

ALPHA-SYNUCLEIN BINDERS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit or priority to U.S. Provisional Application No. 63/485,159, filed February 15, 2023, the disclosure of which is incorporated herein by its entirety.

BACKGROUND OF THE INVENTION

[0002] Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease (PD), Huntington's disease, amyotrophic lateral sclerosis and prion diseases are debilitating diseases which affect cognition and/or muscle control. These diseases are a subset of protein misfolding diseases. Protein folding is an essential process for protein function in all organisms, and conditions that disrupt protein folding present a threat to cell viability. In some cases, the disease arises because a specific protein is no longer functional when adopting a misfolded state. In other diseases, the pathological state originates because misfolding occurs concomitantly with aggregation, and the underlying aggregates are detrimental. Even though neurodegenerative diseases such as Alzheimer's and Parkinson's are caused by different proteins, both involve the accumulation of insoluble fibrous protein deposits, called amyloids. For example, Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA), which are collectively referred to as "synucleinopathies," have been linked to the accumulation of aggregated forms of the alpha-synuclein protein in neurons in the brain (see *Nat. Rev. Neuro.* 2013, 9, 13-24 and *J. Parkinson's Disease* 2013, 3, 565-567). As the primary neuropathologic change of PD, the degeneration of dopaminergic neurons occurs in the substantia nigra, as well as Lewy bodies (LB) and Lewy neurites (LN). To date, the pathogenic mechanism of PD has not been fully discovered.

[0003] Alpha-synuclein is a presynaptic terminal protein that consists of a 140-amino acid protein that plays an important function in the central nervous system including synaptic vesicle recycling and synthesis, vesicular storage, and neurotransmitter release. It is specifically upregulated in a discrete population of presynaptic terminals of the brain during acquisition-related synaptic rearrangement. Alpha-synuclein naturally exists in a highly soluble, unfolded state. Evidence suggests that filamentous aggregates of alpha-synuclein accumulate at the presynaptic membrane and trigger synapse dysfunction and neuronal cell death in synucleinopathies and may be the cause of Parkinson's and DLB. Alpha-synuclein aggregation has been identified

by antibody immunohistological studies as the major component of Lewy bodies, which are microscopic protein deposits in deteriorating nerve cells. Accumulation of misfolded, fibrillar alpha-synuclein in Lewy bodies (LB) and Lewy neurites (LN) is considered a hallmark of PD.

[0004] The diagnosis of PD is mainly based on the clinical symptoms such as rest tremor, bradykinesia, and rigidity, although these methods have their limitations (see *J. Neurology* **2019**, 266, 1927-1936). The current desired treatment for PD is to slow the disease progression and minimize the disease symptoms in the patients. Therefore, a method of diagnosing PD in the very early stage can greatly help the physicians to design the therapeutic paradigm accordingly, and to slow the disease progression. There remains a need for improved diagnostic methods for identifying aggregations of misfolded proteins, including alpha-synuclein for early detection and ongoing monitoring of PD in subjects (see *J. Parkinson's Disease* 2013, 3, 565-567).

[0005] An alpha-synuclein positron emission tomography (PET) tracer would be a valuable non-invasive diagnostic biomarker for spatial and temporal quantification of aggregated pathological alpha-synuclein in human brain as a Parkinson's Disease biomarker. Additionally, an alpha-synuclein PET tracer could be useful for patient selection for PD clinical trials. In this mode, an alpha-synuclein tracer could be developed as a companion diagnostic for co-registration of a therapeutic agent. Additionally, an alpha-synuclein PET tracer could be a critical disease-relevant tool for quantifying a stabilization or decrease of alpha-synuclein formation for disease-modifying PD therapeutics.

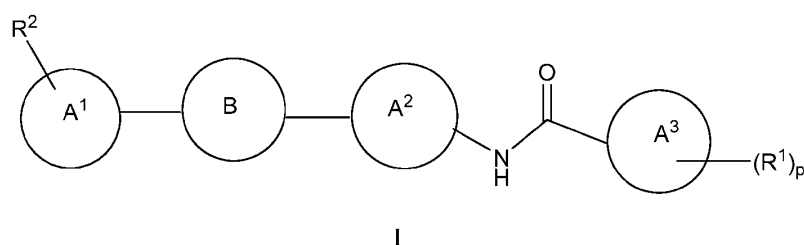
[0006] Therefore, a need exists for neuroimaging radiotracers that would allow *in vivo* imaging of alpha-synuclein pathology thereby providing insight into the deposition of alpha-synuclein aggregates in the human brain. The successful neuroimaging radiotracer must cross the blood-brain barrier, have rapid clearance from tissue and plasma, and possess high affinity and specificity for alpha-synuclein aggregates with high selectivity over binding to beta-amyloid and tau aggregated proteins due to co-expression in many PD patient populations (see *Biol Psychiatry* 2015, 78, 672-683 and *J Neuropath Exper Neurol* 2003, 62, 389-397). While alpha synuclein binding ligands have been described that have reduced selectivity over aggregated beta-amyloid (WO 2019/121661), there is a need for compounds with high levels of selectivity over co-expressed aggregated proteins in PD in order to quantify an alpha synuclein specific signal in an *in vivo* imaging study for PD patients.

[0007] The present invention advances these interests by providing compounds of Formula I as aggregated alpha-synuclein binding ligands with high selectivity over binding of aggregated beta-amyloid pathology. The instant invention also relates to a method of using the compounds

of Formula I as tracers in PET imaging to study alpha-synuclein deposits in brain *in vivo* to allow diagnosis of neurodegenerative diseases characterized by alpha-synuclein pathology. The invention further relates to a method of measuring clinical efficacy of therapeutic agents targeting alpha-synuclein pathology.

SUMMARY OF THE INVENTION

[0008] The invention is directed to compounds of Formula I, pharmaceutical salts thereof, pharmaceutical compositions comprising them, diagnostic and therapeutic uses and processes for making such compounds. An embodiment of the invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-C_{1-6}$ alkyl, OR^c or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^d or halo;

R^d is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

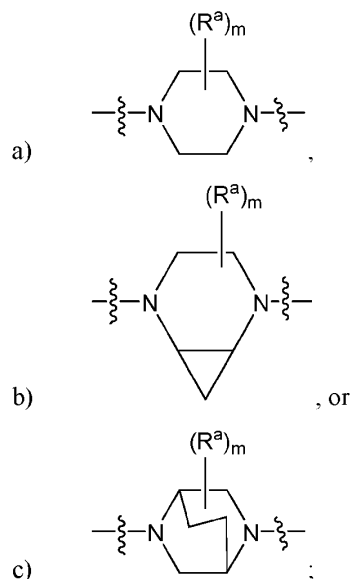
R^2 is selected from hydrogen, OR^c , NO_2 , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R ;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, imidazopyridinyl, 3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazine or phenyl;

Ring B is selected from



m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1, 2 or 3; and

q is selected from 1, 2 or 3.

[0009] The present invention is also directed to isotopically-labeled compounds of Formula I. Additionally, the present invention provides pharmaceutical compositions comprising a compound of Formula I and at least one pharmaceutically acceptable carrier.

[0010] The present invention is directed to compounds of Formula I which may be useful for binding alpha-synuclein aggregated proteins and/or tau aggregated proteins, and hence are useful in binding and imaging alpha-synuclein aggregated protein pathology in PD and non-PD synucleinopathy patients as well as aggregated Tau protein pathology Alzheimer's Disease (AD) and non-AD tauopathy patients via PET imaging techniques known commonly in the field (see *J. Nucl. Med.* 2019, 60, 93-99 and 107-114). This invention also relates to methods of using compounds of Formula I to identify patients with abnormal levels of aggregated alpha-synuclein pathology in the brain. This invention also relates to methods of using a compound of Formula I as a to measure progression of alpha-synuclein pathology over time as a biomarker in clinical assessment of potential therapeutic agents that can modify Parkinson's Disease progression.

[0011] Compounds of this invention may also be useful for imaging and detecting for other neurodegenerative diseases characterized by the deposition of alpha-synuclein aggregates such as multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB).

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1: Saturation binding experiment in aggregated beta-amyloid rich AD tissue homogenate for [³H]-105.

[0013] FIG. 2: Saturation binding experiment in triton-insoluble fraction from PD tissue homogenate enriched in aggregated alpha-synuclein for [³H]-1.

[0014] FIG. 3: [³H]-1 radioligand saturation binding data in human cortical PD tissue homogenate enriched in aggregated alpha-synuclein pathology.

[0015] FIG. 4: [³H]-1 radioligand saturation binding data in human cortical AD tissue homogenate enriched in aggregated A β .

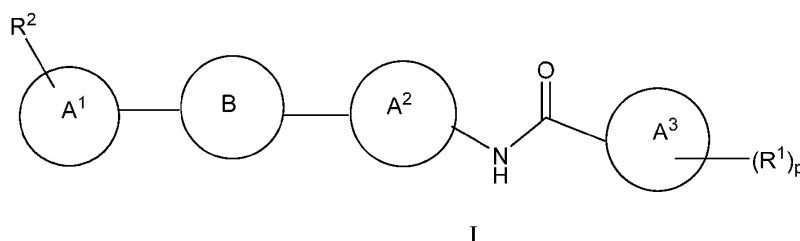
[0016] FIG. 5: [^3H]-**24** radioligand saturation binding data in human cortical PD tissue homogenate enriched in aggregated alpha-synuclein pathology.

[0017] FIG. 6: [^3H]-**24** radioligand saturation binding data in human cortical AD tissue homogenate enriched in aggregated A β .

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention provides novel substituted heterocyclic piperazine amide compounds, synthetic methods for making the compounds, pharmaceutical compositions containing them, isotopically-labeled compounds and methods of using the compounds as imaging agents.

[0019] In an embodiment, the present invention is directed to a compound of Formula I:



or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, OR^c or halo, where said alkyl is optionally substituted with one to three groups from $-\text{C}_{1-6}\text{alkyl}$, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-\text{C}_{1-6}\text{alkyl}$, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-\text{C}_{1-6}\text{alkyl}$, halo, $-(\text{CH}_2)_n\text{OR}^c$, $-\text{CN}$, $-\text{NR}^c_2$, $-(\text{CH}_2)_n\text{halogen}$, or $-\text{O}(\text{CH}_2)_n\text{halo}$;

R^c is independently selected from H or $-\text{C}_{1-6}\text{alkyl}$, where said alkyl is optionally substituted with one to three groups from $-\text{C}_{1-6}\text{alkyl}$, OR^d or halo;

R^d is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

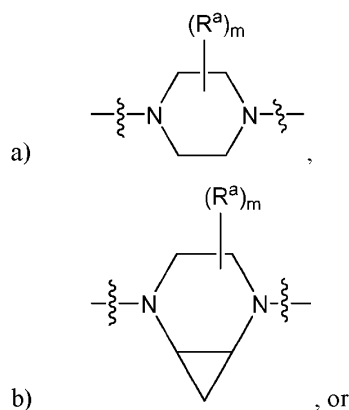
R^2 is selected from hydrogen, OR^c , NO_2 , halo or $-C_{1-6}$ alkyl;

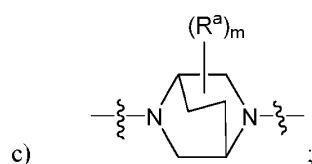
Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, imidazopyridinyl, 3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazine or phenyl;

Ring B is selected from





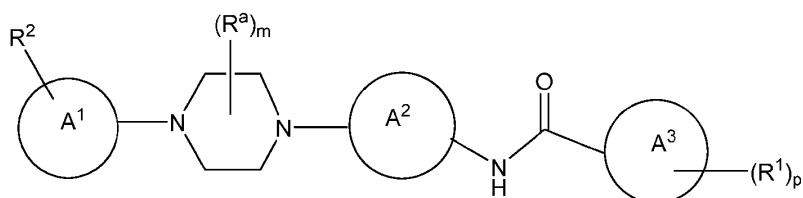
m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1, 2 or 3; and

q is selected from 1, 2 or 3.

[0020] In a further embodiment, the present invention is directed to a compound of Formula IA,



IA

or a pharmaceutically acceptable salt thereof, wherein;

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl or $-(CH_2)_{1-3}O-(CH_2)_{0-3}R$, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^d or halo;

R^d is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, $-NR_2$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R ;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2*H*-pyrido[3,2,*b*][1,4]oxazine or phenyl;

m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 0, 1, 2 or 3.

[0021] In a further embodiment, the present invention is directed to a compound of Formula IA, or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-C_{1-6}$ alkyl, OR^c or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl or $-(CH_2)_{1-3}O-(CH_2)_{0-3}R$, said alkyl optionally substituted with 1 to 3 groups of R ;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or

$-\text{O}(\text{CH}_2)_n\text{halo}$;

R^c is independently selected from H or $-\text{C}_{1-6}\text{alkyl}$, where said alkyl is optionally substituted with one to three groups from $-\text{C}_{1-6}\text{alkyl}$, OR^d or halo;

R^d is independently selected from H or $-\text{C}_{1-6}\text{alkyl}$;

R^1 is independently selected from $-(\text{CH}_2)_n\text{OR}^c$, $-(\text{CH}_2)_n\text{O}(\text{CH}_2)_n\text{R}$, $-(\text{CH}_2)_n\text{O}(\text{CH}_2)_n\text{OR}^c$, halo, $-\text{NR}_2$, unsubstituted or substituted $\text{C}_{1-6}\text{alkyl}$, unsubstituted or substituted phenyl, unsubstituted or substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , $-\text{NO}_2$, halo or $-\text{C}_{1-6}\text{alkyl}$;

Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, imidazopyridinyl, 3,4-dihydro-2H-pyrido[3,2,*b*][1,4]oxazine or phenyl;

m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1, 2 or 3; and

q is selected from 1, 2 or 3.

[0022] In a further embodiment, the present invention is directed to a compound of Formula IA, or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-C_{1-6}$ alkyl, OR^c or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

Ring A^1 is selected from pyridyl, pyrazinyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, or pyridyl, where said pyrimidinyl, phenyl, or pyridyl is optionally substituted with 1 to 3 groups of R;

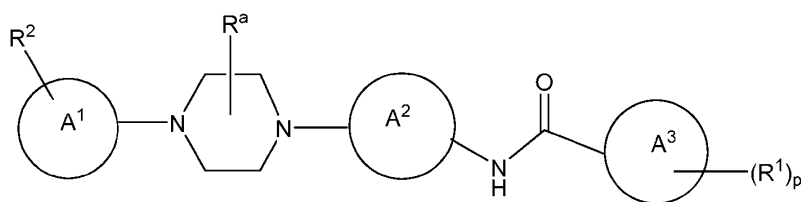
Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, triazolyl or phenyl;

m is selected from 1 or 2;

p is selected from 0, 1 or 2;

and all other substituents and variables are as defined above in Formula I.

[0023] In another embodiment, the present invention is directed to compounds of Formula IB



IB

or a pharmaceutically acceptable salt thereof wherein:

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, pyrazolyl, oxazolyl, thiazolyl or pyrimidinyl;

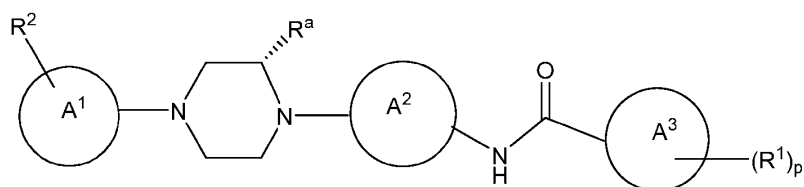
Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R ;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, pyrrolopyrazinyl, oxadiazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 1 or 2.

[0024] In another embodiment, the present invention is directed to compounds of Formula IC



IC

or a pharmaceutically acceptable salt thereof wherein:

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine or phenyl;

n is independently selected from 0, 1, 2, 3 or 4; and
p is selected from 0, 1, 2 or 3.

[0025] In another embodiment, the present invention is directed to compounds of Formula IC, or a pharmaceutically acceptable salt thereof wherein:

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-NR_2$, pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl, where said pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl can be optionally substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, pyrimidinyl, thiazolyl or pyrazolyl;

Ring A^2 is selected from pyrimidinyl, pyridyl or pyrazinyl, where said pyrimidinyl, pyridyl, or pyrazinyl is optionally substituted with 1 to 3 groups of R;

Ring A^3 is selected from pyridyl, pyrazinyl or phenyl;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 0, 1, 2 or 3.

[0026] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein Ring A^1 is selected from pyridyl, pyrazinyl, pyrimidinyl, thiazolyl or pyrazolyl. In another embodiment, Ring A^1 is selected from pyridyl, pyrazinyl, pyrazolyl or pyrimidinyl. In another embodiment, Ring A^1 is selected from pyridyl or pyrazinyl.

[0027] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein Ring A² is selected from pyrimidinyl, pyridyl or pyrazinyl, where said pyrimidinyl, pyridyl or pyrazinyl is optionally substituted with 1 to 3 groups of R. In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein Ring A² is selected from pyrimidinyl or pyrazinyl, where said pyrimidinyl or pyrazinyl is optionally substituted with 1 to 3 groups of R. In a further embodiment, Ring A² is pyrimidinyl, which is optionally substituted with 1 to 3 groups of R. In a further embodiment, Ring A² is pyrazinyl, which is optionally substituted with 1 to 3 groups of R.

[0028] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, triazolyl or phenyl. In another embodiment, Ring A³ is selected from pyridyl, pyrazinyl or phenyl.

[0029] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein R^c is independently selected from H or -C₁₋₆alkyl, where said alkyl is optionally substituted with one to three groups from -C₁₋₆alkyl, OR^d or halo. In another embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein R^c is independently selected from H or -C₁₋₆alkyl.

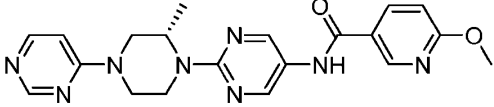
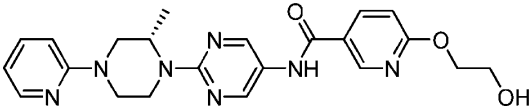
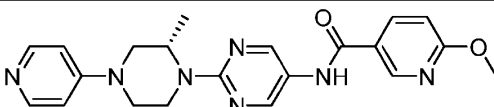
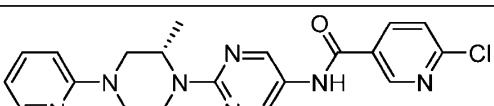
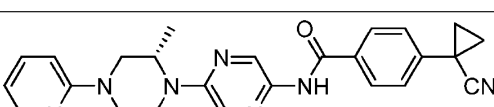
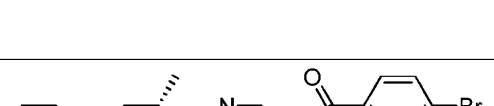
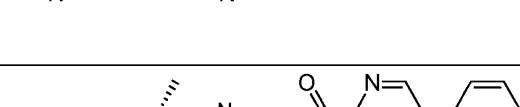
[0030] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein R¹ is selected from -(CH₂)_nOR^c, -(CH₂)_nO(CH₂)_nR, -(CH₂)_nO(CH₂)_nOR^c, halo, -NR₂, -C₁₋₆alkyl, cyclopropyl, imidazolyl, pyridyl, indolyl, pyrazolyl, triazolyl, azetidyl, phenyl, azepanyl, pyrrolopyrazinyl, pyrrolidinyl, azabicyclo-heptanyl, furyl, thiazolyl, pyrimidinyl, oxa-azabicycloheptanyl, pyridazinyl, thienyl, isoxazolyl, oxazolyl, dihydropyrrolylpyrazolyl, morpholinyl, tetrazolyl, or piperazinyl, where said alkyl, cyclopropyl, imidazolyl, pyridyl, indolyl, pyrazolyl, triazolyl, azetidyl, phenyl, azepanyl, pyrrolopyrazinyl, pyrrolidinyl, azabicyclo-heptanyl, furyl, thiazolyl, pyrimidinyl, oxa-azabicycloheptanyl, pyridazinyl, thienyl, isoxazolyl, oxazolyl, dihydropyrrolylpyrazolyl, morpholinyl, tetrazolyl, piperazinyl can be optionally substituted with one to three groups of R^b.

[0031] In an embodiment, the invention provides a compound of Formula I, IA, IB or IC, wherein R¹ is selected from -(CH₂)_nOR^c, -(CH₂)_nO(CH₂)_nR, -NR₂, pyridyl, pyrazolyl, azetidyl, pyrrolidinyl, furyl, where said pyridyl, pyrazolyl, azetidyl, pyrrolidinyl, or furyl can be optionally substituted with one to three groups of R^b.

[0032] Representative compounds of the present invention include compounds selected from

Ex. No.	Structure	Name
1		(S)-6-methoxy-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
2		N-[2-[(3S)-3-ethyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-imidazol-1-yl-pyridine-3-carboxamide
3		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-4-(3-pyridyl)benzamide
4		5-fluoro-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-1H-indole-2-carboxamide
5		6-imidazol-1-yl-N-[2-[4-(5-methyl-2-pyridyl)-3-(2,2,2-trifluoroethyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
6		6-methoxy-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
7		6-imidazol-1-yl-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
8		6-methoxy-N-[2-[(2S)-2-methyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
9		5-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrazine-2-carboxamide
10		6-methoxy-N-[2-[(2S)-4-(5-methoxy-2-pyridyl)-2-methylpiperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
11		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
12		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrazin-2-yl-piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
13		N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide
14		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide

Ex. No.	Structure	Name
15		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrimidin-4-yl]piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
16		6-(2-hydroxyethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)]piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
17		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-pyridyl)]piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
18		6-chloro-N-[2-[(2S)-2-methyl-4-(2-pyridyl)]piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
19		4-(1-cyanocyclopropyl)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)]piperazin-1-yl]pyrazin-2-yl]benzamide
20		6-bromo-N-[2-[(2S)-2-methyl-4-(2-pyridyl)]piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
21		N-[2-[(2S)-2-methyl-4-(2-pyridyl)]piperazin-1-yl]pyrimidin-5-yl]-5-phenyl-pyrazine-2-carboxamide

Ex. No.	Structure	Name
22		6-methoxy-N-[2-[(2R)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
23		6-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
24		2-methoxy-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-4-carboxamide
25		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
26		4-(1-cyanocyclopropyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
27		N-[2-[(2S)-4-(6-fluoro-2-pyridyl)-2-methyl-piperazin-1-yl]pyrimidin-5-yl]-6-methoxy-pyridine-3-carboxamide
28		6-(difluoromethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

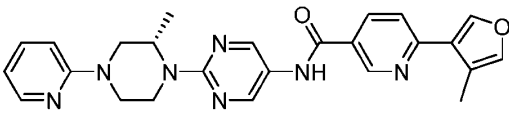
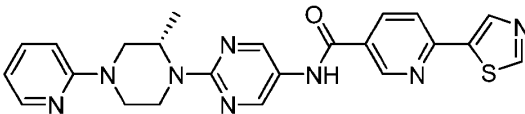
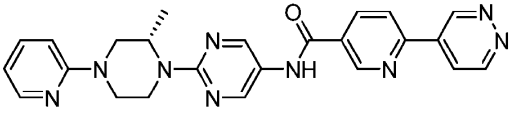
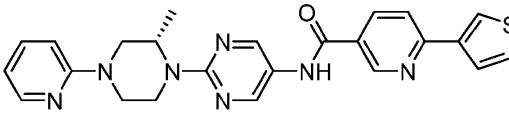
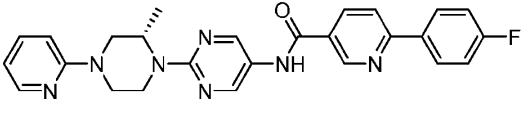
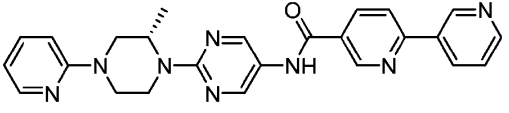
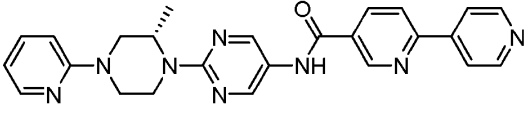
Ex. No.	Structure	Name
29		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyridine-2-carboxamide
30		6-(2-fluoroethoxy)-N-[6-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-3-pyridyl]pyridine-3-carboxamide
31		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-2-pyridyl]pyridine-2-carboxamide
32		2-(2-fluoroethoxy)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyrimidine-5-carboxamide
33		6-methoxy-N-[2-[(3R)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
34		6-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
35		N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide

Ex. No.	Structure	Name
36		2-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrimidine-5-carboxamide
37		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide
38		6-(4-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
39		6-(4-fluoropyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
40		6-(3-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
41		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(triazol-1-yl)pyridine-3-carboxamide
42		6-(3-methylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

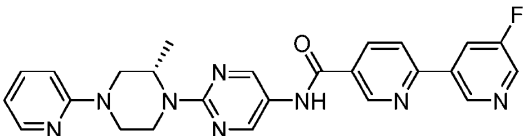
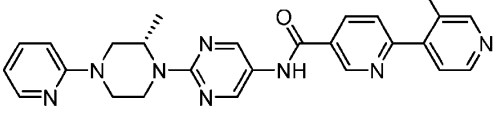
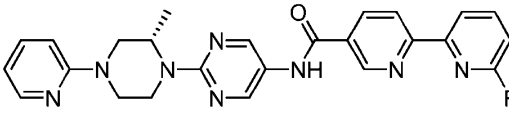
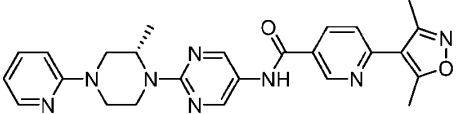
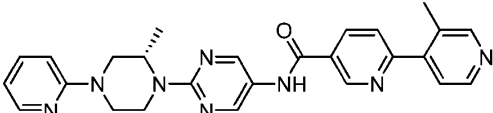
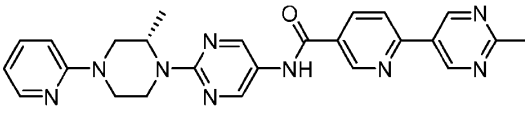
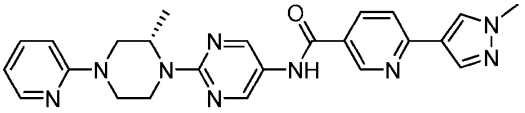
Ex. No.	Structure	Name
43		6-(2-methylimidazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
44		(S)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(2H-1,2,3-triazol-2-yl)nicotinamide
45		6-(3,5-dimethylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
46		6-(3,3-difluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
47		6-[(3R)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
48		6-[rac-(4S)-2-azabicyclo[2.2.1]heptan-2-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
49		6-[(3S)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
50		6-(3,3-dimethylpyrrolidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
51		6-(3-fluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
52		6-(3-methylazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
53		6-(azepan-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
54		6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
55		6-[methyl(propyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
56		6-(azetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
57		6-(methylamino)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
58		6-(dimethylamino)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
59		6-[ethyl(2-hydroxyethyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
60		6-(3-hydroxyazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
61		6-[isobutyl(methyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
62		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrrolidin-1-yl-pyridine-3-carboxamide
63		6-(3-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

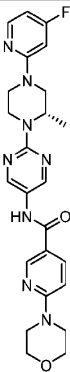
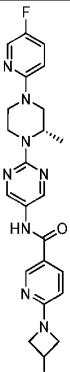
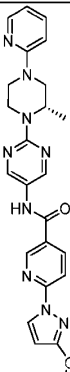
Ex. No.	Structure	Name
64		6-(4-methyl-3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
65		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-thiazol-5-yl-pyridine-3-carboxamide
66		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyridazin-4-yl-pyridine-3-carboxamide
67		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-thienyl)pyridine-3-carboxamide
68		6-(4-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
69		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-pyridyl)pyridine-3-carboxamide
70		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(4-pyridyl)pyridine-3-carboxamide

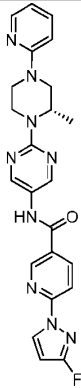
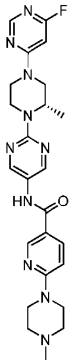
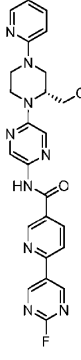
Ex. No.	Structure	Name
71		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-phenyl-pyridine-3-carboxamide
72		6-(3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
73		6-(4-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
74		6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
75		6-(2-methylpyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
76		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrimidin-5-yl-pyridine-3-carboxamide
77		6-(2-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

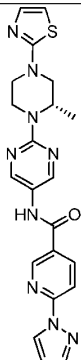
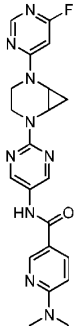
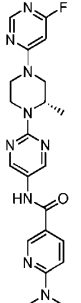
Ex. No.	Structure	Name
78		6-(5-fluoro-3-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
79		6-(3-fluoro-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
80		6-(6-fluoro-2-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
81		6-(3,5-dimethylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
82		6-(3-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
83		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(2-methylpyrimidin-5-yl)pyridine-3-carboxamide
84		6-(1-methylpyrazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

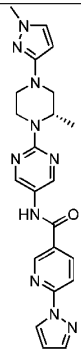
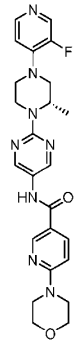
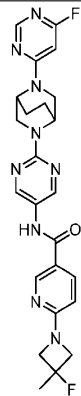
Ex. No.	Structure	Name
85		6-(3-methylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
86		4-(3-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
87		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
88		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(2-methyl-4-(4-nitropyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
89		(S)-N-(2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
90		(S)-N-(2-(2-methyl-4-(2-nitropyridin-4-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
91		(S)-6-(1H-imidazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

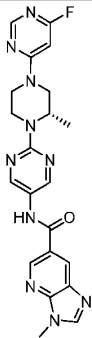
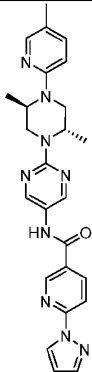
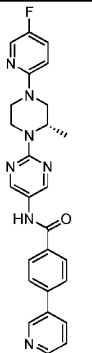
Ex. No.	Structure	Name
92		N-(2-((2S,6R)-2,6-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-5'-fluoro-[2,3'-bipyridine]-5-carboxamide
93		N-(2-((S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-((R)-3-fluoropyrrolidin-1-yl)nicotinamide
94		(R)-6-(1H-imidazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
95		(S)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide
96		(S)-6-(3-fluoroazetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
97		(S)-6-(3-methoxy-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
98		(S)-6-(3-fluoro-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
99		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(4-methylpiperazin-1-yl)nicotinamide
100		(R)-6-(2-fluoropyrimidin-5-yl)-N-(5-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)nicotinamide

Ex. No.	Structure	Name
101		(S)-N-(2-(2-methyl-4-(thiazol-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
102		6-(dimethylamino)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyrimidin-5-yl)nicotinamide
103		(S)-6-(dimethylamino)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
104		(S)-N-(2-(2-methyl-4-(1-methyl-1H-pyrazol-3-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
105		(S)-N-(2-(4-(3-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide
106		6-(3-fluoro-3-methylazetidin-1-yl)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
107		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide
108		N-(2-((2S,5R)-2,5-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
109		(S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-4-(pyridin-3-yl)benzamide

Ex. No.	Structure	Name
110		6-(3,3-difluoroazetidin-1-yl)-N-(2-((2R,3R)-4-(4-fluoropyridin-2-yl)-2,3-dimethylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
111		(S)-N-(2-(4-(2-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide
112		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
113		(S)-6-(azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
114		(R)-6-(4-(fluoromethyl)-1H-pyrazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
115		(S)-N-(5-(4-(6-fluoropyrimidin-4-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
116		(S)-6-(3-fluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
117		(R)-N-(5-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
118		(S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
119		(R)-N-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
120		(R)-N-(2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
121		(R)-N-(4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

Ex. No.	Structure	Name
122		(S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(pyrrolidin-1-yl)nicotinamide
123		(S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
124		(R)-N-(5-(3-((2-fluoroethoxy)methyl)-4-(5-fluoropyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
125		(S)-2-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)pyrimidine-5-carboxamide
126		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
127		(S)-N-(2-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
128		(R)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

Ex. No.	Structure	Name
129		(R)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
130		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
131		(R)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
132		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
133		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
134		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
135		(S)-6'-amino-6-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-[2,3'-bipyridine]-5-carboxamide

Ex. No.	Structure	Name
136		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(5-fluoropyrazin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
137		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
138		(R)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
139		(S)-6-(3-fluoroazetidin-1-yl)-N-(6-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyridin-3-yl)nicotinamide
140		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
141		(S)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

Ex. No.	Structure	Name
142		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
143		(S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
144		(S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

or a pharmaceutically acceptable salt thereof.

[0033] The present invention is directed to compound of Formula I for use as an imaging agent.

[0034] An embodiment of the invention comprises a compound selected from Ex. No. 1, 6, 9, 11, 12, 37, 39, 47, 51, 57, 58, 64, 72, 75, 78, 79, 80, 91, 96, 112, 113, 115, 116, 118, 134, 138 and 141, or a pharmaceutically acceptable salt thereof. A further embodiment of the invention comprises a compound selected from Ex. No. 39, 47, 51, 78, 79, 96, 112, 116 and 141 or a pharmaceutically acceptable salt thereof. Another embodiment of the invention comprises a compound selected from Ex. No. 96, 112, 113, 115, 116, 118, 134, 138 and 141, or a pharmaceutically acceptable salt thereof. A further embodiment of the invention comprises a compound selected from Ex. No. 96, 112, 116 and 141, or a pharmaceutically acceptable salt thereof.

[0035] Another aspect of the invention is directed to compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are labeled with an isotope selected from ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}CL , ^{82}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I or ^{131}I . In a further aspect of the invention, the compounds of Formula I are isotopically labeled with ^3H , ^{11}C or ^{18}F . Examples of isotopically labeled a compound of Formula I, or

pharmaceutically acceptable salts thereof, include, but are not limited to, ³H-**1**, ³H-**24**, ¹⁸F-**39**, ¹⁸F-**47**, ¹⁸F-**51**, ¹⁸F-**78**, ¹⁸F-**79**, ¹¹C-**94**, ¹⁸F-**96**, ¹¹C-**97**, ¹⁸F-**116**, ¹¹C-**117**, ¹¹C-**118**, ¹⁸F-**141**, and ¹¹C-**143**, and the like. Further examples of isotopically labeled a compound of Formula I, or pharmaceutically acceptable salts thereof, include, but are not limited to ³H-**1**, ³H-**24**, ¹⁸F-**39**, ¹⁸F-**47**, ¹⁸F-**51**, ¹⁸F-**78**, ¹⁸F-**79**, ¹⁸F-**96**, ¹⁸F-**116**, and ¹⁸F-**141**, and the like. Further examples of isotopically labeled a compound of Formula I, or pharmaceutically acceptable salts thereof, include, but are not limited to ¹¹C-**118**, and ¹¹C-**143**, and the like. Further examples of isotopically labeled a compound of Formula I, or pharmaceutically acceptable salts thereof, include, but are not limited to ¹⁸F-**96**, ¹⁸F-**116**, and ¹⁸F-**141**, and the like. Further examples of isotopically labeled a compound of Formula I, or pharmaceutically acceptable salts thereof, include, but are not limited to ¹⁸F-**78**, ¹⁸F-**79**, ¹⁸F-**96**, ¹⁸F-**116**, and ¹⁸F-**141**, and the like. Further examples of isotopically labeled a compound of Formula I, or pharmaceutically acceptable salts thereof, include, but are not limited to ¹⁸F-**96**, ¹⁸F-**116**, and ¹⁸F-**141**, and the like.

[0036] Another aspect of the invention is directed to compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are labeled with an isotope selected from ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶CL, ⁸²Br, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I or ¹³¹I, for use as an imaging agent.

[0037] In one embodiment the present invention provides pharmaceutical compositions comprising a compound of the invention, for example, a compound of Formula I, and at least one pharmaceutical excipient.

[0038] Compounds of Formula I are inhibitors and/or binders of aggregated alpha-synuclein or tau protein. Compounds of Formula I, and isotopically labeled variants thereof, may be useful for the diagnosis and/or treatment of Parkinson's disease and/or Alzheimer's disease. Means of detecting labels are well known to those skilled in the art. For example, isotopic labels may be detected using imaging techniques, photographic film or scintillation counters. In a preferred embodiment, the label is detected *in vivo* in the brain of the subject by imaging techniques, for example positron emission tomography (PET).

[0039] The compounds of Formula (I) may also form a component of bifunctional compounds that are targeted protein degrader compounds that bind aggregated alpha-synuclein proteins. Such targeted alpha-synuclein protein degrader compounds contain a target protein binding moiety which is formed from a compound of Formula (I) and an E3 ubiquitin ligase-binding moiety. The

targeted alpha-synuclein protein degrader compounds typically contain a linker group joining the alpha-synuclein protein binding moiety and the E3 ubiquitin ligase-binding moiety. The E3 ubiquitin ligase-binding moieties in the alpha-synuclein targeted protein degrader compounds can be, but are not limited to, binders to the E3 ligase von Hippel-Lindau protein, binders to the E3 ligase cereblon protein, or binders to the MDM2 protein. Such compounds can be administered in pharmaceutical compositions to treat disease conditions, including but not limited to, the conditions disclosed herein.

[0040] In the description that follows conventional structural representation is employed and includes conventional stereochemical notation for certain asymmetric carbon centers. Thus, structural representation of compounds of the invention includes conventional stereochemical notation for some asymmetric carbon centers shown in the example compounds. Accordingly, in such instances, solid black “wedge” bonds represent bonds projecting from the plane of the reproduction medium, “hashed wedge” bonds representing descending bonds into the plane of the reproduction medium, and a “wavey” line appended to a carbon bearing a double bond indicates both possible cis and trans orientations are included. As is conventional, plain solid lines represent all spatial configurations for the depicted bonding. Accordingly, where no specific stereochemical notation is supplied the representation contemplates all stereochemical and spatial orientations of the structural features.

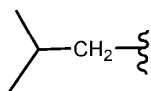
[0041] As is shown in the examples of the invention, and mentioned above, particular asymmetric carbon centers are structurally represented using conventional “Solid Wedge” and “Hash Wedge” bonding representation. For the most part, absolute configuration has not been determined for the example compounds, but has been assigned by analogy to specific example compounds of known stereochemical configurations (determined by X-ray crystallography) prepared using the same or analogous reaction conditions and starting reagents and isolated under the same chromatographic conditions. Accordingly, specific assignment of the configurations structurally represented herein is meant to identify the specific compounds prepared has having an excess of one particular stereoisomer and is not put forth herein necessarily as being a statement of the absolute determination of the stereochemical structure of said compound unless otherwise noted in the data presented.

[0042] It will be appreciated that where isomeric mixtures are obtained, the preparation of individual stereoisomers in significant percentages of enantiomeric excess can be carried out, if desired, by separation of the mixture using customary methods, for example by chromatography or crystallization, or by the use of stereochemically uniform starting materials for the synthesis

described, or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of Formula I or it can be done on a final racemic product.

[0043] Where indicated herein, absolute stereochemistry is determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Unless a particular isomer, salt, solvate (including hydrates) or solvated salt of such racemate, enantiomer, or diastereomer is indicated, the present invention includes all such isomers, as well as salts, solvates (including hydrates) and solvated salts of such racemates, enantiomers, diastereomers and mixtures thereof.

[0044] Where a wavy line terminates a conventional bond (as opposed to connecting two atoms within a structure) it indicates a point of bonding to a structure, e.g.:



indicates a the secondary-butyl moiety is bonded via the methylene group via the bond terminated with the wavy line. Where an alphabetical notation is used to depict a substituent moiety, a dash is employed to indicate the point of bonding to the indicated substrate, e.g.: -CH₂-C(O)-CH₂Cl indicates the acetyl chloride moiety is bonded via the methylene portion of the moiety.

[0045] Where compounds of Formula I are capable of tautomerization, all individual tautomers as well as mixtures thereof are included in the scope of this invention.

[0046] When any variable (e.g., R, R¹, n, heteroaryl, alkyl, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence unless otherwise specified at the point of definition. One of ordinary skill in the art will recognize that choice of combinations of the various substituents defined in a structural representation, i.e., R¹, R², etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability, and combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0047] A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic

administration to a subject). The compounds of the present invention are limited to stable compounds embraced by Formula I.

[0048] Where any variable or moiety is expressed in the form of a range, e.g., $(-\text{CH}_2-)_{1-4}$, both of the extrema of the specified range are included (i.e., 1 and 4 in the example) as well as all of the whole number values in between (i.e., 2 and 3 in the example).

[0049] It is understood that reference to "Formula I" also encompasses compounds of Formula IA, Formula IB and Formula IC, unless indicated otherwise.

[0050] As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

[0051] "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

[0052] As used herein, "cycloalkyl" is intended to include cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Preferably, cycloalkyl is C₃-C₁₀ cycloalkyl. Examples of such cycloalkyl elements include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0053] As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In an embodiment of the instant invention, aryl is phenyl or naphthyl. In a further embodiment, aryl is phenyl.

[0054] The term heterocyclyl, heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic can include heteroaryl moieties when two rings are fused together. Examples of heterocyclic elements include, but are not limited to, azabicyclo[2.2.1]heptanyl, azepanyl, azetidiny, benzodioxolyl, chromanyl, dihydrobenzofuryl, dihydrobenzothieryl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydro-pyrrolo[1,2-b]pyrazolyl, 1,3-dioxolanyl, imidazolidinyl, indolinyl, isochromanyl, isoindolinyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptanyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyrazolidinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, and thiamorpholinyl.

[0055] In an embodiment, heterocyclyl is selected from azabicyclo[2.2.1]heptanyl, azepanyl, azetidiny, dihydro-pyrrolo[1,2-b]pyrazolyl, morpholiny, oxa-5-azabicyclo[2.2.1]heptanyl, piperidyl, piperaziny, pyrazolidiny, pyrrolidiny, pyrroly, and tetrahydrofuryl. In another embodiment, heterocyclyl is selected from azabicyclo[2.2.1]heptanyl, azepanyl, azetidiny, dihydro-pyrrolo[1,2-b]pyrazolyl, oxa-5-azabicyclo[2.2.1]heptanyl, piperaziny, and pyrrolidiny.

[0056] "Heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, azepiny, furanyl, furyl, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoxazolyl, isoquinoliny, isothiazolyl, naphthyridiny, oxazolyl, oxadiazolyl, pyridyl, pyraziny, pyrazolyl, pyridaziny, pyrimidiny, 5H-pyrrolo[2,3-b]pyraziny, pyrroly, quinazoliny, quinoliny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, thiazolyl, thienofuryl, thienothienyl, thienyl, triazolyl and the like. In an embodiment, heteroaryl is selected from furyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyraziny, pyrazolyl, pyridaziny, pyrimidiny, 5H-pyrrolo[2,3-b]pyraziny, tetrazolyl, thiazolyl, thienyl, triazolyl and the like.

[0057] For use in medicine, the salts of the compounds of Formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

[0058] When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

[0059] The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

[0060] If the compounds of Formula I simultaneously contain acidic and basic groups in the molecule the invention also includes zwitterions, in addition to the salt forms described above.

[0061] The present invention also embraces isotopically-labeled compounds of the present invention which are structurally identical to those recited herein, but for the fact that a statistically significant percentage of one or more atoms in that form of the compound are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number of the most abundant isotope usually found in nature, thus altering the naturally occurring abundance of that isotope present in a compound of the invention. Another aspect of the invention relates to use of the isotopically labeled compounds as neuroimaging radiotracers for *in vivo* imaging of the brain for alpha-synuclein aggregates in the diagnosis, monitoring, and/or treatment of Parkinson's Disease (PD). Another aspect of the invention is use of the isotopically labeled compounds in PET, which is an *in vivo* analysis technique in the diagnosis, monitoring, and/or treatment of PD. The ^3H , ^{11}C or ^{18}F labeled compounds can be used in *in vitro* and *in vivo* methods for the determination of binding, receptor occupancy and metabolic studies including covalent labeling.

[0062] Another aspect of the invention relates to the use of the isotopically labeled compounds to screen for new chemical matter. In particular, various isotopically labeled compounds find utility in magnetic resonance imaging, autoradiography and other similar analytical tools. The present invention is meant to include all suitable isotopic variations of the compounds of Formula I. Examples of isotopes that can be preferentially incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, iodine, fluorine and chlorine, for example, but not limited to: ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I or ^{131}I isotopically labeled substituted heterocyclic derivative

compounds of Formula I. It will be appreciated that other isotopes may be incorporated by known means also. In particular, the present invention is directed to ^{11}C , ^{13}C , ^{14}C , ^{18}F , ^{15}O , ^{13}N , ^{35}S , ^2H , and ^3H isotopes of compounds of Formula I, compositions and methods of their preparation and use as radiotracers or PET tracers in diagnosing and measuring the effects of a compound in the treatment of PD. In a further embodiment, the present invention is directed to compounds of Formula I that are isotopically labeled with ^3H , ^{11}C or ^{18}F , along with compositions and methods of their preparation and use as PET tracers in diagnosing and measuring the effects of a compound in the treatment of PD. The present invention also relates to non-toxic alpha-synuclein protein binding compounds that can rapidly cross the blood brain barrier, have low non-specific binding properties and are rapidly cleared from the system. This and other aspects of the invention will be realized upon review of the specification in its entirety.

[0063] Isotopically-enriched compounds within Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0064] As indicated herein the present invention includes isotopically labeled compounds of the invention. An "isotopically-labeled", "radio-labeled", "tracer", "radiotracer", "labeled tracer" or "radioligand" compound, is a compound where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides (i.e., "detectable isotopes") that may be incorporated in compounds of the present invention include but are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I and ^{131}I . The isotopically labeled compounds of the invention need only to be enriched with a detectable isotope to, or above, the degree which allows detection with a technique suitable for the particular application. The radionuclide that is incorporated in the instant radiolabeled compounds will depend on the specific application of that radiolabeled compound. In another embodiment of the invention the radionuclides are represented by ^{11}C , ^{13}C , ^{14}C , ^{18}F , ^{15}O , ^{13}N , ^{35}S , ^2H , and ^3H , preferably ^{11}C , ^3H , and ^{18}F .

[0065] The isotopically labeled compounds of this invention are prepared by incorporating a selected isotope into the substrate molecule. This is accomplished by utilizing reagents that have had one or more of the atoms contained therein made radioactive by placing them in a source of radioactivity such as a nuclear reactor, a cyclotron and the like. Additionally, many isotopically labeled reagents, such as $^2\text{H}_2\text{O}$, $^3\text{H}_3\text{Cl}$, $^{14}\text{C}_6\text{H}_5\text{Br}$, $\text{ClCH}_2^{14}\text{COCl}$ and the like, are commercially

available. The isotopically labeled reagents are then used in standard organic chemistry synthetic techniques to incorporate the isotope atom, or atoms, into a compound of Formula I as described below. The following Schemes illustrate how to make the compounds of Formula I.

[0066] This invention further relates to a pharmaceutical composition comprising an effective amount of at least one compound of Formula I and a pharmaceutically acceptable carrier. The composition may comprise, but is not limited to, one or more buffering agents, wetting agents, emulsifiers, suspending agents, lubricants, adsorbents, surfactants, preservatives and the like. The composition may be formulated as a solid, liquid, gel or suspension for oral administration (e.g., drench, bolus, tablet, powder, capsule, mouth spray, emulsion); parenteral administration (e.g., subcutaneous, intramuscular, intravenous, epidural injection); topical application (e.g., cream, ointment, controlled-released patch, spray); intravaginal, intrarectal, transdermal, ocular, or nasal administration. In a further embodiment, the pharmaceutical composition of the present invention may be formulated for parenteral administration, such as an intravenous formulation.

