

SUBSTITUTED PYRROLO[2,3-D]PYRIMIDINES, THEIR PREPARATION
AND THEIR THERAPEUTIC APPLICATION

Disclosed herein are substituted pyrrolo[2,3-d]pyrimidine compounds, crystalline form, processes for their preparation, pharmaceutical compositions containing the
5 compounds, as well as therapeutic uses thereof.

BACKGROUND

Parkinson's disease (PD) is an age-dependent neurodegenerative disorder with high unmet medical need, in the context of an aging population. Mutations in several genes segregate PD in families. Among them, seven leucine rich repeat kinase 2 (LRRK2)
10 mutations are linked to autosomal dominant forms of PD. LRRK2 polymorphs were identified as risk factors for sporadic PD in Genome Wide Association Studies (J.H. Kluss, Biochemical Society Transactions 2019). LRRK2 carriers share similar clinical symptoms, disease onset and progression with sporadic patients (H. Tomiyama, Hum. Mov. Disord. 2006) suggesting that LRRK2 signaling pathways may be central to the processes
15 underlying both LRRK2 familial and sporadic late onset PD. All pathogenic LRRK2 mutations, as well as VPS35 D620N mutation which is another target genetically linked to PD, induce increased LRRK2 kinase activity (M. Steger et al., eLife 2016; R. Mir et al., Biochem J. 2018). Beyond familial PD, increased LRRK2 activity or level was reported in human brains from idiopathic PD patients (R. Di Maio et al., Sci. Transl. Med. 2018).
20 These results support the hypothesis that dysregulated LRRK2 kinase activity may contribute to pathogenesis, suggesting the therapeutic potential of LRRK2 kinase inhibitors to block aberrant LRRK2-dependent signaling in both LRRK2 and idiopathic form of PD (A.B. West Exp. Neurol. 2017). Accumulation of synuclein aggregates and loss of dopaminergic neurons are the main hallmarks of PD. Blockade of these
25 phenotypes after LRRK2 kinase inhibitor treatment was demonstrated in numerous reports (E.M. Rocha et al, Neurobiol. Of Disease 2019). These results support the hypothesis that potent, brain penetrant LRRK2 kinase inhibitors have therapeutic potential for the treatment of PD.

A growing body of evidence suggests a role of LRRK2 in the regulation of
30 lysosomal activity (J. Schapansky et al, Neurobiol. of Disease 2018). Increased bis(monoacylglycerol)phosphate levels, a marker of lysosomal storage diseases such as

Pick's disease, was observed in fluids from LRRK2 gain of function mutations carriers (R.N. Alcalay, Movement Disorders, 2020). Lysosomal glucocerebrosidase (GBA) mutations are the largest risk factor for development of PD (GBA-PD). Decreased glucocerebrosidase activity was reported in neurons from GBA and LRRK2 mutation carriers (D. Ysselstein, Nature com. 2019). Conversely, normalization of glucocerebrosidase activity and level were achieved in vitro and in vivo after treatment with LRRK2 kinase inhibitors, suggesting a potential benefit in patients from lysosomal storage diseases such as GBA-PD (A. Sanyal et al, Mov. Disorders 2020).

Immunofluorescence experiments in human brain showed colocalization of LRRK2 with neurofibrillary tangles (J. Miklossy, J Neuropathol. Exp. Neurol. 2006). Moreover, LRRK2 has been reported to phosphorylate tubulin-associated Tau (F. Kawakami et al., PloS One 2012), and Tau hyperphosphorylation was observed in LRRK2 kinase activating mutant transgenic mice (Y. Li et al., Nat. Neurosci. 2009). These data indicate that LRRK2 kinase inhibitor treatment might be useful in treating tauopathy disorders such as Pick's disease, progressive supranuclear palsy and frontotemporal dementia.

LRRK2 is expressed in brain glial cells, and attenuation of neuroinflammation was achieved after LRRK2 kinase inhibitor treatment in various in vivo models (M.S. Moehle et al., J. Neurosci. 2012). Neuroinflammation is often observed in neurodegenerative diseases such as Parkinson's disease, Alzheimer disease, multiple sclerosis, HIV-induced dementia and Amyotrophic lateral sclerosis; LRRK2 kinase inhibitors may therefore have utility in the treatment of these pathologies.

WO2017106771 discloses compounds having a pyrrolopyrimidine core substituted by a (hetero)arylamine group and by a cyano group. These compounds are capable of inhibiting certain protein kinases, and especially the leucine-rich repeat kinase 2 (LRRK2) protein and can be used to treat disorders including neurodegenerative diseases such as Parkinson's disease.

US2020239474 discloses a novel pyrrolo-pyrimidine derivative compound for preventing or treating a protein kinase-related disease.

WO2020149715 discloses compounds having a pyrrolopyrimidine core substituted by a (hetero)arylamino group and by a cyano group, which can be advantageously used

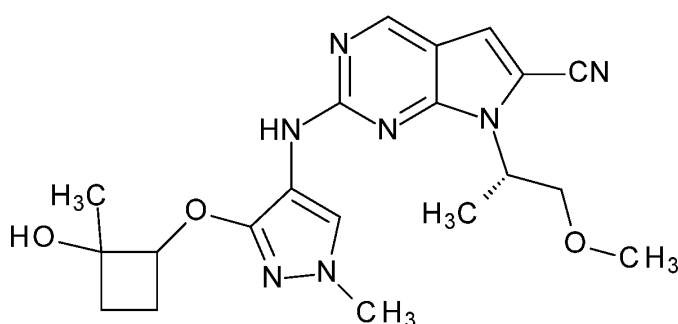
for treating or preventing protein kinase-related diseases, cancer and degenerative brain diseases.

In general, there is a desire to produce solid forms of pharmacologically active substances with advantageous physical properties, for example in terms of optimal chemical and physical stability, acceptable solubility, better handling properties, etc. From a chemistry point of view, generating a crystalline form of an active ingredient allows access to purification processes, which permits easier control of the final impurity profile of the compound.

There is a need to provide LRRK2 kinase inhibitors with good efficacy and there is a need to develop solid forms of the compound of Formula (I) with advantageous properties.

SUMMARY OF THE INVENTION

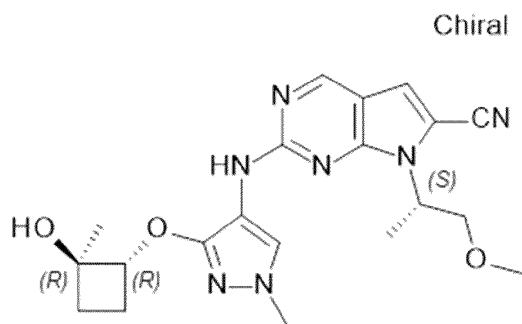
In accordance with one aspect, disclosed herein is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof.

Another aspect of the present disclosure is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Herein is therefore provided a specific crystalline form of a compound of Formula (Ia):



;

wherein the crystalline form is Form A, having an X-ray powder diffraction pattern comprising characteristic peaks at $6.8^{\circ} \pm 0.2^{\circ} 2\theta$, $17.8^{\circ} \pm 0.2^{\circ} 2\theta$, and $19.9^{\circ} \pm 0.2^{\circ} 2\theta$.

The compounds of Formula (I) above and pharmaceutically acceptable salts thereof exhibit inhibitory activity against wild type and mutant LRRK2 and are useful in the treatment of neurodegenerative diseases.

DESCRIPTION

As used herein, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, the term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of a compound of Formula (I). These salts can be prepared *in situ* during the final isolation and purification of the compounds.

As used herein, the term "pharmaceutically acceptable excipient" refers to a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present disclosure in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. The said excipients are selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

As used herein, the term "pharmaceutically effective amount" or "therapeutically effective amount" means an amount of a compound/composition according to the present disclosure effective in producing the desired therapeutic effect.

As used herein, the term "substantially enantiomerically pure" means that 90% or more of a particular compound in the composition is in the first enantiomeric form, and 10% or less is in the second enantiomer.

As used herein, the term "enantiomerically pure" means that 95% or more of the particular compound in the composition is in the first enantiomeric form, and 5% or less is in the second enantiomer. In some instance, it means 97% or 99% or more of the particular compound in the composition is in the first enantiomeric form.

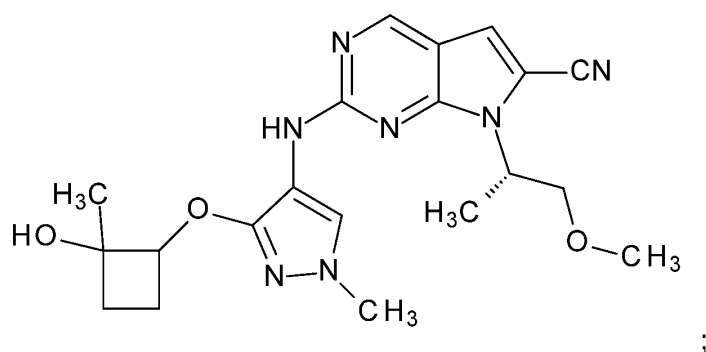
As used herein, the term "enantiomeric excess" means the difference between the amount of one particular compound in the composition and the amount of the other compound(s) in the composition. Thus, for example, an excess of 96% of the enantiomer indicates a composition having 98% of one particular compound and 2% of the other one particular compound(s).

As used herein, the term "treating" or "treatment" means to arrest, slow down or reduce the progression of the disease; to cause regression of its biological manifestations and/or clinical symptom; to inhibit further progression or worsening of at least one symptom, i.e. by reducing the severity or frequency of at least one symptom.

As used herein, the term "patient" refers to a human suffering from disease.

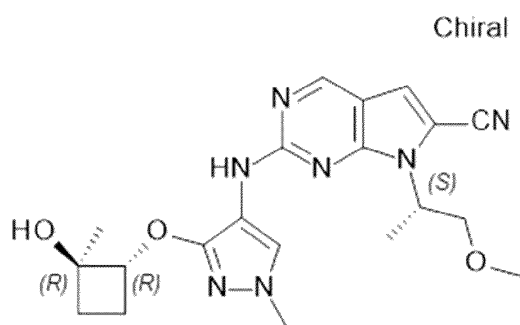
As used herein, the term "Compounds of Formula (I)", and equivalent expressions, are meant to include racemic compounds of Formula (I), and their enantiomers, epimers, diastereoisomers, geometric isomers, tautomers and mixtures thereof, where the context so permits.

Provided herein is a compound of the formula (I):



or pharmaceutically acceptable salt thereof.

Provided herein is a compound of the formula (I-a):



or pharmaceutically acceptable salt thereof.

