropyrimidiny, dioxoliny, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO₂ groups
35 are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholiny such as tetrahydrothiene 1,1-dioxide and thiomorpholiny 1,1-dioxide. A

suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group via any suitable atom, such as via a carbon or nitrogen atom. However, reference herein to piperidino or morpholino refers to a piperidin-1-yl or morpholin-4-yl ring that is linked via the ring nitrogen.

[00131] By “bridged ring systems” is meant ring systems in which two rings share more than two atoms, see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages 131-133, 1992. Examples of bridged heterocyclyl ring systems include, aza-bicyclo[2.2.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.1]octane, quinuclidine, 6-azabicyclo[3.1.1]heptane, 8-azabicyclo[3.2.1]octane, bicyclo[3.2.1]octane, 7-oxabicyclo[2.2.1]hept-2-ene and 3-oxa-8-azabicyclo[3.2.1]octane.

[00132] The term “heteroaryl” or “heteroaromatic” means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. The term heteroaryl includes both monovalent species and divalent species. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[00133] Examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl,

- benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzoquinolyl, pyridopyrazinyl, thieno[2,3-*b*]furanyl, 2H-furo[3,2-*b*]pyranyl, 5H-pyrido[2,3-*d*]-o-oxazinyl, 1H-pyrazolo[4,3-*d*]-oxazolyl, 4H-imidazo[4,5-*d*]thiazolyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*b*][1,2,4]triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a non-aromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or sulfur. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolyl, tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl and 3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazinyl.
- 15 **[00134]** Examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.
- [00135]** Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.
- 20 **[00136]** A bicyclic heteroaryl group may be, for example, a group selected from:
- a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
 - a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
 - a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
 - 25 a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - 30 a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;
 - a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a cyclohexyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms; and

5 a cyclopentyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms.

[00137] Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuranyl, benzthiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indoliziny, indoliny, isoindoliny, puriny (e.g., adeniny, 10 guaniny), indazolyl, benzodioxolyl and pyrazolopyridiny groups.

[00138] Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoliny, isoquinoliny, chromanyl, thiochromanyl, chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinoliziny, benzoxaziny, benzodiaziny, pyridopyridiny, quinoxaliny, quinazoliny, cinnoliny, 15 phthalaziny, naphthyridiny and pteridiny groups.

[00139] The term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In particular embodiment, an aryl is phenyl.

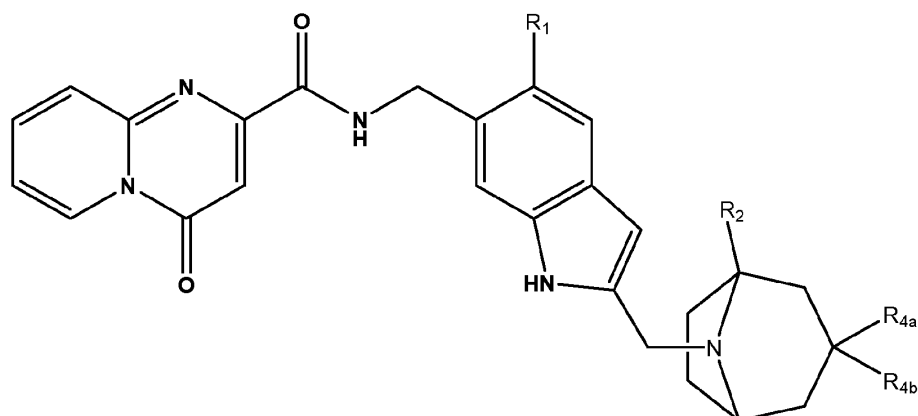
20 [00140] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

[00141] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

25 [00142] The phrase "compound of the invention" means those compounds which are disclosed herein, both generically and specifically.

Compounds of the invention

[00143] In one aspect, the present invention relates to compounds of the formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R₁ is selected from hydrogen or fluoro;

5 R₂ is selected from hydrogen or methyl; and

R_{4a} and R_{4b} are each independently selected from hydrogen, fluoro, methyl or fluoromethyl (e.g. CF₃, CF₂H, CFH₂), with the proviso that at least one of R_{4a} and R_{4b} is not hydrogen.

[00144] In certain embodiments, R₁ is hydrogen. In other embodiments, R₁ is fluoro.

10 [00145] In certain embodiments, R₂ is methyl. In other embodiments, R₂ is hydrogen.

[00146] Suitably, R_{4a} and R_{4b} are each independently selected from hydrogen, fluoro, methyl, CF₂H, with the proviso that at least one of R_{4a} and R_{4b} is not hydrogen.

[00147] Suitably, at least one of R_{4a} and R_{4b} is hydrogen, and the other is selected from fluoro, methyl, fluoromethyl (e.g. CF₃, CF₂H, CFH₂), or both R_{4a} and R_{4b} are fluoro.

15 [00148] Suitably, at least one of R_{4a} and R_{4b} is hydrogen, and the other is selected from methyl or fluoromethyl (e.g. CF₃, CF₂H, CFH₂).

[00149] More suitably, R_{4a} and R_{4b} are as defined below:

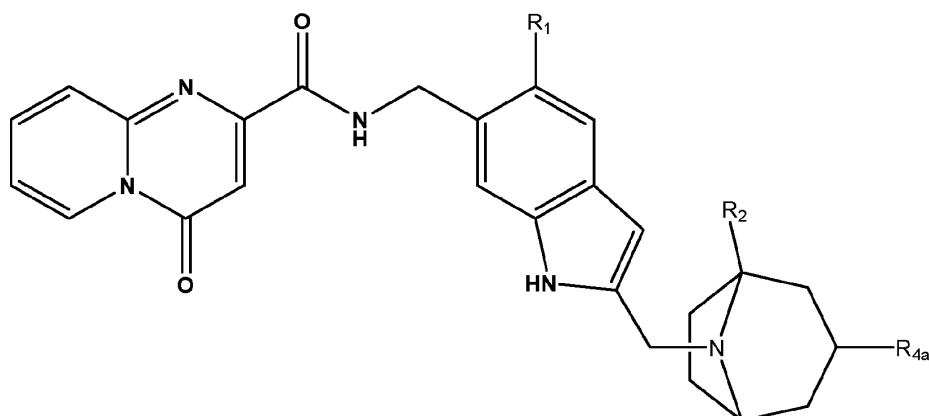
- a) one of R_{4a} and R_{4b} is methyl and the other is hydrogen;
- b) one of R_{4a} and R_{4b} is CF₂H and the other is hydrogen;
- 20 c) R_{4a} and R_{4b} are both fluoro.

[00150] More suitably, R_{4a} and R_{4b} are as defined below:

- a) one of R_{4a} and R_{4b} is methyl and the other is hydrogen;
- b) one of R_{4a} and R_{4b} is CF₂H and the other is hydrogen;

[00151] In a particular group of compounds of the invention, the compounds have the structural formula (II) below:

25



(II)

wherein R₁, R₂ and R_{4a} each have any one of the meanings defined herein, or a pharmaceutically acceptable salt thereof.

5 [00152] In an embodiment of the compounds of Formula (II):

R₁ is hydrogen or fluoro;

R₂ is hydrogen or methyl; and

R_{4a} is methyl or CF₂H.

[00153] In an embodiment of the compounds of Formula (II):

10 R₁ is hydrogen or fluoro;

R₂ is hydrogen; and

R_{4a} is methyl or CF₂H.

[00154] In an embodiment of the compounds of Formula (II):

R₁ is hydrogen or fluoro;

15 R₂ is hydrogen or methyl; and

R_{4a} is methyl.

[00155] In an embodiment of the compounds of Formula (II):

R₁ is hydrogen or fluoro;

R₂ is hydrogen; and

20 R_{4a} is CF₂H.

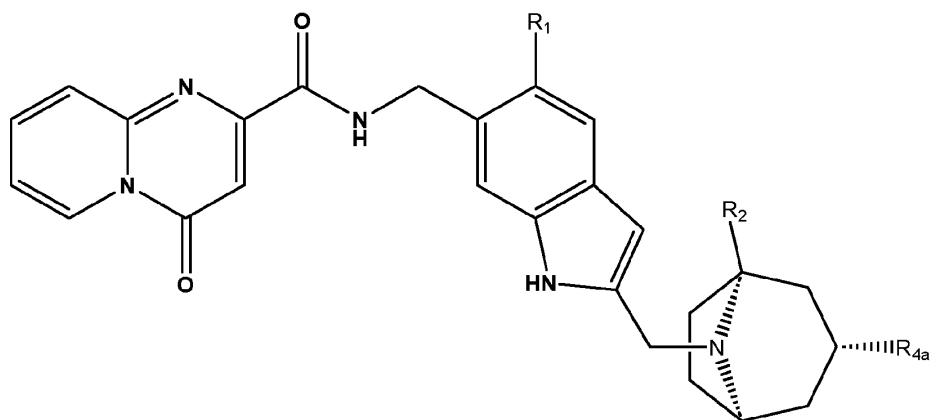
[00156] In an embodiment of the compounds of Formula (II):

R₁ is fluoro;

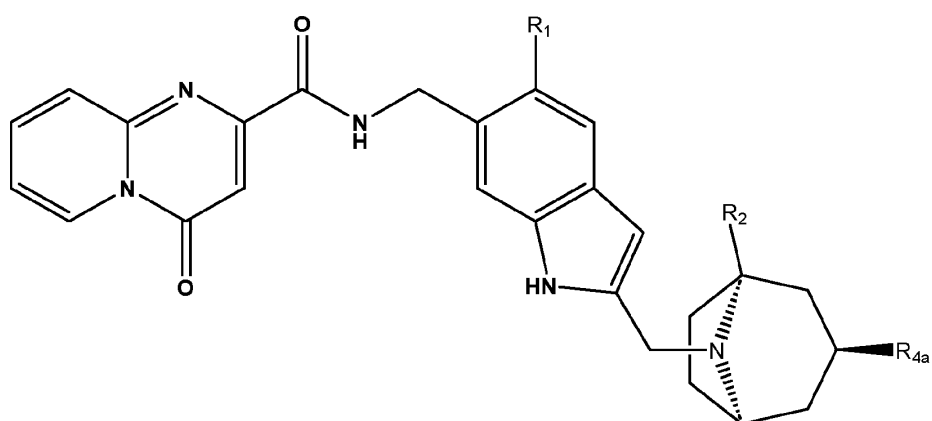
R₂ is hydrogen or methyl; and

R_{4a} is methyl.

[00157] In a particular group of compounds of the invention, the compounds have the structural formula (IIa), (IIb), (IIc) or (IId) below:

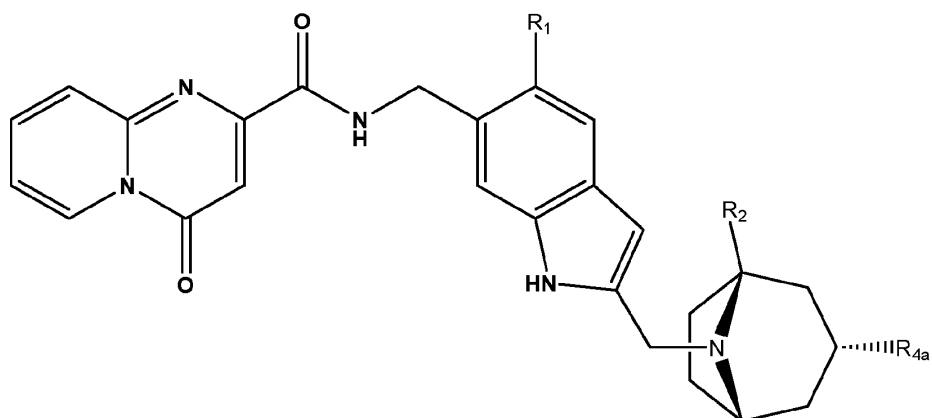


(IIa)

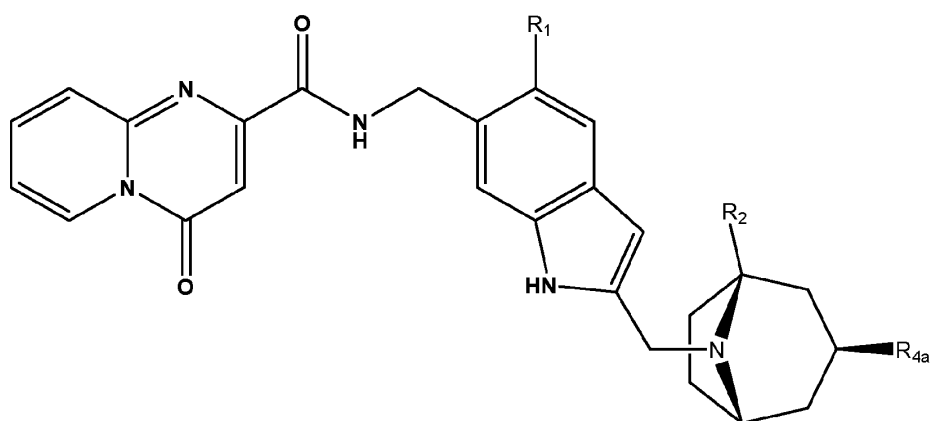


(IIb)

29



(IIc)



(IIId)

5

wherein R_1 , R_2 and R_{4a} each have any one of the meanings defined herein, or a pharmaceutically acceptable salt thereof.

10 **[00158]** In an embodiment of the compounds of Formula (IIa), (IIb), (IIc) and (IIId):

R_1 is hydrogen or fluoro;

R_2 is hydrogen or methyl; and

R_{4a} is methyl or CF_2H .

15 **[00159]** In an embodiment of the compounds of Formula (IIa), (IIb), (IIc) and (IIId):

R_1 is hydrogen or fluoro;

R_2 is hydrogen; and

R_{4a} is methyl or CF₂H.

[00160] In an embodiment of the compounds of Formula (IIa), (IIb), (IIc) and (IId):

R₁ is hydrogen or fluoro;

R₂ is hydrogen or methyl; and

5 R_{4a} is methyl.

[00161] In an embodiment of the compounds of Formula (IIa), (IIb), (IIc) and (IId):

R₁ is hydrogen or fluoro;

R₂ is hydrogen; and

R_{4a} is CF₂H.

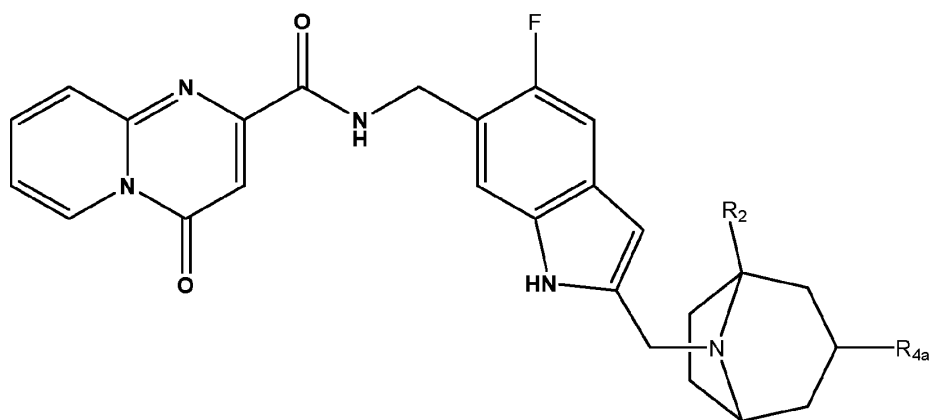
10 [00162] In an embodiment of the compounds of Formula (IIa), (IIb), (IIc) and (IId):

R₁ is fluoro;

R₂ is hydrogen or methyl; and

R_{4a} is methyl.