[0067] This invention provides radiolabeled compounds of Formula I as alpha-synuclein imaging agents and synthetic precursor compounds from which they are prepared. The compounds of Formula I bind aggregated alpha-synuclein to potentially track the progression of age-related diseases such as PD, as well as other synucleinopathies and neurodegenerative diseases, such as Multiple Systems Atrophy (MSA), Dementia with Lewy Bodies (DLB), etc. The compounds of this invention may also be used in combination with a broad range of cognition deficit enhancement agents. Thus, in another embodiment of this invention a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of Formula (I) is administered concurrently, simultaneously, sequentially or separately with another pharmaceutically active compound or compounds used in AD / PD therapies including for example donepezil, memantine, tacrine, carvidopa, levodopa, MOA-B inhibitors, catechol O-methyltransferase (COMT) inhibitors, etc. and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

[0068] An objective of the present invention is to provide a radiopharmaceutical agent, such as an isotopically labeled compound of Formula I, that is useful in alpha-synuclein imaging and has high specific radioactivity and high target tissue selectivity by virtue of its high affinity for alpha-synuclein aggregates.

[0069] In accordance with the present invention, a method for imaging alpha-synuclein deposits in a patient, wherein an isotopically-labeled compound of Formula I is employed as the imaging agent, comprises the steps of: a) placing a human patient in a supine position in a PET camera; b)

administering, intravenously, about 0.1 to about 10 mCi of an isotopically-labeled compound of Formula I to the patient; and c) performing an emission scan of the cerebral region of the patient's head to identify aggregations of alpha-synuclein in the brain tissue of the patient. The technique for performing an emission scan of the head is well known to those of skilled in the art. PET techniques are described in Freeman *et al.*, Freeman and Johnson's Clinical Radionuclide Imaging, 3rd. Ed. Vol. 1 (1984); Grune & Stratton, New York; Ennis *et Q.* Vascular Radionuclide Imaging: A Clinical Atlas, John Wiley & Sons, New York (1983).

[0070] The term "labeled tracer" refers to any molecule which can be used to follow or detect a defined activity *in vivo*, for example, a preferred tracer is one that accumulates in the regions where alpha-synuclein aggregates may be found. Preferably, the labeled tracer is one that can be viewed in a living experimental animal, healthy human or patient (referred to as a subject), for example, by positron emission tomography (PET) scanning. Suitable labels include, but are not limited to radioisotopes, fluorochromes, chemiluminescent compounds, dyes, and proteins, including enzymes.

[0071] The present invention also provides methods of determining *in vivo* activity of an enzyme or other molecule. In an embodiment, an isotopically labeled compound of Formula I is used as a tracer to track the binding activity of aggregated alpha-synuclein protein in the brain and central nervous system.

[0072] Biomarkers of Parkinson's disease state, prognosis and progression will all be useful for general diagnostic utilities as well as for clinical development plans for therapeutic agents for Parkinson's disease. Compounds of Formula I may be used to provide biomarker information for patients in clinical trials for novel symptomatic and disease-modifying Parkinson's disease treatments and to assist in patient selection and assignment to cohorts. The present invention will serve as one of the biomarkers of disease state in order to get the correct patients into the proper PhIIb trial cohort. In addition, the present invention can serve as one marker of disease prognosis as an entry inclusion criterion in order to enhance the probability that the disease will progress in the placebo treatment arm, an issue that continues to plague Parkinson's disease clinical trials. Finally, the present invention can serve as one biomarker of disease progression to monitor the clinical course of patients on therapy and could provide an independent biomarker measure of treatment response by a therapeutic drug. The tracer can be selected in accordance with the detection method chosen. Before conducting the method of the present invention, a diagnostically effective amount of a labeled or unlabeled compound of the invention is administered to a living body, including a human.

[0073] The present invention also provides a method of measuring the clinical efficacy of therapeutic agents useful for treating Parkinson's Disease (PD) comprising the steps of: a) administering an isotopically-labeled compound of Formula I to the patient diagnosed with PD before treatment with said therapeutic agent, b) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue, c) administering an isotopically-labeled compound of Formula I to the patient after treatment with said therapeutic agent, d) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue after treatment, and e) analyzing whether said therapeutic agent stopped or decreased the progression of alpha-synuclein aggregate formation in the patient's brain tissue.

[0074] The diagnostically effective amount of the labeled or unlabeled compound of the invention to be administered before conducting the *in-vivo* method for the present invention is within a range of from 0.1 ng to 100 mg per kg body weight, preferably within a range of from 1 ng to 10 mg per kg body weight.

[0075] The compounds of the present invention have utility in diagnosing, monitoring, and measuring Parkinson's disease and other non-PD synucleinopathies such as Multiple Systems Atrophy (MSA), Dementia with Lewy Bodies (DLB).

[0076] In preferred embodiments, the compounds of the invention are useful in diagnosing, monitoring or measuring Parkinson's Disease, non-PD synucleinopathies, neurodegenerative disease, cognitive disorders, schizophrenia, pain disorders and sleep disorders.

[0077] The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

[0078] In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of Formula I, is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

[0079] As the term is used herein, “patients” (alternatively “subjects”) refers to an animal, preferably a mammal, and in particular a human, in need of assessment via an imaging study. As used herein, the term “administration” and variants thereof (*e.g.*, “administering” a compound) in reference to a compound of Formula I means providing the compound, or a pharmaceutically acceptable salt thereof, to a subject in need of treatment.

[0080] The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the invention.

[0081] The compounds described herein can be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. Deuterated versions of the compounds of the invention can be prepared by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. Reagents and starting materials for preparing the intermediates and example compounds are commercially available, unless indicated otherwise. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). ¹H NMR spectra were recorded at 300-500 MHz.

List of Abbreviations

AD	=	Alzheimer's disease
(^{ipc} ADI)NiBr ₂	=	N,N'-bis(1R,2R,3R,5S)-(-)-isopinocampheyl-2,3-butanediimine nickel(II) bromide
Anal.	=	analytical
calc.	=	calculated
BSA	=	Bovine Serum Albumin
Cellulose SC	=	immobilized-type polysaccharide stationary phase [Cellulose tris(3,5-dichlorophenylcarbamate) selector]

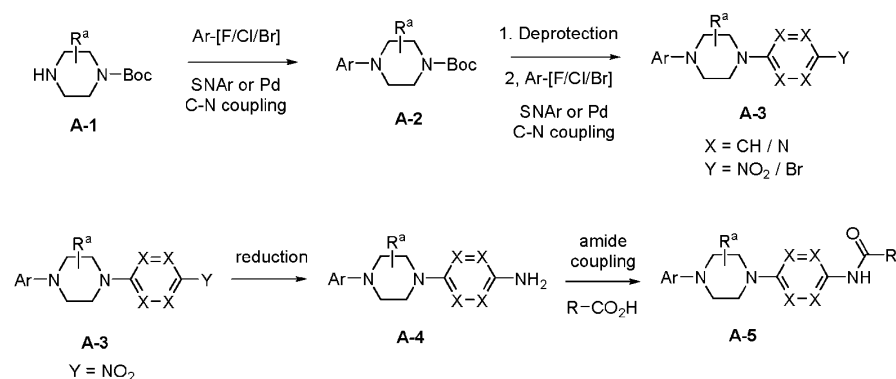
CPME	=	cyclopentyl methylether
Crabtree's catalyst	=	(1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(i) hexafluorophosphate
Cs ₂ CO ₃	=	cesium carbonate
CsF	=	cesium fluoride
DAST	=	diethylaminosulfur trifluoride
DCM	=	dichloromethane
DEA	=	diethylamine
DIPEA	=	<i>N,N</i> -diisopropylethylamine
DMF	=	dimethylformamide
DMSO	=	dimethyl sulfoxide
DMA	=	dimethylacetamide
DPBS	=	Dulbecco's phosphate-buffered saline
EDTA	=	Ethylenediaminetetraacetic acid
EtOAc	=	ethyl acetate
EtOH	=	ethanol
h	=	hour(s)
HATU	=	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5- b]pyridinium 3-oxide hexafluorophosphate
HPLC	=	high-pressure liquid chromatography
IHC	=	immunohistochemistry
IPA	=	<i>iso</i> -propyl alcohol
IPAc	=	<i>iso</i> -propyl acetate
K ₂ CO ₃	=	potassium carbonate
K ₃ PO ₄	=	potassium phosphate tribasic
LCMS	=	Liquid Chromatography coupled to Mass Spectrometry
mCi	=	millicurie
MeCN	=	acetonitrile
MeOH	=	methyl alcohol
MgSO ₄	=	magnesium sulfate
MS	=	mass spectroscopy
NaHBEt ₃	=	sodium triethylborohydride
NaHCO ₃	=	sodium bicarbonate

Na ₂ SO ₄	=	sodium sulfate
NH ₄ Cl	=	ammonium chloride
NH ₄ OH	=	ammonium hydroxide
NMP	=	N-methylpyrrolidone
NMR	=	nuclear magnetic resonance spectroscopy
PD	=	Parkinson's Disease
Pd/C	=	10% palladium on carbon by weight
PdCl ₂ (dppf)	=	1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PE or Pet Ether	=	petroleum ether
PEI	=	Polyethylenimine
RuPhos Pd G2	=	2nd Generation RuPhos Precatalyst, Chloro(2- dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2- (2'-amino-1,1'-biphenyl)]palladium(II)
rt	=	room temperature
SNAr	=	nucleophilic aromatic substitution reaction
TFA	=	trifluoroacetic acid
TLC	=	thin-layer chromatography
tR	=	retention time
THF	=	tetrahydrofuran
wt%	=	percentage by weight
XPhos Palladacycle-G2	=	2nd Generation XPhos Precatalyst, Chloro(2- dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'- biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

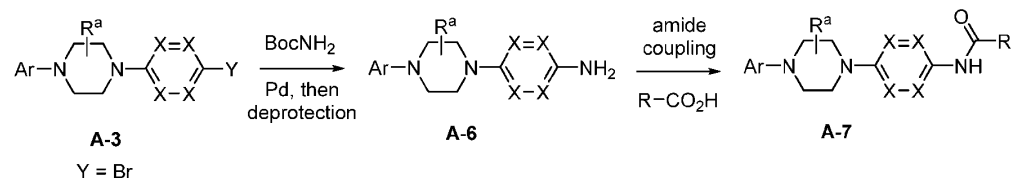
[0082] Compounds described herein were synthesized as a racemic mixture unless otherwise stated in the experimental procedures. In some cases, the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases, the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following schemes and examples are provided so that the invention might be more

fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

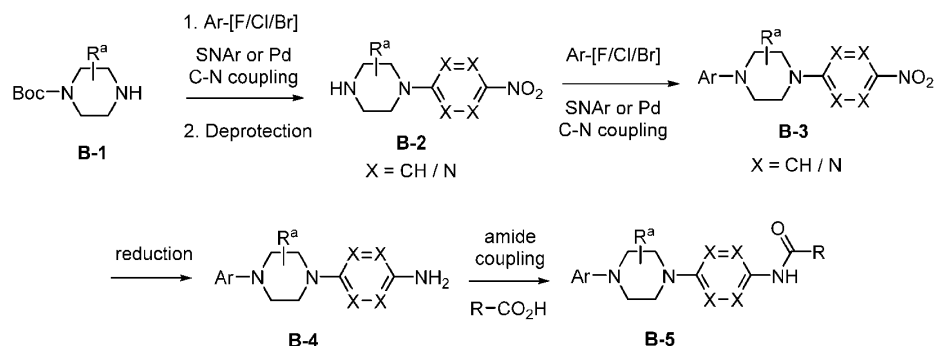
Generic Scheme A



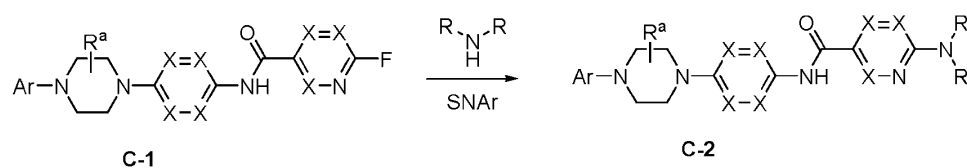
[0083] Substituted piperazines (**A-1**) can be transformed to aryl piperazines **A-2** via SNAr or Pd-mediated C-N coupling reactions. Deprotection followed by SNAr or Pd-mediated C-N couplings with aryl halides provide intermediates **A-3**. If Y is nitro in **A-3**, reductions (such as hydrogenation) can provide aniline intermediates **A-4** and subsequent amide couplings provide target molecules **A-5**.



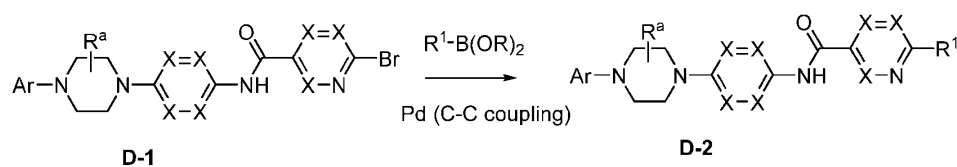
[0084] Alternatively, if Y is bromide (or Cl), intermediates **A-6** can result from Pd-mediated C-N coupling with Boc-amine and subsequent amide couplings provide target molecules **A-7**.

Generic Scheme B

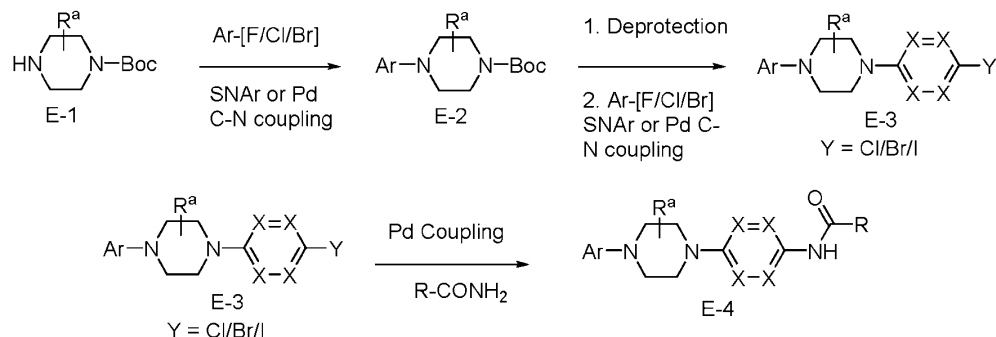
[0085] Substituted piperazines (**B-1**) can be transformed to aryl piperazines **B-2** via SNAr or Pd-mediated C-N coupling reactions followed by deprotection. **B-2** can undergo SNAr or Pd-mediated C-N couplings with aryl halides provide intermediates **B-3**. **B-3** can be engaged in reduction reactions to provide aniline intermediates **B-4** and subsequent amide couplings provide target molecules **B-5**.

Generic Scheme C

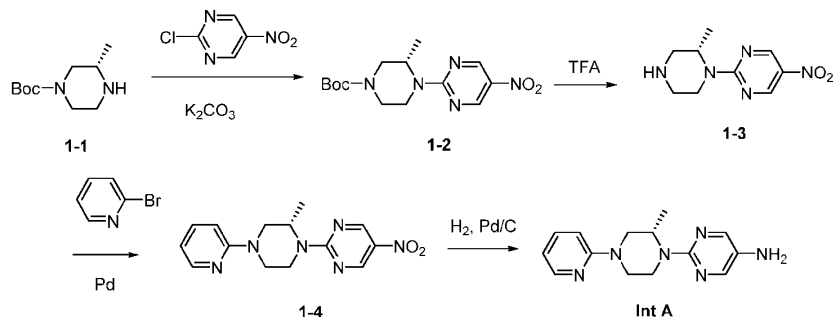
[0086] Intermediates **C-1** can engage in SNAr reactions with amines or NH-containing heterocycles to afford target compounds **C-2**.

Generic Scheme D

[0087] Intermediates **D-1** can engage in Pd-mediated C-C coupling reactions to afford target compounds **D-2**.

Generic Scheme E

[0088] Substituted piperazines (**E-1**) can be transformed to aryl piperazines **E-2** via SNAr or Pd-mediated C-N coupling reactions. Deprotection followed by SNAr or Pd-mediated C-N couplings with aryl halides provide intermediates **E-3**. Halide **E-3** can undergo Pd-mediated C-N coupling with preformed primary amides to provide target molecules **E-4**.

Preparation of Intermediates**Synthesis of Intermediate A: (S)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine****Synthesis of 1-2: (S)-tert-butyl 3-methyl-4-(5-nitropyrimidin-2-yl)piperazine-1-carboxylate**

[0089] To a solution of (S)-tert-butyl 3-methylpiperazine-1-carboxylate (**1-1**, 13.6 g, 67.9 mmol) in DMF (150 mL) was added K_2CO_3 (14.08 g, 102 mmol) and 2-chloro-5-nitropyrimidine (12.46 g, 78 mmol). The mixture was stirred for 12 h at 25 °C under N_2 balloon. TLC showed the starting material was consumed completely. Water (450 mL) was added and the mixture was stirred at 25 °C (rt) for 30 min. The precipitated solid was collected by filtration, washed with water (100 mL x 3) and dried to give the **1-2** as a solid.

¹H NMR (500 MHz, Chloroform-d): δ = 9.07 (s, 2H), 5.06 (br s, 1H), 4.67 (br s, 1H), 3.91~4.29 (m, 2H), 3.28~3.36 (m, 1H), 3.13 (br s, 1H), 2.83~3.01 (m, 1H), 1.45~1.52 (m, 9H), 1.26 (d, J = 6.5 Hz, 3H)

Synthesis of 1-3: (S)-2-(2-methylpiperazin-1-yl)-5-nitropyrimidine

[0090] To a solution of 1-2 (21 g, 64.9 mmol) in DCM (160 mL) was added TFA (40 mL) at 0 °C. The mixture was stirred for 2 h at 25 °C. TLC showed most of the starting material was consumed completely. The mixture was concentrated under reduced pressure to give the crude product (S)-2-(2-methylpiperazin-1-yl)-5-nitropyrimidine (25 g, 78 mmol) as an oil. The product was diluted with DCM (200 mL) and H₂O (160 mL). Then the Na₂CO₃ was added to solution to adjust pH to 7~8. The solution was extracted with DCM (200 mL*2). The organic layer was dried over Na₂SO₄, filtered and concentrated to give 1-3 as a solid.

¹H NMR (400 MHz, DMSO-d₆): δ = 9.44 (s, 1H), 8.92~9.10 (m, 1H), 5.13~5.24 (m, 1H), 4.82 (d, J = 14.4 Hz, 1H), 3.31~3.49 (m, 3H), 3.26 (d, J = 7.2 Hz, 1H), 3.06 (d, J = 8.8 Hz, 1H), 1.52 (s, 1H), 1.33 (d, J = 7.2 Hz, 3H). MS (ESI) m/z : 224.0 [M+H]⁺.

Synthesis of 1-4: (S)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)-5-nitropyrimidine

[0091] To a solution of 1-3 (2.5 g, 11.20 mmol) in Dioxane (50 mL) was added 2-bromopyridine (3.72 g, 23.52 mmol), Cs₂CO₃ (14.96 g, 45.9 mmol) and chloro(2-dicyclohexylphosphino-2', 6'-dimethoxy-1, 1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.968 g, 1.344 mmol). The mixture was stirred for 12 h at 110 °C under N₂ balloon. TLC showed most of the starting material was consumed completely. The mixture was filtered and concentrated. The residue was extracted with EtOAc (3*50 mL) and H₂O (60 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified using a silica gel column eluting with 15~30% EtOAc / PE to give the **1-4** as a solid.

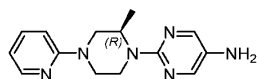
¹H NMR (400 MHz, Chloroform -d): δ = 9.10 (s, 2H), 8.17~8.24 (m, 1H), 7.47~7.59 (m, 1H), 6.62~6.71 (m, 2H), 5.11 (dt, J = 6.4, 3.2 Hz, 1H), 4.74 (dt, J = 13.6, 3.6 Hz, 1H), 4.24 (d, J = 12.8 Hz, 1H), 4.13 (d, J = 13.2 Hz, 1H), 3.53~3.63 (m, 1H), 3.37 (dd, J = 13.2, 4.0 Hz, 1H), 3.12 (td, J = 12.0, 3.6 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H). MS (ESI) m/z : 301.0 [M+H]⁺.

Synthesis of (S)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine (Int A)

[0092] To a solution of 1-4 (2.5 g, 8.32 mmol) in MeOH (40 mL) was added Pd/C (0.2 g, 1.879 mmol). The mixture was stirred for 2 h at 25 °C under H₂ balloon. TLC showed most of the starting material was consumed completely. The mixture was filtered, and the filter cake was washed with MeOH (3*200 mL). The combined organic extracts were concentrated under reduced pressure to give the Int A as an oil.

¹H NMR (400 MHz, Chloroform -d): δ = 8.19 (dd, J = 4.8, 1.2 Hz, 1H), 8.01 (s, 2H), 7.45~7.50 (m, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 6.8, 5.2 Hz, 1H), 4.76~4.85 (m, 1H), 4.32~4.40 (m, 1H), 4.19~4.26 (m, 1H), 4.10 (dt, J = 12.8, 2.0 Hz, 1H), 3.23~3.41 (m, 2H), 3.15 (s, 2H), 3.01~3.08 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H). MS (ESI) m/z : 271.1 [M+H]⁺.

Synthesis of Intermediate B: (R)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine

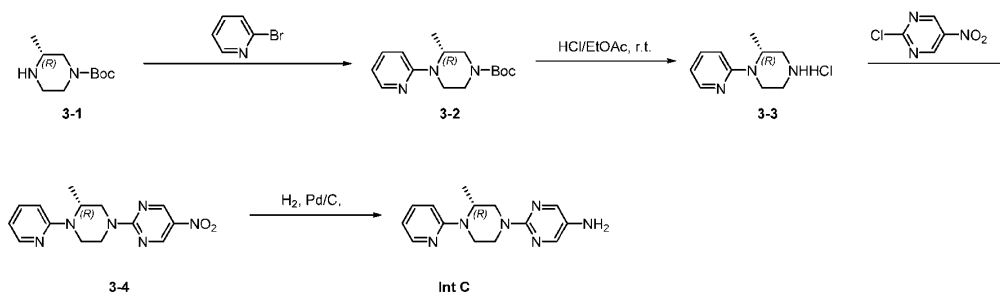


Int B

[0093] (R)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine (Int B) was isolated as an oil by an analogous sequence to the synthesis of Int A.

¹H NMR (400 MHz, DMSO-d₆): δ = 8.07 (dd, J = 4.8, 1.3 Hz, 1H), 7.90 (s, 2H), 7.48~7.54 (m, 1H), 6.82 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 6.8, 5.2 Hz, 1H), 4.54~4.72 (m, 3H), 4.12~4.25 (m, 3H), 3.05~3.13 (m, 1H), 2.79~2.91 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H). MS (ESI) m/z : 271.0 [M+H]⁺.

Synthesis of Intermediate C: (R)-2-(3-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine



Synthesis of 3-2: (R)-tert-butyl 3-methyl-4-(pyridin-2-yl)piperazine-1-carboxylate

[0094] To a solution of (R)-tert-butyl 3-methylpiperazine-1-carboxylate (**3-1**, 2 g, 9.99 mmol) in dioxane (40 mL) was added 2-bromopyridine (3.31 g, 20.97 mmol), Cs₂CO₃ (13.34 g, 40.9 mmol) and chloro(2-dicyclohexylphosphino-2', 6'-dimethoxy-1, 1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.864 g, 1.198 mmol). The mixture was stirred for 12 h at 110 °C under N₂ balloon. TLC showed most of the starting material was consumed completely. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified using a silica gel column eluting with 15% EtOAc / PE to give the 3-2 as an oil.

¹H NMR (400 MHz, Chloroform-*d*): δ = 8.18 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.42~7.52 (m, 1H), 6.54~6.64 (m, 2H), 4.46 (br s, 1H), 3.78~4.25 (m, 3H), 2.93~3.23 (m, 3H), 1.48 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H). MS (ESI) *m/z*: 278.1 [M+H]⁺.

Synthesis of 3-3: (R)-2-methyl-1-(pyridin-2-yl)piperazine

[0095] To a solution of 3-2 (2 g, 7.21 mmol) in EtOAc (17 mL) was added EtOAc/ HCl (34 mL). The mixture was stirred for 5 h at 25 °C. TLC showed the starting material was consumed completely. The obtained solid was collected by filtration. The cake was washed with EtOAc (5 mL) and dried to give the 3-3 as an oil.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.07 (br d, *J* = 7.2 Hz, 1H), 9.72 (br s, 1H), 8.02~8.12 (m, 2H), 7.40 (br d, *J* = 9.2 Hz, 1H), 7.03 (t, *J* = 6.4 Hz, 1H), 4.79 (br s, 1H), 4.38 (br d, *J* = 14.4 Hz, 1H), 3.58 (br t, *J* = 12.0 Hz, 1H), 3.22~3.36 (m, 3H), 3.09 (br d, *J* = 10.4 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H).

Synthesis of 3-4: (R)-2-(3-methyl-4-(pyridin-2-yl)piperazin-1-yl)-5-nitropyrimidine

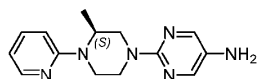
[0096] To a solution of **3-3** (1.7 g, 9.59 mmol) in DMF (20 mL) was added 2-chloro-5-nitropyrimidine (1.836 g, 11.51 mmol) and K₂CO₃ (5.30 g, 38.4 mmol). The mixture was stirred for 2 h at 80 °C under N₂ balloon. TLC showed most of the starting material was consumed completely. Water (150 mL) was added and the mixture was stirred at 25 °C (r.t.) for 30 min. The precipitated solid was collected by filtration, washed with water (100 mL x 3) and dried to give the **3-4** as an oil.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.15 (d, *J* = 4.4 Hz, 2H), 8.14 (d, *J* = 3.6 Hz, 1H), 7.51~7.60 (m, 1H), 6.82 (s, 1H), 6.65 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.62~4.76 (m, 3H), 4.13~4.24 (m, 1H), 3.53 (d, *J* = 4.0 Hz, 1H), 3.33~3.40 (m, 1H), 3.11~3.23 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H). MS (ESI) *m/z*: 301.1 [M+H]⁺.

Synthesis of (R)-2-(3-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine (Int C)

[0097] To a solution of 3-4 (1.8 g, 5.99 mmol) in MeOH (30 mL) was added Pd/C (0.2 g, 1.879 mmol). The mixture was stirred for 2 h at 25 °C under H₂ balloon. TLC showed most of the starting material was consumed completely. The mixture was filtered, and the filter cake was washed with MeOH (3*200 mL). The combined organic extracts were concentrated under reduced pressure to give the Int C as an oil.

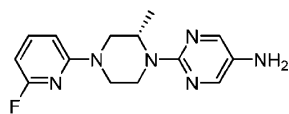
¹H NMR (400 MHz, DMSO-d₆): δ = 8.12 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.91 (s, 2H), 7.50~7.55 (m, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.60 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.54~4.64 (m, 3H), 4.27~4.45 (m, 2H), 4.08 (s, 1H), 2.99~3.10 (m, 2H), 2.83~2.90 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H). MS (ESI) *m/z*: 271.0 [M+H]⁺.

Synthesis of Intermediate D: (S)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine

Int D

[0098] (S)-2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine was isolated as an oil in an analogous synthetic sequence to Int C above.

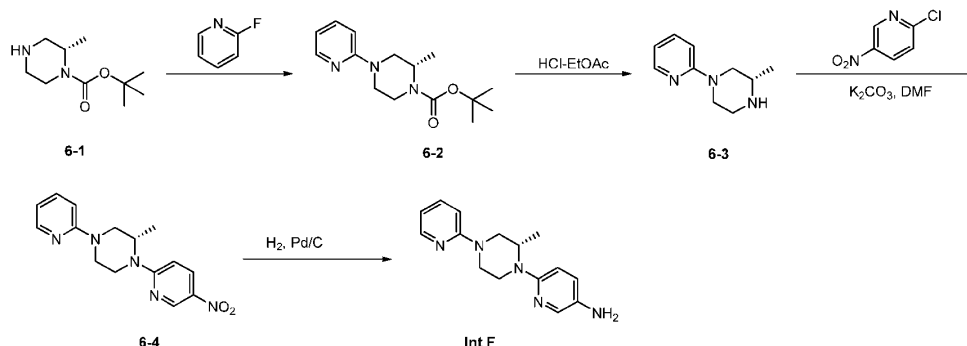
¹H NMR (400 MHz, DMSO-d₆): δ = 8.09 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.89 (s, 2H), 7.48~7.52 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.58 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.51~4.60 (m, 3H), 4.28~4.41 (m, 2H), 3.98~4.11 (m, 1H), 2.99~3.08 (m, 2H), 2.84 (td, *J* = 12.0, 3.6 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H). MS (ESI) *m/z*: 271.1 [M+H]⁺.

Synthesis of Intermediate E: (S)-2-(4-(6-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine

Int E

[0099] (S)-2-(4-(6-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine was isolated as an oil in an analogous synthetic sequence to that described for **Int A**.

Synthesis of Intermediate F: (S)-6-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyridin-3-amine



Synthesis of 6-2: (S)-tert-butyl 2-methyl-4-(pyridin-2-yl)piperazine-1-carboxylate

[0100] A mixture of (S)-1-N-BOC-2-methylpiperazine (15 g, 74.9 mmol), 2-fluoropyridine (36.4 g, 374 mmol) was heated at 135 °C for 48 h. LCMS showed starting material was remained and new product formed. LCMS (ESI) calc'd for $C_{15}H_{23}N_3O_2$ $[M+H]^+$: 278.1, found: 278.2, tR = 0.684 min. The mixture was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 4: 1 to give 6-2 as a colorless liquid.

Synthesis of 6-3: (S)-3-methyl-1-(pyridin-2-yl)piperazine dihydrochloride

[0101] Hydrogen chloride in EtOAc (37.9 ml, 151 mmol) was added to 6-2 (7 g, 25.2 mmol) at room temperature, it was stirred at 20 °C for 18 h. LCMS (ESI) showed starting material was consumed and new product formed. LCMS (ESI) calc'd for $C_{10}H_{15}N_3 \cdot 2ClH$ $[M+H]^+$: 178.1, found: 178.1, tR = 0.170 min. The mixture was evaporated under reduced pressure. Then added EtOAc (25 ml *3) to the residue. It was evaporated under reduced pressure to give 6-3 as a solid.

Synthesis of 6-4: (S)-2-methyl-1-(5-nitropyridin-2-yl)-4-(pyridin-2-yl)piperazine

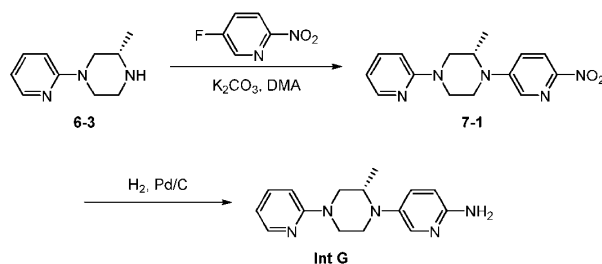
[0102] 2-chloro-5-nitropyridine (0.697 g, 4.40 mmol) was added to a stirred mixture of 6-3 (1 g, 4.00 mmol) and K_2CO_3 (2.210 g, 15.99 mmol) in DMF (12 ml) and the mixture was stirred at 80 °C for 15 h. LCMS (ESI) showed starting material was consumed and new product formed. LCMS (ESI) calc'd for $C_{15}H_{17}N_5O_2$ $[M+H]^+$: 300.1, found: 300.1, tR = 0.351 min. Then poured into 30 mL of ice-water, the mixture was filtered, and the filter cake was washed with Water (15 mL * 3), dried under vacuum and dried to give 6-4 as a brown solid.

Synthesis of (S)-6-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyridin-3-amine (Int F)

[0103] Iron (0.933 g, 16.70 mmol) was added to a stirred mixture of 6-4 (1.0g, 3.34mmol), ammonium chloride (1.787 g, 33.4 mmol) in EtOH (20 ml) and Water (10 ml) at room temperature and the mixture was stirred at room temperature (Temp: 40 °C) for under N₂ atmosphere. LCMS (ESI) showed starting material was consumed and new product formed. LCMS (ESI) calc'd for C₁₅H₁₉N₅ [M+H]⁺: 270.1, found: 270.1, t_R = 0.128 min. The mixture was cooled to room temperature, filtered and the solvent was evaporated under reduced pressure. Water (25 mL) was added and the mixture was extracted with EtOAc (30 mL* 3). The combined organic fractions were dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure and dissolved in EtOAc (10 ml), dropwise 0.5 ml HCl (4 M EtOAc solution), the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with Acetonitrile/Water + 0.1% TFA, to give Int F as a brown solid.

¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.31 (d, *J*=6.26 Hz, 3 H) 3.61 - 3.76 (m, 2 H) 3.86 (dd, *J*=13.69, 3.91 Hz, 1 H) 4.01 - 4.16 (m, 3 H) 4.52 (br d, *J*=6.65 Hz, 1 H) 7.03 (t, *J*=6.65 Hz, 1 H) 7.10 (d, *J*=9.39 Hz, 1 H) 7.40 (d, *J*=9.39 Hz, 1 H) 7.64 (dd, *J*=9.39, 3.13 Hz, 1 H) 7.81 (s, 1 H) 7.97 - 8.11 (m, 2 H); LCMS (ESI) calc'd for C₁₅H₁₉N₅ [M+H]⁺: 270.1, found: 270.1

Synthesis of Intermediate G: (S)-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyridin-2-amine



Synthesis of 7-1: (S)-2-methyl-1-(6-nitropyridin-3-yl)-4-(pyridin-2-yl)piperazine

[0104] 5-fluoro-2-nitropyridine (1.2 g, 8.45 mmol) and 6-3 (2.42 g, 13.65 mmol) in DMA (20mL) was added K₂CO₃ (4.67 g, 33.8 mmol). The mixture was stirred at 100 °C for 18 hours. TLC (Petroleum ether: ethyl acetate = 1:1) showed little starting material left. LCMS (ESI) calc'd for C₁₅H₁₇N₅O₂ [M+H]⁺: 300.1, found: 300.5, t_R = 0.57 min. The mixture was cooled, diluted with ethyl acetate (20 mL) and water (20 mL), organic layer was washed with aqueous Na₂CO₃ (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under

reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / ethyl acetate = 1:1 to give **7-1** as a solid.

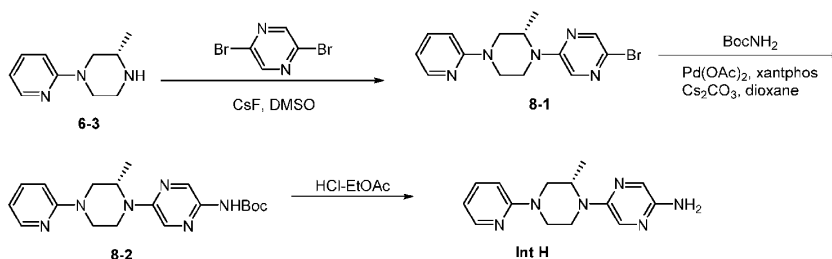
^1H NMR (400 MHz, Chloroform- d) δ 8.36 - 8.58 (m, 1H) 8.17 - 8.28 (m, 2H) 8.12 (d, J = 3.1 Hz, 1H) 7.46 - 7.72 (m, 1H) 7.18 (dd, J =9.2, 2.9 Hz, 1H) 6.50 - 6.82 (m, 2H) 4.17 - 4.38 (m, 2H) 4.04 - 4.43 (m, 1H) 3.69 - 3.95 (m, 1H) 3.44 - 3.62 (m, 2H) 3.27 - 3.38 (m, 1H) 3.01 (s, 7H) 2.94 (s, 7H) 2.08 (s, 7H) 1.30 (d, J =6.7 Hz, 4H); LCMS (ESI) calc'd for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$: 300.1, found: 300.5.

Synthesis of (S)-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyridin-2-amine (Int G)

[0105] **7-1** (1.1 g, 3.67 mmol) and Pd-C (300 g, 2819 mmol) in MeOH (20 mL) was treated with H_2 (15 Psi), the mixture was stirred at 20 °C for 18 hours. TLC (DCM: MeOH = 10:1) showed no starting material was remained. Desired mass was detected, LCMS (ESI) calc'd for $\text{C}_{15}\text{H}_{19}\text{N}_5$ $[\text{M}+\text{H}]^+$: 270.2, found: 269.8, t_R = 0.596 min. Solvent was filtered, filtrate was concentrated, the residue was purified by silica gel column flash chromatography, eluting with ethyl acetate: EtOH = 10:1 to 20:1 to afford Int G as a solid.

^1H NMR (500 MHz, Chloroform- d) δ 8.20 (dd, J = 4.9, 1.1 Hz, 1H) 7.86 (d, J = 2.4 Hz, 1H) 7.48 (ddd, J = 8.6, 7.1, 2.0 Hz, 1H) 7.26 (dt, J = 5.8, 2.8 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H) 6.58 - 6.63 (m, 1H) 6.50 (d, J =8.7 Hz, 1H) 4.30 (br s, 2H) 3.92 (m, 1H) 3.73 - 3.81 (m, 1H) 3.53 (m, 1H) 3.32 (m, 1H) 3.21 (dd, J =12.4, 7.4 Hz, 1H) 3.08 - 3.14 (m, 1H) 3.00 - 3.07 (m, 1H) 0.97 (d, J = 6.3 Hz, 3H); LCMS (ESI) calc'd for $\text{C}_{15}\text{H}_{19}\text{N}_5$ $[\text{M}+\text{H}]^+$: 270.2, found: 269.8.

Synthesis of Intermediate H: (S)-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-amine



Synthesis of 8-1: (S)-2-bromo-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrazine

[0106] In a clean dry sealed tube 2,5-dibromopyrazine (1.046 g, 4.40 mmol) and **6-3** (1g, 4.00 mmol) in DMSO (10 ml) was added CsF (3.04 g, 19.99 mmol), then the resulting mixture was stirred at 90 °C for 18h. LCMS (ESI) showed starting material was consumed and new product formed. The mixture was cooled to room temperature, filtered and the filter cake was washed

with DCM (10 mL * 3). The solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 4: 1 to give (S)-2-bromo-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrazine as a gum. LCMS (ESI) calc'd for C₁₄H₁₆BrN₅ [M+H]⁺: 336.0, found: 335.9.

Synthesis of 8-2: (S)-tert-butyl (5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)carbamate

[0107] (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.519 g, 0.898 mmol) and diacetoxypalladium (0.101 g, 0.449 mmol) was added to a stirred mixture of **8-1** (1.5 g, 4.49 mmol), tert-butyl carbamate (1.052 g, 8.98 mmol) and cesium carbonate (4.39 g, 13.46 mmol) in dioxane (25 ml) at room temperature under N₂ atmosphere and the mixture was heated with stirring at (Temp: 70 °C) for 18 h. LCMS (ESI) showed starting material was consumed and new product formed. Filtered and concentrated, the residue was purified by silica gel flash chromatography (ISCORF150; Sepa flash column), eluting with petroleum ether / EtOAc = 3:1 to give **8-2** as a solid.

¹H NMR (400 MHz, Chloroform-d) δ 8.72 (brs, 1H), 8.10-8.28 (m, 1H), 7.74 (s, 1H), 7.41-7.55 (m, 1H), 6.99 (brs, 1H), 6.51-6.74 (m, 2H), 4.47 (brdd, *J* = 3.06, 5.99 Hz, 1H), 4.22 (brd, *J* = 12.23 Hz, 1H), 4.10 (brdd, *J* = 1.47, 12.72 Hz, 1H), 3.97 (brdd, *J* = 2.69, 12.72 Hz, 1H), 3.26-3.42 (m, 2H), 3.05-3.20 (m, 1H), 1.51-1.58 (m, 9H), 1.19 (dd, *J* = 2.32, 6.48 Hz, 3H); LCMS (ESI) calc'd for C₁₈H₂₄N₆O₂ [M+H]⁺: 357.2, found: 357.2.

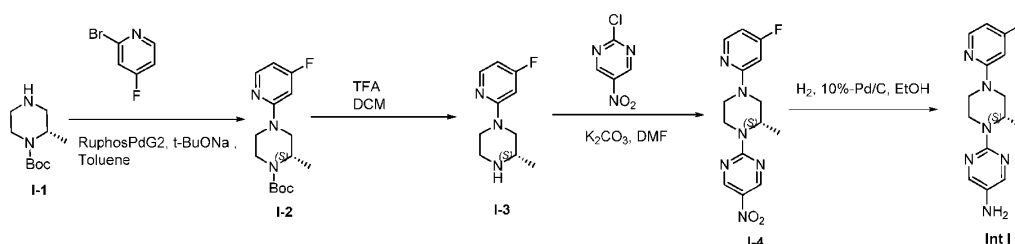
Synthesis of (S)-5-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-amine (Int H)

[0108] HCl/EtOAc (0.675 ml, 2.70 mmol) was added to a stirred mixture of 8-2 (1.0 g, 2.70 mmol) in Ethyl acetate (5 ml) at room temperature and the mixture was stirred at room temperature (Temp: 20 °C) for 48 h. LCMS (ESI) showed starting material was consumed and new product formed. Then concentrated, the residue was adjusted to pH 9 with saturated Na₂CO₃, extracted with EtOAc (20 mL, 3 times), then washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated, The residue was purified by silica gel flash chromatography (ISCORF150; Sepa flash column), eluting with petroleum ether / EtOAc = 1:1 to give Int H as a solid.

¹H NMR (500 MHz, Chloroform-d) δ 8.18-8.22 (m, 1H), 7.72 (d, *J* = 1.53 Hz, 1H), 7.67 (d, *J* = 1.22 Hz, 1H), 7.46-7.53 (m, 1H), 6.68 (d, *J* = 8.54 Hz, 1H), 6.63 (dd, *J* = 5.19, 7.02 Hz, 1H), 5.47-5.50 (m, 1H), 4.34 (td, *J* = 3.32, 6.48 Hz, 1H), 4.20 (brdd, *J* = 1.68, 12.05 Hz, 1H), 3.96-

4.07 (m, 3H), 3.76 (td, $J = 3.55, 12.13$ Hz, 1H), 3.38 (dd, $J = 3.81, 12.66$ Hz, 1H), 3.27 (dt, $J = 3.51, 11.52$ Hz, 1H), 3.15-3.21 (m, 1H), 1.15 (d, $J = 6.71$ Hz, 3H); LCMS (ESI) calc'd for $C_{14}H_{18}N_6$ $[M+H]^+$: 271.2, found: 271.1.

Preparation of compound Intermediate I: (S)-2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine



Synthesis of I-2: tert-butyl (S)-4-(4-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxylate

[0109] To a stirred solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**I-1**, 5 g, 24.96 mmol) in toluene (200 mL) (purged with Argon gas for 10 min) were added 2-bromo-4-fluoropyridine (4.39 g, 24.96 mmol), sodium tert-butoxide (2.399 g, 24.96 mmol) and Chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (19.39 g, 24.96 mmol) at room temperature. Reaction mixture was again purged with Argon for 10 min and stirred at 120°C for 12h. The reaction mixture was diluted with water (80 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to get crude product. The crude product was purified by 100-200 mesh silica gel (300 g cartridge), eluted with 20% EtOAc/Pet ether as gradient. Pure fractions concentrated under reduced pressure to afford compound **I-2** as a yellow liquid. M/Z (ESI): 296.37 $[M+H]^+$.

Synthesis of I-3: (S)-1-(4-(4-fluoropyridin-2-yl)-3-methylpiperazine

[0110] To a stirred solution of compound **I-2** (5 g, 16.93 mmol) in DCM (80 mL) were added TFA (6.52 mL, 85 mmol) at 0°C. The reaction mixture was stirred room temperature for 12h. The reaction mixture was concentrated under reduced pressure to afford compound **I-3** as a pale yellow liquid. M/Z (ESI): 196.23 $[M+H]^+$.

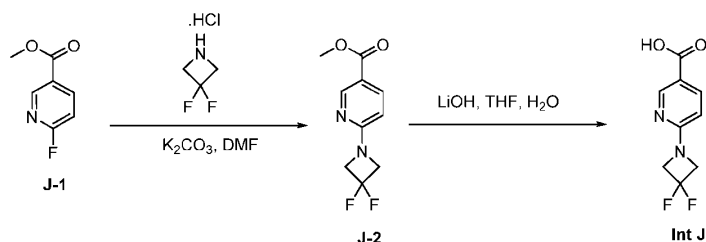
Synthesis of I-4: (S)-2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-nitropyrimidine

[0111] To a stirred solution of compound **I-3** (3.5 g, 17.93 mmol) in DMF (80 mL) were added 2-chloro-5-nitropyrimidine (3.43 g, 21.51 mmol) and K_2CO_3 (9.91 g, 71.7 mmol) at room temperature. The reaction mixture was stirred 80°C for 2h. The reaction mixture was diluted with ice cold water (20 mL), obtained solid was filtered and washed with water (2 x 50 mL), dried under reduced pressure to afford compound **I-4** as a pale yellow solid. M/Z (ESI): 319.20 $[M+H]^+$.

Synthesis of Intermediate I: (S)-2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine

[0112] To a solution of compound **I-4** (3.5 g, 11 mmol) in EtOH (50 mL) was added 10% Pd-C (1.170 g, 5.50 mmol) at room temperature. The reaction mixture was degassed with nitrogen for 3 times and stirred under balloon pressure of H_2 gas for 16h at room temperature. The reaction mixture was filtered on Buckner funnel through celite bed, washed with EtOAc (50 mL) and concentrated under reduced pressure to afford compound **Int I** as a yellow liquid. M/Z (ESI): 289.17 $[M+H]^+$.

Preparation of compound Intermediate J: 6-(3,3-difluoroazetidin-1-yl)nicotinic acid



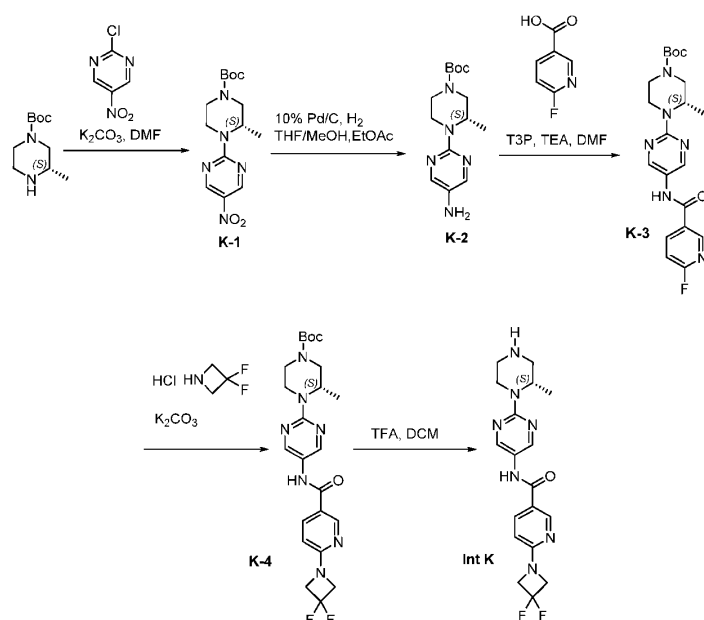
Synthesis of J-2: methyl 6-(3,3-difluoroazetidin-1-yl)nicotinate

[0113] To a stirred solution of 3,3-difluoroazetidine hydrochloride (8.35 g, 64.5 mmol) in DMF (250 mL) was added K_2CO_3 (26.7 g, 193 mmol) at room temperature, followed by methyl 6-fluoronicotinate (**J-1**, 10 g, 64.5 mmol) added at room temperature. The reaction mixture was stirred at 90°C for 12h. Resulting reaction mixture quenched with ice-water (200 mL), separated solid was filtered on Buchner funnel, solid was washed with water (100 mL x 2), dried under reduced pressure to afford compound **J-2** as a white solid. M/Z (ESI): 229.04 $[M+H]^+$.

