

Macrocyclic LRRK2 kinase inhibitors

Field of the invention

5 The present invention relates to novel macrocyclic compounds and compositions containing said compounds acting as kinase inhibitors, in particular as inhibitors of LRRK2 kinase (Leucine-Rich Repeat Kinase 2), for use in the diagnosis, prevention and/or treatment of LRRK2-kinase associated diseases. Moreover, the present invention provides methods of using them, for instance as a medicine or diagnostic agent, in particular for the prevention, treatment
10 and/or diagnosis of diseases characterized by LRRK2 kinase activity such as neurological disorders including Parkinson's disease and Alzheimer's disease. Finally, the present invention also relates to new macrocyclic compounds.

Background of the invention

15 Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopaminergic neurones in the midbrain. In the early stages of the disease the most obvious symptoms are movement-related such as shaking, slowness of movement and difficulty with walking. Later on also cognitive and behavioural problems arise, with dementia commonly
20 occurring in the advanced stages of the disease. Although Parkinson's disease is generally considered to be sporadic, within the last decade, a few mutations in the LRRK2 (leucine rich repeat kinase 2) gene have been linked to Parkinson's disease (WO2006068492 and WO2006045392). LRRK2, also known as dardarin, is a member of the leucine-rich repeat kinase family having mixed-lineage kinase activity, in particular in the brain, but also in other
25 tissues throughout the body. Researchers have identified over 20 *LRRK2* mutations in families with late-onset Parkinson Disease. For example the G2019S mutation co-segregates with autosomal dominant Parkinsonism and accounts for about 6% of familial Parkinson's disease cases and 3% sporadic Parkinson's disease cases in Europe. The G2019S mutation occurs in the highly conserved kinase domain and it has therefore been postulated that the G2019S
30 mutation may have an effect on kinase activity (WO2006068492). Furthermore, amino acid substitutions at a second residue R1441 are also associated with Parkinson's disease and have also been shown to elevate LRRK2 kinase activity. Over-expression of the mutant LRRK2 protein R1441G in transgenic mouse models (Li, Y et al. 2009, Nature Neuroscience 12:826-828) is associated with symptoms of Parkinson's disease as well as reduced dopamine release,
35 suggesting that inhibitors of LRRK2 could also positively regulate dopamine release and have potential utility in treatment of conditions characterized by reduced dopamine levels, such as withdrawal symptoms/relapse associated with drug addiction; Tauopathy diseases such as Alzheimer's disease, argyrophilic grain disease, Pick's disease, corticobasal degeneration;

inherited frontotemporal dementia; and Parkinson's disease. Two further mutations in LRRK2 have been clinically associated with the transition from mild cognitive impairment to Alzheimer's disease (WO200714979). These data further provide evidence that inhibitors of LRRK2 kinase activity could be useful for the treatment of dementias and related neurodegenerative disorders.

5 Thus, pharmacological inhibition of LRRK2 kinase is an attractive strategy towards mechanism-based therapies in neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease. It was therefore an object of the present invention to provide compounds and compositions comprising said compounds, acting as inhibitors of LRRK2 kinases.

10 Untill today several (non-macrocylic) pyrazolopyrimidines have been suggested for the treatment of neuronal disorders, in particular Alzheimer's disease and/or Parkinson's disease (see for example EP1908764, US6194410, EP1354884, EP0729758 and US6194410). However, none of the compounds disclosed in said references have been shown to have LRRK2 inhibitory activity.

15 Furthermore, the currently developed LRRK2 kinase inhibitors, in particular those for the treatment of neuronal disorders, do not comprise macrocyclic pyrazolopyrimidine moieties (see for example WO2009127652, WO2011038572).

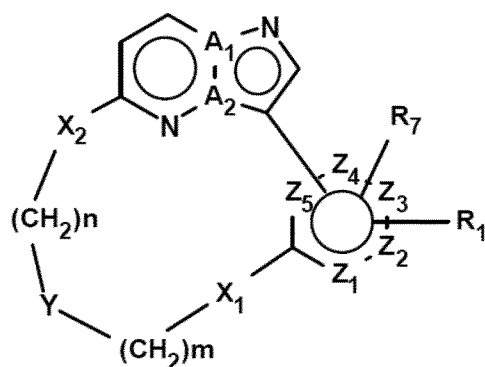
20 Nonetheless, there is a continuing need to design and develop LRRK2 kinase inhibitors for the treatment of neuronal disorders. We have now found that the macrocyclic pyrazolopyrimidines, imidazopyridazines and pharmaceutically acceptable compositions according to this invention are useful for the treatment of several neuronal disorders associated with LRRK2 kinase activity.

SUMMARY OF THE INVENTION

25 We have surprisingly found that the macrocyclic compounds described herein act as LRRK2 kinase inhibitors, and are thus very useful in the diagnosis, prevention and/or treatment of LRRK2-kinase associated diseases.

30 In a first objective the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,

- 3 -



Wherein

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when A₂ is C, then A₁ is N;

5 R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

10 R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

15 R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;

R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;

20 R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

25 R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

30 R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

In a first embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is C and A₂ is N

R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein

each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{15}R_{16}$, $-Het_2$, and $-Ar_3$; R_4 is independently selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{17}R_{18}$, and $-Het_4$;

5 R_5 is selected from $-H$, $-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$; wherein each of said $C_{1-6}alkyl$ or $-C_{3-6}cycloalkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-OC_{1-6}alkyl$, $-SC_{1-6}alkyl$, $-Het_5$, and $-NR_{31}R_{32}$;

R_6 is selected from $-H$, $-OH$, $-halo$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{33}R_{34}$, and $-Het_8$;

10 R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{37} and R_{38} are each independently selected from $-H$, $=O$, $-C_{1-6}alkyl$, and $-Het_1$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{35}R_{36}$, $-Het_7$, and $-Ar_4$;

15 R_{35} and R_{36} are each independently selected from $-H$, $=O$, and $-C_{1-6}alkyl$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

20 X_1 is selected from $-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-(C=O)-$, $-NR_3-(C=O)-$, $-C_{1-6}alkyl-NR_3-$, $-NR_3-$, $-(C=O)-$, $-NR_3-(C=O)-NR_{37}-$, $-NR_3-C_{1-6}alkyl-$, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}alkyl-$, $-(C=O)-NR_3-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_3-C_{1-6}alkyl-$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-phenyl$, and $-NR_{23}R_{24}$;

25 X_2 is selected from $-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-(C=O)-$, $-NR_2-(C=O)-$, $-C_{1-6}alkyl-NR_2-$, $-NR_2-$, $-(C=O)-$, $-NR_2-(C=O)-NR_{38}-$, $-NR_2-C_{1-6}alkyl-$, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}alkyl-$, $-(C=O)-NR_2-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_2-C_{1-6}alkyl-$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-phenyl$ and $-NR_{25}R_{26}$;

Y is selected from a direct bond, $-CHR_6-$, $-O-$, $-S-$, and $-NR_5-$;

30 Ar_2 , Ar_3 , and Ar_4 are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar_2 , Ar_3 , and Ar_4 is optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{19}R_{20}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

35 Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 is optionally substituted with from 1 to 3 substituents selected from $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, and $-NR_{21}R_{22}$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 $-halo$;

Z_1 , Z_2 , Z_3 , Z_4 and Z_5 are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

In yet a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is N and A₂ is C

R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;

R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;

R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-,

- 7 -

$-(C=O)-NR_2-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_2-C_{1-6}alkyl-$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-phenyl$ and $-NR_{25}R_{26}$;

Y is selected from a direct bond, $-CHR_6-$, $-O-$, $-S-$, and $-NR_5-$;

5 Ar_2 , Ar_3 , and Ar_4 are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar_2 , Ar_3 , and Ar_4 is optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{19}R_{20}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

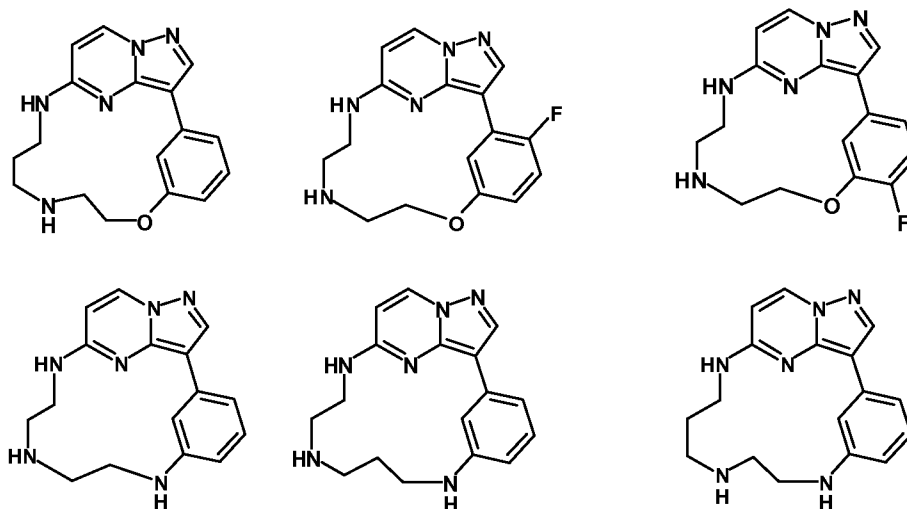
10 Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 is optionally substituted with from 1 to 3 substituents selected from $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, and $-NR_{21}R_{22}$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 -halo;

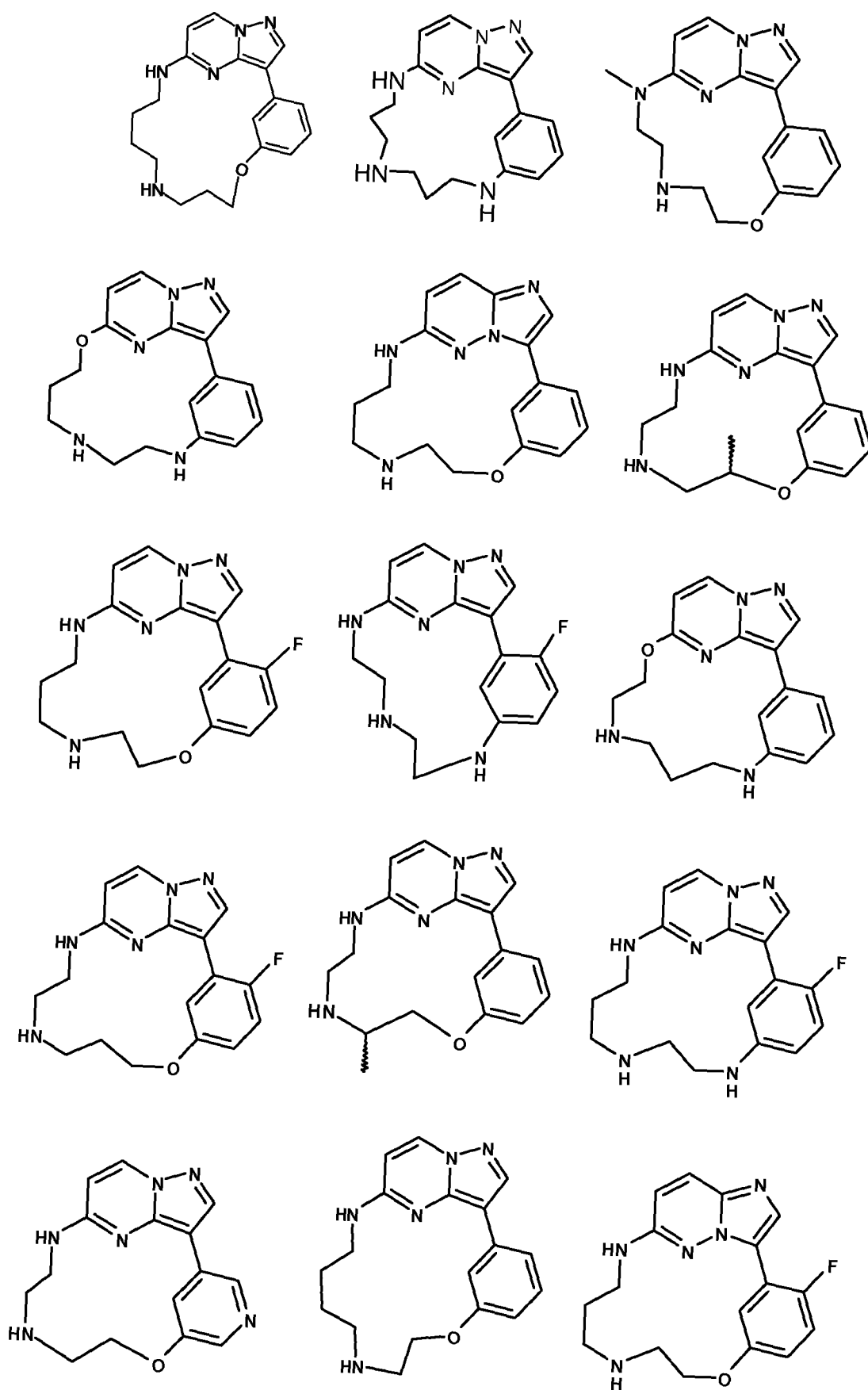
15 Z_1 , Z_2 , Z_3 , Z_4 and Z_5 are each independently selected from C and N;

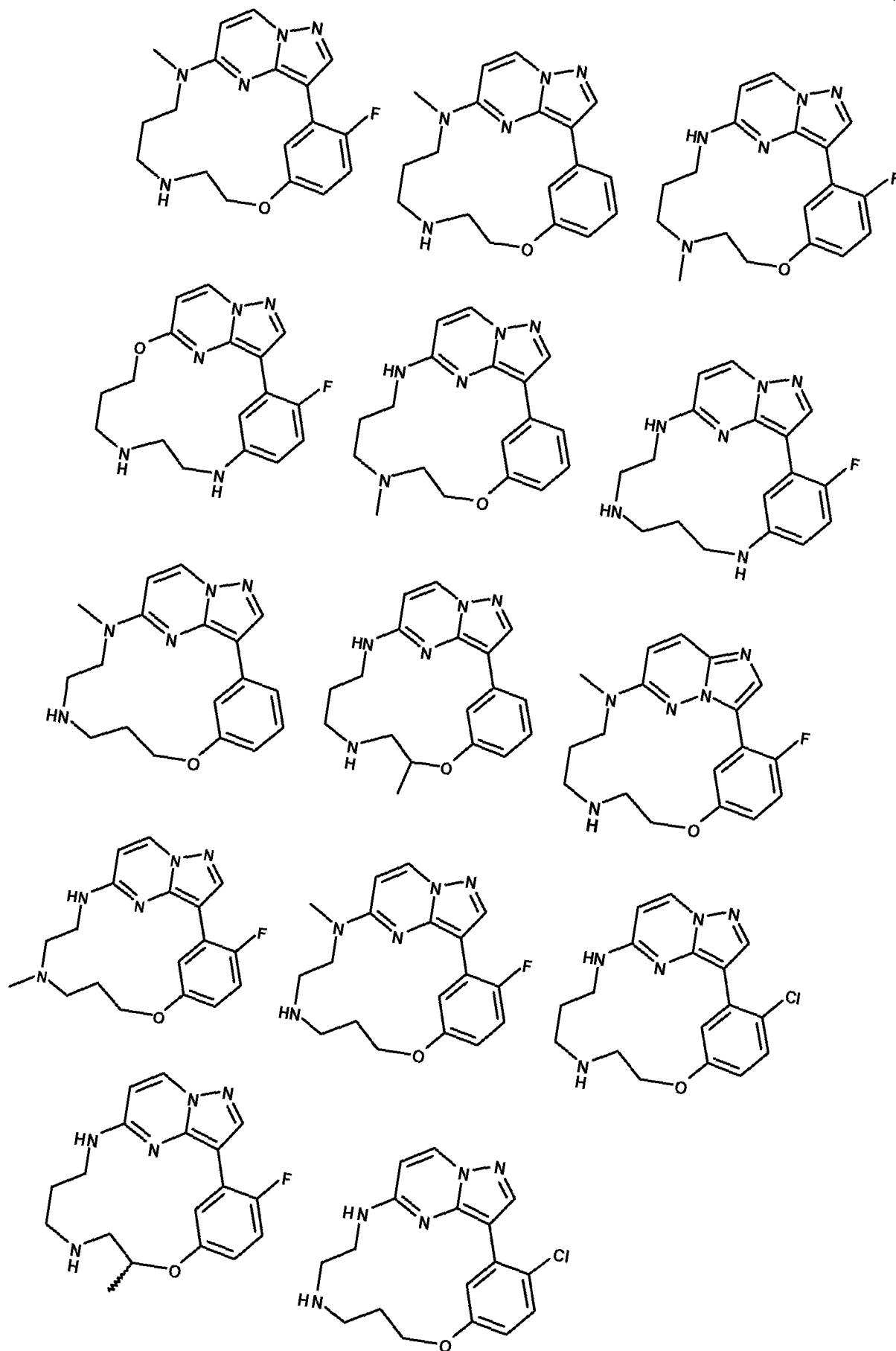
m and n are each independently 1, 2, 3, or 4.

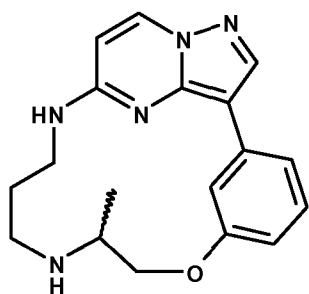
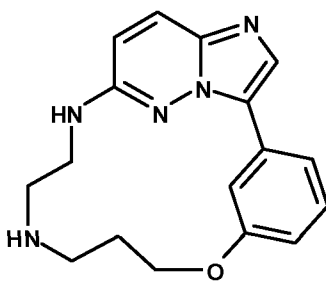
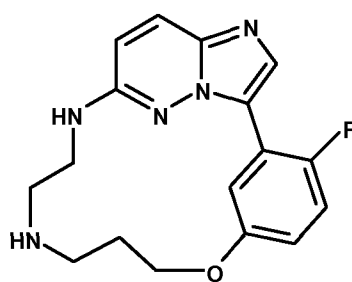
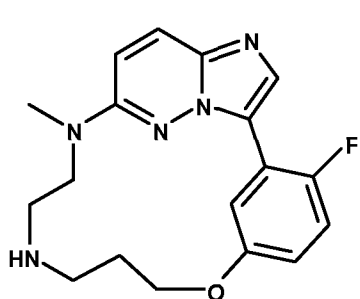
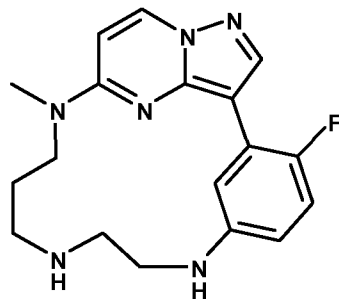
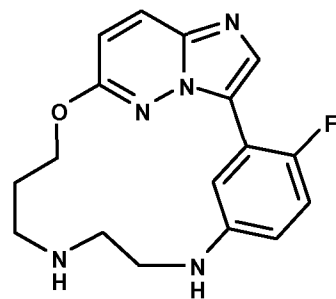
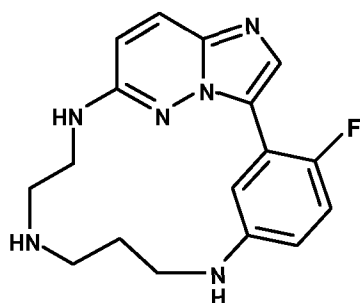
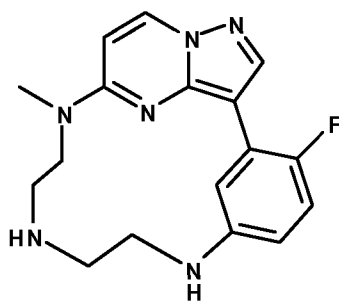
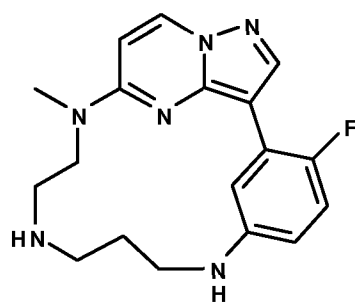
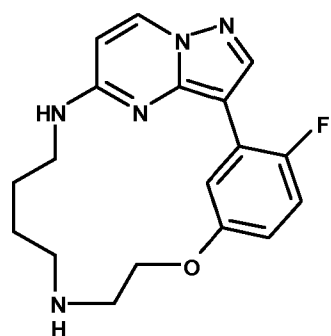
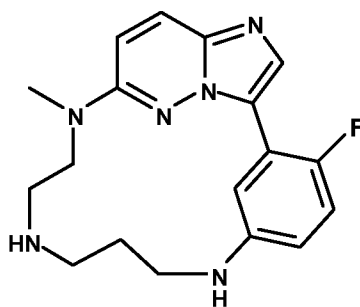
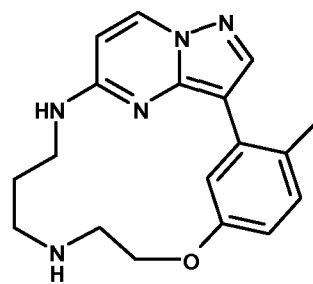
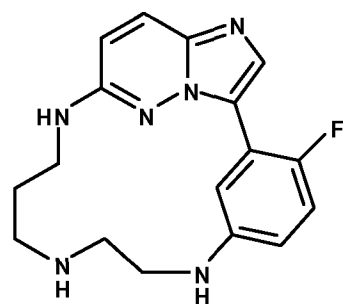
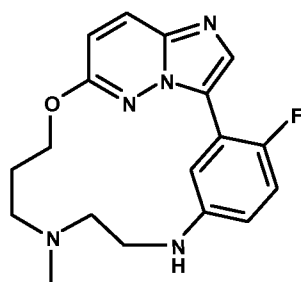
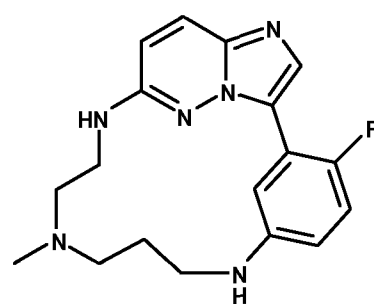
for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

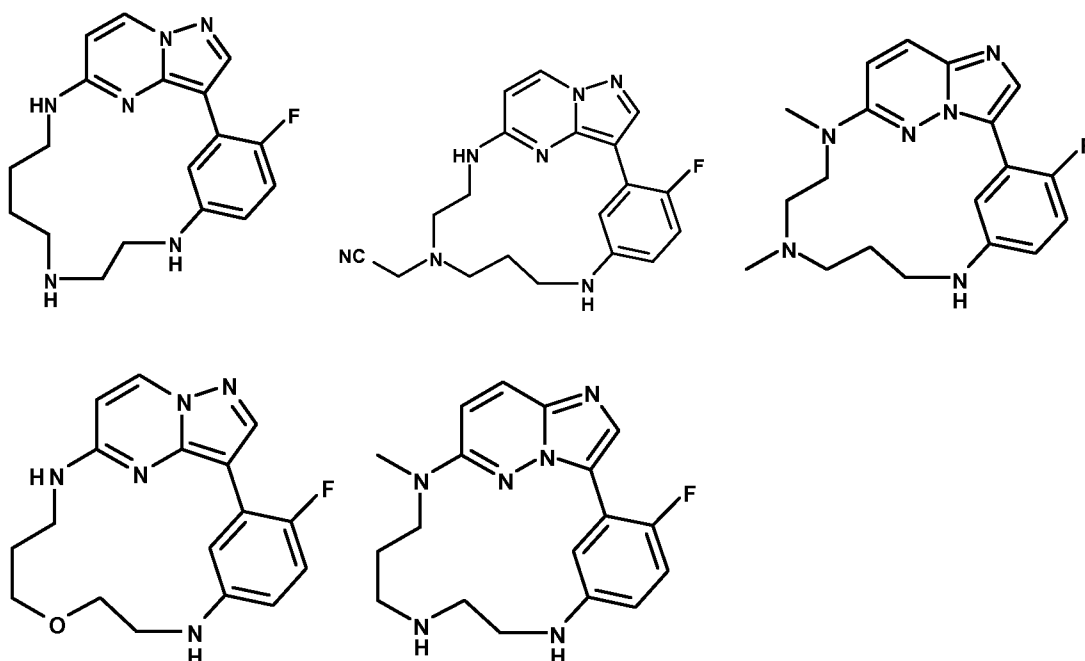
20 In a particular embodiment, the present invention provides compounds for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein said compounds are selected from:



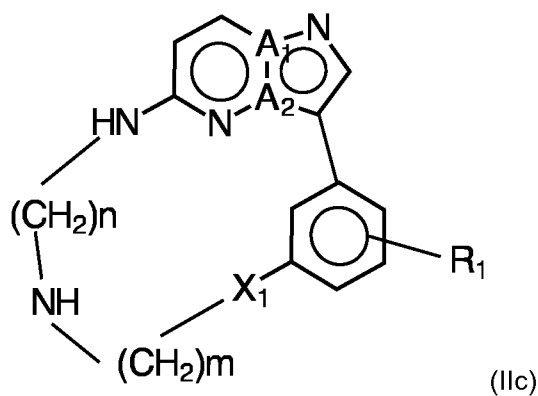








- 5 In particular in the compounds according to this invention, the pyrazolopyrimidine or the imidazopyridazine moiety is linked to the aryl or heteroaryl moiety at position Z_4 or Z_5 , in accordance with the numbering as provided in Formula I. Furthermore, the R_1 of the compounds according to this invention is preferably linked to the aryl or heteroaryl moiety at position Z_1 , Z_2 or Z_3 , in accordance with the numbering as provided in Formula I.
- 10 In a further embodiment, the present invention provides a compound of Formula (IIc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

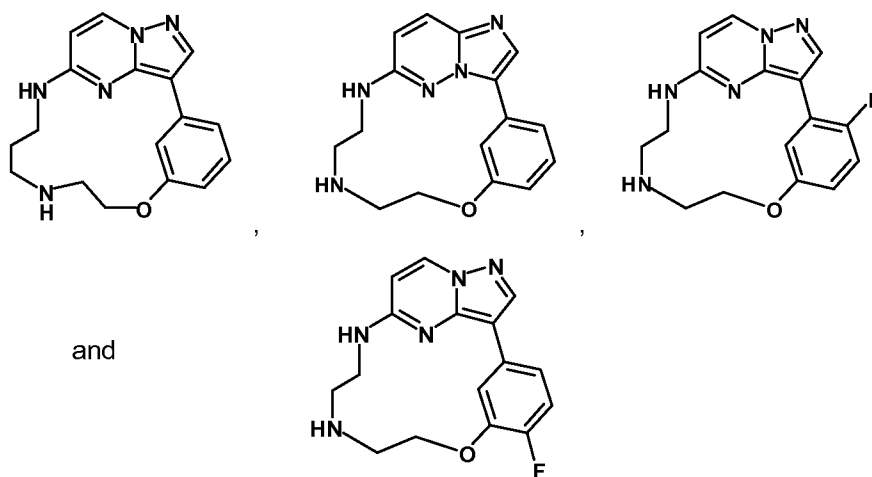
R_1 is selected from the list comprising -H, -F, -CH₃, and -CN

5 X_1 is selected from the list comprising -NH- and -O-

m and n are each independently 1, 2, 3, or 4

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

In a particular embodiment, the present invention provides compounds for use in the diagnosis,
prevention and/or treatment of a LRRK2-kinase associated disease wherein said compounds
10 are selected from:



In a particular embodiment, the LRRK2-kinase associated disease is chosen between Crohn's
15 disease, leprosy, and a neurological disorder. Preferably, the neurological disorder is Parkinson's disease or Alzheimer's disease.

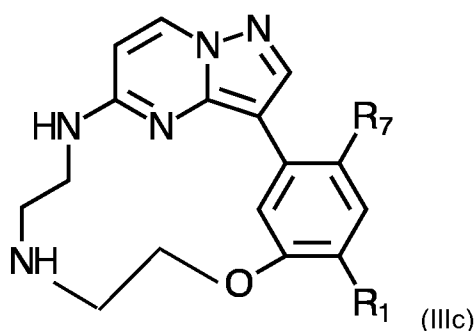
The present invention further provides a pharmaceutical composition for use in the diagnosis,
prevention and/or treatment of a LRRK2-kinase associated disease comprising a compound
20 according to the present invention.

The present invention also provides the use of a compound, or a composition according to this
invention, suitable for inhibiting the activity of a kinase; in particular a LRRK2 kinase.

Furthermore, the present invention provides the use of a compound or a composition according to this invention, for the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

- 5 Moreover, the present invention provides a method for the prevention and/or treatment of a LRRK2-kinase associated disease; said method comprising administering to a subject in need thereof a compound or a composition according to this invention.

Furthermore, the present invention provides new compounds of Formula (IIIc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or
 10 solvate thereof,

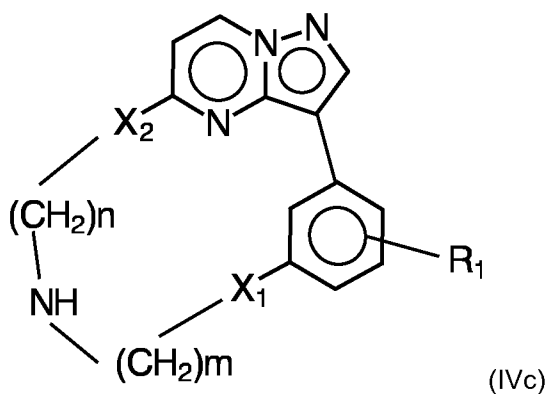


wherein

R_1 is -H and R_7 is -F; or

R_7 is -H and R_1 is -F.

- 15 In another embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof:



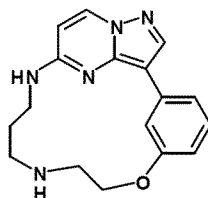
wherein

- 20 R_1 is selected from the list comprising -H, -F, -CH₃, and -CN

X_1 and X_2 are each independently selected from the list comprising $-NH-$ and $-O-$

m and n are each independently 1, 2, 3, or 4.

with the proviso that said compound is not

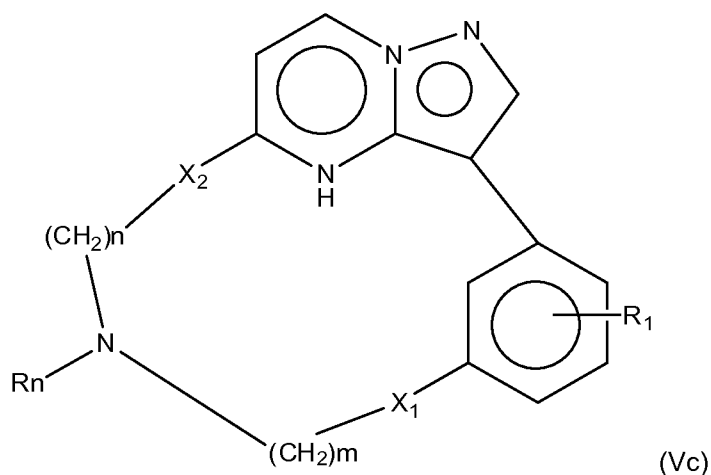


- 5 In a further aspect, the present invention provides a compound according to this invention for use as a medicine or diagnostic agent.

