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(71) Applicant: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 541-0045 (JP).

(72) Inventors: **LIWICKI, Gemma**; c/o TAKEDA GmbH, Byk-Gulden-Str.2, Konstanz, 78467, Germany (DE). **MACK, Stephen**; c/o TAKEDA GmbH, Byk-Gulden-Str.2, Konstanz, 78467, Germany (DE). **RUPRAH, Parminder Kaur**; c/o TAKEDA GmbH, Byk-Gulden-Str.2, Konstanz, 78467, Germany (DE). **REEVES, Jennifer**; c/o TAKEDA GmbH, Byk-Gulden-Str.2, Konstanz, 78467, Germany (DE).

(74) Agent: **TAKASHIMA, Hajime** et al.; Meiji Yasuda Seimei Osaka Midouji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka, 541-0044 (JP).

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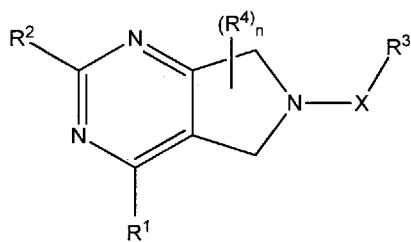
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(54) Title: THERAPEUTIC COMPOUNDS



(I)

(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof : in which n, X, R¹, R², R³ and R⁴ are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.



DESCRIPTION

Title of Invention: THERAPEUTIC COMPOUNDS

The present invention relates to muscarinic receptor modulators, particularly M4 muscarinic modulators, processes for their preparation, pharmaceutical compositions
5 containing them and their use in therapy, particularly for the treatment or prevention of psychiatric and neurological conditions.

Dysregulation of the dopaminergic system is known to play an important role in the pathophysiology of schizophrenia and has been the primary focus of typical and atypical
10 antipsychotic therapy (positive symptomatology). There is increasing evidence that the muscarinic system also plays a role in the disease. Post-mortem studies have shown muscarinic receptor abnormalities in the prefrontal cortex, hippocampus and striatum of schizophrenic patients (review by Raedler TJ *et al* (2007) *Mol Psychiatry* 12:232-246). Studies on M4 knockout mice indicate that the M4 receptor plays a role in locomotor
15 activity, social interaction and sensorimotor gating (Koshimizu H *et al* (2012) *Molecular Brain* 5:10) indicating a role for the M4 receptor in the positive and negative symptomatology of schizophrenia.

Since the beginning of the last century acetylcholine has been recognised as a
20 neurotransmitter in both the central and peripheral nervous systems. There are two families of acetylcholine receptors one which binds muscarine (muscarinic receptors) and one that binds nicotine (nicotinic receptors). Nicotinic cholinergic receptors are composed of five subunits that combine to form a ligand-gated ion channel. Muscarinic cholinergic receptors are members of the class A of the G-protein coupled receptors super-family.
25 There are five known subtypes, M1-M5, which have a high degree of sequence homology at the orthosteric binding site, making it challenging to develop subtype specific ligands. Muscarinic receptors are divided into two groups with differing effects on the G-protein system. M1, M3 & M5 receptors are coupled to Gq and activation results in the activation of phospholipase C and mitogen – activated protein kinase and increases intra-cellular
30 concentrations of inositol triphosphate and calcium. M2 & M4 receptors are coupled to Gi and activation results in a decrease in the formation of cAMP as a result of negative coupling to adenyl cyclase.

Studies suggesting that the muscarinic cholinergic system may be involved in schizophrenia were first published in the 1950s; it was reported that administration of muscarinic agonists to patients with catatonic schizophrenia produced 'lucid' intervals (Pfeiffer CC, and Jenny ERH (1957) *Ann NY Acad Sci* 66:753-764). In 1981 it was reported that a subgroup of patients with schizophrenia responded to physostigmine and lithium (Edelstein P *et al* (1981) *Am J Psychiatry* 138: 1078-1081). Suggestions that the cholinergic system may be involved in schizophrenia have also been derived from psychopharmacological studies (Davis KL *et al* (1978) *Life Sciences* 22(21): 1865-1871; Tandon R, and Greden JK (1989) *Archives of General Psychiatry*: 745-743). These studies hypothesised that abnormalities in the cholinergic system may mediate positive and negative symptomatology. Consistent with these suggestions muscarinic receptor antagonists can produce psychotic-like symptoms including auditory hallucinations, hyperactivity and cognitive disruption (reviewed by Yeomans JS (1995) *Neuropharmacology* 12: 3-16).

Following the findings that the M1, M4 preferring muscarinic agonist Xanomeline significantly reduced psychotic-like behaviours in Alzheimer's disease (Bodick NC *et al* (1997) *Archives of Neurology* 54: 465-473) it was published that Xanomeline (Shannon HE *et al* (2000) *Schizophrenia Research* 42:249-259) and PTAC, an M2,M4 agonist and M1,3,5 antagonist (Bymaster FP *et al* (1998) *Eur J Pharmacol* 356:109-119) were highly efficacious in animal models of schizophrenia. Studies have shown that these effects are greatly reduced in M4 knockout mouse (Bymaster FP *et al* (2003) *Neurochem Res* 28 (12): 437-442; Tzavara ET *et al* (2004) *FASEB J* 18 (12): 1410-1412). This body of data therefore strongly suggested that the antipsychotic effects evoked by muscarinic agonists are mediated by activation of the muscarinic M4 receptor. Xanomeline was subsequently studied in schizophrenia patients and shown to be efficacious against positive and negative symptoms of schizophrenia (Shekhar A *et al* (2008). *Am J Psychiatry*; 165:1033-1039). In addition to the data obtained with Xanomeline, three acetylcholinesterase inhibitors, donepezil, rivastigmine and galantamine have been published to show utility in schizophrenia when used as add-on therapy together with atypical antipsychotics (review by Raedler *et al*, 2007).

The M1/M4 preferring muscarinic partial agonist Xanomeline, when studied in schizophrenia patients displayed equal efficacy against the positive and negative symptoms of schizophrenia (Shekhar *et al*, 2008). Deficits in social behaviour form a major part of the negative symptoms of schizophrenia. An important question posed by this data is the identity of the muscarinic receptor or receptors underlying this efficacy against negative symptoms. The muscarinic M4 receptor is highly expressed in the prefrontal cortex, striatum and the nucleus accumbens (ventral striatum). These areas are known to play major roles in social behaviour in humans, non-human primates and rodents (Shaun Ho S, *et al* (2012). *NeuroImage*; 63: 843-857; Louilot A *et al* (1986). *Brain Research*; 397:395-400; Klein JT *et al* (2013). *Current Biology*; 23: 691-696; Van Kerkhof LWM *et al* (2013). *Neuropsychopharmacology*; 10: 1899-1909). Data from Koshimizu *et al* (2012) has shown that M4 knockout mice display deficits in social interaction studies, in which contacts between the mutant mice were significantly shorter in duration than those of wild-type mice. This body of evidence strongly suggests that selective positive allosteric modulators at the muscarinic M4 receptor may show utility in respect to the treatment of negative symptoms of schizophrenia.

Muscarinic M4 receptors are expressed in regions of the central nervous system that play a role in cognitive function such as the prefrontal cortex and the hippocampus. The muscarinic toxin MT3 has been shown to be selective for the M4 receptor (Jerusalinsky D *et al* (1998). *Neuroreport*; 9: 1407-1411), it has 214 fold selectivity over the M1 receptor and has no significant affinity the M2 M3 or M5 receptors. Jerusalinsky *et al* (1998) and others (Romanelli A *et al* (2003). *Pharmacology, Biochemistry and Behaviour*; 74: 411-415) also demonstrated that MT3 when administered directly into the dorsal hippocampus following training, caused retrograde amnesia in an inhibitory avoidance paradigm. This data is strongly suggestive that the M4 receptor plays a role in memory consolidation. Subsequently it has been demonstrated that MT3 was able to block LTP in the CA1 region of the hippocampus following high frequency stimulation of the Schaffer collateral pathway suggesting that M4 receptor activation plays a permissive role in hippocampal synaptic plasticity (Sanchez G *et al* (2009). *Journal of Neuroscience Research*; 87: 691-700). A more specific physiological role for M4 receptors in the hippocampus was shown by Bell LA *et al* (2013). *Neuropharmacology*; 73:160-173. Using optogenetic technology

combined with whole cell patch clamping in acute mouse hippocampal slices, it was shown that stimulation of the cholinergic medial septum/diagonal bands of Broca inputs to the CA1 region of the hippocampus evoked hyperpolarisations of CA1 GABAergic interneurons that could be enhanced by a selective positive allosteric modulator of the M4 receptor (VU10010). This compound also had an inhibitory effect on bursting activity in these neurones. Hippocampal interneurone function and the bursting activity of these neurones play an important role in hippocampal function, hence cognitive functioning.

There is therefore clear evidence that M4 receptors play an important role in hippocampal and therefore cognitive function and that enhancing M4 receptor activity may show utility against the cognitive symptoms of schizophrenia. In addition to the potential for the therapy of schizophrenia, compounds active at the M4 muscarinic receptor such as PTAC have been shown to have potential for the treatment of drug abuse. Rasmussen T *et al* (2000) *Eur J Pharmacol* 402:241-246 showed that PTAC could decrease cocaine self administration in mice.

Muscarinic receptors have also long been known to be involved in pain perception and muscarinic agonists are very efficacious analgesics with efficacy and potency levels similar to opioid receptor agonists (Sheardown MJ *et al* (1997) *J Pharmacol and Exp Therap* 281: 868-875). Subsequent studies in genetically modified mice have shown that muscarinic analgesia is expressed, at least partially through activation of muscarinic M4 receptors (Duttaroy A *et al* (2002) *Mol Pharmacol* 62(5):1084-1093; Cai Y-Q *et al* (2009) *J Neurochem* 111:1000-1010).

To date, selective tools have not been available to elucidate the roles of the individual muscarinic receptors and lead to viable therapies. Xanomeline and other lead muscarinic agents suffer from lack of sub-type selectivity which result in off-target effects such as bradycardia and gastrointestinal issues which has hindered further development.

An alternative strategy to identify selective muscarinic ligands is to develop ligands that can modulate the response of the receptor in the presence or absence of the endogenous ligand acetylcholine, by binding to an 'allosteric' site that is topographically distinct from

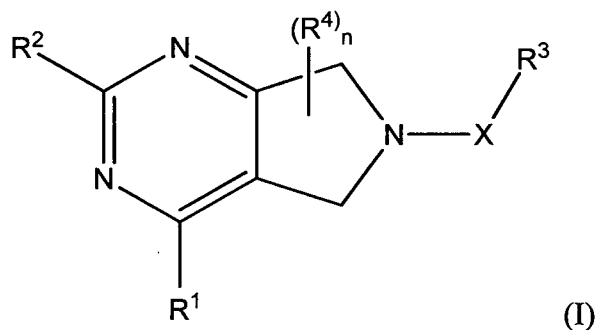
that of the endogenous ligand (Conn PJ *et al* (2009) *Trends in Pharmacological Sciences* 30:148-156; Lindsley CW *et al* (2012) *J Med Chem* 55: 1445-1464).

In this connection, a number of M4 muscarinic allosteric modulators have been described,
 5 for example, in Published PCT Application Nos. WO 2006/047124 (Eli Lilly), WO 2012/154731 (Vanderbilt University), WO 2013/040534 (Vanderbilt University) and WO 2013/126856 (Vanderbilt University), and compounds ML293 (VU0409524) and ML253 (VU0448088) are known from the following journal references: Hopkins C R *et al* (2012) *Bioorg Med Chem Lett* 22: 5084 and Hopkins C R *et al* (2013) *Bioorg Med Chem* 23: 346.

10

We have now discovered a new class of compounds that are muscarinic M4 receptor modulators which have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

15 In accordance with the present invention, there is therefore provided a compound of formula



wherein

R^1 represents $-NR^5R^6$ or a C₅-C₆ heteroaryl group;

20 R^2 represents a hydrogen atom or a group selected from cyano, $-NR^7R^8$, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, C₃-C₈ heterocyclyl, C₆-C₁₀ aryl and C₅-C₁₀ heteroaryl, wherein each of the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl groups may be optionally substituted by at least one substituent independently selected from halogen, hydroxyl, $-NR^9R^{10}$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-
 25 C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ alkylthio, C₁-C₆

alkylsulphinyl, C₁-C₆ alkylsulphonyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkoxy carbonyl, -CONR¹¹R¹², C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy and C₃-C₆ cycloalkylmethyl;

R³ represents a saturated or unsaturated 3- to 10-membered ring system which may
5 comprise at least one ring heteroatom independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by at least one substituent independently selected from halogen, cyano, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyloxy,
10 C₁-C₆ alkoxy carbonyl, -NR¹³R¹⁴, -CONR¹⁵R¹⁶, C₃-C₆ cycloalkyl, phenoxy, phenyl(C₁-C₆alkyl)oxy and sulphonamido (-SO₂NH₂);

n is 0, 1, 2 or 3;

each R⁴ independently represents a C₁-C₆ alkyl group;

X represents C(O), C(O)NH or CO(CHR¹⁷)_y(CHR¹⁸)_z, wherein the latter two groups
15 are oriented such that the NH or (CHR¹⁷)_y(CHR¹⁸)_z moieties are attached to the R³ substituent group;

y is 0 or 1 and z is 0 or 1 provided that y + z is at least 1;

R⁵ and R⁶ each independently represent a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or
R⁵ and R⁶ may together with the nitrogen atom to which they are attached form an
20 azetidiny ring optionally substituted by at least one substituent independently selected from halogen and C₁-C₆ alkyl;

R⁷ and R⁸ each independently represent a hydrogen atom, or a C₁-C₆ alkyl or
C₃-C₆ cycloalkyl group, or R⁷ and R⁸ may together with the nitrogen atom to which they
are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by
25 at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R^9 and R^{10} each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R^9 and R^{10} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R^{11} and R^{12} each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R^{11} and R^{12} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R^{13} and R^{14} each independently represent a hydrogen atom, or a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxy carbonyl or C₁-C₆ alkylsulphonyl group, or R^{13} and R^{14} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R^{15} and R^{16} each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R^{15} and R^{16} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy; and

R^{17} and R^{18} each independently represent a hydrogen atom or C₁-C₆ alkyl group, or R^{17} and R^{18} may together with the carbon atoms to which they are attached form a cyclopropyl ring;

or a pharmaceutically acceptable salt thereof.

In the context of the present specification, unless otherwise stated, an 'alkyl', 'alkenyl' or 'alkynyl' substituent group or an 'alkyl', 'alkenyl' or 'alkynyl' moiety in a substituent group may be linear or branched. Examples of C₁-C₆ alkyl groups/moieties include methyl, ethyl, propyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl. Examples of C₂-C₆ alkenyl groups/moieties include ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl and 1-hexadienyl. Examples of C₂-C₆ alkynyl groups/moieties include ethynyl, propynyl, 1-butyne, 2-butyne, 1-pentyne and 1-hexyne.

A 'C₁-C₆ haloalkyl' or 'C₁-C₆ haloalkoxy' substituent group/moiety will comprise at least one halogen atom, e.g. one, two, three, four or five halogen atoms, examples of which include difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy or pentafluoroethyl.

A 'C₁-C₆ hydroxyalkyl' substituent group/moiety will comprise at least one hydroxyl group, e.g. one, two, three or four hydroxyl groups, examples of which include – CH₂OH, –CH₂CH₂OH, –CH₂CH₂CH₂OH, –CH(OH)CH₂OH, –CH(CH₃)OH and –CH(CH₂OH)₂.