5 In one embodiment, the compound of formula (I-a) is substantially enantiomerically pure.

In one embodiment, the compound of formula (I) is selected from the group consisting of:

- 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-
 10 [(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
- 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-
 2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
- 2-[[3-[trans-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-
 methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
- 15 2-[[3-[(1R,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-
 2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
- 2-[[3-[(1S,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-
 2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;
- 2-[[3-[cis-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-
 20 methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; and
- 2-[[3-[2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-
 methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

5 In one embodiment, the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

10 In one embodiment, the compound of formula (I) is enantiomerically pure 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

15 In one embodiment, the compound of formula (I) is 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

20 In one embodiment, the compound of formula (I) is enantiomerically pure 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; or a pharmaceutically acceptable salt thereof.

25 Another embodiment is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Another embodiment is a pharmaceutical composition comprising as active principle an effective dose of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

30 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of

formula (I) is 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

5 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

10 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

15 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

20 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[trans-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

25 One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[trans-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[(1S,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[cis-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-[[3-[2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile, or a pharmaceutically acceptable salt thereof.

One embodiment is a method for treating a disease or disorder selected from the group consisting of neurodegenerative diseases, said method comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method for treating a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, Lewy body dementia, Pick disease, progressive supranuclear palsy, and frontotemporal dementia, said method comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method for treating a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis and Lewy body dementia, said method

comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method for treating a tauopathy disorder is selected from the group consisting of Pick disease, progressive supranuclear palsy, and frontotemporal dementia, said method comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating Parkinson's disease, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating Parkinson's disease, comprising administering to a patient in need thereof a therapeutically effective amount of substantially enantiomerically pure 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating Parkinson's disease, comprising administering to a patient in need thereof a therapeutically effective amount of 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating Parkinson's disease, comprising administering to a patient in need thereof a therapeutically effective amount of substantially enantiomerically pure 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating Parkinson's disease, comprising administering to a patient in need thereof a therapeutically effective amount of 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is a medicament, characterized in that it comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder selected from the group consisting of neurodegenerative diseases.

One embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, Lewy body dementia, Pick disease, progressive supranuclear palsy and frontotemporal dementia.

One embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, and Lewy body dementia.

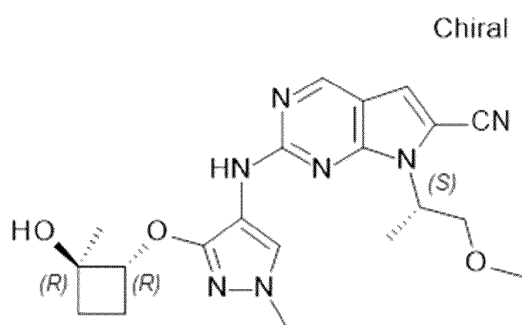
One embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a tauopathy disorder is selected from the group consisting of Pick disease, progressive supranuclear palsy, and frontotemporal dementia.

One embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of Parkinson's disease.

One embodiment is compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of Parkinson's disease, wherein the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of Parkinson's disease, wherein the compound of formula (I) is substantially enantiomerically pure 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile or a pharmaceutically acceptable salt thereof.

One embodiment is a crystalline form of a compound of Formula (Ia):

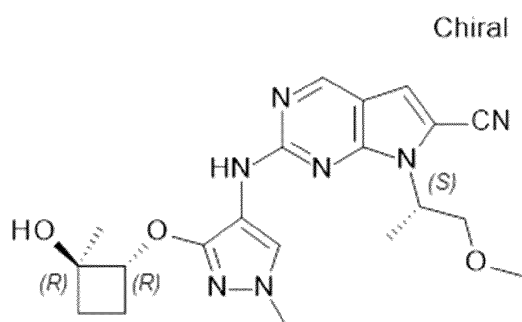


; which is referred herein as Form A.

One embodiment is a solid form of a compound of Formula (I-a) as defined in the present disclosure characterized as crystalline Form A.

- 5 One embodiment is a solid form of a compound of Formula (I-a) which is at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% crystalline.

One embodiment is a crystalline form of a compound of Formula (I-a):



;

- 10 wherein the crystalline form is Form A, having an X-ray powder diffraction pattern comprising characteristic peaks at $6.8^\circ \pm 0.2^\circ 2\theta$, $17.8^\circ \pm 0.2^\circ 2\theta$, and $19.9^\circ \pm 0.2^\circ 2\theta$.

- Crystalline Form A may be characterized by powder X-ray diffraction. Crystalline Form A may have an X-ray powder diffraction pattern comprising characteristic peaks at $6.8^\circ \pm 0.2^\circ 2\theta$, $17.8^\circ \pm 0.2^\circ 2\theta$, and $19.9^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $13.6^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $19.3^\circ \pm 0.2^\circ 2\theta$. The X-ray powder diffraction pattern may further comprise a peak at $17.4^\circ \pm 0.2^\circ 2\theta$. Thus, the X-ray powder diffraction pattern may comprise 3, 4, 5, 6, or more characteristic peaks.
- 15

One embodiment is a solid form of a compound of Formula (I-a) having an X-ray powder diffraction (XRPD) pattern derived using Cu (K α) radiation comprising three, four, five, six, seven or more peaks, in term of 2-theta degrees, chosen from peaks at about 6.8 $\pm$ 0.2, 9.8 $\pm$ 0.2, 13.6 $\pm$ 0.2, 13.9 $\pm$ 0.2, 14.7 $\pm$ 0.2, 16.0 $\pm$ 0.2, 17.4 $\pm$ 0.2, 17.8 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.9 $\pm$ 0.2.

The X-ray powder diffraction pattern of crystalline Form A may comprise peaks at 6.8, 13.6, 17.8, and 19.9, with each peak measured to $\pm$ 0.2° 2 θ .

One embodiment is crystalline form A of compound of formula (I-a) having an XRPD pattern derived using Cu (K α) radiation, in term of 2-theta degrees, having peaks at about 6.8 $\pm$ 0.2, 17.8 $\pm$ 0.2, and 19.9 $\pm$ 0.2.

One embodiment is crystalline form A of compound of formula (I-a) having X-ray powder diffraction pattern that is substantially as illustrated in Fig. 2.

The X-ray powder diffraction pattern of crystalline Form A may comprise peak positions corresponding to 2, 3, 4, 5, 6, 7, or all of the peak positions listed in Table 1 below, which is generated from experimental powder diffraction data:

Angle (2-Theta) (each time $\pm$ 0.20)	Intensity (%)
6.8	100
9.8	4
13.6	12
13.9	7
14.7	6
16.0	6
17.4	9
17.8	22
19.3	11
19.9	14

Crystalline Form A may be characterized by DSC or by TGA. A DSC thermogram of crystalline Form A may have an onset temperature at about $118^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The enthalpy change of the endothermic peak may be about -72 J/g .

5 One embodiment is the solid form of compound of formula (I-a) characterized by a differential scanning calorimetry (DSC) curve with an onset at about $118^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

One embodiment is the solid form of compound of formula (I-a) characterized by a DSC profile substantially in accordance with that shown in Figure 1.

10 Crystalline Form A is thermally stable: this is evident from the DSC of Fig. 1 which shows that crystalline Form A has an onset temperature at about $118^{\circ}\text{C} (\pm 2^{\circ}\text{C})$. TGA analysis also shows the crystalline Form A is chemically stable until close to its melting temperature, as shown in Fig. 3.

One embodiment is the solid form of compound of formula (I-a), wherein Form A is characterized by at least two of:

15 a) an X-ray powder diffraction (XRPD) pattern substantially in accordance with that shown in Figure 2;

 b) an X-ray powder diffraction (XRPD) pattern derived using Cu ($K\alpha$) radiation comprising three, four, five, six, seven or more peaks, in term of 2-theta degrees, at about 6.8 ± 0.2 , 9.8 ± 0.2 , 13.6 ± 0.2 , 13.9 ± 0.2 , 14.7 ± 0.2 , 16.0 ± 0.2 , 17.4 ± 0.2 , 17.8 ± 0.2 , 19.3 ± 0.2 , 19.9 ± 0.2 ;

 c) a DSC profile substantially the same as shown in Figure 1;

 d) a Differential Scanning Calorimetry (DSC) thermogram having an onset at about $118^{\circ}\text{C} \pm 2^{\circ}\text{C}$;

 e) a profile substantially the same as shown in Figure 3;

25 Herein is also provided a pharmaceutical composition comprising crystalline Form A as defined above. Herein is provided a pharmaceutical composition comprising the crystalline Form A and one or more pharmaceutically acceptable excipients, carriers, or diluents.

One embodiment is a pharmaceutical composition comprising the solid form as defined in the present disclosure and a pharmaceutically acceptable carrier.

In various embodiments, the pharmaceutical composition comprises at least about 20 wt% of crystalline Form A, optionally about 30 wt% of crystalline Form A, optionally about 40 wt% of crystalline Form A, optionally about 50 wt% of crystalline Form A, optionally about 60 wt% of crystalline Form A, optionally about 70 wt% of crystalline Form A, optionally about 80 wt% of crystalline Form A, optionally about 90 wt% of crystalline Form A, optionally about 95 wt% of crystalline Form A.

At least about 50 mol% of the compound of Formula (I) in the composition may be in the form of crystalline Form A. For example, at least about 60 mol%, or 70 mol%, or 80 mol%, or 90 mol%, or 95 mol% of the compound of Formula (I) in the composition may be in the form of crystalline Form A. Substantially all of the compound of Formula (I) in the composition may be in the form of crystalline Form A.

Herein is also provided crystalline Form A as defined above, or a pharmaceutical composition as defined herein, for use in therapy, for example in the treatment of a disease or disorder selected from the group consisting of neurodegenerative diseases.

One embodiment is a solid form as defined in the present disclosure for use in treating a neurodegenerative disease in a patient in need thereof.

One embodiment is a use of a solid form as defined in the present disclosure in the manufacture of a medicament for treating a neurodegenerative disease.

Herein is also provided crystalline Form A as defined above, or a pharmaceutical composition as defined herein, for use in the treatment of a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, Lewy body dementia, Pick disease, progressive supranuclear palsy and frontotemporal dementia.

Herein is also provided a method for treating of a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, Lewy body dementia, Pick disease, progressive supranuclear palsy and frontotemporal dementia, which comprises administering to a patient in need of such treatment an effective amount of a crystalline form or a pharmaceutical composition as defined herein.

Herein is also provided the use of a crystalline form or a pharmaceutical composition as defined above for the manufacture of a medicament for the treatment of a neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, Amyotrophic lateral sclerosis, Lewy
5 body dementia, Pick disease, progressive supranuclear palsy and frontotemporal dementia.

Brief Description of the Figures

Figure 1 (also named Fig. 1) shows a differential scanning calorimetry (DSC) plot of crystalline Form A.