The present invention also provides a pharmaceutical composition comprising a compound as defined herein.

In another embodiment, the present invention provides a compound of formula (Vc)

10



wherein

R_1 is selected from the list comprising $-H$, and $-F$,

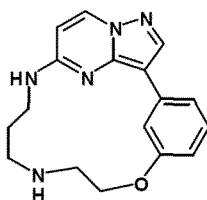
X_1 and X_2 are each independently selected from the list comprising $-NR_x-$ and $-O-$,

- 15 R_x is H or a methyl group,

m and n are each independently 1, 2, 3, or 4,

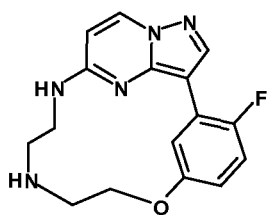
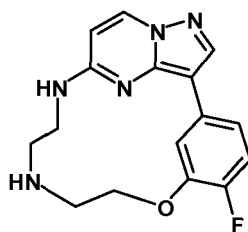
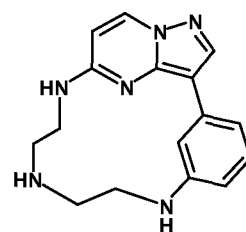
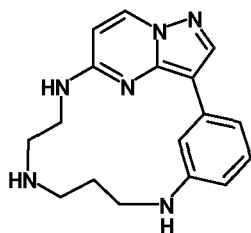
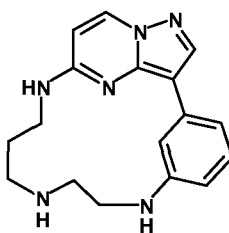
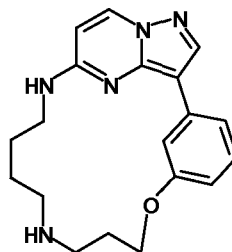
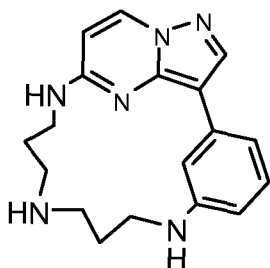
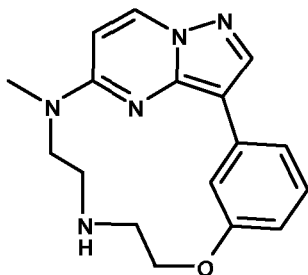
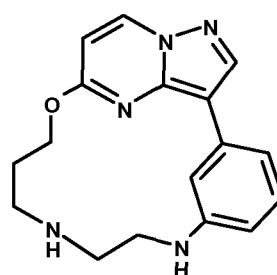
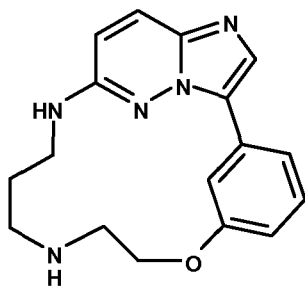
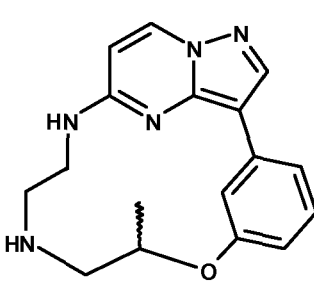
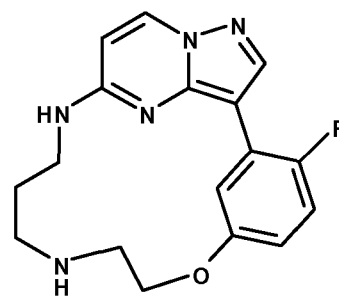
R_n is H or a methyl group,

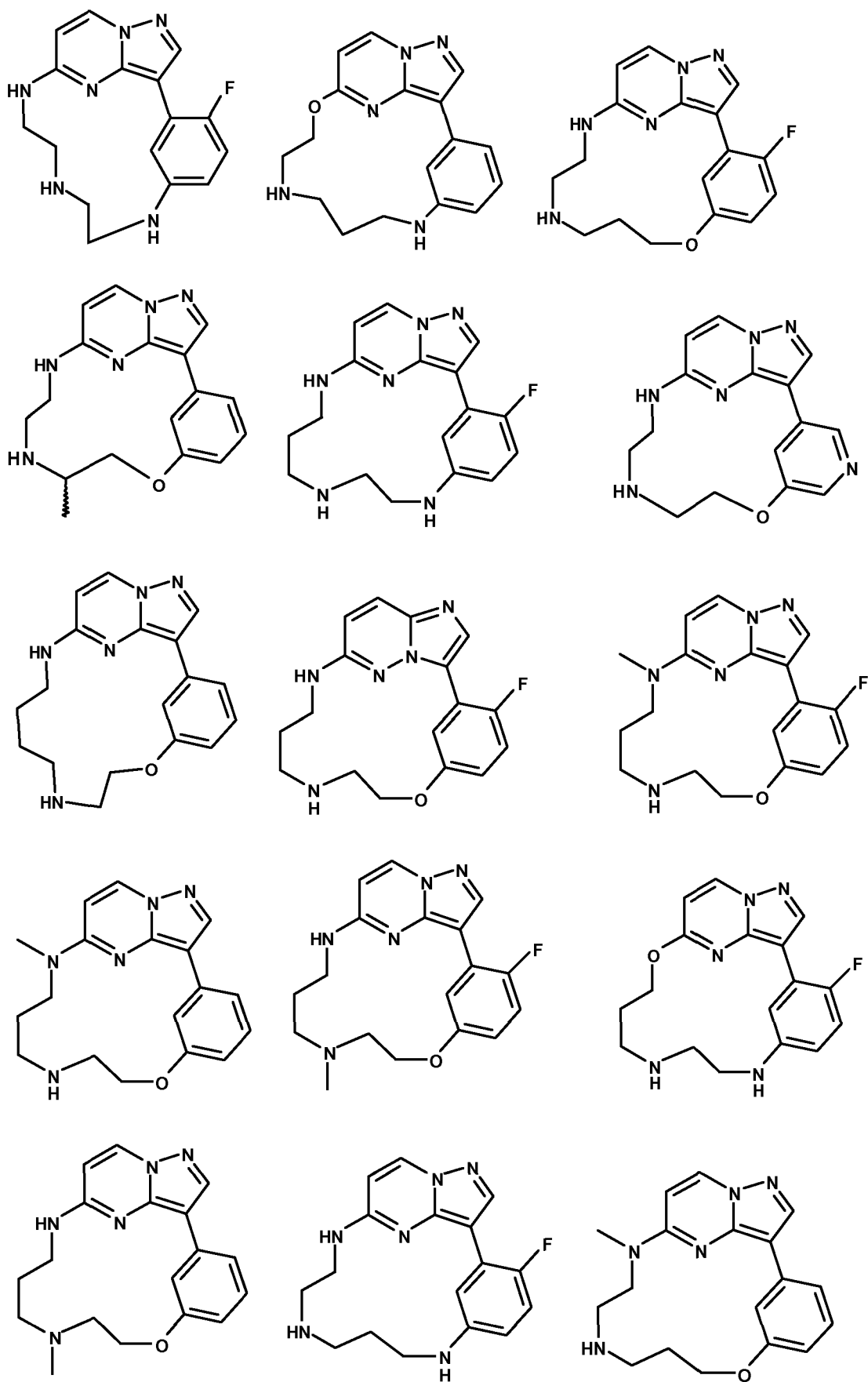
with the proviso that said compound is not

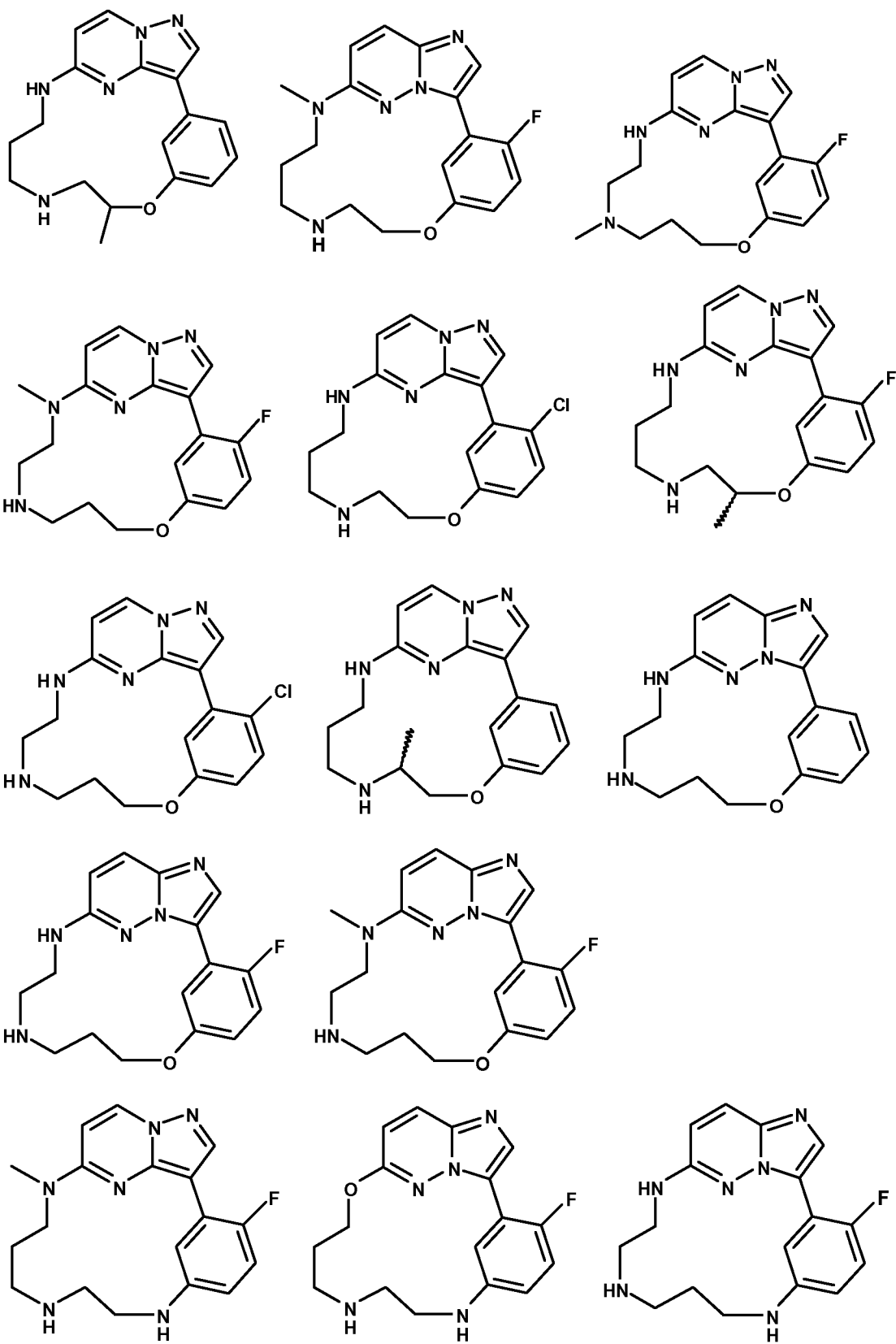


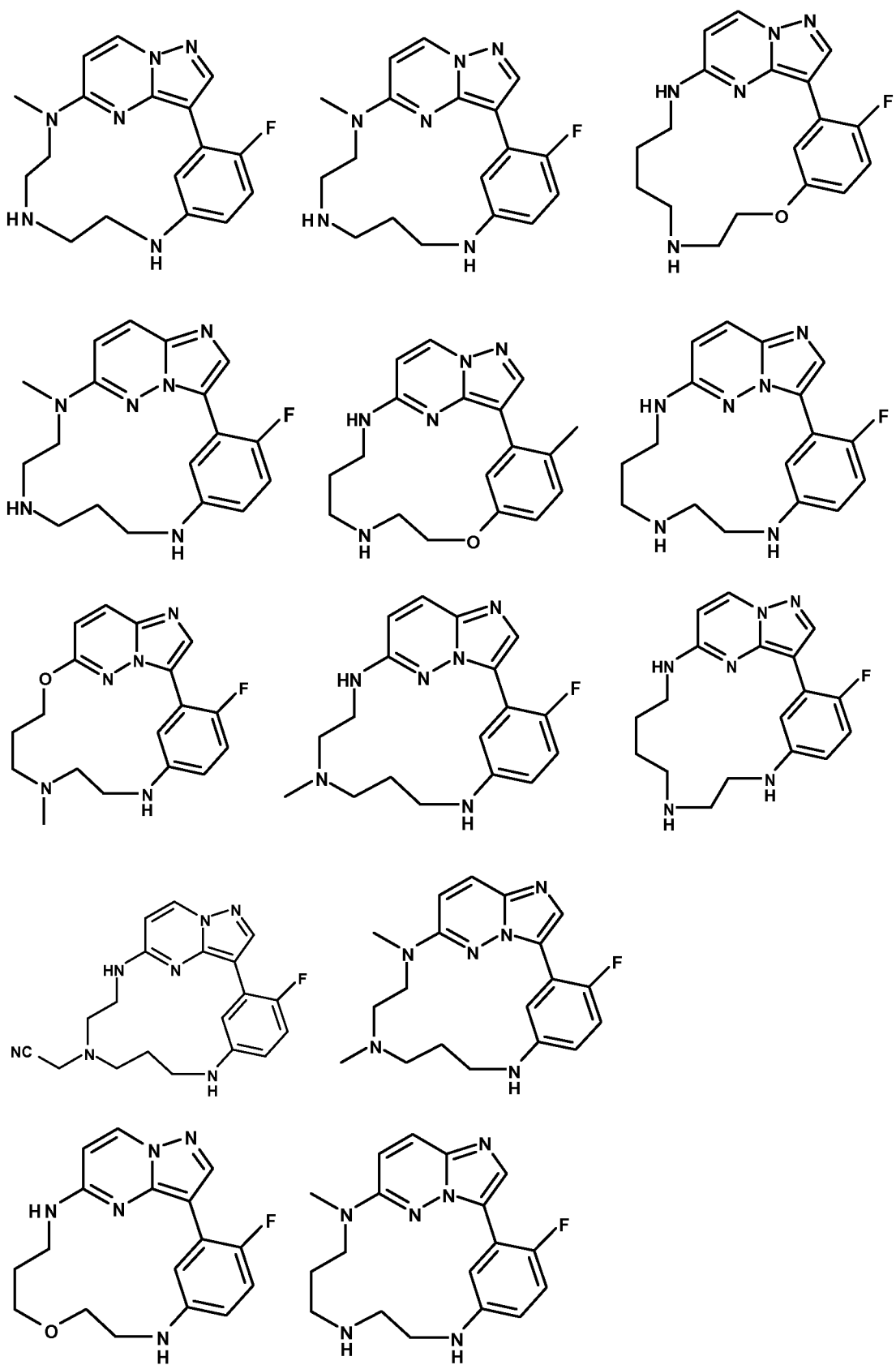
In another embodiment, the present invention provides a compound selected from the list comprising:

5







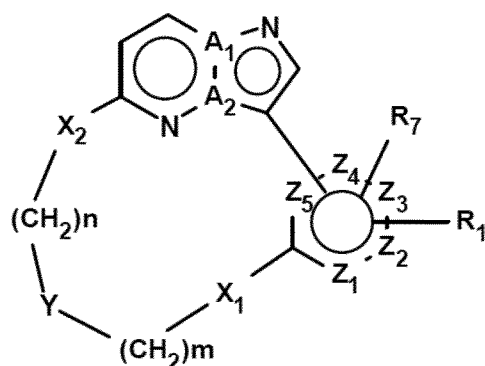


DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

As already mentioned hereinbefore, in a first aspect the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



Wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_7 are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R_2 is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

R_3 is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl, -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;

R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;

R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

Unless indicated otherwise, all of the above radicals can be read both ways. For example, when A is $-(C=O)-NR_5-$, the $-(C=O)-$ may be attached to X_2 and $-NR_5-$ attached to X_1 . Alternatively, the $-(C=O)-$ may be attached to X_1 and $-NR_5-$ attached to X_2 . What is called "left part" of a radical is for example when A is $-(C=O)-NR_5-$, $-(C=O)-$, and the "right part" is $-NR_5-$.

5

Preferably, Y is such as the left part of the possible values of Y (i.e. in particular $-CH$ from $-CHR_6-$) is attached to X_1 . Alternatively, Y is such as the right part of the possible values of Y (i.e. in particular $-R_6-$ from $-CHR_6-$) is attached to X_1 .

10

Preferably, X_1 is such as the left part of the possible values of X_1 (i.e. in particular $-O$ from $-O-C_{1-6}alkyl$, $-S$ from $-S-C_{1-6}alkyl$, $-NR_3$ from $-NR_3-(C=O)$ and $-NR_3-C_{1-6}alkyl$, $-SO_2$ from $-SO_2-NR_3$, etc) is attached to the Z_1-Z_5 aryl or heteroaryl moiety. Alternatively, X_1 is such as the right part of the possible values of X_1 (i.e. in particular $(C_{1-6}alkyl)-$ from $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$ and $-NR_3-C_{1-6}alkyl$, $-(C=O)-$ from $-NR_3-(C=O)$, $(NR_3)-$ from $-SO_2-NR_3$, etc) is attached to the Z_1-Z_5 aryl or heteroaryl moiety.

15

Preferably, X_2 is such as the left part of the possible values of X_2 (i.e. in particular $-O$ from $-O-C_{1-6}alkyl$, $-S$ from $-S-C_{1-6}alkyl$, $-(C=O)-$ from $-(C=O)-NR_2$, $-NR_2$ from $-NR_2-C_{1-6}alkyl$, $-SO_2$ from $-SO_2-NR_2$, etc) is attached to the pyrazolopyrimidine moiety. Alternatively, X_2 is such as the right part of the possible values of X_2 (i.e. in particular $(C_{1-6}alkyl)-$ from $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$ and $-NR_2-C_{1-6}alkyl$, $(NR_2)-$ from $-(C=O)-NR_2$ and $-SO_2-NR_2$, etc) is attached to the pyrazolopyrimidine moiety.

20

The same principle applies to all the radicals of the invention unless specified otherwise.

25

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

30

The term "alkyl" by itself or as part of another substituent refers to fully saturated hydrocarbon radicals. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, $C_{1-6}alkyl$ means an alkyl of one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl, and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers. $C_{1-6}alkyl$ includes all linear, branched, or cyclic alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

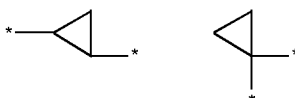
35

The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 3 substituents, for example 1, 2 or 3 substituents or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents include -halo, -OH, primary and secondary amides, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, heteroaryl, aryl, and the like.

The term "cycloalkyl" by itself or as part of another substituent is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbyl group having a cyclic structure. Cycloalkyl includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups having a cyclic structure. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 6 atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylenemethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene.

Generally, alkylene groups of this invention preferably comprise the same number of carbon atoms as their alkyl counterparts. Where an alkylene or cycloalkylene biradical is present, connectivity to the molecular structure of which it forms part may be through a common carbon atom or different carbon atom. To illustrate this applying the asterisk nomenclature of this invention, a C₃ alkylene group may be for example *-CH₂CH₂CH₂*, *-CH(-CH₂CH₃)*, or *-CH₂CH(-CH₃)*. Likewise a C₃ cycloalkylene group may be



The terms "heterocycle" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 6 membered monocyclic ring systems, or 8-10 membered bicyclic rings) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms. An optionally substituted heterocyclic refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

Exemplary heterocyclic groups include piperidinyl, azetidiny, imidazoliny, imidazolidiny, isoxazoliny, oxazolidiny, isoxazolidiny, thiazolidiny, isothiazolidiny, piperidyl, succinimidyl, 3H-indolyl, isoindoliny, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrroliny, 2-pyrroliny, 3-pyrroliny, pyrrolidiny, 4H-quinoliziny, 4aH-carbazolyl, 2-oxopiperaziny, piperaziny, homopiperaziny, 2-pyrazoliny, 3-pyrazoliny, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-

5 dihydro- 2H-pyranyl, phthalazinyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,3-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro- 1,1-dioxothienyl, N- formylpiperazinyl, and morpholinyl; in particular pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, dioxolanyl, dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, thiazolidinyl, tetrahydropyranyl, and tetrahydrofuranyl.

10 8-10 membered heterocyclic groups are also meant to include spiro-groups, which are bicyclic compounds with both rings connected through a single atom, such as for example spiro[4.5]decane, which is a spiro compound consisting of a cyclohexane ring and a cyclopentane ring.

15 The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having from 5-10 atoms. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenyl, biphenylenyl, 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-azulenyl, 1- or 2-naphthyl, 1-, 2-, or 3-indenyl, 1-, 2-, or 9-anthryl, 1- 2-, 3-, 4-, or 5-acenaphtylenyl, 3-, 4-, or 5-acenaphtenyl, 1-, 2-, 3-, 4-, or 10-phenanthryl, 1- or 2-pentalenyl, 1, 2-, 3-, or 4-fluorenyl, 4- or 20 5-indanyl, 5-, 6-, 7-, or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, dibenzo[a,d]cycloheptenyl, and 1-, 2-, 3-, 4-, or 5-pyrenyl; in particular phenyl.

The aryl ring can optionally be substituted by one or more substituents. An "optionally substituted aryl" refers to an aryl having optionally one or more substituents (for example 1 to 5 substituents, for example 1, 2, 3 or 4) at any available point of attachment, selected from those 25 defined above for substituted alkyl.

Where a carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

30 The term "heteroaryl" as used herein by itself or as part of another group refers but is not limited to 5 to 10 carbon-atom aromatic rings in which one or more carbon atoms can be replaced by oxygen, nitrogen or sulfur atoms. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatrizolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, 35 tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-

benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 7-azaindolyl, 6-azaindolyl, 5-azaindolyl, 4-azaindolyl.

- 5 An “optionally substituted heteroaryl” refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term “halo” or “halogen” as a group or part of a group is generic for fluoro, chloro, bromo, or iodo, as well as any suitable isotope thereof.

- 10 Whenever the term “substituted” is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using “substituted” is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture,
15 and formulation into a therapeutic and/or diagnostic agent.

Where groups may be optionally substituted, such groups may be substituted once or more, and preferably once, twice or thrice. Substituents may be selected from, those defined above for substituted alkyl.

- 20 As used herein the terms such as “alkyl, aryl, or cycloalkyl, each being optionally substituted with” or “alkyl, aryl, or cycloalkyl, optionally substituted with” refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

- More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e.
25 enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

- In addition, the invention includes isotopically-labelled compounds and salts, which are identical
30 to compounds of formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of formula (I) are isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^3H , ^{11}C , ^{13}N , ^{14}C , ^{15}O and ^{18}F . Such isotopically-labelled compounds of formula (I) are useful in drug and/or substrate
35 tissue distribution assays. For example ^{11}C and ^{18}F isotopes are particularly useful in PET (Positron Emission Tomography). PET is useful in brain imaging. Isotopically labeled compounds of formula (I) can generally be prepared by carrying out the procedures disclosed

below, by substituting a readily available non-isotopically labeled reagent with an isotopically labeled reagent.

Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general Formula I and any subgroup thereof. This term also refers to the compounds as depicted in Table 1, their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, pro-drugs, esters, and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

In a particular embodiment, the present invention provides compounds of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, *N*-oxide form, or solvate thereof; for use in the diagnosis prevention and/or treatment of a LRRK2-kinase associated disease; wherein one or more of the following applies

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_7 are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R_2 is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

R_3 is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;

R_4 is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;

R_5 is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with
 5 from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

10 X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

15 X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

20 Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

25 Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5-or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -
 30 halo;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

35 In particular, X₁, and X₂ as used herein, represent biradicals, which taken together with the radicals to which they are attached form a macrocyclic pyrazolopyrimidine compound. Said biradicals may be present in either of both directions in the macrocyclic pyrazolopyrimidine, but are preferably present in the direction as described below:

Referring to formula I:

5 X₁ is selected from the list comprising *-C₁₋₆alkyl-, *-O-C₁₋₆alkyl-, *-S-C₁₋₆alkyl-, *-(C=O)-, *-NR₃-(C=O)-, *-C₁₋₆alkyl-NR₃-, *-NR₃-, *-(C=O)-, *-NR₃-(C=O)-NR₃₇-, *-NR₃-C₁₋₆alkyl-, *-NR₃-SO₂-, *-NR₃-(C=O)-C₁₋₆alkyl-, *-(C=O)-NR₃-C₁₋₆alkyl-, *-O-C₁₋₆alkyl-O-C₁₋₆alkyl- and *-C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein said biradical is preferably attached to the aryl or heteroaryl moiety via *;

10 X₂ is selected from the list comprising *-C₁₋₆alkyl-, *-O-C₁₋₆alkyl-, *-S-C₁₋₆alkyl-, *-(C=O)-, *-NR₂-(C=O)-, *-C₁₋₆alkyl-NR₂-, *-NR₂-, *-(C=O)-, *-NR₂-(C=O)-NR₃₈-, *-NR₂-C₁₋₆alkyl-, *-NR₂-SO₂-, *-NR₂-(C=O)-C₁₋₆alkyl-, *-(C=O)-NR₂-C₁₋₆alkyl-, *-O-C₁₋₆alkyl-O-C₁₋₆alkyl- and *-C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein said biradical is preferably attached to the pyrazolopyrimidine moiety via *;

15 In a preferred embodiment, the present invention provides compounds of formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A₁ is C and A₂ is N

20 R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;

25 R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;

30 R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;

R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

35 R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

5 X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

10 X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

15 Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀-, -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, and -S-C₁₋₆alkyl-;

20 Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, and -NR₂₁R₂₂-, wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -halo;

25 Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

30 In yet another particular embodiment, the present invention provides a compound or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease, wherein

A₁ is N and A₂ is C

35 R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀-, -(C=O)-R₄-, -SO₂-R₄-, -CN, -NR₉-SO₂-R₄-, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂-, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈-, -Het₃-, -(C=O)-Het₃-, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl;

wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-Het_3$, $-Ar_2$, and $-NR_{13}R_{14}$;
 R_3 is selected from $-H$, $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-(C=O)-C_{1-6}alkyl$, $-(C=O)-O-C_{1-6}alkyl$, $-Het_2$, $-C_{3-6}cycloalkyl$, $-(C=O)-Het_2$, $-(C=O)-NR_{29}R_{30}$, and $-SO_2-C_{1-6}alkyl$; wherein
5 each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{15}R_{16}$, $-Het_2$, and $-Ar_3$;
 R_4 is independently selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{17}R_{18}$, and $-Het_4$;
 R_5 is selected from $-H$, $-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$; wherein each of said $C_{1-6}alkyl$ or $-C_{3-6}cycloalkyl$ is optionally and independently substituted with from 1 to 3 substituents selected
10 from $-halo$, $-OH$, $-OC_{1-6}alkyl$, $-SC_{1-6}alkyl$, $-Het_5$, and $-NR_{31}R_{32}$;
 R_6 is selected from $-H$, $-OH$, $-halo$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{33}R_{34}$, and $-Het_8$;
 R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{37} and R_{38} are each independently selected from $-H$, $=O$, $-C_{1-6}alkyl$,
15 and $-Het_1$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-NR_{35}R_{36}$, $-Het_7$, and $-Ar_4$;
 R_{35} and R_{36} are each independently selected from $-H$, $=O$, and $-C_{1-6}alkyl$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected
20 from $-halo$, $-OH$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;
 X_1 is selected from $-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-(C=O)-$, $-NR_3-(C=O)-$, $-C_{1-6}alkyl-NR_3-$, $-NR_3-$, $-(C=O)-$, $-NR_3-(C=O)-NR_{37}-$, $-NR_3-C_{1-6}alkyl-$, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}alkyl-$, $-(C=O)-NR_3-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_3-C_{1-6}alkyl-$; wherein each
25 of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-phenyl$, and $-NR_{23}R_{24}$;
 X_2 is selected from $-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-$, $-S-C_{1-6}alkyl-$, $-(C=O)-$, $-NR_2-(C=O)-$, $-C_{1-6}alkyl-NR_2-$, $-NR_2-$, $-(C=O)-$, $-NR_2-(C=O)-NR_{38}-$, $-NR_2-C_{1-6}alkyl-$, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}alkyl-$, $-(C=O)-NR_2-C_{1-6}alkyl-$, $-O-C_{1-6}alkyl-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_2-C_{1-6}alkyl-$; wherein each
30 of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-halo$, $-OH$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, $-phenyl$ and $-NR_{25}R_{26}$;
 Y is selected from a direct bond, $-CHR_6-$, $-O-$, $-S-$, and $-NR_5-$;
 Ar_2 , Ar_3 , and Ar_4 are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar_2 , Ar_3 , and Ar_4 is optionally and independently substituted with from 1 to 3 substituents selected from
35 $-NR_{19}R_{20}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;
 Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 are each independently a 5-or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1 , Het_2 , Het_3 , Het_4 , Het_5 , Het_6 , Het_7 and Het_8 is optionally substituted with from 1 to 3 substituents selected from $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-S-C_{1-6}alkyl$, and $-NR_{21}R_{22}$;

wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N;

m and n are each independently 1, 2, 3, or 4.

- 5 Preferably the present invention provides compounds of Formula (I), for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease, wherein A_1 is N and A_2 is C.

Preferably, the compounds of Formula (I) of the invention are such that both R_1 and R_7 are $-H$.

- 10 Alternatively, the compounds of Formula (I) of the invention are such that R_1 is $-Halo$ and R_7 is $-H$.

Preferably, when R_1 is $-Halo$, R_7 is $-F$.

For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

- 15 R_1 and R_7 are both $-H$;

and one of Z_1, Z_2, Z_3, Z_4 and Z_5 is N and the other ones are each C.

For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

- 20 R_1 and R_7 are both $-H$;

and Z_1, Z_2, Z_3, Z_4 and Z_5 are each C.

For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

- 25 R_1 is $-F$ and R_7 is $-H$;

and Z_1, Z_2, Z_3, Z_4 and Z_5 are each C.

For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

- 30 R_1 is $-F$ and R_7 is $-H$;

and one of Z_1, Z_2, Z_3, Z_4 and Z_5 is N and the other ones are each C.

For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A₁ is C, A₂ is N;

and R₁ is -F and R₇ is -H.

- 5 Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that X₁ is -O-C₁₋₆alkyl or NR₃-.

Preferably, X₁ is -O-C₁₋₆alkyl. Alternatively, X₁ is NR₃-.

Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that X₂ is NR₂- or -O-C₁₋₆alkyl.

- 10 Preferably, X₂ is NR₂-. Alternatively, X₂ is -O-C₁₋₆alkyl, for example -O-CH₂-, -O-CH₂-CH₂- or -O-CH₂-CH₂-.

Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that R₂ is -H.

- 15 Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that R₃ is -H.

Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that Y is -NR₅ or -O-.

Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that Y is -NR₅.

- 20 Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that R₅ is -H or -C₁₋₆alkyl, more preferably R₅ is -H.

Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that Y is -O-.

- 25 Preferably, the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that Z₁, Z₂, Z₃, Z₄ and Z₅ are each C. Alternatively, one of Z₁, Z₂, Z₃, Z₄ and Z₅ is N and the other ones are each C.

Preferably the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that m is 1. Alternatively, m is

- 30 2. Alternatively, m is 3. Alternatively, m is 4.