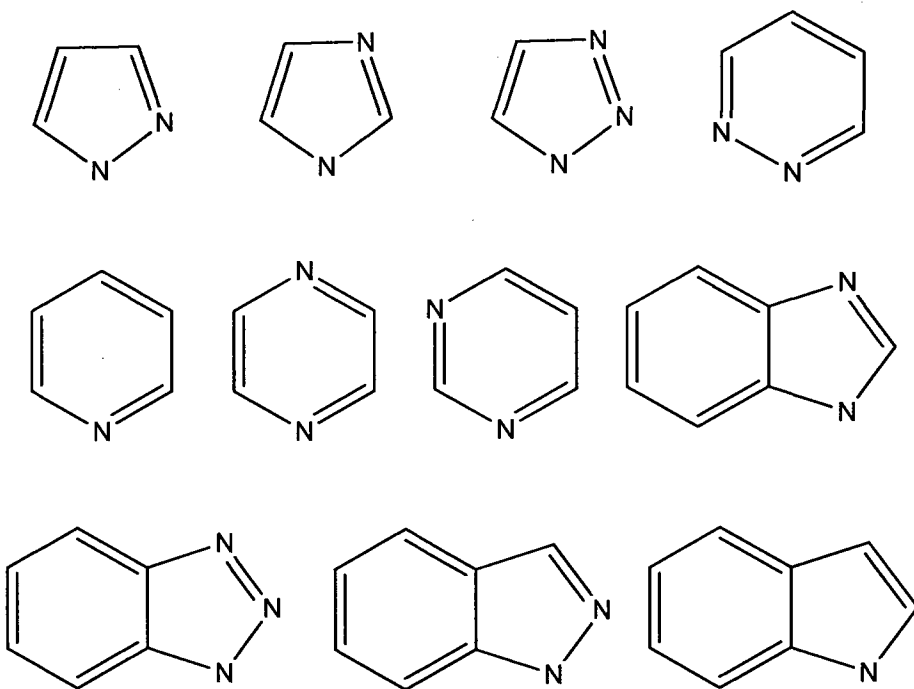
A "cycloalkyl" substituent group/moiety is a saturated hydrocarbyl ring containing, for example, from 3 to 8 ring carbon atoms, examples of which include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

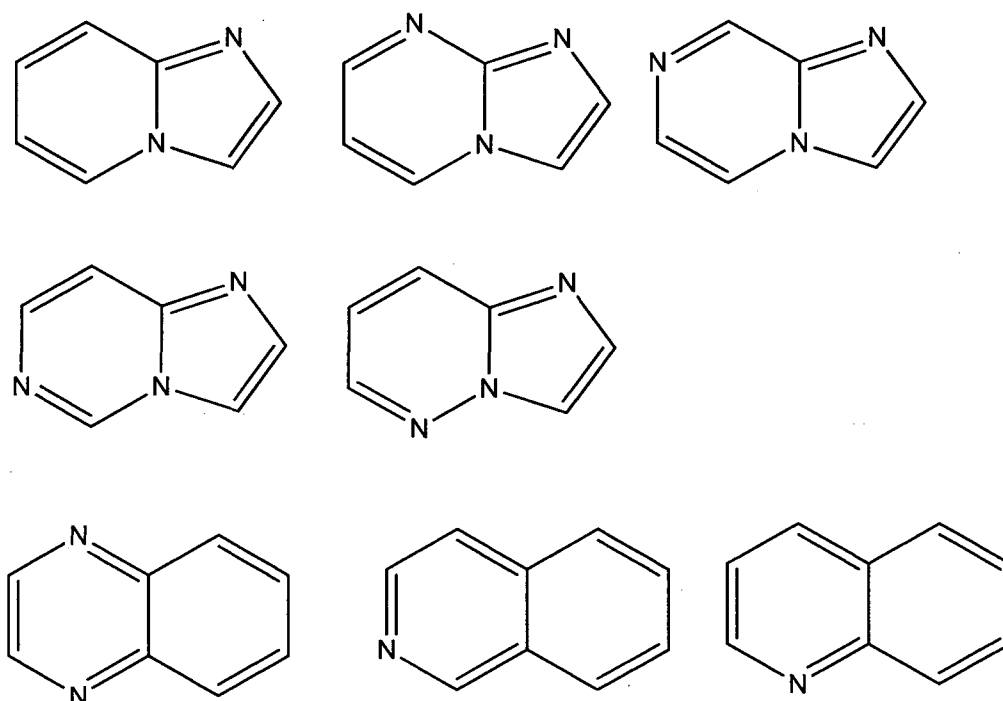
A 'heterocyclyl' substituent group/moiety is a cycloalkyl group in which from 1 to 3 carbon atoms are replaced by heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of heterocyclyl groups include azetidyl, pyrrolidyl,

tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl and 1,4-oxazepanyl.

As used herein, “aryl” is intended to mean any stable monocyclic or bicyclic aromatic hydrocarbon system containing up to 10 carbon atoms, e.g. from 6 to 10 carbon atoms, such as phenyl or naphthyl.

The term “heteroaryl”, as used herein, refers to an aryl group in which from 1 to 4 ring carbon atoms are replaced by nitrogen atoms. Examples of heteroaryl groups include the following:





A 4- to 7-membered saturated heterocyclic ring will contain at least one ring nitrogen atom and may contain one or more (e.g. one or two) further ring heteroatoms independently selected from nitrogen, oxygen and sulphur atoms. It will be understood that the definition is not intended to include unstable structures or any O-O, O-S or S-S bonds and that a substituent, if present, may be attached to any suitable ring atom. Examples of heterocyclic rings include azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl and 1,4-oxaazepanyl.

When any chemical moiety or group in formula (I) is described as being optionally substituted, it will be appreciated that the moiety or group may be either unsubstituted or substituted by one or more of the specified substituents. It will be appreciated that the number and nature of substituents will be selected so as to avoid sterically undesirable combinations.

In an embodiment of the invention R^1 represents $-NR^5R^6$ where R^5 and R^6 each independently represent a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl or C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group, or R^5 and R^6 may together

with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from halogen (e.g. fluorine, chlorine or bromine) and C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl.

5

In one aspect, R⁵ and R⁶ each independently represent a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl group, e.g. methyl group such that -NR⁵R⁶ represents dimethylamino.

10

In another aspect, R⁵ and R⁶ together with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from halogen (e.g. fluorine) and methyl.

15

In a further aspect, R⁵ and R⁶ together with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by a single fluorine or methyl substituent group.

20

In another embodiment, R¹ represents a C₅-C₆ heteroaryl group. This R¹ heteroaryl group comprises one or more, e.g. one, two, three or four, ring heteroatoms selected from nitrogen atoms only. Examples of such 5- or 6-membered heteroaryl groups include pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and tetrazinyl.

In one aspect, R¹ represents a pyrazolyl group.

25

R² represents a hydrogen atom or a group selected from cyano, -NR⁷R⁸, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy, C₃-C₈, or C₃-C₆, cycloalkyl, C₃-C₈, or C₃-C₆, heterocyclyl (e.g. tetrahydropyranyl), C₆-C₁₀ aryl (e.g. phenyl) and C₅-C₁₀ heteroaryl (e.g. pyridinyl), wherein each of the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl groups may be optionally substituted by at least one substituent (e.g. one,

two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, $-NR^9R^{10}$, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₂-C₆, or C₂-C₄, alkenyl, C₂-C₆, or C₂-C₄, alkynyl, C₁-C₆, or C₁-C₄, or C₁-C₂ haloalkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ hydroxyalkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy, C₁-C₆, or C₁-C₄, or C₁-C₂ haloalkoxy, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylthio, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylsulphinyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylsulphonyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylcarbonyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylcarbonyloxy, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxycarbonyl, $-CONR^{11}R^{12}$, C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C₃-C₆ cycloalkyloxy (cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy) and C₃-C₆ cycloalkylmethyl (cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl).

In an embodiment of the invention, R^2 represents a hydrogen atom or a group selected from cyano, $-NR^7R^8$, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy, C₃-C₈, or C₃-C₆, cycloalkyl, C₃-C₈, or C₃-C₆, heterocyclyl, C₆-C₁₀ aryl and C₅-C₁₀ heteroaryl, wherein each of the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl groups may be optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, $-NR^9R^{10}$, C₁-C₄, or C₁-C₂ alkyl, C₁-C₄, or C₁-C₂, haloalkyl, C₁-C₄, or C₁-C₂, hydroxyalkyl, C₁-C₄, or C₁-C₂, alkoxy, C₁-C₄, or C₁-C₂, haloalkoxy, C₁-C₄, or C₁-C₂, alkylcarbonyl, C₁-C₄, or C₁-C₂, alkylcarbonyloxy, C₁-C₄, or C₁-C₂, alkoxycarbonyl, $-CONR^{11}R^{12}$, C₃-C₆, or C₃-C₅, cycloalkyl, C₃-C₆, or C₃-C₅, cycloalkyloxy and C₃-C₆, or C₃-C₅, cycloalkylmethyl.

In another embodiment of the invention, R^2 represents a hydrogen atom or a group selected from cyano, $-NR^7R^8$, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl, wherein each of the alkyl, alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl groups may be optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), $-NR^9R^{10}$, C₁-C₄, or C₁-C₂, alkyl, C₁-C₄, or C₁-C₂, haloalkyl, C₁-C₄, or C₁-C₂, hydroxyalkyl, C₁-C₄, or C₁-C₂, alkoxy, C₁-C₄, or C₁-C₂, haloalkoxy, C₁-C₄, or C₁-C₂, alkylcarbonyl, C₁-C₄, or C₁-C₂, alkylcarbonyloxy, C₁-C₄, or C₁-C₂, alkoxycarbonyl, $-CONR^{11}R^{12}$, C₃-C₆, or C₃-C₅, cycloalkyl, C₃-C₆, or C₃-C₅, cycloalkyloxy and C₃-C₆, or C₃-C₅, cycloalkylmethyl.

In still another embodiment of the invention, R^2 represents a hydrogen atom or a group selected from cyano, $-NR^7R^8$, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl, wherein each of the alkyl, alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl groups may be optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from fluorine, chlorine, $-NR^9R^{10}$ and C₁-C₂ alkoxy.

In yet another embodiment, R^2 represents any one of the following moieties or is selected from a group containing two or more of such moieties in any combination:

- (i) hydrogen,
- (ii) cyano,
- (iii) methyl,
- (iv) ethyl,
- (v) cyclopropyl,
- (vi) trifluoromethyl,
- (vii) methoxymethyl ($-\text{CH}_2\text{-O-CH}_3$)
- (viii) amino (NH_2),

- (ix) methylamino,
- (x) dimethylamino,
- (xi) methylaminomethyl (-CH₂-NHCH₃)
- (xii) dimethylaminomethyl (-CH₂-N(CH₃)₂)
- 5 (xiii) azetidiny,
- (xiv) tetrahydropyranyl,
- (xv) methoxy,
- (xvi) ethoxy,
- (xvii) phenyl, and
- 10 (xviii) pyridinyl (e.g. 2-pyridinyl or 3-pyridinyl).

R³ represents a saturated or unsaturated 3- to 10-membered (e.g. 3-, 4-, 5- or 6- to 7-, 8-, 9- or 10-membered) ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, hydroxyl, oxo, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₂-C₆, or C₂-C₄, alkenyl, C₂-C₆, or C₂-C₄, alkynyl, C₁-C₆, or C₁-C₄, or C₁-C₂ haloalkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ hydroxyalkyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy, C₁-C₆, or C₁-C₄, or C₁-C₂ haloalkoxy, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylthio, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylcarbonyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkylcarbonyloxy, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxycarbonyl, -NR¹³R¹⁴, -CONR¹⁵R¹⁶, C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), phenoxy, phenyl(C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl)oxy and sulphonamido.

This R³ saturated or unsaturated 3- to 10-membered ring system may comprise one or more (e.g. one, two, three or four) ring heteroatoms independently selected from nitrogen, oxygen and sulphur. The ring system may be monocyclic or polycyclic (e.g. bicyclic) in

which the two or more rings are fused, bridged or spiro. Examples of R³ ring systems include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxadiazolyl (e.g. 1,2,4-
 5 oxadiazolyl), tetrahydrofuranyl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, benzoxazolyl, quinolinyl, oxazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl), 2,3-dihydroindenyl, 2,3-dihydrobenzofuranyl, 2,3-dihydroisoindolyl, tetrahydropyranyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl, pyrazolyl, imidazo[1,2-a]pyridinyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, pyrrolyl, furanyl, thiazolyl,
 10 isothiazolyl, indolyl, isoindolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

In one aspect of the invention, the R³ ring system is selected from one or more, in any combination, of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl,
 15 piperidinyl, tetrahydropyranyl, bicyclo[2.2.1]heptyl, oxazolyl, pyrazolyl, phenyl, pyridinyl, pyridazinyl, 2,3-dihydroindenyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl and 2,3-dihydroisoindolyl.

In one embodiment, R³ represents a saturated or unsaturated 3-, 4-, 5- or 6- to 9-membered
 20 ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, hydroxyl, oxo, C₁-C₄, or C₁-C₂ alkyl, C₁-C₄, or C₁-C₂ haloalkyl (e.g.
 25 difluoromethyl or trifluoromethyl), C₁-C₄, or C₁-C₂ hydroxyalkyl, C₁-C₄, or C₁-C₂ alkoxy, C₁-C₄, or C₁-C₂ haloalkoxy (e.g. difluoromethoxy or trifluoromethoxy), C₁-C₄, or C₁-C₂ alkylthio, C₁-C₄, or C₁-C₂ alkylcarbonyl, C₁-C₄, or C₁-C₂ alkylcarbonyloxy, C₁-C₄, or C₁-C₂ alkoxycarbonyl, -NR¹³R¹⁴, -CONR¹⁵R¹⁶, C₃-C₆ cycloalkyl

(cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), phenoxy, phenyl(C₁-C₄, or C₁-C₂ alkyl)oxy and sulphonamido.

In another embodiment, R³ represents a saturated or unsaturated 3-, 4-, 5- or 6- to 9-
5 membered, or 3- to 6-membered, ring system which may comprise one, two, three or four
ring heteroatoms independently selected from nitrogen and oxygen atoms, wherein the ring
system is optionally substituted by at least one substituent (e.g. one, two, three or four
substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or
iodine), cyano, oxo, C₁-C₄, or C₁-C₂ alkyl, C₁-C₄, or C₁-C₂ haloalkyl, C₁-C₄, or
10 C₁-C₂ alkoxy, C₁-C₄, or C₁-C₂ haloalkoxy and phenoxy.

In a further embodiment, R³ represents a saturated or unsaturated 3-, 4-, 5- or 6- to 9-
membered, or 3- to 6-membered, ring system which may comprise one or two ring
heteroatoms independently selected from nitrogen and oxygen atoms (such as cyclopropyl,
15 cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl,
bicyclo[2.2.1]heptyl, oxazolyl, pyrazolyl, phenyl, pyridinyl, pyridazinyl, 2,3-
dihydroindenyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl or 2,3-dihydroisoindolyl),
wherein the ring system is optionally substituted by at least one substituent (e.g. one, two,
three or four substituents) independently selected from fluorine, chlorine, cyano, oxo,
20 methyl, ethyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy,
trifluoromethoxy and phenoxy.

If R³ represents a substituted phenyl group, the substituent(s) is/are preferably attached to
the phenyl ring in the meta or para positions relative to the point of attachment of the group
25 X to R³.

In a still further embodiment, R³ represents any one of the following moieties or is selected
from a group containing two or more of such moieties in any combination:

- (i) 4-chloro-2-methylphenyl,

- (ii) 3-chloro-4-methoxyphenyl,
- (iii) 3-pyridinyl,
- (iv) 4-pyridinyl,
- (v) 3-chlorophenyl,
- 5 (vi) 4-chlorophenyl,
- (vii) cyclobutyl,
- (viii) cyclopentyl,
- (ix) 2-ethylpyridin-4-yl,
- (x) 2-methoxypyridin-4-yl,
- 10 (xi) 2-(trifluoromethyl)pyridin-4-yl,
- (xii) 3-fluoro-4-cyanophenyl,
- (xiii) 3,5-dichloro-4-methoxyphenyl,
- (xiv) 4-fluoro-3-methylphenyl,
- (xv) 2-(trifluoromethyl)pyridin-5-yl,
- 15 (xvi) 3-chloro-5-(trifluoromethyl)phenyl,
- (xvii) 3-chloro-2-methylpyridin-5-yl,
- (xviii) 4-fluorophenyl,
- (xix) 4-trifluoromethylphenyl,
- (xx) 3-fluorophenyl,
- 20 (xxi) 3-trifluoromethylphenyl,
- (xxii) 4-trifluoromethoxyphenyl,
- (xxiii) 3-chloro-4-(trifluoromethoxy)phenyl,
- (xxiv) 3-fluoro-4-(trifluoromethoxy)phenyl,
- (xxv) 4-fluoro-3-(trifluoromethoxy)phenyl,
- 25 (xxvi) 3-methyl-5-(trifluoromethoxy)phenyl,
- (xxvii) 4-(difluoromethoxy)-3,5-dimethylphenyl,
- (xxviii) 4-(difluoromethoxy)phenyl,
- (xxix) 3-(difluoromethoxy)phenyl,
- (xxx) 3-cyano-4-ethylphenyl,
- 30 (xxxi) tetrahydropyranyl,

- (xxxii) 3-cyanophenyl,
(xxxiii) 2,2-dimethylcyclopropyl,
(xxxiv) cyclohexyl,
(xxxv) bicyclo[2.2.1]heptan-2-yl,
5 (xxxvi) 4,4-difluorocyclohexyl,
(xxxvii) 4-methylcyclohexyl,
(xxxviii) 4-cyanophenyl,
(xxxix) 4-chloro-3-fluorophenyl,
(xl) 3-cyano-5-fluorophenyl,
10 (xli) 3-chloro-4-cyanophenyl,
(xlii) 3-cyano-4-chlorophenyl,
(xliii) 3-chloro-5-cyanophenyl,
(xliv) 5-(1-methyl-1,2-dihydropyridin-2-one),
(xlv) 5-chloro-pyridin-2-yl,
15 (xlvi) 5-fluoro-pyridin-2-yl,
(xlvii) 3-methylcyclobutyl,
(xlviii) 3-fluorocyclobutyl,
(xlix) 3,4-dichlorophenyl,
(l) 3-chloro-5-fluorophenyl,
20 (li) 2-methyl-1,3-oxazol-5-yl,
(lii) phenyl,
(liii) 3-chloro-4-methylphenyl,
(liv) 4-methylphenyl,
(lv) 3-fluoro-4-methylphenyl,
25 (lvi) 3,4-difluorophenyl,
(lvii) 3,5-difluorophenyl,
(lviii) 3-chloro-4-fluorophenyl,
(lix) 5-methylpyridin-3-yl,
(lx) 3-methylphenyl,
30 (lxi) cyclopropyl,

- (lxii) 2,3-dihydroinden-2-yl,
(lxiii) 2-methylpyridin-5-yl,
(lxiv) 2,3-dimethylpyridin-5-yl,
(lxv) 3-chloropyridin-5-yl,
5 (lxvi) 2,6-dimethylpyridin-4-yl,
(lxvii) 4-chloro-3-methylphenyl,
(lxviii) 3,5-dichlorophenyl,
(lxix) 2,2-dimethyloxan-4-yl,
(lxx) 3-chloro-5-(trifluoromethoxy)phenyl,
10 (lxxi) 3-chloro-5-methylphenyl,
(lxxii) 4-(trifluoromethyl)cyclohexyl,
(lxxiii) 4-ethylcyclohexyl,
(lxxiv) 4,4-dimethylcyclohexyl,
(lxxv) 3-cyano-4-fluorophenyl,
15 (lxxvi) pyridazinyl,
(lxxvii) 3,3-difluorocyclopentyl,
(lxxviii) 1-methylpyrazol-4-yl,
(lxxix) 1-methylpyrazol-3-yl,
(lxxx) 1-pyrrolidinyl,
20 (lxxxii) 1-piperidinyl,
(lxxxiii) 3-phenoxy-pyrrolidin-1-yl,
(lxxxiv) 3-chloro-4-(difluoromethoxy)phenyl,
(lxxxv) 4-pyrazolyl,
(lxxxvi) 1-methylpyrazol-4-yl,
25 (lxxxvii) 1-ethylpyrazol-4-yl,
(lxxxviii) 2-methylpyridin-4-yl,
(lxxxix) 2-methyl-3-fluoropyridin-5-yl,
(lxxxix) 3-cyano-5-methylphenyl,
(xc) 3-cyano-5-chlorophenyl,
30 (xci) 4-(difluoromethyl)-3-fluorophenyl,

- (xcii) 4-(difluoromethyl)-3-chlorophenyl,
(xciii) 4-chloro-3-(difluoromethyl)phenyl,
(xciv) 2,3-dihydro-isoindol-2-yl,
(xcv) 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl,
5 (xcvi) 4-(difluoromethoxy)-3-fluorophenyl, and
(xcvii) 4-chloro-3-(difluoromethoxy)phenyl.