15 [00163] In a particular group of compounds of the invention, the compounds have the structural formula (III) below:



(III)

wherein R₂ and R_{4a} each have any one of the meanings defined herein, or a pharmaceutically acceptable salt thereof.

20

[00164] In an embodiment of the compounds of Formula (III):

R₂ is hydrogen or methyl; and

R_{4a} is methyl or CF₂H.

[00165] In an embodiment of the compounds of Formula (III):

R_2 is hydrogen; and

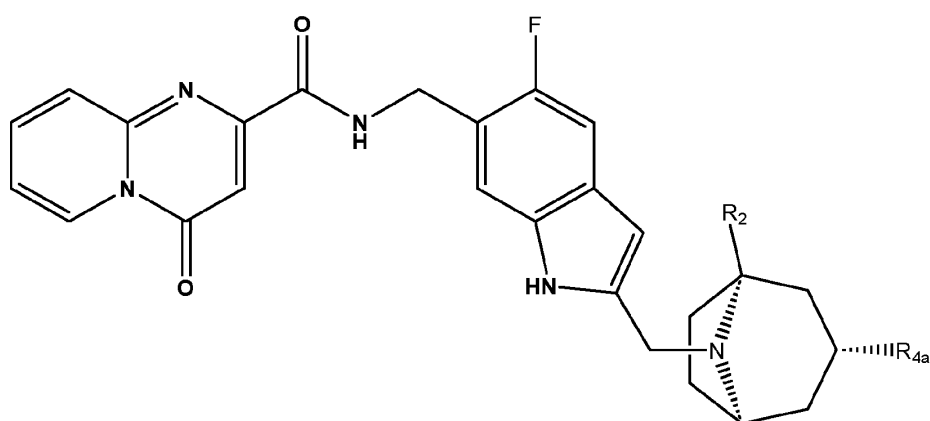
R_{4a} is methyl or CF_2H .

[00166] In an embodiment of the compounds of Formula (III):

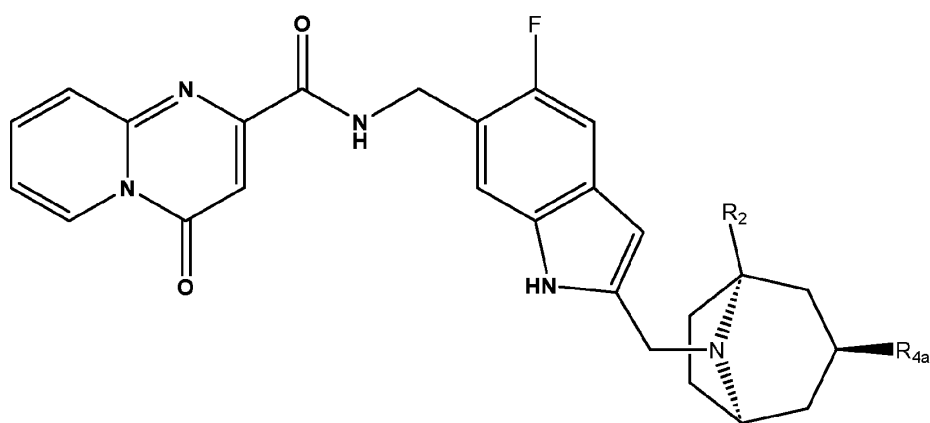
R_2 is hydrogen or methyl; and

5 R_{4a} is methyl.

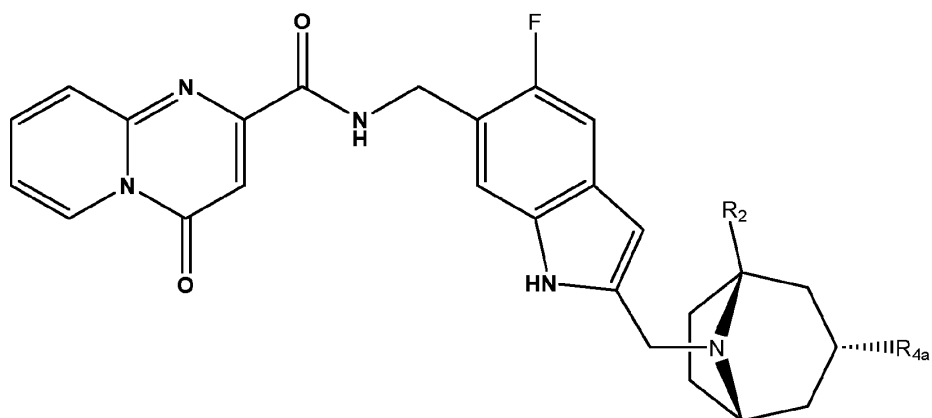
[00167] In a particular group of compounds of the invention, the compounds have the structural formula (IIIa), (IIIb), (IIIc) or (IIId) below:



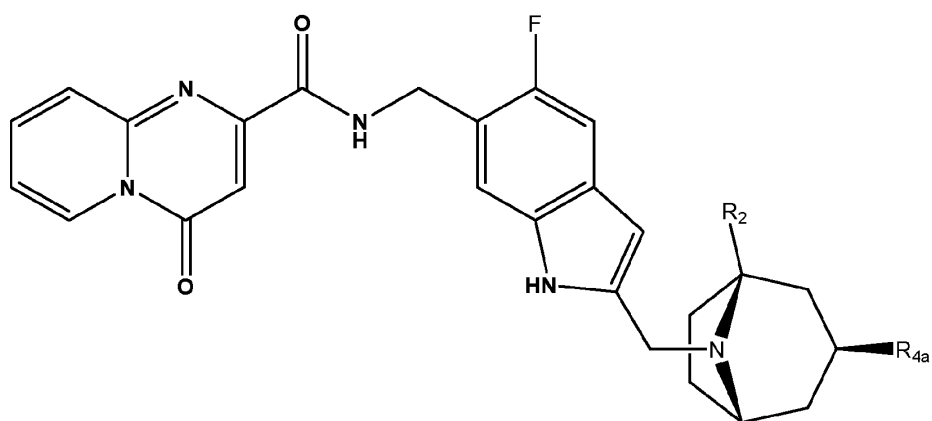
(IIIa)



(IIIb)



(IIIc)



(III d)

5

wherein R_2 and R_{4a} each have any one of the meanings defined herein, or a pharmaceutically acceptable salt thereof.

[00168] In an embodiment of the compounds of Formula (IIIa) or (IIIb):

10 R_2 is hydrogen or methyl; and

R_{4a} is methyl or CF_2H .

[00169] In an embodiment of the compounds of Formula (IIIa) or (IIIb):

R_2 is hydrogen; and

R_{4a} is methyl or CF_2H .

15 **[00170]** In an embodiment of the compounds of Formula (IIIa) or (IIIb):

R_2 is hydrogen or methyl; and

R_{4a} is methyl.

[00171] Particular compounds of the present invention include any of the compounds exemplified in the present application, or a pharmaceutically acceptable salt thereof, and, in particular, any of the following:

- 5 N-[[2-[(3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-((5-fluoro-2-(((1R,3r,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-10 1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-((5-fluoro-2-(((1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
- 15 N-((2-(((1S*,3R*,5R*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide; or
N-((2-(((1R*,3S*,5S*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide.

[00172] The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 900, for example less than 800, or less than 750, or less than 700, or less than 650. More preferably, the molecular weight is less than 600 and, for example, is 550 or less.

[00173] A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid addition salt of a compound of the invention which is sufficiently basic, for example, an acid addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric methane sulfonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt, 30 or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris(2hydroxyethyl)amine.

[00174] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 35

“isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are nonsuperimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R and S sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (–) isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[00175] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of “Advanced Organic Chemistry”, 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the invention may have geometric isomeric centres (E- and Z- isomers). It is to be understood that the present invention encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess antiproliferative activity.

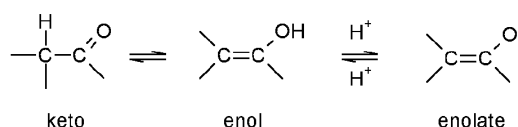
[00176] The present invention also encompasses compounds of the invention as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D), and ^3H (T); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; and O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

[00177] It is also to be understood that certain compounds of the formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess antiproliferative activity.

[00178] It is also to be understood that certain compounds of the formula (I) may exhibit polymorphism, and that the invention encompasses all such forms that possess antiproliferative activity.

[00179] Compounds of the formula (I) may exist in a number of different tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

- 5 Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[00180] Compounds of the formula (I) containing an amine function may also form N-oxides.

- 10 A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such
- 15 as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (*m*CPBA), for example, in an inert solvent such as dichloromethane.

- 20 [00181] The compounds of formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached.
- 25 Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the formula (I) and *in-vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the formula (I).

- [00182] Accordingly, the present invention includes those compounds of the formula I as
- 30 defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the formula (I) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by

way of metabolism of a precursor compound, that is a compound of the formula (I) may be a synthetically-produced compound or a metabolically-produced compound.

[00183] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[00184] Various forms of pro-drug have been described, for example in the following documents :-

- a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);
- f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);
- g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and
- h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[00185] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the formula (I) containing a carboxy group is, for example, a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkyl esters such as methyl, ethyl and *tert*-butyl, C₁₋₆alkoxymethyl esters such as methoxymethyl esters, C₁₋₆alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C₃₋₈cycloalkylcarbonyloxy- C₁₋₆alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C₁₋₆alkoxycarbonyloxy- C₁₋₆alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

[00186] A suitable pharmaceutically acceptable pro-drug of a compound of the formula

(I) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the formula (I) containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C₁₋₁₀alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C₁₋₁₀alkoxycarbonyl groups such as ethoxycarbonyl, *N,N*-(C₁₋₆)₂carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁₋₄alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

15 [00187] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C₁₋₄alkylamine such as methylamine, a (C₁₋₄alkyl)₂amine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a C₁₋₄alkoxy- C₂₋₄alkylamine such as 2-methoxyethylamine, a phenyl-C₁₋₄alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[00188] A suitable pharmaceutically acceptable pro-drug of a compound of the formula (I) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C₁₋₁₀alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁₋₄alkyl)piperazin-1-ylmethyl.

30 [00189] The *in vivo* effects of a compound of the formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the formula (I). As stated hereinbefore, the *in vivo* effects of a compound of the formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

[00190] Though the present invention may relate to any compound or particular group of compounds defined herein by way of optional, preferred or suitable features or otherwise in

terms of particular embodiments, the present invention may also relate to any compound or particular group of compounds that specifically excludes said optional, preferred or suitable features or particular embodiments.

[00191] Suitably, the present invention excludes any individual compounds not
5 possessing the biological activity defined herein.

Synthesis

[00192] The compounds of the present invention can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

10 [00193] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

15 [00194] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[00195] It will be appreciated that during the synthesis of the compounds of the invention in the processes defined herein, or during the synthesis of certain starting materials,
20 it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

[00196] For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher:
25 John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

[00197] Thus, if reactants include, for example, groups such as amino, carboxy or
30 hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[00198] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for

example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

- 5 Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

- 10 [00199] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

- 20 [00200] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

[00201] Resins may also be used as a protecting group.

[00202] The methodology employed to synthesise a compound of formula I will vary depending on the nature of the variable groups. Suitable processes for their preparation are described further in the accompanying Examples.

- 30 [00203] Once a compound of formula I has been synthesised by any one of the processes defined herein, the processes may then further comprise the additional steps of:

- (i) removing any protecting groups present;
- (ii) converting the compound formula I into another compound of formula I;
- (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or

(iv) forming a prodrug thereof.

[00204] The resultant compounds of formula I can be isolated and purified using techniques well known in the art.

Biological Activity

5 [00205] The METTL3 enzyme and cell assays described in accompanying Example section may be used to measure the pharmacological effects of the compounds of the present invention.

[00206] Although the pharmacological properties of the compounds of formula I vary with structural change, as expected, the compounds of the invention were found to be active
10 in these METTL3 assays.

[00207] In general, the compounds of the invention demonstrate an IC_{50} of 10 μM or less in the METTL3 enzyme assay described herein, with preferred compounds of the invention demonstrating an IC_{50} of 5 μM or less and the most preferred compounds of the invention demonstrating an IC_{50} of 2 μM or less.

15 [00208] In the METTL3 cell assay described in the Example section, the compounds of formula (I) suitably possess an activity of less than 10 μM , with preferred compounds of the invention demonstrating an IC_{50} of 5 μM or less and the most preferred compounds demonstrating an activity of 2 μM or less.

[00209] In the cell MDCK-MDR1 Permeability Assay described in the Example section,
20 the compounds of the present invention suitably have an efflux ratio less than 3, with more preferred compounds having an efflux ratio less than 2.5, and the most preferred compounds having an efflux ratio of less than 2.

Pharmaceutical Compositions

[00210] According to a further aspect of the invention there is provided a
25 pharmaceutical composition which comprises a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00211] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions,
30 dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a

sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00212] The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[00213] An effective amount of a compound of the present invention for use in therapy is an amount sufficient to treat or prevent any of the conditions described herein, slow its progression and/or reduce the symptoms associated with the condition and/or disease.

[00214] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00215] The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

[00216] In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

30 Therapeutic Uses and Applications

[00217] The present invention provides compounds that function as inhibitors of METTL3 activity.

[00218] The compounds of the invention may find particular use in the treatment of a disease or disorder in which METTL3 activity is implicated.

[00219] The disease or disorder in which METTL3 activity is implicated may be a proliferative condition.

[00220] The disease or disorder in which METTL3 activity is implicated may be:

- 5 a) cancer, e.g. lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, and other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS));
- 10 b) an autoimmune disease (e.g. colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis);
- 15 c) a neurological disease;
- d) an inflammatory disease;
- e) an infectious disease; (e.g. a viral infection, such as an RNA viral infection; optionally selected from human papillomavirus (HPV) or hepatitis);
- f) type 2 diabetes;
- 20 g) a disorder of the CNS; e.g. a neurodegenerative disorder, e.g. a tauopathy such as Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglialopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy;
- 25 a motor neuron disease, a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease) or Parkinson's Disease; or epilepsy;
- h) a neuropsychiatric behavioural disorder;
- 30 i) a depressive disorder; or
- j) a disease related to the inactivation of the X-chromosome, e.g. RETT syndrome.