Preferably the compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease of the invention are such that n is 1. More preferably, n is 2. Even more preferably, n is 3. Alternatively, n is 4.

For example, m is 1 or 2 and n is 2 or 3.

- 5 For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

X_1 is $-O-C_{1-6}alkyl$ or NR_{3-} ; and

X_2 is NR_{2-} or $-O-C_{1-6}alkyl$.

- 10 For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

X_1 is $-O-methyl$; and

X_2 is NR_{2-} .

- 15 For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

A_1 is N, A_2 is C;

X_1 is NR_{5-} ; and

X_2 is NR_{2-} .

- 20 For example, the present invention provides compounds of Formula (I) for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease wherein

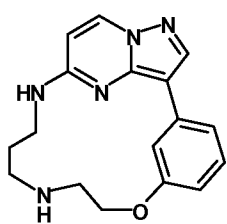
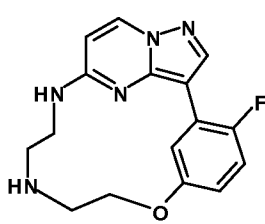
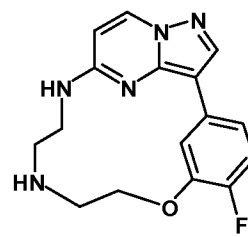
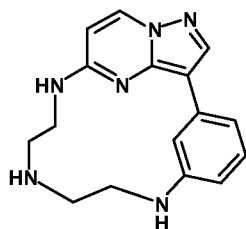
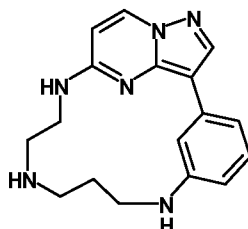
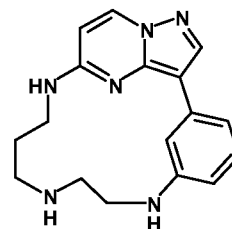
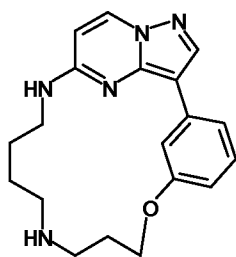
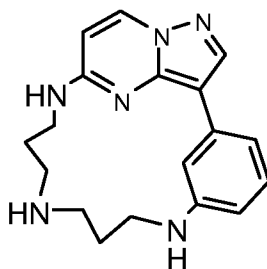
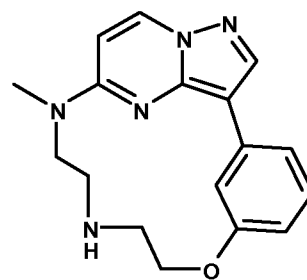
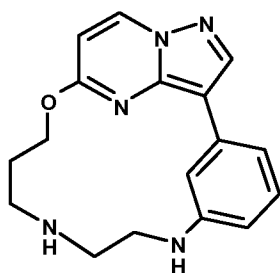
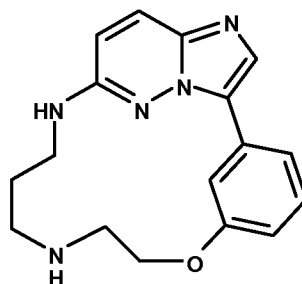
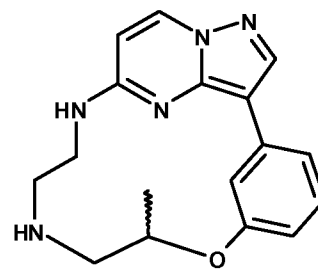
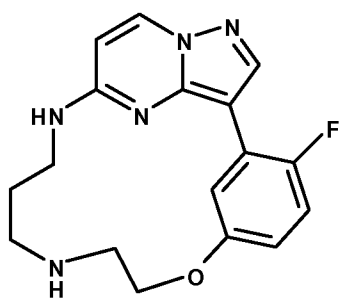
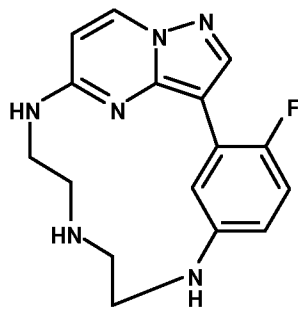
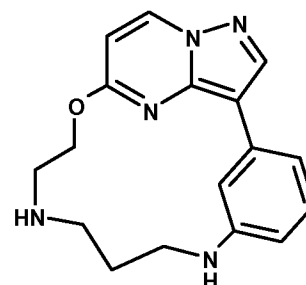
A_1 is N, A_2 is C;

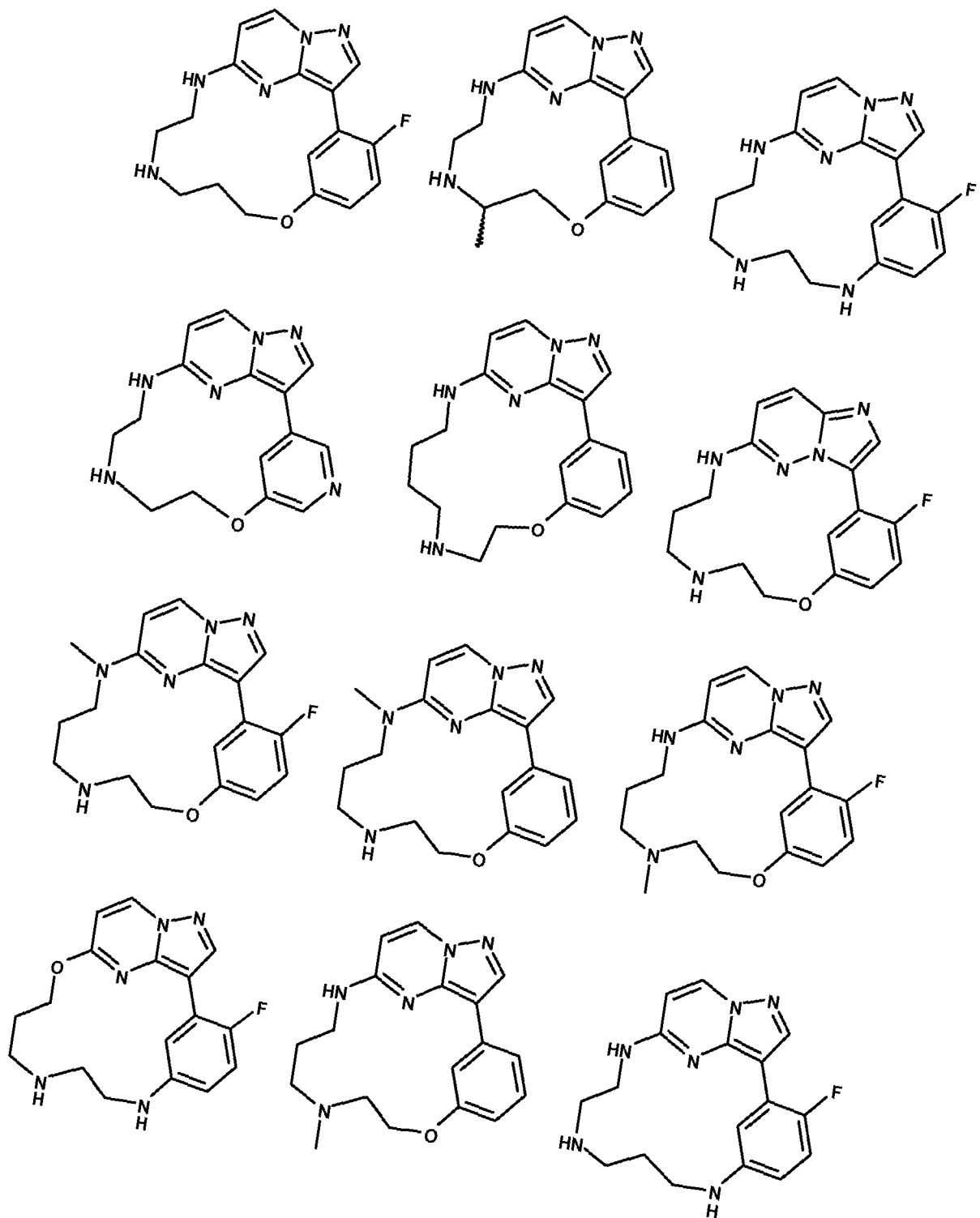
X_1 is $-O-methyl$ or NR_{3-} ;

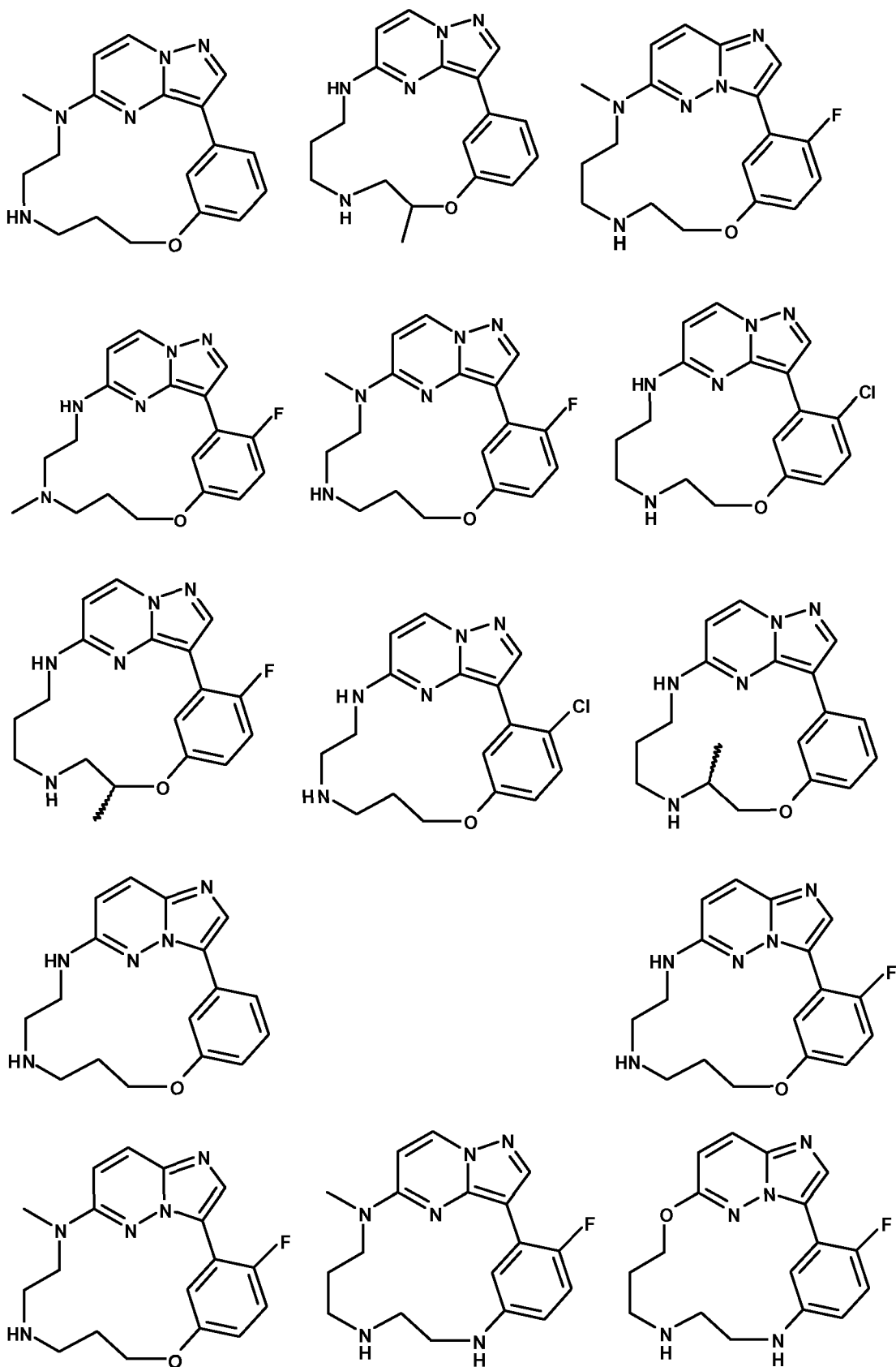
X_2 is NR_{2-} or $-O-methyl$; and

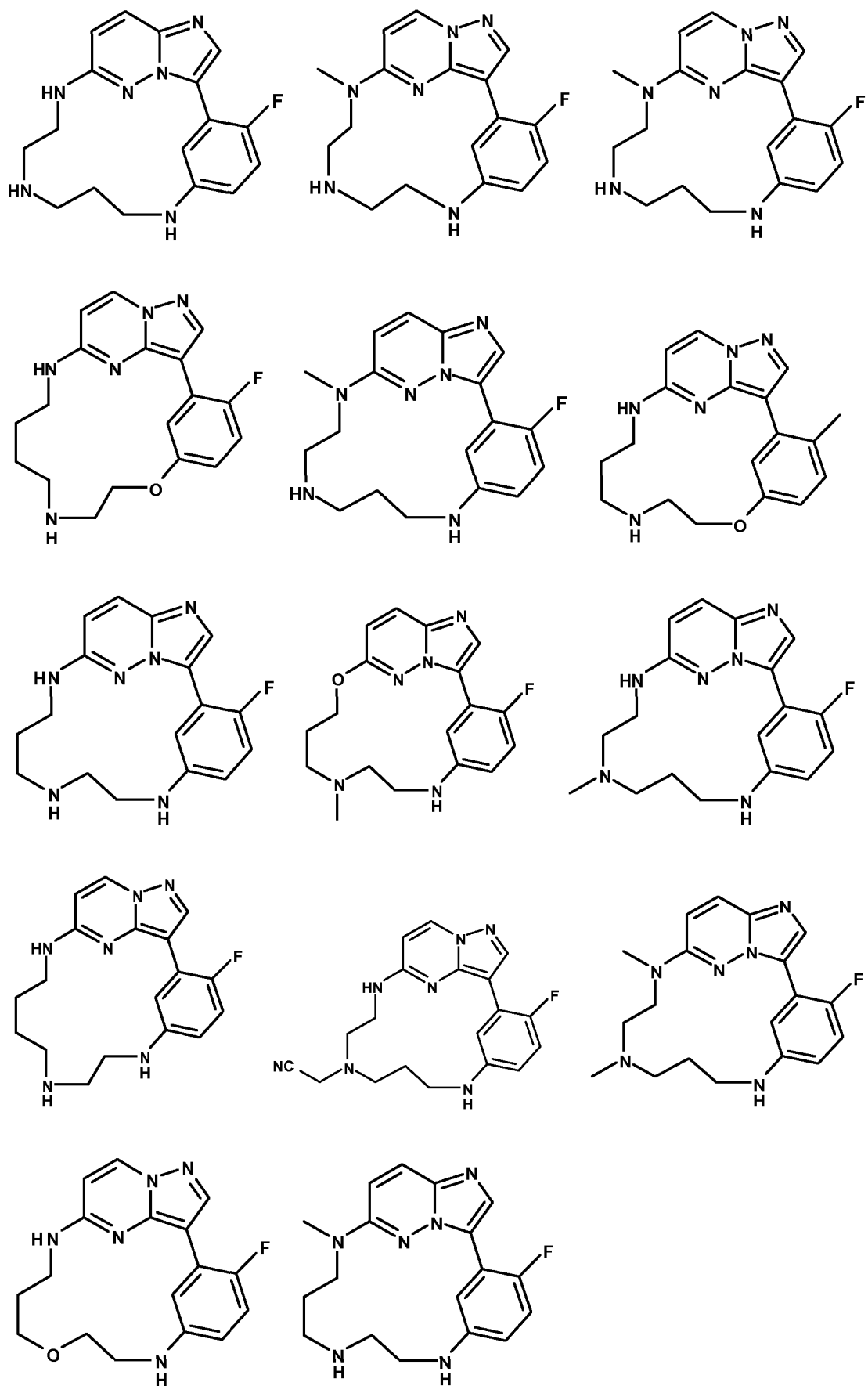
- 25 n and m are each independently 1, 2 or 3.

In particular the present invention provides compounds, for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease, wherein said compounds are selected from:



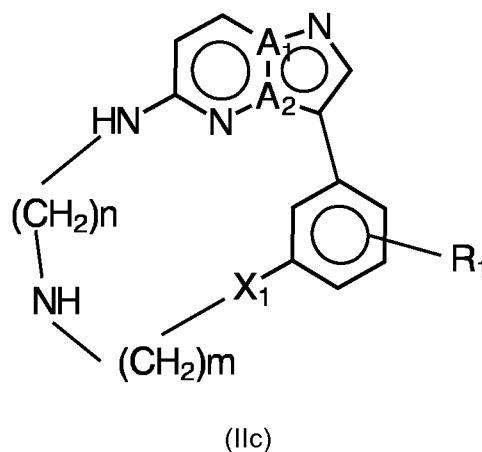






In particular in the compounds according to this invention, the pyrazolopyrimidine moiety is linked to the aryl or heteroaryl moiety at position Z₄ or Z₅, in accordance with the numbering as provided in Formula I. Furthermore, the R₁ of the compounds according to this invention is preferably linked to the aryl or heteroaryl moiety at position Z₁, Z₂ or Z₃, in accordance with the numbering as provided in Formula I.

In a particular embodiment, the present invention provides a compound of Formula (IIc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



wherein

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when A₂ is C, then A₁ is N;

R₁ is selected from the list comprising -H, -F, -CH₃, and -CN

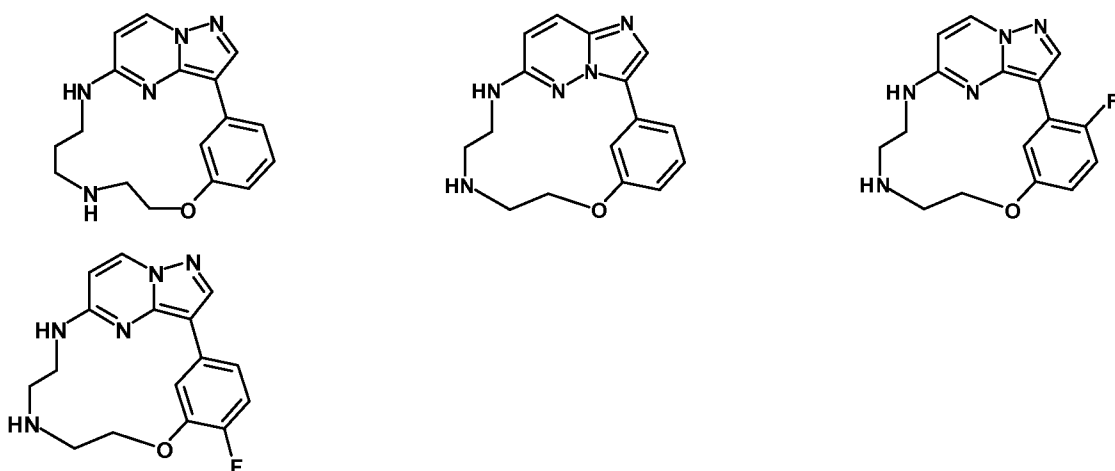
X₁ is selected from the list comprising -NH- and -O-

m and n are each independently 1, 2, 3, or 4

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

In particular the present invention provides compounds, for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease, wherein said compounds are selected from:

- 38 -



- 5 In a particular embodiment, the LRRK2-kinase associated disease is a neurological disorder, in particular selected from the list comprising Parkinson's disease or Alzheimer's disease.

The present invention further provides a pharmaceutical composition for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease comprising a compound
10 according to the present invention.

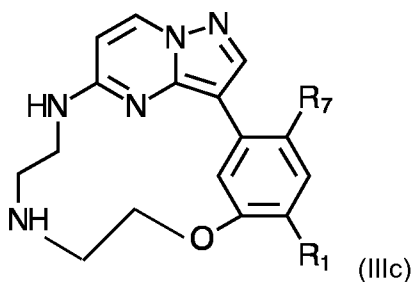
The present invention also provides the use of a compound, or a composition according to this invention, suitable for inhibiting the activity of a kinase; in particular a LRRK2 kinase.

- 15 Furthermore, the present invention provides the use of a compound or a composition according to this invention, for the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

Moreover, the present invention provides a method for the prevention and/or treatment of a
20 LRRK2-kinase associated disease; said method comprising administering to a subject in need thereof a compound or a composition according to this invention.

Finally, the present invention provides new compounds of Formula (IIIc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, according to the general formula (IIIc)

- 39 -

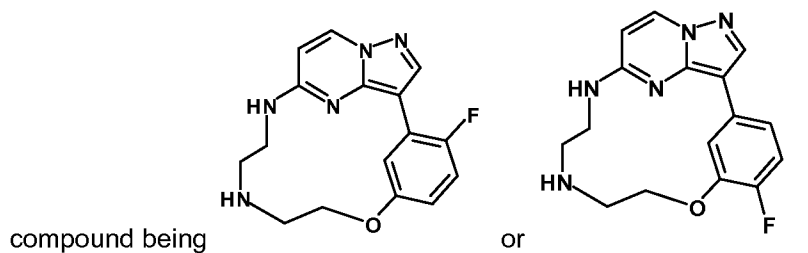


wherein

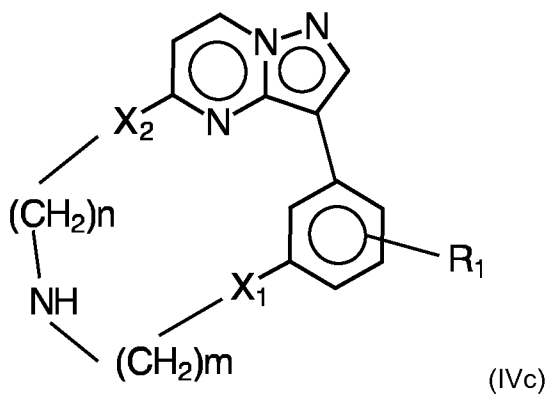
R_1 is $-H$ and R_7 is $-F$; or

R_7 is $-H$ and R_1 is $-F$.

5 In another embodiment, the present invention provides a compound of formula (IIIc), said



As already mentioned hereinbefore, in another aspect the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof:



wherein

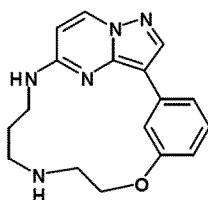
R_1 is selected from the list comprising $-H$, $-F$, $-CH_3$, and $-CN$

X_1 and X_2 are each independently selected from the list comprising $-NH-$ and $-O-$

m and n are each independently 1, 2, 3, or 4.

15 with the proviso that said compound is not

- 40 -



Preferably, R_1 is -H or -F.

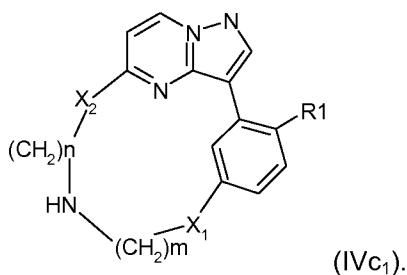
Preferably R_1 is -H.

Alternatively, R_1 is -F, -CH₃ or -CN. Preferably, R_1 is F.

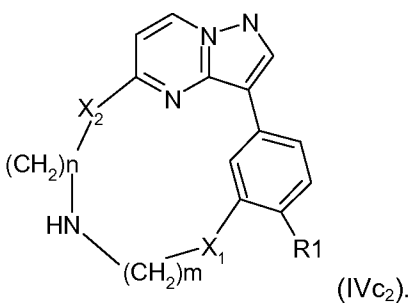
5 Preferably m and n are each independently 2, 3 or 4.

Preferably n is 2 and m is 3. Alternatively, n is 3 and m is 2. Alternatively, n is 4 and m is 3. Alternatively, n is 2 and m is 2.

10 In a particular embodiment, the present invention provides a compound of formula (IVc₁) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein R_1 is -F, -CH₃ or -CN, and X_1 , X_2 , n and m are as defined above

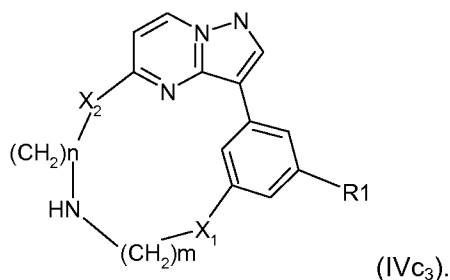


In a particular embodiment, the present invention provides a compound of formula (IVc₂) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein R_1 is -F, -CH₃ or -CN, and X_1 , X_2 , n and m are as defined above



15

In another embodiment, the present invention provides a compound of formula (IVc₃) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein R₁ is -F, -CH₃ or -CN, and X₁, X₂, n and m are as defined above



- 5 In another embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein X₂ is -NH-.

In another embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein X₂ is -O-.

10

In another embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein X₁ is -NH-.

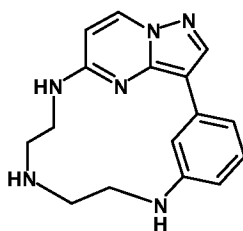
In another embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein X₁ is -O-.

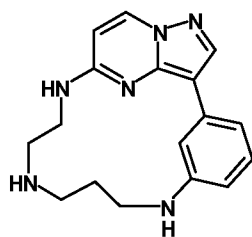
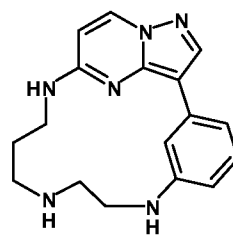
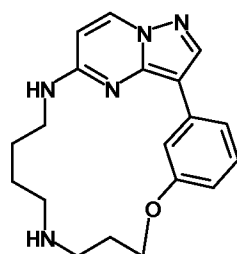
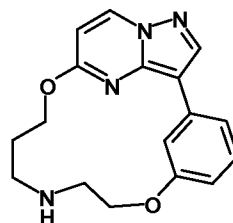
15

Preferably, X₁ and X₂ are -NH-.

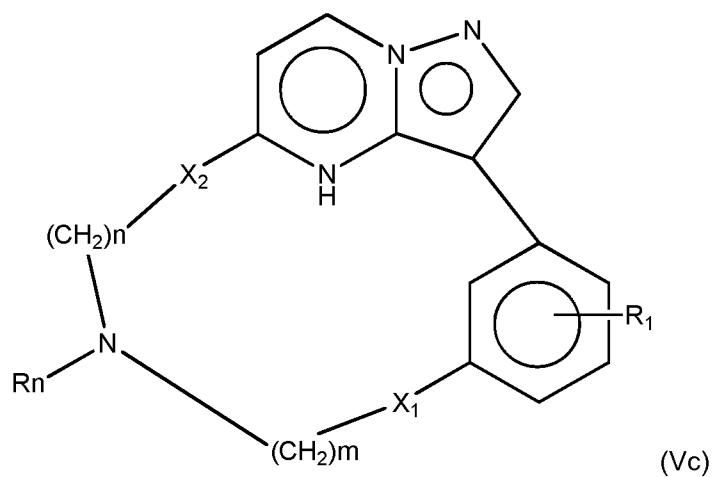
In a particular embodiment, the present invention provides a compound of formula (IVc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, selected from the list comprising:

20





As already mentioned hereinbefore, in another aspect the present invention provides a
 5 compound of formula (Vc)



wherein

R_1 is selected from the list comprising $-H$, and $-F$,

10 X_1 and X_2 are each independently selected from the list comprising $-NR_x-$ and $-O-$,

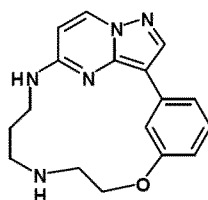
R_x is H or a methyl group,

m and n are each independently 1, 2, 3, or 4,

R_n is H or a methyl group,

with the proviso that said compound is not

- 43 -



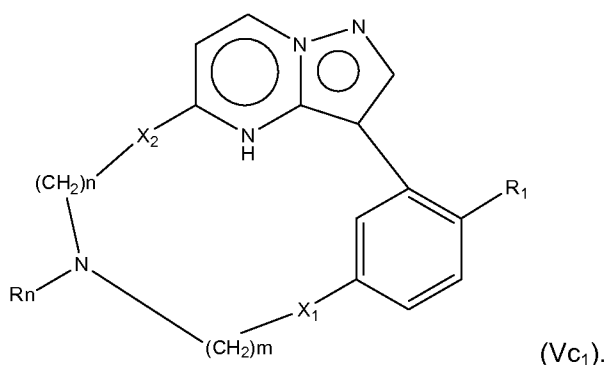
Preferably, R_1 is F.

Preferably m and n are each independently 2, 3 or 4.

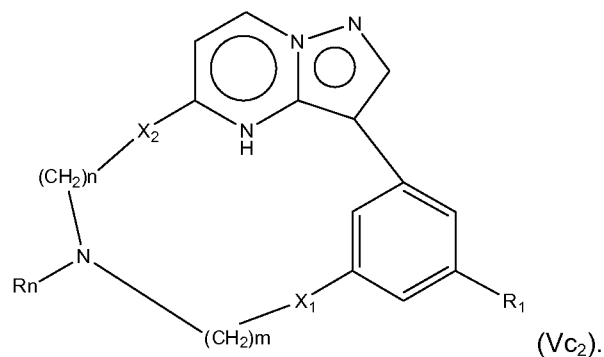
Preferably n is 2 and m is 3. Alternatively, n is 3 and m is 2. Alternatively, n is 4 and m is 3.

5 Alternatively, n is 2 and m is 2.

In a particular embodiment, the present invention provides a compound of formula (Vc₁), wherein R_1 is -F, and X_1 , X_2 , n and m are as defined above

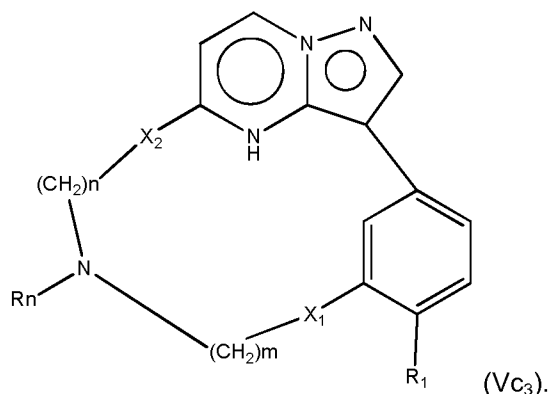


10 In a particular embodiment, the present invention provides a compound of formula (Vc₂), wherein R_1 is -F, and X_1 , X_2 , n and m are as defined above



In another embodiment, the present invention provides a compound of formula (IV₃) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein R_1 is -F, -CH₃ or -CN, and X_1 , X_2 , n and m are as defined above

- 44 -



In another embodiment, the present invention provides a compound of formula (Vc), wherein X₂ is -NR_x-.

5 In another embodiment, the present invention provides a compound of formula (Vc), wherein X₂ is -O-.

In another embodiment, the present invention provides a compound of formula (Vc), wherein X₁ is -NR_x-.

In another embodiment, the present invention provides a compound of formula (Vc), wherein X₁ is -O-.

10 Preferably, X₁ and X₂ are -NR_x-.

The compounds of the present invention can be prepared according to the reaction schemes provided in the examples hereinafter, but those skilled in the art will appreciate that these are only illustrative for the invention and that the compounds of this invention can be prepared by
 15 any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry.