10 Figure 2 (also named Fig. 2) shows an X-ray powder diffraction pattern of crystalline Form A.

Figure 3 (also named Fig. 3) shows TGA plots of crystalline Form A.

Figure 4 (also named Fig. 4) shows an exemplary setup.

GENERAL PROCEDURES:

15 MATERIAL AND METHODS

I. X-RAY POWDER DIFFRACTION (XRPD)

Analyse was carried out at room temperature on a Brucker D4 Endeavor instrument using the Bragg-Brentano parafocusing geometry. A sealed copper anode X-ray tube was used (λ CuK α average = 1.54178 Å). A LynxEye linear detector completed
20 the setup. A counting time of few seconds per step in an angular range of from few 2-Theta degrees to several dozen 2-Theta degrees with a 0.017° step size in 2 θ . For each experiment, the powder was deposited onto the surface of a sample holder.

II. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC analysis was carried out on a DSC2500 calorimeter (TA Instruments).
25 Sample masse of few mg was deposited in an unsealed aluminium pan and the atmosphere was regulated by a constant nitrogen flow. Analyse have been carried out with a scanning rate of 5°C/min.

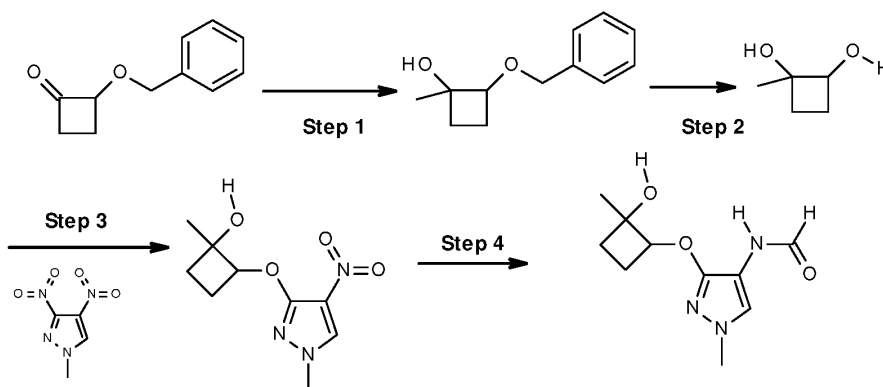
III. THERMOGRAVIMETRIC ANALYSIS (TGA)

Analysis was carried out using a TG209C Netzsch Instrument. A sample mass of a few mg is deposited in an aluminium crucible. The TGA analysis is conducted under a dry nitrogen stream and the sample is heated up to 200°C at a rate of 5°C/min.

Starting materials and solvents used in the synthesis were obtained from chemical vendors such as ABCR, Aldrich, Acros, Apollo, Fluka, Netchem, Lancaster and others.

Generally, crude products were purified by column chromatography or flash chromatography.

Intermediate 1: N-[1-methyl-3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]formamide and N-[1-methyl-3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]formamide (racemic trans)



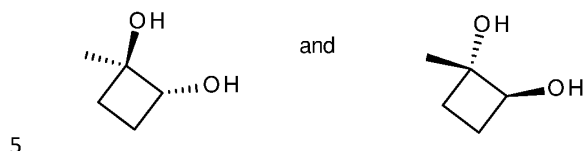
Step 1: Preparation of 2-(benzyloxy)-1-methylcyclobutan-1-ol (racemic trans)



28.4 mL of methyl magnesium bromide (3M in tetrahydrofuran) (1.5 eq.) were added at -78°C to a solution of 10 g of 2-benzyloxycyclobutanone (commercially available) in 240 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 hour then quenched with 150 mL of an aqueous saturated solution of ammonium chloride and extracted twice with 200 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate, concentrated under reduced pressure, and purified on silica,

eluting with 30% of ethyl acetate in heptane to afford 4.9 g of 2-(benzyloxy)-1-methylcyclobutan-1-ol (racemic cis) and 4 g of 2-(benzyloxy)-1-methylcyclobutan-1-ol (racemic trans).

Step 2: Preparation of 1-methylcyclobutane-1,2-diol (racemic trans)

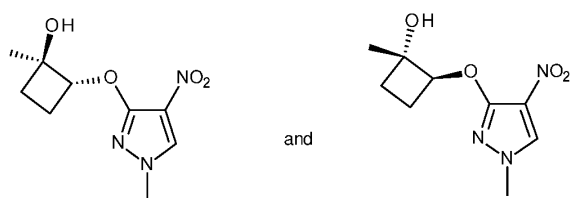


A solution of 4000 mg of 2-(benzyloxy)-1-methylcyclobutan-1-ol (racemic trans) in 150 mL of methanol was treated with 1610 mg of palladium on carbon (10%) under 5 bars of hydrogen at 20°C for 75 minutes. The mixture was filtered with methanol washes and concentrated under reduced pressure to afford 2300 mg of 1-methylcyclobutane-1,2-diol (racemic trans). ¹H NMR (400 MHz, CDCl₃) δ in ppm: 1.29 (s, 3 H); 1.35 (t, J= 10Hz, 1 H); 1.54 (q, J= 11Hz, 1 H); 1.77 (t, J= 10Hz, 1 H); 2.05 (m, 1 H); 2.79 (s, 2 H); 4.07 (t, J= 8.5Hz, 1 H).

10

Step 3: Preparation of (1S,2S)-1-methyl-2-(1-methyl-4-nitro-pyrazol-3-yl)oxy-cyclobutanol and (1R,2R)-1-methyl-2-(1-methyl-4-nitro-pyrazol-3-yl)oxy-cyclobutanol (racemic trans)

15

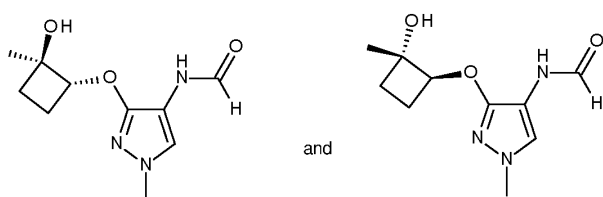


653 mg (1.1 eq.) of 1-methylcyclobutane-1,2-diol (racemic trans) and 3786 mg (2 eq.) of cesium carbonate were added to a solution of 1000 mg (1 eq.) of 1-(methyl)-3,4-dinitro-1H-pyrazole (commercially available) in 20 mL of methyl-THF. The mixture was heated at 80°C for 8 h then allowed to cool to room temperature and poured onto ethyl acetate and water. The aqueous layer was separated and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under

20

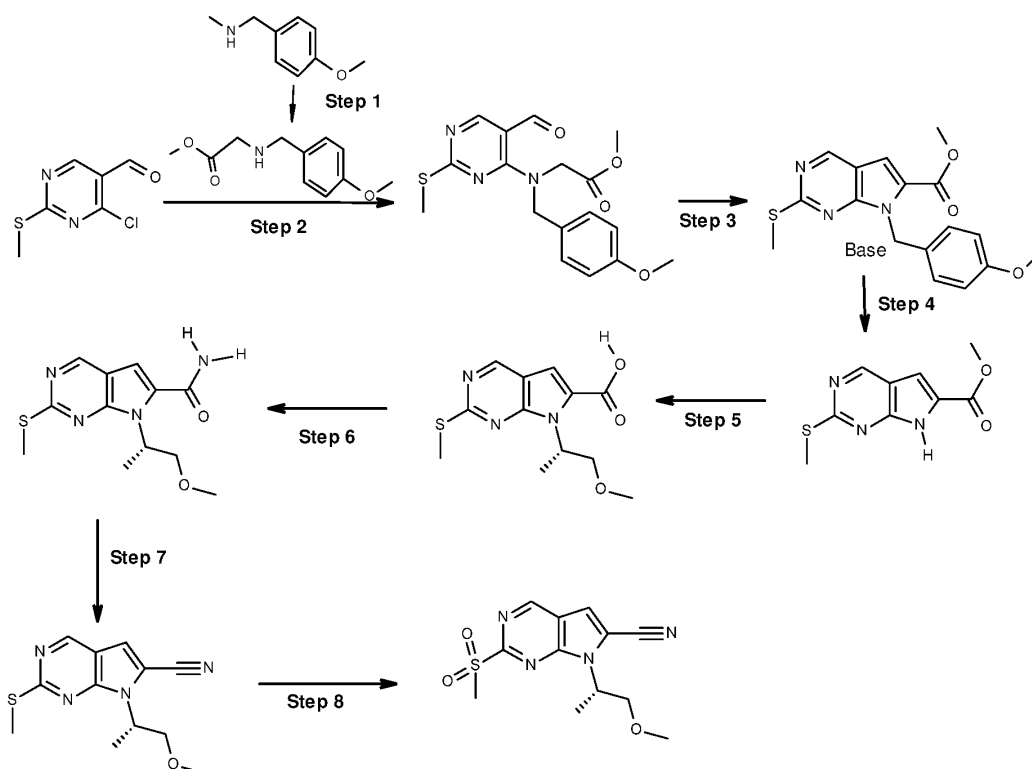
vacuum. The residue was purified on silica gel, eluting with a gradient of 0 to 50% of ethyl acetate in dichloromethane, to afford 794 mg of 1-methyl-2-((1-(methyl)-4-nitro-1H-pyrazol-3-yl)oxy)cyclobutan-1-ol (racemic trans).

Step 4: Preparation of N-[1-methyl-3-[(1R,2R)-2-hydroxy-2-methylcyclobutoxy]pyrazol-4-yl]formamide and N-[1-methyl-3-[rac-(1S,2S)-2-hydroxy-2-methylcyclobutoxy]pyrazol-4-yl]formamide (racemic trans)

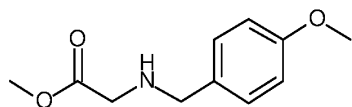


In a microwave vial, a solution of 235 mg of 1-methyl-2-((1-(methyl)-4-nitro-1H-pyrazol-3-yl)oxy)cyclobutan-1-ol (racemic trans) in 5 mL of methanol was treated with 456 mg (7 eq.) of ammonium formate and 85 mg of palladium on carbon (10%) and heated at 70°C for 15 minutes (pressure of 9 bars). The mixture was filtered with methanol washes and concentrated under reduced pressure. The residue was taken into 2 mL of THF and added at 0°C to a mixture of 422 mg of acetic anhydride (4 eq.) and 857 mg (18 eq.) of formic acid that had been premixed for 30 minutes at room temperature. The mixture was stirred for 10 minutes at 0°C then overnight at room temperature. The mixture was concentrated under vacuum. The residue was purified on silica gel, eluting with a gradient of 0 to 10% of methanol in dichloromethane, to afford 185 mg of N-(3-(2-hydroxy-2-methylcyclobutoxy)-1-(methyl)-1H-pyrazol-4-yl)formamide (racemic trans).