[00221] The present invention therefore provides a method of inhibiting METTL3 activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of
35 a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition

as defined herein.

[00222] The present invention also provides a method of treating a disease or disorder in which METTL3 activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein. Suitably, the disease or disorder in which METTL3 activity is implicated is cancer, such as lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS); an autoimmune disease (e.g. colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis); a neuropsychiatric behavioural disorder; a neurological disease; an inflammatory disease; an infection (e.g. viral infection); type 2 diabetes; a disorder of the CNS, such as a neurodegenerative disorder, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy); a motor neuron disease (including ALS); a repeat expansion disease (such as Huntington's Disease); dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease); Parkinson's Disease; a neuropsychiatric behavioural disorder; a depressive disorder; a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome); or a disease related to the inactivation of the Y-chromosome (e.g. Klinefelter syndrome); or epilepsy.

[00223] The present invention provides a method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[00224] The present invention provides a method of treating a proliferative disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00225] The present invention provides a method of treating cancer, said method

comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein. Suitably the cancer is selected from lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS).

[00226] The cancer of the central nervous system may be selected from (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain).

[00227] The present invention provides a method of treating leukaemia (e.g. e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS)), said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00228] The present invention provides a method of treating acute myeloid leukaemia (AML), said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00229] The present invention provides a method of treating chronic myeloid leukaemia, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00230] The present invention provides a method of treating a cancer of the central nervous system (CNS), said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00231] The present invention provides a method of treating an autoimmune disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical

composition as defined herein. Suitably the autoimmune disease is colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis.

[00232] The present invention provides a method of treating a disorder of the CNS, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein. Suitably the disorder of the CNS is a neurodegenerative disorder, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy and chronic traumatic encephalopathy), or a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome)

[00233] The present invention provides a method of treating a neurological disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00234] The present invention provides a method of treating an infectious disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00235] The present invention provides a method of treating an inflammatory disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[00236] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in therapy.

[00237] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a proliferative condition.

[00238] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of cancer. In a particular embodiment, the cancer is human cancer. Suitably the cancer is selected from lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas,

Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS).

[00239] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of leukaemia e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS).

[00240] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of acute myeloid leukaemia (AML).

[00241] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of chronic myeloid leukaemia.

[00242] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a cancer of the CNS. Cancers of the CNS include but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

[00243] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the inhibition of METTL3 activity.

[00244] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of an autoimmune disease. Suitably the autoimmune disease is colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis.

[00245] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a disorder of the CNS. Suitably the disorder of the CNS is a neurodegenerative disorder, for example a tauopathy.

[00246] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a

tauopathy. The tauopathy may be selected from Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglipathy, primary age-related tauopathy (PART), Progressive
5 supranuclear palsy, and chronic traumatic encephalopathy.

[00247] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a motor neuron disease (including ALS). Suitably, the motor neurone disease is selected from amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive
10 muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. More suitably, the motor neuron disease is ALS.

[00248] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a repeat expansion disease (such as Huntington's Disease)

15 **[00249]** The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease).

[00250] The present invention provides a compound, or a pharmaceutically acceptable
20 salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of Alzheimer's Disease.

[00251] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of Parkinson's Disease.

25 **[00252]** The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of multiple sclerosis.

[00253] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of
30 epilepsy.

[00254] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a disease related to the inactivation of the X-chromosome.

[00255] The present invention provides a compound, or a pharmaceutically acceptable

salt thereof, or a pharmaceutical composition as defined herein for use in reactivating expression of a silenced X-chromosome

[00256] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of
5 RETT syndrome.

[00257] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a neurological disease.

[00258] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of an
10 infectious disease.

[00259] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of an inflammatory disease.

15 [00260] The present invention provides a compound, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of a disease or disorder in which METTL3 activity is implicated.

[00261] Suitably, the disease or disorder in which METTL3 activity is implicated is a proliferative condition.

20 [00262] Suitably, the disease or disorder in which METTL3 activity is implicated is cancer. The cancer may be selected from lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain
25 neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS). Suitably, the cancer is a cancer of the CNS.

[00263] Suitably, the disease or disorder in which METTL3 activity is implicated is an
30 autoimmune disease (e.g. colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis)

[00264] Suitably, the disease or disorder in which METTL3 activity is implicated is a neurological disease.

[00265] Suitably, the disease or disorder in which METTL3 activity is implicated is an inflammatory disease.

[00266] Suitably, the disease or disorder in which METTL3 activity is implicated is an infectious disease; (e.g. a viral infection).

5 [00267] Suitably, the disease or disorder in which METTL3 activity is implicated is type 2 diabetes.

[00268] Suitably, the disease or disorder in which METTL3 activity is implicated is a neuropsychiatric behavioural disorder.

10 [00269] Suitably, the disease or disorder in which METTL3 activity is implicated is a depressive disorder.

[00270] Suitably, the disease or disorder in which METTL3 activity is implicated is a disorder of the CNS, such as a neurodegenerative disorder, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's
15 disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy), a motor neuron disease (including ALS), a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease) or Parkinson's Disease;
20 aneuropsychiatric behavioural disorder; a depressive disorder; a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome); or epilepsy.

[00271] Suitably, the disease or disorder in which METTL3 activity is implicated is a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome). Such a disease may be treated by reactivating expression of the silenced gene by administering a
25 METTL3 inhibitor as described herein.

[00272] Disorders related to the inactivation of the X-chromosome which may be treated by the compounds of the invention include those disclosed in Table 4 of WO2022/086935, such as Addison's disease with cerebral sclerosis; Adrenal hypoplasia; siderius X-linked mental retardation syndrome; Agammaglobulinaemia, Bruton type; Choroidoretinal
30 degeneration; Choroidaemia; Albinism, ocular; Dent's disease 2; fragile X syndrome; Rett/ Epileptic encephalopathy, early infantile, 2 (CDKL5 deficiency disorder); Albinism-deafness syndrome; paroxysmal nocturnal hemoglobinuria; Aldrich syndrome; Alport syndrome; Anaemia, hereditary hypochromic; Anemia, sideroblastic, with ataxia; Fabry disease; Spinal muscular atrophy 2; Cataract, congenital; Charcot-Marie-Tooth, peroneal; Spastic paraplegia;
35 Colour blindness; Diabetes insipidus, nephrogenic; DDX3X syndrome; Dyskeratosis

congenita; Ectodermal dysplasia, anhidrotic; Faciogenital dysplasia (Aarskog syndrome); Glucose-6-phosphate dehydrogenase deficiency; Glycogen storage disease type VIII; Gonadal dysgenesis (XY female type); Granulomatous disease (chronic); Haemophilia A; Haemophilia B; Hydrocephalus (aqueduct stenosis); Hypophosphataemic rickets; Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency);
 5 Incontinentia pigmenti; Kallmann syndrome; Keratosis follicularis spinulosa; Lowe (oculocerebrorenal) syndrome; Menkes syndrome; Renpenning Syndrome; Mental retardation, with or without fragile site (numerous specific types); Coffin-Lowry syndrome; Microphthalmia with multiple anomalies (Lenz syndrome); Muscular dystrophy (Becker,
 10 Duchenne and Emery-Dreifuss types); Myotubular myopathy; Night blindness, congenital stationary; Norrie's disease (pseudoglioma); Nystagmus, oculomotor or 'jerky'; Orofaciodigital syndrome (type I); Omithine transcarbamylase deficiency (type I hyperammonaemia); Phosphoglycerate kinase deficiency; Phosphoribosylpyrophosphate synthetase deficiency; Retinitis pigmentosa; Retinoschisis; Rett syndrome; Muscular atrophy /Dihydrotestosterone
 15 receptor deficiency; Spinal muscular atrophy; Spondyloepiphyseal dysplasia tarda; Thrombocytopenia, hereditary; Thyroxine-binding globulin, absence; and McLeod syndrome.

[00273] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a proliferative condition.

20 **[00274]** The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of cancer. Suitably, the medicament is for use in the treatment of human cancers. Suitably the cancer is lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer
 25 of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic
 30 syndromes (MDS) or leukaemia, suitably acute myeloid leukaemia (AML) or chronic myeloid leukaemia.

[00275] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of leukaemia, e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia
 35 (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS).

[00276] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of acute myeloid leukaemia (AML).

5 [00277] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a cancer of the CNS. Cancers of the CNS include but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

10 [00278] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of an autoimmune disease. Suitably the autoimmune disease is colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis.

15 [00279] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a disorder of the CNS. Suitably the disorder of the CNS is a neurodegenerative disorder, for example a tauopathy.

20 [00280] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a tauopathy. The tauopathy may be selected from Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglipathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy.

25 [00281] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a motor neuron disease (including ALS). Suitably, the motor neurone disease is selected from amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome. More suitably, the motor neuron disease is ALS.

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[00282] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a repeat expansion disease (such as Huntington's Disease).

[00283] The present invention provides a use of a compound, or a pharmaceutically

acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease).

5 [00284] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of Alzheimer's Disease.

[00285] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of Parkinson's Disease

10 [00286] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of multiple sclerosis.

[00287] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the
15 treatment of epilepsy.

[00288] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a disease related to the inactivation of the X-chromosome.

[00289] The present invention provides a use of a compound, or a pharmaceutically
20 acceptable salt thereof, as defined herein in the manufacture of a medicament for reactivating expression of a silenced X-chromosome

[00290] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment RETT syndrome.

25 [00291] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a neurological disease.

[00292] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the
30 treatment of an inflammatory disease.

[00293] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of an infectious disease.

[00294] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the inhibition of METTL3 activity.

[00295] The present invention provides a use of a compound, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of a disease or disorder in which METTL3 activity is implicated.

[00296] Suitably, the disease or disorder in which METTL3 activity is implicated is cancer, such as lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS); an autoimmune disease (e.g. colitis, multiple sclerosis, rheumatoid arthritis, lupus, cirrhosis, or dermatitis); a neuropsychiatric behavioural disorder; an inflammatory disease; an infection (e.g. viral infection); type 2 diabetes; a disorder of the CNS, such as a neurodegenerative disorder, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome (also known as corticobasal degeneration), frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy), a motor neuron disease (including ALS), a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease) or Parkinson's Disease; aneuropsychiatric behavioural disorder; a depressive disorder; a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome); or epilepsy.

[00297] Suitably, the disease or disorder in which METTL3 activity is implicated is cancer, such as lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the central nervous system (CNS) (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain), leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS); an autoimmune disease (e.g. colitis, multiple sclerosis, rheumatoid

arthritis, lupus, cirrhosis, or dermatitis); a neuropsychiatric behavioural disorder; a neurological disease; an inflammatory disease; an infection (e.g. viral infection); type 2 diabetes; a disorder of the CNS, such as a neurogenerative disorder, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliaopathy, primary age-related tauopathy and chronic traumatic encephalopathy); a neuropsychiatric behavioural disorder; a depressive disorder; or a disease related to the inactivation of the X-chromosome (e.g. RETT syndrome).

[00298] The term "proliferative disorder" are used herein pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, malignant neoplasms and tumours, cancers, leukaemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain and skin.

[00299] The cancer to be treated may be lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, skin cancer, renal cancer, solid organ cancer, pancreatic cancer, a cancer of the CNS or leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS)). Certain cancers of the CNS include, but are not limited to Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

[00300] Certain disorders of the CNS include, but are not limited to neurodegenerative disorders, for example a tauopathy (including but not limited to Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliaopathy, primary age-related tauopathy and chronic traumatic encephalopathy).

[00301] The anti-proliferative effects of the compounds of the present invention have particular application in the treatment of human cancers (by virtue of their inhibition of METTL3 activity).

[00302] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the

formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death).

5 [00303] In a particular embodiment of the invention, the proliferative condition to be treated is cancer.

Routes of Administration

[00304] The compounds of the invention or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

10 [00305] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by
15 injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Combination Therapies

20 [00306] In one aspect, the present invention provides a combination comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents.

[00307] In another aspect, the present invention relates to a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, with
25 one or more additional therapeutic agents, and one or more pharmaceutically acceptable excipients.

[00308] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in therapy.

30 [00309] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in the treatment of cancer.

[00310] In another aspect, the present invention relates to a use of a combination as defined herein in the manufacture of a medicament for the treatment of cancer.

[00311] In another aspect, the present invention relates to a method of treating of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined herein.

[00312] Suitably, the cancer is any one of the cancers described herein. More suitably, the cancer is a cancer of the CNS.

[00313] The antiproliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- 10 (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine
15 arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and
20 teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate),
25 aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino]thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor
35 antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody

- trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth
- 5 factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth
- 10 factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase
- 15 inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial
- 20 growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as
- 25 those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669,
- 30 WO 01/92224, WO 02/04434 and WO 02/08213;
- (vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;
- (viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (ix) gene therapy approaches, including for example approaches to replace aberrant genes
- 35 such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug

therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;

- (x) immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies; and
- 10 (xi) Agents used to treat AML leukaemia, including for example, cytarabine, FLT3 inhibitors, BCL2 inhibitors or IDH1/2 inhibitors.

[00314] In a particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy.

- 15 **[00315]** Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

- 20 **[00316]** According to this aspect of the invention there is provided a combination for use in the treatment of a cancer (for example a cancer involving a solid tumour) comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and another anti-tumour agent.

- [00317]** According to this aspect of the invention there is provided a combination for use in the treatment of a proliferative condition, such as cancer (for example a cancer involving a solid tumour), comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and any one of the anti-tumour agents listed herein above.
- 25

- [00318]** In a further aspect of the invention there is provided a compound of the invention or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in combination with another anti-tumour agent, optionally selected from one listed herein above.
- 30

[00319] Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention

“combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

5 **[00320]** According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent (optionally selected from one listed herein above), in association with a pharmaceutically acceptable diluent or carrier.

10 **[00321]** In another embodiment, the invention relates to a therapeutic combination comprising a compound as defined herein and another agent used to treat AML leukaemia e.g., cytarabine, FLT3 inhibitors, BCL2 inhibitors or IDH1/2 inhibitors.

[00322] In another embodiment, the invention relates to a therapeutic combination comprising a compound as defined herein and a BCL2 inhibitor (e.g. venetoclax).

15 **[00323]** In another embodiment, the invention relates to a therapeutic combination comprising a compound as defined herein and an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, hypomethylating agent (e.g. 5-azacitidine or decitabine) or FLT3 inhibitor (e.g. quizartinib).

Combinations with immune oncology agent or therapy

20 **[00324]** In one aspect the present invention relates to a combination comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[00325] In another embodiment, the invention relates to a therapeutic combination comprising a compound as defined herein and an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

30 **[00326]** In another embodiment, the invention relates to a therapeutic combination comprising a compound as defined herein and an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor).

[00327] In another embodiment, the invention relates to a therapeutic combination

comprising a compound as defined herein and an immune checkpoint inhibitor.

[00328] Any immune checkpoint inhibitor may be used in the combination therapy defined herein.