In an embodiment of the invention, n is 0, 1 or 2.

- 10 In another embodiment, n is 0.

If present, each R^4 independently represents a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl group.

In one embodiment, each R^4 independently represents a methyl or ethyl group.

15

X represents C(O), C(O)NH or CO(CHR¹⁷)_y(CHR¹⁸)_z, wherein the latter two groups are oriented such that the NH or (CHR¹⁷)_y(CHR¹⁸)_z moieties are attached to the R³ substituent group and wherein y is 0 or 1 and z is 0 or 1 provided that y + z is at least 1, i.e. 1 or 2.

20

R¹⁷ and R¹⁸ each independently represent a hydrogen atom or C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl (e.g. methyl) group, or R¹⁷ and R¹⁸ may together with the carbon atoms to which they are attached form a cyclopropyl ring.

- 25 In an embodiment of the invention, X represents C(O).

In another embodiment, X represents C(O)NH.

In still another embodiment, X represents $\text{CO}(\text{CHR}^{17})_y(\text{CHR}^{18})_z$ where y is 1, z is 0 and R^{17} represents a hydrogen atom; or y is 0, z is 1 and R^{18} represents a hydrogen atom; or y is 1, z is 1 and R^{17} and R^{18} each independently represent a hydrogen atom; or y is 1, z is 1 and R^{17} and R^{18} together with the carbon atoms to which they are attached form a
5 cyclopropyl ring.

R^7 and R^8 each independently represent a hydrogen atom, or a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl or C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group, or R^7 and R^8 may together with the nitrogen atom to which they are attached form a 4-, 5-, 6-
10 or 7-membered saturated heterocyclic ring optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl and C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy.

15 In one aspect, the saturated heterocyclic ring may contain a single ring heteroatom (being the nitrogen atom to which R^7 and R^8 are attached).

In an alternative aspect, the saturated heterocyclic ring may contain a second ring heteroatom selected from a nitrogen or oxygen atom.

20

In one embodiment, R^7 and R^8 each independently represent a hydrogen atom, or a C₁-C₄, or C₁-C₂ alkyl (e.g. methyl) or cyclopropyl group, or R^7 and R^8 may together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered saturated heterocyclic ring (e.g. azetidiny) optionally substituted by at least one substituent (e.g. one,
25 two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C₁-C₂ alkyl and C₁-C₂ alkoxy.

In another embodiment, R⁷ and R⁸ each independently represent a hydrogen atom or a methyl group.

In a further embodiment, R⁷ and R⁸ together with the nitrogen atom to which they are
5 attached form an azetidiny ring.

R⁹ and R¹⁰ are defined as described for R⁷ and R⁸ above.

R¹¹ and R¹² are defined as described for R⁷ and R⁸ above.

10

R¹³ and R¹⁴ each independently represent a hydrogen atom, or a C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl, C₃-C₆ cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C₁-C₆, or C₁-C₄, or C₁-C₂alkylcarbonyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy carbonyl or C₁-C₆, or C₁-C₄, or C₁-C₂ alkylsulphonyl group, or R¹³ and R¹⁴ may together with the
15 nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered saturated heterocyclic ring optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C₁-C₆, or C₁-C₄, or C₁-C₂ alkyl and C₁-C₆, or C₁-C₄, or C₁-C₂ alkoxy.

20 In one aspect, the saturated heterocyclic ring may contain a single ring heteroatom (being the nitrogen atom to which R¹³ and R¹⁴ are attached).

In an alternative aspect, the saturated heterocyclic ring may contain a second ring heteroatom selected from a nitrogen or oxygen atom.

25

In an embodiment, R¹³ and R¹⁴ each independently represent a hydrogen atom, or a C₁-C₄, or C₁-C₂ alkyl, cyclopropyl, C₁-C₄, or C₁-C₂alkylcarbonyl, C₁-C₄, or C₁-C₂ alkoxy carbonyl or C₁-C₄, or C₁-C₂ alkylsulphonyl group, or R¹³ and R¹⁴ may

together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered saturated heterocyclic ring (e.g. azetidiny) optionally substituted by at least one substituent (e.g. one, two, three or four substituents) independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C₁-C₂ alkyl and C₁-C₂ alkoxy.

5

In another embodiment, R¹³ and R¹⁴ each independently represent a hydrogen atom or a methyl group.

10

In a further embodiment, R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form an azetidiny ring.

R¹⁵ and R¹⁶ are defined as described for R⁷ and R⁸ above.

In a particular aspect of the invention,

15

R¹ represents -NR⁵R⁶ or a C₅-C₆ heteroaryl group;

20

R² represents a hydrogen atom or a group selected from cyano, -NR⁷R⁸, C₁-C₂ alkyl, C₁-C₂ alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl, wherein each of the alkyl, alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl groups may be optionally substituted by at least one substituent independently selected from fluorine, chlorine, -NR⁹R¹⁰ and C₁-C₂ alkoxy;

25

R³ represents a saturated or unsaturated 3- to 9-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen and oxygen, wherein the ring system is optionally substituted by at least one substituent independently selected from fluorine, chlorine, cyano, oxo, methyl, ethyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy and phenoxy;

n is 0, 1 or 2;

each R⁴ independently represents a methyl or ethyl group;

X represents C(O), C(O)NH or CO(CHR¹⁷)_y(CHR¹⁸)_z, wherein the latter two groups are oriented such that the NH or (CHR¹⁷)_y(CHR¹⁸)_z moieties are attached to the R³ substituent group;

y is 0 or 1 and z is 0 or 1 provided that y + z is at least 1;

5 R⁵ and R⁶ each independently represent a methyl group, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by at least one substituent independently selected from fluorine and methyl;

R⁷ and R⁸ each independently represent a hydrogen atom or a methyl group, or R⁷ and R⁸ may together with the nitrogen atom to which they are attached form an azetidiny ring;

10 R⁹ and R¹⁰ each independently represent a hydrogen atom or a methyl group; and

R¹⁷ and R¹⁸ each independently represent a hydrogen atom, or R¹⁷ and R¹⁸ may together with the carbon atoms to which they are attached form a cyclopropyl ring.

Examples of preferred compounds of the invention include:

15 1-[6-(4-Chloro-2-methylbenzoyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-{6-[(3-Chloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-3-yl)propan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-4-yl)propan-1-one;

1-{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-[(4-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclobutylethan-1-one;

30 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopentylethan-1-one;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-ethylpyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methoxypyridine;

5 4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-(trifluoromethyl)pyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile;

10 1-{6-[(3,5-Dichloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-fluoro-3-methylphenyl)propan-1-one;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-(trifluoromethyl)pyridine;

15 1-(6-{[3-Chloro-5-(trifluoromethyl)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-3-chloro-2-methylpyridine;

20 1-{6-[(4-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-(2-Methyl-6-{[4-(trifluoromethyl)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-{6-[(3-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-(2-Methyl-6-{[3-(trifluoromethyl)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(2-Methyl-6-{[4-(trifluoromethoxy)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

30 1-(6-{[3-Chloro-4-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[3-Fluoro-4-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[4-Fluoro-3-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(2-Methyl-6-{[3-methyl-5-(trifluoromethoxy)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

5 1-(6-{[4-(Difluoromethoxy)-3,5-dimethylphenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[4-(Difluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

10 1-(6-{[3-(Difluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-ethylbenzonitrile;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopropylpropan-1-one;

15 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopentylpropan-1-one;

1-{2-Methyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-{2-Methyl-6-[(oxan-3-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

1-{6-[(2,2-Dimethylcyclopropyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-Cyclobutanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-Cyclopentanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

30 1-{6-Cyclohexanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[6-({Bicyclo[2.2.1]heptan-2-yl}carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-{{6-[(4,4-Difluorocyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{2-Methyl-6-[(4-methylcyclohexyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 4-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}benzonitrile;

1-{{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 3-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-5-fluorobenzonitrile;

4-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-2-chlorobenzonitrile;

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-2-chlorobenzonitrile;

15 3-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-5-chlorobenzonitrile;

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-1-methyl-1,2-dihydropyridin-2-one;

20 2-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-5-chloropyridine;

2-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-5-fluoropyridine;

1-{{2-Methyl-6-(3-methylcyclobutanecarbonyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{{6-(3-Fluorocyclobutanecarbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

(2R)-1-{{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine;

30 (2S)-1-{{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine;

1-{{6-[(4-Chlorophenyl)carbonyl]-2-ethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{2-Cyclopropyl-6-[(3,4-dichlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

5-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-2-methyl-1,3-oxazole;

15 1-{6-Benzoyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-phenylpropan-1-one;

6-[(3-Chlorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

20 1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-3-fluoroazetidine;

6-[(3-Chloro-4-methylphenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

25 1-{2-Methyl-6-[(4-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3,4-dichlorophenyl)propan-1-one;

1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

30 1-{6-[(3-Fluoro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3,4-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3,5-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chlorophenyl)propan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-chlorophenyl)propan-1-one;

10 1-{6-[(3-Chloro-4-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-methylpyridine;

1-{6-[(3,4-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

15 1-{2-Methyl-6-[(3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyridine;

20 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopropylethan-1-one;

1-{6-[(2,3-Dihydro-1H-inden-2-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{2-Methyl-6-[(2-phenylcyclopropyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-fluoro-4-methylphenyl)propan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chloro-4-fluorophenyl)propan-1-one;

30 5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,3-dimethylpyridine;

3-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-5-chloropyridine;

4-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-2,6-dimethylpyridine;

5 1-{{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-[(4-Fluoro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 1-{{6-[(3,5-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-[(2,2-Dimethyloxan-4-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-(6-{{3-Chloro-5-(trifluoromethoxy)phenyl}carbonyl})-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ylazetidine;

15 1-{{6-[(3-Chloro-5-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-(2-Methyl-6-{{(1R,4R)-4-(trifluoromethyl)cyclohexyl}carbonyl})-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ylazetidine;

1-(2-Methyl-6-{{(1S,4R)-4-ethylcyclohexyl}carbonyl})-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ylazetidine;

1-{{6-[(4,4-Dimethylcyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-2-fluorobenzonitrile;

4-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}pyridazine;

30 1-{{6-[(3,3-Difluorocyclopentyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-1-methyl-1H-pyrazole;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole;

6-[(3-Chloro-5-fluorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

5 1-{6-[(Oxan-4-yl)carbonyl]-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

10 1-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyrrolidine;

1-{[4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}piperidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-phenoxy-pyrrolidine;

15 1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

20 4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

2-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine;

4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonitrile;

25 1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-6-[(4-chlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]azetidine;

30 3-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine;

1-[6-Cyclobutanecarbonyl-2-(oxan-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[6-(4-Chlorobenzoyl)-2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

{[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}(methyl)amine;

5 { [4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}dimethylamine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-(trifluoromethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 1-[(5R)-6-[3-Chloro-4-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

15 1-{6-[(4-Fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

25 4-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1H-pyrazole;

4-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole;

30 4-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-ethyl-1H-pyrazole;

1-{2,5-Dimethyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-Cyclobutanecarbonyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(2,3-Dihydro-1H-inden-2-yl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-{6-[(3-Chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 1-{2-Ethyl-6-[(4-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl} benzonitrile;

1-{2-Ethyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

15 1-{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-{2-Cyclopropyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl} benzonitrile;

1-{6-Cyclobutanecarbonyl-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 4-[6-(4-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]-1H-pyrazole;

1-[(5R)-6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

30 1-[(5R)-6-[(3-Chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[(4-Chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[(3-Chloro-5-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

5 3-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

4-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

10 4-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,6-dimethylpyridine;

5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-3-chloro-2-methylpyridine;

5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-chlorobenzonitrile;

15 1-[(5R)-6-[(3-Chloro-4-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylbenzonitrile;

20 5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile;

5-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-fluoro-2-methylpyridine;

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-methylbenzonitrile;

25 3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-fluorobenzonitrile;

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-chlorobenzonitrile;

30 1-[(5R)-6-(4-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-(3-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

4-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]benzonitrile;

1-[(5R)-6-(3-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

5 1-[(5R)-6-(4-Fluoro-3-methylbenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[4-(Difluoromethyl)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

10 1-[(5R)-6-[3-Chloro-4-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[4-Chloro-3-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

2-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,3-dihydro-1H-isoindole;

15 1-[2,5-Dimethyl-6-({1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl} carbonyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

4-(Azetidin-1-yl)-N-cyclopropyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxamide;

20 1-{6-[(4-Chlorophenyl)carbonyl]-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[(5R)-6-(4-Chlorobenzoyl)-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (Enantiomer 1 substantially as hereinbefore described and with reference to Example 182);

30 1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (Enantiomer 2 substantially as hereinbefore described and with reference to Example 183);

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-{[4-(Azetidin-1-yl)-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

5 1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

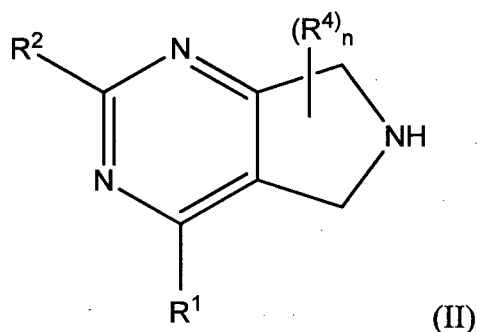
1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (a stereoisomer substantially as hereinbefore described and with reference to Example 189);

15 1-[(5R)-6-[4-(Difluoromethoxy)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine; and

1-[(5R)-6-[4-Chloro-3-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;
and their pharmaceutically acceptable salts.

20 It should be noted that each of the chemical compounds listed above represents a particular and independent aspect of the invention.

The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises
25 reacting a compound of formula



wherein n , R^1 , R^2 and R^4 are as defined in formula (I), with a compound of formula (III), R^3-X-L^1 , wherein L^1 represents a leaving group (e.g. a halogen atom (e.g. chlorine or bromine), a hydroxyl group or hydrocarbyloxy group such as C_1 - C_6 alkoxy (e.g. methoxy or ethoxy) or aryloxy (e.g. phenoxy or benzyloxy)) and X and R^3 are as defined in formula (I);

and optionally thereafter carrying out one or more of the following procedures:

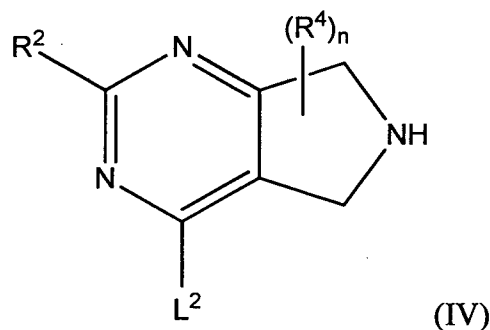
- removing any protecting groups
- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Reaction conditions for the process above will typically require activation of the compound of formula (III) which can be achieved by many of the widely known 'amide coupling' agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxy-7-azabenzotriazole (HOAt), 1-propanephosphonic acid cyclic anhydride or tetramethyluronium tetrafluoroborate (TBTU). This can be carried out in a suitable solvent such as dichloromethane or, in the case of TBTU, dimethylformamide, in the presence of a base such as triethylamine. The amine of formula (II) may be present during activation of the compound of formula (III), or may be added a short while afterwards. The reactions will typically occur at ambient room temperature (20 to 25°C).

As an alternative to carrying out the activation *in situ*, 'pre-activated' variants of the compound of formula (III) such as acid halides, acid anhydrides and esters (e.g. pentafluorophenyl esters) thereof can be used to react with the amine of formula (II) to form compounds of formula (I) under the appropriate conditions which will be known to the person skilled in the art.

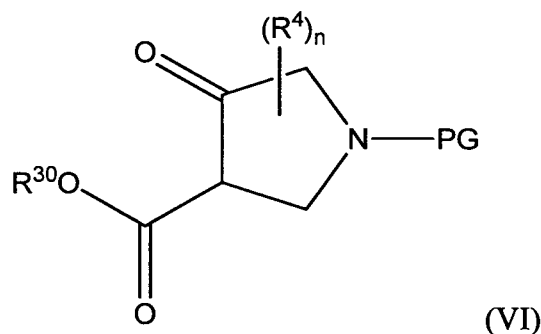
Compounds of formula (II) may be prepared by reacting a compound of formula

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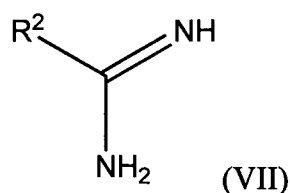


(or a protected derivative thereof in which the amine moiety is protected with a suitable protecting group such as *tert*-butoxycarbonyl (Boc)) in which L^2 represents a leaving group (e.g. a halogen (e.g. chlorine) atom or $-O-SO_2-CF_3$ group) and n , R^2 and R^4 are as defined in formula (I), with a compound of formula (V), R^1-H , wherein R^1 is as defined in formula (I).