Compounds of formula (I), (IIc), (IIIc), (IVc) and (Vc), a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, are inhibitors of
 20 LRRK2 kinase activity and are thus believed to be of potential use in the prevention and/or treatment of neurological disorders including Parkinson's disease, Alzheimer's disease, dementia (including Lewy body dementia and vascular dementia), age related memory dysfunction, mild cognitive impairment, argyrophilic grain disease, Pick's disease, corticobasal degeneration, progressive supranuclear palsy, inherited frontotemporal dementia and
 25 parkinsonism linked to chromosome 17 (FTDP-17), withdrawal symptoms/relapse associated with drug addiction, L-Dopa induced dyskinesia, and renal, breast, lung, prostate cancers as well as acute myelogenous leukemia (AML).

In the context of the present invention, treatment of Parkinson's disease refers to the treatment of idiopathic Parkinson's disease and familial Parkinson's disease. In one embodiment, familial Parkinson's disease includes patients expressing LRRK2 kinase bearing the G2019S mutation or the R1441G mutation. Treatment of Parkinson's disease may be symptomatic or may be disease modifying. In one embodiment, treatment of Parkinson's disease refers to symptomatic treatment. Compounds of the present invention may also be useful in treating patients identified as susceptible to progression to severe Parkinsonism by means of one of more subtle features associated with disease progression such as family history, olfaction deficits, constipation, cognitive defects, gait or biological indicators of disease progression gained from molecular, biochemical, immunological or Imaging technologies. In this context, treatment may be symptomatic or disease modifying.

In the context of the present invention, treatment of Alzheimer's disease refers to the treatment of idiopathic Alzheimer's disease and familial Alzheimer's disease. Treatment of Alzheimer's disease may be symptomatic or may be disease modifying. In one embodiment, treatment of Alzheimer's disease refers to symptomatic treatment.

Similarly, treatment of dementia (including Lewy body dementia and vascular dementia), age related memory dysfunction, mild cognitive impairment argyrophilic grain disease, Pick's disease, corticobasal degeneration, progressive supranuclear palsy, inherited frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP- 7) and renal, breast, lung, prostate cancers as well as acute myelogenous leukemia (AML) may be symptomatic or disease modifying. In one embodiment, treatment of dementia (including Lewy body dementia and vascular dementia), age related memory dysfunction, mild cognitive impairment, argyrophilic grain disease, Pick's disease, corticobasal degeneration, progressive supranuclear palsy, inherited frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP- 17), and renal, breast, lung, prostate cancers as well as acute myelogenous leukemia (A L) refers to symptomatic treatment.

In the context of the present invention, treatment of withdrawal symptoms/relapse associated with drug addiction and L-Dopa induced dyskinesia refers to symptomatic treatment.

Accordingly, the present invention further provides a method for the prevention and/or treatment of neurological disorders such as but not limited to Parkinson's disease and Alzheimer's disease, said method comprising administering to a subject in need thereof a therapeutic effective amount of a compound or a composition as defined herein. The methods of the present invention can be utilized in a variety of settings, including, for example, in selecting the optimal treatment course for a patient, in predicting the likelihood of success when treating an individual patient with a particular treatment regimen, in assessing disease progression, in monitoring treatment efficacy, in determining prognosis for individual patients and in assessing predisposition of an individual to benefit from a particular therapy.

In the invention, particular preference is given to compounds of Formula I or any subgroup thereof that in the inhibition assay for LRRK2 described below inhibit kinase activity with an IC_{50} value of less than 10 μ M, preferably less than 1 μ M, most preferably less than 100 nM.

5 Said inhibition may be effected *in vitro* and/or *in vivo*, and when effected *in vivo*, is preferably effected in a selective manner, as defined above.

The term "LRRK2 kinase-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which the LRRK2 kinase is known to play a role. The term "LRRK2 kinase-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a LRRK2 kinase inhibitor. Accordingly, another embodiment of
10 the present invention relates to treating or lessening the severity of one or more diseases in which the LRRK2 kinase is known to play a role.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g.
15 obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form of a pro-drug or pre-drug, such as an ester. As used herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates,
20 solvates, etc. and the preparation thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or
25 the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride,
30 hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as
35 dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. In addition, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain

halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl-bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

5 Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation or pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

10 By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms – which may be solid, semi-solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-
15 6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye drops, sterile
20 injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and
25 propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers.
30 In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. In particular, the present invention encompasses a pharmaceutical composition comprising an

effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin.

5 In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration.

10 More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

15 The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

20 It may further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

25 Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

35 The preparations may be prepared in a manner known per se, which usually involves mixing at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-

6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

5 The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 10 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, ocular, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention 15 will generally be administered in an "effective amount", by which is meant any amount of a compound of Formula or any subgroup thereof that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram 20 body weight day of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may 25 be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

30 In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

35 For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers, or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum

arabic, magnesias, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

In preferred embodiments, the compounds and compositions of the invention are used orally or parenterally.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

EXAMPLES

5

A. Compound synthesis and physicochemical properties

The compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry. The compounds are generally prepared from starting materials which are either commercially available or prepared by standard means obvious to those skilled in the art.

For some compounds that were purified by reversed phase high-performance liquid chromatography (HPLC) the used method is described below (indicated in the compound procedure with HPLC method A. When necessary, these methods can be slightly adjusted by a person skilled in the art to obtain a more optimal result for the separation.

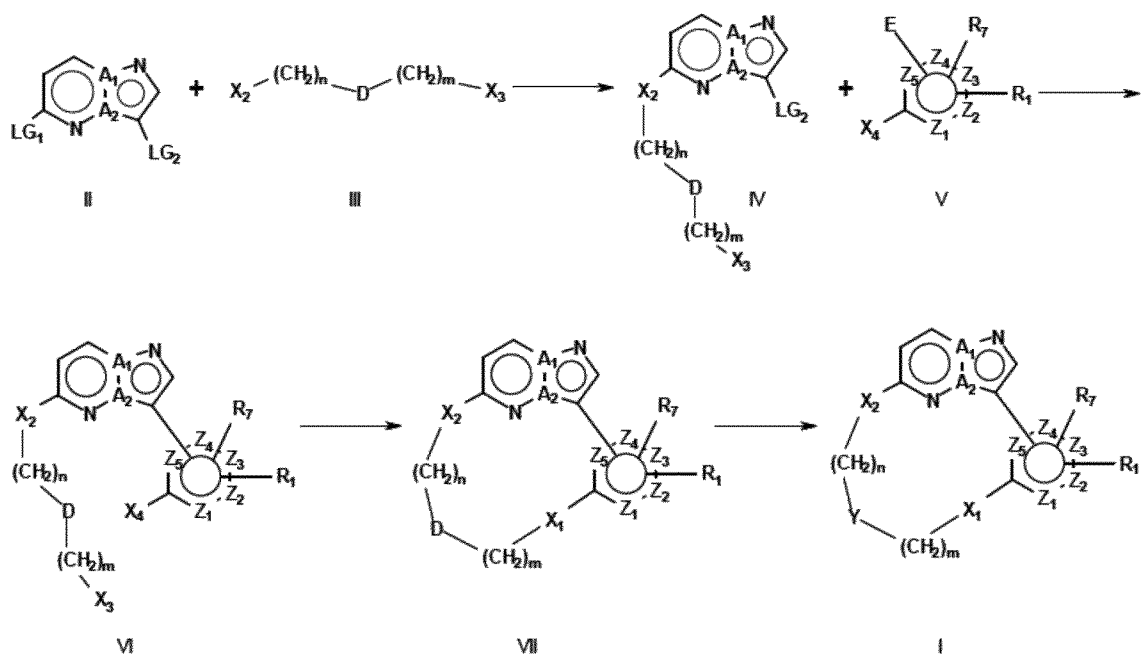
HPLC method A

The crude product was purified by reverse phase HPLC, using a Gilson semi-preparative HPLC system operated by Gilson UNIPPOINT software.

The purification was carried out on a Phenomenex Luna column (100 mm long x 21.2 mm i.d.; 5µm particles) at room temperature, with a constant flow rate of 20.0 mL/min. A gradient elution was performed from 32% (25 mM NH₄HCO₃ aqueous solution) / 68% (Acetonitrile-Methanol 1:1) to 4% (25 mM NH₄HCO₃ aqueous solution) / 96% (Acetonitrile-Methanol 1:1) in 20 minutes. The UV detector was set to 226nm, which corresponds to the wavelength of maximum absorbance observed for the compound.

General schemes:

In general the compounds of formula (I) can be prepared as shown in scheme 1 below wherein a pyrazolo[1,5-a]pyrimidine or a imidazo[2,1-f]pyridazine of formula (II) is converted by reaction with a compound of formula (III) into a compound of formula (IV), which is then reacted with a (hetero-)aryl of formula (V) to form a compound of formula (VI). The compound of formula (VI) can then be optionally deprotected if desired before cyclisation to form a compound of formula (VII). The compound of formula (VII) can be optionally converted into a compound of general formula (I).

Scheme 1

In the above scheme:

5

LG_1 and LG_2 each independently represent suitable leaving or functional groups;

X_3 and X_4 together with the functional moiety to which they are attached represent an unprotected or a protected functional group which upon reaction (after deprotection) produce together X_1 as defined in formula I;

10 E represents a suitable functional group that can be used to form a direct bond between the (hetero-)aryl group and the scaffold.

D represents a functional group such as Y or a protected functional group, which upon further reaction and/or deprotection produces a functional group such as Y as defined in formula I;

15 In the above reaction of the compound of formula (II) with the compound of formula (III) the leaving groups LG_1 and LG_2 are advantageously a halo group such as a chlorine or a bromine group. The reaction can be affected by a substitution for example by treating the compound of formula (II) with the compound of formula (III) in an organic solvent such as acetonitrile with an appropriate base such as for example diisopropylethylamine at an elevated temperature for example under reflux.

20

Compounds of formula (III) can be obtained through various selective protection and deprotection steps. The protection reactions can be effected using for example isoindoline-1,3-dione in a solvent such as toluene at an elevated temperature for example reflux or it can be

effected by using for example benzaldehyde in the presence of a reducing agent for example sodium triacetoxymethylborohydride in a solvent such as 1,2-dichloroethane at room temperature or it can be effected using for example tert-butyldimethylsilyl chloride and triethylamine in a solvent such as N,N-dimethylformamide at room temperature. The deprotection reaction can be effected in a conventional manner using for example hydrazine in a solvent such as ethanol at an elevated temperature for example under reflux.

The compound of formula (IV) can optionally be protected with a suitable protecting group such as a tert-butyloxycarbonylamino group in a conventional manner for example by treatment with tert-butyloxycarbonyl anhydride in basic conditions using for example triethylamine and 4-(dimethylamino)pyridine in a solvent such as tetrahydrofuran at an elevated temperature such as under reflux.

The reaction of the resulting compound (IV) with a (hetero-)aryl compound of formula (V) is advantageously effected through the coupling of a boronic acid E or boronic ester E derivative of the (hetero-)aryl compound under Suzuki conditions using for example tetrakis(triphenylphosphine)palladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) and potassium phosphate tribasic in a solvent mixture such as 1,4-dioxane/water at an elevated temperature for example under reflux.

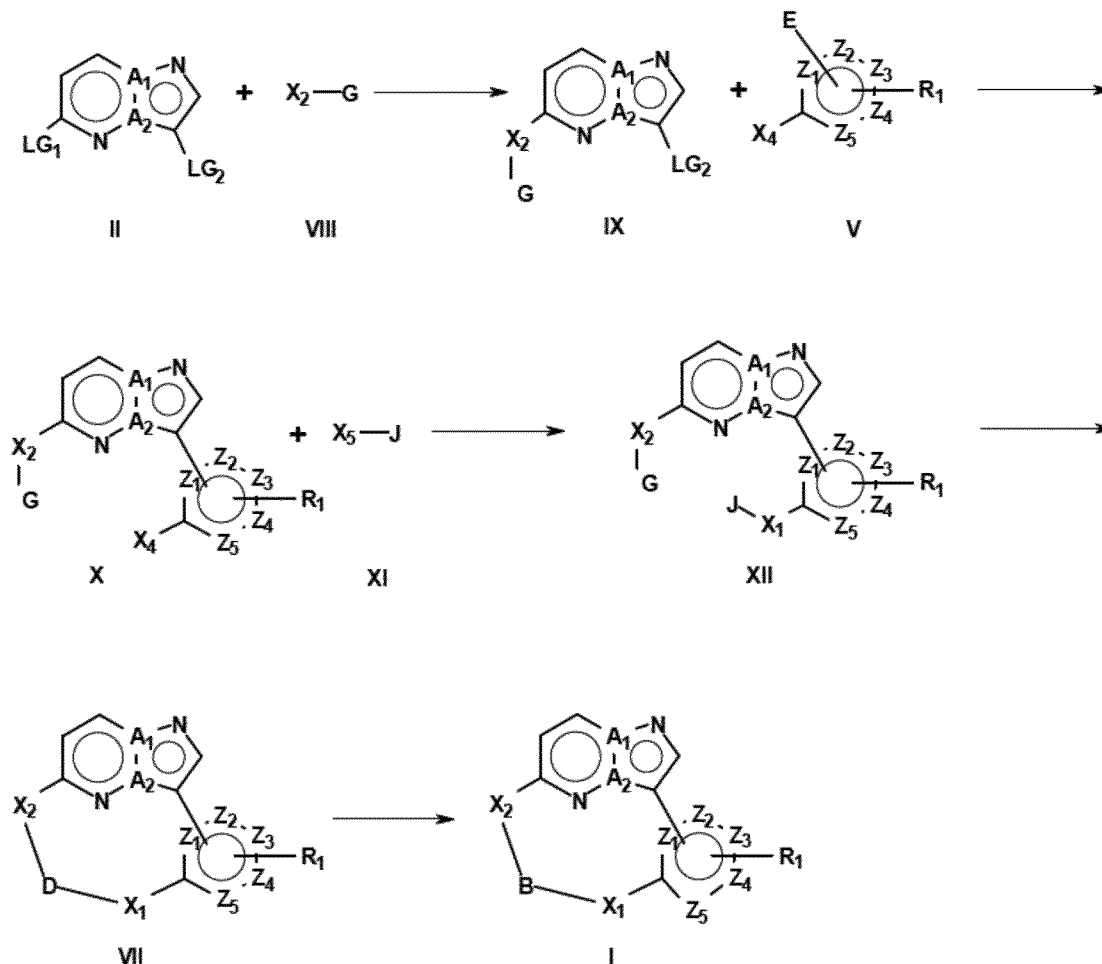
The resulting compound of formula (VI) can optionally be treated to remove any desired protecting groups for example silyl ether groups such as tert-butyldimethylsilyl groups can be converted to the parent free hydroxy group. Such deprotection can be effected in a conventional manner for example using tetrabutylammonium fluoride in tetrahydrofuran at room temperature. The resulting compound of formula (VI) can also optionally be treated to remove any desired protecting groups for example benzyl groups can be removed in a conventional manner for example using hydrogen gas and palladium on activated charcoal (10%) in a solvent such as methanol at a temperature such as room temperature. The compound of formula (VI) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using a 4N acetyl chloride solution in a solvent such as methanol at for example room temperature.

The cyclisation of the compound of formula (VI) can be effected for example under Mitsunobu conditions using for example diisopropyl azodicarboxylate and triphenylphosphine in a solvent mixture such as 2-methyl-1,4-dioxane and toluene at an elevated temperature such as 90°C.

The resulting compound of formula (VII) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using a 4N hydrochloric acid solution in methanol at room temperature.

Compounds C1, C2, D1, D3, D4, D5, G2, G4, G6, G7, G10, G12, G14, G15, G16, G17, G18, G20, G21, G22, G24, G25, G26, G27, G30, G32, G33, G34, G35, G37, G38, G39, G40, G41, G42, G43, G45, G46, G47, G48, G49 and G50 may be prepared according to the synthesis described in Scheme 1.

5

Scheme 2

In the above reaction of the compound of formula (II) with the compound of formula (VIII) the leaving groups LG_1 and LG_2 are advantageously a halo group such as a chlorine or a bromine group. The reaction can be affected by a substitution for example by treating the compound of formula (II) with the compound of formula (VIII) in an organic solvent such as acetonitrile with an appropriate base such as for example diisopropylethylamine at an elevated temperature for example under reflux.

Compounds of formula (VIII) and (XI) can be either commercially acquired or obtained through various selective protection and deprotection steps.

The resulting compound of formula (IX) can optionally be protected with a suitable protecting group such as a tert-butyloxycarbonylamino group in a conventional manner for example by

10

15

treatment with tert-butoxycarbonyl anhydride in basic conditions using for example triethylamine and 4-(dimethylamino)pyridine in a solvent such as tetrahydrofuran at an elevated temperature such as under reflux.

5 The reaction of the resulting compound (IX) with a (hetero-)aryl compound of formula (V) is advantageously effected through the coupling of a boronic acid E or boronic ester E derivative of the (hetero-)aryl compound under Suzuki conditions using for example tetrakis(triphenylphosphine)palladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) and potassium phosphate tribasic in a solvent mixture such as 1,4-dioxane/water at an elevated temperature for example 80°C.

10 The reaction of the resulting compound of formula (X) with a compound of formula (XI) which can be advantageously effected under Williamson conditions using a base such as potassium carbonate in a solvent such as acetonitrile at an elevated temperature such as under reflux. This reaction can also be effected under Mitsunobu conditions using for example diisopropyl azodicarboxylate and triphenylphosphine in a solvent such as tetrahydrofuran at an elevated
15 temperature such as 90°C.

The resulting compound of formula (XII) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group and for example ester groups can be converted to the parent free carboxylic acid groups. Such deprotection can be effected in a conventional manner for
20 example by treatment under acidic conditions for example using an aqueous 6N hydrochloric acid solution in a solvent such as acetonitrile at an elevated temperature for example 60°C or using an acid such as trifluoroacetic acid in a solvent such as dichloromethane at for example room temperature.

The cyclisation of the compound of formula (XII) can be effected for example by treatment with
25 O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and N,N-diisopropylethylamine in a solvent such as N,N-dimethylformamide at for example room temperature. The cyclisation of the compound of formula (XII) can also be advantageously effected under Williamson conditions using a base such as potassium carbonate in a solvent such as acetonitrile at an elevated temperature such as under reflux or at room temperature.
30 This reaction can also be effected under Mitsunobu conditions using for example diisopropyl azodicarboxylate and triphenylphosphine in a solvent such as tetrahydrofuran at an elevated temperature such as 90°C.

The resulting compound of formula (VII) can optionally be treated to form a compound of formula (I).

35

Compounds G1, G3, G8, G11, G13, G19, G23, G28, G31, G36 and G44 may be prepared according to the synthesis described in Scheme 1.

The above general processes are illustrated by the specific processes which are described in the patent applications WO2013/045653 A1 and WO2013/046029 A1.

The process to obtain Example A18 is described in the patent application WO2013/045653.

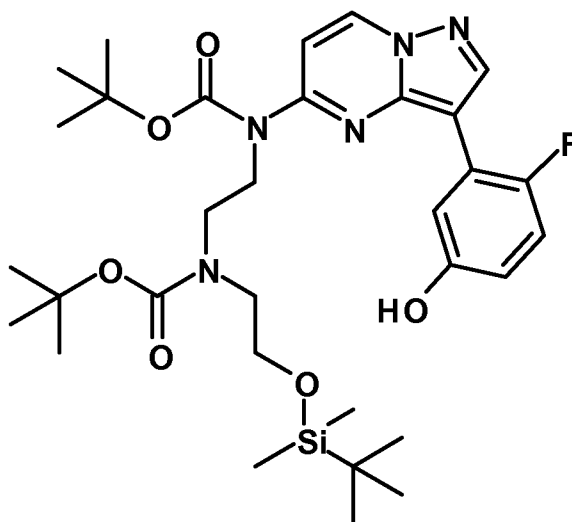
5

Example C1

Example C1 is prepared following general scheme 1.

tert-Butyl N-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)-N-[2-[tert-butoxycarbonyl-[2-(tert-butyl(dimethyl)silyl)oxyethyl]amino]ethyl]carbamate was prepared according to the method described in the patent application WO2013/045653.

Preparation of intermediate 1



15 tert-Butyl N-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)-N-[2-[tert-butoxycarbonyl-[2-(tert-butyl(dimethyl)silyl)oxyethyl]amino]ethyl]carbamate can be prepared according to similar procedures described in the the patent application WO2013/045653 to obtain intermediate 23.

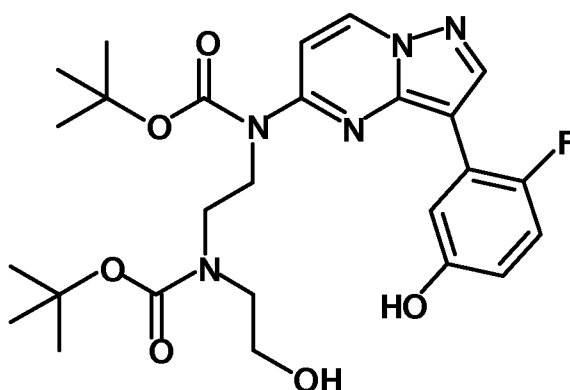
A mixture of 1,4-dioxane and water (3:1, 10,3 ml) was degassed by bubbling nitrogen gas through the mixture. tert-Butyl N-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)-N-[2-[tert-butoxycarbonyl-[2-(tert-butyl(dimethyl)silyl)oxyethyl]amino]ethyl]carbamate (2.11 g, 3.43 mmol), 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.06 g, 4.46 mmol), tris(dibenzylideneacetone)dipalladium(0) (81 mg, 0.07 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (67 mg, 0.14 mmol) and potassium phosphate tribasic (3 eq.) were added and the mixture was stirred under nitrogen gas at 85°C overnight. The reaction mixture was cooled and 1,4-dioxane was removed under reduced pressure. Water was added and the

aqueous layer was extracted with ethyl acetate. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 20% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 950 mg of intermediate 1 (43%)

LCMS method 1: MH^+ = 546 (MW-Boc), RT = 1.585 min

Preparation of intermediate 2

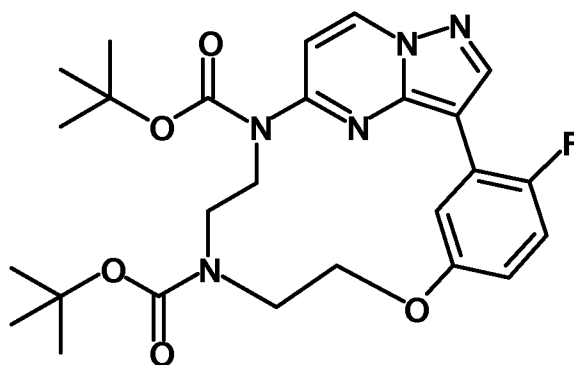


Tetrabutylammonium fluoride (461 mg, 1.76 mmol) was added to a solution of intermediate 1 (950 mg, 1.47 mmol) in tetrahydrofuran (4.41 ml). The reaction mixture was stirred at room temperature for 72 hours. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 70% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 640 mg of intermediate C2 (82%)

LCMS method 1: MH^+ = 532, RT = 1.025 min

Preparation of intermediate 3

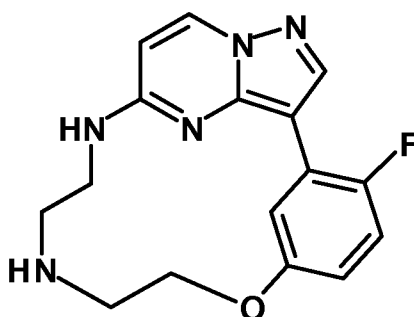


A solution of intermediate 2 (590 mg, 1.11 mmol) in 2-methyltetrahydrofuran (20 ml/mmol) and a solution of diisopropyl azodicarboxylate (660 mg, 3.33 mmol) in toluene (20 ml/mmol) were added drop wise and simultaneously to a solution of triphenylphosphine (873 mg, 3.33 mmol) in toluene (75 ml/mmol). The mixture was stirred at 90°C for 3 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 40% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 573 mg of intermediate 3 (100%)

LCMS method 1: MH^+ = 514, RT = 5.132 min

Preparation of example C1



Intermediate 3 (523 mg, 1.02 mmol) was dissolved in 4N hydrochloric acid in methanol (3 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. Toluene was added and removed under reduced pressure (2 times). The compound was obtained as the hydrochloride salt.

Yield: 145 mg of example C1 (41%)

LCMS method 2: MH^+ = 314, RT = 1.971 min

Example C2

Example C2 was prepared according to the general scheme 1 and more in particular to the methods described to obtain example C1.

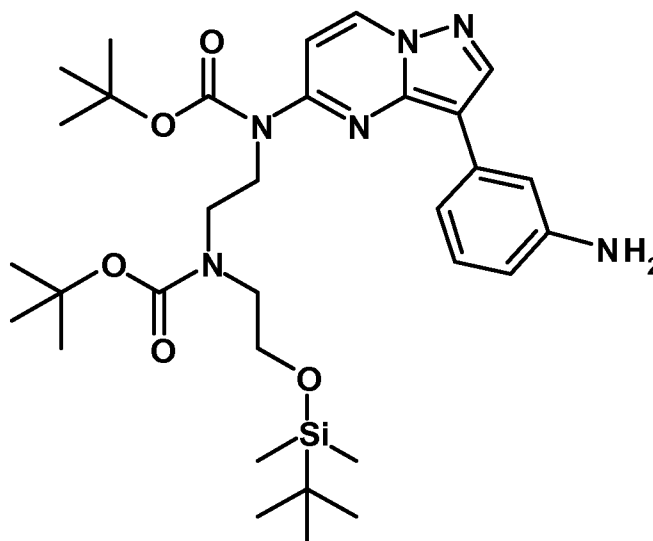
5

Example D1

Example D1 is prepared following general scheme 1.

Preparation of intermediate 4

10



15 A mixture of 1,4-dioxane and water (3:1, 68,46 ml) was degassed by bubbling nitrogen gas through the mixture. tert-Butyl N-(3-bromopyrazolo[1,5-a]pyrimidin-5-yl)-N-[2-[tert-butoxycarbonyl-2-(tert-butyl(dimethyl)silyl)oxyethyl]amino]ethyl]carbamate (14.025 g, 22.82 mmol), (3-aminophenyl)boronic acid hydrate (4.60 g, 29.67 mmol), tris(dibenzylideneacetone)dipalladium(0) (533 mg, 0.46 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (872 mg, 1.83 mmol) and potassium phosphate tribasic (3 eq.)
20 were added and the mixture was stirred under nitrogen gas at 85°C for 4 hours. The reaction mixture was cooled and 1,4-dioxane was removed under reduced pressure. Water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient

- 60 -

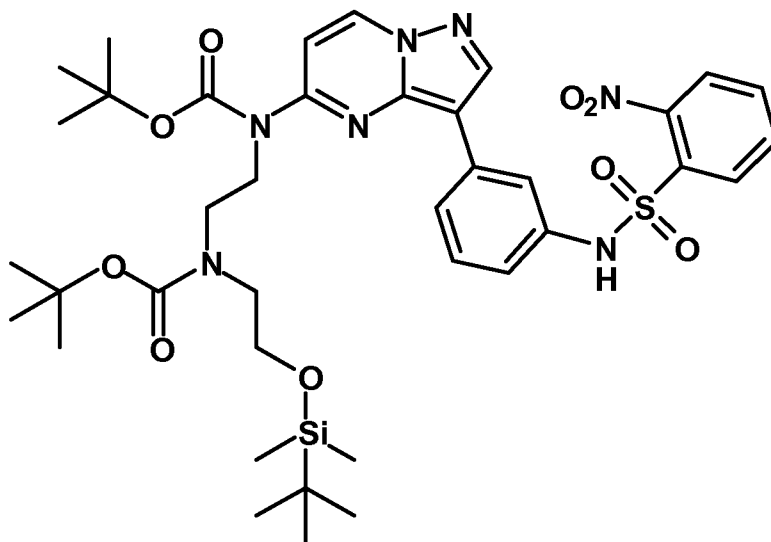
elution from 0% to 60% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 13.741 g of intermediate 4 (96%)

LCMS method 1: $MH^+ = 527$ (MH^+ -Boc), $RT = 1.488$ min

5

Preparation of intermediate 5



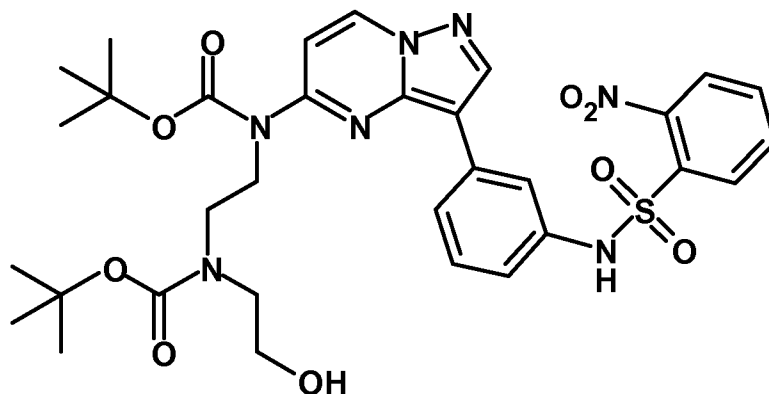
2-Nitrobenzenesulfonyl chloride (6.90 g, 31.14 mmol) was added portion wise at 0°C and under nitrogen atmosphere to a solution of intermediate 4 (13.013 g, 20.76 mmol), triethylamine (4.617 ml, 33.22 mmol) and 4-(dimethylamino)pyridine (127 mg, 1.04 mmol) in dichloromethane (62.28 ml). The reaction mixture was stirred overnight allowing it to reach room temperature. The solvent was removed under reduced pressure. Ethyl acetate was added and the organic layer was washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 80% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 16.85 g of intermediate 5 (100%)

LCMS method 1: $MH^+ = 713$ (MH^+ -Boc), $RT = 1.544$ min

20

Preparation of intermediate 6

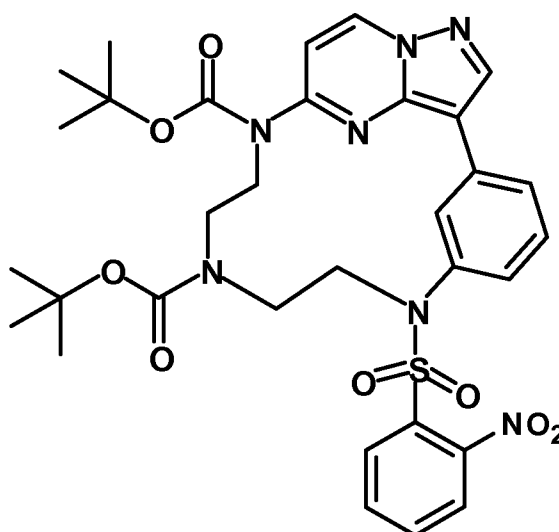


Tetrabutylammonium fluoride (4.39 g, 15.12 mmol) was added to a solution of intermediate 5 (8.184 g, 10.08 mmol) in tetrahydrofuran (30.24 ml). The reaction mixture was stirred at room temperature overnight. More tetrabutylammonium fluoride (2.93 g, 10.08 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 70% ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 3.78 g of intermediate 6 (54%)

LCMS method 1: $MH^+ = 598$ ($MH^+ - Boc$), RT = 1.073 min

Preparation of intermediate 7



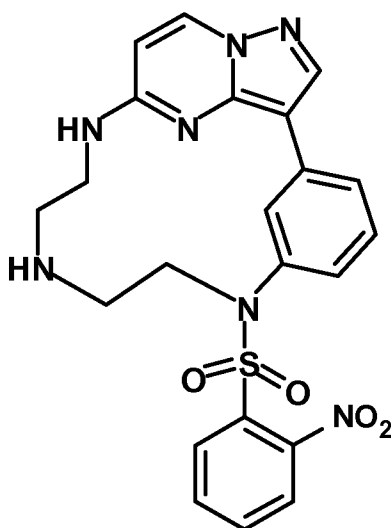
A solution of intermediate 6 (6.25 g, 8.96 mmol) in 2-methyltetrahydrofuran (20 ml/mmol) and a solution of diisopropyl azodicarboxylate (5.40 g, 26.88 mmol) in toluene (20 ml/mmol) were added drop wise and simultaneously to a solution of triphenylphosphine (7.05 g, 26.88 mmol) in

toluene (75 ml/mmol). The mixture was stirred at 90°C for 3 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0% to 70% ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 3.02 g of intermediate 7 (50%)

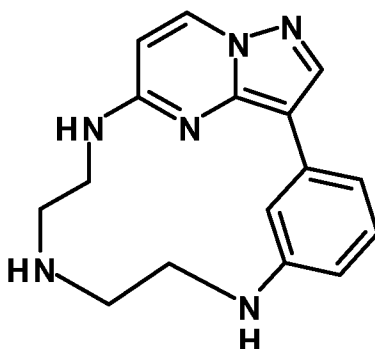
LCMS method 1: MH^+ = 680, RT = 1.348 min

Preparation of intermediate 8



Intermediate 7 (3.02 g, 4.44 mmol) was dissolved in 4N hydrochloric acid in methanol (13.32 ml). The mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the residue was used in the next step without further purification.