[00329] In one embodiment, the immune checkpoint inhibitor is selected from a PD1, PD-L1 inhibitor, a LAG3 inhibitor and a CTLA-4 inhibitor. In a particular embodiment, the immune checkpoint inhibitor is a PD1 or PD-L1 inhibitor.

[00330] PD-1 is a cell surface receptor protein present on T cells. PD-1 plays an important role in down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity. The PD-1 protein is an immune checkpoint that guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T cells in lymph nodes, while simultaneously reducing apoptosis in regulatory T cells (anti-inflammatory suppressive T cells).

[00331] PD-1 therefore inhibits the immune system. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells.

[00332] PD1 binds two ligands, PD-L1 and PD-L2. PD-L1 is of particular interest as it is highly expressed in several cancers and hence the role of PD1 in cancer immune evasion is well established. Monoclonal antibodies targeting PD-1 that boost the immune system are being developed for the treatment of cancer. Many tumour cells express PD-L1, an immunosuppressive PD-1 ligand; inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses *in vitro* and mediate preclinical antitumour activity. This is known as immune checkpoint blockade.

[00333] Examples of drugs that target PD-1 include pembrolizumab (Keytruda) and nivolumab (Opdivo). These drugs have been shown to be effective in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. They are also being studied for use against many other types of cancer. Examples of drugs in development include BMS-936559 (Bristol Myers Squibb), MGA012 (MacroGenics) and MEDI-0680 (MedImmune).

[00334] Examples of drugs that inhibit PD-L1 include atezolizumab (Tecentriq), avelumab (Bavencio) and durvalumab (Imfinzi). These drugs have also been shown to be helpful in treating different types of cancer, including bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma). They are also being studied for use against other types of cancer.

[00335] Examples of LAG3 inhibitors include BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781 and LAG525.

[00336] Examples of CTLA-4 inhibitors include MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab.

[00337] In one embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781, LAG525, MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

[00338] In another embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, MDX-010/Ipilimumab, CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab, or a pharmaceutically acceptable salt thereof.

10 [00339] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

[00340] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

15 [00341] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab and avelumab, or a pharmaceutically acceptable salt thereof.

EXAMPLES

20 [00342] The following abbreviations have been used in the Examples:

Abbreviations

DAST: Diethylaminosulfur trifluoride

DCE: 1,2-Dichloroethane

DCM: Dichloromethane

25 DIPEA: Diisopropylethylamine

DMF: Dimethylformamide

DMSO: Dimethyl sulfoxide

HATU: Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

IPA: Isopropanol

30 RT: Retention Time

SFC: Supercritical fluid chromatography

STAB: Sodium triacetoxymethylborohydride

TEA: Triethylamine

THF: Tetrahydrofuran

35 TMEDA: Tetramethylethylenediamine

The following methodologies have been used in the Examples:**Method A:**

[00343] High pH reverse phase system using a Waters UPLC® BEH C18 column (2.1 mm × 30 mm, 1.7 µm; temperature: 40 °C), with an injection volume of 1 µL at a flow rate of 1 mL/min and a gradient of 5 – 100% B over 0.75 min, then 100% B for 0.1 min, where A = 2 mM ammonium bicarbonate in water, buffered to pH 10, and B = acetonitrile. A second gradient of 100 – 5% B was then applied over 0.05 min and held for 0.1 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Waters Quattro Premier XE detector; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method B:

[00344] High pH reverse phase system using a Waters UPLC® BEH C18 column (2.1 mm × 100 mm, 1.7 µm; temperature: 55 °C), with an injection volume of 1 µL and at a flow rate of 0.6 mL/min and a gradient of 5 – 100% B over 5.3 min, then 100% B for 0.5 min, where A = 2 mM ammonium bicarbonate in water, buffered to pH 10, and B = acetonitrile. A second gradient of 100 – 5% B was then applied over 0.02 min and held for 1.18 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Waters Quattro Premier XE mass detector or a Waters SQD2; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method C:

[00345] LCMS were performed in reverse phase using a Waters UPLC® BEH C18 (2.1 mm x 50 mm, 2.5 µm; temperature: Ambient), with an injection volume of 10 µL maximum at a flow rate of 0.8 mL/min and a gradient of 3-100% of water over 3.00 min at a flow rate of 0.8 mL/min then 100 % B over 0.5min with 1 mL/min flow, where A = 0.1% Formic Acid in water, and B = 0.1% Formic Acid in Water: Acetonitrile (10:90). A second gradient of 100-3% was then applied over 0.01 min and hold for 0.49 min. UV spectra were recorded in spectrum range :200 -400 nm. Mass spectra were obtained using a Acquity Qda detector; ionization mode electrospray positive or negative. Data were integrated and reported using Waters Acquity UPLC and Empower 3 software.

Method D:

[00346] Waters acquity UPLC® H-Class equipped with PDA and attached with QDa detector, column: X-Bridge BEH C18, 50 x 2.1 mm, 2.5 micron, Column temperature: Ambient, Auto sampler temperature: 150C, Mobile Phase A : 2 mM ammonium acetate followed by 0.1%Formic acid in water, Mobile Phase B : 0.1% Formic Acid in Acetonitrile,

Mobile phase gradient details: T = 0 min (95% A, 5% B) flow; T = 0.4 min (95% A, 5% B) ; gradient to T = 0.8 min (65% A, 35% B) ; gradient to T = 1.20 min (45% A, 55% B) ; T = 2.5 min (0% A, 100% B) ; gradient to T = 3.30 min (0% A, 100% B) ; gradient to T = 3.31 min to end of run at T = 4 min (95% A, 5% B), Flow rate: 0.55 mL/min, Run Time: 4 min. UV Detection

5 Method: PDA Mass parameter: Probe: ESI.

Method E:

[00347] Low pH reverse phase system using a Shimadzu LC-20AD MSD: LCMS-2020 Luna C18 (30*2.0mm, 3µm; temperature: 40 °C), with an injection volume of 1 µL and at a flow rate of 1.0 mL/min and a gradient of 0 – 60% B over 2.5 min, then 60% B for 0.5 min, where
10 A = 10 mM ammonium bicarbonate in water, and B = acetonitrile. A second gradient of 95–5% B was then applied over 0.01 min and held for 0.54 min. UV spectra were recorded at 220 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Shimadzu LC-20AD&MS 2020; ionization mode: electrospray positive. Data were integrated and reported using Labsolutions software.

15 **Method F:**

[00348] High pH reverse phase system using a Agilent 1260 HPLC MSD: 6125B single quadrupole MSD. (Column: Xbridge C18, 2.1*50mm, 5µm; Column Temp: 40 °C), with an injection volume of 1 µL and at a flow rate of 0.8 mL/min and a gradient of 5 – 95% B over 3.4 min, then 95% B for 0.45 min, where A = 0.04% TFA in water, and B = 0.02% TFA in
20 acetonitrile. A second gradient of 60 – 0% B was then applied over 0.02 min and held for 0.04 min. UV spectra were recorded at 220 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Agilent 1260 & 6125B; ionization mode: electrospray positive. Data were integrated and reported using Openlab CDS or Openlab ChemStation Edition software.

Method G:

25 [00349] Low pH reverse phase system using a Agilent 1260 HPLC MSD: 6125B single quadrupole MSD. (Column: Luna C18, 2.0*50mm, 5µm; temperature: 40 °C), with an injection volume of 1 µL and at a flow rate of 1.0 mL/min and a gradient of 5% B for 0.4 min, then 5 – 95% B over 2.6 min, then held for 1.0 min, where A = 0.04% TFA in water, and B = 0.02% TFA in acetonitrile. A second gradient of 95–5% B was then applied over 0.01 min and held
30 for 0.5 min. UV spectra were recorded at 220 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Agilent 1260 & 6125B; ionization mode: electrospray positive. Data were integrated and reported using Openlab ChemStation software.

Method H:

[00350] Low pH reverse phase system using a Shimadzu LC-20AD MSD: LCMS-2020
35 Halo C18 30*3.0mm, 5µm; temperature: 40 °C), with an injection volume of 1 µL and at a flow

rate of 1.0 mL/min and a gradient of 5 – 95% B over 2.5 min, then 95% B for 0.5 min, where A = 0.04% TFA in water, and B = 0.02% TFA in acetonitrile. A second gradient of 95– 5% B was then applied over 0.01 min and held for 0.01 min. UV spectra were recorded at 220 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Shimadzu LC-20AD&MS
2020; ionization mode: electrospray positive. Data were integrated and reported using Labsolutions software.

Chiral analytical methods

Method A SFC:

[00351] Waters UPCC with PDA; column: Chiralpak IG-3, 50×4.6mm I.D., 3 µm;
10 temperature: 35 °C), with an injection volume of 2.0 µL and at a flow rate of 4.0 mL/min and a gradient of 50% A and 50% B for 6 min, where A = sCO₂, and B = MeOH:acetonitrile=1:1(0.1%IPA). UV spectra were recorded at 254 nm; spectrum range: 200 – 400 nm.

Method B SFC:

15 [00352] Waters UPCC with PDA; column: Chiralpak IH-3, 50×4.6mm I.D., 3µm; temperature: 35 °C), with an injection volume of 5.3 µL and at a flow rate of 3.4 mL/min and a gradient of 5% B for 0.2 min, then 5 – 50% B over 1.0 min, then held for 1.0 min, where A = sCO₂, and B = IPA[0.2%NH₃(7M in MeOH). A second gradient of 50– 5% B was then applied over 0.4 min and held for 0.4 min. UV spectra were recorded at 220 nm; spectrum range: 200
20 – 400 nm.

Preparative HPLC methods

Method A:

[00353] High pH purification reverse phase using a Waters Xbridge C18 column (30 mm × 100 mm, 5 µm; temperature: room temperature), with an injection volume of 1500 µL at a
25 flow rate of 40 mL/min at 30% B for 2.0 min then a gradient of 30 – 95% B over 9.5 min and held for 2.0 min, where A = 0.2% ammonium hydroxide in water and B = 0.2% ammonium hydroxide in acetonitrile. A second gradient of 95 – 30% B was then applied over 0.3 min and held for 1.3 min. UV spectra were recorded at 215 nm.

Method B:

30 [00354] High pH purification reverse phase using column: Phenomenex Gemini NX-C18 (75*30mm*3µm); mobile phase: [A = H₂O (0.05% NH₃H₂O+10mM NH₄HCO₃); B = acetonitrile]; gradient: XX%-YY% B over 8.0 min).

Method C:

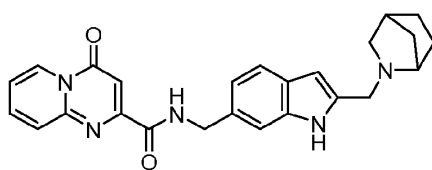
[00355] High pH purification reverse phase using column: Waters Xbridge BEH C18 (250*70 mm*10 μ m); mobile phase: [A = H₂O (0.05% NH₃H₂O); B = acetonitrile]; gradient: XX%-YY% B over 20.0 min.

Method D:

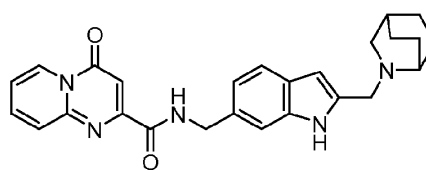
- 5 **[00356]** High pH purification reverse phase using column: Waters Xbridge Prep OBD C18 (150*40 mm*10 μ m); mobile phase: [A = H₂O (0.05% NH₃H₂O + 10 mM NH₄HCO₃); B = acetonitrile]; gradient: XX%-XX% B over 8.0 min.

Examples

Reference compounds



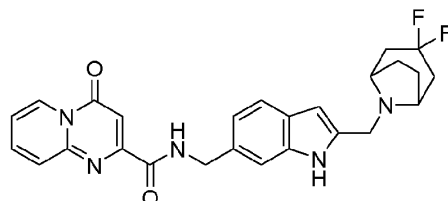
Reference compound 1



Reference compound 2

[00357] Reference compounds 1 and 2 were prepared according to previously described procedures (WO 2021/111124, examples 139 and 21 respectively).

Example 1: N-[(2-(3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

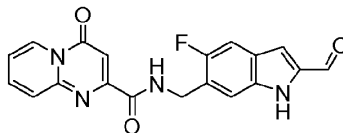


[00358] A mixture of STAB (92 mg, 0.43 mmol), 3,3-difluoro-8-azabicyclo[3.2.1]octane;hydrochloride (53 mg, 0.29 mmol), DIPEA(0.076 mL, 0.43 mmol) and N-[(2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide (50 mg, 0.14 mmol, prepared according to previous report: WO 2021/111124, Example 2, steps1-4) in DCE (4 mL) were stirred at 50 °C overnight. LCMS method A showed 94% conversion to the product. The reaction was worked up at this point. The reaction mixture was quenched with water (30 mL) and extracted with DCM (30 mL). The pH of the aqueous layer was then adjusted to pH 11 by addition of 1 M NaOH solution, and the aqueous layer was then extracted with DCM (2 x 30 mL). The combined organic layers were passed through an Isolute phase separator and concentrated in vacuo. The residue was purified by prep HPLC (method A). The product containing fractions were combined, concentrated in vacuo and freeze dried

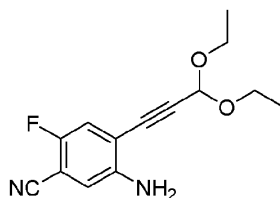
overnight to give N-[[2-[(3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide (47 mg, 69% yield) as a white solid.

[00359] Method B: LCMS (electrospray): m/z = 478.2. $(M+H)^+$, RT = 3.66 min, purity = 100%.

- 5 **Intermediate 1:** N-((5-fluoro-2-formyl-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



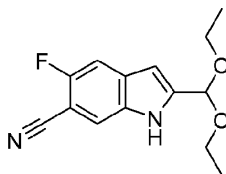
Step 1: 5-amino-4-(3,3-diethoxyprop-1-yn-1-yl)-2-fluorobenzonitrile



- 10 **[00360]** To a stirred solution of 5-amino-4-bromo-2-fluorobenzonitrile (90.0 g, 420.5 mmol) in THF (900 mL) were added $Pd(PPh_3)_2Cl_2$ (2.9 g, 4.2 mmol), TPP (2.2 g, 8.4 mmol), CuI (1.5 g, 8.4 mmol) and TEA (297.3 g, 2943.9 mmol) at room temperature. The resulting reaction mixture was degassed with nitrogen gas for 15 min. 3,3-Diethoxy-1-propyne (107.6 g, 841.1 mmol) was added and the resulting reaction mixture was stirred at 70 °C for 12 h. The reaction
- 15 mixture was diluted with water (2000 mL) and extracted with ethyl acetate (1500 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and the filtrate concentrated under vacuum. The crude product was purified by column chromatography on silica 60-120 using 12% ethyl acetate in hexane to afford 5-amino-4-(3,3-diethoxyprop-1-yn-1-yl)-2-fluorobenzonitrile (90.0 g, 82%) as a tan solid.
- 20 **[00361]** 1H NMR (400 MHz, DMSO- d_6) δ ppm: 7.40 (d, J = 10.0 Hz, 1H), 7.05 (d, J = 5.6 Hz, 1H), 5.71 (s, 2H), 5.59 (s, 1H), 3.69 – 3.65 (m, 2H), 3.62 – 3.54 (m, 2H), 1.16 (t, J = 7.2 Hz, 6H).