Intermediate 2: (S)-7-(1-methoxypropan-2-yl)-2-(methylsulfonyl)-7H-pyrrolo[2,3d]pyrimidine-6-carbonitrile

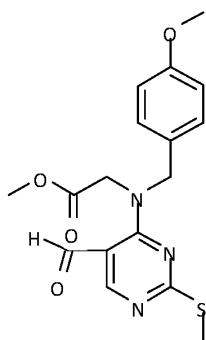


Step 1: Preparation of methyl (4-methoxybenzyl)glycinate



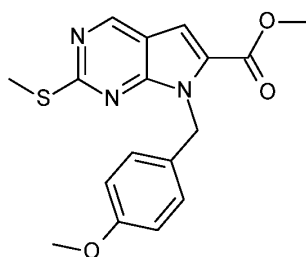
53 mL (1 eq.) of methyl 2-bromoacetate in 225 mL of tetrahydrofuran was slowly added (35 minutes) to a solution of 71 mL (1 eq.) of (4-methoxyphenyl)methanamine and 116 mL of triethylamine (1.5 eq.) in 750 mL of tetrahydrofuran at 0°C (ice water/methanol bath) under argon. After 5 hours at room temperature and completion of the reaction, the mixture was filtered. The filtrate was taken into 975 mL of ethyl acetate and 375 mL of water was added. After drying of the organic layer on magnesium sulfate and concentration under vacuum, the residue was purified on silica gel eluting with dichloromethane 100% then dichloromethane/ethyl acetate (90/10) then dichloromethane/ethyl acetate (70/30) to give 60.9 g of methyl(4-methoxybenzyl)glycinate.

Step 2: Preparation of methyl N-(5-formyl-2-(methylthio)pyrimidin-4-yl)-N-(4-methoxybenzyl)glycinate



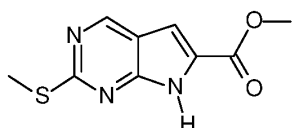
5 52.5 mL of triethylamine (1.5 eq.) was added to a solution of 49 g of 4-chloro-2-(methylthio)pyrimidine-5-carbaldehyde (1 eq.) in 500 mL of tetrahydrofuran and 50 mL of dichloromethane at 0°C. 63 g of methyl (4-methoxybenzyl)glycinate (1.1 eq) was added dropwise. The mixture was stirred at room temperature for 17 hours. The reaction mixture was diluted with 500 mL of ethyl acetate and water. The organic layer was separated,
 10 washed twice with 1000 mL of water and then 1000 mL of a 0.5N HCl aqueous solution. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken into 500 mL of heptane and stirred for 12 hours. The resulting precipitate was filtered and dried under vacuum to afford 90 g of methyl N-(5-formyl-2-(methylthio)pyrimidin-4-yl)-N-(4-methoxybenzyl)glycinate.

15 Step 3: Preparation of methyl 7-(4-methoxybenzyl)-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate



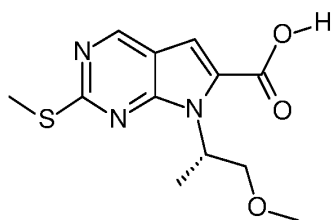
167 mL (4 eq.) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added dropwise to a solution of 99 g of methyl N-(5-formyl-2-(methylthio)pyrimidin-4-yl)-N-(4-methoxybenzyl)glycinate (1 eq.) in 1000 mL of acetonitrile. The reaction mixture was heated at 85°C for 40 minutes. After cooling down to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was taken into 800 mL of ethyl acetate and 500 mL of water. The organic layer was washed with 300 mL of a 1N HCl aqueous solution, 300 mL of a saturated aqueous sodium hydrogenocarbonate solution, 500 mL of water, and then 300 mL of brine and concentrated under reduced pressure to afford 82.4 g of methyl 7-(4-methoxybenzyl)-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate.

Step 4: Preparation of methyl 2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate



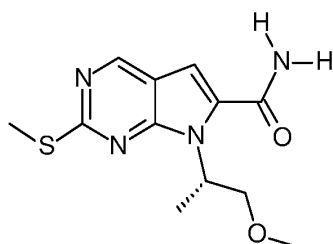
169 mL of trifluoromethanesulfonic acid (10 eq.) was added dropwise to a solution of 62.8 g of methyl 7-(4-methoxybenzyl)-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (1 eq.) in 604 mL of trifluoroacetic acid (44 eq.). The reaction mixture was heated at 75°C for 90 minutes. After cooling down to room temperature, the trifluoroacetic acid was concentrated under reduced pressure. The reaction mixture was diluted with 500 mL of dichloromethane and cooled to -15°C. 360 mL of 5M sodium hydroxide solution was added dropwise while maintaining the temperature below 5 °C. When pH 6 was reached a precipitate was formed. The precipitate was filtered then washed with water (twice with 250 mL) and 250 mL of heptane then dried under vacuum to afford 37.72 g of methyl 2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate.

Step 5 : Preparation of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



To a solution of 62.5 g (1 eq.) of methyl 2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, 37.84 g (1.5 eq.) of (2R)-1-methoxypropan-2-ol and 110.1 g (1.5 eq.) of triphenylphosphine in 1100 mL of anhydrous tetrahydrofuran cooled at -10°C was added
 5 84.9 g (1.5eq.) of diisopropyl azodicarboxylate in 30 minutes, keeping the temperature below 10°C. The mixture was stirred at room temperature for 4.5 hours. 58.74 g of Lithium hydroxide hydrate (5 eq.) in 450 mL of water were added. The mixture was stirred for overnight at room temperature then diluted with 450 mL of water and extracted 4 times with 500 mL of ethyl acetate. The two phases were separated. The aqueous layer was
 10 acidified to pH 1 with HCl 5N. The precipitate formed upon acidification was filtered-off, washed with 100 mL of water, 100 mL of pentane, and dried under vacuum at 50°C to afford 26.6 g of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid.

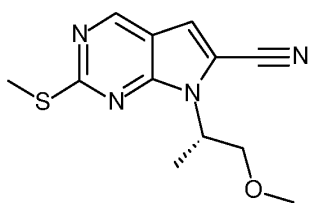
Step 6 : preparation of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-
 15 d]pyrimidine-6-carboxamide



82.04 g (2 eq.) of di(1H-imidazol-1-yl)methanone (CDI) was added to a solution of 71.17 g (1 eq.) of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid in 720 mL of dimethylformamide. The mixture was stirred at room
 20 temperature for 1 hour and 180 mL of a 28% ammonium hydroxide solution was added.

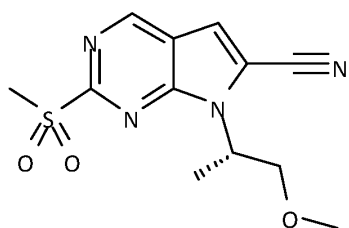
The reaction mixture was stirred at room temperature for 3 hours. It was then diluted with 3500 mL of water and extracted 4 times with 750 mL of ethyl acetate. The organic layers were combined, washed with 2000 mL of water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on silica gel, eluting with a gradient of 20 to 100% of ethyl acetate in heptane, to afford 60.73 g of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carboxamide.

Step 7 : preparation of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile



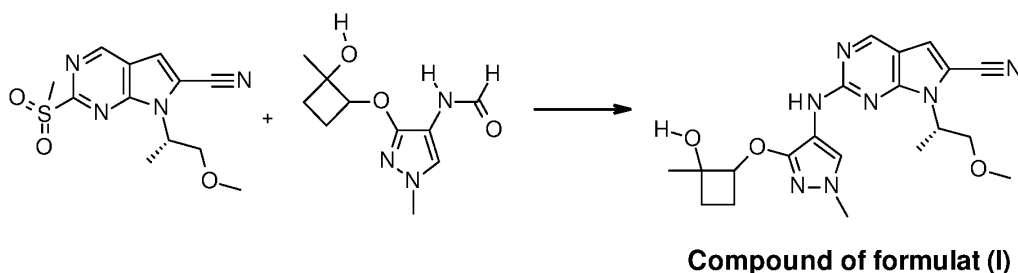
98.6 g (4.5 eq.) of triethylamine was added to a solution of 60.7 g (1 eq.) of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carboxamide in 750 mL of anhydrous tetrahydrofuran at 0°C under argon, followed by 164 g (3.6 eq.) of trifluoroacetic anhydride (addition in 30 minutes, maintaining the temperature below 6°C). The mixture was stirred for 45 minutes allowing the temperature to warm up to room temperature. It was then diluted with 3600 mL of water and 3600 mL of ethyl acetate. The organic layer was washed twice with 1800 mL of water, twice with 1800 mL of aqueous saturated sodium hydrogenocarbonate solution twice with 1800 mL of water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford 67.82 g of an orange oil. The crude material was taken into 50 mL of diisopropyl ether, the formed solid filtered and washed with 80 mL of di isopropyl ether and 80 mL of pentane to afford 43.04 g of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfanyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile.

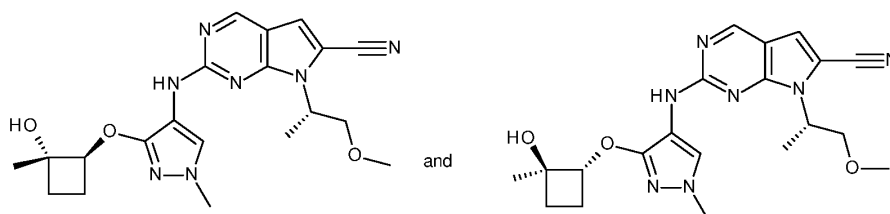
Step 8: Preparation of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfonyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile



179.4 g of potassium peroxymonosulfate (2 eq.) in 685 mL of water was added dropwise in 15 minutes to a solution of 38.27 g (1 eq.) of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfonyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile in 760 mL of methanol at room temperature. The mixture was stirred at room temperature overnight then diluted with 400 mL of water and 600 mL of dichloromethane. The aqueous layer was washed with 400 mL of dichloromethane. The combined organic layers were washed with 400 mL of aqueous saturated hydrogenocarbonate solution, then 400 mL of water, dried over magnesium sulfate, and concentrated under reduced pressure to afford 34.5 g of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfonyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile.

Example 1 : 2-[[1-methyl-3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile and 2-[[1-methyl-3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile





245 mg (1 eq.) of tert-butylimino-tri(pyrrolidino)phosphorane (BTTP) was added to a solution of 230 mg (1 eq.) of 7-[(1S)-2-methoxy-1-methyl-ethyl]-2-methylsulfonyl-pyrrolo[2,3-d]pyrimidine-6-carbonitrile and 184 mg (1.05 eq.) of a racemic mixture of N-[1-methyl-3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]formamide and N-[1-methyl-3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]formamide (intermediate 1) in 8 mL of acetonitrile and the mixture was stirred at room temperature for 2 hours, a diluted with 50 mL of ethyl acetate and 50 mL of water. The organic layer was washed twice with 50 mL of water then dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken in 10 mL of methanol and 50 mL of a 7N methanolic ammonia solution, stirred for 15 minutes at room temperature, concentrated under reduced pressure. The residue was purified on silica, eluting with a gradient of 20 to 50% of ethyl acetate in dichloromethane to afford 153 mg of an isomeric mixture of 2-[[1-methyl-3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile and 2-[[1-methyl-3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile.