Preparation of example D1



Intermediate 8 (150 mg, 0.29 mmol) and cesium carbonate (377 mg, 1.16 mmol) were suspended in N,N-dimethylformamide (0.87 ml). Thiophenol (40 μ l, 0.35 mmol) was added and the mixture was stirred at room temperature for 18 hours. Sodium hydroxide was added and the solvent was removed under reduce pressure. The residue was suspended in a mixture of dichloromethane and methanol and filtered. The product was purified by reversed phase column chromatography (HPLC method A). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 25 mg of example D1 (29%)

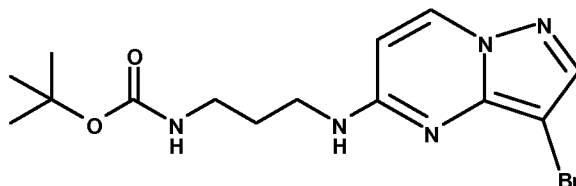
LCMS method 2: MH^+ = 295, RT = 1.753 min

Examples D3, D4 and D5 may be prepared according to the synthesis as described above.

Example G1

Example G1 is prepared following general scheme 2.

Preparation of intermediate 9

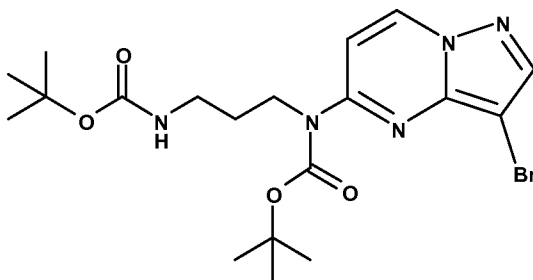


A mixture of 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine (6.0 g, 25.812 mmol), tert-butyl N-(3-aminopropyl)carbamate (4.95 g, 28.39 mmol) and N,N-diisopropylethylamine (5.27 ml, 30.97 mmol) in acetonitrile (77 ml) was refluxed for 4 hours. More tert-butyl N-(3-aminopropyl)carbamate (450 mg, 2.58 mmol) was added and the reaction mixture was refluxed overnight. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 20 % to 100 % of ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 6.99 g of intermediate 9 (73%)

LCMS method 1: MH^+ = 371, RT = 0.792 min

Preparation of intermediate 10

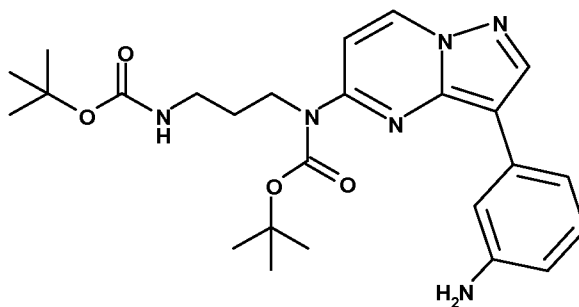


A mixture of intermediate 9 (14.43 g, 38.97 mmol) in tetrahydrofuran (117 ml) were added tert-butoxycarbonyl anhydride (8.93 g, 40.92 mmol), triethylamine (6 ml, 42.87 mmol) and 4-(dimethylamino)pyridine (238 mg, 1.95 mmol) was stirred under reflux overnight. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0 % to 33 % of ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 14.53 g of intermediate 10 (79%)

LCMS method 1: $MH^+ = 494$, RT = 1.184 min

Preparation of intermediate 11



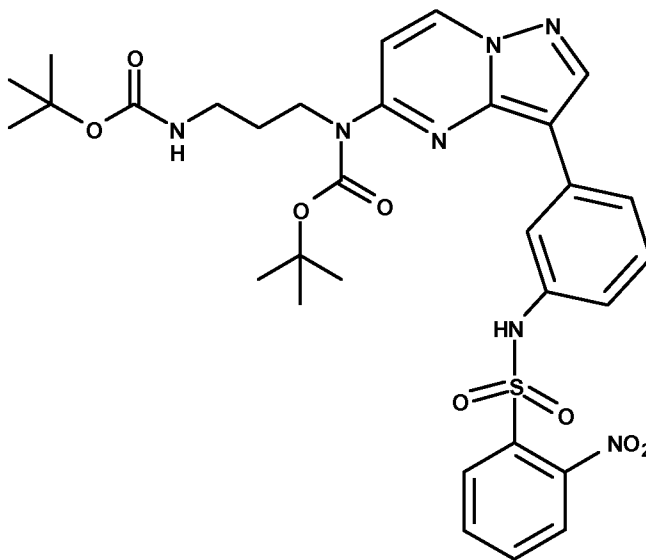
15

A mixture of 1,4-dioxane and water (3:1, 53 ml) was degassed by bubbling nitrogen gas through the mixture. Intermediate 10 (4.00 g, 8.50 mmol), (3-aminophenyl)boronic acid (1.71 g, 11.05 mmol), tetrakis(triphenylphosphine)palladium(0) (197 mg, 0.17 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (162 mg, 0.34 mmol) and potassium phosphate tribasic (5.41 g, 3 eq.) were added and the mixture was stirred under nitrogen gas at 80°C for 5 hours. The reaction mixture was cooled, diluted with ethyl acetate and the organic layer was washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 20 % to 100 % of ethyl

acetate). The product fractions were collected and the solvent was removed under reduced pressure.

LCMS method 1: MH^+ = 483, RT = 1.492 min

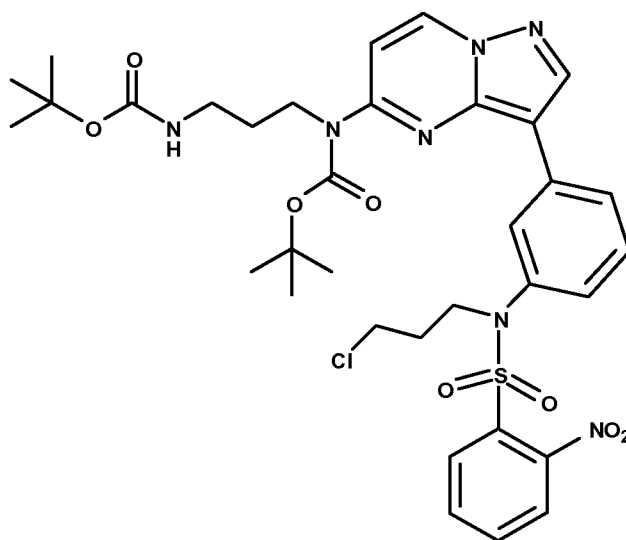
5 Preparation of intermediate 12



2-Nitrobenzenesulfonyl chloride (3.24 g, 14.61 mmol) was added to a solution of intermediate 11 (4.70 g, 9.74 mmol) and triethylamine (4 ml, 29.22 mmol) in dichloromethane (50 ml). 4-Dimethylaminopyridine (60 mg, 0.49 mmol) was added and the reaction mixture was stirred at room temperature overnight. More 2-nitrobenzenesulfonyl chloride (716 mg, 3.23 mmol) was added and the mixture was stirred at room temperature for 2 days. The crude reaction mixture was diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate solution and water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0 % to 50 % of ethyl acetate). The product fractions were collected and the solvent was evaporated.

Yield: 4.40 g of intermediate 12 (68%)

Preparation of intermediate 13

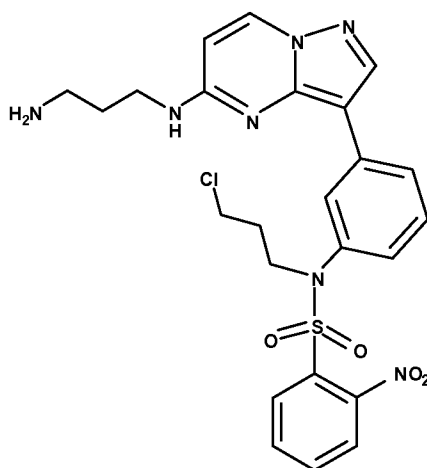


A mixture of intermediate 12 (4.40 g, 6.59 mmol), cesium carbonate (5.37 g, 16.48 mmol) and 1-bromo-3-chloro-propane (1.31 ml, 13.18 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature overnight. More 1-bromo-3-chloro-propane (650 μ l, 6.59 mmol) and cesium carbonate (1.15 g, 6.59 mmol) were added and the reaction mixture was stirred at 75°C overnight. The reaction mixture was cooled and concentrated under reduced pressure. The residue was diluted with ethyl acetate and the organic layer was washed with water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The product was used in the next step without further purification.

Yield: 1.82 g of intermediate 13 (37%)

LCMS method 1: MH^+ = 644 (MW – Boc), RT = 1.278 min

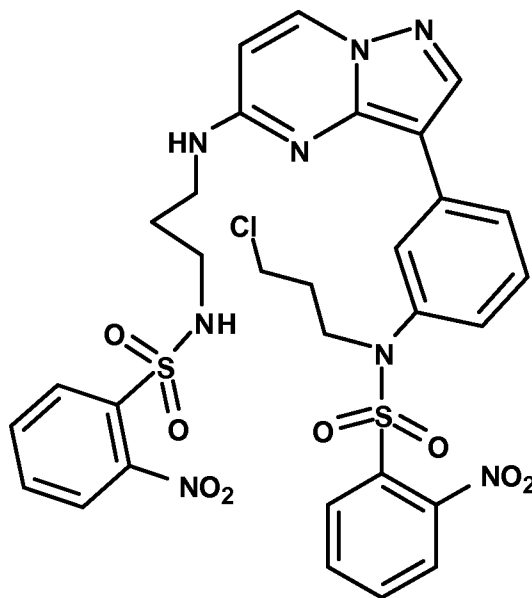
Preparation of intermediate 14



Intermediate 13 (1.82 g, 2.45 mmol) was dissolved in 4N hydrochloric acid in methanol (7.35 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The compound was obtained as the hydrochloride salt and was used in the next step without further purification.

5

Preparation of intermediate 15



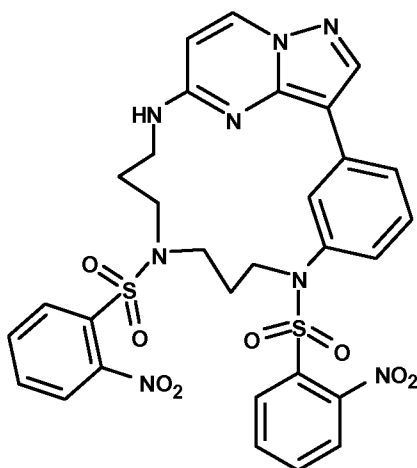
2-Nitrobenzenesulfonyl chloride (0.60 g, 2.69 mmol) was dissolved in N,N-dimethylacetamide (2 ml) and added drop wise at 0°C to a stirred solution of intermediate 14 (2.45 mmol) and triethylamine (1.70 ml, 12.25 mmol) in N,N-dimethylacetamide (5.35 ml). The reaction mixture was stirred at 0°C for 1 hour. The crude reaction mixture was diluted with dichloromethane and washed with water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents. The product fractions were collected and the solvent was evaporated.

Yield: 1.618 g of intermediate 15 (91%)

LCMS method 1: MH^+ = 730, RT = 1.844 min

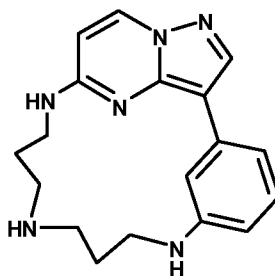
Preparation of intermediate 16

- 68 -



To a stirred suspension of cesium carbonate (3.61 g, 11.10 mmol) in N,N-dimethylformamide (56 ml) was added drop wise at 90°C a solution of intermediate 15 (1.618 g, 2.22 mmol) in N,N-dimethylformamide (166 ml). The reaction mixture was stirred at 90°C for 1 hour. The solvent
5 was removed under reduced pressure. The product was used in the next step without further purification.

Preparation of example G1

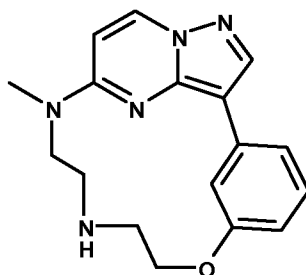


10

Intermediate 16 (2.22 mmol) and cesium carbonate (2.886 g, 8.88 mmol) were suspended in N,N-dimethylformamide (6.7 ml). Thiophenol (500 μ l, 4.88 mmol) was added and the mixture was stirred at room temperature for 2 hours. Tert-butoxycarbonyl anhydride (1.06 g, 2.20 mmol) was added and the mixture was stirred at room temperature for 4 hours. The reaction mixture
15 was diluted with ethyl acetate and washed with brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was dissolved in 4N hydrochloric acid in methanol (10 ml). The mixture was stirred at room temperature for 1 hour. The solid was filtered and washed with diethyl ether and methanol. The product was obtained as the HCl salt.

20 Yield: 0.470 g of example G1 (82%)

LCMS method 1: MH^+ = 323, RT = 0.416 min

Example G2

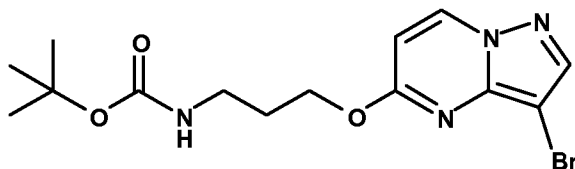
Example G2 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G3

Example G3 is prepared following general scheme 2.

10 Preparation of intermediate 17

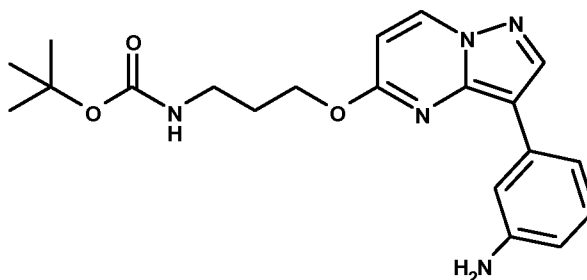


Sodium hydride (60% in mineral oil, 2.58 g, 64.53 mmol) and tert-butyl N-(3-hydroxypropyl)carbamate (30.15 g, 172.08 mmol) were dissolved in anhydrous tetrahydrofuran and stirred at room temperature for 30 minutes. 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine (10.00 g, 43.02 mmol) was added portion wise and the reaction mixture was stirred at room temperature for 1 hour. Water was added and the tetrahydrofuran was removed under reduced pressure. The residue was diluted with dichloromethane and washed with water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 10 % to 80 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure. The product was triturated with diethyl ether, filtered and dried under reduced pressure.

15 Yield: 14.06 g of intermediate 17 (88%)

25 LCMS method 2: MH^+ = 315, RT = 3.401 min

Preparation of intermediate 18

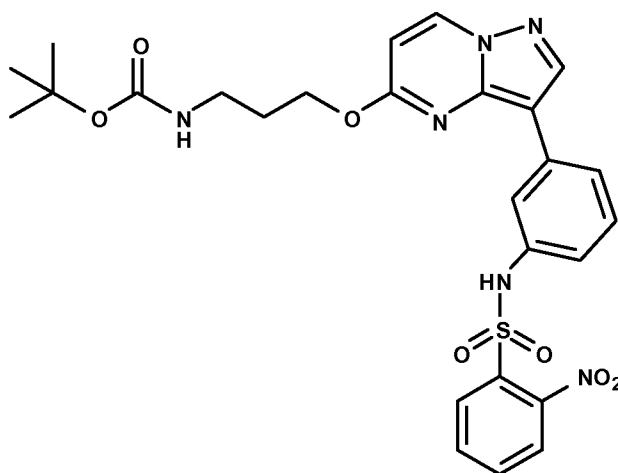


- 5 A mixture of 1,4-dioxane and water (3:1, 65 ml) was degassed by bubbling nitrogen gas through the mixture. Intermediate 17 (4.00 g, 10.77 mmol), (3-aminophenyl)boronic acid (2.17 g, 14.00 mmol), tetrakis(triphenylphosphine)palladium(0) (255 mg, 0.22 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (205 mg, 0.43 mmol) and potassium phosphate tribasic (85 g, 3 eq.) were added and the mixture was stirred under nitrogen gas at 80°C for 3 hours. The reaction mixture was cooled, diluted with ethyl acetate and the organic layer was washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 30 % to 100 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.
- 10
- 15

Yield: 3.12 g of intermediate 18 (76%)

LCMS method 1: MH^+ = 384, RT = 1.012 min

Preparation of intermediate 19



20

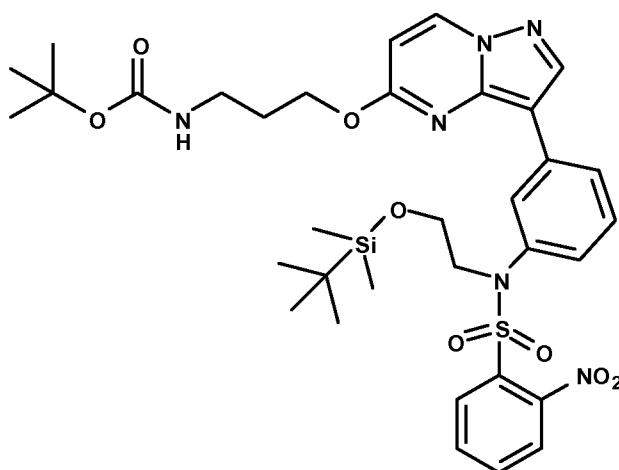
2-Nitrobenzenesulfonyl chloride (3.38 g, 15.52 mmol) was added portion wise to a solution of intermediate 18 (3.90 g, 10.17 mmol) and triethylamine (4.24 ml, 30.51 mmol) in

- 71 -

dichloromethane (42 ml). 4-Dimethylaminopyridine (62 mg, 0.51 mmol) was added and the reaction mixture was stirred at room for 18 hours. The reaction mixture was diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate solution and water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0 % to 40 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 5.71 g of intermediate 19 (99%)

Preparation of intermediate 20

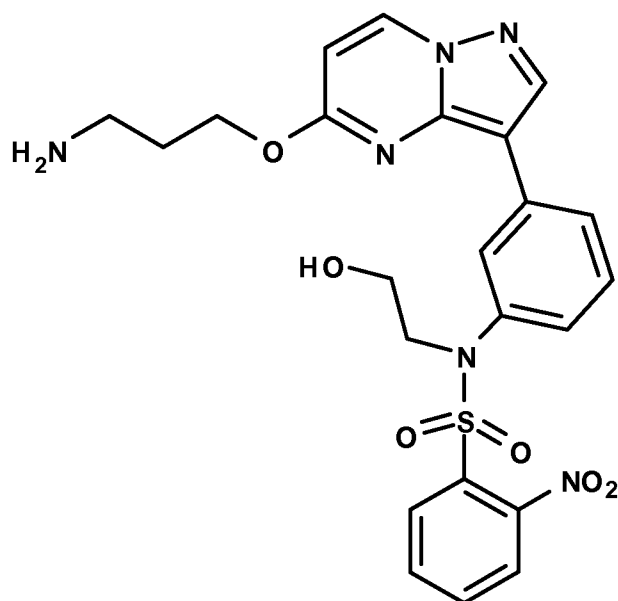


2-Bromoethoxy-tert-butyl-dimethyl-silane (360 mg, 1.68 mmol) was added to a mixture of intermediate 19 (716 mg, 1.53 mmol) and cesium carbonate (600 mg, 1.84 mmol) in N,N-dimethylformamide (4.6 ml). The reaction mixture was stirred at 75°C overnight. The reaction mixture was cooled and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 10 % to 60 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 560 mg of intermediate 20 (58%)

LCMS method 2: MH^+ = 627, RT = 4.960 min

Preparation of intermediate 21

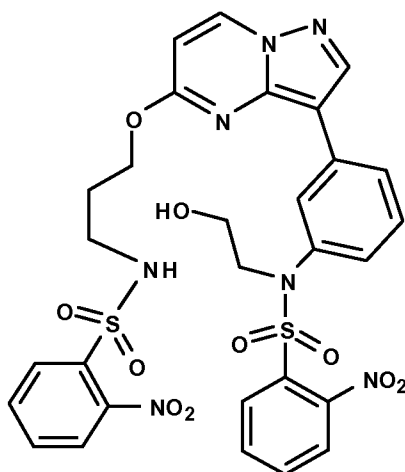


- 5 Intermediate 20 (3.42 g, 4.70 mmol) was dissolved in 4N hydrochloric acid in methanol (14.1 ml). The mixture was stirred at room temperature for overnight. The solvent was removed under reduced pressure, toluene was added twice and removed twice under reduced pressure. The residue was used in the next step without further purification.

LCMS method 2: MH^+ = 513, RT = 2.276 min

10

Preparation of intermediate 22



- 15 2-Nitrobenzenesulfonyl chloride (510 mg, 2.29 mmol) dissolved in N,N-dimethylacetamide (8.2 ml) was added at 0°C to a solution of intermediate 21 (2.29 mmol) and triethylamine (1.592 ml,

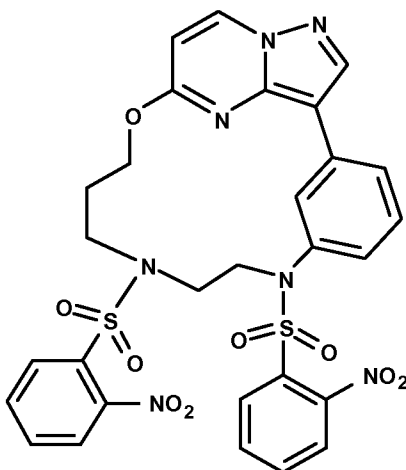
- 73 -

11.45 mmol) in N,N-dimethylacetamide (6.9 ml). The reaction mixture was stirred at 0°C for 1 hour. More triethylamine (1.0 ml, 7.19 mmol) was added and the mixture was stirred at room temperature overnight. The crude mixture was diluted with ethyl acetate and washed with water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 30 % to 80 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 1.40 g of intermediate 22 (88%)

LCMS method 1: MH^+ = 698, RT = 2.011 min

Preparation of intermediate 23



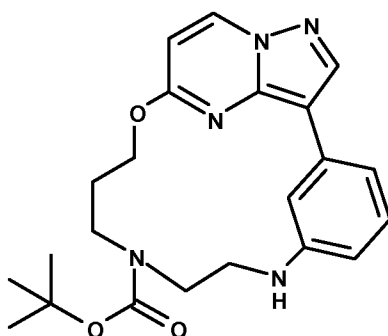
A solution of intermediate 22 (1.40 g, 2.01 mmol) in 2-methyltetrahydrofuran (20 ml/mmol) was degassed by bubbling nitrogen gas through the mixture. A degassed solution of diisopropyl azodicarboxylate (1.20 g, 6.03 mmol) in toluene (20 ml/mmol) was added drop wise at 90°C and simultaneously to a degassed solution of triphenylphosphine (1.582 g, 6.03 mmol) in toluene (75 ml/mmol). The mixture was stirred at 90°C for 30 minutes. The reaction mixture was cooled and the solvent was removed under reduced pressure. Methanol was added, the solid was filtered and washed with diethyl ether. The residue was dried under reduced pressure and without further purification used in the next step.

Yield: 1.05 g of intermediate 23 (77%)

LCMS method 2: MH^+ = 680, RT = 3.810 min

Preparation of intermediate 24

- 74 -

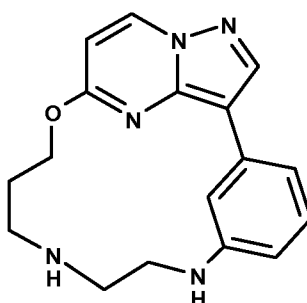


Intermediate 23 (1.05 g, 1.54 mmol) and cesium carbonate (2.00 g, 6.16 mmol) were suspended in N,N-dimethylformamide (4.6 ml). Thiophenol (350 μ l, 3.39 mmol) was added and the mixture was stirred at room temperature overnight. Tert-butoxycarbonyl anhydride (740 mg, 3.39 mmol) was added and the mixture was stirred at room temperature for 4 hours. An aqueous solution of 1N sodium hydroxide was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 30 % to 80 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

Yield: 392 mg of intermediate 24 (62%)

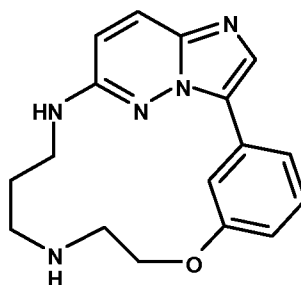
LCMS method 2: MH^+ = 410, RT = 3.502 min

Preparation of example G3



Intermediate 24 (392 mg, 0.96 mmol) was dissolved in 4N hydrochloric acid in dioxane (2.88 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, toluene was added twice and removed twice under reduced pressure. The product was obtained as the HCl salt.

LCMS method 2: MH^+ = 310, RT = 1.940 min

Example G4

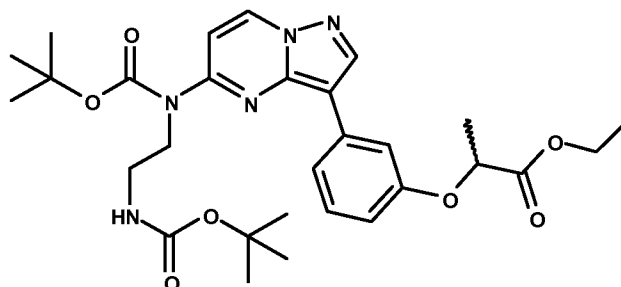
Example G4 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G5

Example G5 may be prepared following general scheme 2.

Preparation of intermediate 25



10

Tert-butyl N-[2-(tert-butoxycarbonylamino)ethyl]-N-[3-(3-hydroxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl]carbamate is prepared according to the method described in the patent application WO2013/0460029. A mixture of tert-butyl N-[2-(tert-butoxycarbonylamino)ethyl]-N-[3-(3-hydroxyphenyl)pyrazolo[1,5-a]pyrimidin-5-yl]carbamate (1.65 g, 3.51 mmol), ethyl 2-bromopropanoate (690 μ l, 5.26 mmol) and potassium carbonate (970 mg, 7.02 mmol) in N,N-dimethylformamide (10.5 ml) was stirred at 80°C for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using heptane and ethyl acetate as eluents (gradient elution from 0 % to 50 % of ethyl acetate). The product fractions were collected and the solvent was removed under reduced pressure.

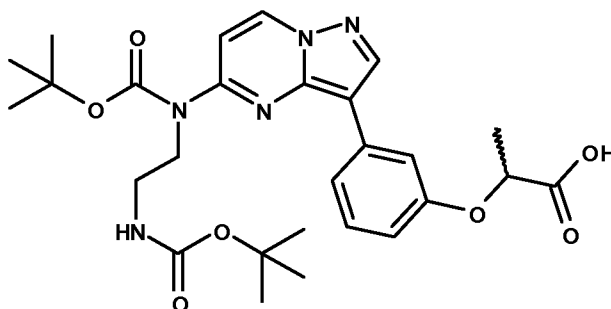
15

20

Yield: 1,60 g of intermediate 25 (80%)

LCMS method 1: $MH^+ = 470$ ($=MH^+ - Boc$), RT = 1.320 min

Preparation of intermediate 26

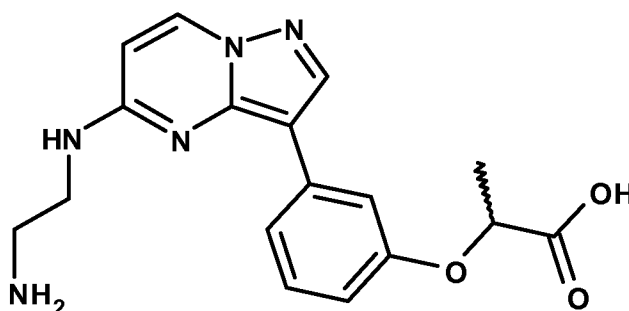


- 5 Intermediate 25 (1.60 g, 2.81 mmol) was dissolved in a mixture of tetrahydrofuran, methanol and water (2;2;1, 8.43 ml) and lithium hydroxide monohydrate (340 mg, 8.43 mmol) was added. The reaction mixture was stirred at 50°C for 4 hours. The solvent was removed under reduced pressure and the residue was used in the next step without further purification.

LCMS method 1: $MH^+ = 542$, RT = 1.129 min

10

Preparation of intermediate 27



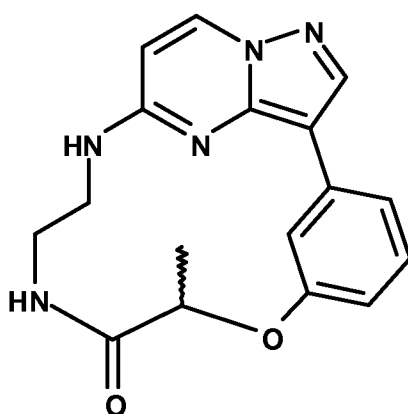
15

Intermediate 26 (2.81 mmol) was dissolved in 4N hydrochloric acid in dioxane (8.43 ml). The mixture was stirred at room temperature for 72 hours. The solvent was removed under reduced pressure, toluene was added twice and removed twice under reduced pressure. The product was obtained as the HCl salt.