Compounds of formula (IV) may be prepared by reacting a compound of formula



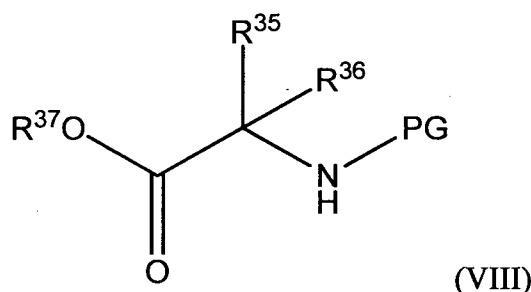
in which R^{30} represents a hydrocarbyl group such as an alkyl group (e.g. C_1 - C_6 alkyl, particularly ethyl, group), PG represents a nitrogen protecting group such as *tert*-butoxycarbonyl (Boc) and n and R^4 are as defined in formula (I), with a compound of formula



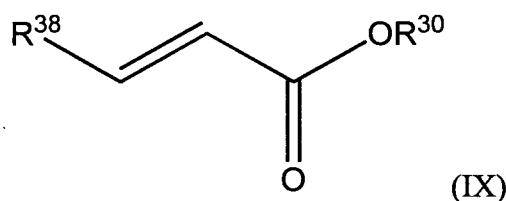
in which R^2 is as defined in formula (I), to obtain a compound of formula (IV) in which L^2 represents a hydroxyl group and, thereafter, reacting the compound obtained with a

halogenating agent or triflic anhydride to obtain a compound of formula (IV) in which L^2 represents a halogen or an $-O-SO_2-CF_3$ leaving group.

Compounds of formula (VI) may be prepared by reacting a compound of formula



in which R^{35} and R^{36} each independently represent a hydrogen atom or R^4 , R^{37} represents a hydrocarbyl group such as an alkyl group (e.g. C_1 - C_6 alkyl, particularly methyl, group) and R^4 and PG are as defined in formula (VI), with a compound of formula



in which R^{38} represents a hydrogen atom or R^4 , and R^4 and R^{30} are as defined in formula (VI).

Compounds of formulae (III), (V), (VII), (VIII) and (IX) are either commercially available, are well known in the literature or may be prepared using known techniques.

The compounds of formula (II) are novel and therefore the present invention further provides an intermediate of formula (II).

It will be appreciated by those skilled in the art that in the above processes certain functional groups such as phenol, hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of compounds of formula (I) may involve the addition and removal of one or more protecting groups during their synthesis.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-
5 Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a formate, hemi-formate, hydrochloride, hydrobromide, benzenesulphonate (besylate), saccharin (e.g.
10 monosaccharin), trifluoroacetate, sulphate, nitrate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, valerate, propanoate, butanoate, malonate, oxalate, 1-hydroxy-2-napthoate (xinafoate), methanesulphonate or *p*-toluenesulphonate salt.

In one aspect of the invention, compounds of formula (I) defined above may bear one or
15 more radiolabels. Such radiolabels may be introduced by using radiolabel-containing reagents in the synthesis of the compounds of formula (I) or may be introduced by coupling the compounds of formula (I) to chelating moieties capable of binding to a radioactive metal atom. Such radiolabeled versions of the compounds may be used, for example, in diagnostic imaging studies.

20 Compounds of formula (I) and their salts may be in the form of hydrates or solvates which form an aspect of the present invention. Such solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

25 Compounds of formula (I) above are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present
30 invention. Enantiomerically pure forms are particularly desired.

Compounds of formula (I) and their salts may be amorphous or in a polymorphic form or a mixture of any of these, each of which forms an aspect of the present invention.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as
5 pharmaceuticals, in particular as M4 muscarinic receptor modulators, e.g. positive allosteric modulators, and thus may be used in the treatment of schizophrenia and other psychotic disorders (e.g., schizophreniform disorder, schizoaffective disorder and psychosis), dementia (including behavioural and psychological symptoms of dementia, BPSD) and other cognitive disorders, anxiety disorders (e.g., generalized anxiety disorder,
10 post-traumatic stress disorder and panic attack), mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression), sleep disorders, disorders usually first diagnosed in infancy, childhood, or adolescence (e.g., attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X syndrome, Asperger syndrome and disruptive behaviour disorders), pain (e.g.
15 neuropathic pain including chemotherapy induced pain), neurodegenerative disorders (e.g. Parkinson's or Alzheimer's disease) and addiction (e.g. drug addiction, alcohol addiction and nicotine addiction).

Thus, the present invention provides a compound of formula (I) or a pharmaceutically
20 acceptable salt thereof as hereinbefore defined for use in therapy, in particular for the treatment of conditions whose development or symptoms are linked to M4 muscarinic receptor activity.

The present invention also provides the use of a compound of formula (I) or a
25 pharmaceutically acceptable salt thereof as hereinbefore defined for the preparation of a medicament for the treatment of conditions whose development or symptoms are linked to M4 muscarinic receptor activity.

In the context of the present specification, the term "therapy" also includes "prophylaxis"
30 unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

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

In particular, the compounds of the invention (including pharmaceutically acceptable salts)
10 may be used in the treatment of the positive symptoms of schizophrenia, schizophreniform disorder or schizoaffective disorder (e.g. voices or hallucinations), cognitive disorders (such as dementia and impaired learning) and also pain (such as neuropathic pain).

The invention also provides a method of treating at least one symptom or condition
15 associated with schizophrenia and other psychotic disorders (e.g., schizophreniform disorder, schizoaffective disorder and psychosis), dementia and other cognitive disorders, anxiety disorders (e.g., generalized anxiety disorder, post-traumatic stress disorder and panic attack), mood disorders (e.g., depressive disorders, major depressive disorders, bipolar disorders including bipolar I and II, bipolar mania, bipolar depression), sleep
20 disorders, disorders usually first diagnosed in infancy, childhood, or adolescence (e.g., attention-deficit disorder, autistic spectrum disorders, Rett syndrome, Fragile X syndrome, Asperger syndrome and disruptive behaviour disorders), pain (e.g. neuropathic pain including chemotherapy induced pain), neurodegenerative disorders (e.g. Parkinson's or Alzheimer's disease) and addiction (e.g. drug addiction, alcohol addiction and nicotine
25 addiction) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

Such symptoms and conditions include, but are not limited to, anxiety, agitation, hostility,
30 panic, an eating disorder, an affective symptom, a mood symptom, a negative and positive psychotic symptom commonly associated with psychosis and neurodegenerative disorder.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of a compound according to the invention (i.e. a compound of formula (I) or a pharmaceutically acceptable salt thereof), if inhaled, may be in the range from 0.05 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 micrograms per kilogram body weight ($\mu\text{g/kg}$). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

Therefore the present invention further provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention still further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceutics - The Science of Dosage Form Design", M. E. Aulton, Churchill Livingstone, 1988.

Pharmaceutically acceptable adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins,

such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, 5 polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene- polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of the present invention may be administered orally, 10 parenterally, by inhalation spray, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral administration is preferred. The pharmaceutical compositions of the invention may contain any conventional non-toxic pharmaceutically acceptable adjuvants, diluents or carriers. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, 15 intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. The suspension may be formulated according to techniques known in the art using suitable dispersing or wetting 20 agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable diluents and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are 25 conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long- 30 chain alcohol diluent or dispersant such as that described in Ph. Helv. or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders, granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions of the invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active ingredient. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above may also be administered in conjunction with other compounds used for the treatment of the above conditions.

5 The invention therefore further relates to combination therapies wherein a compound of formula (I) or a pharmaceutically acceptable salt thereof as previously defined or a pharmaceutical composition or formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as previously defined is administered with another therapeutic agent or agents, for the treatment of one or more of the conditions previously
10 indicated. Such therapeutic agents may be selected from the following:

(i) **antidepressants** such as, for example, amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, nortriptyline, nefazodone,
15 paroxetine, phenelzine, protriptyline, reboxetine, robaizotan, sertraline, sibutramine, thionisoxetine, tranlycypromaine, trazodone, trimipramine, venlafaxine, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(ii) **atypical antipsychotics** including, for example, quetiapine and pharmaceutically
20 active isomer(s) and/or metabolite(s) thereof;

(iii) **antipsychotics** including, for example, amisulpride, aripiprazole, asenapine, benisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, loxapine,
25 mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclonidine, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

30

(iv) **anxiolytics** including, for example, alnespirone, azapirones, benzodiazepines, barbiturates, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s)

thereof. Example anxiolytics include adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, quazepam, reclazepam, tracazolate, trepipam, temazepam, triazolam, uldazepam, and zolazepam; and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(v) **anticonvulsants** including, for example, carbamazepine, valproate, lamotrigine, and gabapentin, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(vi) **Alzheimer's therapies** including, for example, donepezil, memantine, tacrine, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(vii) **Parkinson's therapies** including, for example, deprenyl, L-dopa, Requip, Mirapex, monoamine oxidase type B (MAO-B) inhibitors such as selegiline and rasagiline, catechol-O-methyl transferase (COMT) inhibitors such as Tasmar, A-2 inhibitors, dopamine re-uptake inhibitors, NMDA antagonists, Nicotine agonists, and Dopamine agonists and inhibitors of neuronal nitric oxide synthase, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(viii) **migraine therapies** including, for example, almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, and zomitriptan, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(ix) **stroke therapies** including, for example, abciximab, activase, NXY-059, citicoline, crobenetine, desmoteplase, repinotan, traxoprodil, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(x) **urinary incontinence therapies** including, for example, darafenacin, falvoxate,

oxybutynin, propiverine, robalzotan, solifenacin, and tolterodine, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xi) **neuropathic pain therapies** including, for example, gabapentin, lidoderm, and pregablin, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xii) **nociceptive pain therapies** such as, for example, celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, and paracetamol, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xiii) **insomnia therapies** including, for example, allobarbitol, alonimid, amobarbital, benzocetamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, ethchlorvynol, etomidate, glutethimide, halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midafur, nisobamate, pentobarbital, phenobarbital, propofol, roletamide, triclofos, secobarbital, zaleplon, and Zolpidem, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xiv) **mood stabilizers** including, for example, carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, and verapamil, and equivalents and pharmaceutically active isomer(s) and/or metabolite(s) thereof;

(xv) 5HT_{1B} ligands such as, for example, compounds disclosed in WO 99/05134 and WO 02/08212;

(xvi) mGluR2 agonists;

(xvii) alpha 7 nicotinic agonists such as, for example, compounds disclosed in WO 96/006098, WO 97/030998, WO 99/003859, WO 00/042044, WO 01/029034, WO 01/60821, WO 01/36417, WO 02/096912, WO 03/087102, WO 03/087103, WO 03/087104, WO 2004/016617, WO 2004/016616, and WO 2004/019947;

(xviii) chemokine receptor CCRI inhibitors; and

(xix) delta opioid agonists such as, for example, compounds disclosed in WO 97/23466 and WO 02/094794.

5

Such combination products employ the compound of formula (I) or a pharmaceutically acceptable salt thereof as previously defined within the dosage range described herein and the other pharmaceutically active agent within approved dosage ranges and/or the dosage such as described in the publication reference.

10

In a further aspect the present invention provides a combination (for example for the treatment of schizophrenia, cognitive disorders or pain) of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined and one or more agents independently selected from carbamazepine, olanzapine, quetiapine, verapamil,

15

lamotrigine, oxcarbazepine, risperidone, aripiprazole, ziprasidone and lithium.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, and a preparation of a
20 second active ingredient which is carbamazepine, olanzapine, quetiapine, verapamil, lamotrigine, oxcarbazepine, risperidone, aripiprazole, ziprasidone or lithium, for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active
25 ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, and a preparation of a second active ingredient which is carbamazepine, olanzapine, quetiapine, verapamil, lamotrigine, oxcarbazepine, risperidone, aripiprazole, ziprasidone or lithium, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

30

The present invention will now be further explained by reference to the following illustrative examples, in which the starting materials and reagents used are available from commercial suppliers.

5 Nuclear magnetic resonance (NMR) spectra were recorded at 400MHz or 300MHz as stated and at 300.3K unless otherwise stated; the chemical shifts (δ) are reported in parts per million. Spectra were recorded using a Bruker 400 AVANCE instrument fitted with a 5mm BBFO probe with instrument controlled by Bruker TopSpin 2.1 software, or by a Bruker 300MHz AVANCE II instrument fitted with a 5mm DUL probe with instrument
10 controlled by Bruker TopSpin 1.3 software, or by a Jeol Lambda spectrometer (JN-LMA400) instrument fitted with a 5mm Jeol TH5 probe with instrument controlled by Jeol Delta software v4.3.5

In respect of NMR analysis, compounds of the formula (I) frequently exhibit signal
15 splitting and/or broadening due to conformationally restricted motion of the pendant substituents of the *N*-acyl pyrrolidine ring. These effects are temperature and solvent dependent and can complicate the assignment of signals and coupling constants. For the avoidance of doubt, such split or broadened signals have been assigned a chemical shift range as observed and have been designated as multiplets.

20

Purity was assessed using one or more of the following:

- UPLC with UV (photodiode array) detection over a wide range of wavelengths, normally 220-450nm, using a Waters Acquity UPLC system equipped with Acquity UPLC BEH or HSS C18 columns (2.1mm id x 50mm long) operated at 50
25 or 60°C. Mobile phases typically consisted of acetonitrile or methanol mixed with water containing either 0.05% formic acid or 0.025% ammonia. Mass spectra were recorded with a Waters SQD single quadrupole mass spectrometer using atmospheric pressure ionisation.
- Perkin Elmer 200 series system equipped with Agilent Poroshell 120 column (SB-
30 C18, 4.6mm id x 30mm, 2.7 μ m) operated at 20°C. Mobile phases consisted of acetonitrile and water, both containing 0.1%v/v formic acid. Mass spectra were

recorded with a PE SCIEX API 2000 MS/MS mass spectrometer. The system was controlled by Analyst software (version 1.5.1).

Compounds were purified using normal phase chromatography on silica, using Biotage or Isolute KP-Sil cartridges or Kinesis Telos Silica cartridges, or on basic silica, using Biotage or Isolute KP-NH cartridges, or by reverse phase chromatographic methods, using Biotage or Isolute KP-C18-HS cartridges or by SCX-2 catch-release cartridges, or by Preparative HPLC, or by Supercritical Fluid Chromatography (SFC).

Preparative HPLC was performed using one or more of the following:

- Agilent Technologies 1100 Series system or a Waters autopurification LC/MS system typically using Waters 19mm id x 100mm long C18 columns such as XBridge or SunFire 5 μ m materials at room temperature.
- Gilson HPLC system using Waters XBridge Column (C18, 5 μ m, 19mm id x 250mm), controlled by UniPoint software (version 2.10)
- Waters autopurification LC/MS system using Varian Column (C18, 5 μ m, 21.2mm id x 150mm), controlled by MassLynx software (version 4.0 SP4)

Mobile phases typically consisted of acetonitrile or methanol mixed with water containing either 0.1% formic acid or 0.1% ammonia, unless stated otherwise.

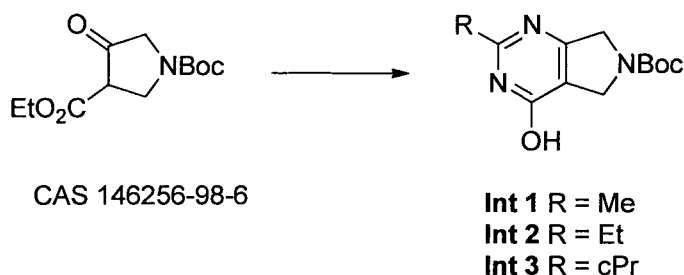
Room temperature in the following examples means a temperature in the range from 20°C to 25°C.

The following abbreviations are used in the Examples:

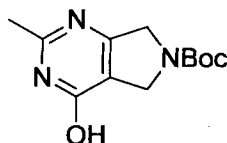
AcOH	acetic (ethanoic) acid
aq.	aqueous
Boc	<i>tert</i> -butoxy carbonyl
<i>Tert</i> - or <i>t</i> - BuOH	<i>tert</i> -butanol
CDCl ₃	deuterated chloroform

CD ₃ OD	deuterated methanol
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
EtOH	ethanol
g	grams
HCl	hydrochloric acid
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	high pressure liquid chromatography
LCMS	liquid chromatographic mass spectrometry
MgSO ₄	magnesium sulphate
MeOH	methanol
mg	milligrams
mins	minutes
mL	millilitres
mmol	millimoles
MS	mass spectrometry
NaBH ₄	sodium borohydride
NaH	sodium hydride
NaHCO ₃	sodium hydrogen carbonate
Na ₂ SO ₄	sodium sulphate
NH ₃	ammonia
NMR	nuclear magnetic resonance
ppm	parts per million
<i>iso</i> - or <i>i</i> -PrOH	isopropanol

RT	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Scheme 1**Intermediate 1**

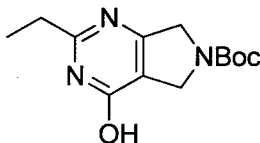
- 5 ***tert*-Butyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



A mixture of 1-*tert*-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 146256-98-6) (20 g, 78 mmol), acetamidine hydrochloride (7.35 g, 78 mmol), and triethylamine (28.2 mL, 202 mmol) in *tert*-butanol (100 mL) was heated under reflux overnight. The reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was partitioned between EtOAc and water. The organic layer was dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-15 % MeOH in EtOAc to afford the title compound.