Chiral separation performed on 153 mg of the isomeric mixture gave 73 mg of the first eluting isomer and 74 mg of the second eluting isomer (conditions: column Chiralpak AD, 20 μ m, 350x76.5 mm; liquid phase: heptane 70/ethyl alcohol 30 / 0.1 TEA; flow rate: 400 mL/min).

Peak 1 (1st isomer): ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 1.19 (s, 3 H) 1.39 - 1.58 (m, 2 H) 1.55 (d, J=7.0 Hz, 3 H) 1.62 - 1.74 (m, 1 H) 1.99 - 2.09 (m, 1 H) 3.19 (s, 3 H) 3.65 (dd, J=10.5, 5.0 Hz, 1 H) 3.68 (s, 3 H) 3.96 (dd, J=10.5, 9.5 Hz, 1 H) 4.59 - 4.64 (m, 1 H) 4.88 - 4.97 (m, 1 H) 5.03 (s, 1 H) 7.40 (s, 1 H) 7.72 (s, 1 H) 8.48 (br s, 1 H) 8.77 (s, 1 H); MS m/z 412 [M+1]⁺; t=1.45 min (absolute configuration not determined)

Peak 2 (2nd isomer): ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 1.19 (s, 3 H) 1.39 - 1.58 (m, 2 H) 1.55 (d, J=7.0 Hz, 3 H) 1.62 - 1.74 (m, 1 H) 1.99 - 2.09 (m, 1 H) 3.19 (s, 3 H) 3.65 (dd, J=10.5, 5.0 Hz, 1 H) 3.68 (s, 3 H) 3.96 (dd, J=10.5, 9.5 Hz, 1 H) 4.59 - 4.64 (m, 1 H) 4.88 - 4.97 (m, 1 H) 5.03 (s, 1 H) 7.40 (s, 1 H) 7.72 (s, 1 H) 8.48 (br s, 1 H) 8.77 (s, 1 H); MS m/z 412 [M+1]⁺; t=1.45 min (absolute configuration not determined)

LCMS Method Info : **LC/MS system : Waters UPLC-SQD2**

Ionisation : electrospray in positive and negative mode (ES+/-)

Acquisition : 85 to 1500 uma

UV detection : DAD from 195 380

ELS detection

Chromatographic conditions :

Column : ACQUITY CSH C18 - 1.7 μm - 2.1 x 50 mm at 60°C

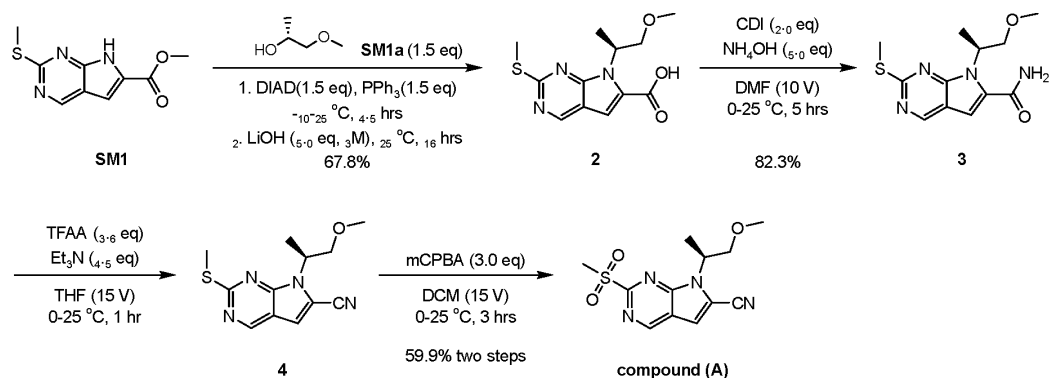
Solvents : A : H₂O (0.1 % formic acid) - B : CH₃CN (0.1 % formic acid)

Flow rate : 1 ml/min

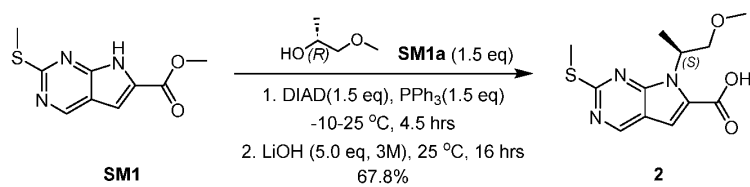
3 min gradient : 0 to 0.1 min 3% of B - 0.1 to 2.1min, from 3 to 97% of B - 2.1 to 2.45 min 97% of B - 2.45 to 2.5 min, from 97 to 3% of B - 2.5 to 3 min 3% of B

Example 2: Process of making compound of formula (I-a)

SCHEME 1



Preparation of compound 2



5

To a mixture of compound SM1 (1.40 kg, 6.27 mol, 1.00 eq), compound SM1a (847 g, 9.41 mol, 1.50 eq) and PPh₃ (2.47 kg, 9.41 mol, 1.50 eq) in THF (21.0 L) was added DIAD (1.90 kg, 9.41 mol, 1.82 L, 1.50 eq) slowly at -10 °C, and stirred at 25 °C for 4 hrs. LCMS (ET70918-8-P1A2, Product RT= 1.960 min) showed one peak with desired MS was detected. LiOH.H₂O (3 M, 10.4 L, 5.00 eq) was added to the mixture and stirred at 25 °C for 12 hrs. LCMS (Product RT = 1.117 min) showed one peak with desired MS was detected. The mixture was poured into water (30.0 L) and extracted with ethyl acetate (10.0 L * 3). The organic phase was poured into water (20.0 L) and diluted with NaOH (10.0 L, 1 M) and separated. The aqueous phase was combined and the PH value was adjusted to 3-4 with HCl (10.0 L, 5M), the solution was filtered and the filter cake was washed with water (6.00 L) and heptane (5.00 L). The solid was dried in vacuum to give the compound 2 (1.20 kg, 4.24 mol, 67.8% yield) as white solid.

15

LCMS: RT = 1.960 min, M+H = 296.2

Method Info : Instrument: Shimadzu LC-20AD MSD:LCMS-2020

Column:XBridge C18 2.1*50mm,5um

Column Temp:40°C

Mobile Phase:A:H2O+10mM NH4HCO3

5 Mobile Phase:B:Acetonitrile

Flow Rate:1.0ml/min

Time B% Flow(ml/min)

0.01 5 1.0

2.50 95 1.0

10 3.00 95 1.0

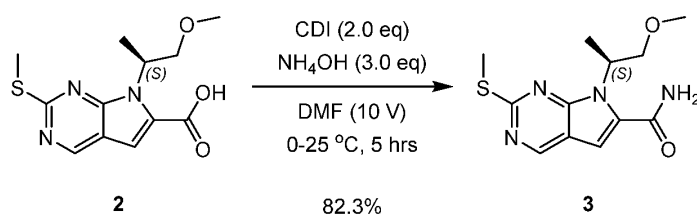
3.01 5 1.0

3.50 5 1.0

HNMR: 400 MHz DMSO-*d*6

15 δ 8.91 (s, 1H), 7.17 (s, 1H), 5.88-5.93 (m, 1H), 4.23 (t, *J* = 9.6 Hz, 1H), 3.72 (q, *J* = 5.6 Hz, 1H), 3.14 (s, 3H), 2.53 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H).

Preparation of compound 3



To a solution of compound **2** (1.20 kg, 4.27 mol, 1.00 eq) in DMF (12.0 L) was added CDI (1.38 kg, 8.53 mol, 2.00 eq) and stirred for 1 hr at 25 °C. NH₃.H₂O (2.67 kg, 21.3 mol,

2.93 L, 28% purity, 5.00 eq) was added to the mixture slowly at 0 °C and the mixture was stirred at 25 °C for 4 hrs. LCMS (Product RT = 1.451 min) showed one peak with desired MS was detected. The mixture was poured into water (15.0 L) and extracted with ethyl acetate (10.0 L * 3). The organic phase was washed with water (10.0 L) and brine (10.0 L), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 0/1, 100/1 to 0/1, Product R_f=0.40) to afford the compound **3** (1.00 kg, 3.51 mol, 82.3% yield) as yellow oil.

LCMS: RT = 1.451 min, M+H = 281.1

10 Method Info: Instrument: Shimadzu LC-20AD MSD:LCMS-2020

Column: XBridge C18 2.1*50mm,5um

Column Temp: 40°C

Mobile Phase: A: H₂O+10mM NH₄HCO₃

Mobile Phase: B: Acetonitrile

15 Flow Rate: 1.0ml/min

Time B% Flow(ml/min)

0.01 5 1.0

2.50 95 1.0

3.00 95 1.0

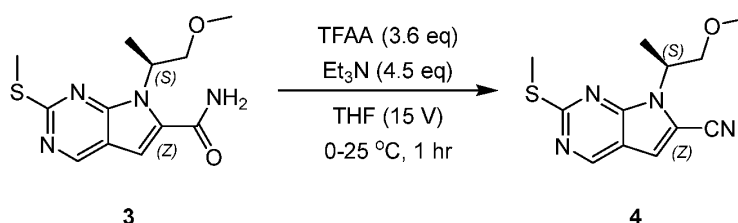
20 3.01 5 1.0

3.50 5 1.0

¹H NMR: 400 MHz DMSO-*d*₆

δ 8.92 (s, 1H), 7.07 (s, 1H), 5.66-5.71 (m, 1H), 4.21 (t, $J = 9.6$ Hz, 1H), 3.68 (q, $J = 5.6$ Hz, 1H), 3.14 (s, 3H), 2.55 (s, 3H), 1.57 (d, $J = 6.8$ Hz, 3H).

Preparation of compound 4



- 5 To a solution of compound **3** (1.00 kg, 3.57 mol, 1.00 eq) in THF (15.0 L) was added TEA (1.62 kg, 16.0 mol, 2.23 L, 4.50 eq) and TFAA (2.70 kg, 12.8 mol, 1.78 L, 3.60 eq) dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hr. LCMS (Product RT = 1.863 min) showed one peak with desired MS was detected. The mixture was cooled to 0 °C and the mixture was quenched with NaHCO₃ (aq, 10.0 L) and the PH value was adjusted
- 10 to 7-8. The solution was extracted with ethyl acetate (10.0 L * 3). The combined organic phase was washed with brine (8.00 L), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the crude product (1.10 kg, crude) as a yellow solid.