20

LCMS method 1: $MH^+ = 342$, RT = 0.391 min

Preparation of intermediate 28



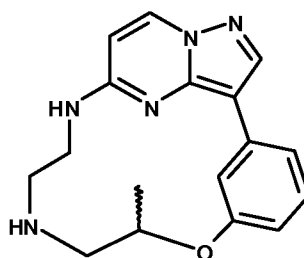
A solution of intermediate 27 (2.81 mmol) and N,N-diisopropylethylamine (2.4 ml, 5 eq.) in N,N-dimethylformamide (93 ml) was added drop wise to a solution O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (3.21 g, 8.43 mmol) and N,N'-diisopropylmethanediiimine (4.9 ml, 10 eq.) in N,N-dimethylformamide (188 ml). The reaction mixture was stirred at room temperature for 1 hour after the addition was completed. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using dichloromethane and methanol as eluents (gradient elution from 2 % to 10 % of methanol). The product fractions were collected and the solvent was evaporated. The residue was purified by reversed phase column chromatography (HPLC method A).

Yield: 150 mg of intermediate 28 (17%)

LCMS method 2: $MH^+ = 324$, RT = 2.126 min

15

Preparation of example G5



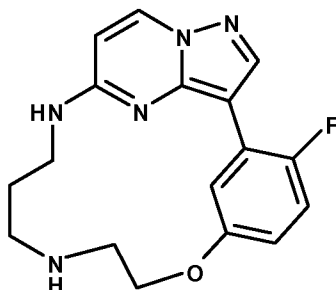
Intermediate 28 (130 mg, 0.4 mmol) was dissolved in 2N borane dimethylsulfide in tetrahydrofuran (1 ml). The reaction mixture was stirred at room temperature for 18 hours. More 2N borane dimethylsulfide in tetrahydrofuran (0.5 ml) was added. The reaction mixture was stirred at room temperature for 24 hours. An aqueous 2N hydrochloric acid solution was added and the reaction mixture was stirred at 100°C for 1 hour. The reaction mixture was neutralized to pH 7 with a saturated aqueous sodium bicarbonate solution. The product was extracted with

a mixture of dichloromethane and methanol (9:1). The solvent of the organic layer was removed under reduced pressure. The residue was purified by reversed phase column chromatography (HPLC method A).

Yield: 14 mg of example G5 (1%)

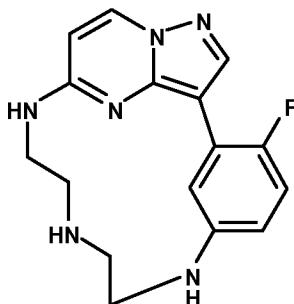
- 5 LCMS method 2: MH^+ = 310, RT = 1.990 min

Example G6



- 10 Example G6 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

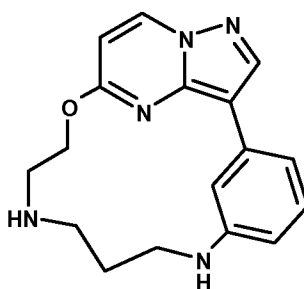
Example G7



- 15 Example G7 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

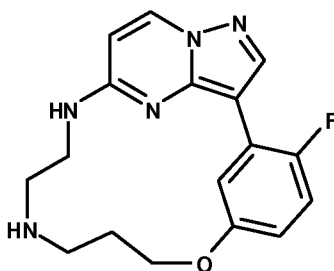
Example G8

- 79 -



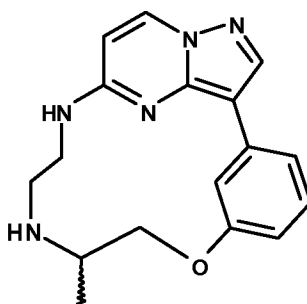
Example G8 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G3.

5 Example G10



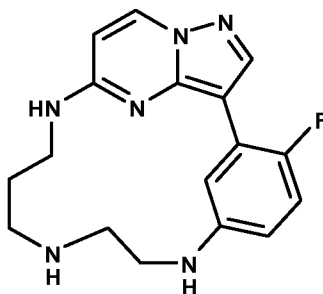
Example G10 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

10 Example G11



Example G11 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G5.

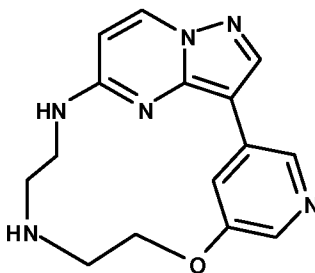
Example G12



Example G12 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

5

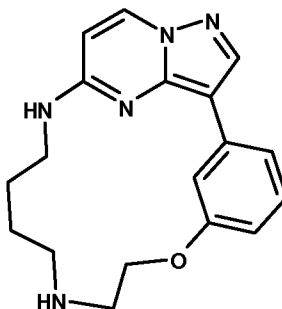
Example G13



Example G13 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G5.

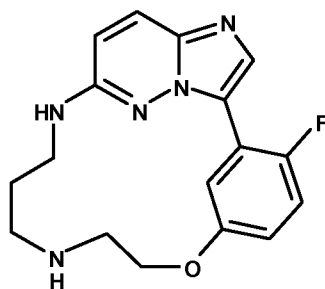
10

Example G14



Example G14 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

15

Example G15

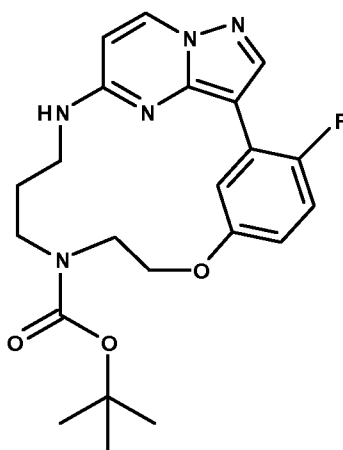
Example G15 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G16

Example G16 may be prepared following general scheme 1.

Preparation of intermediate 29



10

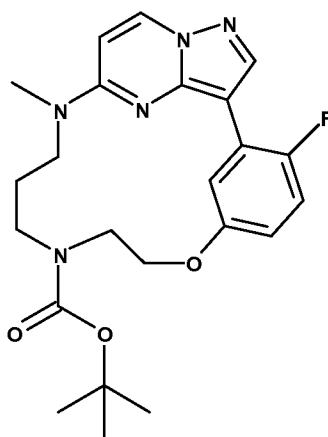
Example G6 (HCl salt, 400 mg, 1.10 mmol) and triethylamine (306 μ l, 2.20 mmol) were suspended in tetrahydrofuran (3.3 ml). tert-Butoxycarbonyl anhydride (0.38 g, 1.65 mmol) was added and the mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using dichloromethane and methanol as eluents (gradient elution from 0 % to 3 % of methanol). The product fractions were collected and the solvent was evaporated.

15

Yield: 389 mg of intermediate 29 (83%)

LCMS method 1: $MH^+ = 428$, RT = 1.084 min

Preparation of intermediate 30

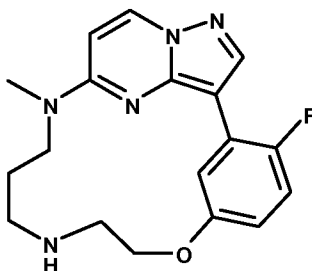


Sodium hydride (60% in mineral oil, 180 mg, 4.60 mmol) was added in one portion to a solution of intermediate 29 (460 mg, 0.195 mmol) in anhydrous N,N-dimethylformamide (5 ml). The mixture was stirred at room temperature for 50 minutes. Methyl iodide (33 μ l, 0.53 mmol) was added and the mixture was stirred at room temperature for 2 hours. More methyl iodide (0.2 eq) was added and the mixture was stirred at room temperature for 90 minutes. More sodium hydride (60% in mineral oil, 180 mg, 4.60 mmol) and methyl iodide (33 μ l, 0.53 mmol) were added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into a cold saturated aqueous ammonium chloride solution and the product was extracted with ethyl acetate. The combined organic layers were dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using dichloromethane and methanol as eluents (gradient elution from 0 % to 2 % of methanol). The product fractions were collected and the solvent was evaporated.

Yield: 133 mg of intermediate 30 (65%)

LCMS method 2: $MH^+ = 442$, RT = 4.471 min

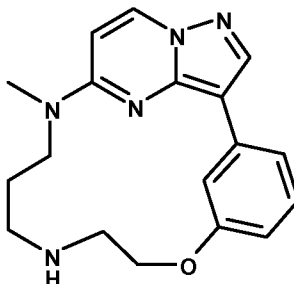
Preparation of example G16



Intermediate 30 (133 mg, 0.30 mmol) was dissolved in 4N hydrochloric acid in dioxane (0.90 ml). The mixture was stirred at 50°C for 2 hours. The solvent was removed under reduced pressure, diethyl ether was added twice and removed twice under reduced pressure. The product was dried at 55°C under reduced pressure. The product was obtained as the HCl salt.

Yield: 112 mg of example G16 (99%)

LCMS method 2: MH^+ = 342, RT = 1.907 min

10 Example G17

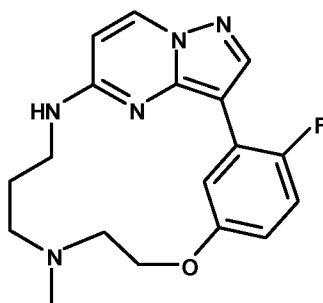
Example G17 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G16.

15 Example G18

Example G18 may be prepared following general scheme 1.

Preparation of example G18

- 84 -



Example G6 (157 mg, 0.48 mmol) and formaldehyde (37% aqueous solution) were suspended in a mixture of dichloromethane/methanol (1:1, 1.44 ml) and the mixture was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (203 mg, 0.96 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 16 hours. Ethyl acetate was added and the organic layer was washed with a saturated sodium bicarbonate solution and brine. The organic layer was dried and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography over silica gel using dichloromethane and methanol as eluents (gradient elution from 0 % to 5 % of methanol). The product fractions were collected and the solvent was evaporated.

Yield: 119 mg of example G18 (73%)

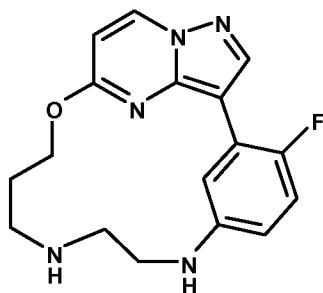
LCMS method 2: MH^+ = 342, RT = 1.865 min

Example G18 (119 mg, 0.35 mmol) was dissolved in a mixture of dichloromethane/methanol (4:1, 1.05 ml) and 4N hydrochloric acid in dioxane (0.13 ml, 0.52 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, diethyl ether was added twice and removed twice under reduced pressure. The product was dried at 60°C under reduced pressure for 8 hours. The product was obtained as the HCl salt.

Yield: 117 mg of example G18 as HCl salt (883%)

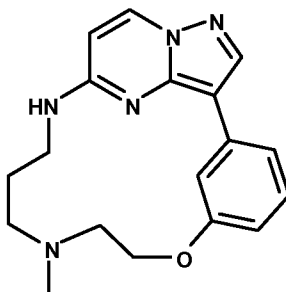
LCMS method 2: MH^+ = 342, RT = 1.853 min

Example G19



Example G19 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G3.

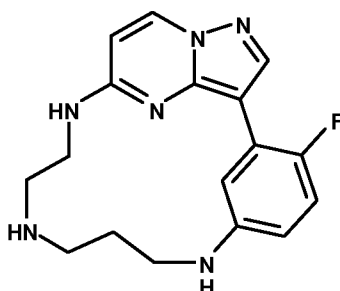
Example G20



5

Example G20 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G18.

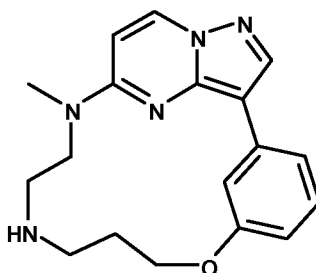
Example G21



10

Example G21 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

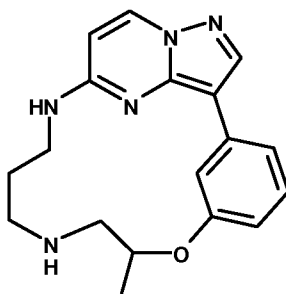
Example G22



15

Example G22 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G16.

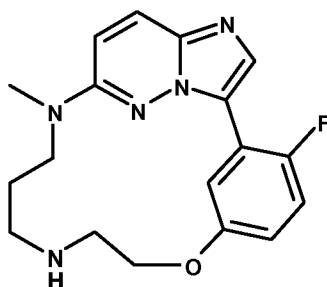
Example G23



5

Example G23 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G5.

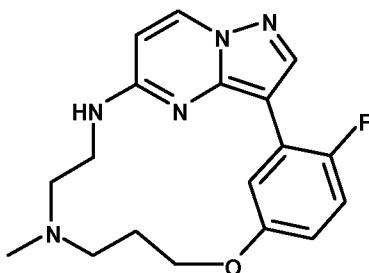
Example G24



10

Example G24 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G16.

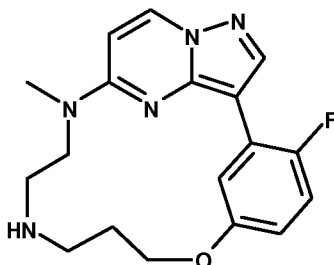
Example G25



15

Example G25 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G18.

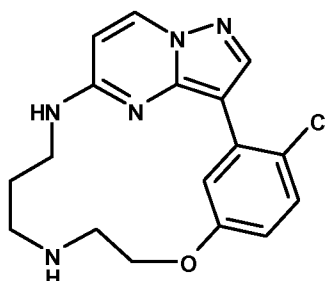
Example G26



5

Example G26 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G16.

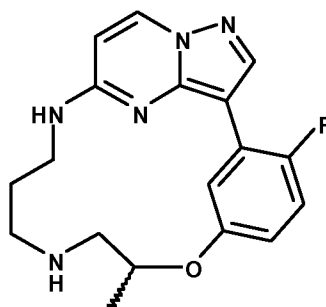
Example G27



10

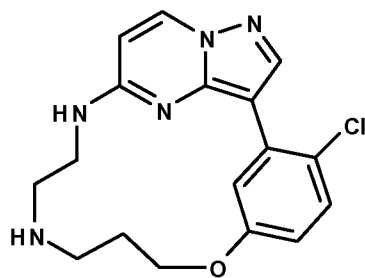
Example G27 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

Example G28



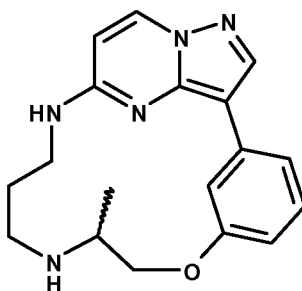
15

Example G28 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G5.

Example G30

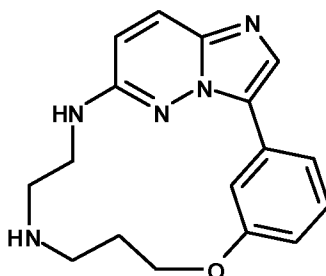
Example G30 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G31

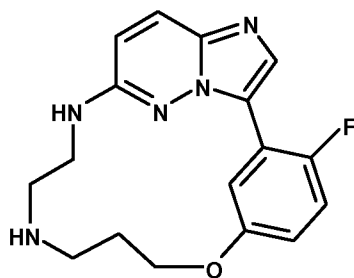
Example G31 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G5.

10

Example G32

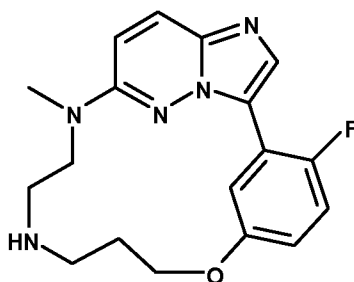
Example G32 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

15

Example G33

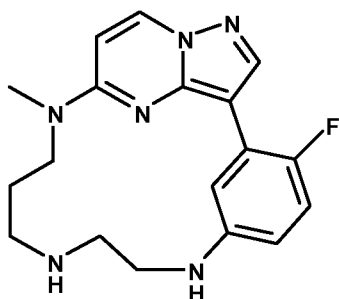
Example G33 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G34

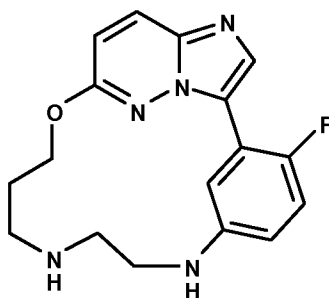
Example G34 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example G16.

10

Example G35

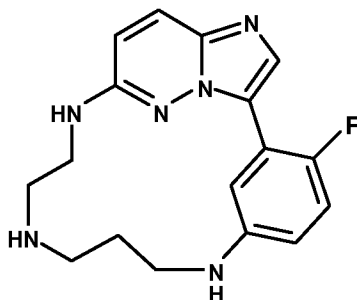
Example G35 may be prepared following general scheme 1.

15

Example G36

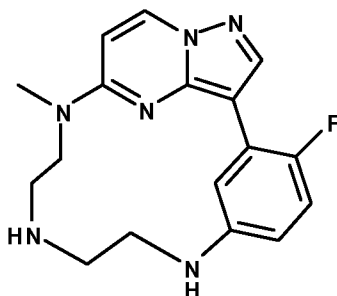
Example G36 may be prepared following general scheme 2 and according to the procedures illustrated above for the preparation of example G3.

5

Example G37

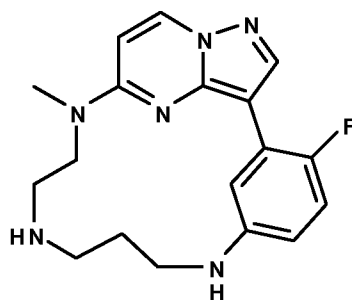
Example G37 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

10

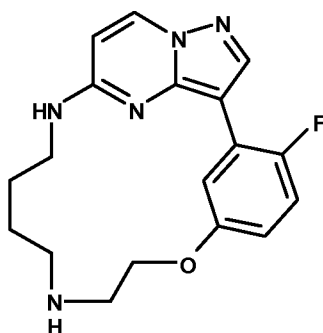
Example G38

Example G38 may be prepared following general scheme 1.

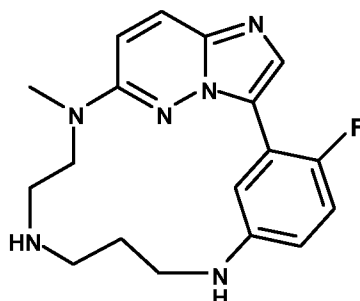
15

Example G39

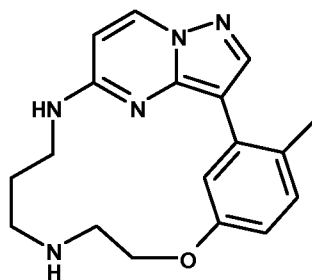
Example G39 may be prepared following general scheme 1.

5 Example G40

Example G40 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

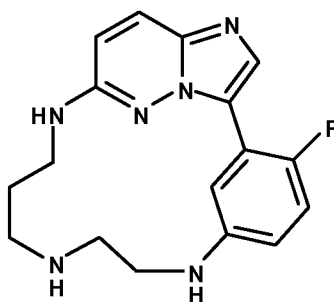
10 Example G41

Example G41 may be prepared following general scheme 1.

Example G42

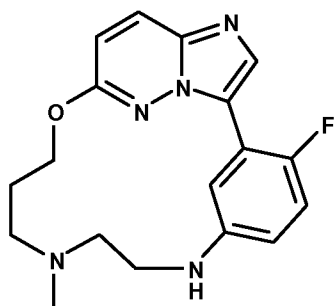
Example G42 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example C1.

5

Example G43

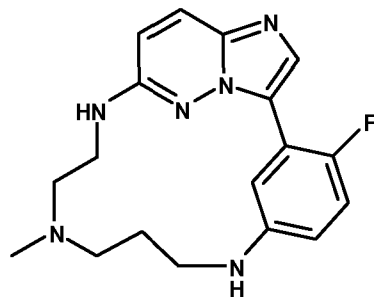
Example G43 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

10

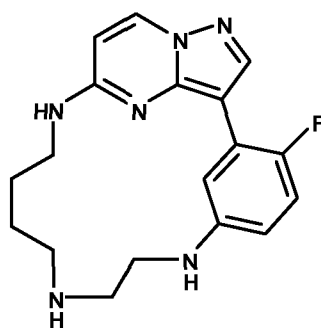
Example G44

Example G44 may be prepared following general scheme 2.

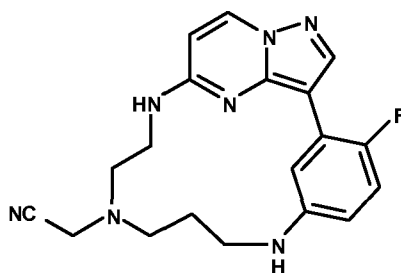
15

Example G45

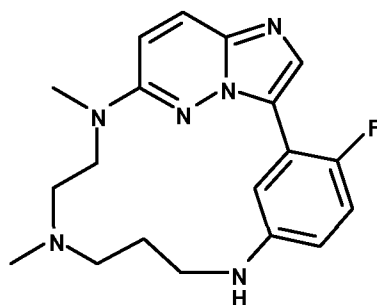
Example G45 may be prepared following general scheme 1.

5 Example G46

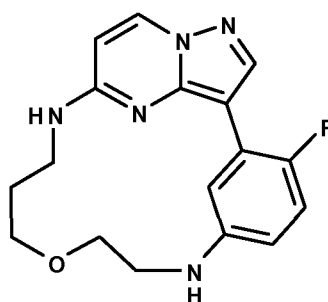
Example G46 may be prepared following general scheme 1 and according to the procedures illustrated above for the preparation of example D1.

10 Example G47

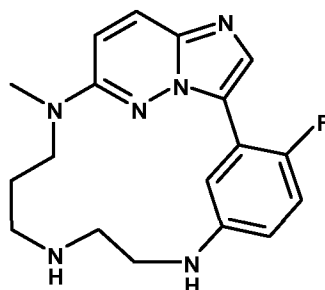
Example G47 may be prepared following general scheme 1.

Example G48

Example G48 may be prepared following general scheme 1.

5 Example G49

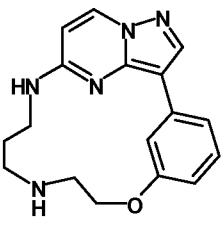
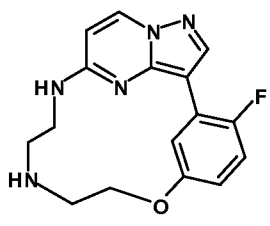
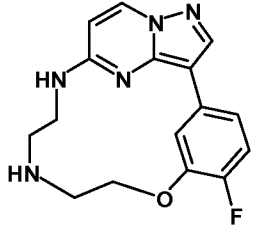
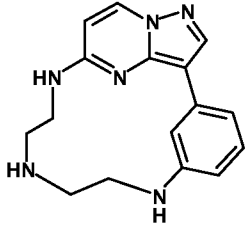
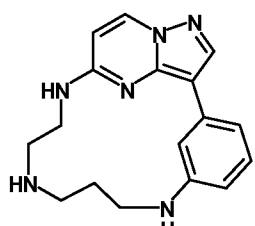
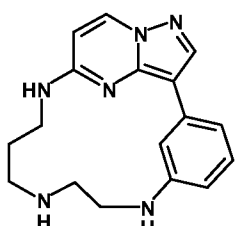
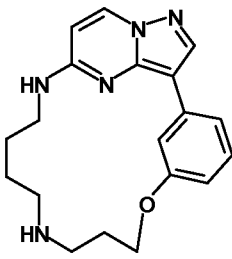
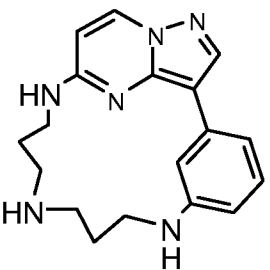
Example G49 may be prepared following general scheme 1.

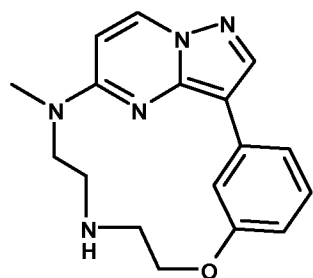
Example G50

Example G50 may be prepared following general scheme 1.

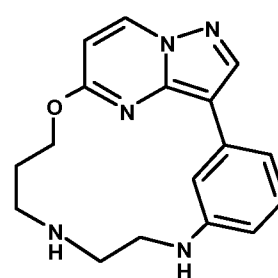
The compounds in Table 1 were prepared according to one of the procedures described above.

Table 1

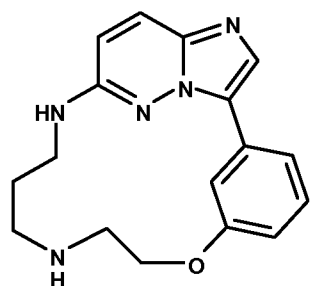
 <p>Compound A33, Example A18</p>	 <p>Compound C1, Example C1</p>
 <p>Compound C2, Example C2</p>	 <p>Compound D1, Example D1</p>
 <p>Compound D3, Example D3</p>	 <p>Compound D4, Example D4</p>
 <p>Compound D5, Example D5</p>	 <p>Compound G1, Example G1</p>