[00362] Method C: LCMS (electrospray): m/z = 261.1 $(M-H)^-$, RT = 2.23 min.

Step2 : 2-(diethoxymethyl)-5-fluoro-1H-indole-6-carbonitrile.

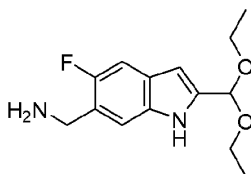


[00363] To a stirred solution of 5-amino-4-(3, 3-diethoxyprop-1-yn-1-yl)-2-fluorobenzonitrile (90 g, 343.5 mmol) in NMP (900 mL) were added KOtBu (76.94 g, 687.0 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 2 h then poured into cold water (1500 mL). The aqueous layer was extracted with ethyl acetate (1000 mL x 3). The combined organic layers were washed with brine solution and dried over anhydrous Na₂SO₄, filtered and the filtrate concentrated under vacuum. The crude product was purified by column chromatography on silica 60-120 using 8% ethyl acetate in hexane to give 2-(diethoxymethyl)-5-fluoro-1H-indole-6-carbonitrile (50.0 g, 62.5%) as a yellow solid.

10 [00364] ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 11.79 (s, 1H), 7.80 (d, J = 5.6, Hz 1H), 7.57 (d, J = 10.4 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 5.77 (s, 1H), 3.62 – 3.55 (m, 4H), 1.18 (t, J = 7.2 Hz, 6H).

[00365] Method D: LCMS (electrospray): m/z = 261.1 (M-H)⁺, RT = 2.30 min.

[00366] **Step 3:** (2-(diethoxymethyl)-5-fluoro-1H-indol-6-yl) methanamine

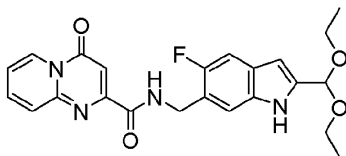


15

[00367] To a stirred mixture of 2-(diethoxymethyl)-5-fluoro-1H-indole-6-carbonitrile (50.0 g, 190.8 mmol) in MeOH (500 mL) were added Raney Ni (81.7 g, 954.1 mmol) and aqueous NH₃ (500 mL) into a hydrogenation vessel. The resulting reaction mixture was charged with H₂ atmosphere (30 kg/cm²) and stir at 70 °C for 3 h. The reaction mixture was filtered through a Buchner funnel and washed with additional MeOH (1000 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford (2-(diethoxymethyl)-5-fluoro-1H-indol-6-yl)methanamine (52 g, quantitative) as a yellow solid, that was used in the subsequent step without further purification.

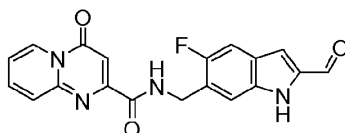
25 [00368] ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 11.11 (s, 1H), 7.38 (d, J = 6.4, 1H), 7.18 (d, J = 11.2 Hz, 1H), 6.34 (d, J = 1.6 Hz, 1H), 5.68 (s, 1H), 3.78 (s, 1H), 3.62 – 3.50 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H).

[00369] **Step 4:** N-((2-(diethoxymethyl)-5-fluoro-1H-indol-6-yl) methyl)-4-oxo-4H-pyrido [1,2-a]pyrimidine-2-carboxamide



[00370] To a stirred solution of (2-(diethoxymethyl)-5-fluoro-1H-indol-6-yl)methanamine (52.0 g, 195.4 mmol) and 4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylic acid (44.6 g, 234.5 mmol) in DMF (520 mL) were added DIPEA (75.65 g, 586.4 mmol) at room temperature. The resulting reaction mixture was stirred for 15 minutes and HATU (111.4 g, 293.2 mmol) was added into reaction mixture. The resulting reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was poured into ice-cold water, and the precipitate that formed filtered and the solid dried under vacuum to afford N-((2-(diethoxymethyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (52.0 g, 61%) that was used in the subsequent step without further purification.

10 [00371] **Step 5:** N-((5-fluoro-2-formyl-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

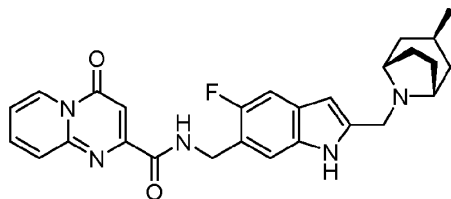


[00372] To a stirred solution of N-((2-(diethoxymethyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (52.0 g, 118.7 mmol) in THF (520 mL) was added glacial CH₃COOH (52 mL). The resulting reaction mixture was stirred at room temperature for 1 h and then concentrated and diluted with ice cold water (2000 mL) with continuous stirring to obtain a solid precipitate. The precipitate that formed was filtered and the solid dried under vacuum. The crude solid was further purified by trituration with methanol. The solid was collected and dried under vacuum to afford N-((5-fluoro-2-formyl-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide **Intermediate 1** (40.0 g, 93%) as an off-white solid.

[00373] ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 11.98 (s, 1H), 9.82 (s, 1H), 9.40 (t, J = 6.4 Hz, 1H), 9.03 (d, J = 6.4 Hz, 1H), 8.11 – 8.07 (m, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 10.8 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.36 (d, J = 1.2 Hz, 1H), 6.90 (s, 1H), 4.64 (d, J = 6.0 Hz, 2H);

[00374] Method D: LCMS (electrospray): m/z = 263.1 (M-H)⁺, RT = 1.82 min.

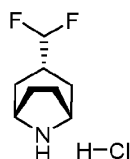
Example 2: N-((5-fluoro-2-(((1R,3r,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



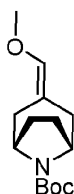
[00375] A mixture of STAB (87 mg, 0.41 mmol), (1S,3r,5R)-3-methyl-8-azabicyclo[3.2.1]octane;hydrochloride (44 mg, 0.274 mmol), N-[(5-fluoro-2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide **Intermediate 1** (50 mg, 0.14 mmol) and DIPEA (0.07 mL, 0.41 mmol) in DCE (4 mL) was stirred at 50 °C for 2 h. LCMS method A showed 93% conversion to the product. The reaction was worked up at this point. The reaction mixture was quenched with water (30 mL) and extracted with DCM (30 mL). The pH of the aqueous layer was then adjusted to pH 11 by addition of 1 M NaOH solution, and the aqueous layer was then extracted with DCM (2 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The residue was purified by prep HPLC (method A), and the product containing fractions were combined, concentrated in vacuo and freeze dried overnight to give N-[[5-fluoro-2-[(1S,5R)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide (45 mg, 66% yield) as a white solid.

[00376] Method B: LCMS (electrospray): m/z = 474.32 (M+H)⁺, RT = 3.94 min, purity = 96%.

Intermediate 2: (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane;hydrochloride



[00377] **Step 1:** tert-butyl-3-(methoxymethylene)-8-azabicyclo[3.2.1]octane-8-carboxylate



To a solution of methoxymethyl-triphenylphosphonium chloride (22.8 g, 66.6 mmol) in THF (150 mL) was added t-BuOK (6.97 g, 62.1 mmol) at 0 °C. N-(tert-Butoxycarbonyl)nortropinone (10 g, 44.4 mmol), was added and the mixture was stirred at 15 °C for 3 h. TLC (petroleum ether/ethyl acetate = 3:1, R_f = 0.5) indicated that the starting ketone was consumed completely, and one new spot had formed. The reaction was quenched with NH₄Cl (60 mL), diluted with H₂O (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 0/1), to give tert-butyl-3-(methoxymethylene)-8-azabicyclo[3.2.1]octane-8-carboxylate (7.00 g, 24.3 mmol, 55% yield, 88% purity) as a colorless oil.

[00378] TLC: Petroleum ether: ethyl acetate = 3:1, R_f = 0.5

[00379] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm: 5.76 (s, 1H) 3.99 – 3.86 (m, 2H) 3.35 – 3.27 (m, 3H) 2.34 – 2.26 (m, 1H) 2.18 – 2.03 (m, 1H) 1.92 – 1.71 (m, 1H) 1.62 (br d, J = 11.8 Hz, 3H) 1.46 – 1.31 (m, 2H) 1.24 (s, 9H)

- 5 [00380] **Step 2:** tert-butyl (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

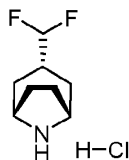


- [00381] A mixture of tert-butyl-3-(methoxymethylene)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.00 g, 7.89 mmol), 1.0 M HCl (88.0 mL) in acetonitrile (60 mL) was degassed and purged with N_2 three times at 0 °C, and then the mixture was stirred at 15 °C for 6 h under a N_2 atmosphere. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.4) indicated the starting material was completely consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue of tert-butyl (1R,3s,5S)-3-formyl-8-azabicyclo[3.2.1]octane-8-carboxylate that solidified as an off-white solid on standing (1.00 g) that was used directly in the next step without further purification.

- [00382] To a solution of tert-butyl (1R,3s,5S)-3-formyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 4.18 mmol) in DCM (12 mL) was added DAST (1.68 g, 10.5 mmol, 1.38 mL) at 0 °C. The mixture was stirred at 15 °C for 1 h. LCMS showed the starting material was consumed completely and one peak with desired mass was detected. The reaction was quenched with saturated NH_4Cl (10 mL). The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and the filtrate concentrated under reduced pressure to give tert-butyl (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate as a colorless oil (700 mg). This was used without further purification.

- 25 [00383] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm: 5.70 – 5.36 (m, 1H) 4.12 (br s, 2H) 1.93 – 1.84 (m, 2H) 1.66 – 1.59 (m, 2H) 1.53 – 1.46 (m, 4H) 1.43 – 1.39 (m, 1H) 1.38 – 1.35 (m, 9H)

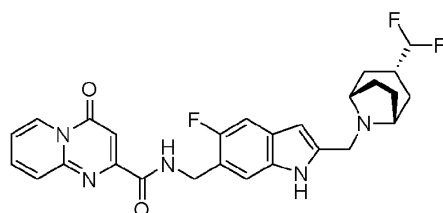
[00384] **Step 3:** (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane;hydrochloride



[00385] A mixture of tert-butyl (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (200 mg, 765 μ mol), and 4 M HCl in ethyl acetate (2.0 mL) in ethyl acetate (2.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 15 °C for 0.5 h under a N₂ atmosphere. LCMS showed that the starting material was completely consumed and one new peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue of (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane;hydrochloride **Intermediate 2** (100 mg) as a colourless oil.

[00386] Method E: LCMS (electrospray): m/z = 162.1 (M+H)⁺, RT = 0.987 min.

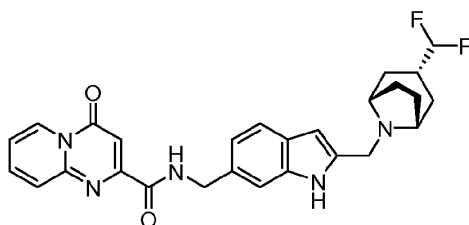
Example 3: N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



[00387] A mixture of (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane;hydrochloride **Intermediate 2** (90.0 mg, 455.3 μ mol), N-[(5-fluoro-2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide **Intermediate 1** (120 mg, 329.4 μ mol), STAB (209 mg, 988.1 μ mol) and DIPEA (223 mg, 1.72 mmol, 300 μ L) in DCE (4 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 50 °C for 12 h under a N₂ atmosphere. LCMS showed **intermediate 1** was completely consumed and one new peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Method B, gradient: 30%-70% B) to give N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (70 mg, 42% yield) as a white solid.

[00388] Method F: LCMS (electrospray): m/z = 510.2 (M+H)⁺, RT = 3.03 min, purity 99.7%.

Example 4: N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

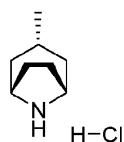


[00389] A mixture of (1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octane;hydrochloride **Intermediate 2** (68 mg, 346.5 μmol), N-[(2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide (80 mg, 231 μmol , prepared according to previous report: WO 2021/111124, Example 2, step1-4)), STAB (147 mg, 693 μmol), DIPEA (90 mg, 693 μmol , 121 μL) in DCE (4 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 50 $^\circ\text{C}$ for 12 h under a N_2 atmosphere.

[00390] LCMS showed N-[(2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide was completely consumed and one new peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Method B, gradient: 30%-55% B) to give N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (60 mg 53% yield) as a white solid.

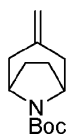
[00391] Method F: LCMS (electrospray): m/z = 492.2 ($\text{M}+\text{H}$) $^+$, RT = 2.94 min, purity 99.5%.

[00392] **Intermediate 3:** (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane; hydrochloride



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[00393] Step 1: tert-butyl-3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate



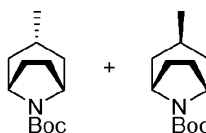
[00394] To a stirred suspension of Me-PPh₃Br (134 g, 390 mmol) in THF (1200 mL), *t*-BuOK (40.5 g, 360 mmol) was added at 0 $^\circ\text{C}$. The mixture was stirred at 15 $^\circ\text{C}$ for 1 h. A solution of N-(tert-Butoxycarbonyl)nortropinone (58.0 g, 257 mmol) in THF (300 mL) was added dropwise to the mixture and stirred at 15 $^\circ\text{C}$ for 12 h. TLC indicated the starting ketone was consumed completely and one new spot had formed. After stirring at 25 $^\circ\text{C}$ for a further 1 h, the reaction was quenched with acetone (250 mL) and the precipitate that formed was filtered off. The filtrate was concentrated in vacuo, then water was added (250 mL) and the crude mixture was extracted with ethyl acetate (3 $\times$ 250 mL). The combined organic phases were dried over anhydrous Na_2SO_4 , then filtered and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 10/1) to give tert-butyl-3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (42.0 g, 66% yield, as a yellow oil.

[00395] TLC: petroleum ether/ethyl acetate=10/1, R_f = 0.53

30

[00396] ^1H NMR (400 MHz, CHCl_3 - d) δ ppm: 4.9 (t, J = 2.0 Hz, 2H) 4.2 (br s, 2H) 2.5 (br d, J = 12.8 Hz, 2H) 2.1 (dd, J = 12.8, 1.2 Hz, 2H) 1.8 – 1.9 (m, 2H) 1.6 (d, J = 7.6 Hz, 2H) 1.5 (s, 9H).