- 15 ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.42 - 1.47 (m, 9H), 2.31 (s, 3H), 4.25 - 4.39 (m, 4H), 12.52 (br s, 1H).

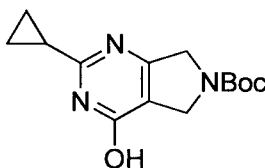
MS ES+ 252

Intermediate 2***tert*-Butyl 2-ethyl-4-hydroxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

Prepared in a similar manner to **Intermediate 1** using propionamidine hydrochloride (CAS 3599-89-1) and 1-*tert*-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 146256-98-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.18 (t, *J*=7.6 Hz, 3 H) 1.44 (s, 9 H) 2.58 (q, *J*=7.6 Hz, 2 H) 4.12 - 4.49 (m, 4 H) 12.50 (br. s., 1 H).

MS ES+ 266

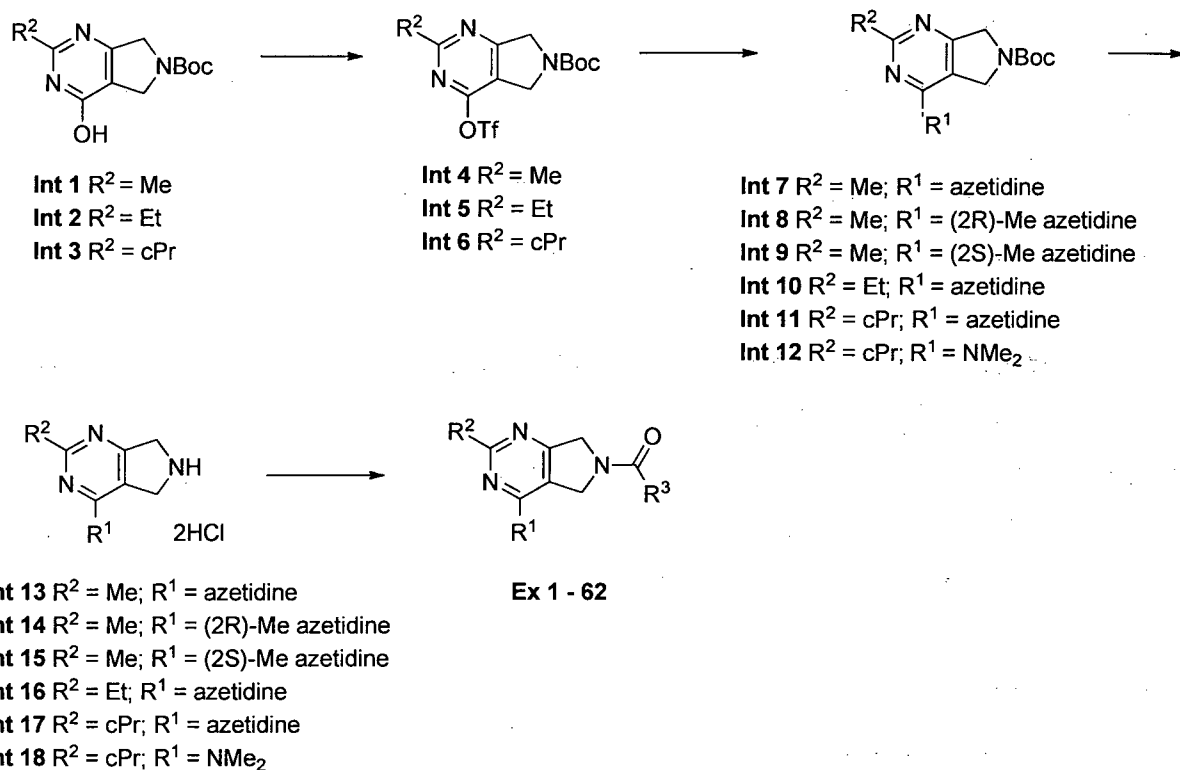
Intermediate 3***tert*-Butyl 2-cyclopropyl-4-hydroxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

Prepared in a similar manner to **Intermediate 1** using cyclopropylcarboxamidine hydrochloride (CAS 57297-29-7) and 1-*tert*-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 146256-98-6).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 0.93 - 1.08 (m, 4H), 1.38 - 1.47 (m, 9H), 1.91 - 1.99 (m, 1H), 4.22 - 4.34 (m, 4H), 12.73 (br s, 1H).

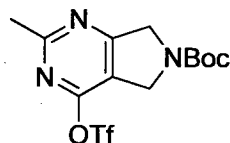
MS ES+ 278

Scheme 2



Intermediate 4

5 *tert*-Butyl 2-methyl-4-[(trifluoromethane)sulfonyloxy]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



10 Five solutions of *tert*-butyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 1**, 1.00 g, 3.98 mmol) in DCM (30 mL) were cooled to 0 °C under nitrogen. Triethylamine (0.67 mL, 4.78 mmol) was added to each, followed by triflic anhydride (0.74 mL, 4.38 mmol) dropwise. The reaction mixtures were stirred at 0 °C for 1 hour. The reactions were combined, diluted with DCM and washed with water. The organic layer was dried (phase separator) and concentrated *in vacuo* to afford the title compound which was taken on to the next step without further purification.

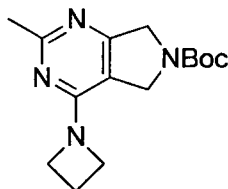
15

^1H NMR (400 MHz, DMSO- d_6): δ ppm 1.46 (s, 9H), 2.67 (s, 3H), 4.59 - 4.71 (m, 4H).

MS ES+ 291

Intermediate 7

***tert*-Butyl 4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



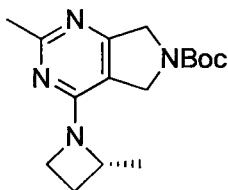
Azetidine (2.68 mL, 39.8 mmol) was added dropwise to a solution of *tert*-butyl 2-methyl-4-[(trifluoromethane)sulfonyloxy]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 4**, 7.63 g, 19.9 mmol) and triethylamine (3.32 mL, 23.9 mmol) in DCM (65 mL). The reaction mixture was stirred at RT for 30 minutes. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on basic silica, eluting with 0-30 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, CDCl₃): δ ppm 1.48 - 1.55 (m, 9H), 2.36 - 2.47 (m, 2H), 2.48 - 2.53 (m, 3H), 4.19 - 4.28 (m, 4H), 4.40 - 4.51 (m, 2H), 4.58 - 4.67 (m, 2H).

MS ES+ 291

Intermediate 8

***tert*-Butyl 2-methyl-4-[(2R)-2-methylazetidin-1-yl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



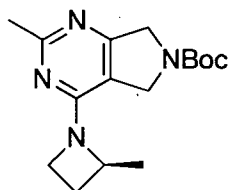
Prepared in a similar manner to **Intermediate 7** using **Intermediate 1** and (2R)-2-methylazetidine hydrochloride (CAS 791614-71-6).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.39 - 1.66 (m, 12 H) 2.05 (s, 2 H) 2.35 - 2.60 (m, 3 H) 3.93 - 4.27 (m, 3 H) 4.29 - 4.76 (m, 4 H)

MS ES+ 305

Intermediate 9

***tert*-Butyl 2-methyl-4-[(2*S*)-2-methylazetidin-1-yl]-5*H*,6*H*,7*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**



5

Prepared in a similar manner to **Intermediate 7** using **Intermediate 1** and (2*S*)-2-methylazetidine hydrochloride (CAS 935669-67-3)

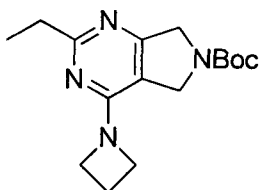
¹H NMR (400 MHz, CDCl₃) δ ppm 1.43 - 1.66 (m, 12 H) 1.89 - 2.12 (m, 2 H) 2.40 - 2.63

10 (m, 3 H) 3.92 - 4.27 (m, 3 H) 4.27 - 4.72 (m, 4 H)

MS ES+ 305

Intermediate 10

***tert*-Butyl 4-(azetidin-1-yl)-2-ethyl-5*H*,6*H*,7*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**



15

Prepared in a similar manner to **Intermediate 7** using **Intermediate 2**, triflic anhydride and then azetidine (CAS 503-29-7)

¹H NMR (400 MHz, CD₃OD) δ ppm 1.21 - 1.30 (m, 3 H) 1.51 (s, 9 H) 2.33 - 2.48 (m, 2 H)

20 2.59 - 2.74 (m, 2 H) 4.18 - 4.34 (m, 4 H) 4.36 - 4.69 (m, 4 H).

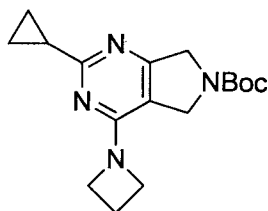
MS ES+ 305

Intermediate 11

***tert*-Butyl 4-(azetidin-1-yl)-2-cyclopropyl-5*H*,6*H*,7*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**

25

58

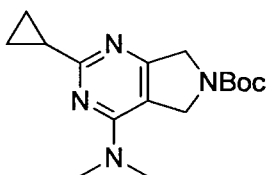


Prepared in a similar manner to **Intermediate 7** using **Intermediate 3**, triflic anhydride and then azetidine (CAS 503-29-7)

¹H NMR (400 MHz, CD₃OD): δ ppm 0.84 - 1.05 (m, 4H), 1.51 (s, 9H), 1.90 - 2.00 (m, 1H), 2.40 (m, 2H), 4.16 - 4.27 (m, 4H), 4.34 - 4.39 (m, 2H), 4.56 - 4.64 (m, 2H).
MS ES+ 317

Intermediate 12

tert-Butyl 2-cyclopropyl-4-(dimethylamino)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



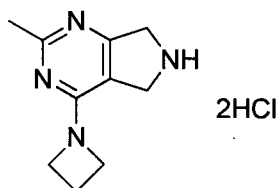
Prepared in a similar manner to **Intermediate 7** using **Intermediate 3**, triflic anhydride and then dimethylamine hydrochloride (CAS 506-59-2)

15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.70 - 1.00 (m, 4 H) 1.45 (s, 9 H) 1.84 - 2.00 (m, 1 H) 2.92 - 3.16 (m, 6 H) 4.03 - 4.37 (m, 2 H) 4.58 - 4.89 (m, 2 H)
MS ES+ 305

Intermediate 13

1-{2-Methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



Hydrogen chloride (4.0 M in dioxane, 3.4 mL, 13.8 mmol) was added to a solution of *tert*-butyl 4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 7**, 1.0 g, 3.44 mmol) in DCM (12 mL). The reaction was stirred at RT for 18 hours and was then concentrated *in vacuo* to afford the title compound.

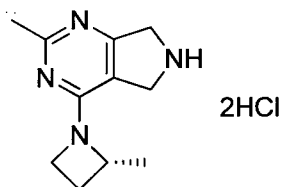
5

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.35 - 2.45 (m, 2H), 2.52 (br s, 3H), 4.25 - 4.64 (m, 8H), 10.77 (br s, 2H).

MS ES+ 191

10 **Intermediate 14**

(2R)-2-Methyl-1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



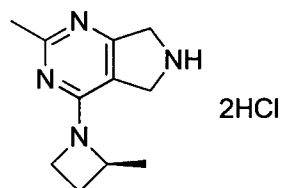
Prepared in a similar manner to **Intermediate 13** using **Intermediate 8**. The crude material was taken directly on to the next step.

15

MS ES+ 205

Intermediate 15

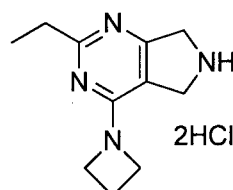
(2S)-2-Methyl-1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



Prepared in a similar manner to **Intermediate 13** using **Intermediate 9**. The crude material was taken directly on to the next step.

25

MS ES+ 205

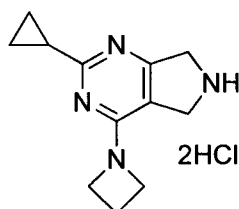
Intermediate 16**1-{2-Ethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride**

5 Prepared in a similar manner to **Intermediate 13** using **Intermediate 10**.

¹H NMR (400 MHz, CD₃OD) δ ppm 1.36 (t, *J*=7.5 Hz, 3 H) 2.45 - 2.64 (m, 2 H) 2.85 (q, *J*=7.5 Hz, 2 H) 4.32 - 4.50 (m, 2 H) 4.63 - 4.81 (m, 6 H).

MS ES+ 205

10

Intermediate 17**1-{2-Cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride**

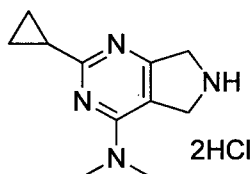
Prepared in a similar manner to **Intermediate 13** using **Intermediate 11**.

15

¹H NMR (400 MHz, CD₃OD) δ ppm 1.18 - 1.36 (m, 4 H) 1.92 - 2.16 (m, 1 H) 2.35 - 2.61 (m, 2 H) 4.21 - 4.46 (m, 2 H) 4.52 - 4.77 (m, 6 H).

MS ES+ 217

20

Intermediate 18**2-Cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine dihydrochloride**

Prepared in a similar manner to **Intermediate 13** using **Intermediate 12**.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.99 - 1.31 (m, 4 H) 2.12 - 2.23 (m, 1 H) 3.23 (s, 6 H) 4.36 - 4.90 (m, 4 H) 10.54 (br. s, 2 H).

5 MS ES+ 205

Compounds of formula (I) were synthesized *via* one of the following methods.

Method A

10 To a solution of acid (1.2 equiv.), 1-propanephosphonic acid cyclic anhydride (50 % in EtOAc, 1.5 equiv.), and triethylamine (1.2 equiv.) in DCM was added amine (1 equiv.). The reaction mixture was stirred at RT overnight. The mixture was diluted with DCM and washed with water and saturated sodium bicarbonate solution. The organics were dried (phase separator, MgSO_4 or Na_2SO_4) and concentrated *in vacuo*. The crude product was
15 purified by column chromatography on silica or basic silica (typically eluting with 0-15 % MeOH in DCM or 0-100 % EtOAc in petrol) or reverse phase preparative HPLC (typically eluting with acetonitrile/0.1 % NH_3 in water) to afford the compound of formula (I).

Method B

20 To a solution of amine (1 equiv.), acid (1.1 equiv.) and triethylamine (2.5 equiv.) in DMF was added HATU (1.5 equiv.) and the reaction stirred at RT for ~ 2 h. The mixture was diluted with DCM and washed with saturated sodium bicarbonate solution. The organics were dried (phase separator, MgSO_4 or Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica or basic silica (typically eluting
25 with 0-15 % MeOH in DCM or 0-100 % EtOAc in petrol) or reverse phase preparative HPLC (typically eluting with acetonitrile/0.1 % NH_3 in water) to afford the compound of formula (I).

Method C

30 A mixture of amine (1 equiv.), acid (1.1 equiv.), triethylamine (2.5 equiv.), EDC.HCl (1.5 equiv.) and HOAt (1.5 equiv.) in DCM was stirred at RT for 2 hours. The mixture was diluted with DCM and washed with saturated sodium bicarbonate solution. The organics

were dried (phase separator, MgSO₄ or Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica or basic silica (typically eluting with 0-15 % MeOH in DCM or 0-100 % EtOAc in petrol) or reverse phase preparative HPLC (typically eluting with acetonitrile/0.1 % NH₃ in water) to afford the compound of formula (I).

Method D

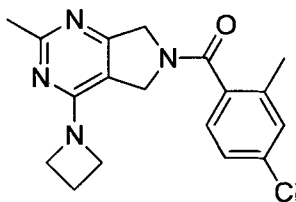
A solution of acid chloride (1.1 equiv.) in DCM was added to a solution/suspension of amine (1 equiv.) and triethylamine (3.2 equiv.) in DCM (5 mL) and THF (5 mL) at RT. The mixture was partitioned between DCM and water. The organic phase was dried (phase separator, MgSO₄ or Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica or basic silica (typically eluting with 0-15 % MeOH in DCM or 0-100 % EtOAc in petrol) or reverse phase preparative HPLC (typically eluting with acetonitrile/0.1 % NH₃ in water) to afford the compound of formula (I).

Method E

To a solution of amine (1 equiv.) and acid (1.2 equiv.) in DMF at 0 °C was added TBTU (1.2 equiv.). The reaction was stirred at this temperature for 20 minutes then DIPEA (3 equiv.) was added. The reaction was stirred at RT for ~ 2 hours. The reaction was diluted with EtOAc and was washed with water then brine. The organic phase was dried (phase separator, MgSO₄ or Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica or basic silica (typically eluting with 0-15 % MeOH in DCM or 0-100 % EtOAc in petrol) or reverse phase preparative HPLC (typically eluting with acetonitrile/0.1 % NH₃ in water) to afford the compound of formula (I).

Example 1

1-[6-(4-Chloro-2-methylbenzoyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



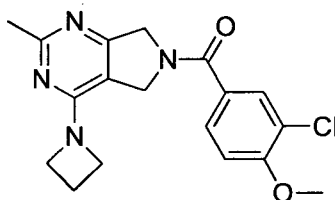
Prepared via Method C using **Intermediate 13** and 4-chloro-2-methylbenzoic acid (CAS 7499-07-2).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.17 - 2.25 (m, 4 H), 2.30 - 2.40 (m, 4 H), 3.99 - 4.06 (m, 2 H), 4.16 - 4.86 (m, 6 H), 7.29 - 7.38 (m, 2 H), 7.41 (s, 1 H).