Synthesis of Intermediate J: 6-(3,3-difluoroazetidin-1-yl)nicotinic acid

[0114] To a stirred solution of compound **J-2** (10 g, 43.5 mmol) in THF (70 mL), water (140 mL) was added LiOH (3.13 g, 131 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was concentrated acidified (PH = 5) with saturated solution of KHSO₄ and extracted with DCM (3 x 200 ml), dried over Na₂SO₄, filtered and concentrated and washed with pentane, dried under reduced pressure to afford compound **Int J** as an off white solid. M/Z (ESI): 215.04 [M+H]⁺.

Preparation of compound Intermediate K: (S)-2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine



Synthesis of K-1: tert-butyl (S)-3-methyl-4-(5-nitropyrimidin-2-yl)piperazine-1-carboxylate

[0115] To a stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (5 g, 24.96 mmol) in DMF (50 mL) was added potassium carbonate (6.90 g, 49.9 mmol) and 2-chloro-5-nitropyrimidine (4.78 g, 30.0 mmol) and stirred for 3 h at 60 °C under N₂ atmosphere. The reaction mixture was quenched with ice water (200 mL), stirred at room temperature for 30 min. Obtained solid precipitate filtered, washed with water (100 mL x 3) and dried under suction vacuum to afford **K-1** as a pale yellow solid.

¹H NMR (400MHz, CHLOROFORM-d) δ : 9.08 (s, 2H), 4.97-5.14 (m, 1H), 4.61-4.76 (m, 1H), 3.87-4.32 (m, 2H), 3.26-3.43 (m, 1H), 3.14 (br d, J=11.8 Hz, 1H), 2.90-2.99 (m, 1H), 1.50 (s, 9H), 1.27 (d, J=6.8 Hz, 3H).

Synthesis of K-2: tert-butyl (S)-4-(5-aminopyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0116] To a solution of **K-1** (3 g, 9.28 mmol) in THF/MeOH/Ethyl Acetate (1:1:1) (50 ml) was added palladium on carbon (1.975 g, 18.56 mmol) and stirred for 15 h at 25 °C under Hydrogen Balloon atmosphere. The reaction mixture was filtered, washed with MeOH/THF (3 x 50 mL), combined organic layer concentrated under reduced pressure to afford **K-2** as a yellow solid. M/Z (ESI): 294.15 [M+H]⁺.

Synthesis of K-3: tert-butyl (S)-4-(5-(6-fluoronicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0117] To a stirred solution of **K-2** (1.20 g, 4.09 mmol) and 6-fluoronicotinic acid (1.154 g, 8.18 mmol) in DMF (20 ml) was added 50% 1-Propanephosphonic anhydride solution in EtOAc (5.21 g, 8.18 mmol) and TEA (1.710 ml, 12.27 mmol) at room temperature and stirred at room temperature for 15h. The reaction mixture was diluted with EtOAc (100 ml) and washed with brine (100 ml) and sat NaHCO₃ solution (100 ml), organic phase dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford **K-3** as a solid. M/Z (ESI): 417.42 [M+H]⁺.

Synthesis of K-4: tert-butyl (S)-4-(5-(6-(3,3-difluoroazetidin-1-yl)nicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

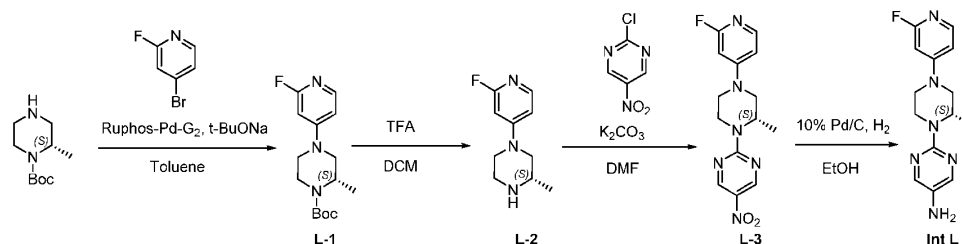
[0118] To a stirred solution of 3,3-difluoroazetidine hydrochloride (641 mg, 4.95 mmol) in DMF (10 ml) was added K₂CO₃ (912 mg, 6.60 mmol), **K-3** (700 mg, 1.649 mmol) at room temperature and stirred at 100 °C for overnight. Reaction mixture was quenched with ice cold water (30 ml), extracted with EtOAc (3 x 25 ml), organic layer washed with brine solution (2 x 25 ml), dried over Na₂SO₄, filtered and concentrated to afford **K-4** as brown solid. M/Z (ESI): 490.45 [M+H]⁺.

Synthesis of Intermediate K: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0119] To a stirred solution of **K-4** (700 mg, 1.158 mmol) in DCM (10 ml) was added TFA (0.268 ml, 3.47 mmol) at 0 °C and stirred at 0 °C for 5h. Reaction mixture was concentrated and

co-distilled with toluene twice to afford **Int K** as a yellow semisolid. M/Z (ESI): 390.18 [M+H]⁺.

Preparation of compound Intermediate L: (S)-2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine



Synthesis of L-1: tert-butyl (S)-4-(2-fluoropyridin-4-yl)-2-methylpiperazine-1-carboxylate

[0120] To a stirred solution of 4-bromo-2-fluoropyridine (1.142 g, 6.49 mmol) in Toluene (20 ml) was added chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (1.939 g, 2.496 mmol), tert-butyl (S)-2-methylpiperazine-1-carboxylate (1 g, 4.99 mmol), sodium tert-butoxide (1.200 g, 12.48 mmol) at room temperature and stirred at 110 °C for 18 h. The reaction mixture quenched with ice cold water (10 mL), extracted with ethyl acetate (2 x 200 mL), combined organic layer washed with brine solution (2 x 30 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and crude compound purified by 100-200 silica gel Biotage flash column chromatography using 50% EtOAc/pet-ether as eluent. Pure fractions concentrated under reduced pressure to afford compound **L-1** as a yellow sticky solid. M/Z (ESI): 296.31 [M+H]⁺.

Synthesis of L-2: (S)-1-(2-fluoropyridin-4-yl)-3-methylpiperazine

[0121] To a stirred solution of compound **L-1** (1.0 g, 3.39 mmol) in DCM (12 ml) was added TFA (0.777 ml, 10.16 mmol) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was quenched with NaHCO₃ solution (10 ml), extracted with DCM (2 x 50 mL), washed with water (2 x 30 ml), combined organic layer was washed with brine solution (20 ml), dried over Na₂SO₄, filtered, concentrated under reduced pressure to afford compound **L-2** as a yellow solid. M/Z (ESI): 196.07 [M+H]⁺.

Synthesis of L-3: (S)-2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)-5-nitropyrimidine

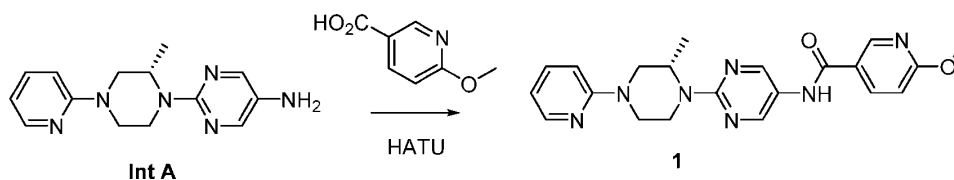
[0122] To a stirred solution of compound **L-2** (700 mg, 3.59 mmol) in DMF (12 ml) was added Potassium carbonate (1487 mg, 10.76 mmol), 2-chloro-5-nitropyrimidine (858 mg, 5.38 mmol) at room temperature and stirred at 80 °C for 3 h. The reaction mixture was quenched with ice cold water (20 ml), the precipitated solid was filtered, dried under vacuum to afford compound **L-3** as off white solid. M/Z (ESI): 319.24 [M+H]⁺.

Synthesis of Intermediate L: (S)-2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-amine

[0123] To a stirred solution of compound **L-3** (600 mg, 1.885 mmol) in EtOH (15 ml) was added Pd-C (241 mg, 2.262 mmol) at room temperature and stirred for 12 h at room temperature under hydrogen balloon. The reaction mixture was filtered on Buckner funnel through celite bed, washed with EtOAc (2 x 50 ml), concentrated under reduced pressure to afford compound **Int L** as sticky solid. M/Z (ESI): 289.25 [M+H]⁺.

EXAMPLES

Example 1: Synthesis of (S)-6-methoxy-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



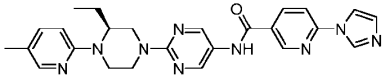
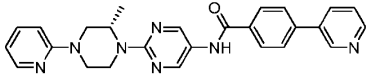
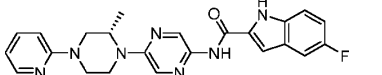
[0124] To a solution of Int A (185 mg, 0.684 mmol) in DMF (3422 µl) was added 6-methoxynicotinic acid (131 mg, 0.855 mmol), DIEA (359 µl, 2.053 mmol), and HATU (325 mg, 0.855 mmol). The mixture was stirred for 16 h at 25 °C. The mixture was then purified by preparative HPLC (reverse phase C-18 column), eluting with Acetonitrile/Water + 0.1% TFA, to give **1** as a solid.

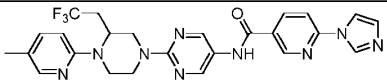
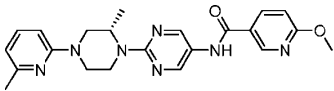
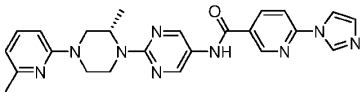
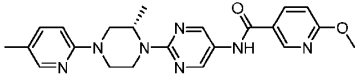
¹H NMR (500 MHz, Chloroform-d) δ 8.72 (d, J = 2.2 Hz, 1H), 8.57 (s, 2H), 8.22 (dd, J = 4.9, 1.2 Hz, 1H), 8.11 (dd, J = 8.7, 2.5 Hz, 1H), 7.52 (ddd, J = 8.9, 7.2, 2.0 Hz, 1H), 7.43 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 6.8, 5.2 Hz, 1H), 4.96 (dt, J = 6.6, 3.6 Hz, 1H), 4.55 (dt, J = 13.5, 3.4 Hz, 1H), 4.24 (d, J = 12.5 Hz, 1H), 4.14 (dd, J = 12.7, 2.0 Hz, 1H),

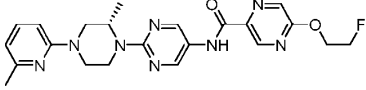
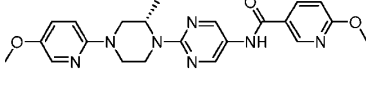
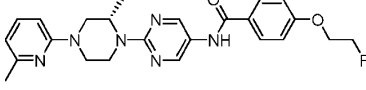
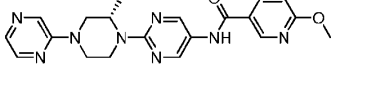
4.03 (s, 3H), 3.48 (ddd, J = 13.5, 11.3, 3.8 Hz, 1H), 3.34 (dd, J = 12.8, 3.9 Hz, 1H), 3.11 (td, J = 12.2, 3.8 Hz, 1H), 1.30 (d, J = 6.6 Hz, 3H). **MS** (ESI) m/z: 406.4 [M+H]⁺.

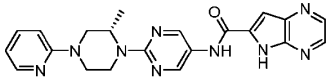
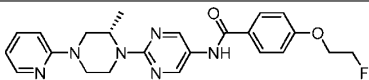
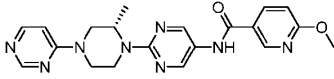
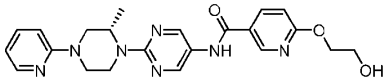
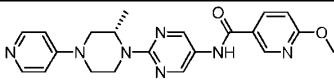
[0125] The compounds contained in Table 1 were synthesized by analogous methods from synthetic sequences used to prepare the Intermediates, utilizing the amide coupling reaction shown in Example 1. Commercially available reagents were substituted where necessary to produce the examples below.

Table 1

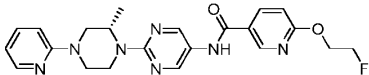
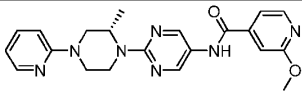
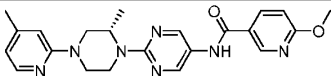
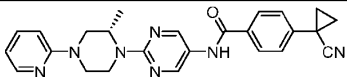
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
2		N-[2-[(3S)-3-ethyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-imidazol-1-yl-pyridine-3-carboxamide	470.3	469.2
3		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-4-(3-pyridyl)benzamide	452.3	451.2
4		5-fluoro-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-1H-indole-2-carboxamide	432.4	431.2

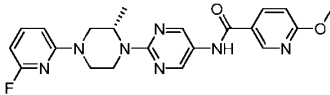
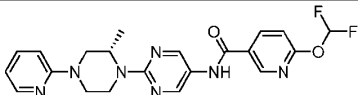
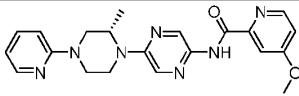
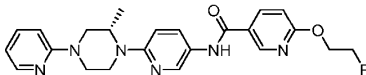
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
5		6-imidazol-1-yl-N-[2-[4-(5-methyl-2-pyridyl)-3-(2,2,2-trifluoroethyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	524.3	523.2
6		6-methoxy-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	420.2	419.2
7		6-imidazol-1-yl-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.3	455.2
8		6-methoxy-N-[2-[(2S)-2-methyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	420.2	419.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
9		5-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrazine-2-carboxamide	453.3	452.2
10		6-methoxy-N-[2-[(2S)-4-(5-methoxy-2-pyridyl)-2-methylpiperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	436.3	435.2
11		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide	451.3	450.2
12		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrazin-2-ylpiperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	407.2	406.2

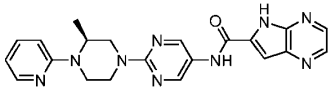
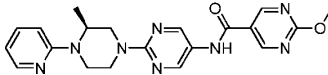
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
13		N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide	416.4	415.2
14		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide	437.3	436.2
15		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrimidin-4-yl-piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	407.4	406.2
16		6-(2-hydroxyethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	436.3	435.2
17		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	406.3	405.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
18		6-chloro-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	410.10	409.1
19		4-(1-cyanocyclopropyl)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]benzamide	440.4	439.2
20		6-bromo-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	454.2	453.1
21		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-5-phenyl-pyrazine-2-carboxamide	453.3	452.2
22		6-methoxy-N-[2-[(2R)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	406.3	405.2

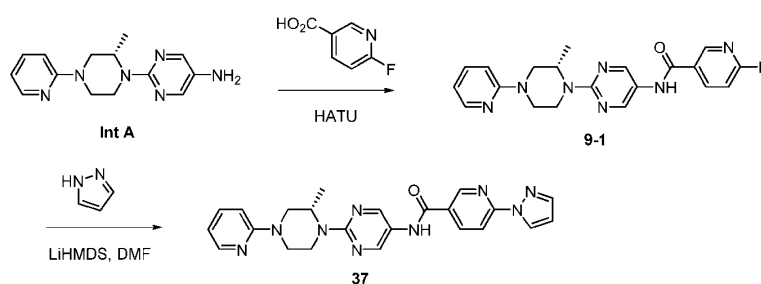
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
23		6-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	438.2	437.2
24		2-methoxy-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-4-carboxamide	406.3	405.2
25		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	420.2	419.2
26		4-(1-cyanocyclopropyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide	440.3	439.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
27		N-[2-[(2S)-4-(6-fluoro-2-pyridyl)-2-methylpiperazin-1-yl]pyrimidin-5-yl]-6-methoxy-pyridine-3-carboxamide	424.2	423.2
28		6-(difluoromethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	442.3	441.2
29		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyridine-2-carboxamide	406.4	405.2
30		6-(2-fluoroethoxy)-N-[6-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-3-pyridyl]pyridine-3-carboxamide	437.4	436.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
31		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-2-pyridyl]pyridine-2-carboxamide	405	404.2
32		2-(2-fluoroethoxy)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyrimidine-5-carboxamide	438.2	437.5
33		6-methoxy-N-[2-[(3R)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	406.2	405.2
34		6-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	406.1	405.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
35		N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide	416.5	415.2
36		2-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrimidine-5-carboxamide	407.4	406.2

Example 37: Synthesis of N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide



Synthesis of 9-1: (S)-6-fluoro-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0126] A solution of Int A (200 mg, 0.740 mmol), 6-fluoronicotinic acid (157 mg, 1.110 mmol), HATU (422 mg, 1.110 mmol), and Hunig's Base (517 μ l, 2.96 mmol) was made in DMF (2466 μ l) at 50 °C. After 18h, the reaction was complete by LCMS. The reaction was diluted with EtOAc and washed with saturated NaHCO₃, water and brine; the organic phase dried over

MgSO₄, filtered, and concentrated. The material was purified by normal phase column chromatography (0 to 100% EtOAc in hexanes, ISCO 24g column; 25 minute gradient) to afford **9-1** as a solid.

¹H NMR (500 MHz, DMSO-d₆) δ 10.42 (s, 1H), 8.83 (d, J = 2.0 Hz, 1H), 8.69 (s, 2H), 8.51 (td, J = 8.3, 2.4 Hz, 1H), 8.12 (d, J = 3.5 Hz, 1H), 7.60 – 7.47 (m, 1H), 7.39 (dd, J = 8.6, 2.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.64 (dd, J = 6.8, 5.1 Hz, 1H), 4.95 – 4.74 (m, 1H), 4.44 (d, J = 13.4 Hz, 1H), 4.24 (dd, J = 24.0, 12.8 Hz, 2H), 3.33 – 3.25 (m, 1H), 3.18 (dd, J = 12.9, 3.8 Hz, 1H), 2.95 (td, J = 12.1, 3.7 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H). LCMS (ESI) calc'd for C₂₀H₂₀N₇O [M+H]⁺: 394.2, found: 394.3.

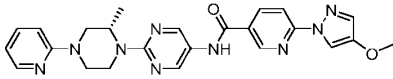
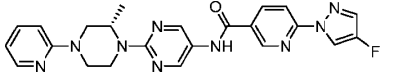
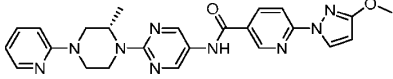
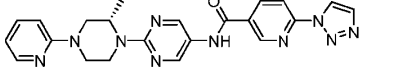
Synthesis of N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide (**37**)

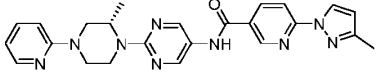
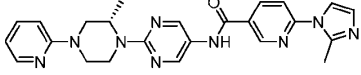
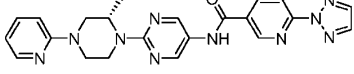
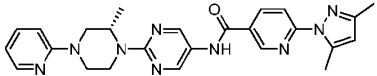
[0127] To a solution of **9-1** (25 mg, 0.064 mmol) and 1H-pyrazole (8.65 mg, 0.127 mmol) in DMF (635 μl) at ambient temperature was added LiHMDS (63.5 μl, 0.095 mmol; 1.5M in THF) and the reaction was heated to 100 °C. After 4h, the reaction was complete. The reaction was diluted with EtOAc and quenched with water and brine; the organic phase dried over MgSO₄, filtered, and concentrated. The material was purified by normal phase column chromatography (0 to 100% EtOAc in hexanes, ISCO 12g column; 20 minute gradient) to afford **37** as a solid.

¹H NMR (500 MHz, DMSO-d₆) δ 10.44 (s, 1H), 9.03 (d, J = 1.8 Hz, 1H), 8.72 (d, J = 4.4 Hz, 2H), 8.52 (dd, J = 8.6, 2.2 Hz, 1H), 8.18 – 8.02 (m, 2H), 7.97 – 7.82 (m, 1H), 7.61 – 7.46 (m, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.69 – 6.56 (m, 2H), 4.94 – 4.77 (m, 1H), 4.52 – 4.36 (m, 1H), 4.24 (dd, J = 24.2, 12.8 Hz, 2H), 3.29 (d, J = 3.7 Hz, 1H), 3.19 (dd, J = 13.0, 3.8 Hz, 1H), 2.96 (td, J = 12.2, 3.8 Hz, 1H), 1.16 (d, J = 6.6 Hz, 3H). LCMS (ESI) calc'd for C₂₃H₂₃N₉O [M+H]⁺: 442.2, found: 442.3.

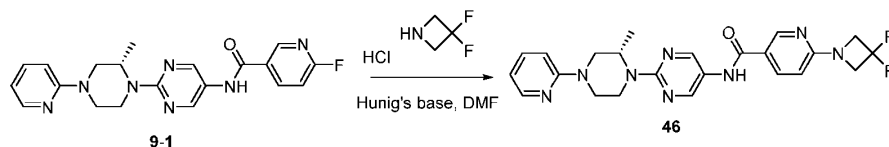
[0128] The compounds contained in Table 2 were synthesized by analogous methods from synthetic sequence in Example 37. Commercially available reagents were substituted where necessary to produce the examples below.

Table 2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
38		6-(4-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	472.2	471.2
39		6-(4-fluoropyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	460.2	459.2
40		6-(3-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	472.2	471.2
41		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(triazol-1-yl)pyridine-3-carboxamide	443.2	442.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
42		6-(3-methylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.2	455.2
43		6-(2-methylimidazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.2	455.2
44		(S)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(2H-1,2,3-triazol-2-yl)nicotinamide	443.2	442.2
45		6-(3,5-dimethylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	470.2	469.2

Example 46: Synthesis of 6-(3,3-difluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide



[0129] A solution of **9-1** (30 mg, 0.076 mmol) and Hunig's Base (80 μ l, 0.458 mmol) in DMF (763 μ l) was added to 3,3-difluoroazetidine hydrochloride (29.6 mg, 0.229 mmol) and heated to 100 °C. After 18h, the reaction was complete by LCMS. The reaction was cooled and diluted with EtOAc. The organic phase was washed with water/saturated NH_4Cl , dried over MgSO_4 , and concentrated. The residue was purified by normal phase column chromatography (20 to 100% EtOAc in hexanes, ISCO 12g column; 20 minute gradient) to afford **46** as a solid.

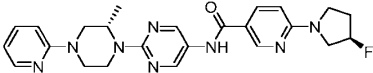
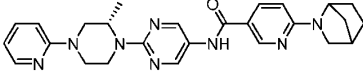
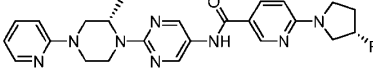
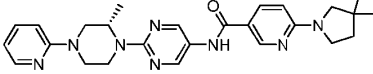
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.07 (s, 1H), 8.76 (d, $J = 1.9$ Hz, 1H), 8.67 (s, 2H), 8.25 – 8.03 (m, 2H), 7.60 – 7.47 (m, 1H), 6.86 (d, $J = 8.6$ Hz, 1H), 6.72 – 6.56 (m, 2H), 4.90 – 4.79 (m, 1H), 4.57 – 4.35

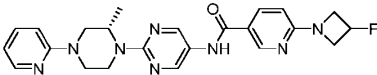
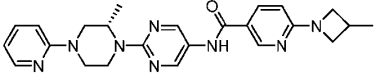
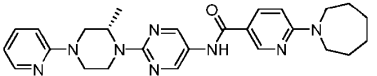
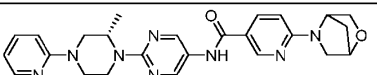
(m, 6H), 4.24 (dd, $J = 24.8, 12.7$ Hz, 2H), 3.31 – 3.24 (m, 1H), 3.22 – 3.11 (m, 1H), 2.95 (td, $J = 12.1, 3.7$

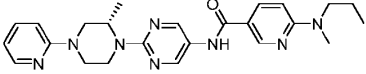
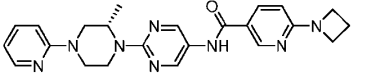
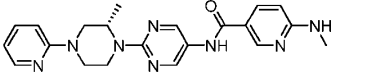
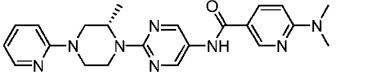
Hz, 1H), 1.14 (d, $J = 6.6$ Hz, 3H); LCMS (ESI) calc'd for $\text{C}_{23}\text{H}_{24}\text{F}_2\text{N}_8\text{O}$ $[\text{M}+\text{H}]^+$: 467.2, found: 467.3.

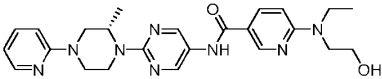
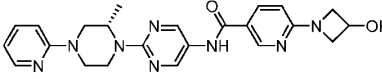
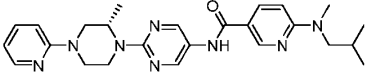
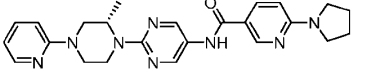
[0130] The compounds contained in Table 3 were synthesized by analogous methods from synthetic sequence in Example 46. Commercially available reagents were substituted where necessary to produce the examples below.

Table 3

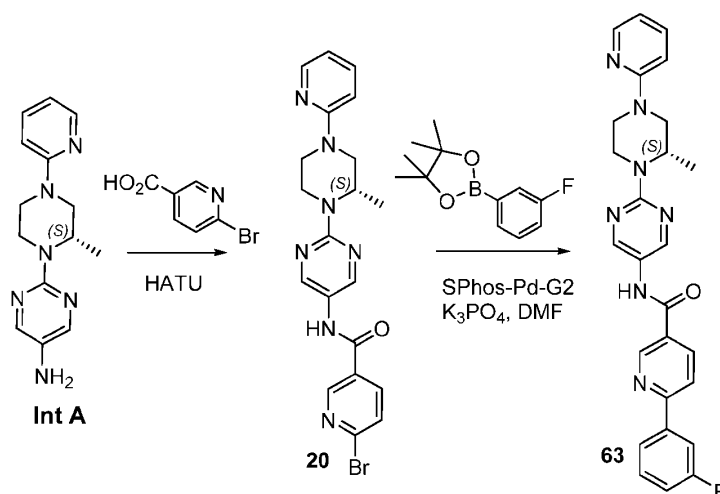
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
47		6-[(3R)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	467.2	466.2
48		6-[rac-(4S)-2-azabicyclo[2.2.1]heptan-2-yl]-N-[2-[rac-(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	463.3	462.2
49		6-[(3S)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	471.3	470.3
50		6-(3,3-dimethylpyrrolidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	463.3	462.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
51		6-(3-fluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)pyrimidin-5-yl]pyridine-3-carboxamide	473.4	472.3
52		6-(3-methylazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)pyrimidin-5-yl]pyridine-3-carboxamide	463.4	462.2
53		6-(azepan-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)pyrimidin-5-yl]pyridine-3-carboxamide	445.4	444.2
54		6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-[2-[rac-(2S)-2-methyl-4-(2-pyridyl)pyrimidin-5-yl]pyridine-3-carboxamide	473.4	472.3

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
55		6-[methyl(propyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	447.5	446.3
56		6-(azetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	431.3	430.2
57		6-(methylamino)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	405.3	404.2
58		6-(dimethylamino)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	433.3	432.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
59		6-[ethyl(2-hydroxyethyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	463.5	462.2
60		6-(3-hydroxyazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	447.5	446.2
61		6-[isobutyl(methyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	461.5	460.3
62		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrrolidin-1-yl-pyridine-3-carboxamide	445.4	444.2

Example 63: Synthesis of 6-(3-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide



Synthesis of 6-bromo-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide (20)

[0131] A solution of Int A (200 mg, 0.740 mmol), 6-bromonicotinic acid (224 mg, 1.110 mmol), HATU (422 mg, 1.110 mmol), and Hunig's Base (517 μ l, 2.96 mmol) was made in DMF (2466 μ l) and heated to 50 °C. After 18h, the reaction was complete by LCMS. The reaction was diluted with EtOAc and washed with saturated NaHCO₃, water and brine; the organic phase dried over MgSO₄, filtered, and concentrated. The material was purified by normal phase column chromatography (20 to 100% EtOAc in hexanes, ISCO 24g column; 25 minute gradient) to afford 20 as a solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 8.93 (d, *J* = 2.1 Hz, 1H), 8.69 (s, 2H), 8.24 (dd, *J* = 8.3, 2.5 Hz, 1H), 8.16 – 8.03 (m, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.45 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 6.8, 5.1 Hz, 1H), 4.84 (dd, *J* = 6.3, 3.2 Hz, 1H), 4.52 – 4.35 (m, 1H), 4.23 (dd, *J* = 23.9, 12.8 Hz, 2H), 3.32 – 3.25 (s, 1H), 3.18 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.07 – 2.86 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H). LCMS (ESI) calc'd for C₂₀H₂₀BrN₇O [M+H]⁺: 454.1, found: 454.2.

Synthesis of 6-(3-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide (63)

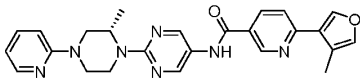
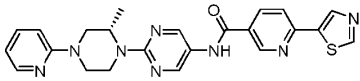
[0132] A solution of 20 (8.2 mg, 0.018 mmol), 3-fluorophenyl pinacolboronate (15.9 mg, 0.072 mmol), SPhos-Pd-G2 (2.6 mg, 0.033 mmol), and K₃PO₄ (23 μ l of 1.5M solution in water, 0.036 mmol) was made in DMF (2466 μ l) and heated to 80 °C. After 18h, the reaction was complete by

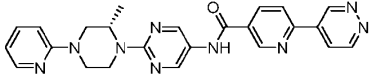
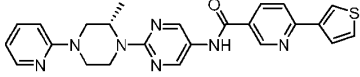
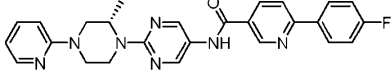
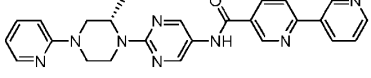
LCMS. The reaction was diluted with DMF (1.0 mL) and the mixture was purified by RP HPLC (reverse phase column chromatography; MeCN in water, 0.1% NH₄OH modifier, Phenomenex C18 Luna column, 100 x 21.2 mm, 5 micron) to afford 63 as a solid after concentration.

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 9.22 (s, 1H), 8.73 (s, 2H), 8.43 (dd, *J* = 8.4, 1.9 Hz, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 4.4 Hz, 1H), 8.04 (dd, *J* = 25.7, 9.0 Hz, 2H), 7.68 – 7.49 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.57 (m, 1H), 4.96 – 4.75 (m, 1H), 4.44 (d, *J* = 13.4 Hz, 1H), 4.25 (dd, *J* = 24.5, 12.8 Hz, 2H), 3.32 – 3.25 (m, 1H) 3.19 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.96 (td, *J* = 12.0, 3.5 Hz, 1H), 1.16 (d, *J* = 6.6 Hz, 4H).; LCMS (ESI) calc'd for C₂₆H₂₄N₇O [M+H]⁺: 470.2, found: 470.2.

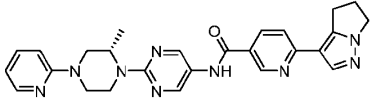
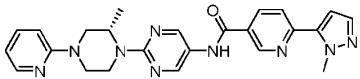
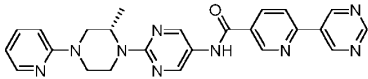
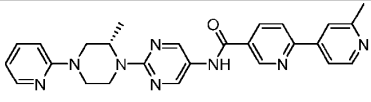
[0133] The compounds contained in Table 4 were synthesized by analogous methods from synthetic sequence in Example 63. Commercially available reagents were substituted where necessary to produce the examples below.

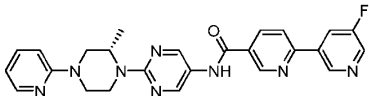
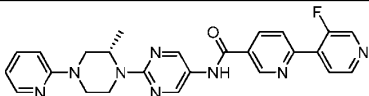
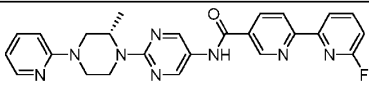
Table 4

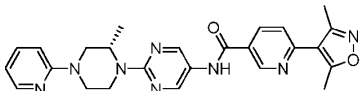
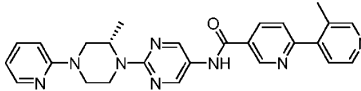
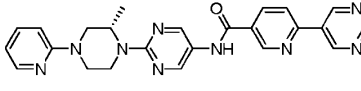
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
64		6-(4-methyl-3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.2	455.2
65		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-thiazol-5-yl-pyridine-3-carboxamide	459.2	458.2

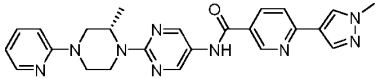
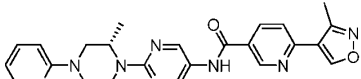
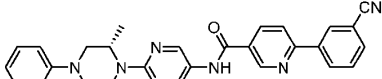
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
66		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyridazin-4-yl-pyridine-3-carboxamide	454.2	453.2
67		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-thienyl)pyridine-3-carboxamide	458.2	457.2
68		6-(4-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	470.2	469.2
69		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-pyridyl)pyridine-3-carboxamide	453.2	452.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
70		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(4-pyridyl)pyridine-3-carboxamide	453.2	452.2
71		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-phenylpyridine-3-carboxamide	452.3	451.2
72		6-(3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	442.2	441.2
73		6-(4-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	477.2	476.2

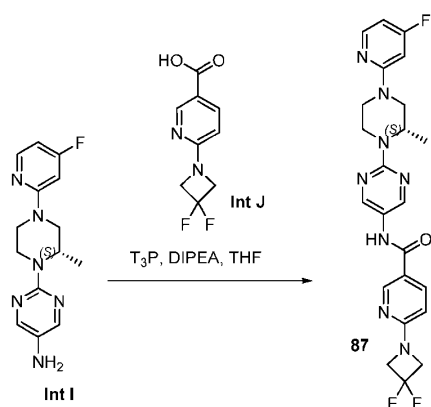
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
74		6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	482.3	481.2
75		6-(2-methylpyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.2	455.2
76		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrimidin-5-yl-pyridine-3-carboxamide	454.2	453.2
77		6-(2-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-	467.3	466.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
		yl]pyridine-3-carboxamide		
78		6-(5-fluoro-3-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	471.2	470.2
79		6-(3-fluoro-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	471.2	470.2
80		6-(6-fluoro-2-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	471.2	470.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
81		6-(3,5-dimethylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	471.2	470.2
82		6-(3-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	467.3	466.2
83		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(2-methylpyrimidin-5-yl)pyridine-3-carboxamide	468.2	467.2

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
84		6-(1-methylpyrazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	456.3	455.2
85		6-(3-methylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	457.2	456.2
86		4-(3-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide	476.4	475.2

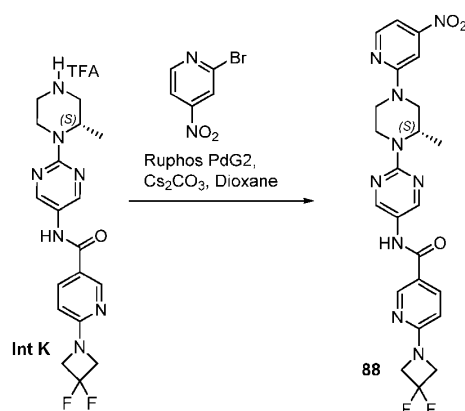
Example 87: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0134] To a stirred solution of compound **Intermediate I** (500 mg, 1.734 mmol) in THF (10 mL) were added compound **Intermediate J** (557 mg, 2.60 mmol), DIPEA (0.909 mL, 5.20 mmol) and 50% 1-Propanephosphonic anhydride solution in EtOAc (1104 mg, 3.47 mmol) at room temperature. The reaction mixture was stirred at 50°C for 12h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). Combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to get crude compound. The crude compound was submitted prep HPLC purification (method: MOBILE PHASE - 10mM Ammonium Bicarbonate IN H₂O: MeCN, COLUMN - LUNA pack C18 (21.2X250) mm 5um Flow-18ml/min, gradient method: 0/45, 12/70, 12.05/98, 14/98, 14.05/45, 17/45) **87** as a pale brown solid. M/Z (ESI): 485.30 [M+H]⁺.

¹H NMR (DMSO-d₆, 400 MHz): δ (ppm) 8.73 (t, J = 2 Hz, 1H), 8.65 (s, 2H), 8.09-8.15 (m, 2H), 6.65-6.71 (m, 2H), 6.51-6.55 (m, 1H), 4.81 (br s, 1H), 4.32-4.53 (m, 5H), 4.22 (t, J = 13.2 Hz, 2H), 3.21-3.32 (m, 2H), 2.95-3.2 (m, 1H), 1.12 (d, J = 2 Hz, 3H).

Example 88: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(2-methyl-4-(4-nitropyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

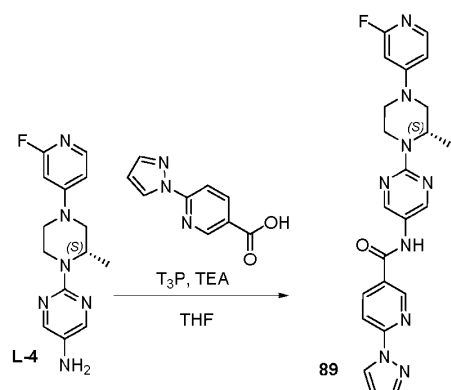


Synthesis of 88: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(2-methyl-4-(4-nitropyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0135] To a stirred solution of **Int K** (250 mg, 0.465 mmol) in Dioxane (3 ml) was added Cs_2CO_3 (455 mg, 1.396 mmol), 2-bromo-4-nitropyridine (123 mg, 0.605 mmol) at room temperature, degassed under nitrogen for 10 min, followed by chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (18.08 mg, 0.023 mmol) stirred at 100 °C in for 16h. Reaction mixture was filtered on celite bed, washed with ethyl acetate. Filtrate was dried over sodium sulfate and evaporated under reduced pressure and crude compound was purified by Prep-HPLC (method: MOBILE PHASE - 10mM Ammonium Bicarbonate IN H_2O : MeCN, COLUMN - LUNA Omega C18 (21.2X250) mm 5um Flow-18ml/min, GRADIENT METHOD-0/50, 10.2/84, 10.25/100, 12/100, 12.05/50, 16/50) and lyophilized to afford **88** as a yellow solid. M/Z (ESI): 512.35 $[\text{M}+\text{H}]^+$.

^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 10.07 (s, 1H), 8.76 (d, $J=2.0$ Hz, 1H), 8.68 (s, 2H), 8.41 (d, $J=5.4$ Hz, 1H), 8.15 (dd, $J=8.8, 2.4$ Hz, 1H), 7.49 (d, $J=1.5$ Hz, 1H), 7.26 (dd, $J=5.5, 1.8$ Hz, 1H), 6.66 (d, $J=8.8$ Hz, 1H), 4.85 (dt, $J=6.3, 3.3$ Hz, 1H), 4.29-4.59 (m, 7H), 3.33-3.41 (m, 2H), 3.11-3.20 (m, 1H), 1.14 (d, $J=6.6$ Hz, 3H).

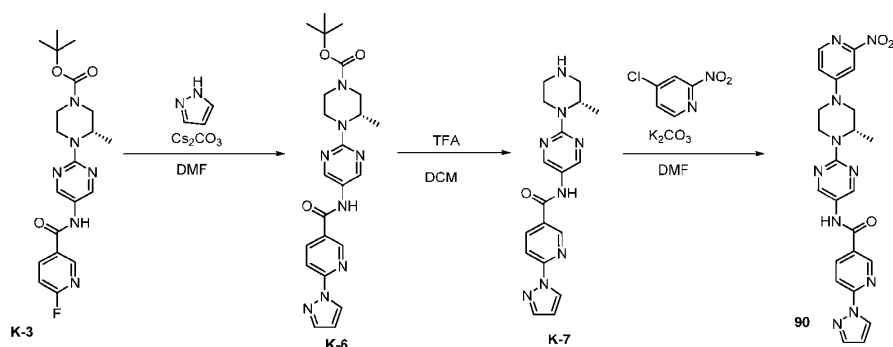
Example 89: (S)-N-(2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide



[0136] To a stirred solution of compound **Int L** (150 mg, 0.520 mmol) in THF (3 ml) was added TEA (0.290 ml, 2.081 mmol), 50% 1-Propanephosphonic anhydride solution in EtOAc (0.312 ml, 1.040 mmol), 6-(1H-pyrazol-1-yl)nicotinic acid (128 mg, 0.676 mmol) at 0 °C and stirred for 12 h at room temperature. The reaction mixture was quenched with NaHCO₃ solution (10 ml), extracted with EtOAc (2 x 50 mL), washed with water (2 x 10 ml), combined organic layer was washed with brine solution (20 ml), dried over Na₂SO₄, filtered, concentrated under reduced pressure and prep HPLC (conditions: MOBILE PHASE - 10mM Ammonium Bicarbonate IN H₂O: MeCN COLUMN - X-Select Phenyl Hexyl (19X250) mm 5u Flow-18ml/min GRADIENT METHOD - 0/35,9.3/70,9.4/99,11/99,11.05/35,15/35). Pure fractions concentrated and lyophilized to afford **89** as off white solid. M/Z (ESI): 460.15 [M+H]⁺.

¹H NMR (400MHz, DMSO-d₆) δ: 10.44 (s, 1H), 9.03 (d, J=2.2 Hz, 1H), 8.72 (s, 3H), 8.51 (dd, J=8.6, 2.2 Hz, 1H), 8.08 (d, J=8.6 Hz, 1H), 7.87-7.96 (m, 1H), 7.81 (d, J=6.1 Hz, 1H), 6.81 (br d, J=6.1 Hz, 1H), 6.61-6.68 (m, 1H), 6.49 (s, 1H), 4.78 (dt, J=6.7, 3.1 Hz, 1H), 4.33-4.41 (m, 1H), 3.86-3.98 (m, 2H), 3.34-3.48 (m, 2H), 3.09-3.18 (m, 1H), 1.16 (d, J=6.6 Hz, 3H).

Example 90: (S)-N-(2-(2-methyl-4-(2-nitropyridin-4-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide



Synthesis of K-6: *tert*-butyl (S)-4-(5-(6-(1H-pyrazol-1-yl)nicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0137] To a stirred solution of 1H-pyrazole (82 mg, 1.201 mmol), cesium carbonate (391 mg, 1.201 mmol) in DMF (5 ml) was added **K-3** (250 mg, 0.600 mmol) at room temperature under nitrogen atmosphere and stirred at 90 °C for 3 h. Progress of the reaction monitored by LCMS and TLC. TLC showed that the reaction was completed. Then the reaction mixture was diluted with ethyl acetate (100 mL) and water (60 mL). Organic layer was separated and aqueous layer was re extracted with ethyl acetate (2 x 40 mL) and the combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain compound **K-6** as a pale brown color gummy solid. M/Z (ESI): 465.36 [M+H]⁺.

Synthesis of K-7: (S)-N-(2-(2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide

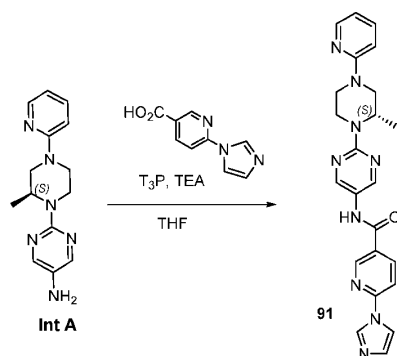
[0138] To a stirred solution of compound **K-6** (190 mg, 0.409 mmol) in DCM (5.7 ml) was added TFA (1.565 ml, 20.45 mmol) at room temperature and stirred under nitrogen atmosphere at room temperature for 2 h. Progress of the reaction monitored by TLC. TLC showed that the reaction was completed. Then the reaction mixture was concentrated under reduced pressure and crude residue was diluted with DCM (100 ml) and H₂O (60 ml). Then the Na₂CO₃ was added to adjust pH to 7~8 and extracted with DCM (100 ml x 3). Combined organic layer dried over sodium sulphate, filtered and concentrated under reduced pressure to give compound **K-7** as a pale brown solid. M/Z (ESI): 365.15 [M+H]⁺.

Synthesis of 90: (S)-N-(2-(2-methyl-4-(2-nitropyridin-4-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide

[0139] To a stirred solution of compound **K-7** (105 mg, 0.288 mmol), potassium carbonate (119 mg, 0.864 mmol) in DMF (5 ml) was added 4-chloro-2-nitropyridine (91 mg, 0.576 mmol) at room temperature under nitrogen atmosphere and stirred at 50 °C for 6 h. Progress of the reaction monitored by LCMS and TLC. TLC showed that the reaction was completed. Then the reaction mixture was diluted with ethyl acetate (60 mL) and water (50 mL). Organic layer was separated and aqueous layer was re extracted with ethyl acetate (2 x 30 mL) and combined organic layer dried over sodium sulphate, filtered and concentrated under reduced pressure and crude was purified by Prep HPLC (conditions: MOBILE PHASE - 10mM Ammonium Bicarbonate IN H₂O: MeCN COLUMN - X-BRIDGE C18 (19X250) mm 5u Flow-18ml/min GRADIENT METHOD-0/30, 9/75, 9.05/100, 11/100, 11.05/30, 13.5/30. The obtained compound further purified by SFC method (conditions: Column: Chiralpak IG (4.6*250 mm), 5µ Mobile Phase- A: MeOH/DCM/DEA(50/50/0.2) Isocratic of A: 100% Flow Rate: 1.0 mL/min Diluent: EtOH). Pure fractions concentrated and lyophilized to afford **90** as a yellow solid. M/Z (ESI): 487.12 [M+H]⁺.

¹H NMR (500MHz, DMSO-d₆) δ: 10.45 (s, 1H), 9.00-9.05 (m, 1H), 8.69-8.76 (m, 3H), 8.52 (dd, J=8.5, 2.4 Hz, 1H), 8.18 (d, J=5.8 Hz, 1H), 8.05-8.10 (m, 1H), 7.89-7.94 (m, 1H), 7.63 (d, J=2.4 Hz, 1H), 7.23 (dd, J=6.1, 2.4 Hz, 1H), 6.65 (dd, J=2.6, 1.7 Hz, 1H), 4.77-4.85 (m, 1H), 4.35-4.42 (m, 1H), 3.98-4.09 (m, 2H), 3.45-3.55 (m, 2H), 3.22-3.29 (m, 1H), 1.17 (d, J=6.4 Hz, 3H).

Example 91: (S)-6-(1H-imidazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0140] To a stirred solution of **Intermediate A** (150 mg, 0.555 mmol), 6-(1H-imidazol-1-yl)nicotinic acid (157 mg, 0.832 mmol) in THF (30 ml) was added TEA (0.193 ml, 1.387 mmol), 1-propanephosphonic anhydride (0.495 ml, 0.832 mmol) at 25 °C and stirred for 16 h at 25 °C. The reaction mixture quenched with ice cold water (10 mL), extracted with ethyl acetate (2 x 100

mL), combined organic layer washed with brine solution (2 x 10 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and crude compound purified by Prep HPLC (MOBILE PHASE - 10mM Ammonium Bicarbonate IN H₂O: MeCN COLUMN - X-Select C18 (19X250) mm 5u Flow-18ml/min GRADIENT METHOD-0/45, 6.9/76, 6.95/100, 9/100, 9.05/45, 12/45). Pure fractions concentrated and lyophilized to afford **91** as a pale yellow solid. M/Z (ESI): 442.14 [M+H]⁺.