[00397] **Step 2:** tert-butyl (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

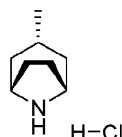
**Exo****Endo**

[00398] To a solution of $\text{Pd}(\text{OH})_2$ (2.00 g, 10% wt.) in ethyl acetate (50 mL) was added tert-butyl-3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (15.0 g, 22.4 mmol) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 12 h. TLC (petroleum ether: ethyl acetate = 10:1, R_f = 0.46) indicated the starting alkene was completely consumed and one new spot had formed. The suspension was filtered through a pad of Celite® and the pad was washed with ethyl acetate (40 mL $\times$ 3). The combined filtrates were concentrated to dryness to give tert-butyl (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (14.0 g) as a yellow oil. This material was used directly in the next step without further purification. ^1H NMR analysis gave an exo/endo ratio of isomers of 8:1.

[00399] TLC: Petroleum ether/ethyl acetate=10/1, R_f = 0.46

[00400] ^1H NMR **exo isomer** (400 MHz, $\text{DMSO}-d_6$) δ ppm: 4.0 (br s, 2H) 1.7 – 2.0 (m, 3H) 1.6 – 1.7 (m, 2H) 1.5 (br s, 2H) 1.4 (s, 9 H) 1.1 – 1.3 (m, 2H) 0.8 (d, J = 6.4 Hz, 3H).

[00401] **Step 3:** (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane; hydrochloride

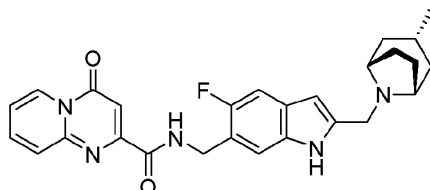


[00402] tert-butyl (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (14.0 g, 62.1 mmol) in ethyl acetate (75 mL) was added HCl in ethyl acetate (4.0 M, 75 mL). The mixture was stirred at 15 °C for 12 h. LCMS showed complete conversion to a new peak with the desired mass. The reaction mixture was concentrated under reduced pressure to give a residue (9.0 g), which was then dissolved in acetonitrile (180 mL). Insoluble material was removed by filtration and then isopropyl ether (1000 mL) was added slowly to the filtrate and stirred at 25 °C for 3 h. The precipitate was collected by filtration, the filter cake was dried in vacuo to afford (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane; hydrochloride **intermediate 3** (7.05 g, 66% yield) as a white solid. ^1H NMR analysis gave an exo/endo ratio of isomers of 16:1.

[00403] TLC: Ethyl acetate: methanol = 10:1, R_f = 0.03

[00404] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 8.7 – 9.2 (m, 2H) 3.9 (br s, 2H) 1.9 – 2.0 (m, 2H) 1.7 – 1.9 (m, 3H) 1.6 – 1.7 (m, 2H) 1.4 – 1.6 (m, 2H) 0.9 (d, J = 6.4 Hz, 3H).

Example 5: N-((5-fluoro-2-(((1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

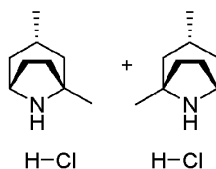


[00405] To a solution of (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane; hydrochloride **intermediate 3** (4.15 g, 25.7 mmol) in DCE (680 mL) was added DIPEA (9.05 g, 12.2 mL, 70.0 mmol), STAB (14.8 g, 70 mmol), and N-[(5-fluoro-2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide **Intermediate 1** (8.5 g, 23.3 mmol). The mixture was stirred at 50 °C for 12 h. LCMS showed **Intermediate 1** was completely consumed and the desired mass was detected. The reaction mixture was quenched with H_2O (700 mL) and extracted with DCM (700 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and the filtrate concentrated in vacuo. The residue was purified by *prep*-HPLC (method C, gradient 45-80% B) to give the desired compound (6.0 g, 54% yield) as a yellow solid. ^1H NMR analysis gave an exo/endo ratio of isomers of 15:1.

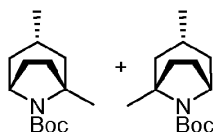
[00406] Method F: LCMS (electrospray): m/z = 474.2 ($\text{M}+\text{H}$) $^+$, RT = 3.01 min, purity 97.8%.

[00407] 2.0 g of material was further separated by SFC (column: DAICEL CHIRALPAK IG (250 mm*50 mm, 10 μm); mobile phase: [CO_2 -MeOH: acetonitrile = 1:1 (0.1% $\text{NH}_3\text{H}_2\text{O}$)]; B%:60%, isocratic elution mode; 620 minute run time) to afford N-((5-fluoro-2-(((1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (1.30 g, 65% yield) as a yellow solid. SFC chromatogram analysis (SFC method A) gave an exo/endo ratio of isomers of >99:1 (endo: 0.33%, RT = 2.87 min; exo: 99.67%, RT = 3.86 min).

[00408] Method G: LCMS (electrospray): m/z = 474.2 ($\text{M}+\text{H}$) $^+$, RT = 2.11 min, purity 98.6%. **Intermediate 4:** ($\pm$)-(1R,3S,5S)-1,3-dimethyl-8-azabicyclo[3.2.1]octane;hydrochloride



[00409] **Step 1:** ($\pm$)-tert-butyl (1S,3R,5R)-1,3-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate

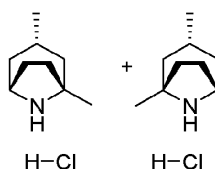


[00410] To a solution of TMEDA (516 mg, 4.44 mmol, 670 μ L) in THF (6 mL) was added s-BuLi (1.3 M, 3.41 mL) at -70°C , the reaction was stirred for 30 min, tert-butyl (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (500 mg, 2.22 mmol, exo/endo ratio = 8:1) in THF (2 mL) was added and the reaction stirred at -20°C for 30 min. Dimethyl sulfate (920 mg, 7.29 mmol, 690 μ L) was added at -70°C and then the reaction mixture was allowed to warm to room temperature and stirred for 12 h. TLC indicated tert-butyl (1R,3s,5S)-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate remained and that one new spot had formed. The reaction mixture was added to water (10 mL), extracted with ethyl acetate (10 mL X 2), and the combined organics dried over Na_2SO_4 , filtered and the filtrate concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0-50% ethyl acetate/petroleum ether gradient @ 120 mL/min). Product containing fractions were combined to give ($\pm$)-tert-butyl (1S,3R,5R)-1,3-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 28% yield) as a white solid. ^1H NMR analysis suggested the isolated product was a 7:1 mixture of exo/endo isomers.

[00411] TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.53)

[00412] ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm: 4.18 (dt, J = 7.4, 2.6 Hz, 1H) 1.78 – 1.91 (m, 2H) 1.56 – 1.75 (m, 3H) 1.34 – 1.46 (m, 1H) 1.17 – 1.28 (m, 1H) 1.07 (d, J = 7.6 Hz, 0.4H) 0.80 (d, J = 6.6 Hz, 2.8 H)

[00413] **Step 2:** ($\pm$)-(1R,3S,5S)-1,3-dimethyl-8-azabicyclo[3.2.1]octane;hydrochloride



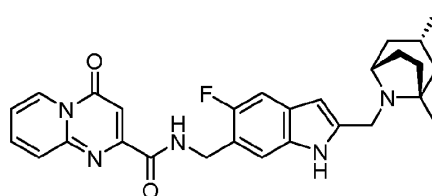
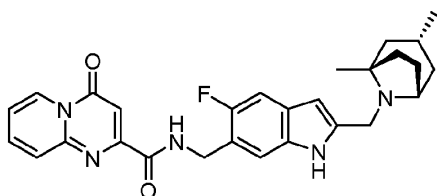
[00414] A solution of ($\pm$)-tert-butyl (1S,3R,5R)-1,3-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 627 μ mol, exo/endo ratio = 7:1) in HCl in ethyl acetate (4.0 M, 1.87 mL) was stirred at 20°C for 1 h. TLC indicated the starting material was completely consumed and one new baseline spot had formed. The reaction mixture was concentrated in vacuo to give ($\pm$)-(1R,3S,5S)-1,3-dimethyl-8-azabicyclo[3.2.1]octane;hydrochloride **intermediate 4** (120 mg, exo/endo ratio = 7:1) as a white solid.

[00415] TLC: Petroleum ether: ethyl acetate = 5:1, R_f = 0

Example 6: N-((2-(((1S*,3R*,5R*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

and

Example 7: N-((2-(((1R*,3S*,5S*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



Example 6

Example 7

- 5 **[00416]** A solution of N-[(5-fluoro-2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide **Intermediate 1** (200 mg, 549 μ mol) and ($\pm$)-(1R,3S,5S)-1,3-dimethyl-8-azabicyclo[3.2.1]octane;hydrochloride **intermediate 4** (116 mg, 659 μ mol, exo/endo ratio = 7:1) and STAB (349 mg, 1.65 mmol) and DIPEA (213 mg, 1.65 mmol, 287
- 10 μ L) in DCE (16 mL) was stirred at 70 $^{\circ}$ C for 12 h. LCMS showed **intermediate 1** was completely consumed and the desired mass was detected. The reaction mixture was concentrated in vacuo and the residue was purified by prep-HPLC (Method D, gradient 40%-70% B). Fractions containing pure ($\pm$)-N-((2-(((1S,3R,5R)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-
- 15 a]pyrimidine-2-carboxamide were combined and the enantiomers separated by SFC (column: DAICEL CHIRALPAK AY-H(250 mm $\times$ 30mm,10 μ m); mobile phase: [CO₂-EtOH: acetonitrile=1:1 (0.1% NH₃H₂O)]; B%:50%, isocratic elution mode 96 minute run time) to give the separated enantiomers of unknown absolute configuration. Assignment is arbitrary and based on the retention time.
- 20 **Enantiomer 1, example 6:** N-((2-(((1S*,3R*,5R*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (40 mg, 15% yield), was obtained as a white solid. SFC chromatogram analysis (SFC method B) gave an enantiomeric ratio of >95:1 (enantiomer 1: 95.2%, RT = 1.80 min; enantiomer 2: 4.78%, RT = 2.01 min).
- 25 **[00417]** Method H: LCMS (electrospray): m/z = 488.3 (M+H)⁺, RT = 1.46 min, purity 99.4%. **Enantiomer 2, example 7:** N-((2-(((1R*,3S*,5S*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (33 mg, 12% yield), was obtained as a white solid. SFC chromatogram analysis (SFC method B) gave an enantiomeric ratio of >99:1 (enantiomer 1: 0.03%, RT = 1.82 min; enantiomer 2:
- 30 99.97%, RT = 2.06 min).
- [00418]** Method H: LCMS (electrospray): m/z = 488.2 (M+H)⁺, RT = 1.45 min, purity 99.4%.

METTL3/14 methyltransferase assay**[00419] Biochemical assay**

[00420] The enzymatic assay was established to determine IC₅₀ values for inhibition of RNA methyltransferase activity. More specifically, the enzymatic reaction was performed at room temperature in 384-well plates using a final reaction volume of 20 µL containing 20 mM TrisCl pH 7.6, 1 mM DTT, 0.01% Tween-20. 5 nM final concentration of METTL3/14 was pre-incubated with various compound concentrations for 10 minutes, followed by addition of 0.2 µM final concentration ssRNA and 0.5 µM final concentration S-adenosyl-methionine (SAM). The reaction was incubated for further 60 minutes at room temperature, and then 40 µL 7.5% TCA with two internal product standards (D₄-SAH and ¹³C₁₀-SAH) was added to quench the reaction. After termination, plates were sealed, centrifuged and stored at 4°C until analysis.

Mass spectrometry analysis

[00421] RNA methyltransferase activity was measured label free using the RapidFire™ mass spectrometry (RF/MS) platform. Stopped and stable assay plates were analyzed on the Agilent RF300 integrated autosampler/solid-phase extraction (SPE) system coupled to an ABSciex 4000 mass spectrometer for the generation of the product S-adenosyl homocysteine (SAH) and normalized to the ratio of signal of the two internal product standards, respectively. Solvent A was water containing 0.1% (v/v) TCA. Solvent B was acetonitrile/0.1% TCA in water (8:2, v/v). More specifically, plates were centrifuged at 4350 rpm for 10 min, samples were aspirated under vacuum for 600 ms, then loaded onto a C18 solid-phase extraction cartridge and washed for 3 s with solvent A at a flow rate of 1.5 mL/min. Retained product and internal standards were eluted with solvent B at a flow rate of 1 mL/min for 3 s and finally the cartridge was reequilibrated with solvent A for 500 ms. The mass transition for the product (SAH) was 384.9/135.9 Da. Transitions of the two internal product standards (IS1: D₄-SAH and IS2: ¹³C₁₀-SAH) were 389.1/135.8 Da and 395.0/134.2 Da, respectively. Ratios of SAH/IS1 and SAH/IS2 were used for normalization of matrix effects. IC₅₀ values were calculated based on dilution series of individual compounds. Potency of a compound was measured at varied inhibitor concentrations and normalized to control wells with full inhibition (w/o RNA) and no inhibition (DMSO only).

30 CTG assay (Caov-3 cell line)

[00422] Cell culture: Caov-3 cells (HTB-75, Lot number: 70016791, ATCC) were grown in DMEM (11960-04431053-028, Gibco) supplemented with 10% fetal bovine serum (HyClone™ 10309433, Fisher), 1 mM sodium pyruvate (11360-039, Gibco) and 2mM Glutamax (35050-038, Gibco) at 37°C with 5% CO₂.

35 Cell treatment and cell growth assessment: 18 hours post-seeding in white 384-Viewplate (6007480, PerkinElmer) at 1500 cells/well, Caov-3 cells were treated for 120 hours with compounds inhibiting the METTL3/14 activity (10 serial semi-log dilutions, 30 µM as top

concentration). Upon treatment, Caov-3 cells were incubated for 10 min at RT with the CellTiter-Glo reagent (G7571, Promega). Measurement of the luminescence signal was performed on a microplate reader.

MDCK-MDR1 Permeability Assay

5 [00423] **Cell culture:** MDR1-MDCK II cells (obtained from Piet Borst at the Netherlands Cancer Institute) were seeded onto Polycarbonate membranes (PC) in 96-well insert systems at 3.33×10^5 cells/mL for 4-7 days until confluent cell monolayer formation.

[00424] Transport method: Test compounds were diluted with the transport buffer (HBSS with 10mM Hepes, pH7.4) from DMSO stock solution to a concentration of 2 μ M (DMSO<1%) and applied to the apical or basolateral side of the cell monolayer. Permeation of the test compounds from A to B direction or B to A direction was determined in duplicate. P-gp substrate control compound Digoxin was tested at 10 μ M from A to B direction or B to A direction as well, while nadolol (low permeability control compound) and metoprolol (high permeability control compound) were tested at 2 μ M in A to B direction in duplicate. The plate was incubated for 2.5 hours in CO₂ incubator at $37 \pm 1^\circ\text{C}$, with 5% CO₂ at saturated humidity without shaking. In addition, the efflux ratio of each compound was also determined. Test and reference compounds were quantified by LC/MS/MS analysis based on the peak area ratio of analyte/IS.