LCMS: RT = 1.863 min, M+H = 263.1

Method Info : Instrument: Shimadzu LC-20AD MSD:LCMS-2020

- 15 Column: XBridge C18 2.1*50mm,5um

Column Temp: 40°C

Mobile Phase: A: H₂O+10mM NH₄HCO₃

Mobile Phase: B: Acetonitrile

Flow Rate:1.0ml/min

- 20 Time B% Flow(ml/min)

0.01 5 1.0

2.50 95 1.0

3.00 95 1.0

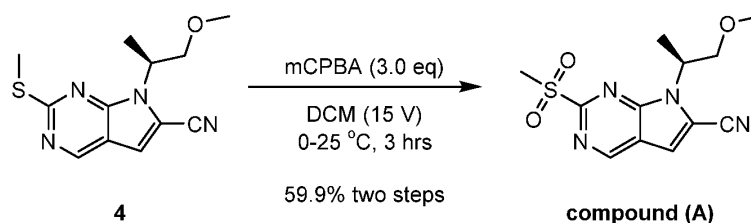
3.01 5 1.0

3.50 5 1.0

5 **HNMR:** 400 MHz DMSO-*d*₆

δ 9.01 (s, 1H), 7.59 (s, 1H), 4.98-5.04 (m, 1H), 4.01-4.06 (m, 1H), 3.66-3.70 (m, 1H), 3.19 (s, 3H), 2.56 (s, 3H), 1.63 (d, *J* = 7.2 Hz, 3H).

Preparation of compound (A)



10 Five reactions were carried out in parallel.

To a solution of compound **4** (220 g, 561 mmol, 1.00 eq) in DCM (3.30 L) was added MCPBA (342 g, 1.69 mol, 85% purity, 3.00 eq) at 0 °C. The mixture was stirred at 25 °C for 3 hrs. LCMS (Product Rt = 1.407 min) showed one peak with desired MS was detected. The mixture was cooled to 0 °C and the mixture was quenched with Na₂S₂O₃ (aq, 1.50 L) and the five reactions were worked up together. The solution was filtered, the filter cake was washed with DCM (3.00 L *2). The filtrate was separated and the water phase was extracted with DCM (4.00 L). The combined organic phase was washed with Na₂S₂O₃ (aq, 5.00 L *2), NaHCO₃ (aq, 5.00 L), brine (5.00 L), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with MTBE : DCM (15 : 1, 3.50 L) at 25 °C for 2 hrs. The suspension was filtered and the filter cake was washed with MTBE (800 mL * 2) and the filter cake was dried in vacuum to give **compound (A)** (704 g, 2.37 mol, 75.2% yield, 99.07% purity) as a white solid.

LCMS: RT = 1.407 min, M+H = 295.2

Method Info: Instrument: Shimadzu LC-20AD MSD:LCMS-2020

Column: XBridge C18 2.1*50mm,5um

Column Temp: 40°C

5 Mobile Phase: A: H₂O+10mM NH₄HCO₃

Mobile Phase: B: Acetonitrile

Flow Rate:1.0ml/min

Time B% Flow(ml/min)

0.01 5 1.0

10 2.50 95 1.0

3.00 95 1.0

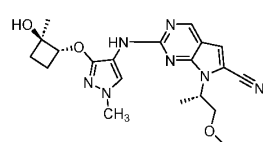
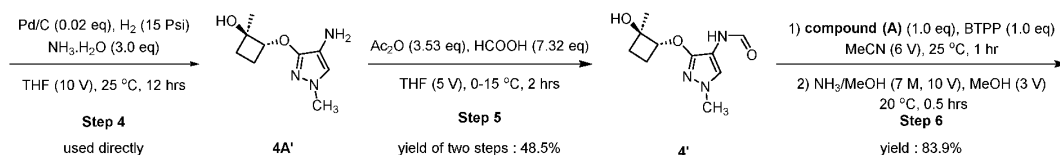
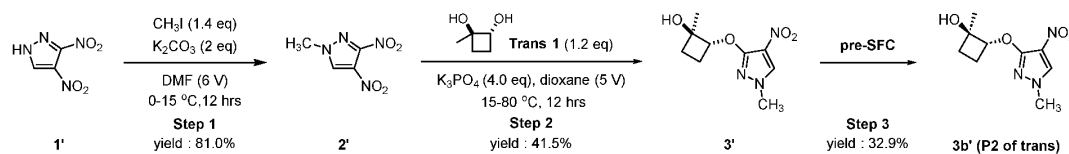
3.01 5 1.0

3.50 5 1.0

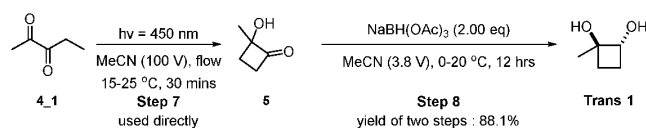
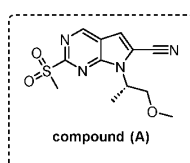
HNMR: 400 MHz DMSO-*d*₆

15 δ 9.47 (s, 1H), 7.90 (s, 1H), 5.14-5.19 (m, 1H), 4.02 (t, *J* = 10.0 Hz, 1H), 3.73 (q, *J* = 4.4 Hz, 1H), 3.48 (s, 3H), 3.19 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H).

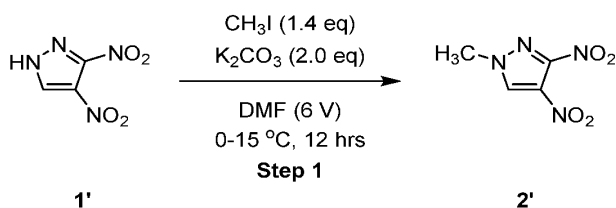
SCHEME 2



I-a
36.5 g, 99.1% HPLC, 99.8% ee



Preparation of compound 2'

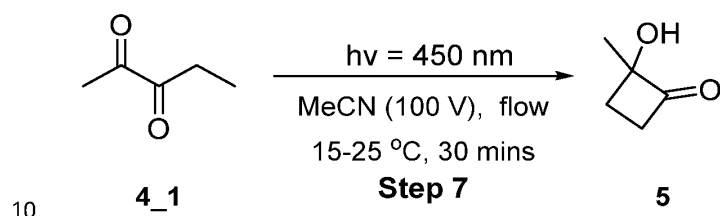


- 5 Seven reactions were carried out in parallel (total 2.21 mol).

To a solution of 3,4-dinitro-1H-pyrazole (compound 1', 50.0 g, 316 mmol, 1.00 eq) in DMF (300 mL) was added K₂CO₃ (87.4 g, 633 mmol, 2.00 eq) at 15 °C. CH₃I (62.9 g, 443 mmol, 27.6 mL, 1.40 eq) was added dropwise to the reaction mixture at 0 °C. The mixture

was stirred at 15 °C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 1/1, compound 1': R_f = 0.50, compound 2: R_f = 0.60) indicated compound 1 was consumed completely and one new spot formed. The four reactions were combined for work up. The crude product were combined for work up. The reaction mixture was poured into ice-water (2.50 L) at 5 25 °C. The suspension was stirred for 30 mins and filtered. The filter cake was washed with water (200 mL x 3), the filter cake was dissolved with 2-MeTHF (1.00 L) and the solution was used into the next step. Compound 2' (2.38 kg, 81.0% yield, 13.0% purity) (a solution in 2-MeTHF) was obtained as a yellow oil.

Preparation of compound 5



Six reactions were carried out in parallel (total 5.93 mol).

15

20

Instrument:	peristaltic pump		
Pipe material:	PFA		
Pipe size:	Ø6 (OD = 6 mm, ID = 4 mm)		
Volume:	750 mL		
Pump A:	A mixture of compound 4_1 (100 g, 0.998 mol, 1.00 eq) in MeCN (100 L) was degassed and purged with N ₂ for 3 times and then the mixture was stirred and irradiated with 450 nm at 15-25 °C for 30 mins under N ₂ atmosphere.		
Condition:		RT	Temp
	Step 1	30 min	15-25 °C
Cooling/Heating Method:	Circulating bath temperature: 20 °C		

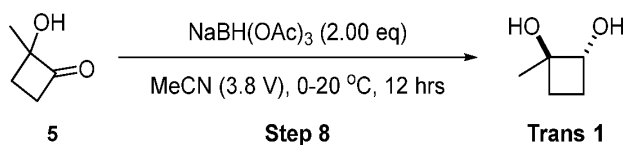
(see Figure 4)

Six reactions were combined for work up. The reaction mixture was concentrated in vacuum. Compound **5** (1.13 kg, crude) (MeCN solution) was obtained as a yellow oil.

HNMR: 400 MHz, DMSO-*d*₆

5 δ 2.80-2.95 (m, 3H), 2.01-2.15 (m, 2H), 1.46 (s, 3H).

Preparation of compound *Trans 1*



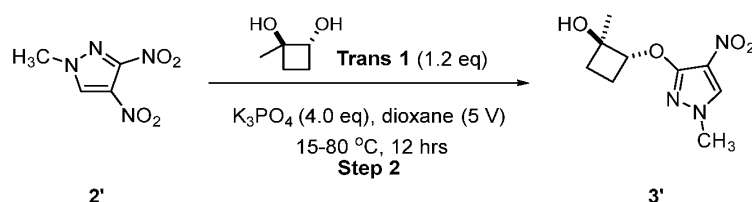
To a solution of compound **5** (158 g, 791 mmol, 1.00 eq) in MeCN (600 mL) was added NaBH(OAc)₃ (335 g, 1.58 mol, 2.00 eq) at 0 °C. The mixture was stirred at 20 °C for 12

hrs. TLC (Petroleum ether/Ethyl acetate = 0/1, compound **5**: R_f = 0.60, compound **Trans 1**: R_f = 0.20) indicated compound **5** was consumed completely and one main spot formed. The reaction mixture was quenched by addition MeOH (70.0 mL, 2.00 eq) at 15 °C and stirred at 15 °C for 30 mins. The reaction mixture was concentrated in vacuum, then
 5 purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1) to give compound **Trans 1** (345 g, crude) as a yellow oil.

¹H NMR: 400 MHz, DMSO-*d*₆

δ 4.89 (d, J = 4.8 Hz, 1H), 4.77 (s, 1H), 3.80 (t, J = 7.2 Hz, 1H), 1.75-1.79 (m, 1H), 1.51-1.54 (m, 1H), 1.35-1.38 (m, 1H), 1.15-1.20 (m, 1H), 1.07 (s, 3H).