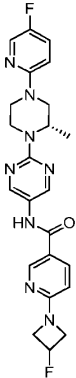
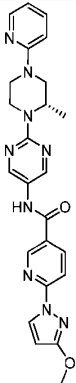
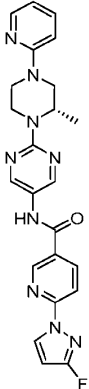
¹H NMR (400MHz, DMSO-d₆) δ: 10.43 (s, 1H), 9.04 (d, J=2.0 Hz, 1H), 8.71 (s, 2H), 8.66 (s, 1H), 8.52 (dd, J=8.7, 2.3 Hz, 1H), 8.12 (dd, J=4.9, 1.2 Hz, 1H), 8.06 (t, J=1.2 Hz, 1H), 8.01 (d, J=8.6 Hz, 1H), 7.55 (ddd, J=8.6, 7.0, 2.2 Hz, 1H), 7.18 (s, 1H), 6.86 (d, J=8.8 Hz, 1H), 6.60-6.67 (m, 1H), 4.85 (dt, J=6.4, 3.2 Hz, 1H), 4.41-4.49 (m, 1H), 4.17-4.31 (m, 2H), 3.28 (br d, J=3.7 Hz, 1H), 3.19 (br dd, J=13.1, 3.8 Hz, 1H), 2.90-3.01 (m, 1H), 1.16 (d, J=6.6 Hz, 3H).

[0141] The compounds contained in Table 5 were synthesized by analogous methods from synthetic sequences above. Commercially available reagents were substituted where necessary to produce the examples below.

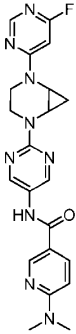
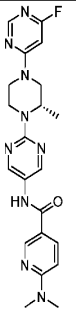
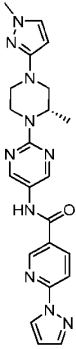
Table 5

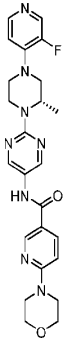
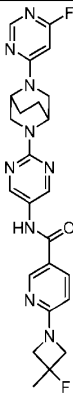
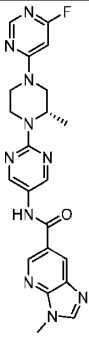
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
92		N-(2-((2S,6R)-2,6-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-5'-fluoro-[2,3'-bipyridine]-5-carboxamide	499.2	498.23

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
93		N-(2-((S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-((R)-3-fluoropyrrolidin-1-yl)nicotinamide	481.3	480.22
94		(R)-6-(1H-imidazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide	472.4	471.21
95		(S)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide	479.4	478.22

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
96		(S)-6-(3-fluoroazetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide	467.4	466.20
97		(S)-6-(3-methoxy-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide	472.4	471.21
98		(S)-6-(3-fluoro-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide	460.3	459.19

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
99		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(4-methylpiperazin-1-yl)nicotinamide	493.3	492.25
100		(R)-6-(2-(2-fluoropyrimidin-5-yl)-N-(5-(2-methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)nicotinamide	502.4	501.20
101		(S)-N-(2-(2-methyl-4-(thiazol-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide	448.1	447.16

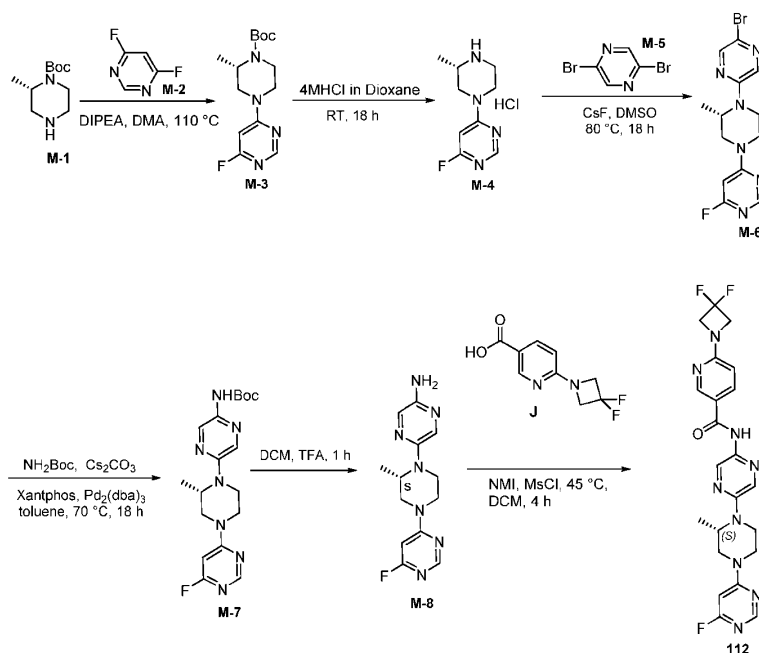
Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
102		6-(dimethylamino)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyrimidin-5-yl)nicotinamide	436.4	435.19
103		(S)-6-(dimethylamino)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide	438.2	437.21
104		(S)-N-(2-(2-methyl-4-(1-methyl-1H-pyrazol-3-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide	445.3	444.21

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
105		(S)-N-(2-(4-(3-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide	479.3	478.22
106		6-(3-fluoro-3-methylazetidin-1-yl)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidin-5-yl)nicotinamide	494.4	493.22
107		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide	449.2	448.19

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
108		N-(2-((2S,5R)-2,5-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide	470.3	469.23
109		(S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-4-(pyridin-3-yl)benzamide	470.6	469.20
110		6-(3,3-difluoroazetidin-1-yl)-N-(2-((2R,3R)-4-(4-fluoropyridin-2-yl)-2,3-dimethylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide	499.5	498.21

Example Number	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
111		(S)-N-(2-(4-(2-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide	479.2	478.22

Example 112: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide



Synthesis of **M-3**: tert-butyl (S)-4-(6-fluoropyrimidin-4-yl)-2-methylpiperazine-1-carboxylate

[0142] To a stirred solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**M-1**) (2.0 g, 9.99 mmol) in DMA (20 ml) was added N,N-Diisopropylethylamine (5.2 mL, 30.0 mmol) at 0

°C followed by 4,6-difluoropyrimidine (**M-2**) (1.28 g, 11.0 mmol) and the mixture was stirred for 18 h at 110 °C. Reaction mixture was poured into crushed ice, extracted with EtOAc and organic layer was washed with brine solution and dried over Na₂SO₄ and evaporated under reduced pressure to afford compound **M-3**. M/Z (ESI): 297.12 [M+H⁺].

Synthesis of **M-4**: (S)-4-fluoro-6-(3-methylpiperazin-1-yl)pyrimidine

[0143] To a stirred solution of **M-3** (2.2 g, 7.42 mmol) in DCM (10 ml) was added 4M HCl in 1,4-Dioxane (9.25 g, 74.2 mmol) at 0 °C and stirred for 18 h. Reaction mixture was concentrated by under reduced pressure and washed with saturated NaHCO₃ solution, extracted with EtOAc. Organic phase was washed with brine solution, dried over Na₂SO₄ and concentrated under reduced pressure to give compound **M-4**. M/Z (ESI): 197.06 [M+H⁺].

Synthesis of **M-6**: (S)-4-(4-(5-bromopyrazin-2-yl)-3-methylpiperazin-1-yl)-6-fluoropyrimidine

[0144] To a stirred solution of **M-4** (1.9 g, 9.68 mmol) in DMSO (20 ml) was added cesium fluoride (2.94 g, 19.4 mmol) and 2,5-dibromopyrazine (**M-5**) (1.843 g, 7.75 mmol) at 0 °C and stirred for 18 h at 80 °C. Reaction mixture was poured into ice cold water and extracted with EtOAc and organic layer was washed with brine solution, dried over Na₂SO₄ and evaporated under vacuum to afford compound **M-6**. M/Z (ESI): 353.04 [M+H⁺].

Synthesis of **M-7**: tert-butyl (S)-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)carbamate

[0145] To a stirred solution of **M-6** (800 mg, 2.265 mmol) in toluene (10 ml) was added cesium carbonate (996 mg, 3.06 mmol), tris(dibenzylideneacetone)dipalladium(0) (104 mg, 0.113 mmol), xantphos (131 mg, 0.227 mmol) and tert-butyl carbamate (292 mg, 2.492 mmol) at 0 °C and stirred for 18 h at 70 °C. Reaction mixture was poured into ice water (5 mL) and extracted with EtOAc (5mL x 3) and organic layer was washed with brine solution and dried over anhydrous Na₂SO₄, evaporated under reduced pressure to afford compound **M-7**. M/Z (ESI): 390.17 [M+H⁺].

Synthesis of **M-8**: (S)-5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-amine

[0146] To a stirred solution of **M-7** (600 mg, 1.541 mmol) in DCM (8 ml) was added TFA (0.590 ml, 7.70 mmol) at 0 °C and stirred for 18 h at room temperature. Reaction mixture evaporated and quenched with saturated NaHCO₃ solution (10 ml), and extracted with EtOAc (10

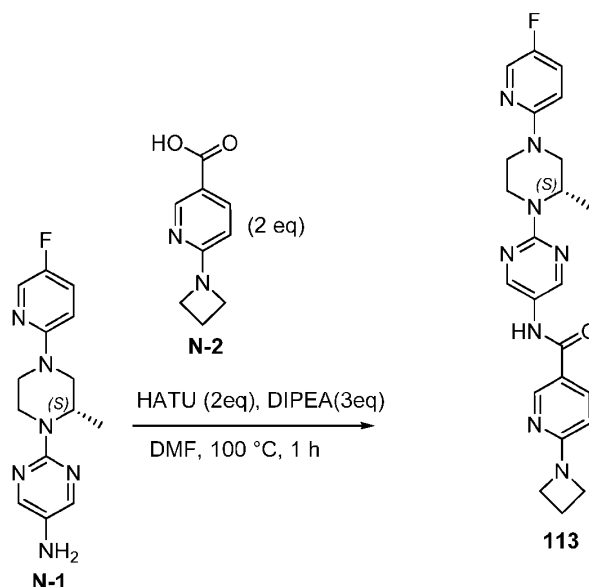
ml x 3). Organic layer was washed with brine solution and dried over Na₂SO₄ and evaporated under reduced pressure to give **M-8**. M/Z (ESI): 290.21 [M+H⁺].

Synthesis of **112**: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide:

[0147] To a stirred solution of **int J** (89 mg, 0.415 mmol) in DCM (5 ml) was added 1-methylimidazole (0.083 ml, 1.037 mmol) at 0 °C, followed by methanesulfonyl chloride (0.035 ml, 0.456 mmol) at 0 °C and stirred for 15 min then **M-8** (60 mg, 0.207 mmol) was added and stirred for 4 h at 45 °C. Reaction mixture was poured into ice cold water (2 mL) and extracted with DCM (3 mL x 3). Organic layer was washed with brine solution and dried over anhydrous Na₂SO₄ and evaporated under reduced pressure and crude compound was purified by prep HPLC (MOBILE PHASE - 10mM Ammonium Bicarbonate in H₂O: MeCN, Column - X-Bridge C18 (19X250) mm 5u Flow-18ml/min, Gradient Method-0/30, 9.2/78, 9.25/99, 11.2/99, 11.25/30, 15.2/30) and lyophilized to afford **112**. M/Z (ESI): 484.18 [M+H⁺].

¹H NMR (400MHz, DMSO-d₆) δ: 10.57 (s, 1H), 8.82 (br dd, J=17.7, 1.6 Hz, 2H), 8.32 (br d, J=2.7 Hz, 1H), 8.20 (br dd, J=8.8, 2.4 Hz, 1H), 8.12 (br d, J=1.2 Hz, 1H), 6.58-6.65 (m, 2H), 4.60 (br dd, J=6.4, 2.7 Hz, 1H), 4.42-4.54 (m, 4H), 4.31-4.40 (m, 2H), 4.06-4.11 (m, 1H), 3.75-3.81 (m, 1H), 3.43 (br dd, J=13.7, 3.7 Hz, 1H), 3.24 (br dd, J=8.4, 4.5 Hz, 2H), 1.06 (d, J=6.4 Hz, 3H).

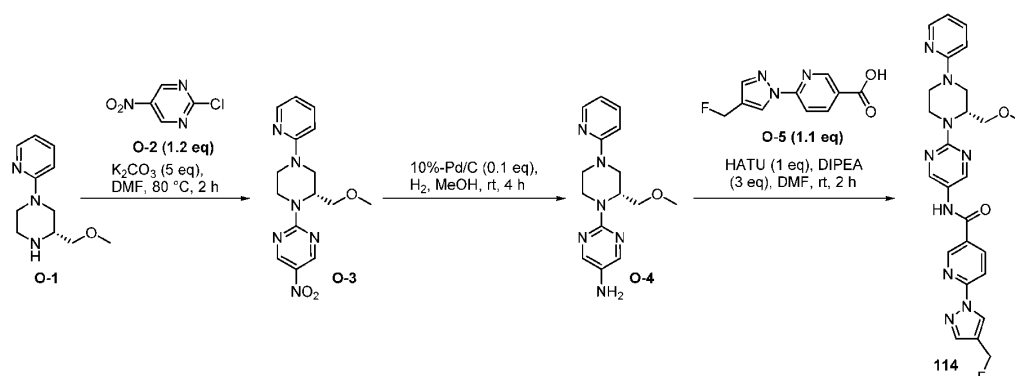
Example **113**: (S)-6-(azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0148] To a stirred solution of **N-1** (prepared in an analogous manner as **M-8**) (0.060 g, 0.208 mmol) and **N-2** (prepared in an analogous manner as **J**) (0.074 g, 0.416 mmol) in DMF (2 mL) was added HATU (0.158 g, 0.416 mmol) and DIPEA (0.109 mL, 0.624 mmol) at 0 °C and stirred at 100 °C for 1 h. The reaction mixture was quenched with ice cold water (10 mL), extracted with ethyl acetate (2 x 50 mL), and the combined organic layer was washed with brine solution (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure and the crude compound was purified by Prep HPLC (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Bridge C18 (19X250) mm 5u Flow-18ml/min Gradient Method-0/40, 8/73, 8.05/99, 10/99, 10.05/40, 13/40). Pure fractions were concentrated and lyophilized to afford **113**. M/Z (ESI): 449.46 [M+H]⁺.

¹H NMR (400MHz, DMSO-d₆) δ: 9.94 (s, 1H), 8.61-8.75 (m, 3H), 8.10 (d, J=3.2 Hz, 1H), 8.03 (dd, J=8.9, 2.3 Hz, 1H), 7.53 (td, J=8.8, 3.2 Hz, 1H), 6.92 (dd, J=9.4, 3.3 Hz, 1H), 6.40 (d, J=8.8 Hz, 1H), 4.84 (br s, 1H), 4.42 (br d, J=13.4 Hz, 1H), 4.10-4.24 (m, 2H), 4.04 (t, J=7.5 Hz, 4H), 3.23-3.30 (m, 1H), 3.13 (dd, J=13.0, 3.9 Hz, 1H), 2.91 (br d, J=3.7 Hz, 1H), 2.30-2.42 (m, 2H), 1.15 (d, J=6.6 Hz, 3H).

Example 114: (R)-6-(4-(fluoromethyl)-1H-pyrazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



Synthesis of **O-3**: (R)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)-5-nitropyrimidine

[0149] To a stirred solution of **O-1** (made in an analogous method as int **3-3**) (300 mg, 1.231 mmol) in DMF (4 mL) were added K_2CO_3 (851 mg, 6.15 mmol) and 2-chloro-5-nitropyrimidine (**O-2**) (236 mg, 1.477 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. Reaction mixture was quenched with H_2O (25 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford **O-3**. M/Z (ESI): 331.17 $[M+H]^+$.

Synthesis of **O-4**: (R)-2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-amine

[0150] To a stirred solution of **O-3** (50 mg, 0.151 mmol) in MeOH (5 mL) was added 10% Pd/C (16.11 mg, 0.015 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h under hydrogen atmosphere. Reaction mixture was diluted with EtOAc (15 mL), filtered through celite pad and washed with EtOAc (2 x 15 mL). Filtrate was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford **O-4**. M/Z (ESI): 301.24 $[M+H]^+$.

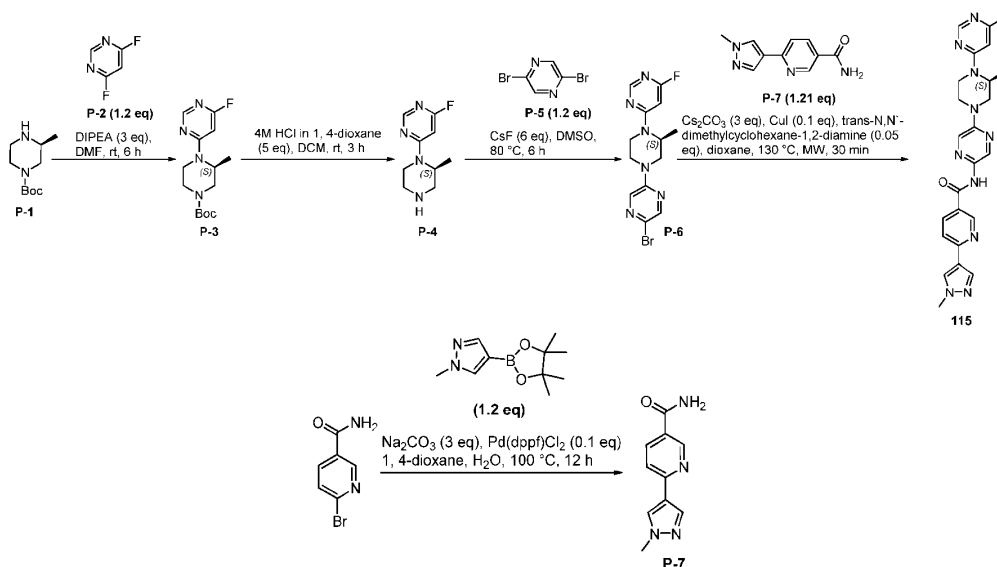
Example **114**: (R)-6-(4-(fluoromethyl)-1H-pyrazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0151] To a stirred solution of **O-4** (40 mg, 0.133 mmol) in DMF (1 mL) were added HATU (50.6 mg, 0.133 mmol), **O-5** (32.4 mg, 0.146 mmol) and DIPEA (0.070 mL, 0.4 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. Reaction mixture was quenched with water (15 mL) and extracted with EtOAc (2 x

20 mL). Combined organic layer was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H_2O : MeCN, Column - X-Select C18 (19X250) mm 5u, Flow-18ml/min Gradient, Method - 0/45, 8/81, 8.05/99, 10/99, 10.05/45.13/45). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **114**. M/Z (ESI): 504.32 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.46 (s, 1H), 9.05 (s, 1H), 8.90 (d, J = 3.2 Hz, 1H), 8.71 (s, 2H), 8.53 (d, J = 8.4 Hz, 1H), 7.98-8.17 (m, 3H), 7.56 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.65 (t, J = 6.4 Hz, 1H), 5.32-5.55 (m, 2H), 4.88 (br s, 1H), 4.48 (d, J = 13.6 Hz, 1H), 4.37 (d, J = 13.2 Hz, 1H), 4.26 (d, J = 12.4 Hz, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.38-3.45 (m, 1H), 3.23 (s, 4H), 3.14 (dd, J = 13.2 Hz, 3.6 Hz, 1H), 2.89-3.04 (m, 1H).

Example 115: (S)-N-(5-(4-(6-fluoropyrimidin-4-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of P-3: tert-butyl (S)-4-(6-fluoropyrimidin-4-yl)-3-methylpiperazine-1-carboxylate

[0152] To a stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (**P-1**) (5 g, 24.96 mmol) in DMF (50 mL) were added DIPEA (13.08 mL, 74.9 mmol) and 4,6-difluoropyrimidine (**P-2**) (3.48 g, 30.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6 h. Reaction mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was washed with brine (100 mL), dried over

anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 silica) cartridge and compound eluted with 20% EtOAc in petroleum ether. Pure fractions were combined and concentrated under vacuum to afford **P-3**. M/Z (ESI): 297.16 [M+H]⁺.

Synthesis of **P-4**: (S)-4-fluoro-6-(2-methylpiperazin-1-yl)pyrimidine

[0153] To a stirred solution of **P-3** (2.3 g, 7.76 mmol) in DCM (30 mL) was added 4M HCl in 1, 4-dioxane (9.70 mL, 38.8 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. Reaction mixture was concentrated and dried under reduced pressure to afford **P-4**. M/Z (ESI): 197.09 [M+H]⁺.

Synthesis of **P-6**: (S)-4-(4-(5-bromopyrazin-2-yl)-2-methylpiperazin-1-yl)-6-fluoropyrimidine

[0154] To a stirred solution of **P-4** (500 mg, 2.149 mmol) in DMSO (8 mL) were added cesium fluoride (1958 mg, 12.89 mmol) and 2, 5-dibromopyrazine (**P-5**) (613 mg, 2.58 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 6 h under argon atmosphere. Reaction mixture was quenched with ice cold water (50 mL) and extracted with EtOAc (3x 50 mL). Combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using silica gel cartridge and compound eluted with 25% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **P-6**. M/Z (ESI): 353.06 [M+H]⁺.

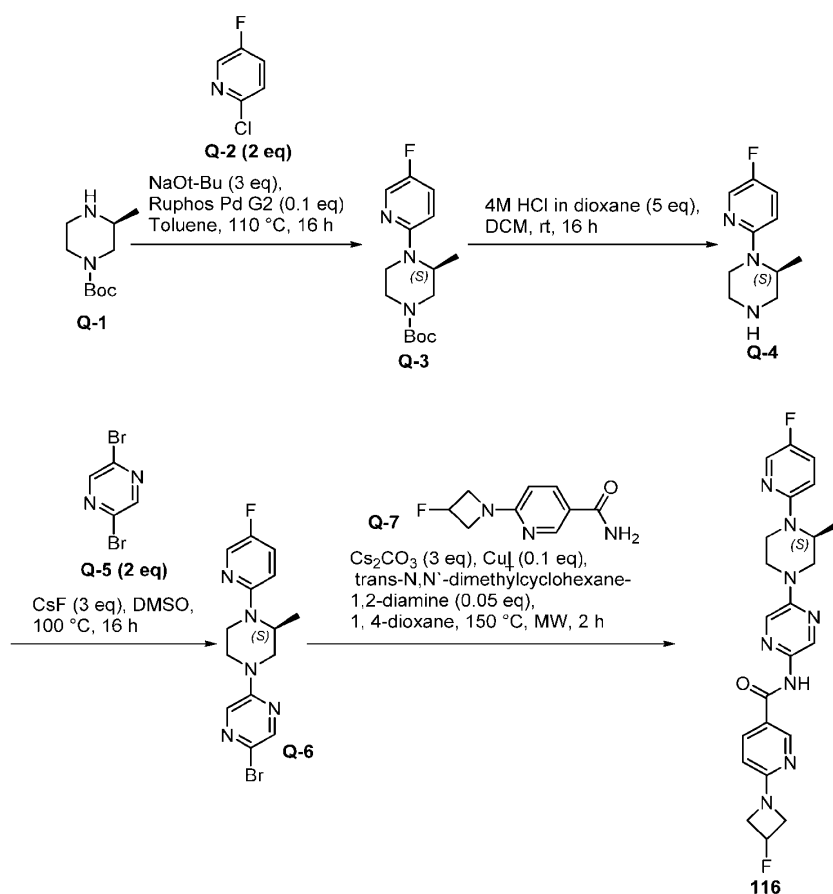
Synthesis of **P-7**: 6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0155] To a solution of 6-bromonicotinamide (3 g, 14.92 mmol) in 1, 4-dioxane (40 mL), and H₂O (10 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.73 g, 17.91 mmol), Na₂CO₃ (4.75 g, 44.8 mmol) at room temperature. The reaction mixture was degassed and purged with argon for 5 min. Then to this reaction mixture was added PdCl₂ (dppf) (1.092 g, 1.492 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 12 h. Reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 50mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 10-15% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure to afford **P-7**. M/Z (ESI): 203.02 [M+H]⁺.

Example 115: (S)-N-(5-(4-(6-fluoropyrimidin-4-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0156] To a stirred solution of **P-6** (100 mg, 0.283 mmol) in 1, 4-dioxane (2 mL) were added **P-7** (69 mg, 0.341 mmol), Cs₂CO₃ (277 mg, 0.849 mmol), copper(I) iodide (5 mg, 0.026 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (4 mg, 0.028 mmol) at room temperature. Reaction mixture was degassed and purged with argon gas for 10 min. The reaction mixture was stirred in a microwave at 130 °C for 30 min. Reaction mixture was quenched with water (30 mL) and extracted with DCM (3 x 20 mL). Combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was triturated with diethyl ether (2 x 10 mL) and dried under reduced pressure. Obtained compound was again purified by prep-HPLC purification (conditions: Mobile Phase - 0.1%FA in H₂O: MeCN Column - X-Bridge C18 (19X250) mm, 5μ Flow-15.0 ml/min Gradient Method - 0/35,2/35,6/45,10.5/48.7,10.55/100,12.5/100,12.55/35,16/35). Pure compound was combined, concentrated under reduced pressure and lyophilized to afford **115**. M/Z (ESI): 475.18 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.84 (s, 1H), 9.09 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 8.88 (d, *J* = 1.6 Hz, 1H), 8.41 (s, 1H), 8.32-8.39 (m, 2H), 8.23 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 0.4 Hz, 1H), 7.78 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 6.58 (d, *J* = 1.2 Hz, 1H), 4.69 (br s, 1H), 4.15-4.39 (m, 3H), 3.91 (s, 3H), 3.35-3.48 (m, 2H), 3.08-3.20 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H).

Example 116: (S)-6-(3-fluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide



Synthesis of **Q-3**: tert-butyl (S)-4-(5-fluoropyridin-2-yl)-3-methylpiperazine-1-carboxylate

[0157] To a stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (**Q-1**) (1 g, 4.99 mmol) in toluene (20 mL) were added 2-chloro-5-fluoropyridine (**Q-2**) (0.995 mL, 9.99 mmol) and sodium tert-butoxide (1.440 g, 14.98 mmol) at room temperature. Reaction mixture was degassed and purged with argon gas for 25 min. Then to this reaction mixture was added RuPhos Pd G2 (0.388 g, 0.499 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 16 h under nitrogen atmosphere in a sealed tube. Reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 85 mL). Combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 15% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **Q-3**. M/Z (ESI): 296.11 [M+H]⁺.

Synthesis of **Q-4**: (S)-1-(5-fluoropyridin-2-yl)-2-methylpiperazine

[0158] To a stirred solution of **Q-3** (100 mg, 0.339 mmol) in DCM (2 mL) was added 4M HCl in 1, 4-dioxane (0.423 mL, 1.693 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h under nitrogen atmosphere. Reaction mixture was concentrated under reduced pressure. Crude compound was triturated with 20% EtOAc in diethyl ether and dried under reduced pressure to afford **Q-4**. M/Z (ESI): 196.12 [M+H]⁺.

Synthesis of **Q-6**: (S)-2-bromo-5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazine

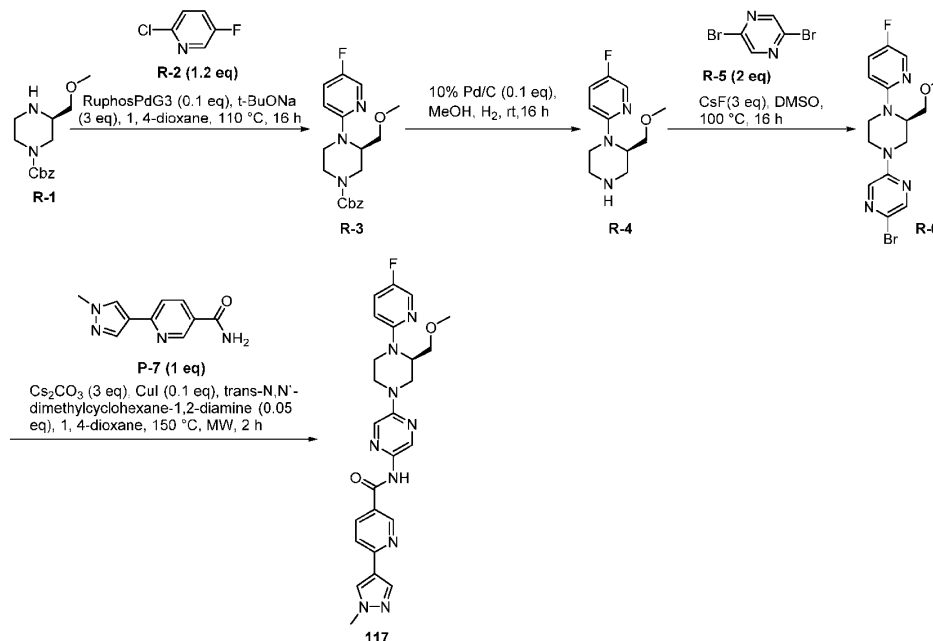
[0159] To a stirred solution of **Q-4** (80 mg, 0.345 mmol) in DMSO (2 mL) were added CsF (157 mg, 1.036 mmol) and 2, 5-dibromopyrazine (**Q-5**) (164 mg, 0.691 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h under nitrogen atmosphere in a sealed tube. Reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 35 mL). Combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 25% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **Q-6**. M/Z (ESI): 352.97 [M+H]⁺.

Example 116: (S)-6-(3-fluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

[0160] To a stirred solution of **Q-6** (60 mg, 0.170 mmol) in 1, 4-dioxane (1.5 mL) were added Cs₂CO₃ (167 mg, 0.511 mmol), copper(I) iodide (3.24 mg, 0.017 mmol), trans-N, N'-dimethylcyclohexane-1, 2-diamine (1.212 mg, 8.52 μmol) and (**Q-7**) (made in an analogous manner as **X-5**) (61.4 mg, 0.170 mmol) at room temperature. The reaction mixture was stirred in a microwave at 150 °C for 2 h under nitrogen atmosphere. Reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 75 mL). Combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 40 g silica (230-400 mesh) cartridge and compound eluted with 3% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure. Obtained compound was further re-purified by achiral prep-purification [Cellulose SC (250X30X5μ), MeCN:MeOH (90:10)]. Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **116**. M/Z (ESI): 467.28 [M+H]⁺.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.50 (s, 1H), 8.83 (d, J = 1.6 Hz, 1H), 8.76-8.82 (m, 1H), 8.10-8.26 (m, 3H), 7.49-7.59 (m, 1H), 6.87 (dd, J = 9.4 Hz, 3.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.40-5.72 (m, 1H), 4.50-4.63 (m, 1H), 4.32-4.49 (m, 2H), 3.98-4.32 (m, 5H), 3.16-3.30 (m, 2H), 3.00-3.12 (m, 1H), 1.09 (d, J = 6.4 Hz, 3H).

Example 117: (R)-N-(5-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of R-3: benzyl (R)-4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazine-1-carboxylate

[0161] To a stirred solution of **R-1** (2 g, 7.57 mmol) in 1,4-dioxane (30 mL) were added sodium tert-butoxide (2.182 g, 22.70 mmol), 2-chloro-5-fluoropyridine (**R-2**) (1.194 g, 9.08 mmol) at room temperature. Reaction mixture was degassed and purged with argon gas for 5 min. Then to this reaction mixture was added (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (0.633 g, 0.757 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 16 h in a sealed tube. Reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 30 mL). Combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Crude compound was purified by silica gel column and

compound eluted with 20% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **R-3**. M/Z (ESI): 360.07 [M+H]⁺.

Synthesis of **R-4**: (R)-1-(5-fluoropyridin-2-yl)-2-(methoxymethyl)piperazine

[0162] To a stirred solution of **R-3** (800 mg, 2.226 mmol) in MeOH (10 mL) was added 10% Pd/C (237 mg, 0.223 mmol). The reaction mixture was stirred at room temperature for 16 h under hydrogen atmosphere. Reaction mixture was filtered through celite pad and filtrate was concentrated and dried under reduced pressure to afford **R-4**. M/Z (ESI): 226.00 [M+H]⁺.

Synthesis of **R-6**: (R)-2-bromo-5-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrazine

[0163] To a stirred solution of **R-4** (600 mg, 2.66 mmol) in DMSO (10 mL) were added CsF (1214 mg, 7.99 mmol) and 2, 5-dibromopyrazine (**R-5**) (1267 mg, 5.33 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h under nitrogen atmosphere in a sealed tube. Reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 30 mL). Combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by silica gel column and compound eluted with 20% EtOAc in petroleum ether. Pure fractions were combined and concentrated under reduced pressure to afford **R-6**. M/Z (ESI): 382.17 [M+H]⁺.

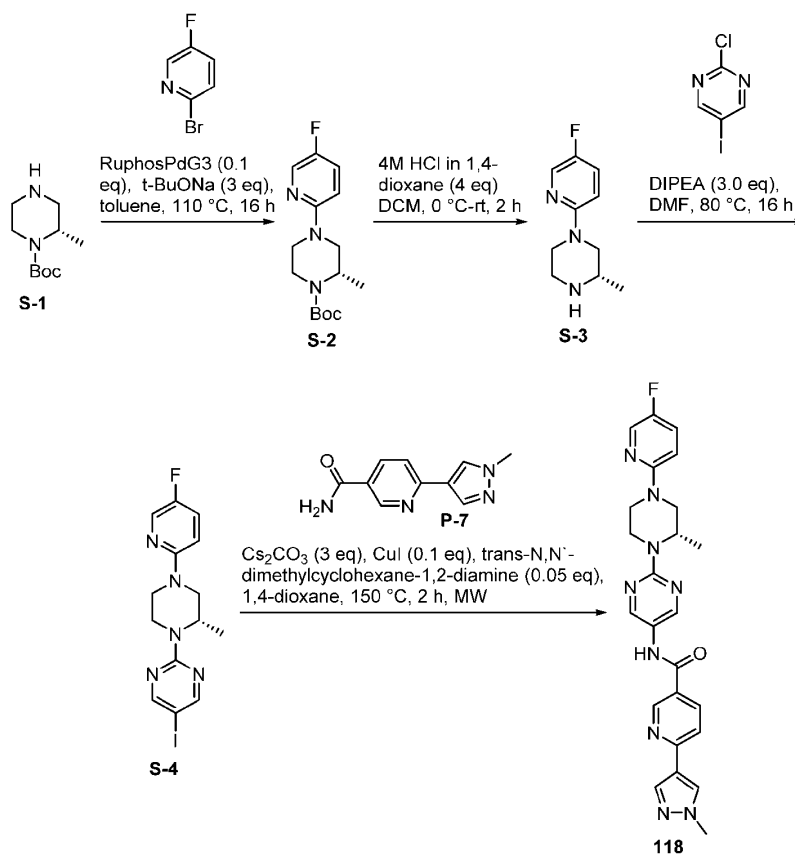
Example 117: (R)-N-(5-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0164] To a stirred solution of **R-6** (70 mg, 0.183 mmol) and **P-7** (37.0 mg, 0.183 mmol) in 1, 4-dioxane (1 mL) were added Cs₂CO₃ (179 mg, 0.549 mmol), copper(I) iodide (3.49 mg, 0.018 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (1.302 mg, 9.16 μmol) at room temperature. Reaction mixture was degassed and purged with argon gas for 10 min. The reaction mixture was stirred in a microwave at 150 °C for 2 h. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). Combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC Purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate IN H₂O: MeCN COLUMN - X-Bridge, C18 (25X250) mm, 5μ Flow-15.0 ml/min Gradient Method 0/35,1/35,10.3/70,10.35/98,13.5/98,13.55/35,16/35). Pure fractions were

combined, concentrated under reduced pressure and lyophilized to afford **117**. M/Z (ESI): 504.15 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.84 (s, 1H), 9.09 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 8.88 (d, *J* = 1.6 Hz, 1H), 8.41 (s, 1H), 8.34 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 8.08-8.15 (m, 2H), 7.78 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 7.49-7.59 (m, 1H), 6.88 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 4.54-4.63 (m, 1H), 4.38 (d, *J* = 13.2 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 3.99-4.13 (m, 1H), 3.91 (s, 3H), 3.46 (t, *J* = 9.2 Hz, 1H), 3.33-3.39 (m, 1H), 3.20-3.29 (m, 5H), 3.11-3.20 (m, 1H).

Example 118: (S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of S-2: tert-butyl (S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxylate

[0165] To a stirred solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**S-1**) (2 g, 9.99 mmol) and 2-bromo-5-fluoropyridine (2.109 g, 11.98 mmol) in toluene (50 mL) was added sodium tert-butoxide (2.88 g, 30.0 mmol) at room temperature and degassed with argon for 5 min. Then

RuPhos Pd G2 (0.776 g, 0.999 mmol) was added to the reaction mixture at room temperature and again degassed with argon for 1 min. The reaction mixture was stirred at 110 °C for 16 h. Reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 24 g silica gel cartridge and compound eluted with 50% EtOAc in petroleum ether. Pure fractions were combined and concentrated under reduced pressure to afford **S-2**. M/Z (ESI): 296.11 [M+H]⁺.

Synthesis of **S-3**: (S)-1-(5-fluoropyridin-2-yl)-3-methylpiperazine

[0166] To a stirred solution of **S-2** (1.5 g, 5.08 mmol) in DCM (20 mL) was added 4M HCl in 1,4-dioxane (5.08 mL, 20.31 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h. Reaction mixture was concentrated under reduced pressure to afford **S-3**. M/Z (ESI): 196.01 [M+H]⁺.

Synthesis of **S-4**: (S)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-iodopyrimidine

[0167] To a stirred solution of **S-3** (1.2 g, 5.18 mmol) in DMF (20 mL) under argon were added 2-chloro-5-iodopyrimidine (1.494 g, 6.21 mmol) and DIPEA (2.71 mL, 15.54 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. Reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). Combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by silica column and compound eluted with 10% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **S-4**. M/Z (ESI): 400.19 [M+H]⁺.

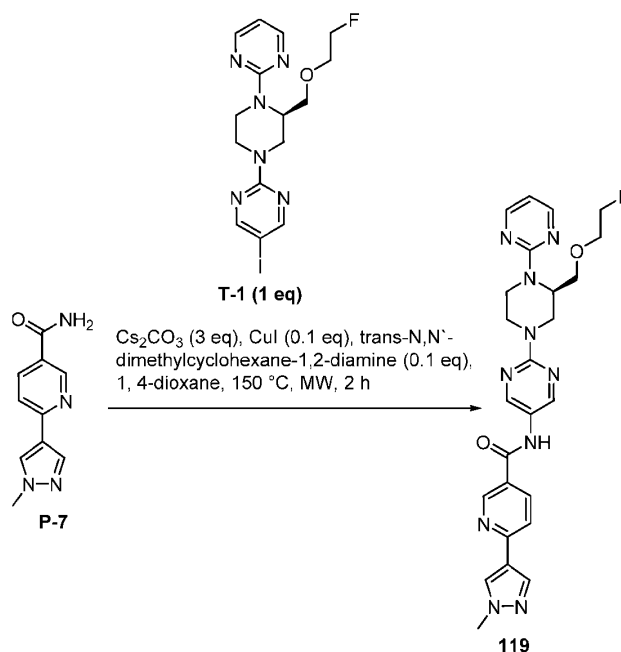
Example 118: (S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0168] To a stirred solution of **S-4** (50 mg, 0.125 mmol) and **P-7** (25.3 mg, 0.125 mmol) in 1,4-dioxane (1 mL) were added Cs₂CO₃ (122 mg, 0.376 mmol), copper(I) iodide (2.385 mg, 0.013 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.891 mg, 6.26 μmol) at room temperature and degassed with argon for 10 min. The reaction mixture was stirred at 150 °C for 2 h under microwave irradiation. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). Combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Prep

HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate IN H₂O: MeCN COLUMN - X-Bridge , C18 (19X250) mm, 5 μ Flow-12.0 ml/min Gradient Method : 0/50, 2/50, 8.66/60, 8.7/100, 12/100, 12.05/50, 16/50). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **118**. M/Z (ESI): 474.21 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ = 10.31 (s, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 8.70 (s, 2H), 8.41 (s, 1H), 8.28 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 8.07-8.15 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.49-7.58 (m, 1H), 6.92 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 4.80-4.90 (m, 1H), 4.10-4.50 (m, 3H), 3.91 (s, 3H), 3.25-3.30 (m, 1H), 3.15 (dd, *J* = 12.8 Hz, 4.0 Hz, 1H), 2.92 (td, *J* = 12.0 Hz, 3.6 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H).

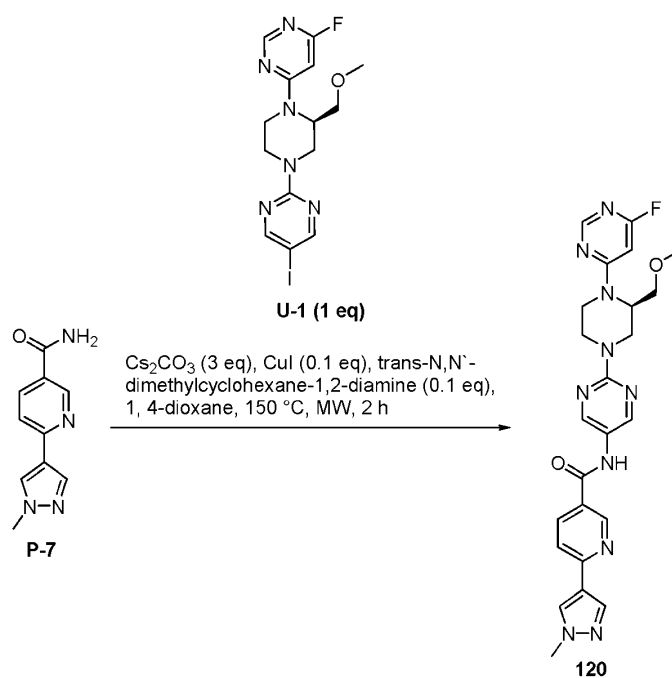
Example 119: (R)-N-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



[0169] To solution of **T-1** (prepared in an analogous manner as **R-6**) (100 mg, 0.225 mmol) in 1, 4-dioxane (2 mL) were added **P-7** (54.6 mg, 0.270 mmol), Cs₂CO₃ (220 mg, 0.675 mmol), copper (I) iodide (4.29 mg, 0.023 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (3.20 mg, 0.023 mmol) at room temperature. The reaction mixture was degassed and purged with argon for 10 min. Then this reaction mixture was stirred in microwave at 150 °C for 2 h.

[0170] Reaction mixture was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). Combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was triturated with diethyl ether (2 x 5 mL) and concentrated under reduced pressure. Obtained compound was purified by prep-HPLC purification (conditions: Instrument ID ANL-MCL5-PREP-020 Column Name Betasil Phenyl Hexyl (21.2X250)MM, 5 μ Column No# 250*19 Mobile Phase-A 10mM Ammonium BiCarbonate in water Mobile Phase-B Acetonitrile Gradient program (T/%B) 0/35, 2/35, 10/55, 11.63/55, 11.65/100, 15/100, 15.01/35, 18/35). Pure fractions were combined and concentrated under reduced pressure to afford **119**. M/Z (ESI): 519.31 [M+H]⁺.

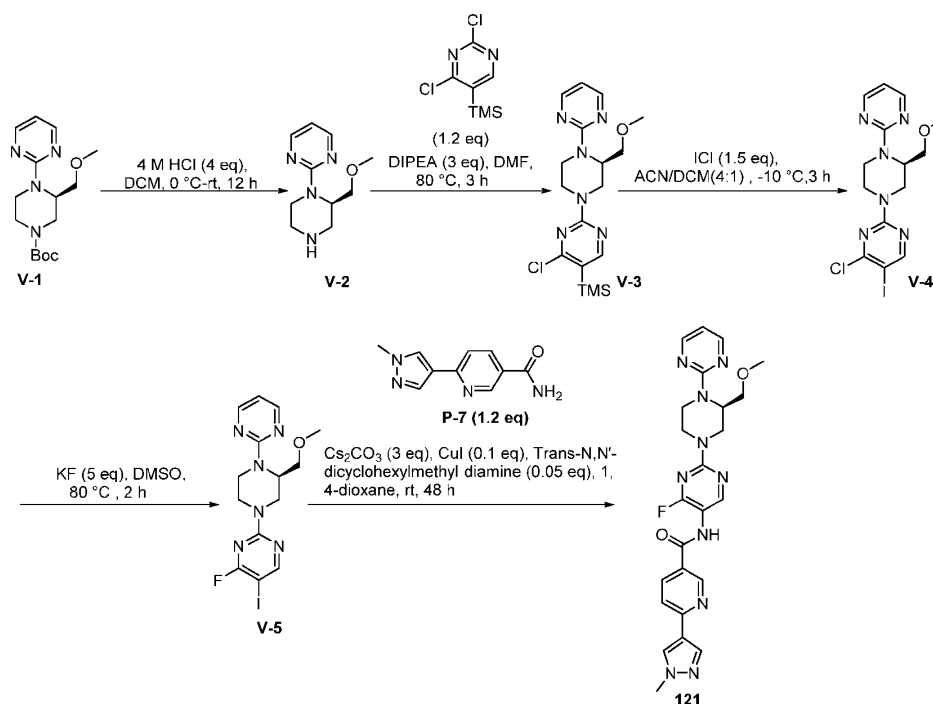
Example 120: (R)-N-(2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



[0171] To solution of **P-7** (100 mg, 0.232 mmol) in 1, 4-dioxane (2 mL) were added **U-1** (prepared in an analogous manner as **Q-6**) (56.4 mg, 0.279 mmol), Cs₂CO₃ (227 mg, 0.697 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (3.31 mg, 0.023 mmol) at room temperature. The reaction mixture was degassed and purged with argon for 10 min. The reaction mixture was stirred in microwave at 150 °C for 2 h. Reaction mixture was quenched with water (30 mL) and extracted with DCM (3 x 30 mL). Combined organic layer was washed with brine

(20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Crude compound was triturated with diethyl ether (2 x 10 mL) and concentrated under reduced pressure. Obtained compound was purified by prep-HPLC purification (conditions: MOBILE PHASE - 10mM Ammonium Bicarbonate IN H_2O : MeCN Column - X-Bridge, C18 (19X250) mm, 5 μ Flow-14.0 ml/min Gradient Method :- 0/35,2/35,8.60/45,8.65/100,11.65/100,11.70/35,15.0/35). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **120**. M/Z (ESI): 505.25 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) = 10.33 (s, 1H), 9.05 (d, $J = 2.0$ Hz, 1H), 8.71 (s, 2H), 8.41 (s, 1H), 8.35 (d, $J = 2.4$ Hz, 1H), 8.28 (dd, $J = 8.2$ Hz, 2.2 Hz, 1H), 8.10 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 6.58 (s, 1H), 4.57 - 4.96 (m, 2H), 4.11 - 4.56 (m, 2H), 3.91 (s, 3H), 3.43 - 3.50 (m, 2H), 3.11 - 3.29 (m, 6H).

Example 121: (R)-N-(4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of V-2: (R)-2-(2-(methoxymethyl)piperazin-1-yl)pyrimidine

[0172] To a stirred solution of **V-1** (made in an analogous manner as **3-2**) (2 g, 6.49 mmol) in DCM (40 mL) was added HCl in 1, 4-dioxane (3.08 mL, 25.9 mmol) at 0 °C. The reaction

mixture was stirred at room temperature for 12 h. Reaction mixture was concentrated and dried under reduced pressure to afford **V-2**. M/Z (ESI): 209.18 [M+H]⁺.