[00425] After the transport assay, the Lucifer yellow rejection assay was applied to determine the cell monolayer integrity. Buffers were removed from both apical and basolateral chambers, followed by the addition of 75 μ L of 100 μ M lucifer yellow in transport buffer and 250 μ L transport buffer in apical and basolateral chambers, respectively. The plate was incubated for 30 minutes at 37°C with 5% CO₂ and 95% relative humidity without shaking. After 30 minutes incubation, 20 μ L of Lucifer yellow samples were taken from the apical sides, followed by the addition of 60 μ L of Transport Buffer, and then 80 μ L of lucifer yellow samples were taken from the basolateral sides. The relative fluorescence unit (RFU) of Lucifer yellow was measured at 425/528 nm (excitation/emission) with an Envision plate reader.

[00426] **Data analysis:** The apparent permeability coefficient Papp (cm/s) was calculated using the equation:

30
$$\text{Papp} = (\text{dCr}/\text{dt}) \times \text{Vr} / (\text{A} \times \text{C0})$$

[00427] Where dCr/dt is the cumulative concentration of compound in the receiver chamber as a function of time (μ M/s); Vr is the solution volume in the receiver chamber (0.075 mL on the apical side, 0.25 mL on the basolateral side); A is the surface area for the transport, i.e. 0.143 cm² for the area of the monolayer; C0 is the initial concentration in the donor chamber (μ M).

[00428] The efflux ratio was calculated using the equation:

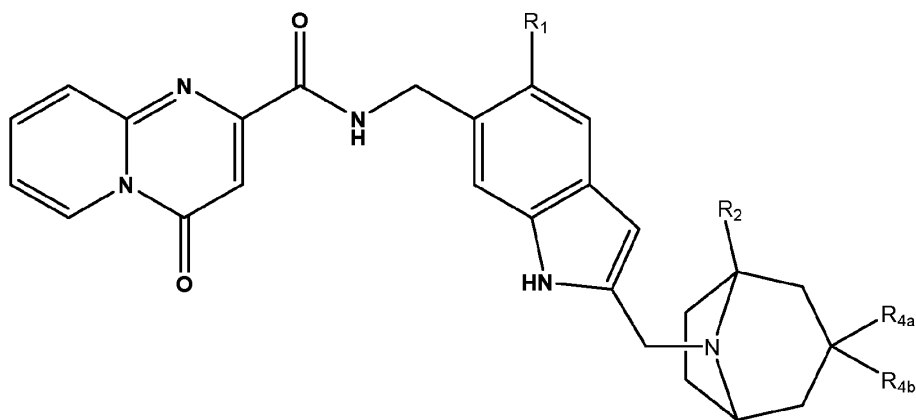
$$\text{Efflux Ratio} = \text{Papp (BA)} / \text{Papp (AB)}$$

Results Table 1

Example Number	METTL3_14 RFMS IC ₅₀ (nM)	Caov-3 CTG IC ₅₀ (nM)	MDCK-MDR1 A-B (10 ⁻⁶ cm/s)	MDCK-MDR1 B-A (10 ⁻⁶ cm/s)	Efflux ratio
1	<6	573	6.27	9.43	1.50
2	10.5	374	4.43	11.9	2.69
3	<6	271	4.20	6.19	1.47
4	<6	289	4.95	13.4	2.71
5	<6	171	5.05	9.12	1.81
6	21.6	515	3.94	7.00	1.78
7	9.7	45.2	4.94	6.72	1.36
Ref cmp 1	24.4	1942	0.88	37.8	43.0
Ref cmp 2	6.6	746	1.31	35.4	27.0

CLAIMS

1. A compound of formula (I) shown below, or a pharmaceutically acceptable salt thereof:



5

(I)

wherein:

R₁ is selected from hydrogen or fluoro;

R₂ is selected from hydrogen or methyl; and

10 R_{4a} and R_{4b} are each independently selected from hydrogen, fluoro, methyl or fluoromethyl (e.g. CF₃, CF₂H, CFH₂), with the proviso that at least one of R_{4a} and R_{4b} is not hydrogen.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,
15 wherein R₁ is hydrogen.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,
wherein R₁ is fluoro.

20 4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R₂ is hydrogen.

5. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R₂ is methyl.

25

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R_{4a} and R_{4b} are each independently selected from hydrogen, fluoro, methyl, CF_2H , with the proviso that at least one of R_{4a} and R_{4b} is not hydrogen.

5 7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein one of the following applies:

- a) one of R_{4a} and R_{4b} is methyl and the other is hydrogen;
- b) one of R_{4a} and R_{4b} is CF_2H and the other is hydrogen; or
- c) R_{4a} and R_{4b} are both fluoro.

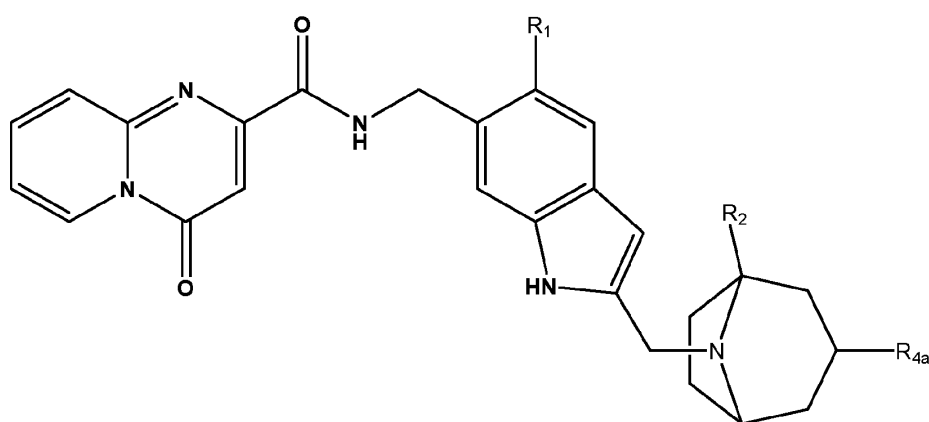
10

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein one of the following applies:

- a) one of R_{4a} and R_{4b} is methyl and the other is hydrogen; or
- b) one of R_{4a} and R_{4b} is CF_2H and the other is hydrogen.

15

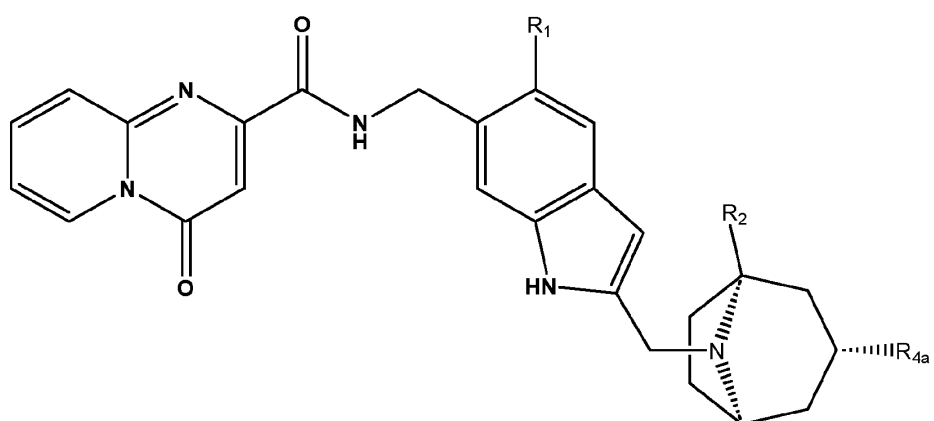
9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, having a structural formula (II), (IIa), (IIb), (IIc), (IId), (III), (IIIa), (IIIb), (IIIc) or (IIId) below:



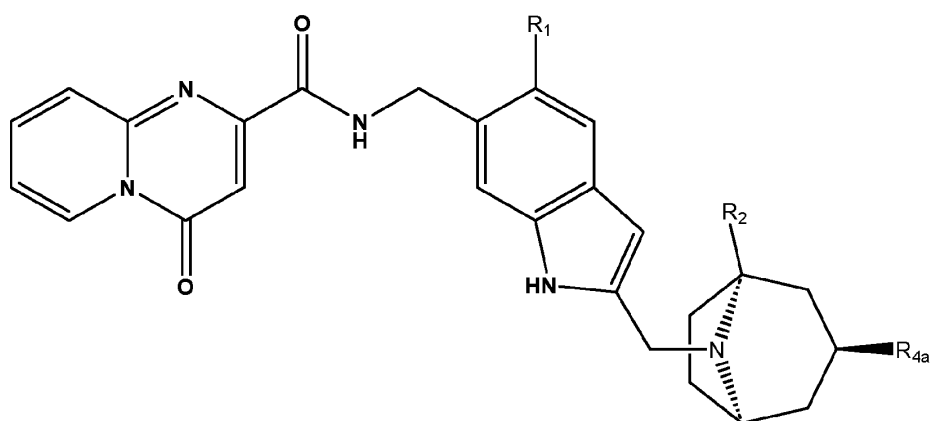
20

(II)

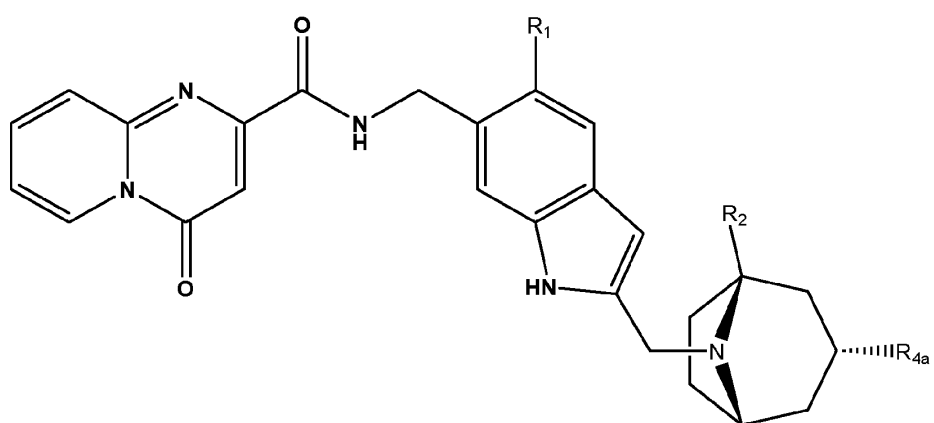
82



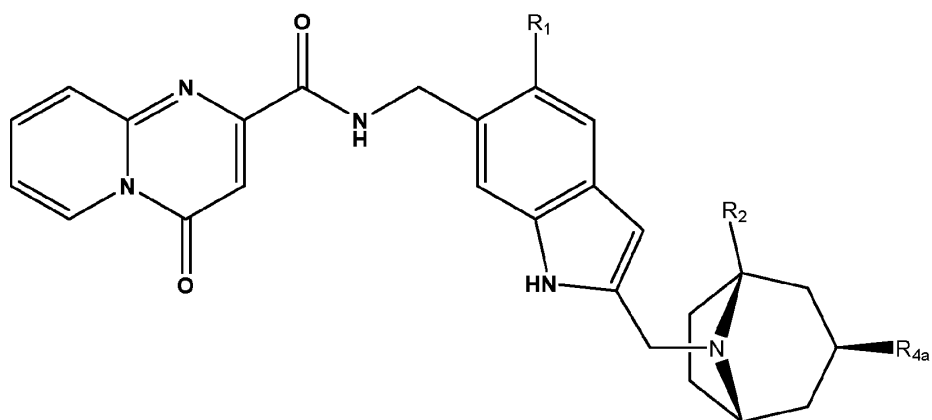
(IIa)



(IIb)

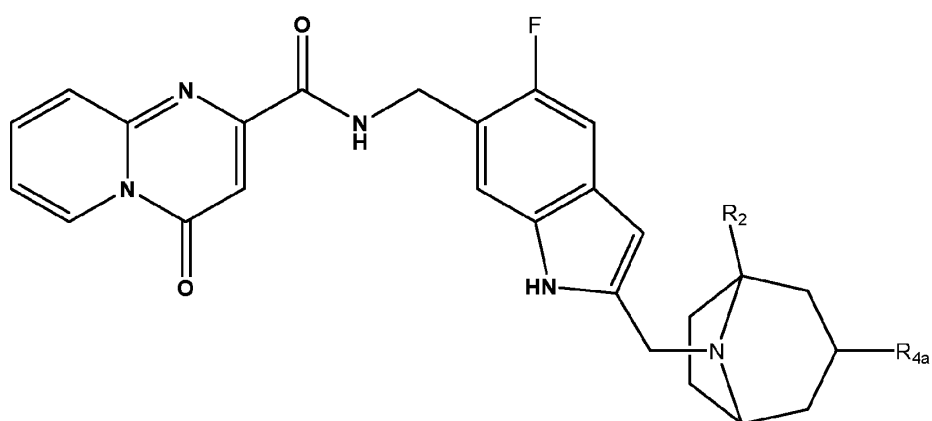


(IIc)

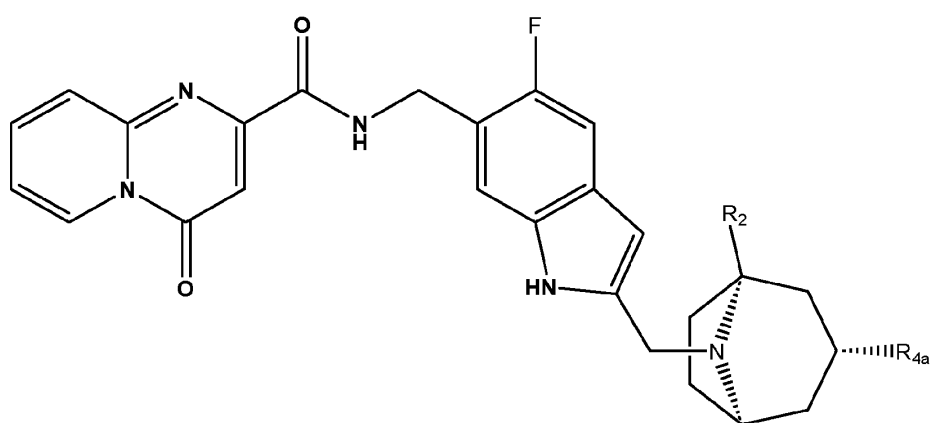


(IIId)

5

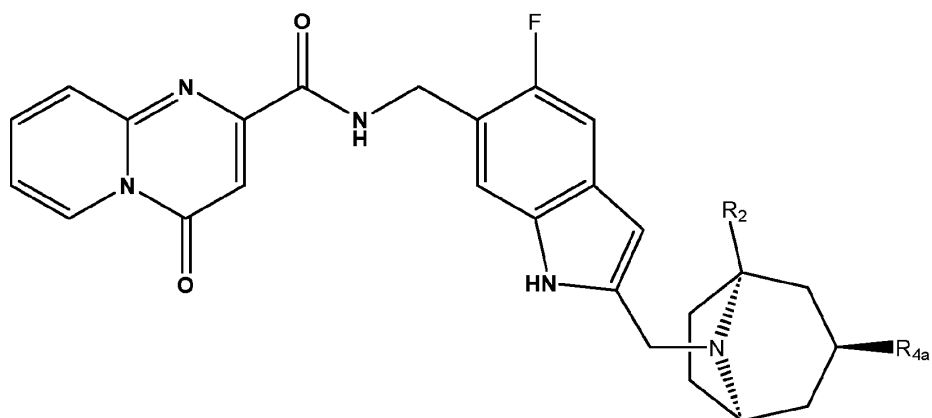


(III)