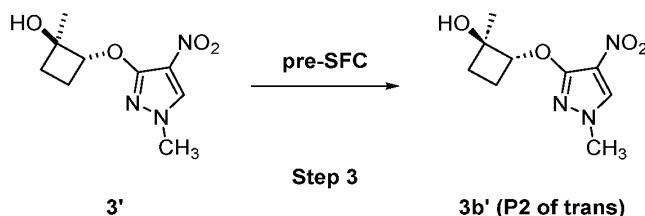
10 **Preparation of compound 3'**



To a solution of compound **2'** (310 g, 1.80 mol, 1.00 eq) in dioxane (1.55 L) was added K₃PO₄ (1.53 kg, 7.21 mol, 4.00 eq) and compound **Trans 1** (248 g, 2.16 mol, 1.20 eq) at 15 °C. The mixture was stirred at 80 °C for 12 hrs. HPLC (compound **3'**: RT = 8.457 min,
 15 compound **2'**: RT = 8.113 min) showed ~12.1 % compound **2'** remained and one main peak with desired m/z. The reaction mixture was poured with water (2.00 L) and stirred for 10 mins. The aqueous phase was extracted with ethyl acetate (2.50 L x 2). The combined organic phase was washed with brine (1.00 L), dried over Na₂SO₄ and concentrated in vacuum. The crude product was triturated with PE/MTBE = 1/1 (300 mL)
 20 at 25 °C for 12 hrs and compound **3'** (170 g, 748 mmol, 41.5% yield) was obtained as a yellow solid.

¹H NMR: 400 MHz, DMSO-*d*₆

δ 8.65 (s, 1H), 4.79 (t, J = 8.0 Hz, 1H), 3.71 (s, 3H), 2.14-2.16 (m, 1H), 1.76-1.78 (m, 1H), 1.29-1.63 (m, 2H), 1.08 (s, 3H).

Preparation of compound 3b' (P2 of trans)

The crude compound **3'** (170 g, 748 mmol) was purified by pre-SFC (column: DAICEL
 5 CHIRALPAK IG (250 mm * 50 mm, 10 μ m); mobile phase: [CO₂-MeOH (0.1% NH₃H₂O)];
 B%: 20%, isocratic elution mode). Compound **3b' (P2 of trans)** (56.0 g, 246 mmol, 32.9%
 yield) was obtained as a yellow oil.

LCMS: compound **3b'**: RT = 1.100 min, M+H = 228

Method Information

10 Instrument: Shimadzu LC-20ADXR MSD:LCMS-2020

Mobile Phase:A:0.04% TFA in H₂O

Mobile Phase:B:0.02% TFA in ACN

Oven Temperature : 40 °C

Total Flow : 1.0000 mL/min

15 Gradient Program:

Pump A + B

Time(min) / Flow(mL/min) / B.Conc(%) / B.Curve

1 0.00/ 1.0000/ 5.0/ 0

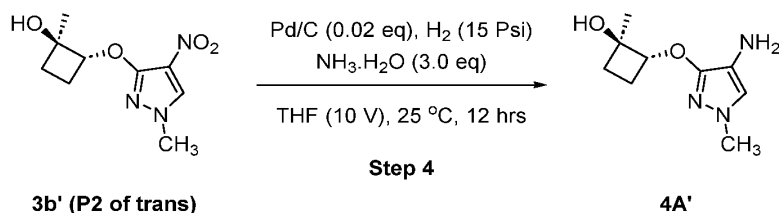
2 2.50/ 1.0000/ 95.0/ 0

20 3 3.00/ 1.0000/ 95.0/ 0

HNMR: 400 MHz, DMSO-*d*₆

δ 8.65 (s, 1H), 5.25 (s, 1H), 4.79 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 2.13-2.14 (m, 1H), 1.76-1.78 (m, 1H), 1.48-1.62 (m, 2H), 1.28 (s, 3H).

Preparation of compound 4A'



5

To a solution of Pd/C (4.60 g, 4.32 mmol, 10.0% purity, 0.02 eq) in THF (400 mL) was added compound **3b' (P2 of trans)** (46.0 g, 200 mmol, 1.00 eq) and NH₃.H₂O (70.0 g, 600 mmol, 77.0 mL, 30.0% purity, 3.00 eq). The mixture was stirred at 25 °C for 12 hrs under H₂ (15 psi). LC-MS (compound **4A'**: RT = 0.366 min) showed compound **3b' (P2 of trans)** was consumed completely and one main peak with desired *m/z*. The reaction mixture was filtered through celite and washed with THF (300 mL x 3). The filter was concentrated in vacuum to give compound **4A'** (40.0 g, crude) as a black oil.

10

LCMS: compound **4A'**: RT = 0.366 min

15 **Method Information**

Instrument: Shimadzu LC-20ADXR MSD:LCMS-2020

Mobile Phase:A:0.04% TFA in H₂O

Mobile Phase:B:0.02% TFA in ACN

Oven Temperature : 40 °C

20 Total Flow : 1.0000 mL/min

Gradient Program:

Pump A + B

Time(min) / Flow(mL/min) / B.Conc(%) / B.Curve

1 0.00/ 1.0000/ 5.0/ 0

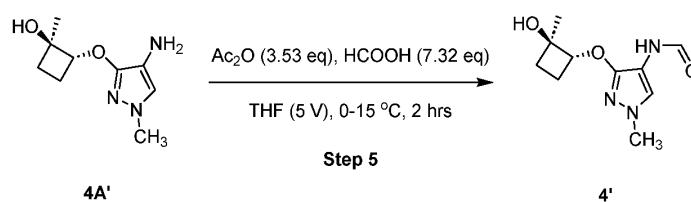
2 2.50/ 1.0000/ 95.0/ 0

5 3 3.00/ 1.0000/ 95.0/ 0

¹H NMR: 400 MHz, DMSO-*d*₆

δ 6.90 (s, 1H), 5.13 (brs, 1H), 4.50 (t, *J* = 8.0 Hz, 1H), 3.51 (s, 3H), 2.04-2.06 (m, 1H), 1.68-1.69 (m, 1H), 1.41-1.55 (m, 2H), 1.23 (s, 3H).

Preparation of compound 4'



10

To a solution of Ac₂O (73.1 g, 716 mmol, 67.2 mL, 3.53 eq) and HCOOH (71.3 g, 1.48 mol, 7.32 eq) was stirred at 15 °C for 1 hr. Compound **4A'** (40.0 g, 203 mmol, 1.00 eq) in THF (200 mL) was added into the mixture at 0 °C, and stirred at 15 °C for 1 hr. LCMS (compound **4'**: RT = 1.301 min) showed compound **4A'** was consumed completely and one main peak with desired *m/z*. The reaction mixture was poured with water (200 mL) and stirred for 10 mins. The pH value of aqueous phase was adjusted to 7~8 with sat. aq. NaHCO₃. The aqueous phase was extracted with ethyl acetate (500 mL x 2). The combined organic phase was washed with brine (200 mL), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, n-heptane/Ethyl acetate = 100/1 to 0/1) to give compound **4'** (20.0 g, 86.1 mmol, 48.5% yield, 97.0% purity) and compound **4** (6.00 g, 24.8 mmol, 13.9% yield, 93.0% purity) as a brown solid.

20

LCMS: compound **4'**: RT = 1.301 min

Method Information

Instrument: Shimadzu LC-20AD MSD: LCMS-2020

Mobile Phase A:0.04%TFA in H₂O

Mobile Phase B:0.02%TFA in ACN

5 Total Flow : 1.0000 mL/min

Oven Temperature: 40 °C

Time Module Command Value Comment

0.01 Pumps B.Conc 0

2.50 Pumps B.Conc 30

10 3.00 Pumps B.Conc 30

3.01 Pumps B.Conc 0

3.01 Pumps T.Flow 1

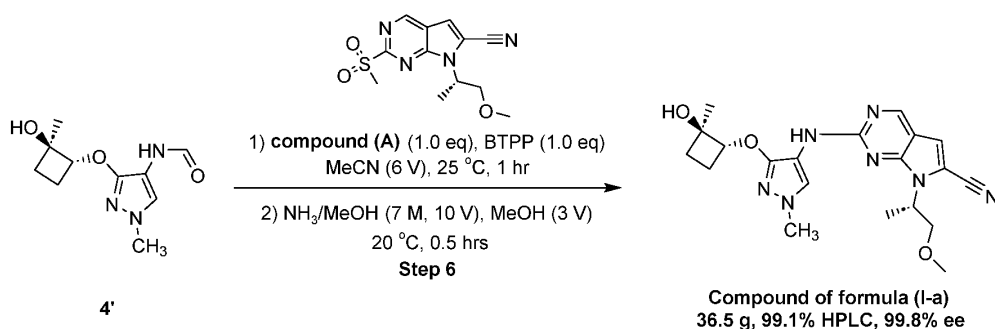
3.02 Pumps T.Flow 1.2

3.50 Controller Stop

15 **¹H NMR:** 400 MHz, CDCl₃

δ 9.62 (s, 1H), 8.12-8.15 (m, 1H), 7.89 (s, 1H), 5.16 (s, 1H), 4.69 (t, *J* = 8.0 Hz, 1H),
3.69 (s, 3H), 2.12-2.16 (m, 1H), 1.76-1.78 (m, 1H), 1.48-1.63 (m, 2H), 1.32 (s, 3H).

Preparation of compound of formula (I-a)



To a solution of compound **4'** (20.0 g, 88.8 mmol, 1.00 eq) and compound **(A)** (26.1 g, 88.8 mmol, 1.00 eq) in MeCN (120 mL) was added BTTPP (27.7 g, 88.8 mmol, 1.00 eq) at 25 °C. The mixture was stirred at 25 °C for 1 hr. LCMS showed compound **4'** was consumed completely and one main peak with desired m/z. The reaction mixture was concentrated in vacuum, then to a solution of **the mixture** (39.0 g, 88.8 mmol, 1.00 eq) in MeOH (120 mL) was added NH_3/MeOH (7.00 M, 390 mL, 30.8 eq) at 20 °C. The mixture was stirred at 20 °C for 0.5 hrs. The reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , n-heptane/Ethyl acetate = 100/1 to 0/1). The product was lyophilized with MeOH to remove ethyl acetate. Compound of formula (I-a) (36.5 g, 88.7 mmol, 83.9% yield, 99.2% purity, 99.8% ee) was obtained as a yellow solid.