Synthesis of **V-3**: (R)-4-chloro-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-(trimethylsilyl)pyrimidine

[0173] To a stirred solution of **V-2** (1.5 g, 6.13 mmol) in DMF (30 mL) were added 2,4-dichloro-5-(trimethylsilyl)pyrimidine (1.627 g, 7.36 mmol) and DIPEA (3.21 mL, 18.39 mmol) at room temperature. The reaction mixture was stirred 80 °C for 3 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by 100 g silica gel (60-120 mesh) cartridge and the compound was eluted with 20% EtOAc in petroleum ether. Pure fractions were combined and concentrated under reduced pressure to afford **V-3**. M/Z (ESI): 393.21 [M+H]⁺.

Synthesis of **V-4**: (R)-4-chloro-5-iodo-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine

[0174] To a stirred solution of **V-3** (1.2 g, 3.05 mmol) in MeCN (10 mL) and DCM (5 mL) was added ICl (0.230 mL, 4.58 mmol) at -10 °C. The reaction mixture was stirred at -10 °C for 3 h. Reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by 100 g silica gel (100-200 mesh) cartridge and compound eluted with 25% EtOAc in petroleum ether. Pure fractions were combined and concentrated under reduced pressure to afford **V-4**. M/Z (ESI): 446.92 [M+H]⁺.

Synthesis of **V-5**: (R)-4-fluoro-5-iodo-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidine

[0175] To a stirred solution of **V-4** (500 mg, 1.119 mmol) in DMSO (10 mL) was added potassium fluoride (325 mg, 5.60 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. Reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by 100 g silica gel (100-200 mesh) column and compound eluted with 20% EtOAc in petroleum ether. Pure fractions were combined and concentrated under reduced pressure to afford **V-5**. M/Z (ESI): 431.00 [M+H]⁺.

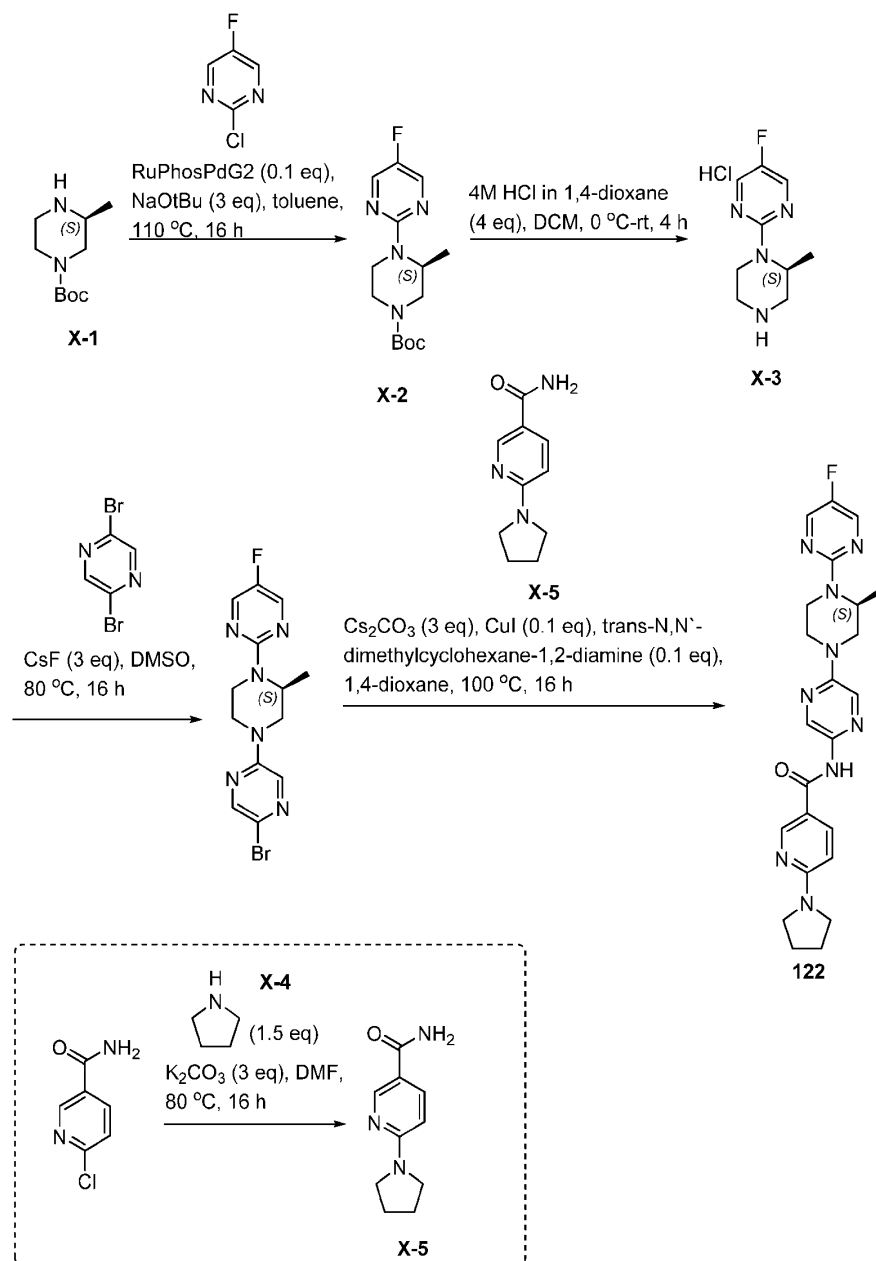
Example 121: (R)-N-(4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0176] To a stirred solution of **V-5** (50 mg, 0.116 mmol) and **P-7** (28.2 mg, 0.139 mmol) in 1,4-dioxane (1 mL) were added Cs₂CO₃ (114 mg, 0.349 mmol), copper(I) iodide (2.213 mg, 0.012 mmol) and trans-N, N'-dimethylcyclohexane-1, 2-diamine (0.827 mg, 5.81 µmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3 x 40 mL). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN, Column - X-Bridge C18 (10X250mm), 5µ Flow-7 ml/min, Gradient Method 0/52, 2/52, 7.5/55.5, 10/55.5, 10.05/100, 12/100, 12.05/52, 16/52). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **121**.

M/Z (ESI): 505.32 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.15 (s, 1H), 9.05 (d, *J* = 1.6 Hz, 1H), 8.54 (d, *J* = 13.2 Hz, 1H), 8.38-8.45 (m, 3H), 8.28 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.10 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 6.68 (t, *J* = 4.6 Hz, 1H), 4.87-4.49 (m, 1H), 4.66 (d, *J* = 13.2 Hz, 1H), 4.49-4.58 (m, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.91 (s, 3H), 3.39-3.48 (m, 3H), 3.27 (d, *J* = 2.4 Hz, 1H), 3.24 (s, 3H), 3.15-3.21 (m, 1H).

Example 122: (S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(pyrrolidin-1-yl)nicotinamide



Synthesis of **X-2**: tert-butyl (S)-4-(5-fluoropyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0177] A stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (**X-1**) (1 g, 4.99 mmol) in toluene (20 mL) was purged with argon gas for 10 min. Then 2-chloro-5-fluoropyrimidine (0.993 g, 7.49 mmol), sodium tert-butoxide (1.440 g, 14.98 mmol) and

chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.388 g, 0.499 mmol) were added to the reaction mixture at room temperature and again purged with argon for another 10 min. The reaction mixture was stirred at 100 °C for 16 h. Reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 25 g silica gel cartridge and compound eluted with 30% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **X-2**. M/Z (ESI): 297.27 [M+H]⁺.

Synthesis of **X-3**: (S)-5-fluoro-2-(2-methylpiperazin-1-yl)pyrimidine hydrochloride

[0178] To a stirred solution of **X-2** (1.1 g, 3.71 mmol) in DCM (20 mL) was added 4M HCl in 1,4-dioxane (3.71 mL, 14.85 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. Reaction mixture was concentrated under reduced pressure to afford **X-3**. M/Z (ESI): 197.02 [M+H]⁺.

Synthesis of **X-4**: (S)-2-(4-(5-bromopyrazin-2-yl)-2-methylpiperazin-1-yl)-5-fluoropyrimidine

[0179] To a stirred solution of **X-3** (800 mg, 3.44 mmol) in DMSO (20 mL) were added CsF (1567 mg, 10.31 mmol) and 2,5-dibromopyrazine (981 mg, 4.13 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. Reaction mixture was quenched with water (120 mL) and extracted with EtOAc (3 x 200 mL). Combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 25 g silica gel cartridge and compound eluted with 30% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **X-4**. M/Z (ESI): 353.09 [M+H]⁺.

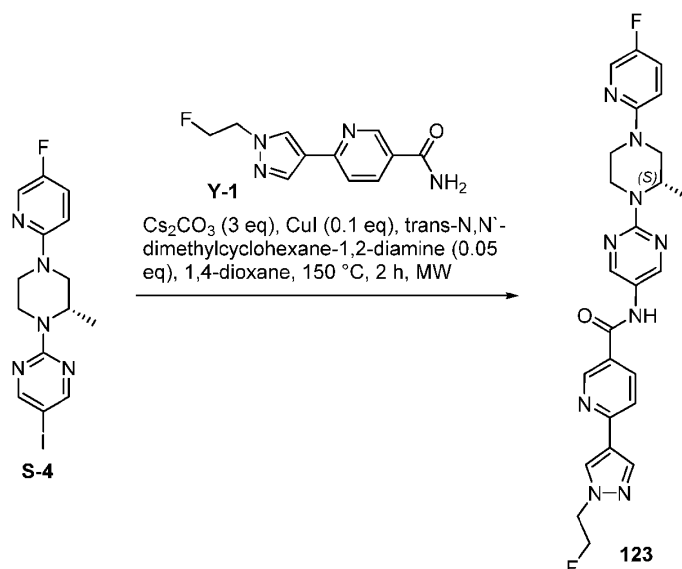
Synthesis of **X-5**: 6-(pyrrolidin-1-yl)nicotinamide

[0180] To a stirred solution of 6-chloronicotinamide (1 g, 6.39 mmol) in DMF (30 mL) were added pyrrolidine (0.681 g, 9.58 mmol) and K₂CO₃ (2.65 g, 19.16 mmol) at room temperature. The reaction mixture was stirred for 80 °C for 16 h. Reaction mixture was quenched with water (80 mL) and extracted with EtOAc (3 x 150 mL). Combined organic layer was dried over Na₂SO₄ filtered and concentrated under reduced pressure. Crude compound was washed with diethyl ether (2 x 30 mL) and concentrated under reduced pressure to afford **X-5**. M/Z (ESI): 192.00 [M+H]⁺.

Example 122: (S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(pyrrolidin-1-yl)nicotinamide

[0181] To a stirred solution of **X-4** (60 mg, 0.170 mmol) and **X-5** (40 mg, 0.204 mmol) in 1,4-dioxane (1 mL) were added Cs₂CO₃ (166 mg, 0.510 mmol), copper(I) iodide (3.24 mg, 0.017 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (2.416 mg, 0.017 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. Reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3 x 30 mL). Combined organic layer was dried over Na₂SO₄ filtered and concentrated under reduced pressure. Crude compound was purified by Prep HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Bridge C18 (10X250mm), 5μ Flow-7 ml/min Gradient Method - 0/52,2/52,7.5/55.5,10/55.5,10.05/100,12/100,12.05/52,16/52). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **122**. M/Z (ESI): 464.28 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ = 10.38 (s, 1H), 8.83 (d, *J* = 1.2 Hz, 1H), 8.77 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 0.8 Hz, 2H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.11 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 4.78-4.87 (m, 1H), 4.38-4.48 (m, 1H), 4.17-4.30 (m, 2H), 3.46 (s, 4H), 3.36-3.40 (m, 1H), 3.22 (dd, *J* = 12.8 Hz, 4.0 Hz, 1H), 3.02 (td, *J* = 11.8 Hz, 4.0 Hz, 1H), 1.96 (t, *J* = 6.6 Hz, 4H), 1.16 (d, *J* = 6.8 Hz, 3H).

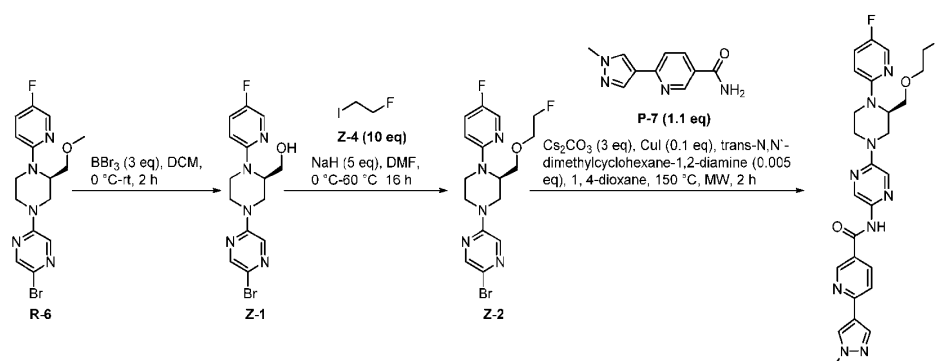
Example 123: (S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0182] To a stirred solution of **S-4** (50 mg, 0.125 mmol) and **Y-1** (prepared in an analogous manner as **P-7**) (29.3 mg, 0.125 mmol) in 1,4-dioxane (1 mL) were added Cs₂CO₃ (122 mg, 0.376 mmol), copper(I) iodide (2.385 mg, 0.013 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.891 mg, 6.26 μmol) at room temperature and degassed with argon for 10 min. The reaction mixture was stirred at 150 °C for 2 h under microwave irradiation. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). Combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Prep HPLC purification (conditions: Mobile Phase - Mobile Phase - 2.5 mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Bridge, C18 (19X250) mm, 5μ Flow-15.0 ml/min Gradient Method-0/45, 2/45, 10.5/62, 10.55/100, 13/100, 13.05/45, 17/45 ANL-MCL-PREP-023). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **123**. M/Z (ESI): 506.21 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ = 10.33 (s, 1H), 9.07 (d, *J* = 1.6 Hz, 1H), 8.70 (s, 2H), 8.49 (s, 1H), 8.30 (dd, *J* = 8.2 Hz, 2.2 Hz, 1H), 8.18 (s, 1H), 8.10 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.53 (td, *J* = 8.6 Hz, 2.9 Hz, 1H), 6.92 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 4.40-4.91 (m, 6H), 4.10-4.25 (m, 2H), 3.24-3.30 (m, 1H), 3.15 (dd, *J* = 12.8 Hz, 4.0 Hz, 1H), 2.93 (td, *J* = 11.8 Hz, 3.4 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H).

Example 124: (R)-N-(5-(3-((2-fluoroethoxy)methyl)-4-(5-fluoropyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of **Z-1**: (R)-(4-(5-bromopyrazin-2-yl)-1-(5-fluoropyridin-2-yl)piperazin-2-yl)methanol

[0183] To a stirred solution of **R-6** (200 mg, 0.523 mmol) in DCM (2 mL) was added BBr_3 (1.570 mL, 1.570 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Reaction mixture was concentrated and quenched with ice cold water (10 mL) and extracted with EtOAc (2 x 10 mL). Combined organic layer was washed with aqueous saturated NaHCO_3 (20 mL) and brine (2 x 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 40 g silica (100-200 mesh) cartridge and compound eluted with 10% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **Z-1**. M/Z (ESI): 369.12 $[\text{M}+\text{H}]^+$.

Synthesis of **Z-2**: (R)-2-bromo-5-(3-((2-fluoroethoxy)methyl)-4-(5-fluoropyridin-2-yl)piperazin-1-yl)pyrazine

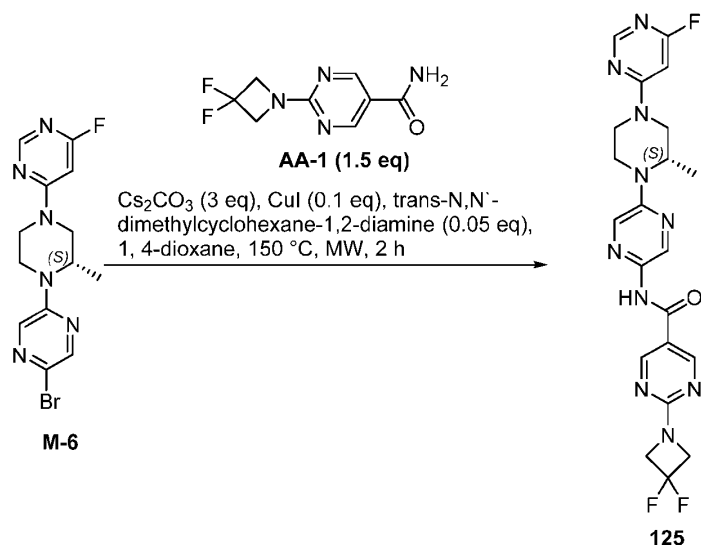
[0184] To a stirred solution of **Z-1** (120 mg, 326 μmol) in DMF (3 mL) was added NaH (39.1 mg, 1.63 mmol) at 0 °C for 10 min. Then to this reaction mixture was added 1-fluoro-2-iodoethane (567 mg, 3.26 mmol) at 0 °C. The reaction mixture was stirred at 60 °C for 16 h. Reaction mixture was quenched with ice cold water (25 mL) and extracted with EtOAc (2 x 25 mL). Combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 40 g silica (100-200 mesh) cartridge and compound eluted with 20% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **Z-2**. M/Z (ESI): 415.15 $[\text{M}+\text{H}]^+$.

Example 124: (R)-N-(5-(3-((2-fluoroethoxy)methyl)-4-(5-fluoropyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0185] To a stirred solution of **Z-2** (80.0 mg, 193 μ mol) and **P-7** (43.0 mg, 212 μ mol) in 1, 4-dioxane (2 mL) was added cesium carbonate (189 mg, 579 μ mol) at room temperature. Reaction mixture was degassed and purged with nitrogen gas for 10 min. Then to this reaction mixture were added copper(I) iodide (3.68 mg, 19.3 μ mol) and Trans-(1r,2r)-N,N'-bismethyl-1,2-cyclohexanediamine (305 mL, 0.966 μ mol). The reaction mixture was stirred in a microwave at 150 °C for 2 h. Reaction mixture was filtered through celite pad and concentrated under reduced pressure. Residue was quenched with water (2 mL) and extracted with 10% MeOH in DCM (2 x 2 mL). Combined organic layer was washed with brine (2 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: MOBILE PHASE – 10mM Ammonium Bicarbonate in H₂O: MeCN Column – X-Select, C18 (10X150) mm, 5 μ Flow-6.0 ml/min Gradient Method:- 0/40,14/40,14.1/100,17.9/100,18/40,22/40). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **124**. M/Z (ESI): 536.31 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.84 (s, 1H), 9.09 (d, *J* = 1.6 Hz, 1H), 8.88 (d, *J* = 1.6 Hz, 1H), 8.41 (s, 1H), 8.34 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.07-8.21 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.54 (td, *J* = 8.8 Hz, 3.2 Hz, 1H), 6.89 (dd, *J* = 9.2 Hz, 3.2 Hz, 1H), 4.55-4.65 (m, 1H), 4.38-4.55 (m, 3H), 4.25 (d, *J* = 12.4 Hz, 1H), 3.99-4.10 (m, 1H), 3.91 (s, 3H), 3.45-3.71 (m, 5H), 3.24-3.28 (m, 1H), 3.12-3.20 (m, 1H).

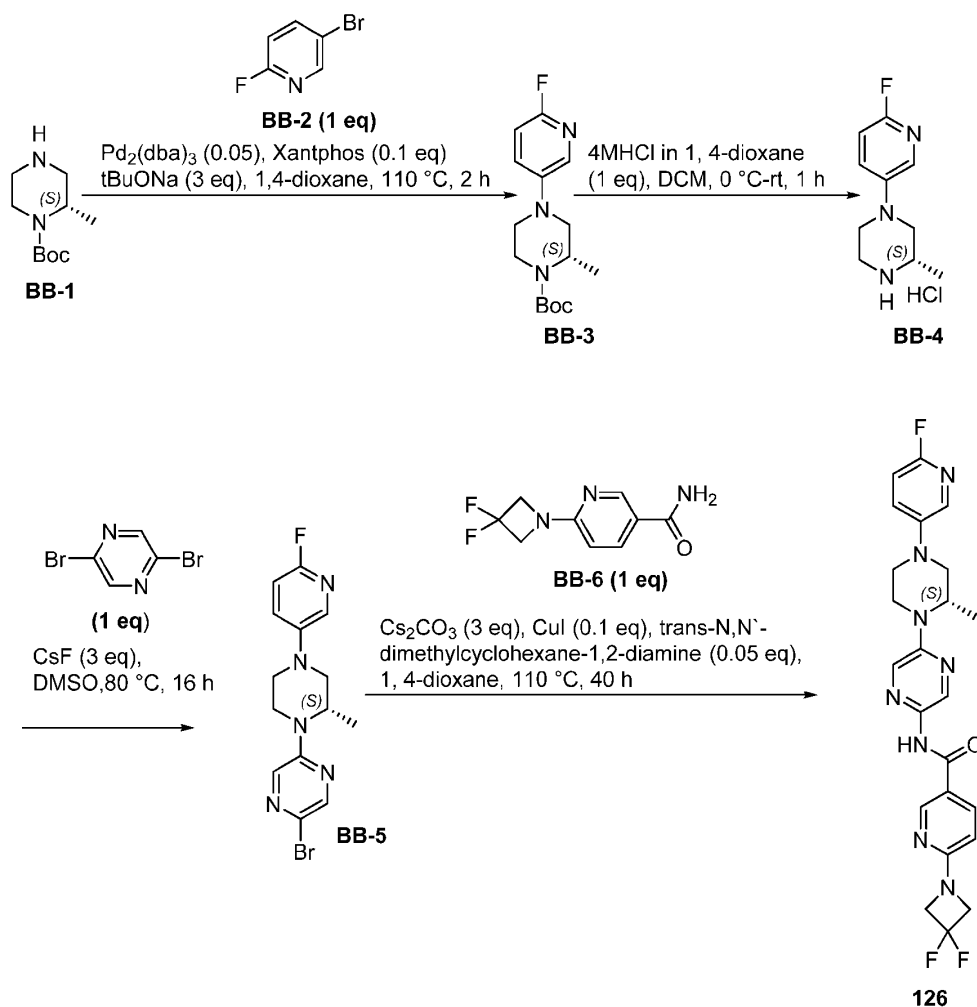
Example 125: (S)-2-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)pyrimidine-5-carboxamide



[0186] To a stirred solution of **M-6** (200 mg, 566 μ mol) in 1,4-dioxane (3 mL) were added Cs₂CO₃ (553 mg, 1.70 mmol), CuI (10.8 mg, 56.6 μ mol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (4.03 mg, 28.3 μ mol) and **AA-1** (made in an analogous manner as **X-5**) (182 mg, 849 μ mol) at room temperature. The reaction mixture was stirred in a microwave at 150 °C for 2 h under nitrogen atmosphere. Reaction mixture was quenched with (20 mL) and extracted with 10% MeOH in DCM (2 x 45 mL). Combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase – 10mM Ammonium Bicarbonate in H₂O: MeCN Column – X-Bridge C18 (19X250) mm, 5 μ , Flow-15.0 ml/min, Gradient Method - 0/40, 3/40, 10.5/65, 10.55/100, 13/100, 13.05/40, 17/40). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **125**. M/Z (ESI): 487.30 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.77 (br s, 1H), 9.00 (s, 2H), 8.87 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.15 (s, 1H), 6.90 (br s, 1H), 6.64 (s, 1H), 4.58 (t, J = 12.4 Hz, 4H), 4.04-4.52 (m, 3H), 3.44 (dd, J = 13.4 Hz, 3.4 Hz, 1H), 3.20-3.28 (m, 2H), 1.07 (d, J = 6.8 Hz, 3H).

Example 126: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide



Synthesis of **BB-3**: tert-butyl (S)-4-(6-fluoropyridin-3-yl)-2-methylpiperazine-1-carboxylate

[0187] To a stirred solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (5 g, 25 mmol) in 1,4-dioxane (100 mL) were added sodium 2-methylpropan-2-olate (8.03 mL, 74.9 mmol) and 5-bromo-2-fluoropyridine (4.39 g, 25 mmol) at room temperature. Reaction mixture was degassed and purged with argon gas for 15 min. Then to this reaction mixture were added Tris(dibenzylideneacetone)dipalladium (1.14 g, 1.25 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (1.44 g, 2.5 mmol) at room temperature. The reaction mixture was stirred at 110°C for 12 h under nitrogen atmosphere in a sealed tube. Reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 75 mL). Combined organic layer was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced

pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 20% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **BB-3**. M/Z (ESI): 296.28 [M+H]⁺.

Synthesis of **BB-4**: (S)-1-(6-fluoropyridin-3-yl)-3-methylpiperazine

[0188] To a stirred solution of **BB-3** (2.5 g, 8.46 mmol) in DCM (30 mL) were added 4M HCl in 1, 4-dioxane (309 mg, 8.46 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Reaction mixture was concentrated and dried under reduced pressure to afford **BB-4**. M/Z (ESI): 196.24 [M+H]⁺.

Synthesis of **BB-5**: (S)-2-bromo-5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazine

[0189] To a stirred solution of **BB-4** (500 mg, 2.16 mmol) in DMSO (10 mL) were added CsF (983 mg, 6.47 mmol) and 2,5-dibromopyrazine (513 mg, 2.16 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 h in a sealed tube. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 25 mL). Combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 12 g silica (230-400 mesh) cartridge and compound eluted with 30% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **BB-5**. M/Z (ESI): 352.23 [M+H]⁺.

Example 126: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

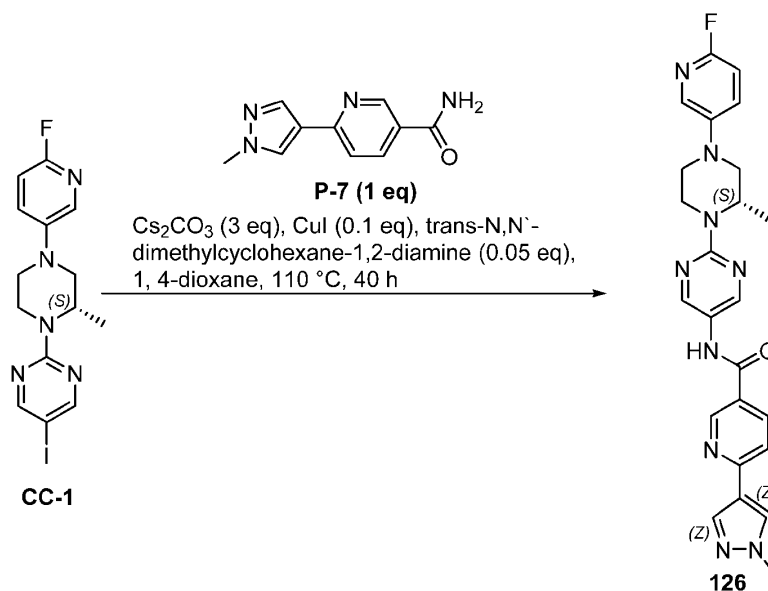
[0190] To a stirred solution of **BB-5** (150 mg, 426 μmol) and **BB-6** (made in an analogous manner as **X-5**) (90.8 mg, 426 μmol) in 1, 4-dioxane (2 mL) were added CuI (8.11 mg, 42.6 μmol), trans-N,N'-bismethyl-1,2-cyclohexanediamine (6.72 μL, 21.3 μmol) and Cs₂CO₃ (416 mg, 1.28 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 40 h in a seal tube. Reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 25 mL). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Column : XBridge C18 (4.6x150) mm, 3.5μm Mobile Phase-A : 10mM Ammonium bicarbonate in water mobile phase -B : 100% Acetonitrile Gradient (T/% B) : 0/10, 12/98, 16/98, 16.1/10, 20/10. Flow Rate : 1.0 mL/min Column ovenTemp : Ambient Diluent : MeCN:water (90:10) V/V). Pure

fractions were combined, concentrated under reduced pressure and lyophilized to afford **126**.

M/Z (ESI): 485.15 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.58 (s, 1H), 8.86 (d, *J* = 1.2 Hz, 1H), 8.80-8.85 (m, 1H), 8.22 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 7.87-7.94 (m, 1H), 7.63-7.72 (m, 1H), 7.06 (dd, *J* = 8.8 Hz, 3.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 4.60-4.69 (m, 1H), 4.50 (t, *J* = 12.4 Hz, 4H), 4.12 (d, *J* = 10.0 Hz, 1H), 3.73 (d, *J* = 12.0 Hz, 1H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.24-3.30 (m, 1H), 3.02 (dd, *J* = 12.4 Hz, 3.6 Hz, 1H), 2.84 (td, *J* = 12.0 Hz, 3.6 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H).

Example 127: (S)-N-(2-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



[0191] To a stirred solution of **CC-1** (prepared in an analogous manner as **BB-5**) (150 mg, 376 μmol) and **P-7** (76 mg, 376 μmol) in 1,4-dioxane (2 mL) were added cesium carbonate (367.0 mg, 1128 μmol), CuI (7.16 mg, 37.6 μmol) and trans-N,N'-bismethyl-1,2-cyclohexanediamine (5.93 μL, 18.8 μmol) at room temperature. The reaction mixture was stirred at 110 °C for 40 h in a sealed tube. Reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 25 mL). Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Column : X Bridge amide (4.6x150) mm, 3.5μm Mobile Phase-A : 20 mM Ammonium

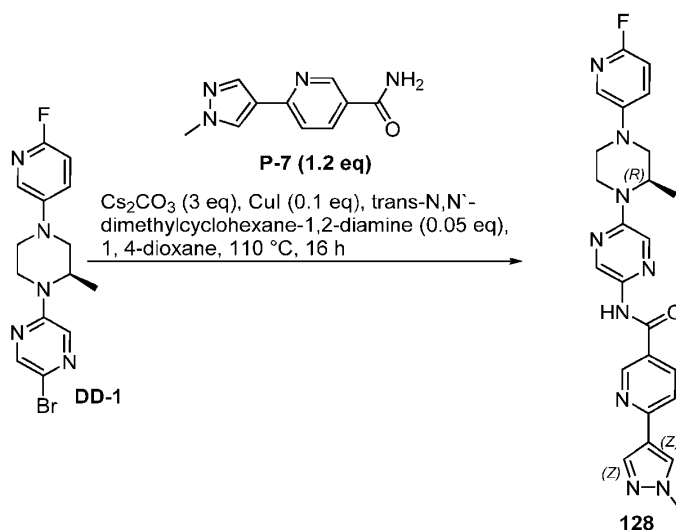
Bicarbonate in Water Mobile Phase-B : 50:50 MeCN : MeOH Gradient (T/% B) :

0/5,1/5,12/60,15/70,20/100.22.1/5,24/5, Flow Rate : 1.0 mL/min Column oven Temp : Ambient

Diluent : MeCN:H₂O). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **127**. M/Z (ESI): 474.19 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.32 (s, 1H), 9.05 (d, *J* = 1.6 Hz, 1H), 8.71 (s, 1H), 8.41 (s, 1H), 8.28 (dd, *J* = 8.2 Hz, 2.2 Hz, 1H), 8.10 (s, 1H), 7.85-7.91 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.62-7.69 (m, 1H), 7.06 (dd, *J* = 9.2 Hz, 3.4 Hz, 1H), 4.85-4.95 (m, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 3.91 (s, 3H), 3.71 (d, *J* = 12.0 Hz, 1H), 3.61 (d, *J* = 12.0 Hz, 1H), 3.33-3.39 (m, 1H), 2.97 (dd, *J* = 12.0 Hz, 4.0 Hz, 2H), 2.77 (td, *J* = 11.6 Hz, 3.6 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H).

Example 128: (R)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

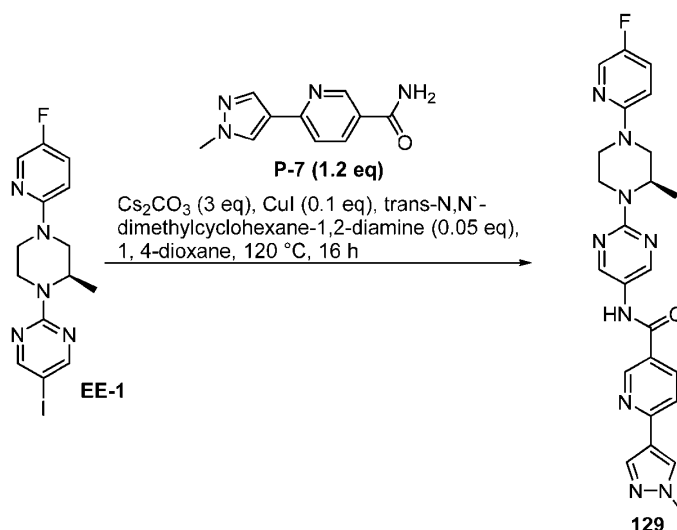


[0192] To a stirred solution of **DD-1** (prepared in an analogous manner as BB-5) (100 mg, 284 μ mol) in 1,4-dioxane (1.5 mL) were added Cs₂CO₃ (278 mg, 852 μ mol), CuI (5.41 mg, 28.4 μ mol), **P-7** (68.9 mg, 341 μ mol) and trans-N,N'-bismethyl-1,2-cyclohexanediamine (4.48 μ L, 14.2 μ mol) at room temperature. The reaction mixture was stirred at 110 °C for 16 h under nitrogen atmosphere in a sealed tube. Reaction mixture was quenched with water (45 mL) and extracted with EtOAc (2 x 85 mL). Combined organic layer was washed with brine (2 x 45 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN Column – Princeton Spher ULTIMA C18 (21.2X250)

0/48,3/48,14/59,14.05/98,17/98,17.05/48,21.0/48). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **128**. M/Z (ESI): 474.36 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.83 (s, 1H), 9.09 (dd, *J* = 2.2 Hz, 0.6 Hz, 1H), 8.90 (d, *J* = 1.2 Hz, 1H), 8.41 (s, 1H), 8.34 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.10 (s, 1H), 7.87-7.94 (m, 1H), 7.78 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 7.62-7.71 (m, 1H), 7.06 (dd, *J* = 8.8 Hz, 3.4 Hz, 1H), 4.58-4.75 (m, 1H), 4.14 (d, *J* = 10.0 Hz, 1H), 3.91 (s, 3H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.27 (dd, *J* = 12.8 Hz, 3.6 Hz, 1H), 3.03 (dd, *J* = 12.0 Hz, 3.6 Hz, 1H), 2.84 (td, *J* = 12.0 Hz, 3.6 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 3H).

Example 129: (R)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



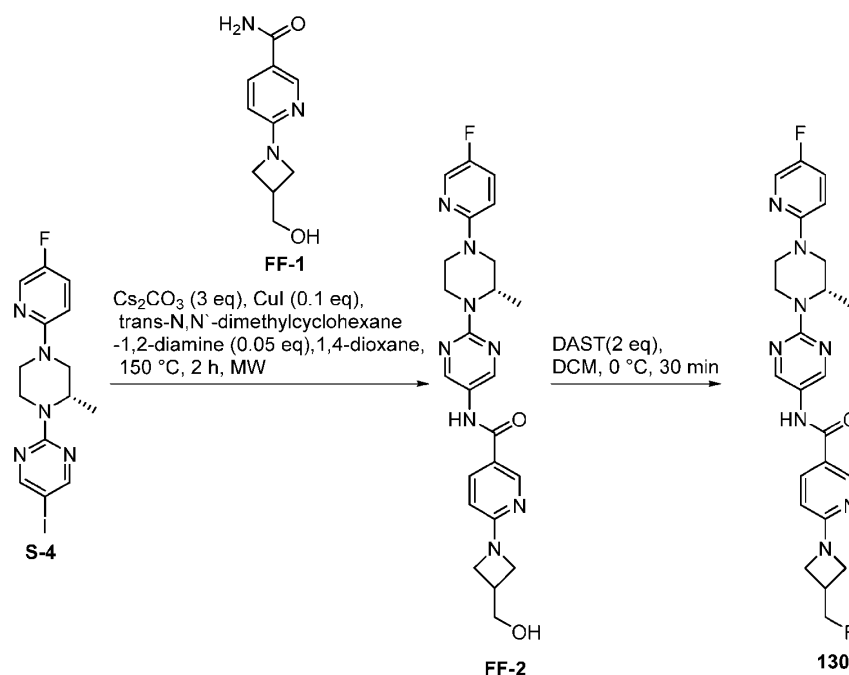
[0193] To a stirred solution of **EE-1** (prepared in an analogous manner as **S-4**) (100 mg, 250 μmol) and **P-7** (60.8 mg, 301 μmol) in 1, 4-dioxane (2 mL) were added trans-N,N'-bismethyl-1,2-cyclohexanediamine (3.95 μL , 12.5 μmol), Cs_2CO_3 (245 mg, 751 μmol) and CuI (4.77 mg, 25.0 μmol) at room temperature. The reaction mixture was stirred at 120 $^\circ\text{C}$ for 16 h under nitrogen atmosphere. Reaction mixture was quenched with aqueous saturated Na_2CO_3 (20 mL) and extracted with 10% MeOH in DCM (2 x 35 mL). Combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase – 10mM Ammonium Bicarbonate in H_2O : MeCN Column – YMC-Actus (20X100) mm, 3 μ Flow

- 12 ml/min Gradient Method- 0/43, 3/43, 9.0/62, 9.05/100, 12/100, 12.05/43, 15/43). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **129**.

M/Z (ESI): 474.26 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.31 (s, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 8.70 (s, 2H), 8.41 (s, 1H), 8.28 (dd, *J* = 8.2 Hz, 2.2 Hz, 1H), 8.08-8.15 (m, 2H), 7.81 (dd, *J* = 8.4 Hz, 0.4 Hz, 1H), 7.49-7.59 (m, 1H), 6.92 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 4.80-4.93 (m, 1H), 4.44 (dt, *J* = 13.2 Hz, 3.2 Hz, 1H), 4.16 (dd, *J* = 21.4 Hz, 12.6 Hz, 2H), 3.91 (s, 3H), 3.27 (d, *J* = 3.6 Hz, 1H), 3.15 (dd, *J* = 13.0 Hz, 3.8 Hz, 1H), 2.92 (td, *J* = 12.2 Hz, 3.6 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H).

Example 130: (S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



Synthesis of FF-2: (S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(3-(hydroxymethyl)azetidin-1-yl)nicotinamide

[0194] To a stirred solution of **S-4** (215 mg, 0.501 mmol) and **FF-1** (prepared in an analogous manner as X-5) (104 mg, 0.501 mmol) in 1,4-dioxane (3 mL) were added Cs_2CO_3 (490 mg, 1.503 mmol), copper(I) iodide (9.54 mg, 0.050 mmol), trans-N,N'-dimethylcyclohexane-1,2-diamine (3.56 mg, 0.025 mmol) at room temperature and degassed with argon for 10 min. The reaction mixture was stirred at 150 °C for 2 h under microwave irradiation. Reaction mixture was

quenched with water (10 mL) and extracted with EtOAc (2 x 30 mL). Combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by silica column and compound eluted with 10% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure to afford **FF-2**. M/Z (ESI): 477.07 [M-H]⁺.

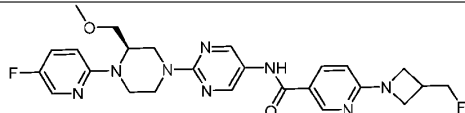
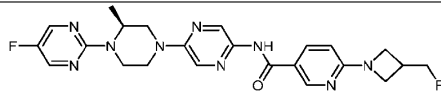
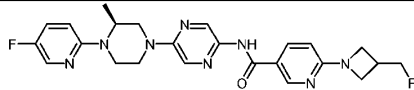
Example 130: (S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0195] To a stirred solution of **FF-2** (70 mg, 0.146 mmol) in DCM (1 mL) was added DAST (0.039 mL, 0.293 mmol) at 0 °C. The reaction mixture was stirred under argon atmosphere at 0 °C for 30 min. Reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 20 mL). Combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Prep HPLC purification (conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Bridge, C18 (19X250) mm, 5μ Flow-12.0 ml/min Gradient Method - 0/50,2/50,10.5/66.5,10.6/100,13/100,13.1/50,16/50). Pure fractions were combined, concentrated under reduced pressure and lyophilized to afford **130**. M/Z (ESI): 481.14 [M+H]⁺.

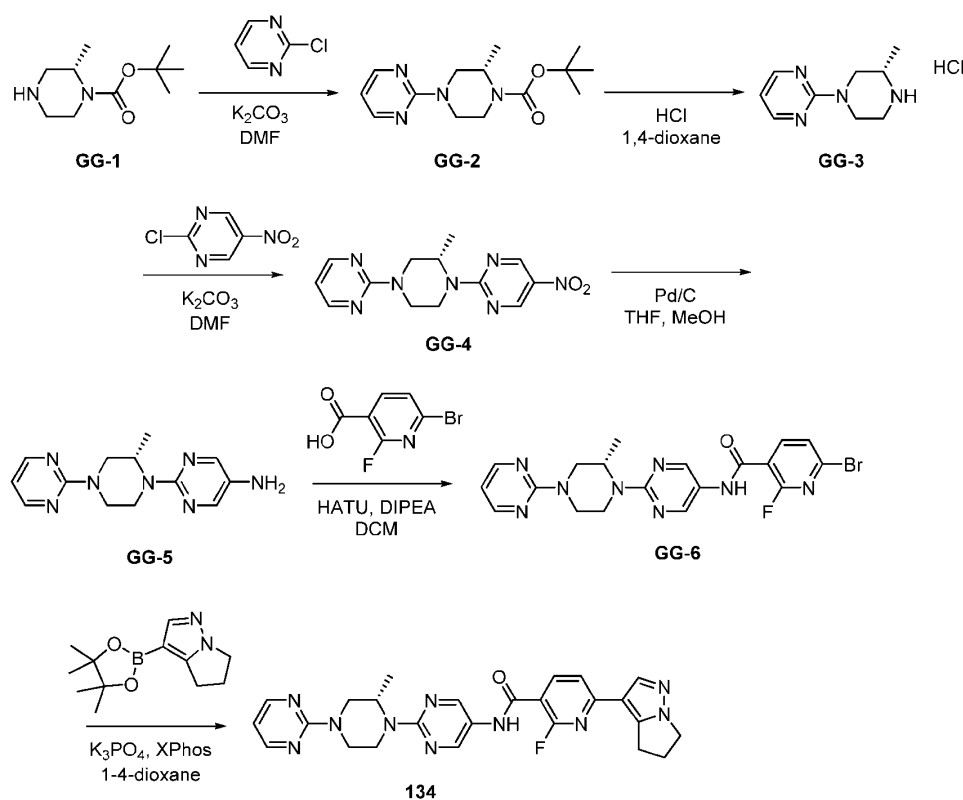
¹H NMR (400 MHz, DMSO-d₆) δ = 9.99 (s, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.66 (s, 2H), 8.10 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.48-7.57 (m, 1H), 6.92 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 4.80-4.89 (m, 1H), 4.54-4.75 (m, 2H), 4.38-4.48 (m, 1H), 4.09-4.25 (m, 4H), 3.80-3.90 (m, 2H), 3.23-3.30 (m, 1H), 3.04-3.20 (m, 2H), 2.91 (td, *J* = 12.0 Hz, 3.6 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H).

[0196] The compounds contained in Table 6 were synthesized by analogous methods from synthetic sequences above. Commercially available reagents were substituted where necessary to produce the examples below.

Table 6

Ex. No.	Structure	Chemical Name	Observed Mass (M+H)	Exact Mass
131		(R)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide	511.30	510.5
132		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide	482.40	481.5
133		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide	481.30	480.5

Example 134: 6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



Synthesis of **GG-2**: tert-butyl (S)-2-methyl-4-(pyrimidin-2-yl)piperazine-1-carboxylate

[0197] To a solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**GG-1**, 1.2 g, 1 Eq, 5.99 mmol) in DMF (24 mL) was added potassium carbonate (2.484 g, 3 Eq, 17.97 mmol) followed by 2-chloropyrimidine (1.029 g, 1.5 Eq, 8.99 mmol). The mixture was stirred for 3 h at 22°C. Water (100 mL) was added to the mixture, stirred for 30 min at 22°C and extracted with EtOAc (100 mL x 3). The organic layer was dried over MgSO₄, filtered through a fritted filter, and concentrated under reduced pressure. The resulting residue was dissolved in DCM (3 mL) and purified using normal-phase chromatography (ISCO 80 g RediSep Gold High Performance Silica, 0-100% Hexane, EtOAc, 26 min gradient). Fractions containing the desired product were combined and concentrated under vacuum to yield **GG-2**. MS (ESI) m/z: 279.3 [M+H]⁺

Synthesis of **GG-3**: (S)-2-(3-methylpiperazin-1-yl)pyrimidine hydrochloride

[0198] To a solution of tert-butyl (S)-2-methyl-4-(pyrimidin-2-yl)piperazine-1-carboxylate (**GG-2**, 1.20 g, 1 Eq, 4.31 mmol) in 1,4-dioxane (12.0 mL) was added 4M hydrogen chloride

(2.16 mL, 4.00 molar, 2 Eq, 8.62 mmol) in 1,4-dioxane. The mixture was stirred for 18 h at 22°. The mixture was concentrated under reduced pressure to yield **GG-3**. MS (ESI) m/z: 179.4 [M+H]⁺

Synthesis of **GG-4**: (S)-2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)-5-nitropyrimidine

[0199] To a solution of (S)-2-(3-methylpiperazin-1-yl)pyrimidine hydrochloride (**GG-3**, 1.00 g, 1 Eq, 3.98 mmol) in DMF (18.0 mL) was added potassium carbonate (2.20 g, 4 Eq, 15.9 mmol) and 2-chloro-5-nitropyrimidine (762 mg, 1.2 Eq, 4.78 mmol). The mixture was stirred for 18 h at 60 °C. Water was added to the mixture and stirred for 30 min at 22°C. The resulting precipitated solid was collected by filtration through a fritted filter, washed with water (100 mL x 3), and dried to give **GG-4**. MS (ESI) m/z: 302.5 [M+H]⁺

Synthesis of **GG-5**: (S)-2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-amine

[0200] A solution of (S)-2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)-5-nitropyrimidine (**GG-4**, 1.00 g, 1 Eq, 3.32 mmol) in THF (8.00 mL) and MeOH (8.00 mL) was degassed and purged with N₂ (x 3) then 10% palladium on carbon (177 mg, 0.5 Eq, 1.66 mmol) was added and degassed and purged with H₂ (x 3). The mixture was stirred for 18 h at 22°C under a H₂ filled balloon. The mixture was filtered through a fritted filter, washed with MeOH (5 mL x 3), and concentrated under vacuum to yield **GG-5**. MS (ESI) m/z: 272.4 [M+H]⁺

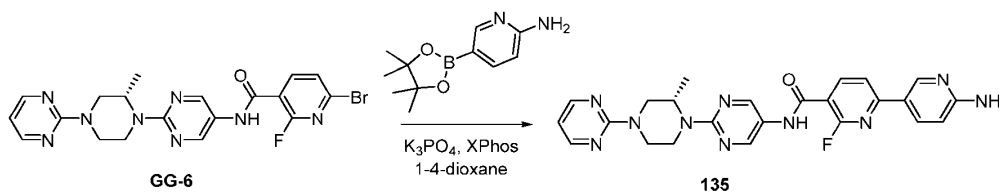
Synthesis of **GG-6**: (S)-6-bromo-2-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0201] To a solution of (S)-2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-amine (**GG-5**, 250.0 mg, 1 Eq, 921.4 µmol) in DCM (6.0 mL) was added diisopropylethylamine (595.4 mg, 793 µL, 5 Eq, 4.607 mmol), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-Oxide Hexafluorophosphate (700.7 mg, 2 Eq, 1.843 mmol), and 6-bromo-2-fluoronicotinic acid (243.2 mg, 1.2 Eq, 1.106 mmol). The mixture was stirred for 30 min at 22°C. The crude mixture was purified using basic reverse-phase chromatography (Waters XBridge Prep C18 5mm - 30x250mm column, 10-100% 5 mM NH₄HCO₃ water solution: acetonitrile, 30 min gradient). Fractions containing the product were combined and extracted between water (100 mL) and DCM (100 mL x 3). The collected organic layer was dried over MgSO₄ then concentrated under vacuum to yield **GG-6**. MS (ESI) m/z: 473.5 [M+H]⁺

Synthesis of Example 134: 6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0202] To a solution of (S)-6-bromo-2-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide (**GG-6**, 60.0 mg, 1 Eq, 127 μ mol) in 1,4-dioxane (0.50 mL) was added 1M potassium phosphate, tribasic (31.5 μ L, 3 Eq, 380 μ mol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (44.5 mg, 1.5 Eq, 190 μ mol). The mixture was purged with N₂ for 5 minutes then XPhos Palladacycle-G2 (9.97 mg, 0.1 Eq, 12.7 μ mol) was added. The mixture was stirred for 3 h at 80°C. The mixture was concentrated and purified using normal phase chromatography (ISCO 12 g RediSep Gold High Performance Silica, 10-100% Hexane, EtOAc, 18 min gradient). Fractions containing the desired product were combined and concentrated under reduced pressure. LCMS showed major byproduct and therefore was redissolved in DCM (1mL) and placed in a TLC chromatography chamber (1:4 Hexane, EtOAc). The desired product was collected from the TLC plate, stirred in EtOAc, and filtered through a fritted filter to yield **134**. MS (ESI) m/z: 501.6 [M+H]⁺
¹H NMR (500 MHz, CDCl₃): δ 8.60 (s, 2H), 8.58 – 8.52 (m, 1H), 8.33 (d, J = 4.7 Hz, 2H), 8.22 (d, J = 15.6 Hz, 1H), 8.07 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 6.51 (t, J = 4.7 Hz, 1H), 4.98 (s, 1H), 4.69 (d, J = 12.7 Hz, 1H), 4.63 (d, J = 13.2 Hz, 1H), 4.55 (d, J = 13.3 Hz, 1H), 4.22 (t, J = 7.3 Hz, 2H), 3.42 – 3.28 (m, 2H), 3.24 (t, J = 7.3 Hz, 2H), 3.16 (td, J = 12.2, 3.5 Hz, 1H), 2.74 (p, J = 7.3 Hz, 2H), 1.23 (d, J = 6.8 Hz, 3H).