MS ES+ 343

10 Example 2

1-[(6-[(3-Chloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine]



Prepared via Method A using **Intermediate 13** and 3-chloro-4-methoxybenzoic acid (CAS 37908-96-6).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.12 - 2.42 (m, 5 H) 3.91 (s, 3 H) 3.99 - 4.29 (m, 4 H) 4.48 - 4.90 (m, 4 H) 7.05 - 7.25 (m, 1 H) 7.28 - 7.38 (m, 1 H) 7.45 - 7.58 (m, 1 H).

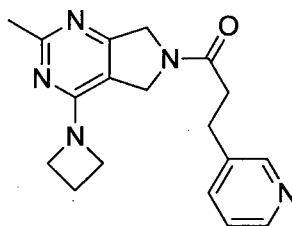
MS ES+ 359

20

Example 3

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-3-yl)propan-1-one

64



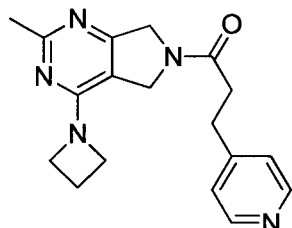
Prepared via Method A using **Intermediate 13** and 3-pyridinepropanoic acid (CAS 3724-19-4).

¹H NMR (400 MHz, CDCl₃) δ ppm 2.28 - 2.58 (m, 5 H) 2.59 - 2.73 (m, 2 H) 2.96 - 3.14 (m, 2 H) 4.00 - 4.35 (m, 4 H) 4.40 - 4.84 (m, 4 H) 7.14 - 7.26 (m, 1 H) 7.55 - 7.69 (m, 1 H) 8.39 - 8.50 (m, 1 H) 8.50 - 8.57 (m, 1 H).

MS ES+ 324

Example 4

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-4-yl)propan-1-one



Prepared via Method A using **Intermediate 13** and 3-(4-pyridyl)propionic acid (CAS 6318-43-0).

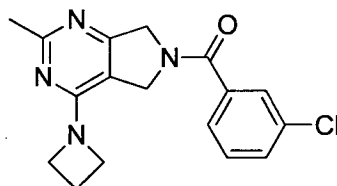
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 - 2.41 (m, 5 H) 2.65 - 2.78 (m, 2 H) 2.78 - 2.94 (m, 2 H) 4.06 - 4.26 (m, 4 H) 4.29 - 4.85 (m, 4 H) 7.19 - 7.42 (m, 2 H) 8.27 - 8.55 (m, 2 H).

MS ES+ 324

Example 5

1-{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

65



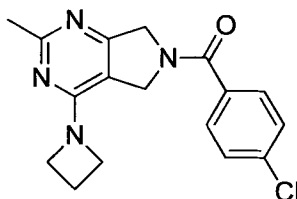
Prepared via Method A using **Intermediate 13** and 3-chlorobenzoic acid (CAS 535-80-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.40 (m, 5 H) 4.05 - 4.08 (m, 2 H) 4.18 -
5 4.26 (m, 2 H) 4.54 - 4.57 (m, 2 H) 4.80 - 4.84 (m, 2 H) 7.48 - 7.54 (m, 1 H) 7.57 - 7.58 (m,
2 H) 7.64 - 7.67 (m, 1 H).

MS ES+ 329

Example 6

10 **1-{6-[(4-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**



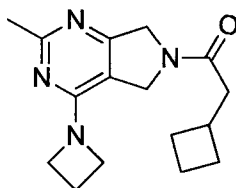
Prepared via Method A using **Intermediate 13** and 4-chlorobenzoic acid (CAS 74-11-3).

15 ¹H NMR (400 MHz, CDCl₃): δ ppm 2.31 - 2.56 (m, 5H), 4.08 - 4.33 (m, 4H), 4.53 - 4.72
(m, 2H), 4.75 - 4.99 (m, 2H), 7.40 - 7.46 (m, 2H), 7.48 - 7.55 (m, 2H).

MS ES+ 329

Example 7

20 **1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclobutylethan-1-one**

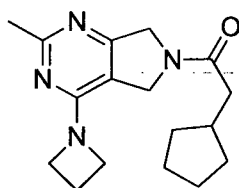


Prepared via Method A using **Intermediate 13** and cyclobutaneacetic acid (CAS 6540-33-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.60 - 1.75 (m, 2 H) 1.77 - 1.91 (m, 2 H) 2.01 - 2.13 (m, 2 H) 2.26 - 2.40 (m, 5 H) 2.45 - 2.49 (m, 2 H) 2.60 - 2.73 (m, 1 H) 4.17 - 4.18 (m, 4 H) 4.29 - 4.32 (m, 1 H) 4.56 - 4.58 (m, 2 H) 4.80 - 4.82 (m, 1 H).
MS ES+ 287

Example 8

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopentylethan-1-one

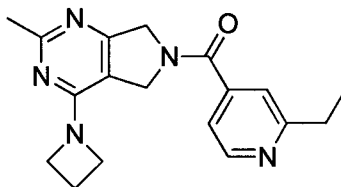


Prepared via Method A using **Intermediate 13** and cyclopentaneacetic acid (CAS 1123-00-8).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.10 - 1.23 (m, 2 H) 1.51 - 1.74 (m, 4 H) 1.84 - 2.00 (m, 2 H) 2.31 - 2.42 (m, 3 H) 2.41 - 2.51 (m, 2 H) 2.53 (s, 3 H) 4.26 - 4.30 (m, 4 H) 4.55 - 4.65 (m, 2 H) 4.75 - 4.77 (m, 2 H).
MS ES+ 301

Example 9

4-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-ethylpyridine



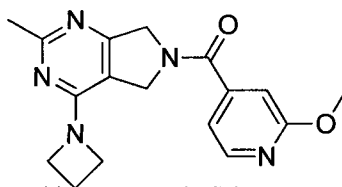
Prepared via Method B using **Intermediate 13** and 2-ethylisonicotinic acid (CAS 3376-96-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.26 (t, *J*=7.5 Hz, 3 H) 1.24 - 1.26 (m, 1 H) 2.18 - 2.42 (m, 5 H) 2.82 (q, *J*=7.5 Hz, 2 H) 4.04 - 4.08 (m, 2 H) 4.18 - 4.25 (m, 2 H) 4.46 - 4.61 (m, 2 H) 4.74 - 4.89 (m, 2 H) 7.36 - 7.38 (m, 1 H) 7.43 - 7.44 (m, 1 H) 8.59 - 8.60 (m, 1 H).

5 MS ES+ 324

Example 10

4-{{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methoxypyridine



10

Prepared via Method B using **Intermediate 13** and 2-methoxypyridine-4-carboxylic acid (CAS 105596-63-2).

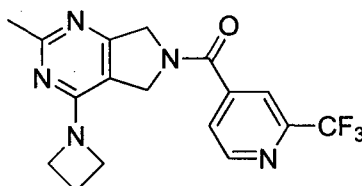
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.41 (m, 5 H) 3.90 (s, 3 H) 4.04 - 4.08 (m, 2 H) 4.20 - 4.22 (m, 2 H) 4.45 - 4.62 (m, 2 H) 4.73 - 4.89 (m, 2 H) 6.98 (s, 1 H) 7.13 - 7.14 (m, 1 H) 8.28 - 8.29 (m, 1 H).

15

MS ES+ 326

20 Example 11

4-{{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-(trifluoromethyl)pyridine



25

Prepared via Method B using **Intermediate 13** and 2-(trifluoromethyl)isonicotinic acid (CAS 131747-41-6).

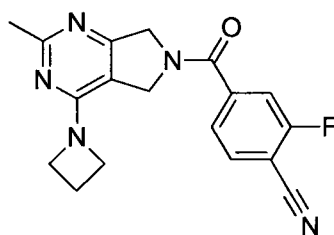
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.16 - 2.42 (m, 5 H) 4.04 - 4.08 (m, 2 H) 4.18 - 4.27 (m, 2 H) 4.56 - 4.60 (m, 2 H) 4.73 - 4.91 (m, 2 H) 7.93 - 7.96 (m, 1 H) 8.07 (s, 1 H) 8.91 - 8.92 (m, 1 H).

MS ES+ 364

5

Example 12

4-{{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile



10 Prepared via Method A using **Intermediate 13** and 4-cyano-3-fluorobenzoic acid (CAS 176508-81-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.42 (m, 5 H) 4.04 - 4.08 (m, 2 H) 4.20 - 4.24 (m, 2 H) 4.49 - 4.64 (m, 2 H) 4.72 - 4.93 (m, 2 H) 7.61 - 7.63 (m, 1 H) 7.77 - 7.79 (m, 1 H) 8.04 - 8.08 (m, 1 H).

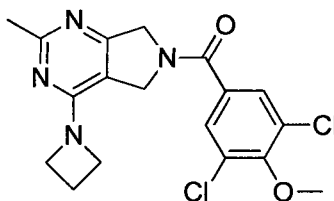
15

MS ES+ 338

Example 13

1-{6-[(3,5-Dichloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

20



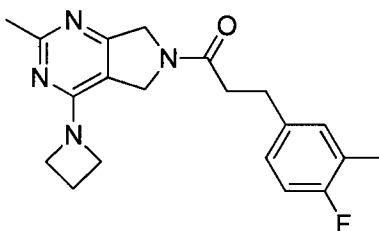
Prepared via Method A using **Intermediate 13** and 3,5-dichloro-4-methoxybenzoic acid (CAS 37908-97-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.21 - 2.43 (m, 5 H) 3.89 (s, 3 H) 4.07 - 4.10 (m, 2 H) 4.17 - 4.27 (m., 2 H) 4.55 - 4.60 (m, 2 H) 4.83 - 4.86 (m, 2 H) 7.68 - 7.80 (m, 2 H).

MS ES+ 393

5 **Example 14**

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-fluoro-3-methylphenyl)propan-1-one



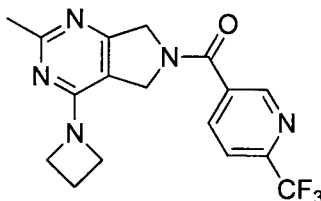
Prepared via Method A using **Intermediate 13** and 4-fluoro-3-methylbenzenepropanoic acid (CAS 881189-64-6).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.20 (s, 3H), 2.26 - 2.39 (m, 5H), 2.59 - 2.70 (m, 2H), 2.77 - 2.86 (m, 2H), 4.09 - 4.25 (m, 4H), 4.32 - 4.57 (m, 2H), 4.59 - 4.81 (m, 2H), 6.97 - 7.06 (m, 1H), 7.07 - 7.13 (m, 1H), 7.15 - 7.20 (m, 1H).

15 MS ES+ 355

Example 15

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-(trifluoromethyl)pyridine



Prepared via Method A using **Intermediate 13** and 6-trifluoromethyl-3-pyridinecarboxylic acid (CAS 231291-22-8).

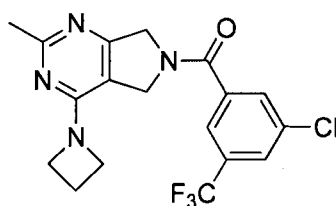
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.45 (m, 5 H) 4.05 - 4.09 (m, 2 H) 4.18 - 4.29 (m, 2 H) 4.57 - 4.65 (m, 2 H) 4.86 - 4.89 (m, 2 H) 8.02-8.04 (m, 1 H) 8.34 - 8.36 (m, 1 H) 8.99 (s, 1 H).

MS ES+ 364

5

Example 16

1-(6-{{3-Chloro-5-(trifluoromethyl)phenyl}carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



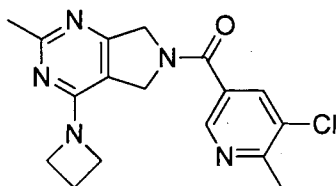
10 Prepared via Method A using **Intermediate 13** and 3-chloro-5-(trifluoromethyl)benzoic acid (CAS 53985-49-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 - 2.41 (m, 5 H) 4.04 - 4.08 (m, 2 H) 4.27 - 4.27 (m, 2 H) 4.54 - 4.61 (m, 2 H) 4.81 - 4.85 (m, 2 H) 7.88 - 8.11 (m, 3 H).

15 MS ES+ 397

Example 17

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-3-chloro-2-methylpyridine



20

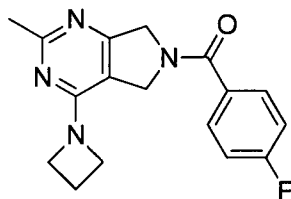
Prepared via Method A using **Intermediate 13** and 5-chloro-6-methyl-3-pyridinecarboxylic acid (CAS 1256835-19-4).

25 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.40 (m, 5 H) 2.58 - 2.74 (m, 3 H) 4.07 - 4.10 (m, 2 H) 4.19 - 4.26 (m, 2 H) 4.53 - 4.69 (m, 2 H) 4.85 - 4.88 (m, 2 H) 8.10 - 8.13 (m, 1 H) 8.63 - 8.70 (m, 1 H).

MS ES+ 344

Example 18

1-{6-[(4-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



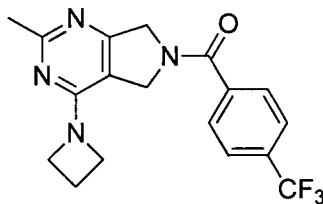
Prepared via Method A using **Intermediate 13** and 4-fluorobenzoic acid (CAS 456-22-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.42 (m, 5 H) 4.05 - 4.09 (m, 2 H) 4.19 - 4.25 (m, 2 H) 4.55 - 4.57 (m, 2 H) 4.81 - 4.85 (m, 2 H) 7.28 - 7.32 (m, 2 H) 7.69 - 7.72 (m, 2 H).

MS ES+ 313

Example 19

1-(2-Methyl-6-{[4-(trifluoromethyl)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



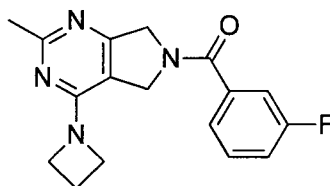
Prepared via Method A using **Intermediate 13** and 4-(trifluoromethyl)benzoic acid (CAS 455-24-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 - 2.43 (m, 5 H) 4.04 - 4.08 (m, 2 H) 4.19 - 4.26 (m, 2 H) 4.46 - 4.64 (m, 2 H) 4.75 - 4.91 (m, 2 H) 7.76 - 7.89 (m, 4 H).

MS ES+ 363

Example 20

1-{6-[(3-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 13** and 3-fluorobenzoic acid (CAS 455-38-9).

5

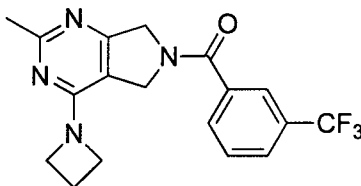
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 - 2.41 (m, 5 H) 4.05 - 4.08 (m, 2 H) 4.17 - 4.27 (m, 2 H) 4.53 - 4.57 (m, 2 H) 4.80 - 4.84 (m, 2 H) 7.33 - 7.37 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.49 - 7.59 (m, 1 H).

MS ES+ 313

10

Example 21

1-(2-Methyl-6-[[3-(trifluoromethyl)phenyl]carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



15 Prepared via Method A using **Intermediate 13** and 3-(trifluoromethyl)benzoic acid (CAS 454-92-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.12 - 2.42 (m, 5 H) 4.03 - 4.07 (m, 2 H) 4.18 - 4.27 (m, 2 H) 4.55 - 4.59 (m, 2 H) 4.78 - 4.93 (m, 2 H) 7.66 - 7.79 (m, 1 H) 7.87 - 7.89 (m, 1 H) 7.92 - 8.00 (m, 2 H).

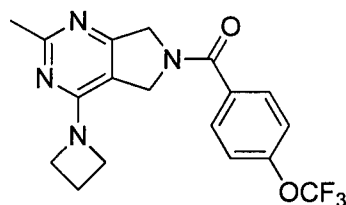
20

MS ES+ 363

Example 22

1-(2-Methyl-6-[[4-(trifluoromethoxy)phenyl]carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine

25

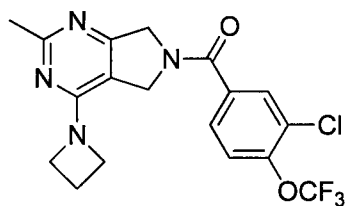


Prepared via Method A using **Intermediate 13** and 4-(trifluoromethoxy)benzoic acid (CAS 330-12-1).

- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.19-2.41 (m, 5H), 4.02-4.11 (m, 2H), 4.14-4.28 (m, 2H), 4.51-4.61 (m, 2H), 4.78-4.88 (m, 2H), 7.41-7.50 (m, 2H), 7.71-7.82 (m, 2H).
MS ES+ 379

Example 23

- 10 **1-(6-([3-Chloro-4-(trifluoromethoxy)phenyl]carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine**

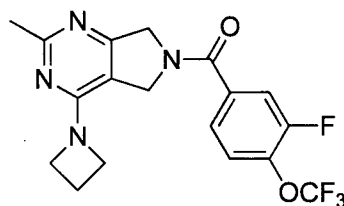


Prepared via Method A using **Intermediate 13** and 3-chloro-4-(trifluoromethoxy)benzoic acid (CAS 158580-93-9).

- 15 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.20-2.39 (m, 6H), 3.99-4.11 (m, 1H), 4.13-4.29 (m, 2H), 4.57 (s, 2H), 4.78-4.88 (m, 2H), 7.58-7.77 (m, 2H), 7.90-7.97 (m, 1H).
MS ES+ 413

20 Example 24

- 1-(6-([3-Fluoro-4-(trifluoromethoxy)phenyl]carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine**

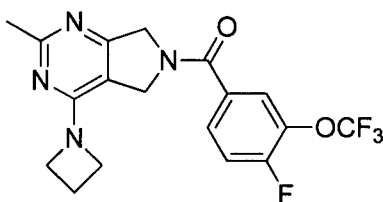


Prepared via Method A using **Intermediate 13** and 3-fluoro-4-trifluoromethoxybenzoic acid (CAS 886498-89-1).

- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.21-2.41 (m, 5H), 4.02-4.12 (m, 2H), 4.14-4.28 (m, 2H), 4.54-4.59 (m, 2H), 4.77-4.89 (m, 2H), 7.51-7.62 (m, 1H), 7.64-7.72 (m, 1H), 7.75-7.83 (m, 1H).
MS ES+ 397

10 **Example 25**

1-(6-{{[4-Fluoro-3-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



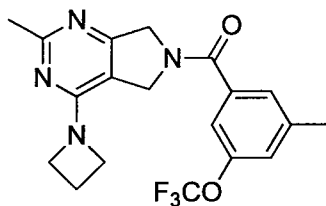
- 15 Prepared via Method A using **Intermediate 13** and 4-fluoro-3-(trifluoromethoxy)benzoic acid (CAS 886496-49-7).

- ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.21-2.40 (m, 5H), 4.00-4.10 (m, 2H), 4.12-4.29 (m, 2H), 4.53-4.60 (m, 2H), 4.80-4.87 (m, 2H), 7.56-7.66 (m, 1H), 7.70-7.78 (m, 1H), 7.82-7.92 (m, 1H).
20 MS ES+ 397

Example 26

1-(2-Methyl-6-{{[3-methyl-5-(trifluoromethoxy)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

75



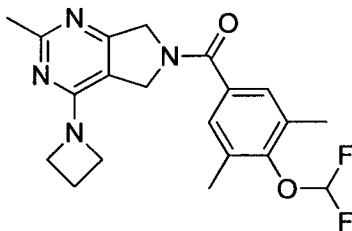
Prepared via Method A using **Intermediate 13** and 3-methyl-5-(trifluoromethoxy)benzoic acid (CAS 916420-51-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19-2.43 (m, 8H), 4.05 (s, 2H), 4.15-4.27 (m, 2H), 4.50-4.58 (m, 2H), 4.83 (s, 2H), 7.34 (s, 1H), 7.37-7.44 (m, 1H), 7.46 (s, 1H).

MS ES+ 393

Example 27

1-(6-([4-(Difluoromethoxy)-3,5-dimethylphenyl]carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



Prepared via Method A using **Intermediate 13** and 4-(difluoromethoxy)-3,5-dimethylbenzoic acid (CAS 1039927-58-6).

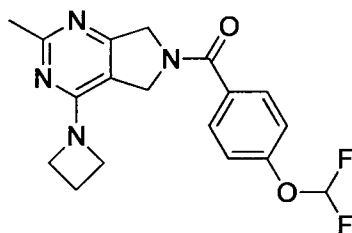
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.41 (m, 11 H) 3.99 - 4.30 (m, 4 H) 4.51 - 4.88 (m, 4 H) 6.73 - 7.25 (m, 1 H) 7.41 (s, 1 H).

MS ES+ 389

Example 28

1-(6-([4-(Difluoromethoxy)phenyl]carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine

76



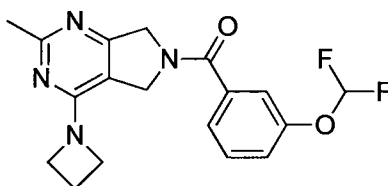
Prepared via Method A using **Intermediate 13** and 4-difluoromethoxybenzoic acid (CAS 4837-20-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.25-2.41 (m, 5H), 4.01-4.10 (m, 2H), 4.13-4.30 (m, 2H), 4.50-4.61 (m, 2H), 4.77-4.89 (m, 2H), 7.12-7.57 (m, 3H), 7.65-7.76 (m, 2H).

MS ES+ 361

Example 29

1-(6-{[3-(Difluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



Prepared via Method A using **Intermediate 13** and 3-(difluoromethoxy)benzoic acid (CAS 4837-19-8).

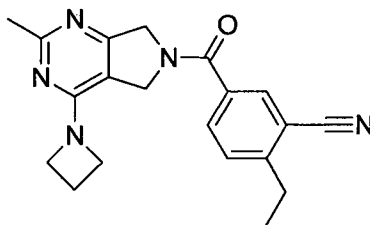
15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20-2.40 (m, 5H), 4.00-4.10 (m, 2H), 4.15-4.28 (m, 2H), 4.49-4.60 (m, 2H), 4.77-4.88 (m, 2H), 7.11-7.59 (m, 5H).

MS ES+ 361

Example 30

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-ethylbenzonitrile



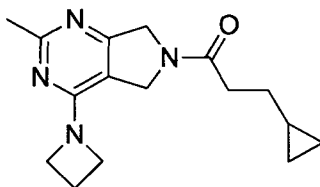
Prepared via Method A using **Intermediate 13** and 3-cyano-4-ethylbenzoic acid (CAS 684249-28-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.18 - 1.38 (m, 3 H) 2.20 - 2.44 (m, 5 H) 2.77 - 2.95 (m, 2 H) 4.02 - 4.29 (m, 4 H) 4.53 - 4.90 (m, 4 H) 7.51 - 7.65 (m, 1 H) 7.83 - 7.94 (m, 1 H) 7.98 - 8.07 (m, 1 H)

MS ES+ 348

Example 31

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopropylpropan-1-one



Prepared via Method A using **Intermediate 13** and 3-cyclopropylpropanoic acid (CAS 5618-03-1).

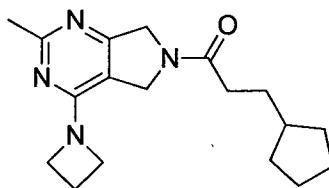
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.00-0.09 (m, 2H), 0.32-0.42 (m, 2H), 0.69-0.81 (m, 1H), 1.39-1.50 (m, 2H), 2.24-2.46 (m, 7H), 4.09-4.24 (m, 4H), 4.28-4.87 (m, 4H).

MS ES+ 287

Example 32

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopentylpropan-1-one

78



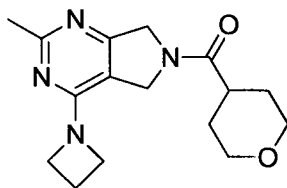
Prepared via Method A using **Intermediate 13** and cyclopentanepropanoic acid (CAS 140-77-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.00 - 1.18 (m, 2 H) 1.37 - 1.66 (m, 6 H) 1.66 - 1.87 (m, 3 H) 2.25 - 2.41 (m, 7 H) 4.03 - 4.26 (m, 4 H) 4.28 - 4.86 (m, 4 H).

MS ES+ 315

Example 33

1-{2-Methyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



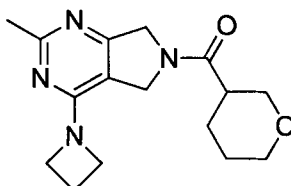
Prepared via Method A using **Intermediate 13** and tetrahydro-2H-pyran-4-carboxylic acid (CAS 5337-03-1).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.52 - 1.70, (m, 4H) 2.27 - 2.42, (m, 5H) 2.70 - 2.89 (m, 1H), 3.35 - 3.44 (m, 2H), 3.82 - 3.94 (m, 2H), 4.11 - 4.25 (m, 4H), 4.31 - 4.63 (m, 2H), 4.65 - 4.93 (m, 2H).

MS ES+ 303

Example 34

1-{2-Methyl-6-[(oxan-3-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



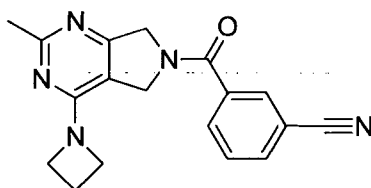
Prepared via Method A using **Intermediate 13** and 3,4,5,6-tetrahydro-2H-pyran-3-carboxylic acid (CAS 873397-34-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.42 - 1.73 (m, 3 H) 1.81 - 1.99 (m, 1 H) 2.19 - 2.41 (m, 5 H) 2.62 - 2.89 (m, 1 H) 3.22 - 3.39 (m, 2 H) 3.70 - 3.99 (m, 2 H) 4.06 - 4.27 (m, 4 H) 4.27 - 5.03 (m, 4 H)

MS ES+ 303

Example 35

3-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}benzonitrile



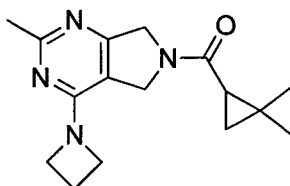
Prepared via Method A using **Intermediate 13** and 3-cyanobenzoic acid (CAS 1877-72-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18-2.42 (m, 5H), 4.00-4.11 (m, 2H), 4.15-4.29 (m, 2H), 4.52-4.61 (m, 2H), 4.76-4.89 (m, 2H), 7.65-7.73 (m, 1H), 7.90-8.01 (m, 2H), 8.05-8.12 (m, 1H).

MS ES+ 320

Example 36

1-{6-[(2,2-Dimethylcyclopropyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 13** and 2,2-dimethylcyclopropanecarboxylic acid (CAS 75885-59-5).

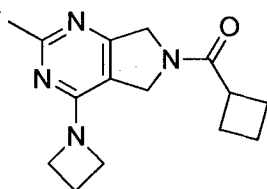
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.54 - 0.77 (m, 1 H) 0.91 - 1.07 (m, 4 H) 1.15 - 1.28 (m, 3 H) 1.68 - 1.81 (m, 1 H) 2.21 - 2.41 (m, 5 H) 4.06 - 4.27 (m, 4 H) 4.27 - 5.11 (m, 4 H).

MS ES+ 287

5

Example 37

1-{6-Cyclobutanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



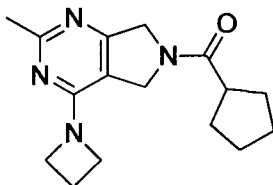
10 Prepared via Method A using **Intermediate 13** and cyclobutanecarboxylic acid (CAS 3721-95-7).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.66 - 2.24 (m, 6H), 2.27 - 2.39 (m, 6H), 4.06 - 4.76 (m, 8H).

15 MS ES+ 273

Example 38

1-{6-Cyclopentanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



20

Prepared via Method A using **Intermediate 13** and cyclopentanecarboxylic acid (CAS 3400-45-1).

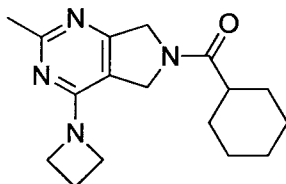
¹H NMR (400 MHz, CDCl₃): δ ppm 1.61 - 1.71 (m, 2H), 1.73 - 1.99 (m, 6H), 2.38 - 2.49 (m, 2H), 2.49 - 2.56 (m, 3H), 2.78 - 2.91 (m, 1H), 4.22 - 4.32 (m, 4H), 4.57 - 4.67 (m, 2H), 4.73 - 4.86 (m, 2H).

25

MS ES+ 287

Example 39

1-{6-Cyclohexanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



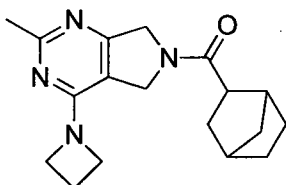
Prepared via Method A using **Intermediate 13** and cyclohexanecarboxylic acid (CAS 98-89-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.06 - 1.43 (m, 5 H) 1.56 - 1.81 (m, 5 H) 2.18 - 2.41 (m, 6 H) 4.06 - 4.27 (m, 4 H) 4.27 - 4.95 (m, 4 H).

MS ES+ 301

Example 40

1-[6-({Bicyclo[2.2.1]heptan-2-yl}carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



Prepared via Method A using **Intermediate 13** and bicyclo[2.2.1]heptane-2-carboxylic acid (CAS 824-62-4).

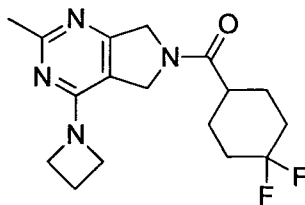
20

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15 - 1.77 (m, 8 H) 2.08 - 2.40 (m, 6 H) 2.57 - 2.73 (m, 1 H) 2.85 - 3.03 (m, 1 H) 4.02 - 4.26 (m, 4 H) 4.28 - 4.99 (m, 4 H).

MS ES+ 313

25 **Example 41**

1-{6-[(4,4-Difluorocyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 13** and 4,4-difluorocyclohexylcarboxylic acid
 5 (CAS 122665-97-8).

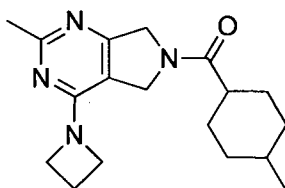
¹H NMR (400 MHz, CDCl₃): δ ppm 1.71 - 2.07 (m, 6H) 2.18 - 2.33 (m, 2H) 2.40 - 2.56 (m, 6H) 4.22 - 4.31 (m, 4H) 4.58 - 4.65 (m, 2H) 4.73 - 4.85 (m, 2H).

MS ES+ 337

10

Example 42

1-{2-Methyl-6-[(4-methylcyclohexyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



15 Prepared via Method A using **Intermediate 13** and 4-methylcyclohexanecarboxylic acid (CAS 4331-54-8).

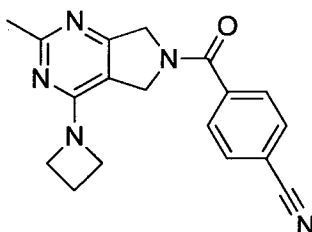
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 0.92 (m, 3 H) 0.92 - 1.09 (m, 2 H) 1.26 - 1.50 (m, 3 H) 1.60 - 1.83 (m, 4 H) 2.22 - 2.42 (m, 6 H) 4.06 - 4.26 (m, 4 H) 4.26 - 4.93 (m,
 20 4 H).

MS ES+ 315

Example 43

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile
 25

83



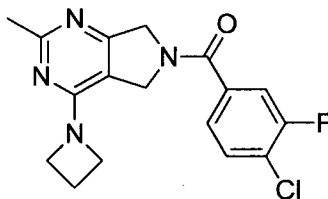
Prepared via Method A using **Intermediate 13** and 4-cyanobenzoic acid (CAS 619-65-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17-2.39 (m, 5H), 3.98-4.08 (m, 2H), 4.14-4.28 (m, 2H), 4.44-4.61 (m, 2H), 4.70-4.88 (m, 2H), 7.74-7.82 (m, 2H), 7.91-7.99 (m, 2H).

MS ES+ 320

Example 44

1-{{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 13** and 4-chloro-3-fluorobenzoic acid (CAS 403-17-8).

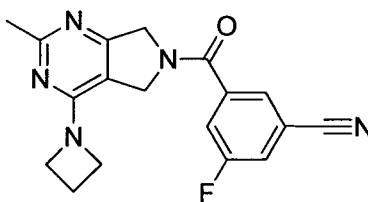
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.26 - 2.41 (m, 5 H) 4.02 – 4.12 (m, 2 H) 4.15 – 4.28 (m, 2 H) 4.52 – 4.60 (m, 2 H) 4.78- 4.87 (m, 2 H) 7.45 – 7.53 (m, 1 H) 7.64 - 7.75 (m, 2 H).

MS ES+ 347

Example 45

3-{{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-fluorobenzonitrile

84



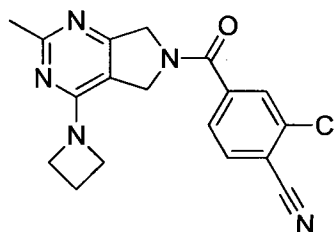
Prepared via Method A using **Intermediate 13** and 3-cyano-5-fluorobenzoic acid (CAS 327056-74-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.43 (m, 5 H) 4.00 - 4.29 (m, 4 H) 4.52 - 4.90 (m, 4 H) 7.79 - 7.91 (m, 1 H) 7.92 - 8.06 (m, 2 H).

MS ES+ 338

Example 46

4-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-chlorobenzonitrile



Prepared via Method C using **Intermediate 13** and 3-chloro-4-cyanobenzoic acid (CAS 1261685-26-0).

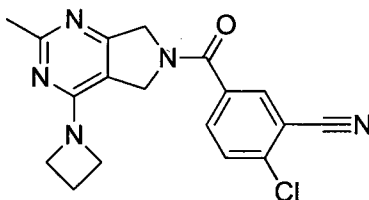
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 - 2.40 (m, 5 H) 4.01 - 4.11 (m, 2 H) 4.15 - 4.28 (m, 2 H) 4.49 - 4.62 (m, 2 H) 4.73 - 4.88 (m, 2 H) 7.72 - 7.79 (m, 1 H) 7.92 - 7.99 (m, 1 H) 8.05 - 8.15 (m, 1 H).

MS ES+ 354

Example 47

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-chlorobenzonitrile

85

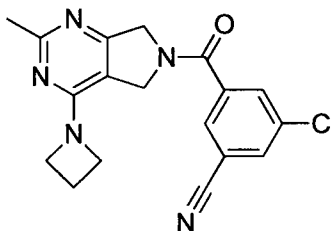


Prepared via Method C using **Intermediate 13** and 4-chloro-3-cyanobenzoic acid (CAS 117738-76-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.41 (m, 5 H) 4.01 - 4.28 (m, 4 H) 4.58 (m, 2 H) 4.77 - 4.90 (m, 2 H) 7.83 - 7.89 (m, 1 H) 7.91 - 7.98 (m, 1 H) 8.21 - 8.26 (m, 1 H).
MS ES+ 354

Example 48

3-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-5-chlorobenzonitrile



Prepared via Method C using **Intermediate 13** and 3-chloro-5-cyanobenzoic acid (CAS 327056-71-3).