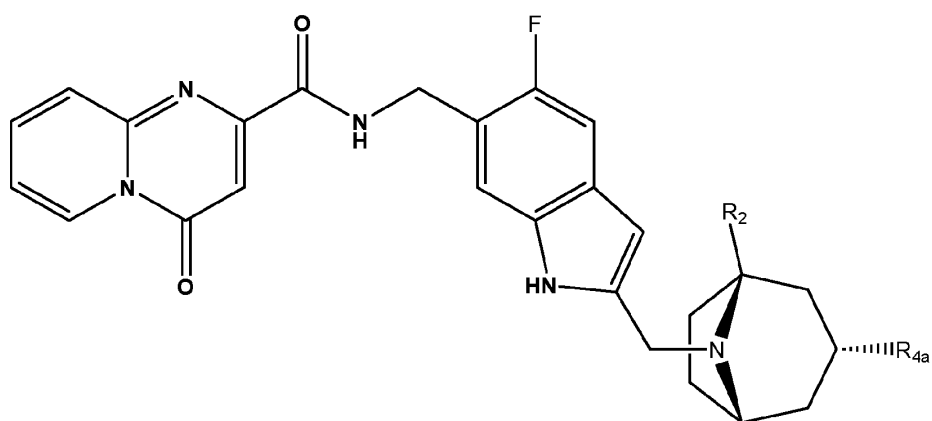


(IIIa)

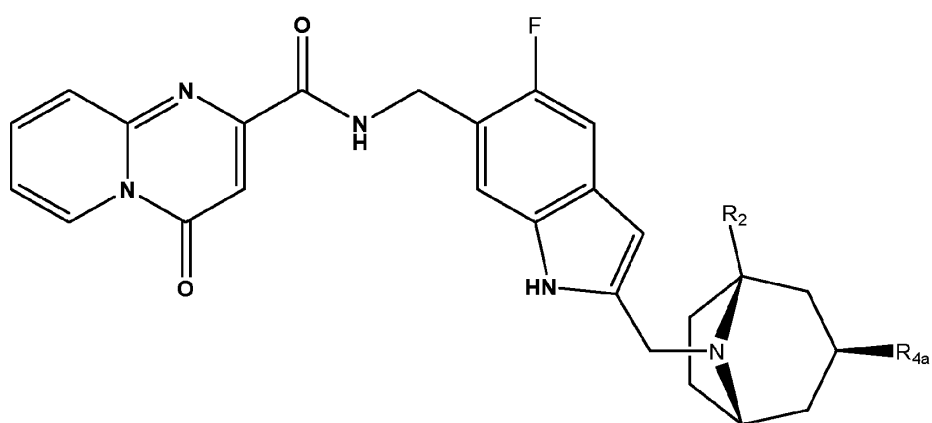
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(IIIb)



(IIIc)



(III d)

wherein R₁, R₂ and R_{4a} are as defined in any one of the preceding claims.

10. A compound, or a pharmaceutically acceptable salt thereof, selected from any one of the following:

N-[[2-[(3,3-difluoro-8-azabicyclo[3.2.1]octan-8-yl)methyl]-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-((5-fluoro-2-(((1R,3r,5S)-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

- 10 N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-((2-(((1R,3s,5S)-3-(difluoromethyl)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

- 15 yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-((2-(((1S*,3R*,5R*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide; and

N-((2-(((1R*,3S*,5S*)-1,3-dimethyl-8-azabicyclo[3.2.1]octan-8-yl)methyl)-5-fluoro-1H-indol-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide.

20

11. A pharmaceutical composition comprising a compound according to any one of claim 1 to 10, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

- 25 12. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, for use in therapy.

13. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, for use in the treatment of a proliferative condition; optionally for use in the treatment of cancer; further optionally for use in the treatment of:

- 35 i. leukaemia, e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS);

- ii. a cancer of the CNS, e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.
- 5 14. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, for use in the treatment of:
- i. a neurodegenerative disorder, e.g. a tauopathy such as Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliaopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy; a motor neuron disease, a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease) or Parkinson's Disease;
 - 10 ii. an autoimmune disease, a disorder of the CNS, a neurological disease, an inflammatory disease, an infectious disease, type 2 diabetes, a neuropsychiatric behavioural disorder, a depressive disorder or a disease related to the inactivation of the X-chromosome;
 - 15 iii. a disease related to the inactivation of the X-chromosome, e.g. Addison's disease with cerebral sclerosis; Adrenal hypoplasia; siderius X-linked mental retardation syndrome; Agammaglobulinaemia, Bruton type; Choroidoretinal degeneration; Choroidaemia; Albinism, ocular; Dent's disease 2; fragile X syndrome; Rett/ Epileptic encephalopathy, early infantile, 2 (CDKL5 deficiency disorder); Albinism-deafness syndrome; paroxysmal nocturnal hemoglobinuria; Aldrich syndrome; Alport syndrome; Anaemia, hereditary hypochromic; Anemia, sideroblastic, with ataxia; Fabry disease; Spinal muscular atrophy 2; Cataract, congenital; Charcot-Marie-Tooth, peroneal; Spastic paraplegia; Colour blindness; Diabetes insipidus, nephrogenic; DDX3X syndrome; Dyskeratosis congenita; Ectodermal dysplasia, anhidrotic; Faciogenital dysplasia (Aarskog syndrome); Glucose-6-phosphate dehydrogenase deficiency; Glycogen storage disease type VIII; Gonadal dysgenesis (XY female type); Granulomatous disease (chronic); Haemophilia A; Haemophilia B; Hydrocephalus (aqueduct stenosis); Hypophosphataemic rickets; Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency);
 - 20
 - 25
 - 30
 - 35 Incontinentia pigmenti; Kallmann syndrome; Keratosis follicularis spinulosa; Lowe (oculocerebrorenal) syndrome; Menkes syndrome; Renpenning Syndrome; Mental retardation, with or without fragile site (numerous specific types); Coffin-Lowry

syndrome; Microphthalmia with multiple anomalies (Lenz syndrome); Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types); Myotubular myopathy; Night blindness, congenital stationary; Norrie's disease (pseudoglioma); Nystagmus, oculomotor or 'jerky'; Orofaciodigital syndrome (type I); Ornithine transcarbamylase deficiency (type I hyperammonaemia); Phosphoglycerate kinase deficiency; 5 Phosphoribosylpyrophosphate synthetase deficiency; Retinitis pigmentosa; Retinoschisis; Rett syndrome; Muscular atrophy /Dihydrotestosterone receptor deficiency; Spinal muscular atrophy; Spondyloepiphyseal dysplasia tarda; Thrombocytopenia, hereditary; Thyroxine-binding globulin, absence; or McLeod 10 syndrome.

15 15. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, for use in the inhibition of METTL3 activity.

15

16. Use of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, in the manufacture of a medicament for the treatment of a proliferative condition; optionally 20 wherein the proliferative condition is cancer; further optionally wherein the cancer is selected from:

- 25 i. leukaemia, e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL) chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL) small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS); or
- ii. a cancer of the CNS, e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain.

30 17. Use of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, in the manufacture of a medicament for the treatment of:

- 35 i. a neurodegenerative disorder, e.g. a tauopathy such as Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astroglipathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy; a motor neuron disease

(including ALS); a repeat expansion disease (such as Huntington's Disease), dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease); multiple sclerosis; or Parkinson's Disease; or

5

- ii. a disease related to the inactivation of the X-chromosome, e.g. Addison's disease with cerebral sclerosis; Adrenal hypoplasia; siderius X-linked mental retardation syndrome; Agammaglobulinaemia, Bruton type; Choroidoretinal degeneration; Choroidaemia; Albinism, ocular; Dent's disease 2; fragile X syndrome; Rett/
10 Epileptic encephalopathy, early infantile, 2 (CDKL5 deficiency disorder); Albinism-deafness syndrome; paroxysmal nocturnal hemoglobinuria; Aldrich syndrome; Alport syndrome; Anaemia, hereditary hypochromic; Anemia, sideroblastic, with ataxia; Fabry disease; Spinal muscular atrophy 2; Cataract, congenital; Charcot-Marie-Tooth, peroneal; Spastic paraplegia; Colour blindness; Diabetes insipidus,
15 nephrogenic; DDX3X syndrome; Dyskeratosis congenita; Ectodermal dysplasia, anhidrotic; Faciogenital dysplasia (Aarskog syndrome); Glucose-6-phosphate dehydrogenase deficiency; Glycogen storage disease type VIII; Gonadal dysgenesis (XY female type); Granulomatous disease (chronic); Haemophilia A; Haemophilia B; Hydrocephalus (aqueduct stenosis); Hypophosphataemic rickets;
20 Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency); Incontinentia pigmenti; Kallmann syndrome; Keratosis follicularis spinulosa; Lowe (oculocerebrorenal) syndrome; Menkes syndrome; Renpenning Syndrome; Mental retardation, with or without fragile site (numerous specific types); Coffin-Lowry syndrome; Microphthalmia with multiple anomalies (Lenz syndrome);
25 Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types); Myotubular myopathy; Night blindness, congenital stationary; Norrie's disease (pseudoglioma); Nystagmus, oculomotor or 'jerky'; Orofaciodigital syndrome (type I); Omithine transcarbamylase deficiency (type I hyperammonaemia); Phosphoglycerate kinase deficiency; Phosphoribosylpyrophosphate synthetase deficiency; Retinitis
30 pigmentosa; Retinoschisis; Rett syndrome; Muscular atrophy /Dihydrotestosterone receptor deficiency; Spinal muscular atrophy; Spondyloepiphyseal dysplasia tarda; Thrombocytopenia, hereditary; Thyroxine-binding globulin, absence; or McLeod syndrome; or
35 iii. an autoimmune disease, a disorder of the CNS, a neurological disease, an inflammatory disease, an infectious disease, type 2 diabetes, a neuropsychiatric behavioural disorder, a depressive disorder or a disease related to the inactivation of the X-chromosome.

18. Use of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11, in the manufacture of a medicament for the inhibition of METTL3 activity.
- 5
19. A method of treating a proliferative disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11;
- 10 optionally wherein the proliferative disorder is cancer;
further optionally wherein the cancer is selected from:
- i. leukaemia, (e.g. acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia, chronic lymphocytic leukaemia (CLL)) small
 - 15 lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS));
 - ii. a cancer of the CNS (e.g. Glioma, Glioblastoma Multiforme (GBM), Astrocytomas, Oligodendrogliomas, Ependyomas, Meningiomas, other brain neoplasms or secondary tumours that have metastasized to the brain).
- 20 20. A method of treating a neurodegenerative disorder, e.g. a tauopathy such as Alzheimer's disease, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementias, Pick's disease, globular glial tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, primary age-related tauopathy (PART), Progressive supranuclear palsy, and chronic traumatic encephalopathy; a motor neuron disease (including ALS); a repeat
- 25 expansion disease such as Huntington's Disease, dementia (including frontotemporal dementia, vascular dementia and dementia caused by a tauopathy such as Alzheimer's Disease); multiple sclerosis; multiple sclerosis; or Parkinson's Disease, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt
- 30 thereof, or a pharmaceutical composition according to claim 11.
21. A method of treating an autoimmune disease, a disorder of the CNS, a neurological diseasean inflammatory disease, an infectious disease, type 2 diabetes, a neuropsychiatric behavioural disorder, a depressive disorder or a disease related to the inactivation of the X-
- 35 chromosome, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 10 or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11.

22. A method of treating a disease related to the inactivation of the X-chromosome, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11; optionally wherein the disease related to the inactivation of the X-chromosome is selected from: Addison's disease with cerebral sclerosis; Adrenal hypoplasia; siderius X-linked mental retardation syndrome; Agammaglobulinaemia, Bruton type; Choroidoretinal degeneration; Choroidaemia; Albinism, ocular; Dent's disease 2; fragile X syndrome; Rett/ Epileptic encephalopathy, early infantile, 2 (CDKL5 deficiency disorder); Albinism-deafness syndrome; paroxysmal nocturnal hemoglobinuria; Aldrich syndrome; Alport syndrome; Anaemia, hereditary hypochromic; Anemia, sideroblastic, with ataxia; Fabry disease; Spinal muscular atrophy 2; Cataract, congenital; Charcot-Marie-Tooth, peroneal; Spastic paraplegia; Colour blindness; Diabetes insipidus, nephrogenic; DDX3X syndrome; Dyskeratosis congenita; Ectodermal dysplasia, anhidrotic; Faciogenital dysplasia (Aarskog syndrome); Glucose-6-phosphate dehydrogenase deficiency; Glycogen storage disease type VIII; Gonadal dysgenesis (XY female type); Granulomatous disease (chronic); Haemophilia A; Haemophilia B; Hydrocephalus (aqueduct stenosis); Hypophosphataemic rickets; Lesch-Nyhan syndrome (hypoxanthine-guanine-phosphoribosyl transferase deficiency); Incontinentia pigmenti; Kallmann syndrome; Keratosis follicularis spinulosa; Lowe (oculocerebrorenal) syndrome; Menkes syndrome; Renpenning Syndrome; Mental retardation, with or without fragile site (numerous specific types); Coffin-Lowry syndrome; Microphthalmia with multiple anomalies (Lenz syndrome); Muscular dystrophy (Becker, Duchenne and Emery-Dreifuss types); Myotubular myopathy; Night blindness, congenital stationary; Norrie's disease (pseudoglioma); Nystagmus, oculomotor or 'jerky'; Orofaciodigital syndrome (type I); Omithine transcarbamylase deficiency (type I hyperammonaemia); Phosphoglycerate kinase deficiency; Phosphoribosylpyrophosphate synthetase deficiency; Retinitis pigmentosa; Retinoschisis; Rett syndrome; Muscular atrophy /Dihydrotestosterone receptor deficiency; Spinal muscular atrophy; Spondyloepiphyseal dysplasia tarda; Thrombocytopenia, hereditary; Thyroxine-binding globulin, absence; or McLeod syndrome.
23. A method of inhibiting METTL3 activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound according to any one of claims 1 to

10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11.

24. A method of inhibiting metastasis *in vitro* or *in vivo*, said method comprising
5 contacting a cell with an effective amount of a compound according to any one claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 11.

25. A combination comprising a compound according to any one of claims 1 to 10, or a
10 pharmaceutically acceptable salt there, with one or more additional therapeutic agents.