LCMS: RT = 1.387 min

Instrument: Shimadzu LC-20AD MSD: LCMS-2020

Mobile Phase A: 0.04% TFA in H_2O

Mobile Phase B: 0.02% TFA in ACN

Total Flow : 1.0000 mL/min

Oven Temperature: 40 °C

Time Module Command Value Comment

0.01 Pumps B.Conc 5

2.50 Pumps B.Conc 95

3.00 Pumps B.Conc 95

3.01 Pumps B.Conc 5

3.01 Pumps T.Flow 1

5 3.02 Pumps T.Flow 1.2

3.50 Controller Stop

¹H NMR: 400 MHz, CDCl₃

10 δ 8.78 (s, 1H), 8.55 (s, 1H), 7.73 (s, 1H), 7.41 (s, 1H), 5.07 (s, 1H), 4.92-4.96 (m, 1H), 4.63 (t, $J = 8.0$ Hz, 1H), 3.97 (t, $J = 10.0$ Hz, 1H), 3.64-3.69 (m, 4H), 3.20 (s, 3H), 2.05-2.07 (m, 1H), 1.67-1.69 (m, 1H), 1.54 (d, $J = 4.4$ Hz, 3H), 1.42-1.50 (m, 2H), 1.19 (s, 3H).

Preparation of seed

15 A reaction on 10 g scale was carried out to prepare seed using compound of formula (I-a) in 6V EtOAc/n-heptane system (2:1, v/v). After adding anti-solvent 28 V EtOAc/n-heptane (1:6, v/v) for 12.2 h and stirring for 9 h at 20-30 °C, the mixture was filtered, and the cake was washed by n-heptane. As a result, 8.259 g crystallized compound of formula (I-a) with 99.6% purity was obtained. The yield was 83.6%.

Preparation of crystallized compound of formula (I-a)

20 A reaction on 385 g scale was carried out to prepare seed using compound of formula (I-a) in 6V EtOAc/n-heptane (2:1, v/v) system. After adding anti-solvent 28 V EtOAc/n-heptane (1:6, v/v) for 14.7 h and stirring for 10 h at 20-30 °C, the mixture was filtered, and the cake was washed with n-heptane. 351.33 g crystallized compound of formula (I-a) with 99.6a% purity and 99.7% assay was obtained. The yield was 92.3%. However, it was found that the particle size was large. So sieving was performed using
25 341.57 g crystallized compound of formula (I-a). After seiving, 334.64 g crystallized

compound of formula (I-a) with 99.6% purity was obtained. The yield was 97.5%. The yield for 2 steps was 90.0%.

Differential scanning calorimetry (DSC):

Differential scanning calorimetry was performed on crystalline Form A as described herein. The results are shown in Fig. 1. Form A exhibits a clean melting/decomposition peak at about 118 °C (± 2 °C) with an enthalpy of -72 J/g.

X-ray powder diffraction:

X-ray powder diffraction was performed on crystalline Form A as described herein. The results are shown in Fig. 2 and are summarised in Table 2:

Table 2

TGA (thermogravimetric analysis)

TGA of crystalline Form A was performed as described herein, at 10 °C/min. The results are shown in Fig. 3. The results show the anhydrate nature of the crystalline form, with nearly no loss of weight until the decomposition temperature.

PHARMACOLOGY

The potency of the compounds in cells were determined using the MSD assay described in the literature (Wang, Y. etc, *Sci Rep* 11, 12900 (2021)) with minor modifications to MSD assay.

Capture antibodies were biotinylated using EZ-Link™ NHS-LC-LC-Biotin (Thermo Fisher, #21343), and detection antibodies were conjugated using Sulfo-TAG NHS-Ester (MSD, R31AA-1). 96-well (or 384-well) MSD GOLD Small Spot Streptavidin plates (MSD L45SSA-1) were coated with 25 µl (or 15 µl for 384 well plates) of capture antibody diluted in Diluent 100 (MSD, R50AA-2) for 1.5-2hr at room temperature with 400 rpm shaking (1000 rpm for 384-well). After three washes with TBST, 25 µl samples were added each well (10 µl for 384-well) and incubated at 4 °C overnight with agitation at 400 rpm. After three additional washes with TBST, 25 µl of detection antibodies (15 µl for 384-well) were added to each well diluted in TBST containing 2.5% MSD blocker A

(MSD R93AA-1) together with rabbit (Rockland Antibodies D610-1000). After 2hr incubation at room temperature at 400 rpm and three washes with TBST, 150 µl MSD read buffer (MSD R92TC, 1:1 diluted with water) was added (35 µl for 384-well), and plates were read on the MSD QuickPlex SQ120.

5

Biologic data

The table below shows the IC50 values obtained as described above for the exemplified compounds.

Compound	Name	LRRK2 /WT IC50 (nM)
I-a	2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile	17 nM
I-b	2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile	211 nM

10

Determine absolute configuration

The absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. The currently most used standard procedure for the determination of the absolute structure with X-ray diffraction techniques is based on the determination of the Flack parameter (x) with its associated standard uncertainty as part of the least-squares refinement procedure (see H.D. Flack, G. Bernardinelli, J. Appl. Cryst. (2000), 33, 1143: "Reporting and evaluating absolute-structure and absolute-configuration determinations"). Expected values are 0 (within 3 esd's) for correct and +1 for inverted absolute structure. An alternative post-

15

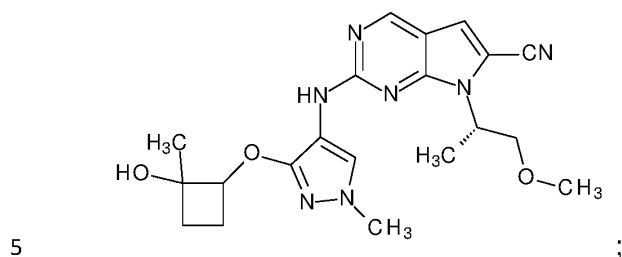
20

refinement procedure based on a Bayesian statistics approach has been applied (a completely different way from Flack approach); see R. W. W. Hooft, L. H. Straver and A. L. Spek, J. Appl. Cryst. (2008), 41, 96: "Determination of absolute structure using Bayesian statistics on Bijvoet differences". Analysis of absolute structure of Compound
5 of formula (I-a) using likelihood method has been performed using Olex2 software package (O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard and H. Puschmann, J. Appl. Cryst. (2009), 42, 339: "OLEX2: a complete structure solution, refinement and analysis program"). The absolute configuration of compound of formula (I-a) has been assigned as 2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-
10 yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile.

Claims

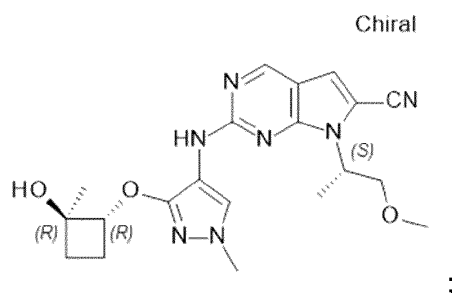
What is claimed is

1. A compound of Formula (I)



or pharmaceutically acceptable salt thereof.

2. A compound of Formula (I-a) according to claim 1



or pharmaceutically acceptable salt thereof.

- 10 3. The compound according to claim 2, wherein the compound is substantially enantiomerically pure.

4. A compound according to claim 1 selected from a group consisting of :

2-[[3-[(1R,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

- 15 2-[[3-[(1S,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

2-[[3-[trans-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-
[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

2-[[3-[(1R,2S)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-
[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

5 2-[[3-[(1S,2R)-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-
[(1S)-2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

2-[[3-[cis-2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-
2-methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile; and

10 2-[[3-[2-hydroxy-2-methyl-cyclobutoxy]-1-methyl-pyrazol-4-yl]amino]-7-[(1S)-2-
methoxy-1-methyl-ethyl]pyrrolo[2,3-d]pyrimidine-6-carbonitrile;

or pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
- 15 6. A medicament, characterized in that it comprises a compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.
7. A compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease.
- 20 8. A compound of formula (I) according to claim 7, or a pharmaceutically acceptable salt thereof, wherein the neurodegenerative disease is selected from the group consisting of Parkinson's disease, multiple sclerosis, HIV-induced dementia, amyotrophic lateral sclerosis, Lewy body dementia, Pick disease, progressive supranuclear palsy, and frontotemporal dementia.
- 25 9. A compound of formula (I) according to claim 7, or a pharmaceutically acceptable salt thereof, wherein the neurodegenerative disease is Parkinson's disease.
10. A solid form of a compound of Formula (I-a) as defined in claim 2, characterized as crystalline Form A.

11. The solid form according to claim 10, which is at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% crystalline.
12. The solid form according to claim 10 or claim 11, having an X-ray powder diffraction (XRPD) pattern derived using Cu (K α) radiation comprising three, four, five, six, seven or more peaks, in term of 2-theta degrees, chosen from peaks at about 6.8 $\pm$ 0.2, 9.8 $\pm$ 0.2, 13.6 $\pm$ 0.2, 13.9 $\pm$ 0.2, 14.7 $\pm$ 0.2, 16.0 $\pm$ 0.2, 17.4 $\pm$ 0.2, 17.8 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.9 $\pm$ 0.2.
13. The solid form according to any one of claims 10 to 12, having an XRPD pattern derived using Cu (K α) radiation, in term of 2-theta degrees, having peaks at about 6.8 $\pm$ 0.2, 17.8 $\pm$ 0.2, and 19.9 $\pm$ 0.2.
14. The solid form according to any one of claims 10 to 13, having an X-ray powder diffraction pattern that is substantially in accordance with that shown in Figure 2.
15. The solid form according to any one of claims 10 to 14, characterized by a differential scanning calorimetry (DSC) curve with an onset at about 118°C $\pm$ 2 °C.
16. The solid form according to any one of claims 10 to 15, characterized by a DSC profile substantially in accordance with that shown in Figure 1.
17. The solid form according to any one of claims 10 to 16, wherein Form A is characterized by at least two of:
- a) an X-ray powder diffraction (XRPD) pattern substantially in accordance with that shown in Figure 2;
 - b) an X-ray powder diffraction (XRPD) pattern derived using Cu (K α) radiation comprising three, four, five, six, seven or more peaks, in term of 2-theta degrees, at about 6.8 $\pm$ 0.2, 9.8 $\pm$ 0.2, 13.6 $\pm$ 0.2, 13.9 $\pm$ 0.2, 14.7 $\pm$ 0.2, 16.0 $\pm$ 0.2, 17.4 $\pm$ 0.2, 17.8 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.9 $\pm$ 0.2;
 - c) a DSC profile substantially the same as shown in Figure 1;
 - d) a Differential Scanning Calorimetry (DSC) thermogram having an onset at about 118 °C $\pm$ 2 °C;

e) a profile substantially the same as shown in Figure 3;

18. A pharmaceutical composition comprising the solid form as defined in any one of claims 10-17 and a pharmaceutically acceptable carrier.

19. A solid form as defined in any one of claims 10-17 for use in treating a
5 neurodegenerative disease in a patient in need thereof.

20. Use of a solid form as defined in any one of claims 10-17 in the manufacture of a medicament for treating a neurodegenerative disease.