Example 135: 6-(4-aminophenyl)-2-fluoro-N-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

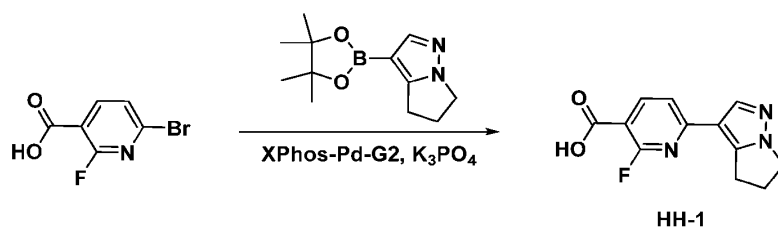


[0203] To a solution of (S)-6-bromo-2-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide (**GG-6**, 15.1 mg, 1 Eq, 0.032 mmol) in 1,4-dioxane (0.50 mL) was added 1M potassium phosphate, tribasic (0.064 mL, 1.00 molar, 2 Eq, 0.064 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (10.5 mg, 1.15 Eq, 0.048 mmol). The mixture was purged with N₂ for 1 min then XPhos Palladacycle-G2 (2.52 mg, 0.1 Eq, 0.003 mmol) was added. The mixture was stirred for 3 h at 80°C. The mixture was filtered through a fritted filter, concentrated, and purified using reverse-phase HPLC (XBridge Prep OBD C18

column, 40-100% water with 0.1% NH₄OH, acetonitrile). Fractions containing the desired product were combined and concentrated under reduced pressure to yield **135**. MS (ESI) *m/z*: 487.5 [M+H]⁺

¹H NMR (500 MHz, DMSO): δ 8.73 (d, *J* = 2.3 Hz, 1H), 8.67 (s, 2H), 8.38 (d, *J* = 4.7 Hz, 2H), 8.24 (dd, *J* = 9.8, 8.0 Hz, 1H), 8.10 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.65 (t, *J* = 4.7 Hz, 1H), 6.56 (d, *J* = 10.6 Hz, 3H), 4.87 (d, *J* = 2.6 Hz, 1H), 4.60 (d, *J* = 13.1 Hz, 1H), 4.56 (d, *J* = 13.0 Hz, 1H), 4.47 – 4.40 (m, 1H), 3.24 (ddd, *J* = 17.1, 11.3, 3.8 Hz, 2H), 3.07 (td, *J* = 12.5, 3.7 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H).

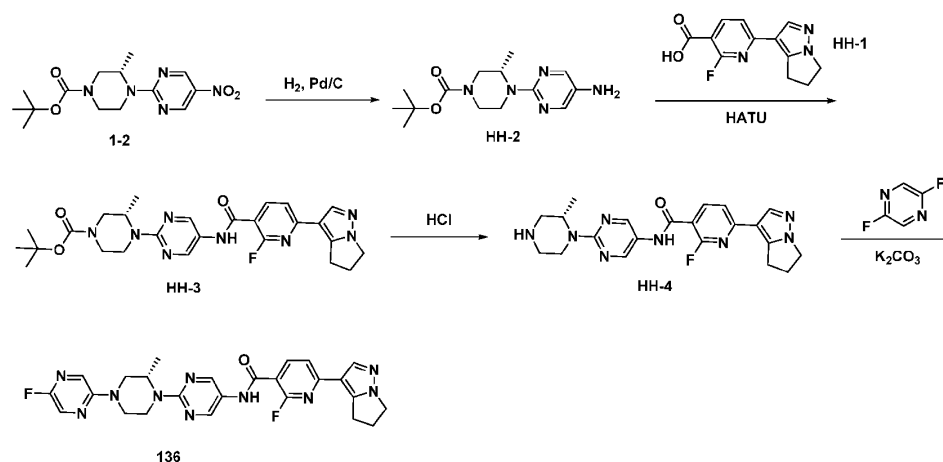
Synthesis of Intermediate **HH-1**: 6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-2-fluoronicotinic acid



Synthesis of **HH-1**: 6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-2-fluoronicotinic acid

[0204] A mixture of 6-bromo-2-fluoronicotinic acid (1.90 g, 8.64 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (3.03 g, 12.9 mmol), and 1M aqueous K₃PO₄ (25.9 mL, 25.9 mmol) in dioxane (57 mL) was purged with nitrogen for 10 minutes. XPhos-Pd-G2 (680 mg, 864 μmol) was added and the mixture was stirred for 2.5 hours at 100 °C. The mixture was cooled and poured onto water (100 mL) and extracted with EtOAc (3 x 30 mL) and DCM (3 x 20 mL). The aqueous layer was acidified with 1M HCl and the resulting precipitated solid was collected by filtration, washed with water (10 mL x 2) and dried to give **HH-1**. MS (ESI) *m/z*: 248.2 [M+H]⁺

Synthesis of Example **136**: (S)-6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-2-fluoro-*N*-(2-(4-(5-fluoropyrazin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



Synthesis of **HH-2**: *tert*-butyl (*S*)-4-(5-aminopyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0205] To a solution of **1-2** (8.88 g, 27.5 mmol) in methanol (137 mL) was added 10% Pd/C (2.00 g, 1.88 mmol). The mixture was stirred for 16 h at 25 °C under a hydrogen balloon. Ice water (300 mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water (20 mL x 2) and dried to give **HH-2**. MS (ESI) *m/z*: 294.3 [*M*+*H*]⁺.

Synthesis of **HH-3**: *tert*-butyl (*S*)-4-(5-(6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-2-fluoronicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0206] A solution of **HH-2** (2.14 g, 7.30 mmol), **HH-1** (1.80 g, 7.30 mmol), HATU (3.33 g, 8.75 mmol), and DIPEA (6.35 mL, 36.5 mmol) in DCM (73 mL) was stirred at 25 °C for 2 hours. The reaction was concentrated and purified by normal phase column chromatography [0 to 100% EtOAc/EtOH (3:1 mix) in hexanes] to afford **HH-3**. MS (ESI) *m/z*: 523.5 [*M*+*H*]⁺.

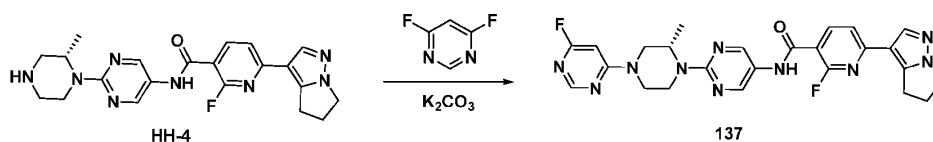
Synthesis of **HH-4**: (*S*)-6-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-2-fluoro-*N*-(2-(2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0207] To a stirred solution of compound **HH-3** (822 mg, 1.57 mmol) in DCM (3.2 mL) was added 4*M* HCl in dioxane (3.93 mL, 15.7 mmol) at 25 °C. The mixture was stirred at room temperature for 2 h and then poured onto saturated aqueous sodium bicarbonate solution (20 mL) and extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **HH-4**. *M/Z* (ESI): 423.4 [*M*+*H*]⁺.

Synthesis of **136**: (S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(5-fluoropyrazin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0208] To a solution of **HH-4** (10.0 mg, 0.024 mmol) in DMF (0.4 mL) was added 2,5-difluoropyrazine (4.1 mg, 0.036 mmol) and DIPEA (1.0 μ L, 0.12 mmol). The mixture was stirred for 16 h at 80 °C. The reaction mixture was purified by reverse phase HPLC (40 to 100% MeCN/H₂O w/ 0.1% NH₄OH gradient on an XBridge Prep OBD C18 column). The desired fractions were concentrated to yield **136**. MS (ESI) m/z: 519.2 [M+H]⁺.

Example **137**: (S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

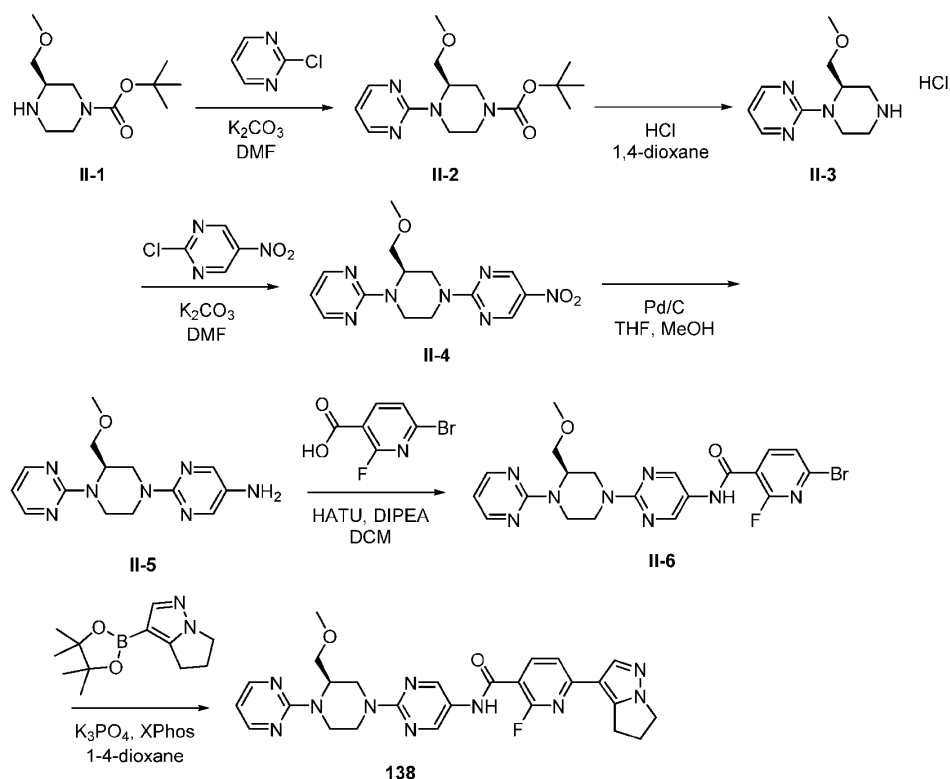


Synthesis of **137**: (S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0209] To a solution of **HH-4** (20.0 mg, 0.0473 mmol) in DMF (0.473 mL) was added 4,6-difluoropyrimidine (8.24 g, 0.0710 mmol) and DIPEA (0.0412 mL, 0.237 mmol). The mixture was stirred for 2 h at 22 °C. The reaction mixture was purified by reverse phase HPLC (40 to 100% MeCN/H₂O w/ 0.1% NH₄OH gradient on a Gemini-NX column). The desired fractions were concentrated to yield **137**. MS (ESI) m/z: 519.4 [M+H]⁺.

¹H NMR (500 MHz, CDCl₃) δ 8.62 (s, 2H), 8.55 (dd, J = 10.3, 8.0 Hz, 1H), 8.35 (d, J = 2.5 Hz, 1H), 8.23 (d, J = 15.7 Hz, 1H), 8.07 (s, 1H), 7.42 (dd, J = 8.0, 2.7 Hz, 1H), 6.02 (s, 1H), 4.99 – 4.94 (m, 1H), 4.56 (dt, J = 13.7, 3.6 Hz, 1H), 4.33 – 4.06 (m, 4H), 3.55 – 3.42 (m, 2H), 3.30 – 3.21 (m, 3H), 2.74 (p, J = 7.4 Hz, 2H), 1.23 (d, J = 6.6 Hz, 3H).

Example **138**: (R)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



Synthesis of II-2: tert-butyl (R)-3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazine-1-carboxylate

[0210] To a solution of tert-butyl (R)-3-(methoxymethyl)piperazine-1-carboxylate (**II-1**, 1.0 g, 1 Eq, 4.34 mmol) in DMF (15 mL) was added diisopropylethylamine (1.68 g, 2.24 mL, 3 Eq, 13.0 mmol) followed by 2-chloropyrimidine (746 mg, 1.5 Eq, 6.51 mmol). The mixture was stirred for 18 h at 130°C. Water (50 mL) was added to the mixture, it was stirred for 30 min at 22°C and then extracted with EtOAc (60 mL x 3). The organic layer was dried over MgSO₄, filtered through a fritted filter, and concentrated under reduced pressure. The resulting residue was dissolved in DCM (3 mL) and purified using normal-phase chromatography (ISCO 80 g RediSep Gold High Performance Silica, 0-100% Hexane, EtOAc, 28 min gradient). Fractions containing the desired product were combined and concentrated under vacuum to yield **II-2**. MS (ESI) m/z: 309.5 [M+H]⁺

Synthesis of II-3: (R)-2-(2-(methoxymethyl)piperazin-1-yl)pyrimidine hydrochloride

[0211] To a solution of tert-butyl (R)-3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazine-1-carboxylate (**II-2**, 870 mg, 1 Eq, 2.82 mmol) in 1,4-dioxane (12.0 mL) was added 4M hydrogen

chloride (1.41 mL, 2 Eq, 5.64 mmol) in 1,4-dioxane. The mixture was stirred for 2 h at 22°C. Additional 4M hydrogen chloride (4 mL) in 1,4-dioxane was added to the mixture and stirred for 1 hour. The mixture was concentrated under reduced pressure to yield **II-3**. MS (ESI) m/z: 209.4 [M+H]⁺

Synthesis of **II-4**: (R)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-nitropyrimidine

[0212] To a solution of (R)-2-(2-(methoxymethyl)piperazin-1-yl)pyrimidine hydrochloride (**II-3**, 790 mg, 1 Eq, 2.81 mmol) in DMF (15.0 mL) was added potassium carbonate (1.55 g, 4 Eq, 11.2 mmol) and 2-chloro-5-nitropyrimidine (538 mg, 1.2 Eq, 3.37 mmol). The mixture was stirred for 18 h at 60 °C. Water was added to the mixture and stirred for 30 min at 22°C. The resulting precipitated solid was collected by filtration through a fritted filter, washed with water (100 mL x 3), and dried to give **II-4**. MS (ESI) m/z: 332.4 [M+H]⁺

Synthesis of **II-5**: (R)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-amine

[0213] A solution of (R)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)-5-nitropyrimidine (**II-4**, 820 mg, 1 Eq, 2.47 mmol) in THF (8.00 mL) and MeOH (8.00 mL) was degassed and purged with N₂ (x 3) then added 10% palladium on carbon (132 mg, 0.5 Eq, 1.24 mmol) and degassed and purged with H₂ (x 3). The mixture was stirred for 18 h at 22°C under a H₂ filled balloon. The mixture was filtered through a fritted filter, washed with MeOH (5 mL x 3), and concentrated under vacuum to yield **II-5**. MS (ESI) m/z: 302.5 [M+H]⁺

Synthesis of **II-6**: (R)-6-bromo-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0214] To a solution of (R)-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-amine (**II-5**, 100.0 mg, 1 Eq, 331.8 µmol) in DCM (2.0 mL) was added diisopropylethylamine (286 µL, 5 Eq, 1.659 mmol), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-Oxide Hexafluorophosphate (252.4 mg, 2 Eq, 663.7 µmol), and 6-bromo-2-fluoronicotinic acid (87.61 mg, 1.2 Eq, 398.2 µmol). The mixture was stirred for 1 h at 22°C. The crude mixture was purified using basic reverse-phase chromatography (Waters XBridge Prep C18 5mm - 30x250mm column, 10-100% 5 mM NH₄HCO₃ water solution: acetonitrile, 26 min gradient). Fractions containing the product were combined and extracted between water (80 mL)

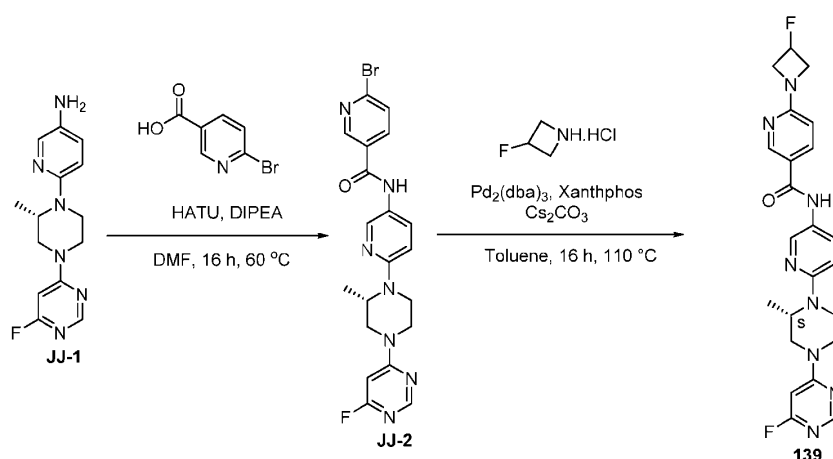
and DCM (80 mL x 3). The collected organic layer was dried over MgSO_4 and then concentrated under vacuum to yield **II-6**. MS (ESI) m/z : 503.5 $[\text{M}+\text{H}]^+$

Example 138: (R)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0215] To a solution of (R)-6-bromo-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide (**II-6**, 20.0 mg, 1 Eq, 39.7 μmol) in 1,4-dioxane (0.50 mL) was added 1M potassium phosphate, tribasic (9.87 μL , 3 Eq, 119 μmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (14.0 mg, 1.5 Eq, 59.6 μmol). The mixture was purged with N_2 for 5 minutes then XPhos Palladacycle-G2 (3.13 mg, 0.1 Eq, 3.97 μmol) was added. The mixture was stirred for 2 h at 80°C. The mixture was filtered through a fritted filter, concentrated, and purified using reverse-phase HPLC (XBridge Prep OBD C18 column, 40-100% water with 0.1% NH_4OH , acetonitrile). Fractions containing the desired product were combined and concentrated under reduced pressure to yield **138**. MS (ESI) m/z : 531.6 $[\text{M}+\text{H}]^+$

¹H NMR (500 MHz, CDCl_3): δ 8.61 (s, 2H), 8.58 – 8.52 (m, 1H), 8.35 (d, $J = 4.7$ Hz, 2H), 8.21 (d, $J = 15.5$ Hz, 1H), 8.07 (s, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 6.53 (t, $J = 4.7$ Hz, 1H), 5.06 (s, 1H), 4.88 (d, $J = 13.4$ Hz, 1H), 4.62 (t, $J = 13.1$ Hz, 2H), 4.22 (t, $J = 7.2$ Hz, 2H), 3.51 (dd, $J = 15.6$, 6.5 Hz, 3H), 3.33 (s, 3H), 3.29 (dd, $J = 13.6$, 3.9 Hz, 1H), 3.26 – 3.16 (m, 3H), 2.78 – 2.69 (m, 2H).

Example 139: (S)-6-(3-fluoroazetidin-1-yl)-N-(6-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyridin-3-yl)nicotinamide



Synthesis of **JJ-2**: (S)-6-bromo-N-(6-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyridin-3-yl)nicotinamide

[0216] To a stirred solution of **JJ-1** (500 mg, 1.734 mmol) in DMF (20 ml) was added 6-bromonicotinic acid (525 mg, 2.60 mmol), HATU (1319 mg, 3.47 mmol) and DIPEA (0.909 ml, 5.20 mmol) at room temperature and stirred for 16 h at 60 °C. Then the reaction mixture was cooled, diluted with ethyl acetate (20 mL), washed with chilled brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and crude was purified using prep-HPLC. (Prep. HPLC Conditions: MOBILE PHASE - 10mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Select C18 (19X250) mm 5u Flow-18ml/min Gradient Method- 0/20,9/78,9.05/99,11/99,11.02/20,14/20. The obtained compound further purified by SFC method (conditions: Column: Chiralpak IG (4.6*250 mm),5μ Mobile Phase- A: MeOH/DCM/DEA(50/50/0.2) Isocratic of A: 100% Flow Rate: 1.0 m L/min Diluent: EtOH. Pure fractions concentrated and lyophilized to afford **JJ-2**. M/Z (ESI): 472.14 [M+H]⁺. ¹H NMR (400MHz, DMSO-d₆) δ: 10.37 (s, 1H), 8.91 (d, J=2.0 Hz, 1H), 8.46 (d, J=2.7 Hz, 1H), 8.32 (d, J=2.4 Hz, 1H), 8.23 (dd, J=8.3, 2.4 Hz, 1H), 7.91 (dd, J=9.3, 2.7 Hz, 1H), 7.85 (d, J=8.3 Hz, 1H), 6.87 (d, J=9.0 Hz, 1H), 6.61 (s, 1H), 4.54-4.60 (m, 1H), 4.26-4.43 (m, 2H), 4.06 (br dd, J=9.5, 3.2 Hz, 1H), 3.41 (br dd, J=13.4, 3.4 Hz, 1H), 3.15-3.25 (m, 2H), 1.03 (d, J=6.4 Hz, 3H).

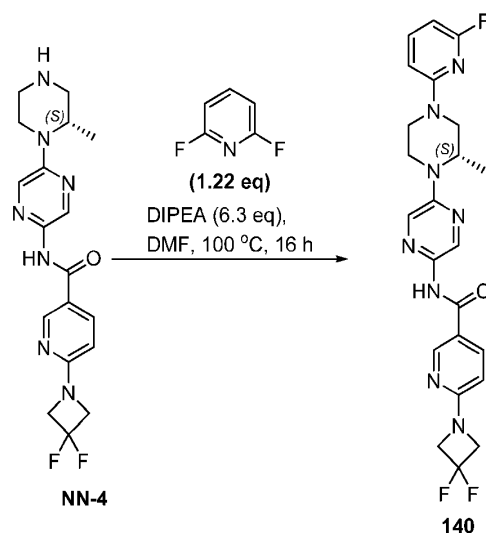
Example 139: (S)-6-(3-fluoroazetidin-1-yl)-N-(6-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyridin-3-yl)nicotinamide

[0217] To a stirred solution of **JJ-2** (90 mg, 0.210 mmol) in toluene (3 ml) was added 3-fluoroazetidine hydrochloride (25.8 mg, 0.231 mmol), Cs₂CO₃ (93 mg, 0.284 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (12.17 mg, 0.021 mmol) at room temperature and purged with argon for 10 min, followed by the addition of Pd₂(dba)₃ (9.63 mg, 10.52 μmol) at room temperature and again purged with argon for another 10 min and stirred for 16 h at 110 °C. Then the reaction mixture was filtered on celite bed and washed with EtOAc. Filtrate was washed with chilled brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and crude was purified by Prep-HPLC. (Conditions: Mobile Phase - 10mM Ammonium Bicarbonate in H₂O: MeCN Column - X-Select C18 (19X250) mm 5u Flow-18ml/min GRADIENT METHOD- 0/60,8/80,8.02/100,10/100,10.08/60,14/60. The obtained compound further purified by SFC method (conditions: Column: Chiralpak IE (4.6*250 mm),5μ Mobile Phase- A: MeOH/DCM/DEA(50/50/0.2) Isocratic of A: 100% Flow Rate: 0.70 mL/m in Diluent: EtOH.

Pure fractions concentrated under reduced pressure and lyophilized to afford **139**. M/Z (ESI): 467.18 [M+H]⁺.

¹H NMR (400MHz, DMSO-d₆) δ: 9.95 (s, 1H), 8.70 (br d, J=2.0 Hz, 1H), 8.45 (br d, J=2.4 Hz, 1H), 8.32 (d, J=2.7 Hz, 1H), 8.09 (br dd, J=8.8, 2.2 Hz, 1H), 7.87-7.94 (m, 1H), 6.88 (br d, J=8.1 Hz, 1H), 6.61 (s, 1H), 6.53 (br d, J=8.6 Hz, 1H), 5.42-5.63 (m, 1H), 4.50-4.56 (m, 1H), 4.43 (br d, J=4.4 Hz, 8H), 3.16-3.24 (m, 2H), 2.54 (s, 1H), 1.03 (br d, J=6.4 Hz, 3H).

Example 140: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

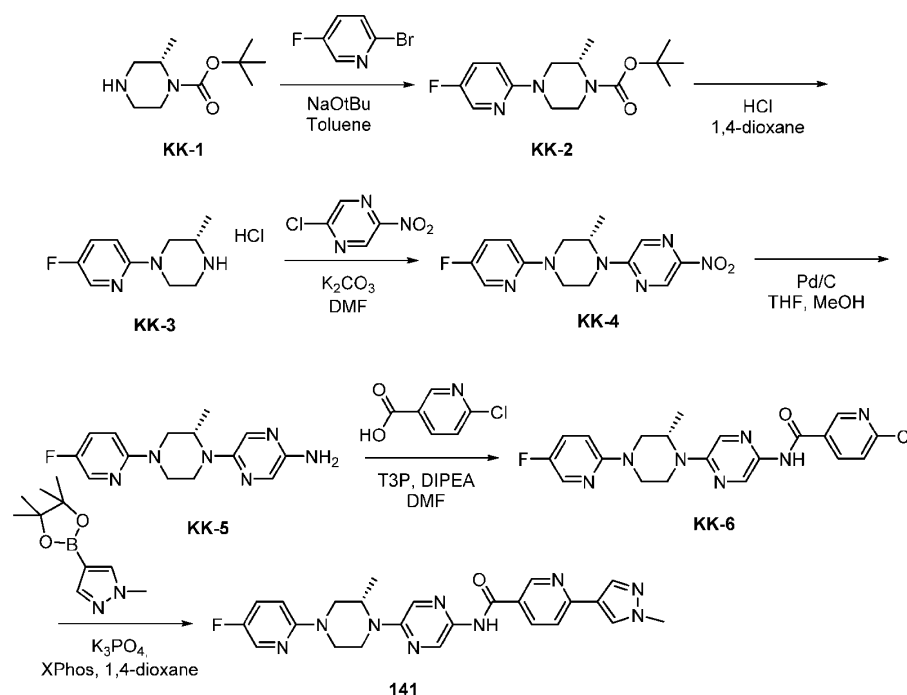


[0218] To a stirred solution of **NN-4** (70 mg, 164 μmol) in DMF (1 mL) were added DIPEA (0.18 mL, 1 mmol) and 2, 6-difluoropyridine (23 mg, 200 μmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h under argon atmosphere. Reaction mixture was quenched with ice cold water (5 mL), precipitated solid was filtered and dried under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: Mobile Phase – 10mM Ammonium Bicarbonate in H₂O: MeCN Column – X-Bridge C18 (19X250) mm, 5μ Flow-15.0 ml/min Gradient Method 0/55,2/55,10/67,10.05/100,12/100,12.05/55,15/55). Pure fractions were combined, concentrated under reduced pressure to afford **140**. M/Z (ESI): 485.29 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 10.58 (s, 1H), 8.86 (d, J = 1.2 Hz, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.22 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 7.69 (q, J = 8.0 Hz, 1H), 6.75

(dd, $J = 8.0$ Hz, 2.4 Hz, 1H), 6.63 (d, $J = 8.8$ Hz, 1H), 6.27 (dd, $J = 7.8$ Hz, 2.6 Hz, 1H), 4.57-4.65 (m, 1H), 4.50 (t, $J = 12.4$ Hz, 4H), 4.02-4.18 (m, 3H), 3.26 (dd, $J = 14.4$ Hz, 3.2 Hz, 2H), 3.09 (td, $J = 12.0$ Hz, 3.6 Hz, 1H), 1.11 (d, $J = 6.4$ Hz, 3H).

Example 141: (S)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of KK-2: tert-butyl (S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxylate

[0219] To a solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**KK-1**, 1.00 g, 1 Eq, 4.99 mmol) in toluene (30.0 mL) was added sodium 2-methylpropan-2-olate (1.44 g, 1.61 mL, 3 Eq, 15.0 mmol) and tert-butyl (S)-2-methylpiperazine-1-carboxylate (1.00 g, 1 Eq, 4.99 mmol). The mixture was purged with N₂ for 5 minutes then chloro(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (194 mg, 0.05 Eq, 250 μmol) was added. The mixture was stirred for 48 h at 110°C. Water (50 mL) was added to the mixture and it was extracted with EtOAc (100 mL x 3). The organic layer was dried over MgSO₄, filtered through a fritted filter, and concentrated under reduced pressure. The resulting residue was dissolved in DCM (3 mL) and purified using normal-phase chromatography (ISCO 80 g

RediSep Gold High Performance Silica, 0-100% Hexane, EtOAc, 26 min gradient). Fractions containing the desired product were combined and concentrated under vacuum to yield **KK-2**. MS (ESI) m/z: 296.4 [M+H]⁺

Synthesis of **KK-3**: (S)-1-(5-fluoropyridin-2-yl)-3-methylpiperazine hydrochloride

[0220] To a solution of tert-butyl (S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxylate (**KK-2**, 1.00 g, 1 Eq, 3.39 mmol) in 1,4-dioxane (14.0 mL) was added 4M hydrogen chloride (3.39 mL, 4 Eq, 13.5 mmol) in 1,4-dioxane. The mixture was stirred for 18 h at 22°C. The mixture was concentrated under reduced pressure to yield **KK-3**. MS (ESI) m/z: 196.3 [M+H]⁺

Synthesis of **KK-4**: (S)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-nitropyrazine

[0221] To a solution of (S)-1-(5-fluoropyridin-2-yl)-3-methylpiperazine hydrochloride (**KK-3**, 900 mg, 1 Eq, 3.36 mmol) in DMF (15.0 mL) was added potassium carbonate (1.86 g, 4 Eq, 13.4 mmol) and 2-chloro-5-nitropyrazine (642 mg, 1.2 Eq, 4.03 mmol). The mixture was stirred for 18 h at 60 °C. Water was added to the mixture and stirred for 30 min at 22°C. The resulting precipitated solid was collected by filtration through a fritted filter, washed with water (100 mL x 3), and dried to give **KK-4**. MS (ESI) m/z: 319.3 [M+H]⁺

Synthesis of **KK-5**: (S)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-nitropyrazine

[0222] A solution of (S)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-nitropyrazine (**KK-4**, 579 mg, 1 Eq, 1.82 mmol) in THF (5.00 mL) and MeOH (5.00 mL) was degassed and purged with N₂ (x 3) then added 10% palladium on carbon (96.8 mg, 0.5 Eq, 909 µmol) and degassed and purged with H₂ (x 3). The mixture was stirred for 18 h at 22°C under a H₂ filled balloon. The mixture was filtered through a fritted filter, washed with MeOH (5 mL x 3), and concentrated under vacuum to yield **KK-5**. MS (ESI) m/z: 289.3 [M+H]⁺

Synthesis of **KK-6**: (S)-6-chloro-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

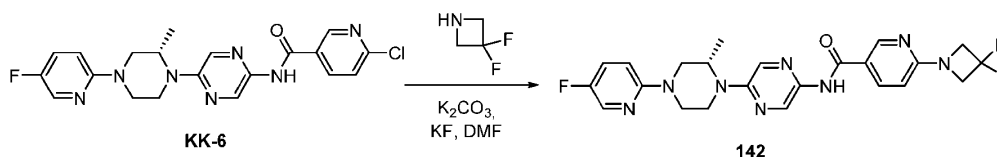
[0223] To a solution of (S)-2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)-5-nitropyrazine (**KK-5**, 520.00 mg, 1 Eq, 1.8035 mmol) in DMF (8.0 mL) was added diisopropylethylamine (1.165 g, 1.57 mL, 5 Eq, 9.0174 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (1.1477 g, 1.22 mL, 50% Wt, 1 Eq, 1.8035 mmol), and 6-chloronicotinic acid (340.97

mg, 1.2 Eq, 2.1642 mmol). The mixture was stirred for 1.5h at 22°C The crude mixture was purified using basic reverse-phase chromatography (Waters XBridge Prep C18 5mm - 50x250mm column, 10-100% 5 mM NH₄HCO₃ water solution: acetonitrile, 33 min gradient). Fractions containing the product were combined and extracted between water (100 mL) and DCM (100 mL x 3). The collected organic layer was dried over MgSO₄ then concentrated under vacuum to yield **KK-6**. MS (ESI) m/z: 428.4 [M+H]⁺

Example 141: (S)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0224] To a solution of (S)-6-chloro-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide (**KK-6**, 20.00 mg, 1 Eq, 46.74 μmol) in 1,4-dioxane (0.30 mL) was added 1M potassium phosphate, tribasic (140.2 μL, 1.00 molar, 3 Eq, 140.2 μmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (11.67 mg, 1.2 Eq, 56.09 μmol). The mixture was purged with N₂ for 5 minutes then XPhos Palladacycle-G2 (3.678 mg, 0.1 Eq, 4.674 μmol) was added. The mixture was stirred for 2 h at 80°C. Post reaction time, LCMS showed high conversion of desired product. Next, the mixture was filtered through a fritted filter, concentrated, and purified using reverse-phase HPLC (XBridge Prep OBD C18 column, 40-100% water with 0.1% NH₄OH, acetonitrile). Fractions containing the desired product were combined and concentrated under reduced pressure to yield **141**. MS (ESI) m/z: 474.5 [M+H]⁺
¹H NMR (500 MHz, DMSO): δ 10.84 (s, 1H), 9.09 (s, 1H), 8.89 (s, 1H), 8.41 (s, 1H), 8.34 (dd, J = 8.3, 2.1 Hz, 1H), 8.16 (s, 1H), 8.12 (d, J = 3.0 Hz, 1H), 8.10 (s, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.54 (td, J = 8.7, 3.1 Hz, 1H), 6.95 (dd, J = 9.3, 3.3 Hz, 1H), 4.62 (s, 1H), 4.25 – 4.09 (m, 3H), 3.91 (s, 3H), 3.30 – 3.23 (m, 1H), 3.20 (dd, J = 12.8, 3.5 Hz, 1H), 2.99 (td, J = 12.0, 3.7 Hz, 1H), 1.14 (d, J = 6.5 Hz, 3H).

Example 142: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

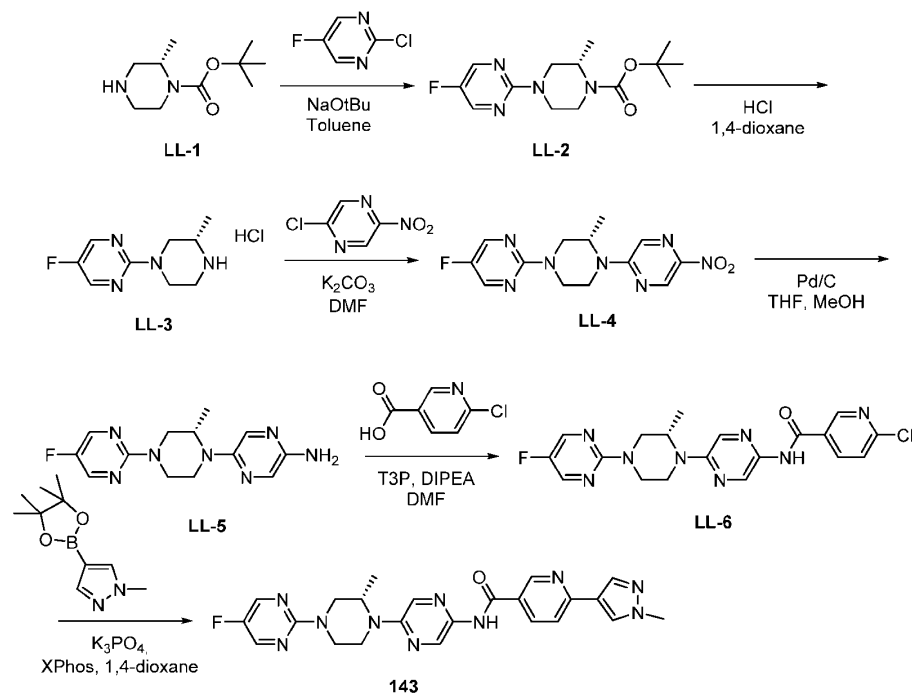


[0225] To a solution of (S)-6-chloro-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide (**KK-6**, 20.00 mg, 1 Eq, 46.74 μmol) in DMF (0.50 mL) was added

potassium carbonate (19.38 mg, 3 Eq, 140.2 μmol), potassium fluoride (8.147 mg, 3.284 μL , 3 Eq, 140.2 μmol) and 3,3-difluoroazetidine (6.526 mg, 1.5 Eq, 70.11 μmol). The mixture was concentrated under vacuum, redissolved in DCM (1 mL), then purified using normal-phase chromatography (ISCO 80 g RediSep Gold High Performance Silica, 0-100% Hexane, EtOAc, 26 min gradient). Fractions containing the desired product were combined and concentrated under vacuum to yield **142**. MS (ESI) m/z : 485.4 $[\text{M}+\text{H}]^+$

^1H NMR (500 MHz, CDCl_3): δ 9.17 (s, 1H), 8.73 (d, $J = 2.1$ Hz, 1H), 8.07 (d, $J = 5.7$ Hz, 3H), 7.82 (s, 1H), 7.32 – 7.28 (m, 1H), 6.65 (dd, $J = 9.2, 3.2$ Hz, 1H), 6.42 (d, $J = 8.7$ Hz, 1H), 4.55 (s, 1H), 4.46 (t, $J = 11.8$ Hz, 4H), 4.15 (d, $J = 12.1$ Hz, 1H), 4.06 (dd, $J = 17.3, 13.6$ Hz, 2H), 3.40 (td, $J = 12.1, 3.6$ Hz, 1H), 3.34 (dd, $J = 12.7, 3.7$ Hz, 1H), 3.13 (qd, $J = 12.2, 4.4$ Hz, 1H), 1.26 (d, $J = 6.5$ Hz, 3H).

Example 143: (S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide



Synthesis of **LL-2**: tert-butyl (S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazine-1-carboxylate

[0226] To a solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (**LL-1**, 5.43 g, 1.00 Eq, 27.1 mmol) in DMF (67.8 mL) was added diisopropylethylamine (17.5 g, 23.6 mL, 5.00 Eq, 136 mmol) and 2-chloro-5-fluoropyrimidine (5.39 g, 3.75 mL, 1.50 Eq, 40.7 mmol). The mixture was stirred for 16 h at 80°C. Water (300 mL) was added to the mixture and extracted with ether (100 mL x 3). The organic layer was dried over Na₂SO₄, filtered through a fritted filter, and concentrated under reduced pressure. The resulting residue was purified using normal-phase chromatography (ISCO 330 g RediSep Gold High Performance Silica, 0-25% Hexane, EtOAc). Fractions containing the desired product were combined and concentrated under vacuum to yield **LL-2**. MS (ESI) m/z: 297.1 [M+H]⁺

Synthesis of **LL-3**: (S)-5-fluoro-2-(3-methylpiperazin-1-yl)pyrimidine hydrochloride

[0227] To a solution of tert-butyl (S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazine-1-carboxylate (**LL-2**, 7.35 g, 1 Eq, 24.8 mmol) in DCM (124 mL) was added 4M hydrogen chloride (62.0 mL, 4.00 molar, 10 Eq, 248 mmol) in DCM. The mixture was stirred for 2 h at 22°C. The mixture was concentrated under reduced pressure to yield **LL-3**. MS (ESI) m/z: 320.2 [M+H]⁺

Synthesis of **LL-4**: (S)-5-fluoro-2-(3-methyl-4-(5-nitropyrizin-2-yl)piperazin-1-yl)pyrimidine

[0228] To a solution of (S)-5-fluoro-2-(3-methylpiperazin-1-yl)pyrimidine hydrochloride (**LL-3**, 1.00 g, 1 Eq, 5.10 mmol) in DMF (25.5 mL) was added potassium carbonate (2.82 g, 4.00 Eq, 20.4 mmol) and 2-chloro-5-nitropyrizine (976 mg, 1.20 Eq, 6.12 mmol). The mixture was stirred for 16 h at 60 °C. Ice water was added to the mixture and the resulting precipitated solid was collected through a fritted filter, washed with water (5 mL x 3), and dried to give **LL-4**. MS (ESI) m/z: 290.2 [M+H]⁺

Synthesis of **LL-5**: (S)-5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-amine

[0229] A solution of (S)-5-fluoro-2-(3-methyl-4-(5-nitropyrizin-2-yl)piperazin-1-yl)pyrimidine (**LL-4**, 1.20 g, 1 Eq, 3.76 mmol) in DCM (9.40 mL) and MeOH (9.40 mL) was degassed and purged with N₂ (x 3) then added 10% palladium on carbon (200.0 mg, 0.500 Eq, 1.879 mmol) and degassed and purged with H₂ (x 3). The mixture was stirred for 6 h at 22°C under a H₂ filled balloon. The mixture was filtered through a fritted filter and concentrated under vacuum to yield **LL-5**. MS (ESI) m/z: 290.2 [M+H]⁺

Synthesis of **LL-6**: (S)-6-chloro-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

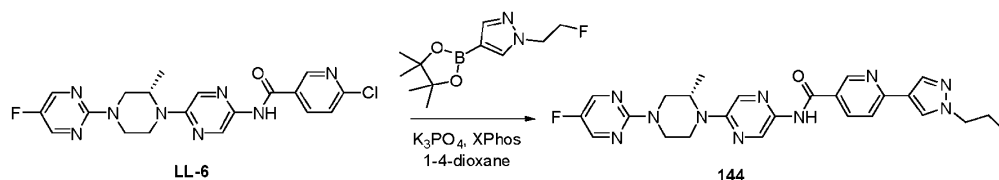
[0230] To a solution of (S)-5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-amine (**LL-5**, 520.00 mg, 1 Eq, 1.8035 mmol) in DMF (8.0 mL) was added diisopropylethylamine (670.11 mg, 903 μ L, 5 Eq, 5.1846 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (659.85 mg, 699 μ L, 50% Wt, 1 Eq, 1.0369 mmol), and 6-chloronicotinic acid (196.04 mg, 1.2 Eq, 1.2443 mmol). The mixture was stirred for 3 h at 22°C. The crude mixture was purified using basic reverse-phase chromatography (Waters XBridge Prep C18 5mm - 50x250mm column, 10-100% 5 mM NH_4HCO_3 water solution: acetonitrile, 33 min gradient). Fractions containing the product were combined and extracted between water (100 mL) and DCM (150 mL x 3). The collected organic layer was dried over MgSO_4 then concentrated under vacuum to yield **LL-6**. MS (ESI) m/z: 429.3 $[\text{M}+\text{H}]^+$

Example 143: (S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

[0231] To a solution of (S)-6-chloro-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide (**LL-6**, 20.00 mg, 1 Eq, 46.64 μ mol) in 1,4-dioxane (0.50 mL) was added 1M potassium phosphate, tribasic (139.9 μ L, 1.00 molar, 3 Eq, 139.9 μ mol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (11.64 mg, 1.2 Eq, 55.96 μ mol). The mixture was purged with N_2 for 5 minutes then XPhos Palladacycle-G2 (3.669 mg, 0.1 Eq, 4.664 μ mol) was added. The mixture was stirred for 2 h at 80°C. The mixture was concentrated and purified using normal phase chromatography (ISCO 12 g RediSep Gold High Performance Silica, 10-100% Hexane, EtOAc, 18 min gradient). Fractions containing the desired product were combined and concentrated under reduced pressure. LCMS showed major byproduct and therefore was redissolved in DMSO (1mL) and re-purified using basic reverse-chromatography (Gilson Waters XBridge Prep OBD C18 5 μ m 10-100% of 0.1% NH_4OH water: acetonitrile, 10 minute gradient). Fractions containing the product were combined and concentrated to yield **143**. MS (ESI) m/z: 475.4 $[\text{M}+\text{H}]^+$

^1H NMR (500 MHz, CDCl_3): δ 9.20 (s, 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.29 – 8.16 (m, 4H), 8.02 (s, 2H), 7.83 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 4.63 (d, J = 13.2 Hz, 1H), 4.56 (d, J = 13.0 Hz, 2H), 4.06 (d, J = 12.7 Hz, 1H), 3.99 (s, 3H), 3.42 – 3.29 (m, 2H), 3.23 (td, J = 12.3, 3.6 Hz, 1H), 1.20 (d, J = 6.5 Hz, 3H).