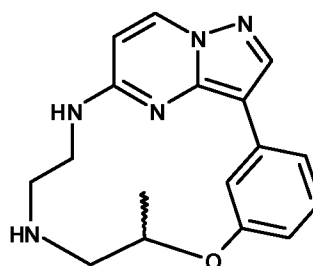
Compound G2, Example G2



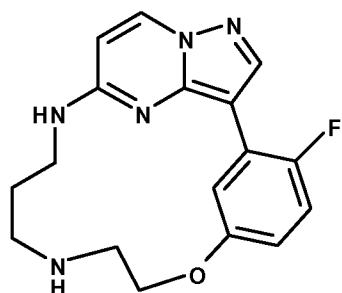
Compound G3, Example G3



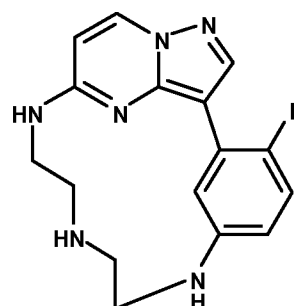
Compound G4, Example G4



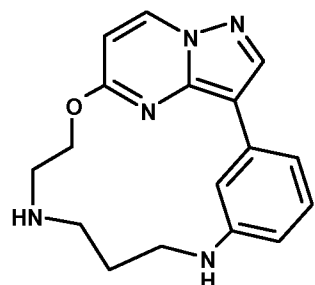
Compound G5, Example G5



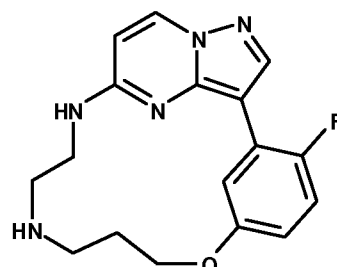
Compound G6, Example G6



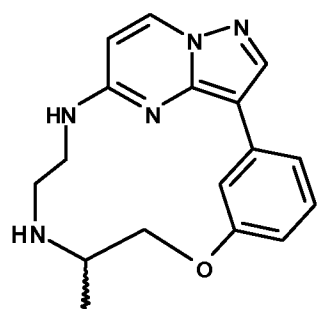
Compound G7, Example G7



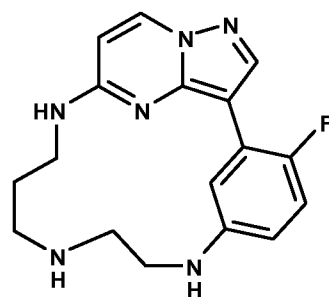
Compound G8, Example G8



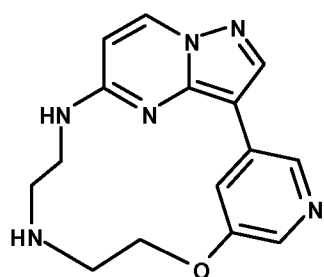
Compound G10, Example G10



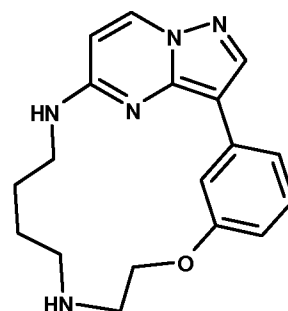
Compound G11, Example G11



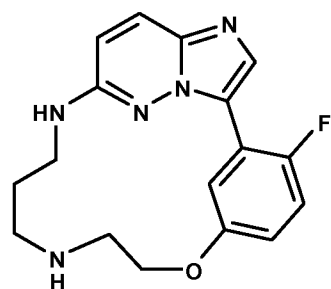
Compound G12, Example G12



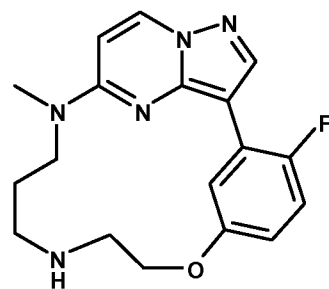
Compound G13, Example G13



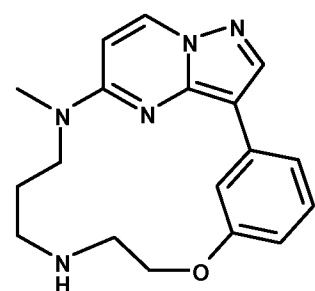
Compound G14, Example G14



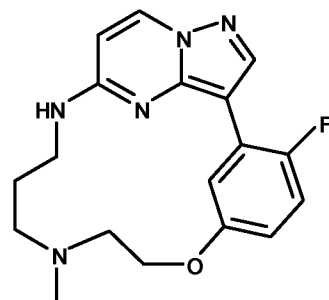
Compound G15, Example G15



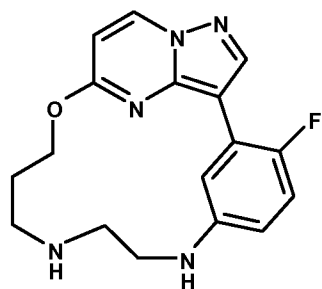
Compound G16, Example G16



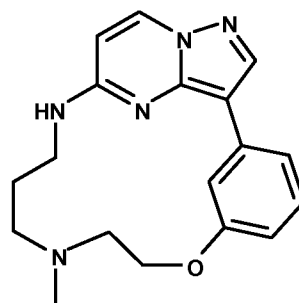
Compound G17, Example G17



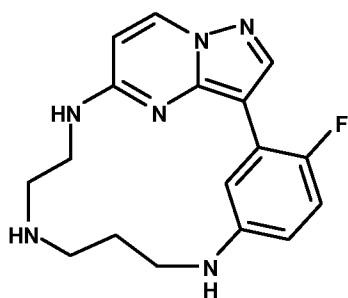
Compound G18, Example G18



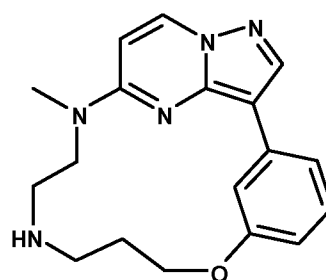
Compound G19, Example G19



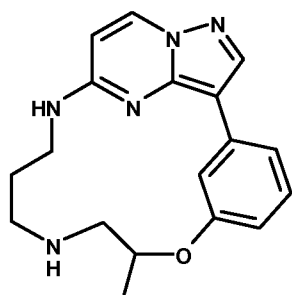
Compound G20, Example G20



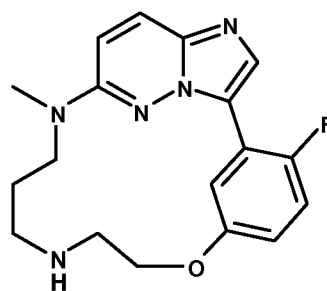
Compound G21, Example G21



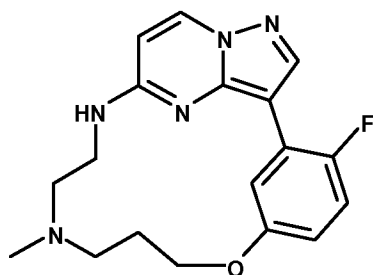
Compound G22, Example G22



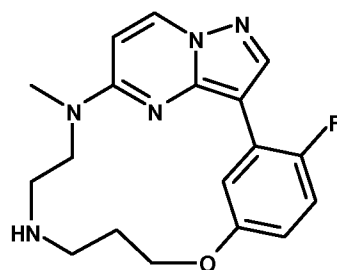
Compound G23, Example G23



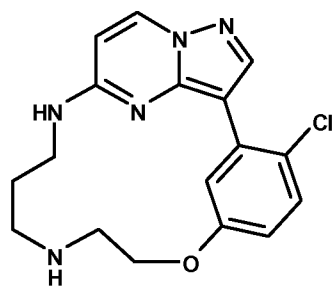
Compound G24, Example G24



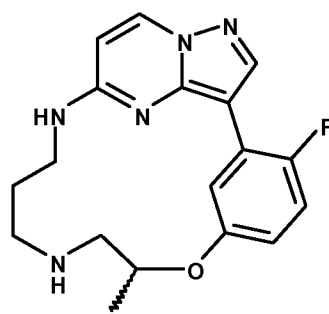
Compound G25, Example G25



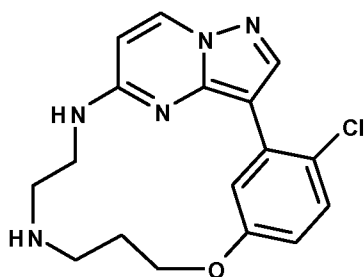
Compound G26, Example G26



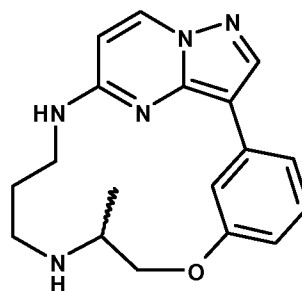
Compound G27, Example G27



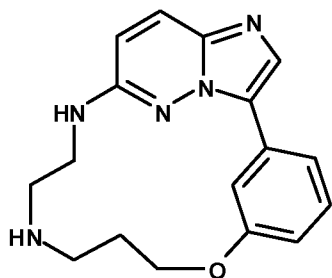
Compound G28, Example G28



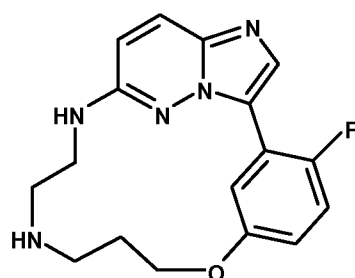
Compound G30, Example G30



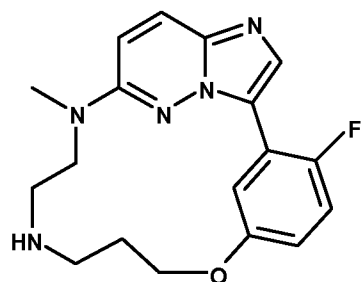
Compound G31, Example G31



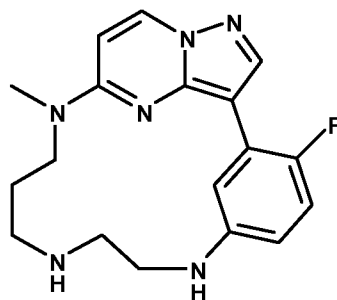
Compound G32, Example G32



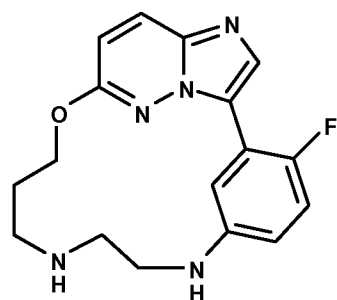
Compound G33, Example G33



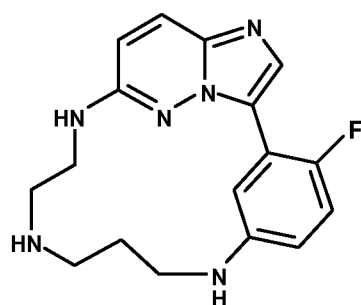
Compound G34, Example G34



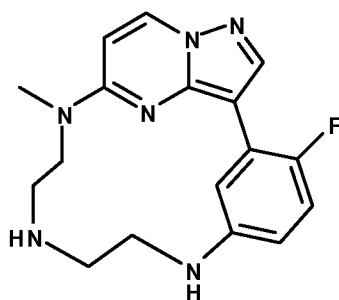
Compound G35, Example G35



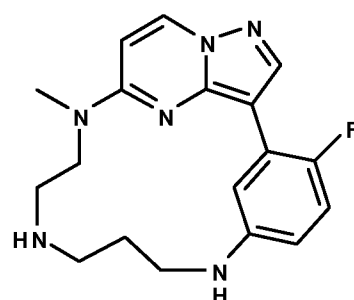
Compound G36, Example G36



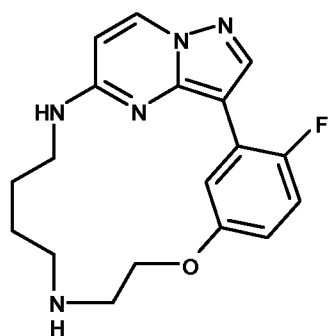
Compound G37, Example G37



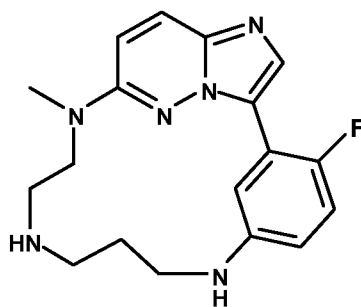
Compound G38, Example G38



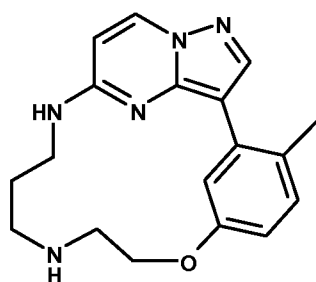
Compound G39, Example G39



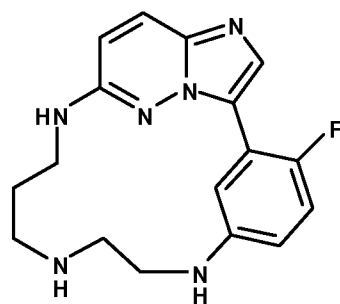
Compound G40, Example G40



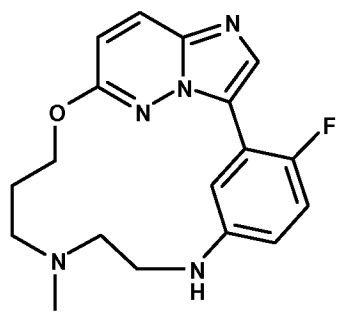
Compound G41, Example G41



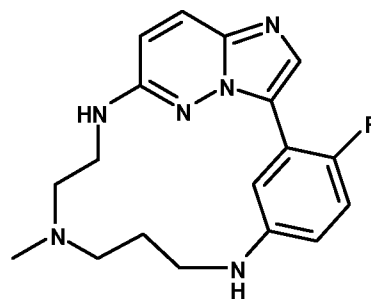
Compound G42, Example G42



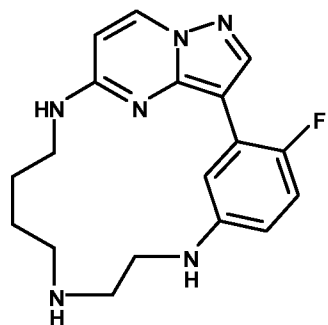
Compound G43, Example G43



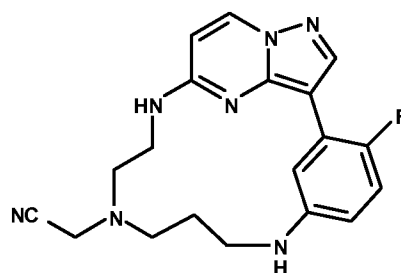
Compound G44, Example G44



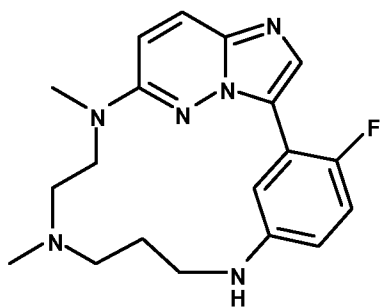
Compound G45, Example G45



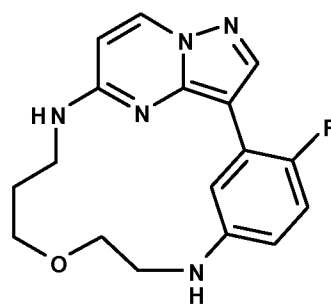
Compound G46, Example G46



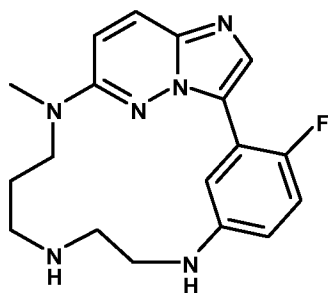
Compound G47, Example G47



Compound G48, Example G48



Compound G49, Example G49



Compound G50, Example G50

Compound identification**Melting points**

5 For the melting point determination of the compounds of the present invention, the following method was used.

Melting point method

10 For a number of compounds, melting points (m.p.) were determined in open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature ranging from 50°C to 300°C , using a gradient of 10 °C/minute. The melting point value was read from a digital display and was not corrected.

Table 2: Melting points

COMPOUND NUMBER	MELTING POINT (°C)
A33	> 300
C1	> 300
C2	> 300
D1	> 300
D3	> 300
D4	296,8
D5	146,9
G1	280,0
G2	> 300
G3	280
G4	> 300
G5	215
G6	197,6
G7	> 300
G8	276,7
G10	> 300
G11	245,9
G12	> 300
G13	283,3
G14	> 300
G15	ND*
G16	> 300
G17	297,5
G18	> 300
G19	279,1
G20	ND*

G21	> 300
G22	286,4
G23	> 300
G24	> 300
G25	168,8
G26	> 300
G27	> 300
G28	> 300
G30	> 300
G31	ND*
G32	> 300
G33	> 300
G34	> 300
G35	284,8
G36	> 300
G37	> 300
G38	286,8
G39	> 300
G40	> 300
G41	263,8
G42	296,8
G43	> 300
G44	242,3
G45	289,1
G46	270,4
G47	262,6
G48	289,4
G49	ND*
G50	ND*

* Not determined

LCMS

- 5 For LCMS-characterization of the compounds of the present invention, the following method was used.

General procedure LCMS

- 10 All analyses were performed using an Agilent 6110 series LC/MSD quadrupole coupled to an Agilent 1290 series liquid chromatography (LC) system consisting of a binary pump with degasser, autosampler, thermostated column compartment and diode array detector. The mass spectrometer (MS) was operated with an atmospheric pressure electro-spray ionization (API-ES) source in positive ion mode. The capillary voltage was set to 3000 V, the fragmentor

voltage to 70 V and the quadrupole temperature was maintained at 100°C. The drying gas flow and temperature values were 12.0 L/min and 350°C respectively. Nitrogen was used as the nebulizer gas, at a pressure of 35 psig. Data acquisition was performed with Agilent Chemstation software.

5

LCMS method 1

In addition to the general procedure LCMS1: Analyses were carried out on a Phenomenex Kinetex C18 column (50 mm long x 2.1 mm i.d.; 1.7 µm particles) at 60°C, with a flow rate of 1.5 mL/min. A gradient elution was performed from 90% (water + 0.1% formic acid) / 10% Acetonitrile to 10% (water + 0.1% formic acid) / 90% acetonitrile in 1.50 minutes, then the final mobile phase composition was held for an additional 0.40 min. The standard injection volume was 2 µL. Acquisition ranges were set to 254 nm for the UV-PDA detector and 80-800 m/z for the MS detector.

15

LCMS method 2

In addition to the general procedure LCMS1: Analyses were carried out on a YMC pack ODS-AQ C18 column (50 mm long x 4.6 mm i.d.; 3 µm particles) at 35°C, with a flow rate of 2.6 mL/min. A gradient elution was performed from 95% (water + 0.1% formic acid) / 5% Acetonitrile to 5% (water + 0.1% formic acid) / 95% Acetonitrile in 4.80 minutes, then the final mobile phase composition was held for an additional 1.00 min. The standard injection volume was 2 µL. Acquisition ranges were set to 190-400nm for the UV-PDA detector and 100-1400 m/z for the MS detector.

20

Table 3: LCMS data

COMPOUND NUMBER	MASS (MH) ⁺ PEAK	RETENTION TIME (min)	LCMS METHOD
A33	310,2	1,753	2
C1	314,1	1,971	2
C2	314,2	1,906	2
D1	295,2	1,000	2
D3	309,2	1,600	2
D4	309,2	1,782	2
D5	338,2	2,030	2
G1	323,2	0,416	2
G2	310,2	1,971	2
G3	310,2	1,940	2
G4	310,2	1,154	2
G5	310,2	1,990	2
G6	327,2	2,023	2

G7	313,2	1,927	2
G8	310,2	1,708	2
G10	328,2	2,122	2
G11	310,2	2,045	2
G12	326,2	1,360	2
G13	311,2	1,690	2
G14	324,2	1,790	2
G15	328,1	1,180	2
G16	342,2	1,907	2
G17	324,2	1,113	2
G18	342,2	1,853	2
G19	328,2	1,860	2
G20	324,2	1,787	2
G21	327,2	1,587	2
G22	324,1	1,859	2
G23	324,2	1,827	2
G24	342,2	1,240	2
G25	342,2	1,980	2
G26	342,2	1,973	2
G27	344,1	1,907	2
G28	342,2	1,940	2
G30	344	2,020	2
G31	324,1	1,887	2
G32	310,2	1,167	2
G33	328,2	1,273	2
G34	342,2	1,313	2
G35	341,2	1,913	2
G36	328,2	1,100	2
G37	327	1,100	2
G38	327	1,853	2
G39	341,2	1,700	2
G40	342,1	1,917	2
G41	341,1	0,359	2
G42	324,1	1,855	2
G43	327,2	2,768	2
G44	342,2	1,360	2
G45	341,2	1,120	2
G46	341,2	1,773	2
G47	366,2	2,330	2
G48	355,3	1,151	2
G49	328,1	2,004	2
G50	341,1	1,180	2

Kinase Activity Assay

The inhibition of LRRK2 kinase was assessed using LRRK2 recombinant protein in an *in vitro* peptide-based kinase assay.

5

Protocol

A radiometric protein kinase assay (³³PanQinase[®] Activity Assay) is used for measuring the kinase activity. All assays are performed in 96-well FlashPlates[™] from Perkin Elmer in a 50 µl reaction volume. The reaction cocktail is 106ipette in 4 steps in the following order:

10

10 µl of non-radioactive ATP solution (in H₂O)

25 µl of assay buffer/ [γ-³³P]-ATP mixture

5 µl of test sample in 10% DMSO

15

10 µl of enzyme/substrate mixture

The assay for LRRK2 contains 70 mM HEPES-NaOH pH 7.5, 3 mM MgCl₂, 3 mM MnCl₂, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG20000, ATP (0.3 µM), [γ-³³P]-ATP (approx. 4 x 1005 cpm per well), protein kinase LRRK2 (7,3 nM) and substrate (GSK3(14-27), 1,0 µg/50 µl).

20

The kinase is obtained from Invitrogen Corporation.

The reaction cocktails were incubated at 30° C for 60 minutes. The reaction was stopped with 50 µl of 2 % (v/v) H₃PO₄, plates were aspirated and washed two times with 200 µl 0.9 % (w/v) NaCl. Incorporation of ³³Pi (counting of "cpm") was determined with a microplate scintillation counter.

25

Compounds

The compounds are dissolved to 10 mM in DMSO. Where needed, solutions are sonicated in a bath sonicator.

30

Table 2 provides the pIC₅₀ values of the compounds according to the invention, obtained using the above mentioned kinase assay.

35

Table 2

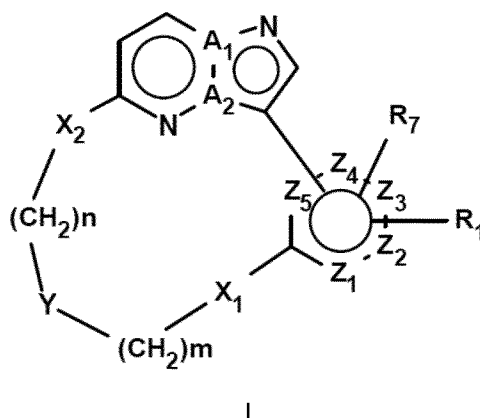
Compound N°	IC ₅₀ for LRRK2
A33	+++
C1	+++
C2	+++
D1	+++
D3	+++
D4	+++
D5	+++
G1	+++
G2	+++
G3	+++
G4	+++
G5	+++
G6	+++
G7	+++
G8	+++
G10	+++
G11	+++
G12	+++
G13	+++
G14	+++
G15	+++
G16	+++
G17	+++
G18	+++
G19	+++
G20	+++
G21	+++
G22	+++
G23	+++
G24	+++
G25	++
G26	+++
G27	+++
G28	+++

G30	++
G31	+++
G32	+++
G33	+++
G34	+++
G35	+++
G36	+++
G37	+++
G38	+++
G39	+++
G40	+++
G41	+++
G42	++
G43	+++
G44	+++
G45	+++
G46	+++
G47	+++
G48	++
G49	+++
G50	+++

- 5 + indicates an IC₅₀ > 1 μ M, ++ indicates an IC₅₀ of between 100 nM and 1 μ M, and +++ indicates an IC₅₀ < 100nM

CLAIMS

1. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



Wherein

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when A₂ is C, then A₁ is N;

- 10 R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;
- 15 R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -Ar₂, and -NR₁₃R₁₄;
- 20 R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl, -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -Het₂, and -Ar₃;
- 25 R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈, and -Het₄;
- R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, -CN and -NR₃₁R₃₂;
- R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;
- 30 R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -

C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

5 R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-,
 10 -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-,
 15 -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

20 Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered
 25 monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -halo;

30 Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

35 2. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is C and A₂ is N

R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆;

- wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{NR}_{11}\text{R}_{12}$, $-\text{O}-C_{1-6}$ alkyl, and $-\text{S}-C_{1-6}$ alkyl;
- R_2 is selected from $-\text{H}$, $-\text{halo}$, $-\text{OH}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-(\text{C}=\text{O})-C_{1-6}$ alkyl, $-(\text{C}=\text{O})-\text{O}-C_{1-6}$ alkyl, $-(\text{C}=\text{O})-\text{NR}_{27}\text{R}_{28}$, $-\text{Het}_3$, $-(\text{C}=\text{O})-\text{Het}_3$, $-\text{SO}_2-C_{1-6}$ alkyl, and $-C_{3-6}$ cycloalkyl; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{Het}_3$, $-\text{Ar}_2$, and $-\text{NR}_{13}\text{R}_{14}$;
- R_3 is selected from $-\text{H}$, $-\text{halo}$, $-\text{OH}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-(\text{C}=\text{O})-C_{1-6}$ alkyl, $-(\text{C}=\text{O})-\text{O}-C_{1-6}$ alkyl, $-\text{Het}_2$, $-C_{3-6}$ cycloalkyl, $-(\text{C}=\text{O})-\text{Het}_2$, $-(\text{C}=\text{O})-\text{NR}_{29}\text{R}_{30}$, and $-\text{SO}_2-C_{1-6}$ alkyl; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{NR}_{15}\text{R}_{16}$, $-\text{Het}_2$, and $-\text{Ar}_3$;
- R_4 is independently selected from $-\text{halo}$, $-\text{OH}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{NR}_{17}\text{R}_{18}$, and $-\text{Het}_4$;
- R_5 is selected from $-\text{H}$, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl; wherein each of said C_{1-6} alkyl or $-C_{3-6}$ cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{OC}_{1-6}$ alkyl, $-\text{SC}_{1-6}$ alkyl, $-\text{Het}_5$, $-\text{CN}$ and $-\text{NR}_{31}\text{R}_{32}$;
- R_6 is selected from $-\text{H}$, $-\text{OH}$, $-\text{halo}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{NR}_{33}\text{R}_{34}$, and $-\text{Het}_8$;
- R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{37} and R_{38} are each independently selected from $-\text{H}$, $=\text{O}$, $-C_{1-6}$ alkyl, and $-\text{Het}_1$; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{NR}_{35}\text{R}_{36}$, $-\text{Het}_7$, and $-\text{Ar}_4$;
- R_{35} and R_{36} are each independently selected from $-\text{H}$, $=\text{O}$, and $-C_{1-6}$ alkyl; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-\text{O}-C_{1-6}$ alkyl, and $-\text{S}-C_{1-6}$ alkyl;
- X_1 is selected from $-C_{1-6}$ alkyl-, $-\text{O}-C_{1-6}$ alkyl-, $-\text{S}-C_{1-6}$ alkyl-, $-(\text{C}=\text{O})-$, $-\text{NR}_3-(\text{C}=\text{O})-$, $-C_{1-6}$ alkyl- NR_3- , $-\text{NR}_3-$, $-(\text{C}=\text{O})-$, $-\text{NR}_3-(\text{C}=\text{O})-\text{NR}_{37}-$, $-\text{NR}_3-C_{1-6}$ alkyl-, $-\text{NR}_3-\text{SO}_2-$, $-\text{NR}_3-(\text{C}=\text{O})-C_{1-6}$ alkyl-, $-(\text{C}=\text{O})-\text{NR}_3-C_{1-6}$ alkyl-, $-\text{O}-C_{1-6}$ alkyl- $\text{O}-C_{1-6}$ alkyl- and $-C_{1-6}$ alkyl- NR_3-C_{1-6} alkyl-; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{phenyl}$, and $-\text{NR}_{23}\text{R}_{24}$;
- X_2 is selected from $-C_{1-6}$ alkyl-, $-\text{O}-C_{1-6}$ alkyl-, $-\text{S}-C_{1-6}$ alkyl-, $-(\text{C}=\text{O})-$, $-\text{NR}_2-(\text{C}=\text{O})-$, $-C_{1-6}$ alkyl- NR_2- , $-\text{NR}_2-$, $-(\text{C}=\text{O})-$, $-\text{NR}_2-(\text{C}=\text{O})-\text{NR}_{38}-$, $-\text{NR}_2-C_{1-6}$ alkyl-, $-\text{NR}_2-\text{SO}_2-$, $-\text{NR}_2-(\text{C}=\text{O})-C_{1-6}$ alkyl-, $-(\text{C}=\text{O})-\text{NR}_2-C_{1-6}$ alkyl-, $-\text{O}-C_{1-6}$ alkyl- $\text{O}-C_{1-6}$ alkyl- and $-C_{1-6}$ alkyl- NR_2-C_{1-6} alkyl-; wherein each of said $-C_{1-6}$ alkyl is optionally and independently substituted with from 1 to 3 substituents selected from $-\text{halo}$, $-\text{OH}$, $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{S}-C_{1-6}$ alkyl, $-\text{phenyl}$ and $-\text{NR}_{25}\text{R}_{26}$;
- Y is selected from a direct bond, $-\text{CHR}_6-$, $-\text{O}-$, $-\text{S}-$, and $-\text{NR}_5-$;

Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

5 Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently
10 substituted with from 1 to 3 -halo;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

3. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or
15 predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is N and A₂ is C

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when
A₂ is C, then A₁ is N;

R₁ and R₇ are each independently selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-
20 C₁₋₆alkyl, -NR₉R₁₀, -(C=O)-R₄, -SO₂-R₄, -CN, -NR₉-SO₂-R₄, -C₃₋₆cycloalkyl, and -Het₆;
wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to
3 substituents selected from -halo, -OH, -NR₁₁R₁₂, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R₂ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -
(C=O)-O-C₁₋₆alkyl, -(C=O)-NR₂₇R₂₈, -Het₃, -(C=O)-Het₃, -SO₂-C₁₋₆alkyl, and -C₃₋₆-
25 cycloalkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted
with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -Het₃, -
Ar₂, and -NR₁₃R₁₄;

R₃ is selected from -H, -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -(C=O)-C₁₋₆alkyl, -
(C=O)-O-C₁₋₆alkyl, -Het₂, -C₃₋₆cycloalkyl, -(C=O)-Het₂, -(C=O)-NR₂₉R₃₀, and -SO₂-C₁₋₆-
30 alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with
from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₅R₁₆, -
Het₂, and -Ar₃;

R₄ is independently selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₁₇R₁₈,
and -Het₄;

35 R₅ is selected from -H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl; wherein each of said C₁₋₆alkyl or -C₃₋₆-
cycloalkyl is optionally and independently substituted with from 1 to 3 substituents
selected from -halo, -OH, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -Het₅, -CN and -NR₃₁R₃₂;

R₆ is selected from -H, -OH, -halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₃R₃₄, and -Het₈;

R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₇ and R₃₈ are each independently selected from -H, =O, -C₁₋₆alkyl, and -Het₁; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR₃₅R₃₆, -Het₇, and -Ar₄;

R₃₅ and R₃₆ are each independently selected from -H, =O, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

X₁ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₃-(C=O)-, -C₁₋₆alkyl-NR₃-, -NR₃-, -(C=O)-, -NR₃-(C=O)-NR₃₇-, -NR₃-C₁₋₆alkyl-, -NR₃-SO₂-, -NR₃-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₃-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl, and -NR₂₃R₂₄

X₂ is selected from -C₁₋₆alkyl-, -O-C₁₋₆alkyl-, -S-C₁₋₆alkyl-, -(C=O)-, -NR₂-(C=O)-, -C₁₋₆alkyl-NR₂-, -NR₂-, -(C=O)-, -NR₂-(C=O)-NR₃₈-, -NR₂-C₁₋₆alkyl-, -NR₂-SO₂-, -NR₂-(C=O)-C₁₋₆alkyl-, -(C=O)-NR₂-C₁₋₆alkyl-, -O-C₁₋₆alkyl-O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂-C₁₋₆alkyl-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -halo, -OH, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -phenyl and -NR₂₅R₂₆;

Y is selected from a direct bond, -CHR₆-, -O-, -S-, and -NR₅-;

Ar₂, Ar₃, and Ar₄ are each independently a 5- or 6-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; wherein each of said Ar₂, Ar₃, and Ar₄ is optionally and independently substituted with from 1 to 3 substituents selected from -NR₁₉R₂₀, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ are each independently a 5- or 6-membered monocyclic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁, Het₂, Het₃, Het₄, Het₅, Het₆, Het₇ and Het₈ is optionally substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -NR₂₁R₂₂; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

4. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when A₂ is C, then A₁ is N;

-114-

R₁ and R₇ are each independently selected from -H, -halo and -C₁₋₆alkyl;

R₂ is selected from -H and -C₁₋₆alkyl;

R₃ is -H;

R₅ is selected from -H and -C₁₋₆alkyl; wherein said -C₁₋₆alkyl may be optionally substituted with -CN

X₁ is selected from -O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl;

X₂ is selected from -O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂;

Y is selected from -O- and -NR₅-;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

5. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is N and A₂ is C

R₁ and R₇ are each independently selected from -H, -halo and -C₁₋₆alkyl;

R₂ is selected from -H and -C₁₋₆alkyl;

R₃ is -H;

R₅ is selected from -H and -C₁₋₆alkyl; wherein said -C₁₋₆alkyl may be optionally substituted with -CN

X₁ is selected from -O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₃-; wherein each of said -C₁₋₆alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C₁₋₆alkyl;

X₂ is selected from -O-C₁₋₆alkyl- and -C₁₋₆alkyl-NR₂;

Y is selected from -O- and -NR₅-;

Z₁, Z₂, Z₃, Z₄ and Z₅ are each independently selected from C and N;

m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

6. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A₁ is C and A₂ is N

R₁ and R₇ are each independently selected from -H, -halo and -C₁₋₆alkyl;

R₂ is selected from -H and -C₁₋₆alkyl;

R₃ is -H;

R₅ is selected from -H and -C₁₋₆alkyl; wherein said -C₁₋₆alkyl may be optionally substituted with -CN

-115-

X_1 is selected from $-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_3-$; wherein each of said $-C_{1-6}alkyl$ is optionally and independently substituted with from 1 to 3 substituents selected from $-C_{1-6}alkyl$;

X_2 is selected from $-O-C_{1-6}alkyl-$ and $-C_{1-6}alkyl-NR_2-$;

5 Y is selected from $-O-$ and $-NR_5-$;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N;

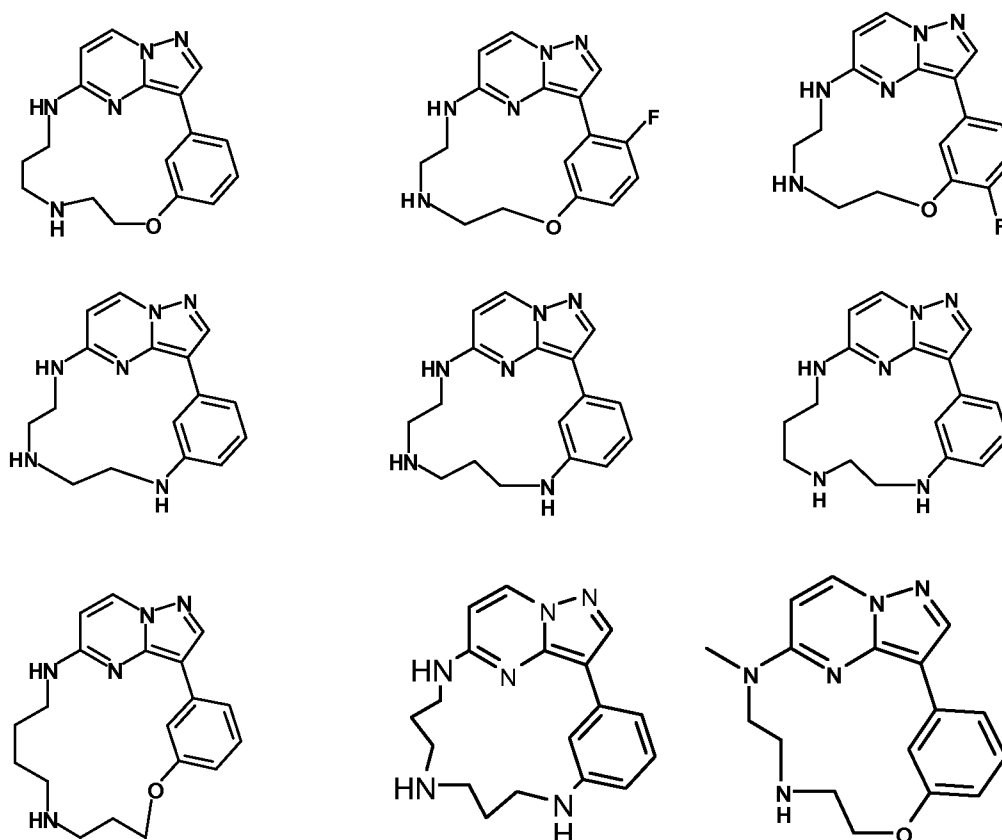
m and n are each independently 0, 1, 2, 3, or 4.