Example 144: (S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

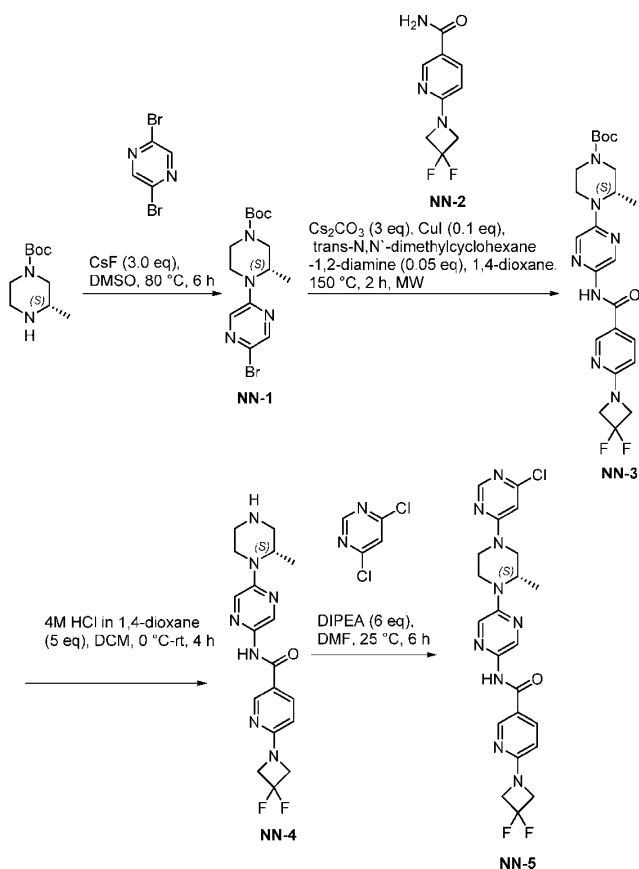


[0232] To a solution of (S)-6-chloro-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide (**LL-6**, 20.00 mg, 1 Eq, 46.64 μmol) in 1,4-dioxane (0.50 mL) was added 1M potassium phosphate, tribasic (139.9 μL , 1.00 molar, 3 Eq, 139.9 μmol) and 1-(2-fluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (13.44 mg, 1.2 Eq, 55.96 μmol). The mixture was purged with N_2 for 5 minutes then XPhos Palladacycle-G2 (3.669 mg, 0.1 Eq, 4.664 μmol) was added. The mixture was stirred for 2 h at 80°C. The mixture was concentrated under a concentrator, dissolved in DCM (1mL), and purified using normal phase chromatography (ISCO 12 g RediSep Gold High Performance Silica, 10-100% Hexane, EtOAc, 18 min gradient). Fractions containing the desired product were combined and concentrated under reduced pressure to yield **144**. MS (ESI) m/z : 507.4 $[\text{M}+\text{H}]^+$

^1H NMR (500 MHz, CDCl_3): δ 9.20 (s, 1H), 9.07 (d, $J = 1.9$ Hz, 1H), 8.25 (s, 1H), 8.23 (s, 2H), 8.20 (dd, $J = 8.3, 2.0$ Hz, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.58 (d, $J = 8.3$ Hz, 1H), 4.87 (t, $J = 4.7$ Hz, 1H), 4.78 (t, $J = 4.7$ Hz, 1H), 4.63 (d, $J = 12.9$ Hz, 1H), 4.56 (d, $J = 13.0$ Hz, 2H), 4.49 (dt, $J = 26.7, 4.8$ Hz, 3H), 4.06 (d, $J = 12.7$ Hz, 1H), 3.41 – 3.30 (m, 2H), 3.23 (td, $J = 12.3, 3.6$ Hz, 1H), 1.20 (d, $J = 6.5$ Hz, 3H).

Synthesis of Radiolabeling intermediates:

Synthesis of Intermediate NN-5: (S)-N-(5-(4-(6-chloropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(3,3-difluoroazetidin-1-yl)nicotinamide



Synthesis of NN-1: tert-butyl (S)-4-(5-bromopyrazin-2-yl)-3-methylpiperazine-1-carboxylate

[0233] To a stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (5 g, 24.96 mmol) in DMSO (100 mL) were added CsF (11.38 g, 74.9 mmol) and 2,5-dibromopyrazine (7.13 g, 30.0 mmol) at room temperature. The reaction mixture was stirred under argon atmosphere at 80 °C for 6 h. Reaction mixture was quenched with cold water (100 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using silica (230-400 mesh) column and compound eluted with 15% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford NN-1. M/Z (ESI): 357.15 [M+H]⁺.

Synthesis of NN-3: tert-butyl (S)-4-(5-(6-(3,3-difluoroazetidin-1-yl)nicotinamido)pyrazin-2-yl)-3-methylpiperazine-1-carboxylate

[0234] To a stirred solution of **NN-1** (1.50 g, 4.20 mmol) in 1,4-dioxane (30 mL) were added **NN-2** (985 mg, 4.62 mmol), Cs₂CO₃ (4.10 g, 12.6 mmol), CuI (80.0 mg, 420 μmol) and trans-(1*r*,2*r*)-N,N'-bismethyl-1,2-cyclohexanediamine (66.2 μL, 210 μmol) at room temperature and degassed with argon for 10 min. The reaction mixture was stirred at 150 °C for 2 h under microwave irradiation. Reaction mixture was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). Combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using silica (230-400 mesh) column and compound eluted with 5% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure to afford **NN-3**. M/Z (ESI): 490.77 [M+H]⁺.

Synthesis of **NN-4**: (S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

[0235] To a stirred solution of **NN-3** (900 mg, 1.84 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (2.30 mL, 9.19 mmol) at 0 °C. The reaction mixture was stirred under argon atmosphere at 25 °C for 4 h. Reaction mixture was concentrated under reduced pressure to afford **NN-4**. M/Z (ESI): 390.23 [M+H]⁺.

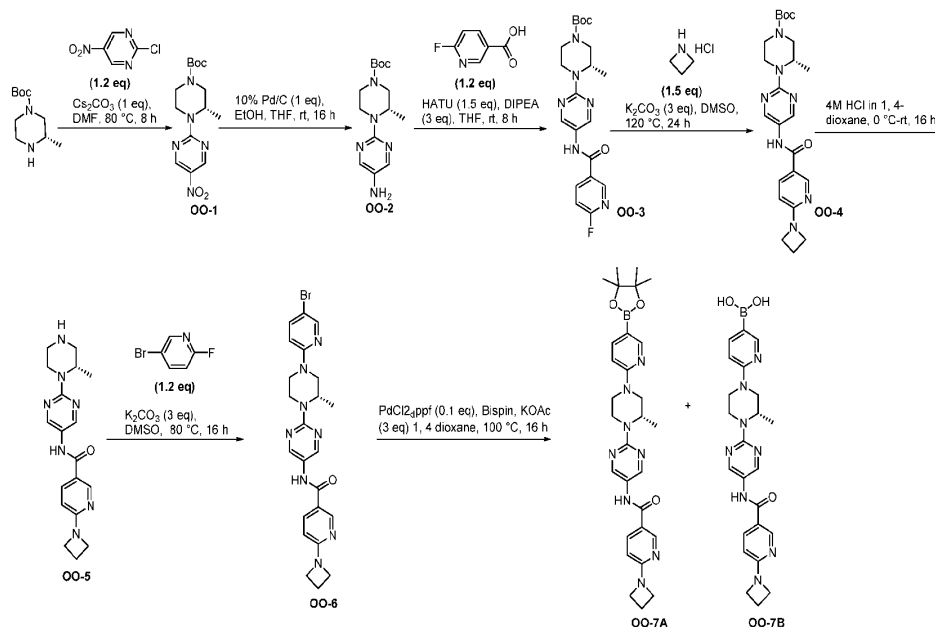
Synthesis of **NN-5**: (S)-N-(5-(4-(6-chloropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(3,3-difluoroazetidin-1-yl)nicotinamide

[0236] To a stirred solution of **NN-4** (150 mg, 352 μmol) in DMF (2 mL) were added DIPEA (0.38 mL, 2.2 mmol) and 4,6-dichloropyrimidine (63.0 mg, 423 μmol) at room temperature. The reaction mixture was stirred under argon atmosphere at 25 °C for 6 h. Reaction mixture was quenched with cold water (10 mL). Precipitated solution was stirred for 10 min, filtered and dried under reduced pressure. Crude compound was triturated with diethyl ether (10 mL) to afford **NN-5**. M/Z (ESI): 502.21 [M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.59 (s, 1H), 8.76-8.94 (m, 2H), 8.37 (s, 1H), 8.22 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 8.13 (s, 1H), 7.06 (s, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 4.21-4.70 (m, 7H), 4.01-4.17 (m, 1H), 3.42 (dd, *J* = 13.2 Hz, 3.6 Hz, 1H), 3.20-3.29 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H).

Synthesis of **OO-7A**: (S)-6-(azetidin-1-yl)-N-(2-(2-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide and **OO-7B** (S)-6-(4-

(5-(6-(azetidin-1-yl)nicotinamido)pyrimidin-2-yl)-3-methylpiperazin-1-yl)pyridin-3-yl)boronic acid



Synthesis of **OO-1**: tert-butyl (S)-3-methyl-4-(5-nitropyrimidin-2-yl)piperazine-1-carboxylate

[0237] To a stirred solution of tert-butyl (S)-3-methylpiperazine-1-carboxylate (10 g, 49.9 mmol) in DMF (100 mL) were added 2-chloro-5-nitropyrimidine (9.56 g, 59.9 mmol) and cesium carbonate (16.3 g, 49.9 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at 80 °C for 8 h. Reaction mixture was quenched with crushed ice and extracted with EtOAc (2 x 100 mL). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 120 g silica gel cartridge and compound eluted with 70% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **OO-1**. M/Z (ESI): 324.23 [M+H]⁺.

Synthesis of **OO-2**: tert-butyl (S)-4-(5-aminopyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0238] To a stirred solution of **OO-1** (15 g, 46.4 mmol) in EtOH (100 mL) and THF (100 mL) was added 10% Pd/C (4.94 g, 46.4 mmol) at room temperature. Reaction mixture was degassed and purged with nitrogen gas. The reaction mixture was stirred at room temperature for 16 h under hydrogen atmosphere. Reaction mixture was filtered through celite pad and filtrate

was concentrated and dried under reduced pressure. Crude compound was triturated with n-pentane and dried under reduced pressure to afford **OO-2**. M/Z (ESI): 294.22 [M+H]⁺.

Synthesis **OO-3**: tert-butyl (S)-4-(5-(6-fluoronicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0239] To a stirred solution of **OO-2** (1 g, 3.41 mmol) and 6-fluoronicotinic acid (577 mg, 4.09 mmol) in THF (20 mL) were added DIPEA (1.78 mL, 10.2 mmol) and HATU (1.94 g, 5.11 mmol) at room temperature. The reaction mixture was stirred at room temperature for 8 h. Reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL). Combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 12 g silica gel cartridge and compound eluted with 40% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **OO-3**. M/Z (ESI): 417.29 [M+H]⁺.

Synthesis of **OO-4**: tert-butyl (S)-4-(5-(6-(azetidin-1-yl)nicotinamido)pyrimidin-2-yl)-3-methylpiperazine-1-carboxylate

[0240] To a stirred solution of **OO-3** (800 mg, 1.92 mmol) in DMSO (5 mL) were added azetidine hydrochloride (270 mg, 2.88 mmol) and K₂CO₃ (796 mg, 5.76 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at 120 °C for 24 h. Reaction mixture was quenched with crushed ice and extracted with EtOAc (2 x 20 mL). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 12 g silica gel cartridge and compound eluted with 80% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **OO-4**. M/Z (ESI): 454.33 [M+H]⁺.

Synthesis of **OO-5**: (S)-6-(azetidin-1-yl)-N-(2-(2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0241] To a stirred solution of **OO-4** (3 g, 6.61 mmol) in DCM (50 mL) was added 4M HCl in 1, 4-dioxane (6.61 mL, 26.5 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was concentrated and dried under reduced pressure to afford **OO-5**. M/Z (ESI): 354.33 [M+H]⁺.

Synthesis of **OO-6**: (S)-6-(azetidin-1-yl)-N-(2-(4-(5-bromopyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

[0242] To a stirred solution of **OO-5** (2 g, 5.13 mmol) and 5-bromo-2-fluoropyridine (1.08 g, 6.16 mmol) in DMSO (10 mL) was added potassium carbonate (2.13 g, 15.4 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 16 h. Reaction mixture was quenched with water (30 mL) and extracted with EtOAc (2 x 50 mL). Combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by silica gel column and compound eluted with 80% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure to afford **OO-6**. M/Z (ESI): 509.23 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 9.94 (s, 1H), 8.64-8.72 (m, 3H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.69 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 4.77-4.90 (m, 1H), 4.36-4.48 (m, 1H), 4.13-4.29 (m, 2H), 4.04 (t, *J* = 7.4 Hz, 4H), 3.21-3.30 (m, 2H), 2.96-3.06 (m, 1H), 2.32-2.43 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 3H).

Synthesis of **OO-7A** (S)-6-(azetidin-1-yl)-N-(2-(2-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide and **OO-7B** (S)-6-(4-(5-(6-(azetidin-1-yl)nicotinamido)pyrimidin-2-yl)-3-methylpiperazin-1-yl)pyridin-3-yl)boronic acid

[0243] To a stirred solution of **OO-6** (300 mg, 588.9 μmol) in 1, 4-dioxane (5 mL) were added potassium acetate (173.4 mg, 1.767 mmol) and bis(pinacolato)diboron (179.5 mg, 706.7 μmol) at room temperature under argon atmosphere. Reaction mixture was degassed and purged with argon gas for 2 min. Then to this reaction mixture was added PdCl₂(dppf)-CH₂Cl₂ adduct (48.09 mg, 58.89 μmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. Reaction mixture was filtered through celite pad and filtrate was concentrated under reduced pressure. Crude compound was purified by prep-HPLC purification (conditions: MOBILE PHASE – 10mM Ammonium Bicarbonate in H₂O: MeCN Column – X-Bridge C18 (19X250) mm, 5μ Flow-15.0 ml/min Gradient Method : 0/40, 2/40, 15/75, 13/75, 13.05/100, 15/100, 15.05/40, 18/40 prep-020). Pure fractions were combined, concentrated under reduced pressure and lyophilized separately to afford **OO-7A** and **OO-7B**.

OO-7A: M/Z (ESI): 557.44 [M+H]⁺.

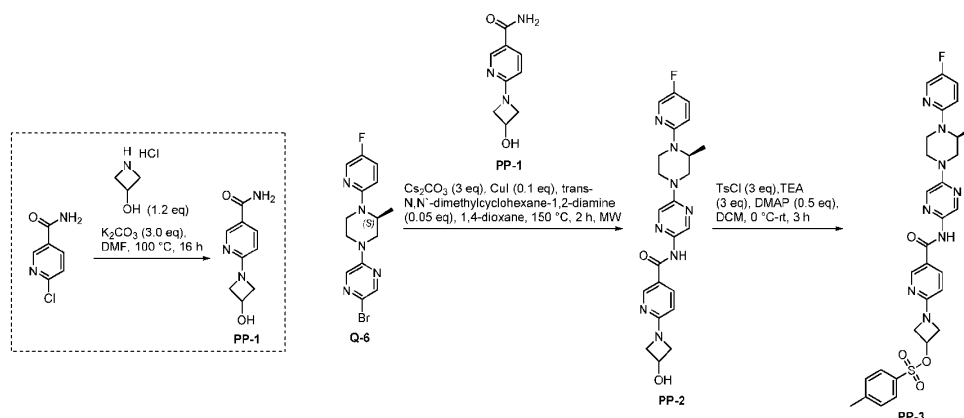
¹H NMR (400 MHz, DMSO-d₆) δ = 9.94 (s, 1H), 8.60-8.73 (m, 3H), 8.34 (d, *J* = 1.2 Hz, 1H), 8.03 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.71 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.40 (d, *J*

= 8.8 Hz, 1H), 4.75-4.85 (m, 1H), 4.25-4.46 (m, 3H), 4.04 (t, $J = 7.6$ Hz, 4H), 3.27 (d, $J = 3.2$ Hz, 2H), 3.05 (td, $J = 11.8$ Hz, 3.6 Hz, 1H), 2.34-2.40 (m, 2H), 1.27 (s, 12H), 1.10 (d, $J = 6.8$ Hz, 3H).

OO-7B: M/Z (ESI): 473.32 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ = 9.94 (s, 1H), 8.63-8.72 (m, 3H), 8.47 (d, $J = 1.2$ Hz, 1H), 8.03 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 7.82-7.91 (m, 3H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.40 (d, $J = 8.8$ Hz, 1H), 4.76-4.89 (m, 1H), 4.22-4.47 (m, 3H), 4.04 (t, $J = 7.4$ Hz, 4H), 3.20-3.30 (m, 2H), 2.99 (td, $J = 12.0$ Hz, 3.6 Hz, 1H), 2.34-2.41 (m, 2H), 1.12 (d, $J = 6.4$ Hz, 3H).

Synthesis of **PP-3**: (S)-1-(5-((5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)carbamoyl)pyridin-2-yl)azetidin-3-yl 4-methylbenzenesulfonate



Synthesis of **PP-1**: 6-(3-hydroxyazetidin-1-yl)nicotinamide

[0244] To a stirred solution of 6-chloronicotinamide (1 g, 6.39 mmol) in DMF (40 mL) were added K₂CO₃ (2.65 g, 19.16 mmol) and 3-hydroxyazetidine hydrochloride (0.840 g, 7.66 mmol) at 0 °C. The reaction mixture was stirred under nitrogen atmosphere at 100 °C for 16 h. Reaction mixture was diluted with EtOAc (50 mL), filtered through celite pad and washed with EtOAc (2 x 50 mL). Filtrate was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 40 g silica (230-400 mesh) cartridge and compound eluted with 12% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure to afford **PP-1**. M/Z (ESI): 194.06 [M+H]⁺.

Synthesis of **PP-2**: (S)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(3-hydroxyazetidin-1-yl)nicotinamide

[0245] To a stirred solution of **Q-6** (300 mg, 0.852 mmol) in 1,4-dioxane (3 mL) were added Cs₂CO₃ (833 mg, 2.56 mmol), copper(I) iodide (16.22 mg, 0.085 mmol), trans-N,N'-dimethylcyclohexane-1,2-diamine (6.66 μ L, 0.043 mmol) and **PP-1** (181 mg, 0.937 mmol) at room temperature. The reaction mixture was stirred under nitrogen atmosphere at 150 °C for 2 h under microwave irradiation. Reaction mixture was quenched with water (80 mL) and extracted with EtOAc (2 x 150 mL). Combined organic layer was washed with brine (2 x 80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 3% MeOH in DCM. Pure fractions were combined and concentrated under reduced pressure to afford **PP-2**. M/Z (ESI): 465.34 [M+H]⁺.

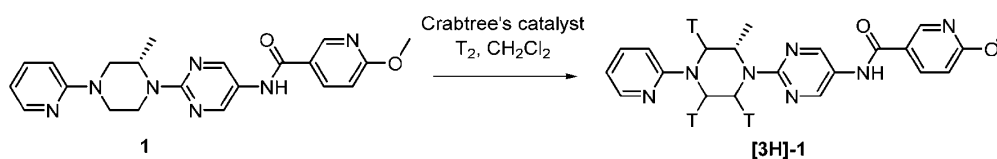
Synthesis of **PP-3**: (S)-1-(5-((5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)carbamoyl)pyridin-2-yl)azetidin-3-yl 4-methylbenzenesulfonate

[0246] To a stirred solution of **PP-2** (200 mg, 0.431 mmol) in DCM (4 mL) were added TEA (0.180 mL, 1.292 mmol), 4-dimethylaminopyridine (26.3 mg, 0.215 mmol) and tosyl-Cl (246 mg, 1.292 mmol) at 0 °C. The reaction mixture was stirred under nitrogen atmosphere at 25 °C for 3 h. Reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 85 mL). Combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Crude compound was purified by Biotage using 80 g silica (230-400 mesh) cartridge and compound eluted with 70% EtOAc in pet ether. Pure fractions were combined and concentrated under reduced pressure. Obtained compound was triturated with 10% diethyl ether in pentane and dried under reduced pressure to afford **PP-3**. M/Z (ESI): 619.33 [M+H]⁺.

¹H NMR (400 MHz, DMSO-d₆) δ = 10.49 (s, 1H), 8.82 (d, J = 1.2 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 8.06-8.25 (m, 3H), 7.86 (d, J = 8.4 Hz, 2H), 7.47-7.60 (m, 3H), 6.87 (dd, J = 9.4 Hz, 3.4 Hz, 1H), 6.45 (d, J = 8.8 Hz, 1H), 5.27-5.36 (m, 1H), 4.50-4.60 (m, 1H), 4.16-4.40 (m, 4H), 4.03 (d, J = 12.8 Hz, 1H), 3.95 (dd, J = 10.0 Hz, 2.8 Hz, 2H), 3.16-3.29 (m, 2H), 3.04 (td, J = 11.8 Hz, 3.4 Hz, 1H), 2.46 (s, 3H), 1.08 (d, J = 6.4 Hz, 3H).

Radiosynthesis Procedures

Synthesis of [³H]-1: [3H]-(S)-6-methoxy-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0247] Crabtree's catalyst (0.15 mg) was added to a Tritium reaction vessel, followed by a solution of Compound **1** (0.5 mg) in CH_2Cl_2 (0.2 mL). The vessel was attached to the Tritium line and pressurized to 0.5 atm with Tritium gas at -200°C . The solution was stirred for 17 hours, cooled to -200°C and excess gas removed. The reaction flask was rinsed with $4 \times 1\text{ mL CH}_3\text{OH}$ transferring each to a 100 mL recovery flask. The combined CH_3OH was removed under vacuum. Crude yield: 90 mCi. The material was purified by HPLC. Mobile phase was removed under vacuum and the product was re-dissolved in absolute Ethanol. Yield: 20.6 mCi, purity $>99\%$. The Specific Activity was determined to be 81.04 Ci/mmol by mass spectrometry; MW for $\text{C}_{21}\text{H}_{20}\text{T}_3\text{N}_7\text{O}_2$ $[\text{M}+\text{H}]^+$: 411.5, found: 412.4.

HPLC Preparatory Separation Conditions

Method: 0-70%8 in 20 minutes

Column: Phenomenex Luna 5flm C18 100 x 21.2mm

Flow Rate: 4 mL/min

Injection Volume: 0.5 mL

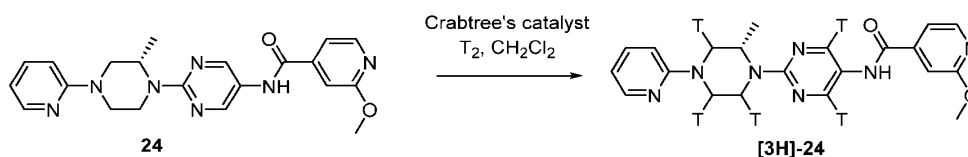
Detection: UV @ 254nm

Mobile Phase A: 0.05%TFA in H_2O

Mobile Phase B: CH_3CN

Product Elution Time: 16.7 minutes

Synthesis of [^3H]-**24**: [^3H]-2-methoxy-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-4-carboxamide



[0248] Crabtree's catalyst (0.3 mg) was added to a Tritium reaction vessel, followed by a solution of Compound **24** (0.4 mg) in CH_2Cl_2 (0.2 mL). The vessel was attached to the Tritium line and pressurized to 0.5 atm with Tritium gas at -200°C . The solution was stirred for 17 hours,

cooled to -200° C and excess gas removed. The reaction flask was rinsed with 4 x 1 mL CH₃OH transferring each to a 100 mL recovery flask. The combined CH₃OH was removed under vacuum. Crude yield: 125 mCi. The material was purified by HPLC. Mobile phase was removed under vacuum and the product was re-dissolved in absolute Ethanol. Yield: 26 mCi, purity >99%. The Specific Activity was determined to be 150.01 Ci/mmol by mass spectrometry; MW for C₂₁H₂₀T₃N₇O₂ [M+H]⁺: 415.5, found: 416.3.

HPLC Prep

Method: 10%8 for 5 minutes; 10-90%8 in 20 minutes

Column: Phenomenex Luna Sum C18 100 x 21.2mm

Flow Rate: 4 mL/min

Injection Volume: 0.5 mL

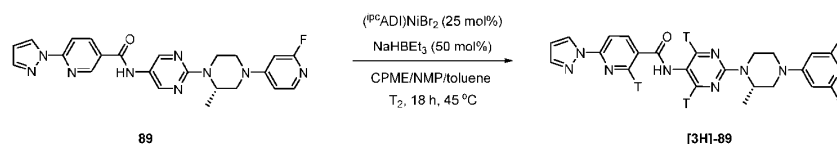
Detection: UV @ 254nm

Mobile Phase A: 0.05% TFA in H₂O

Mobile Phase B: CH₃CN

Product Elution Time: 18.1 minutes

Synthesis of [³H]-89: [3H]-(S)-N-(2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide



[0249] Compound **89** in CH₂Cl₂ was washed with 0.5 M Na₂CO₃ aq. solution, then the organic layer was dried with Na₂SO₄ and the filtrate was evaporated to dryness. The resulting residue (4 mg) was dissolved in CPME (75 μL) and NMP (50 μL). In a glove box, the nickel precatalyst (iPr)₂ADINiBr₂ (6.65 mg) was dissolved in CPME (670 μL) and treated with NaHBEt₃ in toluene (1 M, 23 μL) then stirred for 5 minutes. The substrate solution (100 μL) was added to the active catalyst solution (100 μL) in a tritiation vessel and secured with a portable Swagelok® valve. The valve was attached to the Trisorber and subjected to two freeze-pump-thaw cycles before 155 mmHg tritium gas was introduced. The reaction was thawed, then placed in an oil bath at 45 °C and stirred overnight. After capture of spent tritium on the waste bed, the reaction was transferred into a vial with 10 mL saturated aqueous sodium bicarbonate. The mixture was extracted three times with dichloromethane. The combined organic layers were dried with

sodium sulfate and evaporated. The residue was dissolved in EtOH for LSC and radio-HPLC analysis. Crude yield: 247.2 mCi; RCP: 90%. The material was purified by HPLC. The collected fractions were diluted with an equal volume of water, concentrated on a pair of C18 cartridges and eluted with EtOH. Yield: approx. 20 mL ethanol soln @ 4.22 mCi/mL. The Specific Activity was determined to be 55.52 Ci/mmol by mass spectrometry; MW for C₂₃H₁₉T₄FN₉O [M+H]⁺: 468.2, found: 468.3.

HPLC Analytic Conditions

Method: 10-95%B in 15 minutes, 6 min re-equilibration

Column: Gemini NX C18, 4.6 x 50 mm, 3.5 mm @ 40 °C

Flow Rate: 1 mL/min

Injection Volume: 1 uL

Detection: UV @ 298 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Product Elution Time: 7.08 minutes

HPLC Preparatory Separation Conditions

Column: Gemini NX C18, 10 x 250 mm @ 40 °C

Flow Rate: 5 mL/min

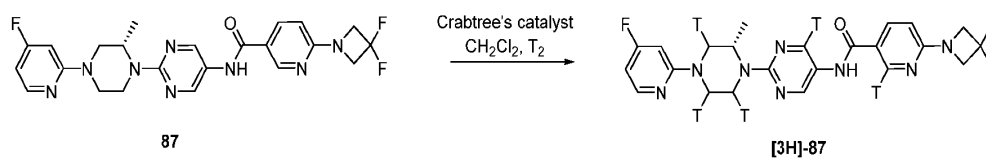
Injection Volume: 0.4 mL

Detection: UV @ 298 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Synthesis of [³H]-87: [³H]-(S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0250] Compound **87** (0.50 mg, 1.03 umol) was weighed into a tritiation vessel. Crabtree's catalyst (1.12 mg, 0.51 umol) was prepared as a solution in CH₂Cl₂ (1.4 mL). The catalyst solution (500 μL) was added to the tritiation vessel which was attached to the ultra torr port on

the Trisorber and subjected to two freeze-pump-thaw cycles before 84 mmHg tritium gas was introduced. The reaction was thawed to room temperature then stirred 4 hours. After capture of spent tritium on the waste bed, the reaction was transferred into a vial with 10 mL saturated aqueous sodium bicarbonate. The mixture was extracted three times with dichloromethane. The combined organic layers were dried with sodium sulfate and evaporated. The residue was dissolved in EtOH for LSC and radio-HPLC analysis. Crude yield: 204.4 mCi; RCP: 89%. The material was purified by HPLC. The collected fractions were diluted with an equal volume of water, concentrated on a pair of C18 cartridges and eluted with EtOH. A portion of the purified batch was dispensed and diluted to 20.0 mL. Yield: 20.0 mL ethanol soln @ 2.45 mCi/mL. The Specific Activity was determined to be 131.4 Ci/mmol by mass spectrometry; MW for $C_{23}H_{19}T_3F_3N_8O$ $[M+H]^+$: 495.2, found: 495.3.

HPLC Analytic Conditions

Method: 10-95%B in 15 minutes, 6 min re-equilibration

Column: Gemini NX C18, 4.6 x 50 mm, 3.5 mm @ 40 °C

Flow Rate: 1 mL/min

Injection Volume: 1.5-2.0 uL

Detection: UV @ 304 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Product Elution Time: 7.63 minutes

HPLC Preparatory Separation Conditions

Method: Isocratic (A:B = 55:45)

Column: Gemini NX C18, 10 x 250 mm @ 40 °C

Flow Rate: 5 mL/min

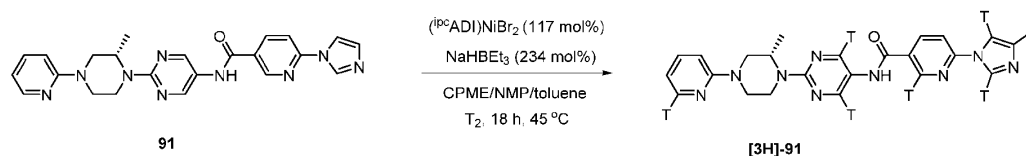
Injection Volume: 0.5 mL

Detection: UV @ 304 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Synthesis of [³H]-91: [3H]-(S)-6-(1H-imidazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide



[0251] In a glove box, Compound **91** (1.33 mg, 3.0 μmol) was dissolved in CPME (75 μL) and NMP (25 μL). The nickel pre-catalyst (i^{ipc} ADI)NiBr₂ (6.73 mg) was dissolved in CPME (670 μL) and treated with NaHBEt₃ in toluene (1 M, 25 μL) then stirred for 5 minutes. The substrate solution (100 μL) was combined with the active catalyst solution (200 μL , 3.5 μmol) in a tritiation vessel and secured with a portable Swagelok® valve. The valve was attached to the Trisorber and subjected to two freeze -pump-thaw cycles before 102 mm tritium gas was introduced. The reaction was thawed, then placed in an oil bath at 45 °C and stirred overnight. After capture of spent tritium on the waste bed, the reaction was transferred into a vial with 10 mL saturated aqueous sodium bicarbonate. The mixture was extracted three times with dichloromethane. The combined organic layers were dried with sodium sulfate and evaporated. The residue was dissolved in EtOH for LSC and radio-HPLC analysis. Crude yield: 120 mCi; RCP: 67%. The material was purified by HPLC. The collected fractions were diluted with an equal volume of water, concentrated on a pair of C18 cartridges and eluted with EtOH. Yield: approx. 20 mL ethanol soln @ 3.18 mCi/mL. The Specific Activity was determined to be 44.9 Ci/mmol by mass spectrometry; MW for C₂₃H₁₇T₇N₉O [M+H]⁺: 456.3, found: 456.0.

HPLC Analytic Conditions

Method: 10-95%B in 12 minutes, hold 3 min, 6 min re-equilibration

Column: Gemini NX C18, 4.6 x 50 mm, 3.5 mm @ 40 °C

Flow Rate: 1 mL/min

Injection Volume: 1.0 μL

Detection: UV @ 294 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Product Elution Time: 6.32 minutes

HPLC Preparatory Separation Conditions

Method: Isocratic (A:B = 65:35)

Column: Gemini NX C18, 10 x 250 mm @ 40 °C

Flow Rate: 5 mL/min

Injection Volume: 0.5 mL

Detection: UV @ 295 nm

Mobile Phase A: 0.05 M pH 10 TEAA in H₂O

Mobile Phase B: CH₃CN

Assay Protocols

Acquisition of Human Post-Mortem Tissue Samples for *In Vitro* Binding Assays

[0252] Frozen human brain tissues from Parkinson's Disease (PD) patients were purchased from Analytic Biological Services Inc. The samples were postmortem tissues from donors with clinical diagnosis of late stage of PD. Alpha-synuclein, tau and amyloid burden was determined through a combination of immunohistochemistry on frozen thin coronal sections, as well as alpha-Lisa-based quantification of protein levels in a detergent insoluble protein fraction. A tissue sample of temporal cortex was identified from one donor as having moderate to high alpha-synuclein burden, low amyloid and minimal to no tau pathology. The detergent insoluble fraction of temporal cortex from this patient was used to support homogenate binding studies.

Preparation Detergent Insoluble Fraction of Human Brain Tissue for *In Vitro* Binding Studies

[0253] Grey matter was dissected out of the temporal cortex tissue with a dissecting blade and minced with fine dissecting scissors. To prepare insoluble fractions, minced tissue was homogenized in ice cold TBS-TX buffer (50mM Tris + 150 mM NaCl + 1% Triton X100 + 1mM EDTA + 1 tablet/10mL of Complete Protease inhibitor + 1 tablet / 10mL PHOSSTOP phosphatase inhibitor tablet) with glass Dounce tissue grinder. Homogenates were centrifuged at 100,000 x g for 45 minutes. The pellet was resuspended in TBS-TX buffer, using a Polytron at highest setting for 30 seconds at 4 °C. Homogenates were centrifuged at 100,000 x g for 45 minutes and the pellet was resuspended in TBS-TX buffer. A BCA protein assay was performed on the final homogenate to determine the protein concentration. Homogenates were aliquoted in 0.5 ml/tube and stored at -70 °C until use.

Procedures for Alpha-Synuclein Tissue Homogenate Binding Assays (Assay 1)

[0254] For hot saturation binding assay, various concentrations of radioligand were prepared in Assay Buffer (DPBS plus 0.1% BSA) for final concentrations of radioligand ranging from 0.84 to 50 nM of [³H]-1. 25 µl of radioligand was added to 200 µl of insoluble fractions of PD brain

homogenates diluted to 150 µg/ml in Assay Buffer (incubation, filtration, and determination of amount of radioligand used in assay are described below). Self-block with unlabeled compound was used to determine non-specific binding. Saturation data was analyzed using GraphPad/Prism software.

[0255] FIG. 2 depicts a saturation binding experiment using [3H]-1 and a triton-insoluble fraction of temporal cortex PD tissue enriched in aggregated alpha-synuclein. This data supports the use of this ligand in radioligand binding assays to optimize potency toward binding pathological alpha synuclein. FIG. 2 shows an example of hot saturation binding of [3H]-1, where the radioligand shows high affinity for alpha synuclein in PD brain homogenates with measured dissociation constant of 25 nM.

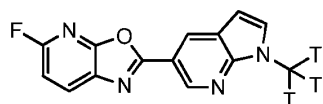
[0256] For displacement alpha synuclein binding assay, unlabeled test compounds were dissolved in DMSO at 10 mM. Dilutions of test compounds to various concentrations were made in 100% DMSO at 1000 x final assay concentration and 0.225 µl aliquots were dispensed into assay plates. Insoluble fractions of PD brain homogenates were diluted to 50 µg/ml from original 10 mg/ml volume in Assay Buffer, and 200 µl were added to the assay plate for a final concentration of 10 µg per well. [3H]-1 was prepared at 10x final concentration in Assay Buffer and 25 µl was added to the assay plate for final assay concentration of 2.0 nM. 200 µL homogenates and 25µL radioligand were added into the assay plates dispensed with titrated compounds. The plates were incubated at RT for 90 minutes. Unbound and bound ligand were separated by filtration of bound onto GF/C filter plates (pre-treated for 60 min with 0.2% PEI at 4 °C) using a Perkin Elmer FilterMate Harvester Unifilter-96 and washing away unbound with 1ml ice cold DPBS three times. Dry filter plates (1 hour at 47 °C with vacuum in oven or overnight at room temp). 50 µl per well Microscint-20 (Perkin Elmer) was added to the plates and plates were counted 1 minute per well on Perkin Elmer TopCount. Data was analyzed using IDBS Activity Base to determine K_i values shown in Data Table 1 (K_d value 25 nM, ligand concentration 2.0 nM; FIG. 2).

Competitive radioligand binding to pathological aggregated beta amyloid in AD tissue (Assay 2):

[0257] Frozen human brain samples of Alzheimer's disease (AD) were purchased from Analytic Biological Services Inc. The samples were postmortem tissue from donors with clinical diagnosis of AD and much of the white matter was dissected out of the frontal cortex in order to enrich the tissue preparations for gray matter. Brain homogenates of gray matter enriched frontal cortex were prepared by homogenizing the tissue in ice cold Phosphate Buffered Saline (PBS), pH 7.4 at 80 mg wet weight tissue per 1 ml for 45 seconds at 4°C on setting 16 of Polytron. The

homogenate was further diluted with ice cold PBS to 30 mg wet weight tissue per 1 ml and homogenized for an additional minute as described above. Homogenates were aliquoted in 5 ml/tube and stored at -70 °C until use.

[0258] Radioligand [³H]-105, prepared as described in ACS Med. Chem. Lett., Vol. 2, pages 498-502, was used in this assay.



[³H]-105

[0259] For hot saturation binding assay, various concentrations of radioligand, [³H]-105 were prepared in Assay Buffer (PBS plus 0.1% BSA) plus 20% DMSO ranging from 3.9 to 500 nM. 25 ul of radioligand was added to 200 ul of crude brain homogenates (diluted to 0.5 mg/ml in Assay Buffer) for final concentration of radioligand ranging from 0.39 to 50 nM and final crude brain homogenates of 100 ug wet weight/assay well (incubation, filtration, and determination of amount of radioligand used in assay are described below). Self-block with unlabeled compound was used to determine non-specific binding. Saturation data was analyzed using Graphpad/Prism software.

[0260] FIG. 1 depicts high affinity saturation binding of [³H]-105 to AD cortical tissue homogenate enriched in aggregated beta-amyloid pathology. FIG. 1 shows an example of hot saturation binding of [³H]-105, where the radioligand shows high affinity for aggregated beta amyloid (abeta) in AD brain homogenates with measured dissociation constant of 11 nM. This data supports the use of this ligand in radioligand binding assays to screen for binding to aggregated beta-amyloid.

[0261] For Assay 2 unlabeled test compounds were dissolved in DMSO at 10 mM. Dilutions of tests compounds to various concentrations were made in 100% DMSO at 1000x final assay concentration and 0.225 ul aliquots were dispensed into assay plates. Brain homogenates were diluted to 0.5 mg/ml from original 30 mg/ml volume in Assay Buffer, and 200 ul were added to the assay plate for a final concentration of 100 ug wet weight/assay well. [³H]-105 was prepared at 10x final concentration in Assay Buffer plus 20% DMSO and 25 ul was added to the assay plate for final assay concentration of 3.0 nM. The plates were incubated at 37 °C for 90 minutes. Unbound and bound ligand were separated by filtration of bound onto GF/B filter plates (pre-treated for 30 min with 0.1% PEI) using a Packard Filtermate and washing away unbound with 2.5 ml ice cold 5 mM Tris at pH 7.4. Filter plates were dried for 1 hr at 57°C and 50 ul

Microscint was added to each well of the plate. The plates were counted for 3H cpm for 1 min per well using PerkinElmer TopCount. Data was analyzed using IDBS Activity Base to determine K_i values shown below in Data Table 1 (K_d value 11.0 nM, ligand concentration 3.5 nM).

Radioligand Binding Data in triton-extracted alpha-synuclein from PD Tissue (Assay 1) and A β -rich AD Tissue (Assay 2) – Data Table 1

(ND = Not Determined)

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
1	60	633	11
2	9	10810	1172
3	10	5850	576
4	14	10810	792
5	15	10810	720
6	22	2162	99
7	24	4545	187
8	26	2162	83
9	28	3085	110
10	30	3619	121
11	31	5996	193
12	36	1225	34
13	43	10810	249
14	52	4699	90
15	62	10810	175
16	66	10810	163
17	79	10810	137
18	85	3937	47
19	86	1538	18
20	93	3603	39
21	94	4595	49

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
22	97	2397	25
23	18	582	32
24	29	590	20
25	34	723	22
26	67	890	13
27	71	552	8
28	82	526	6
29	93	799	9
30	137	10810	79
31	113	2579	23
32	157	2862	18
33	185	3747	34
34	132	4526	34
35	158	10810	68
36	175	10810	62
37	2	10810	4680
38	3	10810	3615
39	3	10810	3593
40	6	10810	1869
41	7	10810	1510
42	9	2773	323
43	25	5762	231
44	40	10810	268
45	43	10810	249
46	54	10810	201
47	9	1388	155
48	14	10810	771
49	15	2383	155
50	21	10810	517
51	26	10810	421

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
52	28	5318	187
53	36	10810	299
54	43	5521	130
55	54	1459	27
56	55	4291	78
57	60	3700	61
58	64	3449	54
59	70	5152	73
60	71	4121	58
61	78	10810	139
62	30	576	19
63	5	10810	2208
64	3	10810	4182
65	3	2453	801
66	5	3429	752
67	5	3603	696
68	6	10810	1842
69	8	10810	1313
70	9	10810	1217
71	9	3603	400
72	9	10810	1141
73	11	10810	952
74	13	10810	839
75	13	1710	132
76	21	3062	145
77	21	4219	199
78	22	2762	125
79	23	2007	88
80	35	10810	313
81	41	10810	263

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
82	44	10810	246
83	55	10810	195
84	73	10810	148
85	6	942	147
86	14	691	51
87	3.8	12000	3158
88	2.8	12000	4286
89	5.1	10	2
90	30	ND	ND
91	5.9	55	9
92	1.0	12000	12000
93	2.0	12000	6000
94	2.1	12000	5714
95	2.4	310	129
96	2.8	12000	4286
97	2.8	2620	936
98	4.4	10000	2273
99	4.8	330	69
100	5.3	12000	2264
101	6.4	20	3
102	6.5	12000	1846
103	7.0	4000	571
104	8.3	220	27
105	9.4	12000	1277
106	11	12000	1091
107	14	12000	857
108	14	12000	857
109	15	30	2
110	20	12000	600
111	30	12000	400

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
112	5.3	12000	2264
113	2.0	12000	6000
114	9.0	12000	1333
115	3.9	ND	ND
116	2.7	ND	ND
117	1.8	ND	ND
118	0.4	ND	ND
119	1.8	ND	ND
120	1.0	ND	ND
121	13	ND	ND
122	1.3	ND	ND
123	0.6	ND	ND
124	2.0	ND	ND
125	36	ND	ND
126	9.2	ND	ND
127	7.6	ND	ND
128	1.7	ND	ND
129	1.3	ND	ND
130	1.6	ND	ND
131	1.9	ND	ND
132	4.5	ND	ND
133	3.7	ND	ND
134	3.7	ND	ND
135	2.9	ND	ND
136	3.0	ND	ND
137	3.0	ND	ND
138	2.3	ND	ND
139	4.9	ND	ND
140	8.7	ND	ND
141	1.2	ND	ND

Example Number	α -synuclein Tissue K_i (Assay 1, nM)	A β Tissue K_i (Assay 2, nM)	Selectivity ratio (Assay 2/Assay 1)
142	3.1	ND	ND
143	3.3	ND	ND
144	1.5	ND	ND

[0262] Procedure for radioligand saturation binding data in human cortical PD tissue homogenate enriched in aggregated alpha-synuclein and human cortical AD tissue homogenate enriched in aggregated A β pathology:

[0263] The Banner Parkinson's disease (PD; Braak Stage 5/6) brain homogenates were obtained through the Michael J. Fox Foundation (MJFF) tissue consortium. Characterization of such brain tissue, as well as preparation of the tissue for binding studies, was done as described in US 2019/0256492, paragraphs 0242-0244. The Banner PD brain homogenates, which are postmortem brain tissue from donors who were diagnosed with PD, were prepared using cingulate cortex collected from multiple PD brains, which were rich of alpha-synuclein pathology, but free from amyloid pathology and tauopathy by neuropathological validation. The final concentration of Banner PD brain homogenates was 333 mg wet tissue per 1mL buffer. Homogenates were aliquoted in 1mL/tube and stored at -70°C prior to use.

[0264] The frozen human brain samples of Alzheimer's disease (AD) were purchased from Analytic Biological Services Inc. They are postmortem tissue from donors with clinical diagnosis of AD and validated by IHC for amyloid pathology. Brain homogenates of frontal cortex were prepared by homogenizing the frontal cortex in ice cold Phosphate Buffered Saline (PBS), pH 7.4, for 30 seconds at 4°C on setting 6 of Polytron. The final concentration of brain homogenates was 10mg wet tissue per 1mL buffer. Homogenates were aliquoted in 5mL/tube and stored at -70°C prior to use.

[0265] [3 H]-1 was synthesized as described in the procedures outlined above. The specific activity of [3 H]-1 is 196.6 Ci/mmol in a volume of 3.9 mCi/mL.

[0266] The hot saturation binding assays used to assess radioligand binding to Banner PD brain homogenates and ABS AD brain homogenates were done separately at nine concentrations from 60.0 nM to 0.6 nM. Brain homogenates were diluted to 2.0 mg/mL (ABS AD) or 2.8 mg/mL (Banner PD) from original 30mg/mL volume with PBS buffer. Total binding was defined in the absence of competing compound, and non-displaceable binding was determined in the presence of 1 μ M unlabeled self-block. Assay buffer was 30 nM Tris pH 7.5 containing 0.1% BSA. The

assay tubes were pre-incubated at room temperature for 30 minutes, then radioligand dilutions (10X) were added into the assay tube (10 μ L each / per tube, separately) to a final volume of 100 μ L per tube. Incubation was carried out at 37°C for 120 minutes, and then the assay samples were filtered onto GF/C filters using Skatron 12 well harvester, washing on setting 5 – 5 – 5 (~ 3x2ml) ice cold buffer (30 nM Tris pH 7.5). The GF/C filter papers for Skatron harvester were pre-soaked in 0.1% BSA for 1 hour at room temperature before use. Filters were punched into scintillation vials and counted in 2mL Ultima Gold on Perkin Elmer Tri-Carb 2900TR for 1 minute. The data analysis was done with Prism software. All assays were done in triplicate, and in the laboratory designated for studies using human tissues.

[0267] The assays on [3 H]-24 were performed in analogous fashion to [3 H]-1.

[0268] Data for these saturation binding assays using [3 H]-1 and [3 H]-24 are illustrated in FIGS. 3-6. Specifically, FIG. 3 depicts a saturation binding experiment using [3 H]-1 and PD cingulate cortical tissue homogenate enriched in aggregated alpha-synuclein. This data demonstrates potent binding to pathological alpha-synuclein in tissue homogenate. FIG. 4 depicts a saturation binding experiment using [3 H]-1 and AD tissue homogenate enriched in aggregated beta-amyloid pathology. (ND= Not determined due to incomplete saturation of binding signal.) This data demonstrates weak binding to pathological beta-amyloid in tissue homogenate. FIG. 5 depicts a saturation binding experiment using [3 H]-24 and PD cortical tissue homogenate enriched in aggregated alpha-synuclein. This data demonstrates potent binding to pathological alpha-synuclein in tissue homogenate. FIG. 6 depicts a saturation binding experiment using [3 H]-24 and AD tissue homogenate enriched in aggregated beta-amyloid pathology. (ND= Not determined due to incomplete saturation of binding signal.) This data demonstrates weak binding to pathological beta-amyloid in tissue homogenate.

In vitro binding of alpha synuclein tracers in human PD brain tissue homogenates

[0269] The frozen human brain samples of Parkinson's disease (PD) were provided by Banner Sun Health Institute (USA) through collaboration with Michael J Fox Foundation (MJFF). They are postmortem tissue from donors with clinical diagnosis of PD and neuropathological validation of PD pathology. Brain homogenates of cerebral cortex were prepared by homogenizing the cortex in ice cold Phosphate Buffered Saline (PBS), pH 7.4, for 30 seconds at 4°C on setting 6 of Polytron. The final concentration of brain homogenates was 30mg wet tissue per 1mL buffer. Homogenates were aliquoted in 1mL/tube and stored at -70°C prior to use.

[0270] [3 H]-87 was synthesized and the specific activities of [3 H]-87 is 131.5 Ci/mmol. For hot saturation binding assay, 9 concentrations of radioligand were used, ranging from 50nM to

0.5 nM and from 10 nM to 0.1 nM. Brain homogenates were diluted from original 30 mg/mL volume to final concentration of 2.8 mg/mL with assay buffer (Tris, pH 7.5, 0.1% BSA), and 250 μ L per assay tube was used in assay. Unlabeled test compounds were dissolved in DMSO at 1mM. Dilution of test compound to various concentrations was made with assay buffer containing 2% DMSO. Total binding was defined in the absence of competing compound, and non-displaceable binding was determined in the presence of 1 μ M unlabeled self block. Compound dilutions (10X) were added into the assay tube (25 μ L each / per tube, separately) containing 200 μ L brain homogenate dilution, and pre-incubate the tubes at room temperature for 30 minutes, then radioligand dilutions (10X) were added into the assay tube (25 μ L each / per tube, separately) to a final volume of 250 μ L per tube. Incubation was carried out at 37°C for 120 minutes, and then the assay samples were filtered onto GF/C filters using Skatron 12 well harvester, washing on setting 5 – 5 – 5 (~ 3x2ml) ice cold buffer (Tris, pH 7.5). GF/C filter papers for Skatron harvester were pre-soaked in 0.1% BSA for 1 hour at room temperature before use. Filters were punched into scintillation vials. Add liquid scintillation fluid (2mL Ultima Gold) into each vial, allow to soak into filters for 4 hours and counted in on Perkin Elmer Tri-Carb 2900TR for 1 minute. The data analysis was done with Prism software. All assays were done in either duplicate or triplicate, depending on assay setting, in the laboratory designated for studies using human tissues.

Data Table 2 – In Vitro Binding data for [³H]-87 in human Parkinson's Disease tissue homogenates

[³ H]-87	PD Cortex
B _{max} (nM)	5.0
K _d (nM)	0.2
B _{max} / K _d	25

[0271] [³H]-89 was synthesized and the specific activities of [³H]-89 is 55.5 Ci/mmol. For hot saturation binding assay, nine concentrations of radioligand were used, ranging from 50nM to 0.5 nM. Brain homogenates were diluted from original 30 mg/mL volume to final concentration of 2.8 mg/mL with assay buffer (Tris, pH 7.5, 0.1% BSA), and 250 μ L per assay tube was used in assay. Unlabeled test compounds were dissolved in DMSO at 1mM. Dilution of test compound to various concentrations was made with assay buffer containing 2% DMSO. Total binding was defined in the absence of competing compound, and non-displaceable binding was determined in

the presence of 1 μ M unlabeled self block. Compound dilutions (10X) were added into the assay tube (25 μ L each / per tube, separately) containing 200 μ L brain homogenate dilution, and pre-incubate the tubes at room temperature for 30 minutes, then radioligand dilutions (10X) were added into the assay tube (25 μ L each / per tube, separately) to a final volume of 250 μ L per tube. Incubation was carried out at 37°C for 120 minutes, and then the assay samples were filtered onto GF/C filters using Skatron 12 well harvester, washing on setting 5 – 5 – 5 (~ 3x2ml) ice cold buffer (Tris, pH 7.5). GF/C filter papers for Skatron harvester were pre-soaked in 0.1% BSA for 1 hour at room temperature before use. Filters were punched into scintillation vials. Add liquid scintillation fluid (2mL Ultima Gold) into each vial, allow to soak into filters for 4 hours and counted in on Perkin Elmer Tri-Carb 2900TR for 1 minute. The data analysis was done with Prism software. All assays were done in either duplicate or triplicate, depending on assay setting, in the laboratory designated for studies using human tissues.

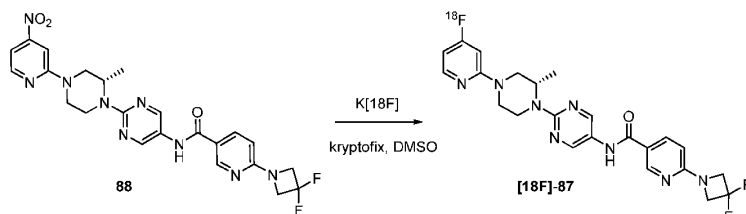
Data Table 3– In Vitro Binding data for [3 H]89 in human Parkinson's Disease tissue homogenates

[3 H]-89	PD Cortex
B _{max} (nM)	134
K _d (nM)	2.9
B _{max} / K _d	46

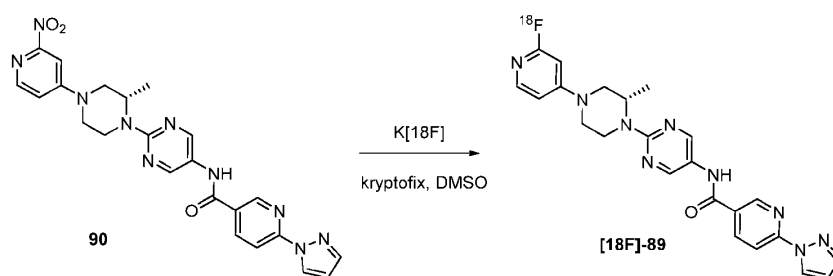
Radiochemical Synthesis of [18 F]-Ligands

General Methods

[0272] [18 F]Fluoride was concentrated on an anion exchange resin and eluted prior to use. Unless specifically stated, the [18 F]fluoride containing anion exchange resin was eluted with Kryptofix 222 (7 mg, 19 μ mol) and K₂CO₃ (2.1 mg, 15 μ mol) in acetonitrile/water (80/20, 0.7 ml) and transferred to a vented 1-ml V-shaped vial in a microwave cavity. The fluoride was dried under argon flow and microwave heating (35 W/90 °C). Additional aliquots of acetonitrile (3 x 0.5 ml) were added for azeotropic drying at 35 W/90 °C.

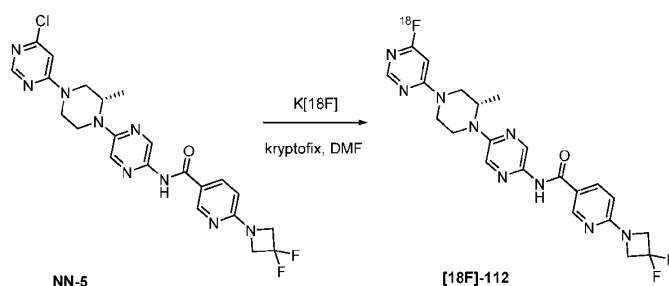
Synthesis of [¹⁸F]-87

[0273] A solution of **88** (0.5 mg, 1.0 μ mol) in DMSO (0.3 mL) was added to the microwave vial containing the dry [¹⁸F]fluoride, the vent line was removed, and the reaction mixture was heated at 170 °C (60 W) for 3 min. After cooling down to < 50 °C, the reaction was diluted with H₂O (0.8 mL), mixed and injected into the semi-preparative HPLC column. The product was purified using Gemini, C6-Phenyl, 110A, 150X10 mm, at a flow rate of 5 mL/min. The mobile phase was acetonitrile / 0.1 % trifluoroacetic acid from 50 to 95 %. The radioactive fraction eluting between 12.5 and 13.5 minutes was collected, diluted with 20 mL of water for injection, and loaded into a Waters Sep-Pak Classic C18 cartridge (Waters, Milford, MA, USA). The Sep-Pak was rinsed with 10 mL of water and then eluted with ethanol (0.5 mL) into 10 mL sterile vial and diluted to the desired formulation. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a ONYX Monolithic, 5 μ , C18, 50X3 mm (Phenomenex) at a flow rate of 1 mL/min. The mobile phase was a mixture consisting of acetonitrile / 0.1% trifluoroacetic acid in water from 10 to 90 % in 10 min. Concentration of [¹⁸F]-**87** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **87**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [¹⁸F]-**87** was 6.3 min.

Synthesis of [¹⁸F]-89

[0274] A solution of **90** (0.5 mg, 1.0 μ mol) in DMSO (0.3 mL) was added to the microwave vial containing the dry [18 F]fluoride, the vent line was removed, and the reaction mixture was heated at 170 $^{\circ}$ C (60 W) for 3 min. After cooling down to < 50 $^{\circ}$ C, the reaction was diluted with H₂O (0.8 mL), mixed and injected into the semi-preparative HPLC column. The product was purified using Gemini, C6-Phenyl, 110A, 150X10 mm, at a flow rate of 5 mL/min. The mobile phase was acetonitrile/ 0.1 % trifluoroacetic acid: 65/35. The radioactive fraction eluting between 7.5 and 8.5 minutes was collected, diluted with 20 mL of water for injection, and loaded into a Waters Sep-Pak Classic C18 cartridge (Waters, Milford, MA, USA). The Sep-Pak was rinsed with 10 mL of water and then eluted with ethanol (0.5 mL) into 10 mL sterile vial and diluted to the desired formulation. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a ONYX Monolithic, 5 μ , C18, 50X3 mm (Phenomenex) at a flow rate of 1 mL/min. The mobile phase was a mixture consisting of acetonitrile / 0.1% trifluoroacetic acid in water from 10 to 90 % in 10 min. Concentration of [18 F]-**89** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **89**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [18 F]-**89** was 5.1 min.

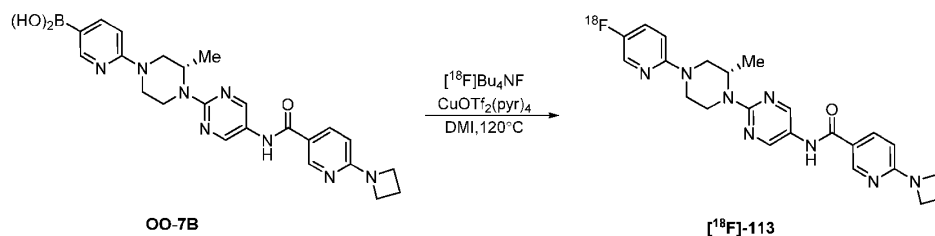
Synthesis of [18 F]-112



[0275] A solution of NN-5 (1.4 mg, 2.40 μ mol) in DMF (0.3 mL) was added to the microwave vial containing the dry [18 F]fluoride, the vent line was removed, and the reaction mixture was heated at 120 $^{\circ}$ C (110 W) for 3 min. After cooling down to < 50 $^{\circ}$ C, the reaction was diluted with H₂O (0.8 mL), mixed and injected into the semi-preparative HPLC column. The product was purified using Zorbax Eclipse XDB-C18 (Agilent), 5 μ , 9.4X250 mm HPLC column, at a flow rate of 5 mL/min. The mobile phase was acetonitrile / Na₂HPO₄ (10 mM) from 30 to 70% in 15 min. The radioactive fraction eluting between 14 and 15 minutes was collected in a flask

containing a 30% β -cyclodextrin solution (1mL), evaporated under negative pressure diluted with saline and transferred into a sterile container. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a ONYX Monolithic, 5 μ , C18, 50X3 mm (Phenomenex) at a flow rate of 1.5 mL/min. The mobile phase was a mixture consisting of acetonitrile / 0.1% formic acid in water from 5 to 50 % in 7 min. Concentration of [18F]-112 was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound 112, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [18F]-112 was 6.0 min.

Synthesis of [18F]-113

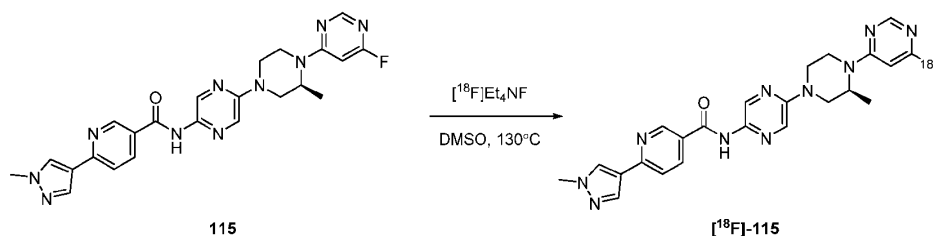


[0276] [18F]Fluoride was concentrated on an anion exchange resin which was pretreated by flushing with EtOH (10 mL) followed by 0.5M KOTf in H₂O (10 mL) and H₂O (10 mL) before use.

[0277] The [18F]fluoride containing anion exchange resin was eluted with tetrabutylammonium triflate (7.5 mg, 19 mmol) and cesium carbonate (0.1 mg, 0.3 mmol) in H₂O (0.5 mL), followed by CH₃CN (1.0 mL) into a vented 2.5 mL v-shaped vial and dried under argon flow using conventional heating at 100 °C. Additional aliquots of CH₃CN (2 x 0.5 mL) were added for azeotropic drying. The v-vial was flushed with air from a syringe (10 mL) and heated to 120 °C after which a solution of OO-7B (2.0 mg, 4.2 mmol), tetrakis(pyridine)copper(II) triflate (11.3 mg, 17 mmol) and pyridine (32 mL, 40 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI ; 0.5 mL) was added. The reaction mixture was heated at 120 °C for 20 min followed by transfer to a vial containing 10% CH₃CN/10 mM Na₂HPO₄ in H₂O pH 7.4 (1.0 mL) at room temperature for dilution, mixing and injection onto a semi-prep HPLC column. The product was purified using a Gemini C18, 5 mm, 110A, 150x10mm HPLC column (Phenomenex) with a flowrate of 5 ml/min and a mobile phase of CH₃CN / 10 mM Na₂HPO₄ pH 7.4 at a gradient of 30 – 50%. The radioactive fraction that eluted between 16.3 and 16.4 min was collected into a round bottom flask containing 10% captisol in H₂O (0.5 mL), evaporated under negative pressure and

transferred to a 10 mL sterile vial. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a Poroshell 120, 4 mm EC-C18 100x4.6mm HPLC column (Agilent) with a flowrate of 1.5 ml/min and a mobile phase of CH₃CN / 10 mM NH₄OAc pH 8.1 at a gradient of 35 – 45%. Concentration of [¹⁸F]-**113** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **113**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [¹⁸F]-**113** was 6.8 min.

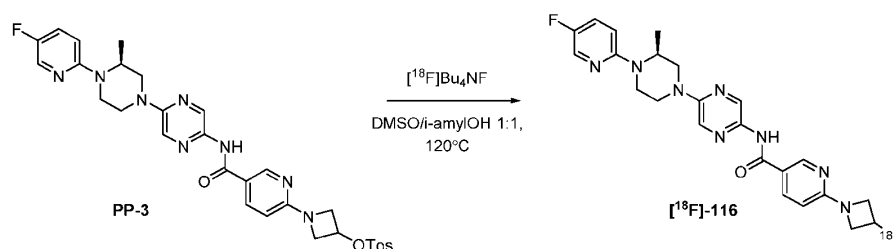
Synthesis of [¹⁸F]-115 by isotope exchange



[0278] The [¹⁸F]fluoride containing anion exchange resin was eluted with tetraethylammonium bicarbonate (4.2 mg, 22 mmol) in CH₃CN/H₂O 1:1 (1.0 mL), followed by CH₃CN (0.5 mL) into a vented 2.5 mL v-shaped vial and dried under argon flow using conventional heating at 100 °C. Additional aliquots of CH₃CN (2 x 0.5 mL) were added for azeotropic drying. The vial containing dried [¹⁸F]Et₄NF was heated to 130 °C after which a solution of **115** (0.3 mg, 0.6 mmol) in DMSO (0.5 mL) was added. The reaction mixture was heated at 130 °C for 10 min followed by transfer to a vial containing H₂O (0.8 mL) at room temperature for dilution, mixing and injection onto a semi-prep HPLC column. The product was purified using a Zorbax XDB-C18, 5 mm, 150x9.4mm HPLC column (Agilent) with a flowrate of 5 ml/min and a mobile phase of 30% CH₃CN / 10 mM Na₂HPO₄ pH 7.4. The radioactive fraction that eluted between 14.3 and 14.7 min was collected into a round bottom flask containing 10% captisol in H₂O (0.5 mL), evaporated under negative pressure to remove CH₃CN and transferred to a 10 mL sterile vial. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a Poroshell 120, 4 mm EC-C18 100x4.6mm HPLC column (Agilent) with a flowrate of 1.5 ml/min and a mobile phase of CH₃CN / 10 mM NH₄OAc pH 8.0 at a gradient of 30 – 40%. Concentration of [¹⁸F]-**115** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a

sample of compound **115**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [^{18}F]-**115** was 4.5 min.

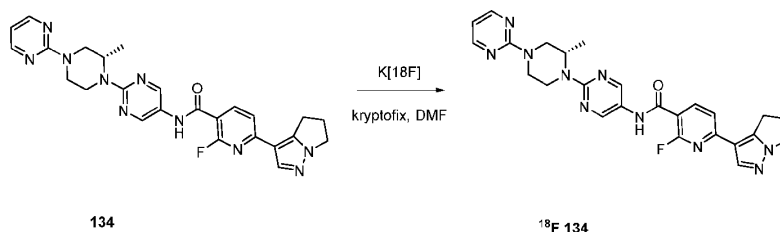
Synthesis of [^{18}F]-**116**



[0279] [^{18}F]Fluoride concentrated on an anion exchange resin which was pretreated by flushing with EtOH (10 mL) followed by 0.5M K_3PO_4 in H_2O (10 mL) and H_2O (10 mL) before use.

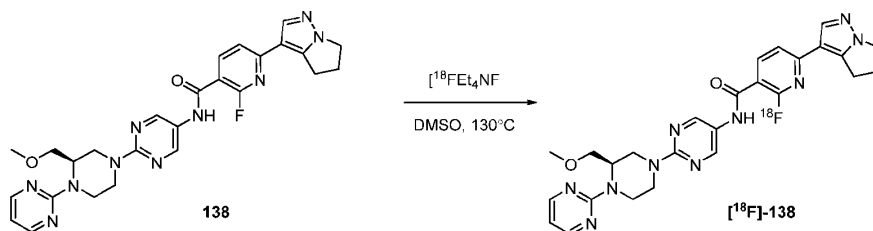
[0280] The [^{18}F]fluoride containing anion exchange resin was eluted with tetrabutylammonium mesylate (6.8 mg, 20 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 1:1 (1.0 mL), followed by CH_3CN (0.5 mL) into a vented 2.5 mL v-shaped vial and dried under argon flow using conventional heating at 100 °C. Additional aliquots of CH_3CN (2 x 0.5 mL) were added for azeotropic drying. The vial containing dried [^{18}F]Bu $_4$ NF was heated to 120 °C after which a solution of **PP-3** (0.9 mg, 1.5 mmol) in DMSO/iso-amyl alcohol 1:1 (0.5 mL) was added. The reaction mixture was heated at 120 °C for 10 min followed by transfer to a vial containing H_2O (1.0 mL) at room temperature for dilution, mixing and injection onto a semi-prep HPLC column. The product was purified using a Zorbax XDB-C18, 5 mm, 150x9.4mm HPLC column (Agilent) with a flowrate of 5 ml/min and a mobile phase of 30% CH_3CN / 10 mM Na_2HPO_4 in H_2O pH 7.4. The radioactive fraction that eluted between 21.5 and 22.1 min was collected into a round bottom flask containing 10% captisol in H_2O (0.5 mL), evaporated under negative pressure to remove CH_3CN and transferred to a 10 mL sterile vial. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a Poroshell 120, 4 mm EC-C18 100x4.6mm HPLC column (Agilent) with a flowrate of 1.5 ml/min and a mobile phase of CH_3CN / 10 mM NH_4OAc pH 8.0 at a gradient of 5 – 95%. Concentration of [^{18}F]-**116** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **116**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [^{18}F]-**116** was 6.6 min.

Synthesis of [^{18}F]-134 by isotope exchange



[0281] A solution of **134** (1.2 mg, 2.40 μ mol) in DMF (0.3 mL) was added to the microwave vial containing the dry [^{18}F]fluoride, the vent line was removed, and the reaction mixture was heated at 140 $^{\circ}\text{C}$ (25 W) for 3 min. After cooling down to $< 50\text{ }^{\circ}\text{C}$, the reaction was diluted with H_2O (0.8 mL), mixed and injected into the semi-preparative HPLC column. The product was purified using Zorbax Eclipse XDB-C18 (Agilent), 5 μ , 9.4X250 mm HPLC column, at a flow rate of 5 mL/min. The mobile phase was acetonitrile / Na_2HPO_4 (10 mM) from 40 to 70% in 15 min. The radioactive fraction eluting between 10 and 10.8 minutes was collected in a flask containing a 30% β -cyclodextrin solution (1mL), evaporated under negative pressure diluted with saline and transferred into a sterile container. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a ONYX Monolithic, 5 μ , C18, 50X3 mm (Phenomenex) at a flow rate of 1.5 mL/min. The mobile phase was a mixture consisting of acetonitrile / 0.1% formic acid in water from 5 to 90 % in 7 min. Concentration of [^{18}F]-**134** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **134**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [^{18}F]-**134** was 4.4 min.

Synthesis of [¹⁸F]-138 by isotope exchange



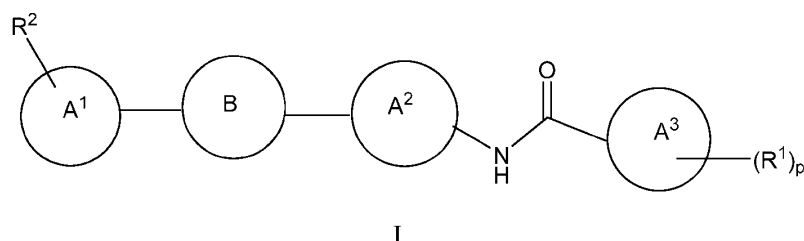
[0282] The [¹⁸F]fluoride containing anion exchange resin was eluted with tetraethylammonium bicarbonate (3.9 mg, 19 mmol) in CH₃CN/H₂O 1:1 (1.0 mL), followed by CH₃CN (0.5 mL) into a vented 2.5 mL v-shaped vial and dried under argon flow using conventional heating at 100 °C.

Additional aliquots of CH₃CN (2 x 0.5 mL) were added for azeotropic drying. The vial containing dried [¹⁸F]Et₄NF was heated to 130 °C after which a solution of **138** (0.2 mg, 0.4 mmol) in DMSO (0.5 mL) was added. The reaction mixture was heated at 130 °C for 10 min followed by transfer to a vial containing 10% CH₃CN/10 mM Na₂HPO₄ in H₂O pH 7.4 (0.8 mL) at room temperature for dilution, mixing and injection onto a semi-prep HPLC column. The product was purified using a Zorbax XDB-C18, 5 mm, 150x9.4mm HPLC column (Agilent) with a flowrate of 5 ml/min and a mobile phase of 35% CH₃CN / 10 mM Na₂HPO₄ in H₂O pH 7.4. The radioactive fraction that eluted between 16.7 and 17.2 min was collected into a round bottom flask containing 10% captisol in H₂O (0.5 mL), evaporated under negative pressure to remove CH₃CN, diluted with saline and transferred to a 10 mL sterile vial. The final product was tested for chemical and radiochemical purity by means of an analytical HPLC system (Agilent) using a Poroshell 120, 4 mm EC-C18 100x4.6mm HPLC column (Agilent) with a flowrate of 1.5 ml/min and a mobile phase of CH₃CN / 10 mM NH₄OAc pH 8.0 at a gradient of 35 – 45%. Concentration of [¹⁸F]-**138** was determined by means of an ultraviolet detector (254 nm). Confirmation of the identity of the product was determined by coinjection of a sample of compound **138**, and radiochemical purity was determined using a sodium iodide detector (Bioscan). The retention time for compound [¹⁸F]-**138** was 5.6 min.

[0283] While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-C_{1-6}$ alkyl, OR^c or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^d or halo;

R^d is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or

substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

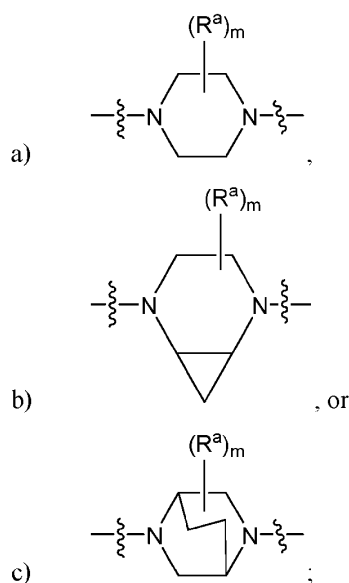
R^2 is selected from hydrogen, OR^c , NO_2 , halo or $-C_{1-6}alkyl$;

Ring A^1 is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R ;

Ring A^3 is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, imidazopyridinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine or phenyl;

Ring B is selected from



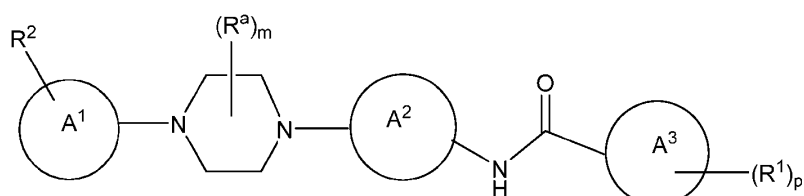
m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1, 2 or 3; and

q is selected from 1, 2 or 3.

2. The compound of Claim 1, having the structure of Formula IA:



IA

or a pharmaceutically acceptable salt thereof, wherein;

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^d or halo;

R^d is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is independently selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, $-NR_2$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, cycloalkyl, phenyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R² is selected from hydrogen, OR^c, halo or -C₁₋₆alkyl;

Ring A¹ is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A² is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R;

Ring A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2*H*-pyrido[3,2,*b*][1,4]oxazine or phenyl;

m is selected from 1, 2 or 3;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 0, 1, 2 or 3.

3. The compound of Claim 1 wherein:

Ring A¹ is selected from pyridyl, pyrazinyl or pyrimidinyl;

Ring A² is selected from pyrimidinyl, phenyl, or pyridyl, where said pyrimidinyl, phenyl, or pyridyl is optionally substituted with 1 to 3 groups of R;

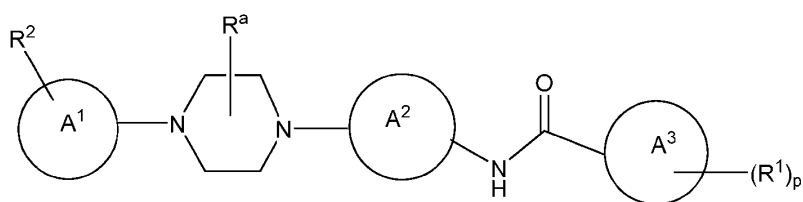
Ring A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, triazolyl or phenyl;

m is selected from 1 or 2; and

p is selected from 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 having the structure of Formula IB

**IB**

or a pharmaceutically acceptable salt thereof wherein;

R is independently selected from H, $-C_{1-6}$ alkyl or halo, where said alkyl is optionally substituted with one to three groups from $-C_{1-6}$ alkyl, OR^c or halo;

R^a is unsubstituted or substituted $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from $-C_{1-6}$ alkyl, halo, $-(CH_2)_nOR^c$, $-CN$, $-NR^c_2$, $-(CH_2)_n$ halogen, or $-O(CH_2)_n$ halo;

R^c is independently selected from H or $-C_{1-6}$ alkyl;

R^1 is selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-(CH_2)_nO(CH_2)_nOR^c$, halo, NR_2 , unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}$ alkyl;

Ring A^1 is selected from pyridyl, pyrazinyl, pyrazolyl, oxazolyl, thiazolyl or pyrimidinyl;

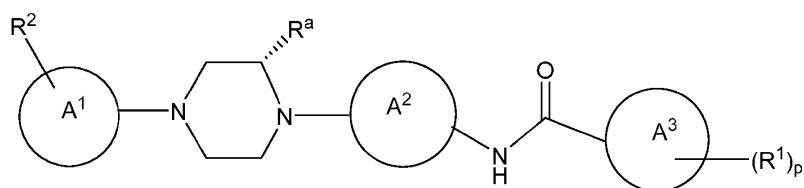
Ring A^2 is selected from pyrimidinyl, phenyl, pyridyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, or pyrazinyl is optionally substituted with 1 to 3 groups of R;

Ring A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, pyrrolopyrazinyl, oxadiazolyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine or phenyl;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 1 or 2.

5. The compound of Claim 1, having the structure of Formula IC



IC

or a pharmaceutically acceptable salt thereof wherein:

R is independently selected from H, -C₁₋₆alkyl or halo, where said alkyl is optionally substituted with one to three groups from -C₁₋₆alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted -C₁₋₆alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from -C₁₋₆alkyl, halo, -(CH₂)_nOR^c, -CN, -(CH₂)_nhalogen, or -O(CH₂)_nhalo;

R^c is independently selected from H or -C₁₋₆alkyl;

R¹ is independently selected from -(CH₂)_nOR^c, -(CH₂)_nO(CH₂)_nR, -(CH₂)_nO(CH₂)_nOR^c, halo, NR₂, unsubstituted or substituted C₁₋₆alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted C₃₋₁₀ cycloalkyl, unsubstituted or substituted heteroaryl or unsubstituted or substituted heterocyclyl, wherein said alkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl can be substituted with one to three groups of R^b;

R² is selected from hydrogen, OR^c, halo or -C₁₋₆alkyl;

Ring A¹ is selected from pyridyl, pyrazinyl, thiazolyl, pyrazolyl, oxazolyl or pyrimidinyl;

Ring A² is selected from pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl, where said pyrimidinyl, phenyl, pyridyl, pyrazinyl or pyridazinyl is optionally substituted with 1 to 3 groups of R;

Ring A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, indolyl, imidazolyl, pyrrolopyrazinyl, oxadiazolyl, triazolyl, thiazolyl, isoxazolyl, oxazolyl, 3,4-dihydro-2*H*-pyrido[3,2,*b*][1,4]oxazine or phenyl;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 0, 1, 2 or 3.

6. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A² is selected from pyrimidinyl, pyridyl or pyrazinyl, where said pyrimidinyl, pyridyl or pyrazinyl is optionally substituted with 1 to 3 groups of R.

7. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A² is pyrimidinyl, where said pyrimidinyl is optionally substituted with 1 to 3 groups of R.

8. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A³ is selected from pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, triazolyl or phenyl.

9. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A³ is selected from pyridyl, pyrazinyl or phenyl.

10. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A¹ is selected from pyridyl, pyrazinyl, pyrazolyl or pyrimidinyl.

11. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A¹ is selected from pyridyl or pyrazinyl.

12. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from -(CH₂)_nOR^c, -(CH₂)_nO(CH₂)_nR, -(CH₂)_nO(CH₂)_nOR^c, halo, -NR₂, unsubstituted or substituted C₁₋₆alkyl, cyclopropyl, imidazolyl, pyridyl, indolyl, pyrazolyl, triazolyl, azetidiny, phenyl, azepanyl, pyrrolopyrazinyl, pyrrolidinyl, azabicyclo-heptanyl, furyl, thiazolyl, pyrimidinyl, oxa-azabicycloheptanyl, pyridazinyl, thienyl, isoxazolyl, oxazolyl, dihydropyrrolylpyrazolyl, morpholinyl, tetrazolyl, or piperazinyl, where said alkyl, cyclopropyl, imidazolyl, pyridyl, indolyl, pyrazolyl, triazolyl, azetidiny, phenyl, azepanyl, pyrrolopyrazinyl, pyrrolidinyl, azabicyclo-heptanyl, furyl, thiazolyl, pyrimidinyl, oxa-azabicycloheptanyl, pyridazinyl, thienyl, isoxazolyl, oxazolyl, dihydropyrrolylpyrazolyl, morpholinyl, tetrazolyl, or piperazinyl can be substituted with one to three groups of R^b.

13. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from -(CH₂)_nOR^c, -(CH₂)_nO(CH₂)_nR, -NR₂, pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl, where said pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl can be substituted with one to three groups of R^b.

14. The compound of Claim 4, wherein R is independently selected from H, -C₁₋₆alkyl or halo, where said alkyl is optionally substituted with one to three groups from -C₁₋₆alkyl, OR^c or halo;

R^a is independently selected from unsubstituted or substituted -C₁₋₆alkyl, said alkyl optionally substituted with 1 to 3 groups of R;

R^b is independently selected from -C₁₋₆alkyl, halo, -(CH₂)_nOR^c, -CN, -(CH₂)_nhalogen, or -O(CH₂)_nhalo;

R^c is independently selected from H or -C₁₋₆alkyl;

R^1 is selected from $-(CH_2)_nOR^c$, $-(CH_2)_nO(CH_2)_nR$, $-NR_2$, pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl, where said pyridyl, pyrazolyl, azetidiny, pyrrolidinyl, or furyl can be substituted with one to three groups of R^b ;

R^2 is selected from hydrogen, OR^c , halo or $-C_{1-6}alkyl$;

Ring A^1 is selected from pyridyl, pyrazinyl, pyrimidinyl, thiazolyl or pyrazolyl;

Ring A^2 is selected from pyridyl, pyrazinyl or phenyl, where said pyridyl, pyrazinyl or phenyl is optionally substituted with 1 to 3 groups of R ;

Ring A^3 is selected from pyrimidinyl, pyridyl or pyrazinyl;

n is independently selected from 0, 1, 2, 3 or 4; and

p is selected from 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

15. A compound selected from

Ex. No.	Structure	Name
1		(S)-6-methoxy-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
2		N-[2-[(3S)-3-ethyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-imidazol-1-yl-pyridine-3-carboxamide
3		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-4-(3-pyridyl)benzamide

Ex. No.	Structure	Name
4		5-fluoro-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-1H-indole-2-carboxamide
5		6-imidazol-1-yl-N-[2-[4-(5-methyl-2-pyridyl)-3-(2,2,2-trifluoroethyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
6		6-methoxy-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
7		6-imidazol-1-yl-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
8		6-methoxy-N-[2-[(2S)-2-methyl-4-(5-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
9		5-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrazine-2-carboxamide
10		6-methoxy-N-[2-[(2S)-4-(5-methoxy-2-pyridyl)-2-methylpiperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
11		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
12		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrazin-2-yl-piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
13		N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide
14		4-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
15		6-methoxy-N-[2-[(2S)-2-methyl-4-pyrimidin-4-yl-piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
16		6-(2-hydroxyethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
17		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
18		6-chloro-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
19		4-(1-cyanocyclopropyl)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]benzamide
20		6-bromo-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
21		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-5-phenyl-pyrazine-2-carboxamide
22		6-methoxy-N-[2-[(2R)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
23		6-(2-fluoroethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
24		2-methoxy-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-4-carboxamide

Ex. No.	Structure	Name
25		6-methoxy-N-[2-[(2S)-2-methyl-4-(4-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
26		4-(1-cyanocyclopropyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
27		N-[2-[(2S)-4-(6-fluoro-2-pyridyl)-2-methyl-piperazin-1-yl]pyrimidin-5-yl]-6-methoxy-pyridine-3-carboxamide
28		6-(difluoromethoxy)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
29		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyridine-2-carboxamide
30		6-(2-fluoroethoxy)-N-[6-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-3-pyridyl]pyridine-3-carboxamide
31		4-methoxy-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]-2-pyridyl]pyridine-2-carboxamide

Ex. No.	Structure	Name
32		2-(2-fluoroethoxy)-N-[5-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrazin-2-yl]pyrimidine-5-carboxamide
33		6-methoxy-N-[2-[(3R)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
34		6-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
35		N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide
36		2-methoxy-N-[2-[(3S)-3-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyrimidine-5-carboxamide
37		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide
38		6-(4-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
39		6-(4-fluoropyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
40		6-(3-methoxypyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
41		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(1,2,3-triazol-1-yl)pyridine-3-carboxamide
42		6-(3-methylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
43		6-(2-methylimidazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
44		(S)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(2H-1,2,3-triazol-2-yl)nicotinamide
45		6-(3,5-dimethylpyrazol-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
46		6-(3,3-difluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
47		6-[(3R)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
48		6-[rac-(4S)-2-azabicyclo[2.2.1]heptan-2-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
49		6-[(3S)-3-fluoropyrrolidin-1-yl]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
50		6-(3,3-dimethylpyrrolidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
51		6-(3-fluoroazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
52		6-(3-methylazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
53		6-(azepan-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
54		6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-[2-[rac-(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
55		6-[methyl(propyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
56		6-(azetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
57		6-(methylamino)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
58		6-(dimethylamino)-N-[2-[(2S)-2-methyl-4-(6-methyl-2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
59		6-[ethyl(2-hydroxyethyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

Ex. No.	Structure	Name
60		6-(3-hydroxyazetidin-1-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
61		6-[isobutyl(methyl)amino]-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
62		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrrolidin-1-yl-pyridine-3-carboxamide
63		6-(3-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
64		6-(4-methyl-3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
65		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-thiazol-5-yl-pyridine-3-carboxamide
66		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyridazin-4-yl-pyridine-3-carboxamide

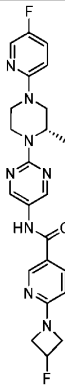
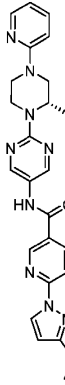
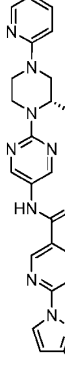
Ex. No.	Structure	Name
67		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-thienyl)pyridine-3-carboxamide
68		6-(4-fluorophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
69		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(3-pyridyl)pyridine-3-carboxamide
70		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(4-pyridyl)pyridine-3-carboxamide
71		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-phenyl-pyridine-3-carboxamide
72		6-(3-furyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
73		6-(4-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide

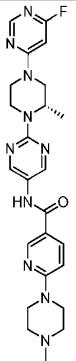
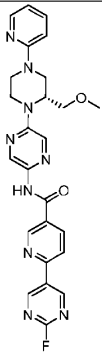
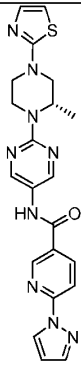
Ex. No.	Structure	Name
74		6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
75		6-(2-methylpyrazol-3-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
76		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-pyrimidin-5-yl-pyridine-3-carboxamide
77		6-(2-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
78		6-(5-fluoro-3-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
79		6-(3-fluoro-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
80		6-(6-fluoro-2-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
81		6-(3,5-dimethylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-

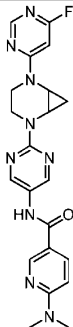
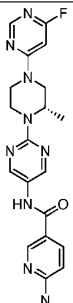
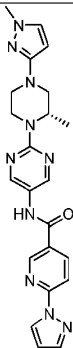
Ex. No.	Structure	Name
		pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
82		6-(3-methyl-4-pyridyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
83		N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]-6-(2-methylpyrimidin-5-yl)pyridine-3-carboxamide
84		6-(1-methylpyrazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
85		6-(3-methylisoxazol-4-yl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide
86		4-(3-cyanophenyl)-N-[2-[(2S)-2-methyl-4-(2-pyridyl)piperazin-1-yl]pyrimidin-5-yl]benzamide
87		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

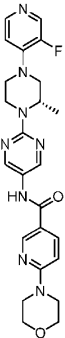
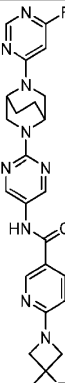
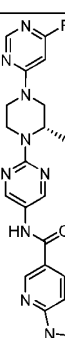
Ex. No.	Structure	Name
88		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(2-(2-methyl-4-(4-nitropyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
89		(S)-N-(2-(4-(2-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
90		(S)-N-(2-(2-methyl-4-(2-nitropyridin-4-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
91		(S)-6-(1H-imidazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
92		N-(2-((2S,6R)-2,6-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-5'-fluoro-[2,3'-bipyridine]-5-carboxamide

Ex. No.	Structure	Name
93		N-(2-((S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-((R)-3-fluoropyrrolidin-1-yl)nicotinamide
94		(R)-6-(1H-imidazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
95		(S)-N-(2-(4-(4-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide

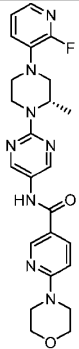
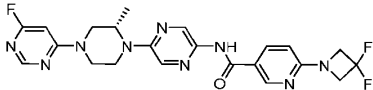
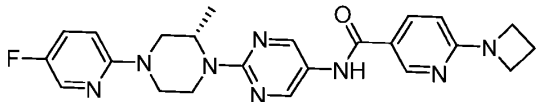
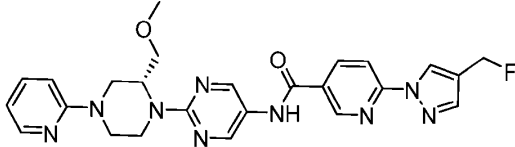
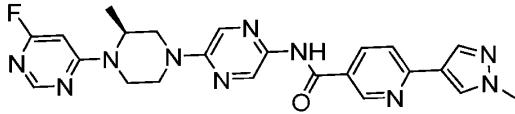
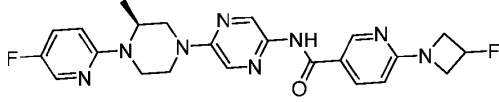
Ex. No.	Structure	Name
96		(S)-6-(3-fluoroazetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
97		(S)-6-(3-methoxy-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
98		(S)-6-(3-fluoro-1H-pyrazol-1-yl)-N-(2-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
99		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(4-methylpiperazin-1-yl)nicotinamide
100		(R)-6-(2-fluoropyrimidin-5-yl)-N-(5-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)nicotinamide
101		(S)-N-(2-(2-methyl-4-(thiazol-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide

Ex. No.	Structure	Name
102		6-(dimethylamino)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)pyrimidin-5-yl)nicotinamide
103		(S)-6-(dimethylamino)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
104		(S)-N-(2-(2-methyl-4-(1-methyl-1H-pyrazol-3-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide

Ex. No.	Structure	Name
105		(S)-N-(2-(4-(3-fluoropyridin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide
106		6-(3-fluoro-3-methylazetidin-1-yl)-N-(2-(5-(6-fluoropyrimidin-4-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)pyrimidin-5-yl)nicotinamide
107		(S)-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

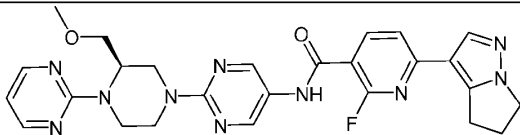
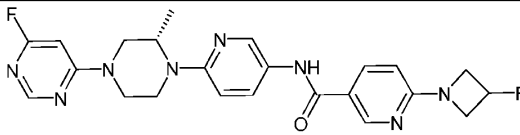
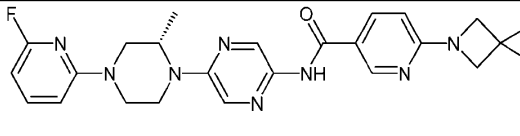
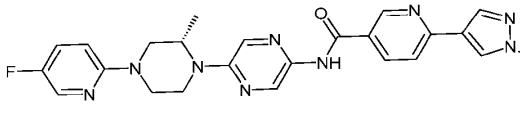
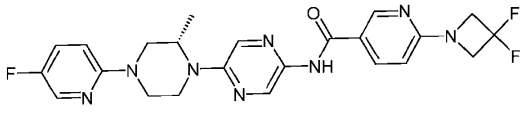
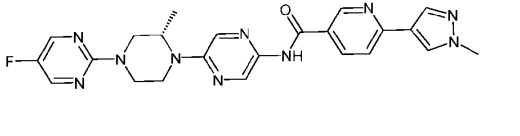
Ex. No.	Structure	Name
108		N-(2-((2S,5R)-2,5-dimethyl-4-(5-methylpyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1H-pyrazol-1-yl)nicotinamide
109		(S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-4-(pyridin-3-yl)benzamide
110		6-(3,3-difluoroazetidin-1-yl)-N-(2-((2R,3R)-4-(4-fluoropyridin-2-yl)-2,3-dimethylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

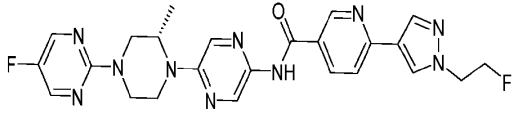
Ex. No.	Structure	Name
111		(S)-N-(2-(4-(2-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-morpholinonicotinamide
112		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
113		(S)-6-(azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
114		(R)-6-(4-(fluoromethyl)-1H-pyrazol-1-yl)-N-(2-(2-(methoxymethyl)-4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
115		(S)-N-(5-(4-(6-fluoropyrimidin-4-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
116		(S)-6-(3-fluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

Ex. No.	Structure	Name
117		(R)-N-(5-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
118		(S)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
119		(R)-N-(2-(3-((2-fluoroethoxy)methyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
120		(R)-N-(2-(4-(6-fluoropyrimidin-4-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
121		(R)-N-(4-fluoro-2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
122		(S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)-6-(pyrrolidin-1-yl)nicotinamide
123		(S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
124		(R)-N-(5-(3-((2-fluoroethoxy)methyl)-4-(5-fluoropyridin-2-yl)piperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
125		(S)-2-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)pyrimidine-5-carboxamide
126		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
127		(S)-N-(2-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
128		(R)-N-(5-(4-(6-fluoropyridin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
129		(R)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
130		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide

Ex. No.	Structure	Name
131		(R)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(2-(4-(5-fluoropyridin-2-yl)-3-(methoxymethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
132		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
133		(S)-6-(3-(fluoromethyl)azetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-3-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
134		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
135		(S)-6'-amino-6-fluoro-N-(2-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)-[2,3'-bipyridine]-5-carboxamide
136		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(5-fluoropyrazin-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
137		(S)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(4-(6-fluoropyrimidin-4-yl)-2-

Ex. No.	Structure	Name
		methylpiperazin-1-yl)pyrimidin-5-yl)nicotinamide
138		(R)-6-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-fluoro-N-(2-(3-(methoxymethyl)-4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-5-yl)nicotinamide
139		(S)-6-(3-fluoroazetidin-1-yl)-N-(6-(4-(6-fluoropyrimidin-4-yl)-2-methylpiperazin-1-yl)pyridin-3-yl)nicotinamide
140		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(6-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
141		(S)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide
142		(S)-6-(3,3-difluoroazetidin-1-yl)-N-(5-(4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide
143		(S)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)nicotinamide

Ex. No.	Structure	Name
144		(S)-6-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)-N-(5-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)nicotinamide

or a pharmaceutically acceptable salt thereof.

16. The compound of Claim 15 selected from Ex. No. 1, 6, 9, 11, 12, 37, 39, 47, 51, 57, 58, 64, 72, 75, 78, 79, 80, 91, 96, 112, 113, 115, 116, 118, 134, 138 and 141, or a pharmaceutically acceptable salt thereof.

17. The compound of Claim 15 selected from Ex. No. 39, 47, 51, 78, 79, 96, 112, 116 and 141 or a pharmaceutically acceptable salt thereof.

18. The compound of Claim 1 or 15, or a pharmaceutically acceptable salt thereof, which is labeled with an isotope selected from 2H , 3H , 11C , 13C , 14C , 13N , 15N , 15O , 17O , 18O , 18F , 35S , 36Cl , 82Br , 76Br , 77Br , 123I , 124I or 131I .

19. The compound of Claim 15, or a pharmaceutically acceptable salt thereof, which is isotopically labeled with 3H , 11C or 18F .

20. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutical excipient.

21. A method of imaging alpha-synuclein deposits in a human patient, using a compound of Claim 18, or a pharmaceutically acceptable salt thereof, as the imaging agent, comprising the following steps:

- a) placing a human patient in a supine position in the PET camera;
- b) administering about 0.1 to about 10 mCi of a compound of Claim 17 to the patient; and

c) performing an emission scan of the cerebral region of the patient's head to identify aggregations of alpha-synuclein in the brain tissue of the patient.

22. A method of measuring the clinical efficacy of therapeutic agents for Parkinson's disease comprising the steps of

a) administering an isotopically-labeled compound of Formula I, according to Claim 18, to the patient diagnosed with PD before treatment with said therapeutic agent,

b) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue,

c) administering an isotopically-labeled compound of Formula I, according to Claim 18, to the patient after treatment with said therapeutic agent,

d) measuring the amount of alpha-synuclein aggregate formation in the patient's brain tissue after treatment, and

e) analyzing whether said therapeutic agent stopped or decreased the progression of alpha-synuclein aggregate formation in the patient's brain tissue.

23. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, for use as an imaging agent.

24. A compound of Claim 18, or a pharmaceutically acceptable salt thereof, for use as an imaging agent.