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

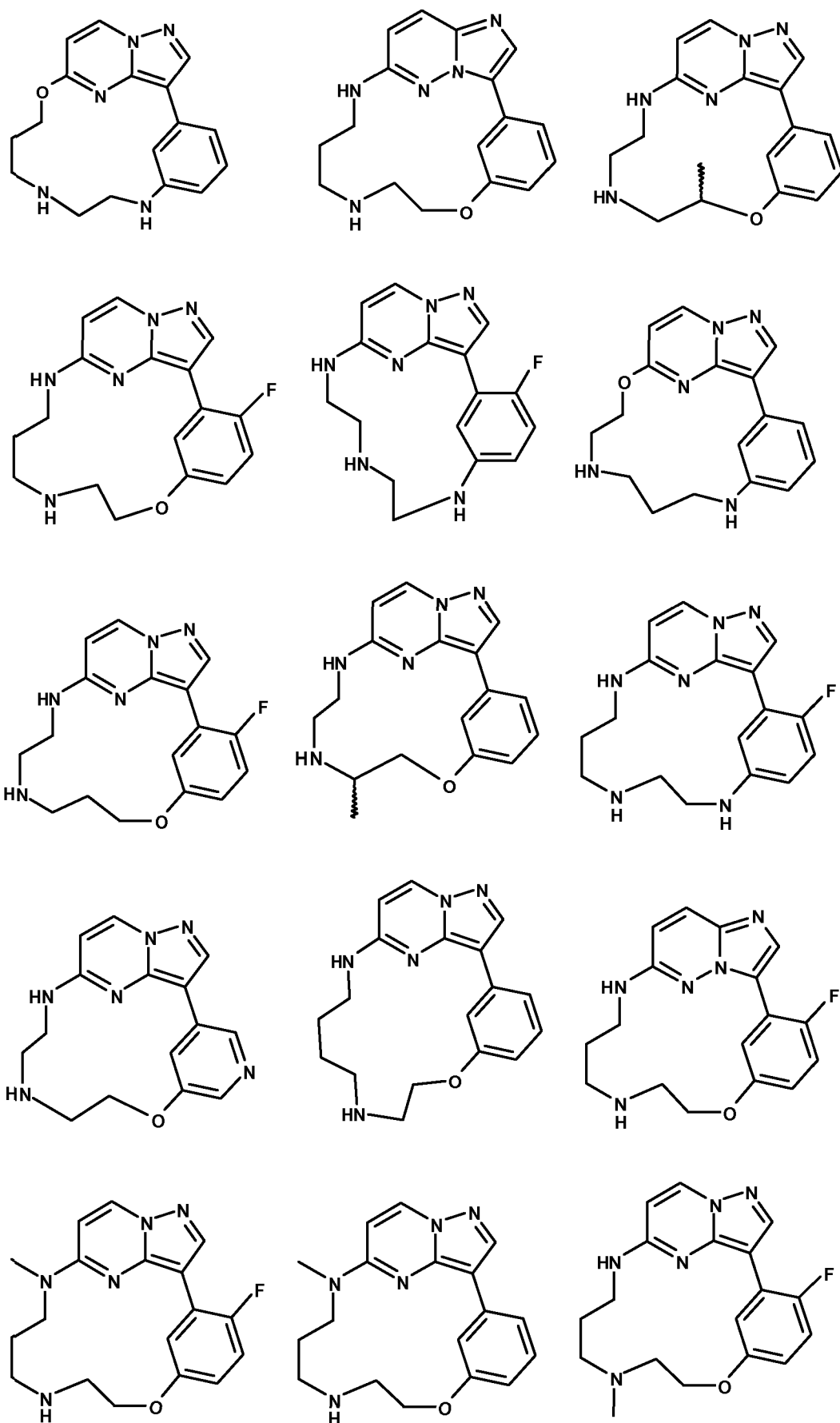
10

7. A compound as defined in any one of claims 1 to 6 for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease; wherein said compound is selected from the list comprising:

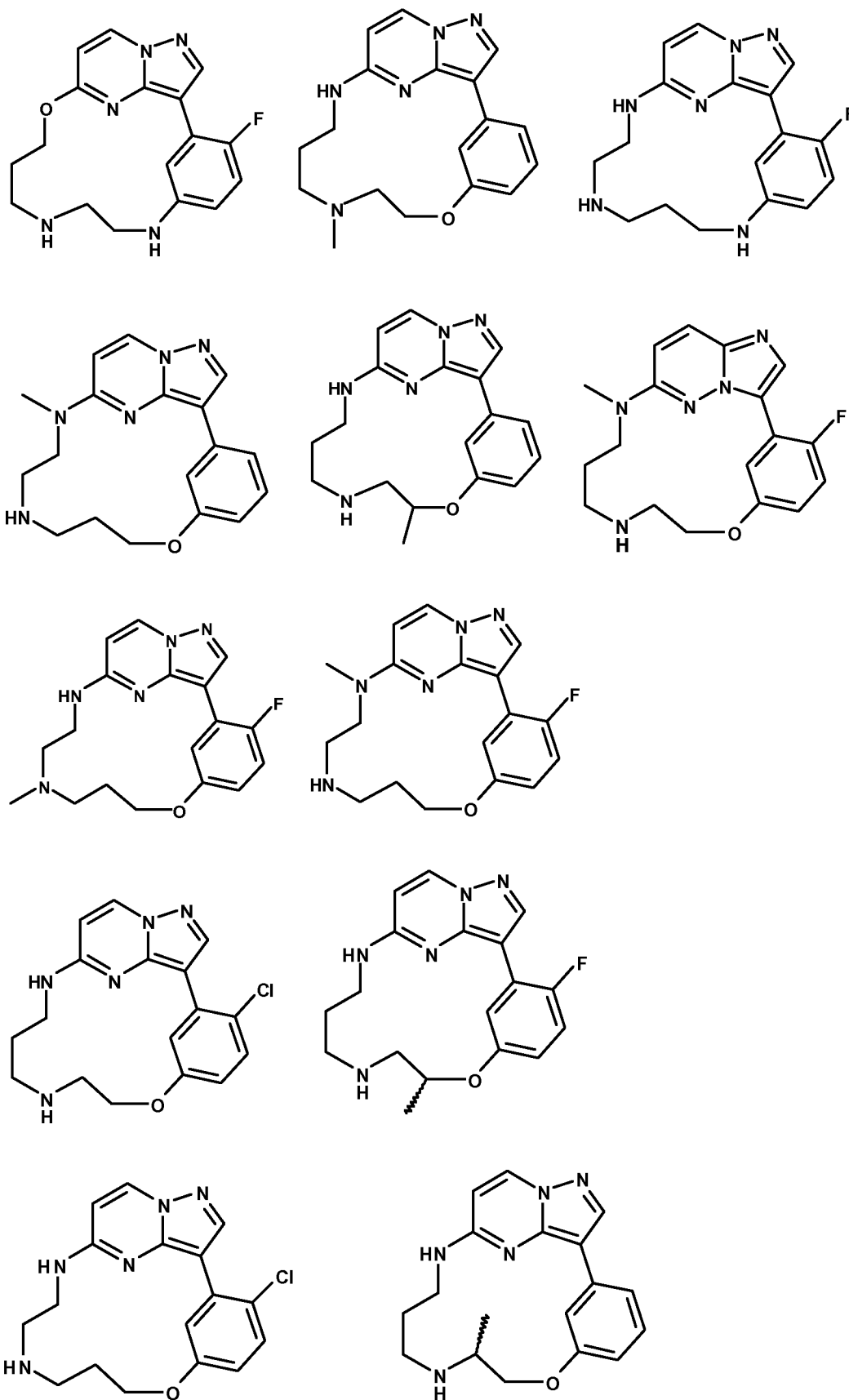
15

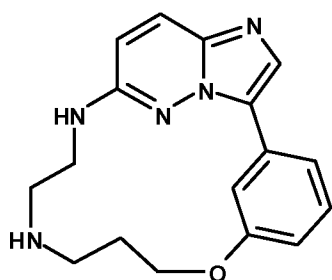
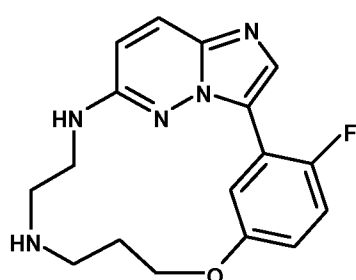
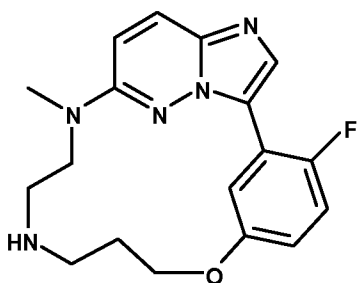
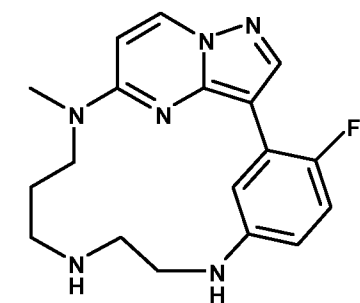
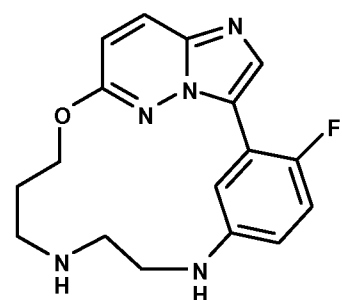
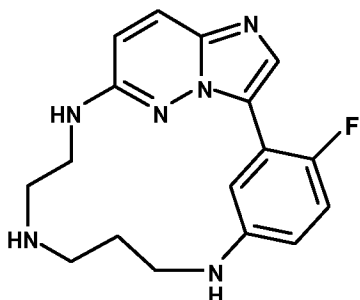
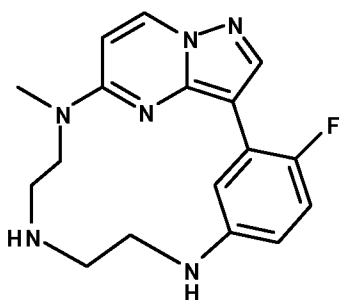
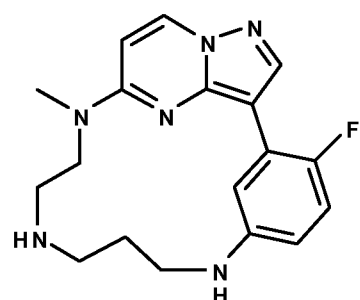


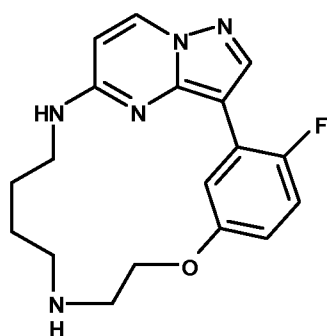
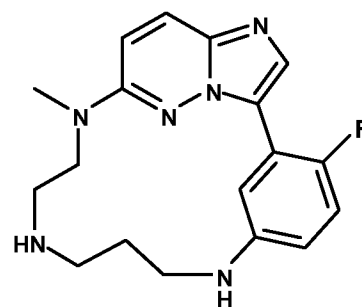
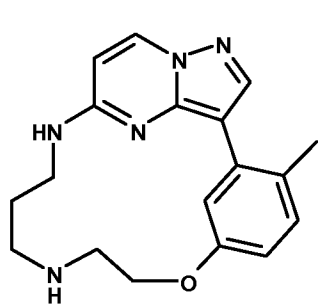
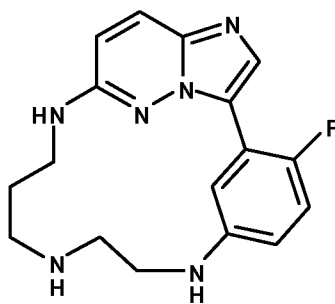
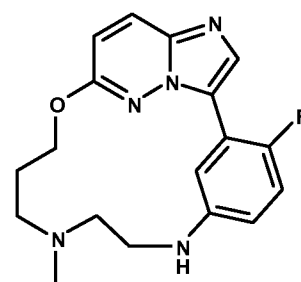
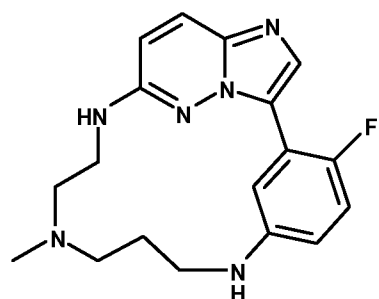
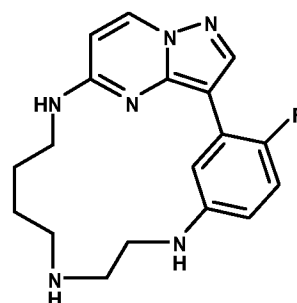
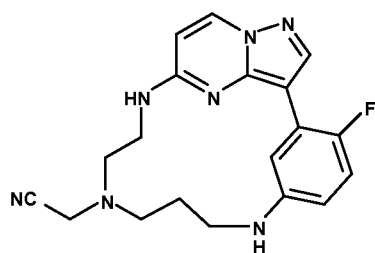
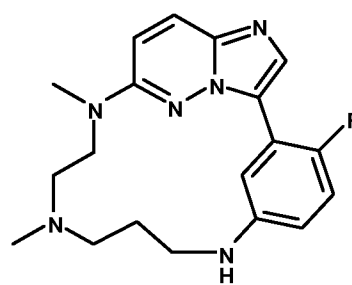
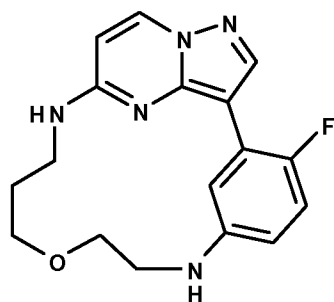
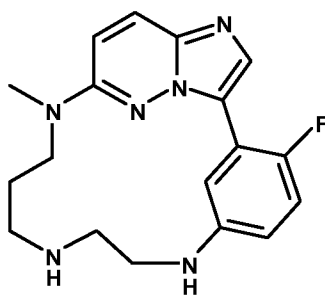
-116-



-117-







8. A compound as defined in any one of claims 1 to 7 for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease; wherein the pyrazolopyrimidine or the imidazopyridazine moiety is linked to the aryl or heteroaryl moiety at position Z₄ or Z₅, in accordance with the numbering as provided in Formula I.

5

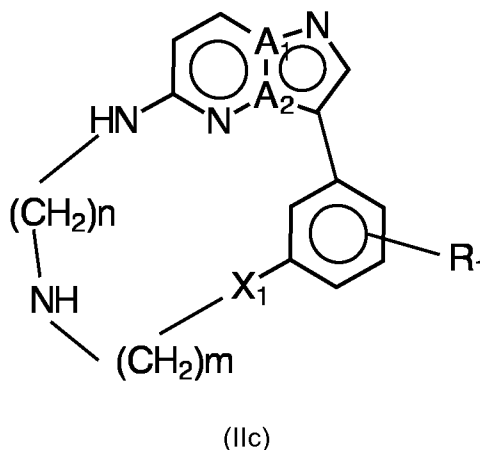
9. A compound as defined in any one of claims 1 to 7 for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease; wherein R₁ is linked to the aryl or heteroaryl moiety at position Z₁, Z₂ or Z₃, in accordance with the numbering as provided in Formula I.

10

10. A compound as defined in any one of claims 1 to 7 for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease; wherein the LRRK2-kinase associated disease is a neurological disorder, in particular selected from the list comprising Parkinson's disease or Alzheimer's disease.

15

11. A compound of Formula (IIc) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



wherein

20

A₁ and A₂ are selected from C and N; wherein when A₁ is C, then A₂ is N; and wherein when A₂ is C, then A₁ is N;

R₁ is selected from the list comprising -H, -F, -CH₃, and -CN

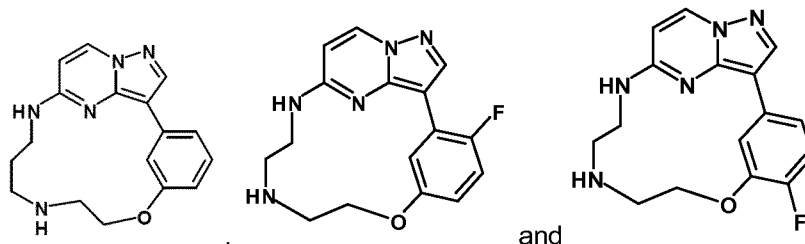
X₁ is selected from the list comprising -NH- and -O-

m and n are each independently 1, 2, 3, or 4

25

for use in the prevention and/or treatment of a LRRK2-kinase associated disease.

12. A compound as defined in any one of claims 1 to 11 for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease; wherein said compound is selected from the list comprising



5

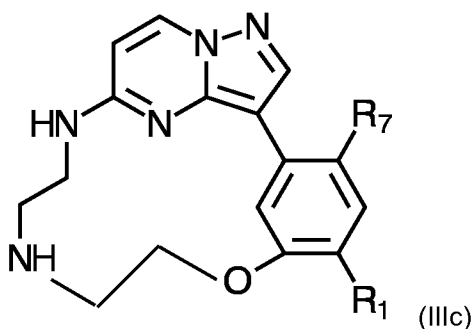
13. A pharmaceutical composition for use in the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease comprising a compound as defined in any one of claims 1 to 12.

10 14. Use of a compound as defined in any one of claims 1 to 12, or a composition as defined in claim 13, suitable for inhibiting the activity of a kinase; in particular a LRRK2 kinase.

15 15. Use of a compound as defined in any one of claims 1 to 12, or a composition as defined in claim 13, for the diagnosis, prevention and/or treatment of a LRRK2-kinase associated disease.

16. A method for the prevention and/or treatment of a LRRK2-kinase associated disease; said method comprising administering to a subject in need thereof a compound according to any one of claims 1 to 12 or a composition as defined in claim 13.

20 17. A compound or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, according to the general formula (IIIc)

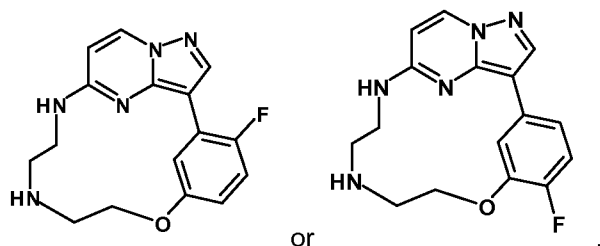


wherein

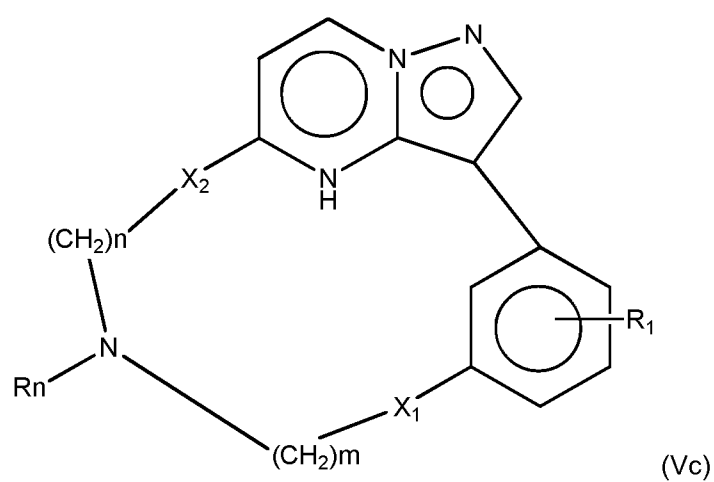
R_1 is -H and R_7 is -F; or

R_7 is $-H$ and R_1 is $-F$.

18. A compound according to claim 17, wherein said compound is:



5 19. A compound of formula (Vc)



wherein

R_1 is selected from the list comprising $-H$, and $-F$,

10 X_1 and X_2 are each independently selected from the list comprising $-NR_x-$ and $-O-$,

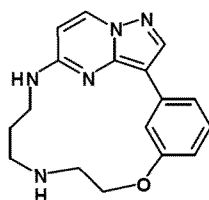
R_x is H or a methyl group,

m and n are each independently 1, 2, 3, or 4,

R_n is H or a methyl group,

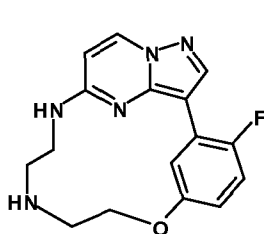
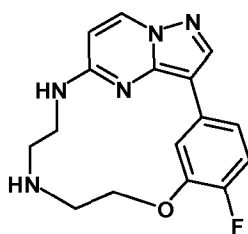
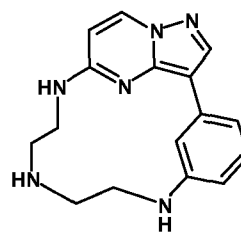
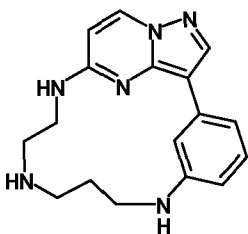
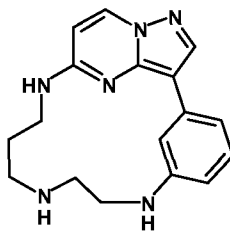
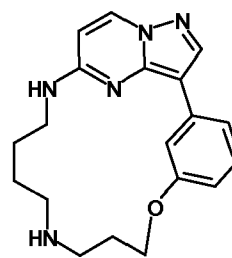
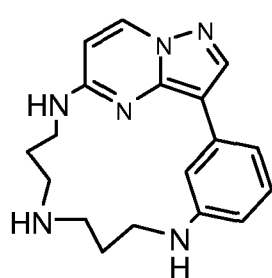
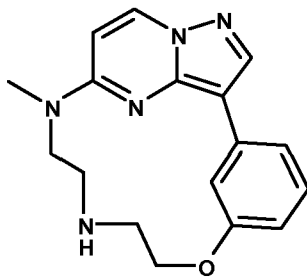
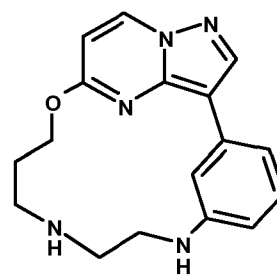
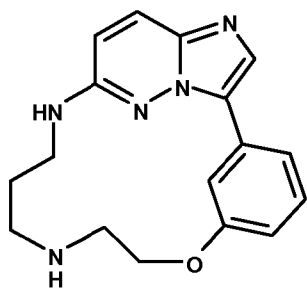
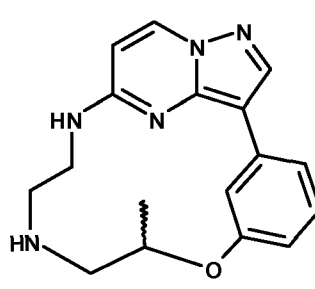
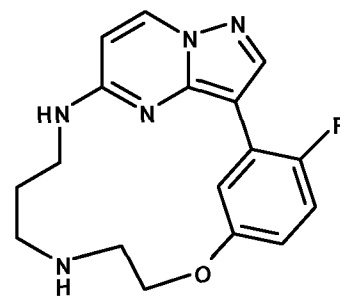
with the proviso that said compound is not

-123-

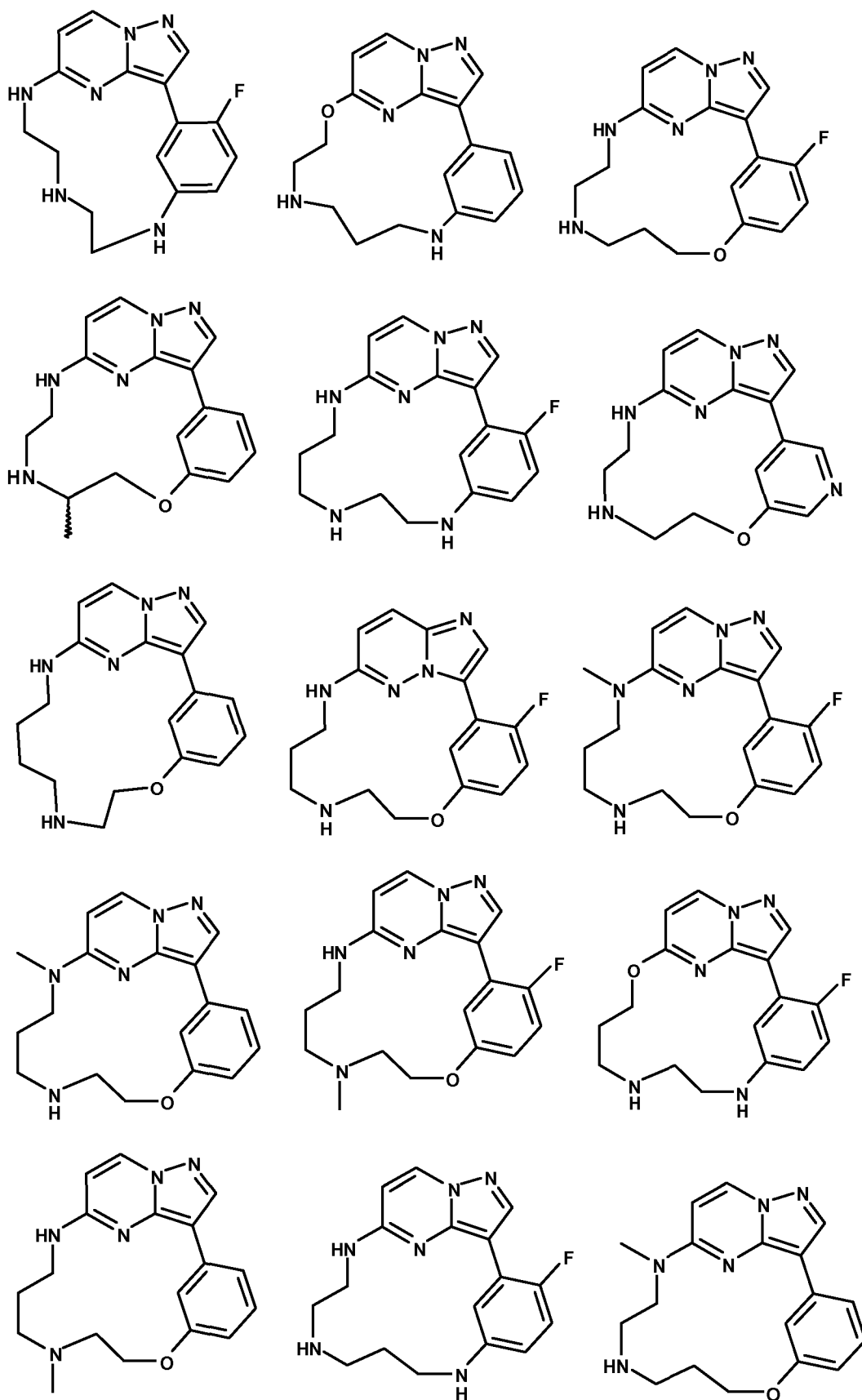


20. A compound selected from the list comprising:

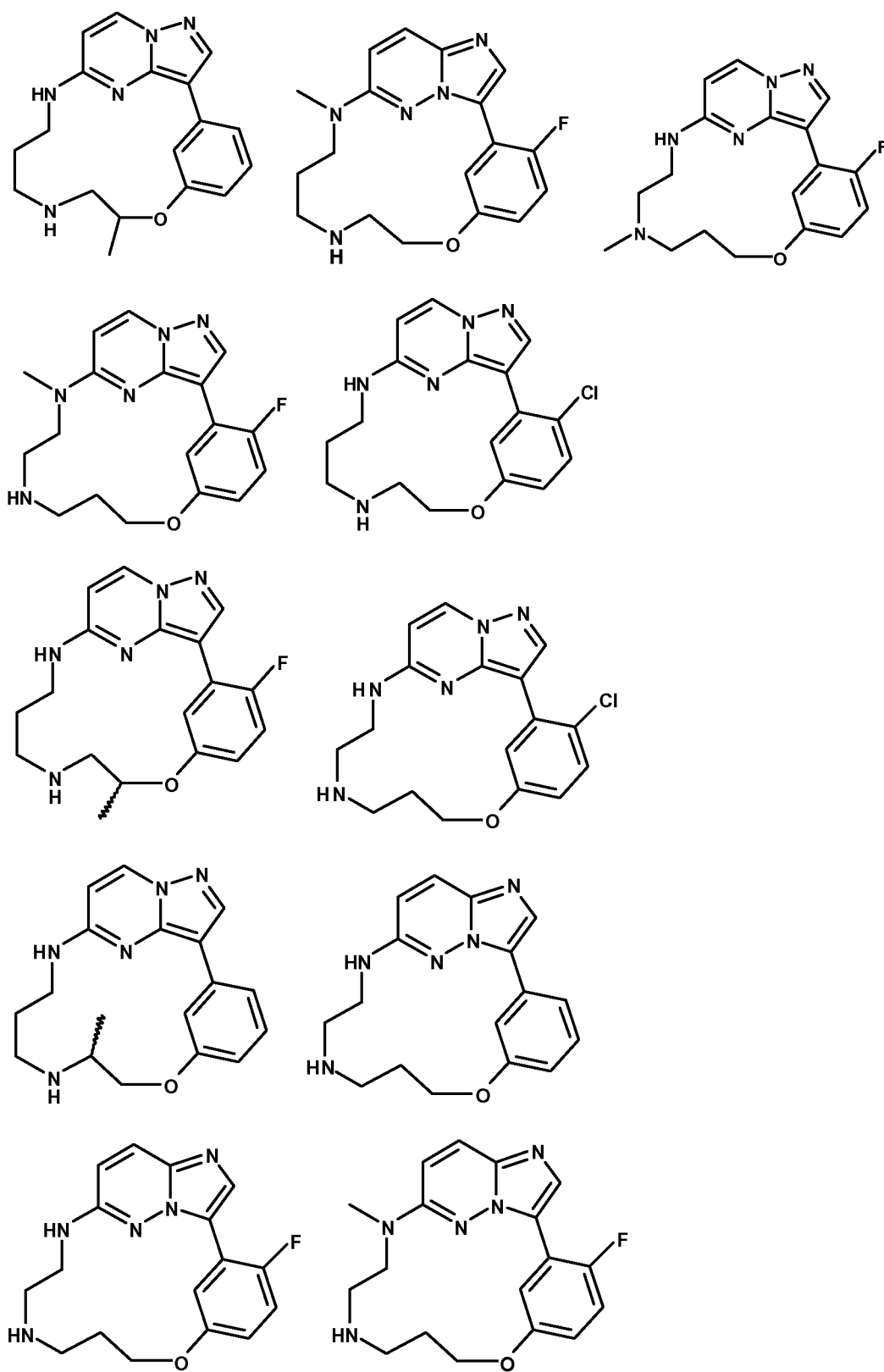
5



-124-



-125-



-126-