15

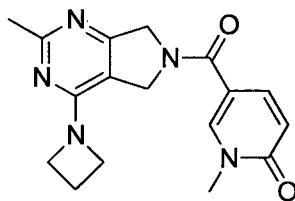
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.14 - 2.44 (m, 5 H) 3.99 - 4.30 (m, 4 H) 4.51 - 4.87 (m, 4 H) 7.93 - 8.04 (m, 1 H) 8.04 - 8.11 (m, 1 H) 8.20 (s, 1 H).
MS ES+ 354

20

Example 49

5-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-1-methyl-1,2-dihydropyridin-2-one

86



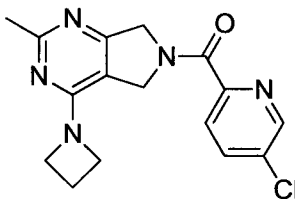
Prepared via Method C using **Intermediate 13** and 1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (CAS 3719-45-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.35 (s, 5 H) 3.49 (s, 3 H) 4.08 - 4.27 (m, 4 H) 4.46 - 5.05 (m, 4 H) 6.36 - 6.46 (m, 1 H) 7.65 - 7.77 (m, 1 H) 8.19 - 8.26 (m, 1 H).

MS ES+ 326

Example 50

2-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-chloropyridine



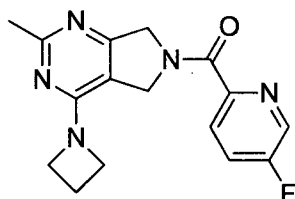
Prepared via Method C using **Intermediate 13** and 5-chloropyridine-2-carboxylic acid (CAS 86873-60-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 - 2.39 (m, 5 H) 4.10 - 4.27 (m, 4 H) 4.61 - 5.10 (m, 4 H) 7.84 - 7.94 (m, 1 H) 8.07 - 8.15 (m, 1 H) 8.64 - 8.77 (m, 1 H).

MS ES+ 330

Example 51

2-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-fluoropyridine



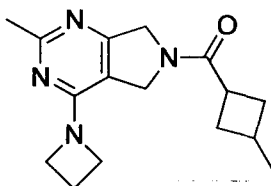
Prepared via Method C using **Intermediate 13** and 5-fluoropyridine-2-carboxylic acid (CAS 107504-08-5)

^1H NMR (300 MHz, DMSO- d_6) δ ppm 2.19 - 2.42 (m, 5 H) 4.02 - 4.30 (m, 4 H) 4.55 - 5.16 (m, 4 H) 7.87 - 8.05 (m, 2 H) 8.59 - 8.73 (m, 1 H).

5 MS ES+ 314

Example 52

1-[2-Methyl-6-(3-methylcyclobutanecarbonyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



10

Prepared via Method C using **Intermediate 13** and 3-methylcyclobutane-1-carboxylic acid (CAS 57252-83-2).

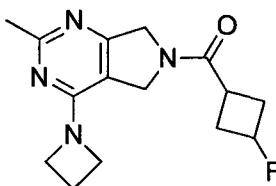
^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.96 - 1.19 (m, 3 H) 1.69 - 1.85 (m, 2 H) 2.24 - 2.38 (m, 8 H) 3.15 - 3.43 (m, 1 H) 4.11 - 4.23 (m, 4 H) 4.29 - 4.51 (m, 2 H) 4.56 - 4.75 (m, 2 H).

15

MS ES+ 287

Example 53

1-[6-(3-Fluorocyclobutanecarbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



20

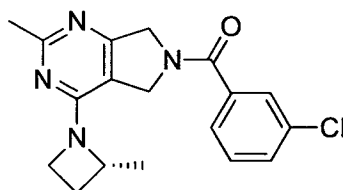
Prepared via Method C using **Intermediate 13** and 3-fluorocyclobutane-1-carboxylic acid (CAS 122665-96-7).

25

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.27 - 2.37 (m, 6 H) 2.37- 2.61 (m, 3 H) 3.34 - 3.47 (m, 1 H) 4.12 - 4.23 (m, 4 H) 4.32 - 4.51 (m, 2 H) 4.59 - 4.77 (m, 2 H) 5.01 - 5.27 (m, 1 H).
MS ES+ 291

5 **Example 54**

(2R)-1-{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine



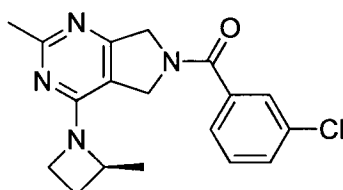
Prepared via Method A using **Intermediate 14** and 3-chlorobenzoic acid (CAS 535-80-8).

10

¹H NMR (400 MHz, CDCl₃) δ ppm 1.32 - 1.68 (m, 3 H) 1.92 - 2.17 (m, 1 H) 2.36 - 2.64 (m, 4 H) 4.06 - 4.34 (m, 2 H) 4.46 - 5.08 (m, 5 H) 7.32 - 7.51 (m, 3 H) 7.56 (s, 1 H).
MS ES+ 343

15 **Example 55**

(2S)-1-{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine



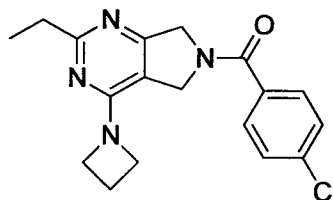
Prepared via Method A using **Intermediate 15** and 3-chlorobenzoic acid (CAS 535-80-8).

20

¹H NMR (400 MHz, CDCl₃) δ ppm 1.43-1.61 (m, 3H), 1.91-2.12 (m, 1H), 2.41-2.67 (m, 4H), 3.92-4.37 (m, 2H), 4.50-5.02 (m, 5H), 7.33-7.49 (m, 3H), 7.55 (s, 1H).
MS ES+ 343

25 **Example 56**

1-{6-[(4-Chlorophenyl)carbonyl]-2-ethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



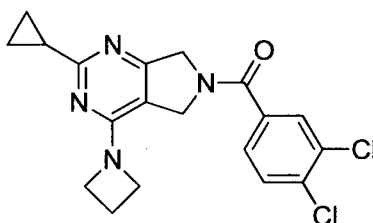
Prepared via Method A using **Intermediate 16** and 4-chlorobenzoic acid (CAS 74-11-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.12 – 1.22 (m, 3 H) 2.19 – 2.42 (m, 2 H) 2.55 – 2.67 (m, 2 H) 4.00 – 4.13 (m, 2 H) 4.14 – 4.30 (m, 2 H) 4.50 – 4.63 (m, 2 H) 4.78 – 4.90 (m, 2 H) 7.49 – 7.58 (m, 2 H) 7.63 – 7.68 (m, 2 H).

MS ES+ 343

Example 57

1-{2-Cyclopropyl-6-[(3,4-dichlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



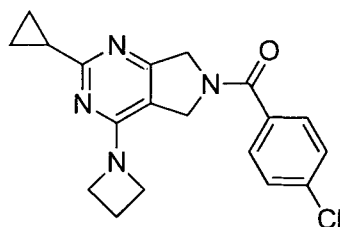
Prepared via Method A using **Intermediate 17** and 3,4-dichlorobenzoic acid (CAS 51-44-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 – 0.97 (m, 4 H) 1.85 – 2.04 (m, 1 H) 2.19 – 2.41 (m, 2 H) 4.03 – 4.07 (m, 2 H) 4.13 – 4.25 (m, 2 H) 4.50 – 4.56 (m, 2 H) 4.78 – 4.81 (m, 2 H) 7.61 (d, *J*=8.3 Hz, 1 H) 7.74 (d, *J*=8.3 Hz, 1 H) 7.82 – 7.95 (m, 1 H).

MS ES+ 389

Example 58

1-{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



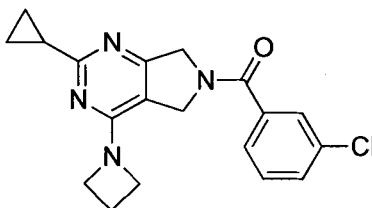
Prepared via Method C using **Intermediate 17** and 4-chlorobenzoic acid (CAS 74-11-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 0.95 (m, 4 H) 1.85 - 2.01 (m, 1 H) 2.17 - 2.40 (m, 2 H) 3.96 - 4.11 (m, 2 H) 4.11 - 4.27 (m, 2 H) 4.46 - 4.57 (m, 2 H) 4.72 - 4.87 (m, 2 H) 7.48 - 7.60 (m, 2 H) 7.60 - 7.71 (m, 2 H).

MS ES+ 354

Example 59

10 **1-{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**



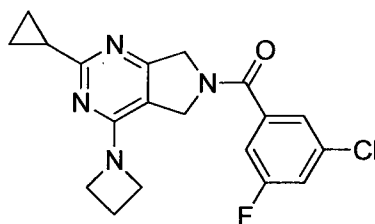
Prepared via Method C using **Intermediate 17** and 3-chlorobenzoic acid (CAS 535-80-8).

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.80 - 0.96 (m, 4 H) 1.86 - 2.00 (m, 1 H) 2.18 - 2.40 (m, 2 H) 3.97 - 4.09 (m, 2 H) 4.13 - 4.26 (m, 2 H) 4.47 - 4.57 (m, 2 H) 4.73 - 4.86 (m, 2 H) 7.46 - 7.54 (m, 1 H) 7.54 - 7.61 (m, 2 H) 7.61 - 7.68 (m, 1 H).

MS ES+ 355

20 Example 60

1-{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



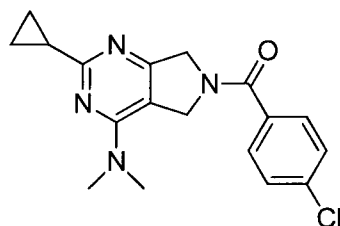
Prepared via Method A using **Intermediate 17** and 3-chloro-5-fluorobenzoic acid (CAS 25026-64-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 0.95 (m, 4 H) 1.86 - 2.01 (m, 1 H) 2.18 - 2.41 (m, 2 H) 3.98 - 4.26 (m, 4 H) 4.47 - 4.55 (m, 2 H) 4.73 - 4.85 (m, 2 H) 7.43 - 7.56 (m, 2 H) 7.55 - 7.64 (m, 1 H).

MS ES+ 373

Example 61

6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine



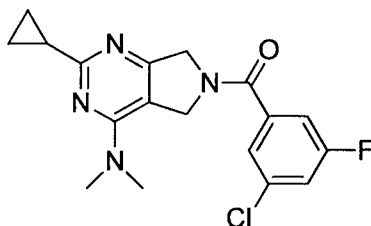
Prepared via Method C using **Intermediate 18** and 4-chlorobenzoic acid (CAS 74-11-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.80 - 0.97 (m, 4 H) 1.86 - 2.02 (m, 1 H) 2.93 - 3.19 (m, 6 H) 4.48 - 4.58 (m, 2 H) 4.98 - 5.09 (m, 2 H) 7.49 - 7.59 (m, 2 H) 7.61 - 7.71 (m, 2 H).

MS ES+ 343

Example 62

6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine

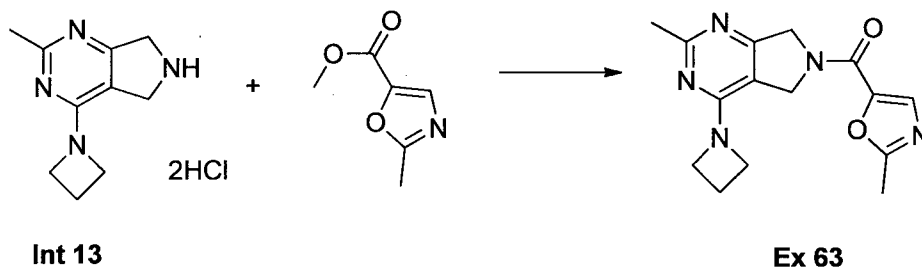


Prepared via Method C using **Intermediate 18** and 3-chloro-5-fluorobenzoic acid (CAS 25026-64-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.77 - 0.98 (m, 4 H) 1.84 - 2.03 (m, 1 H) 2.91 - 3.21 (m, 6 H) 4.38 - 4.63 (m, 2 H) 4.93 - 5.11 (m, 2 H) 7.40 - 7.56 (m, 2 H) 7.57 - 7.66 (m, 1 H).

MS ES+ 361

10 Scheme 3



Example 63

5-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-2-methyl-1,3-oxazole

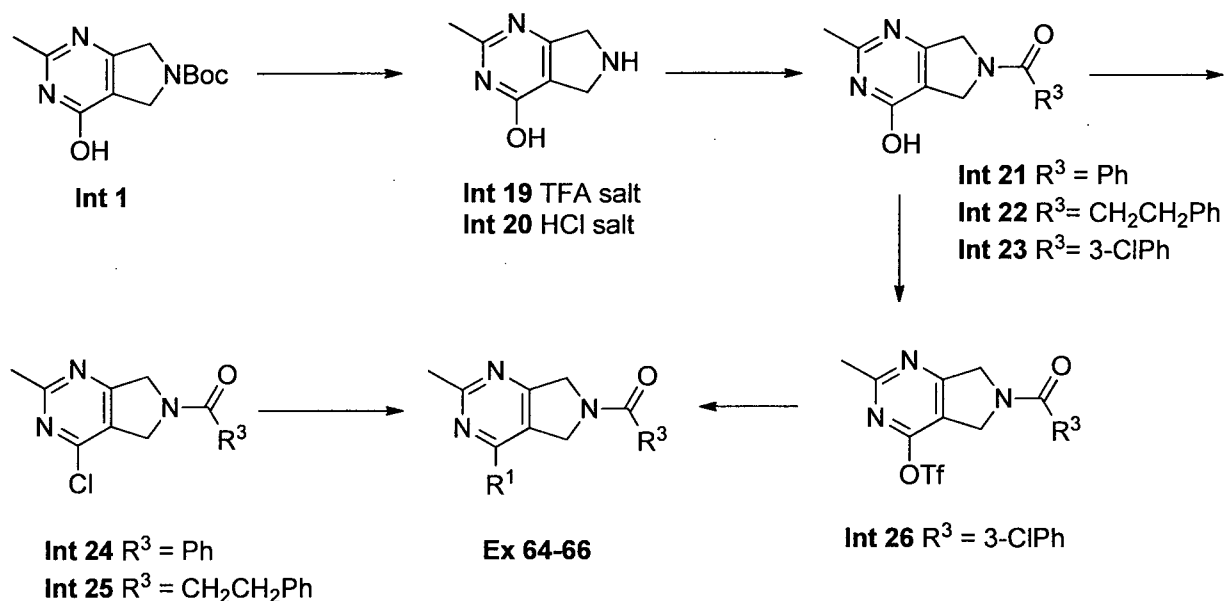
15

A mixture of methyl 2-methyloxazole-5-carboxylate (82 mg, 0.58 mmol) and 1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride (**Intermediate 13**, 69 mg, 0.29 mmol) in methanol (0.5 mL) was stirred at RT for 14 days. The mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC eluting with acetonitrile/water (with 0.1 % ammonia) to afford the title compound.

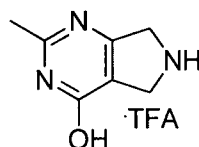
20

¹H NMR (400 MHz, CDCl₃) δ ppm 2.44 - 2.61 (m, 8 H) 4.17 - 4.36 (m, 4 H) 4.75 - 5.14 (m, 4 H) 7.64 (s, 1 H).

ES+ 300

Scheme 4

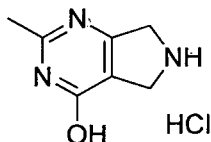
5

Intermediate 19**2-Methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol trifluoroacetate**

- 10 A solution of *tert*-butyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 1**, 6.2 g, 24.7 mmol) and TFA (5.7 mL, 74.0 mmol) in DCM (20 mL) was heated to 40 °C for 4 hours. The reaction mixture was cooled to RT and concentrated *in vacuo* to afford the title compound.

- 15 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 2.34 (s, 3 H) 4.17 - 4.43 (m, 4 H) 9.62 (br. s, 2 H) 12.52 (br. s, 1 H)

Intermediate 20**2-Methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol hydrochloride**

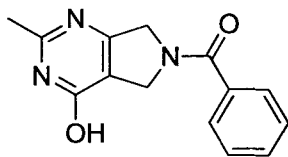


HCl (4M in dioxane, 14.5 mL, 57.8 mmol) was added to a solution of tert-butyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 1**, 2.42 g, 9.6 mmol) in MeOH (19 mL). The reaction was stirred at 40 °C for 1.5 hours. The reaction and
5 was concentrated *in vacuo* and azeotroped with toluene to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.35 (s, 3 H) 4.08 - 4.40 (m, 4 H) 6.62 - 8.48 (m, 2 H) 10.16 (br. s., 1 H).

10 **Intermediate 21**

6-Benzoyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol

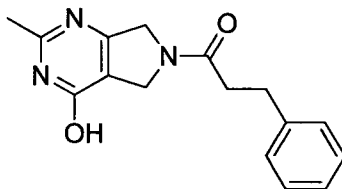


Prepared via Method A using **Intermediate 19** and benzoic acid (CAS 65-85-0).

15 ¹H NMR (400 MHz, CDCl₃) δ ppm 2.44 - 2.61 (m, 3H) 4.55 - 4.71 (m, 2H) 4.90 (br. s., 2H) 7.43 - 7.51 (m, 3H), 7.53 - 7.60 (m, 2H),
MS ES+ 256

Intermediate 22

20 **1-[4-Hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-phenylpropan-1-one**



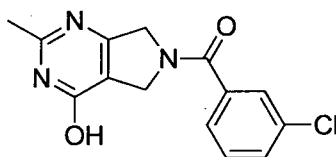
Prepared via Method A using **Intermediate 19** and 3-phenylpropanoic acid (CAS 501-52-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.21 - 2.39 (m, 3 H) 2.58 - 2.74 (m, 2 H) 2.78 - 2.94 (m, 2 H) 4.28 - 4.64 (m, 4 H) 7.11 - 7.33 (m, 5 H) 12.55 (br. s., 1 H).

MS ES+ 284

5 **Intermediate 23**

6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol



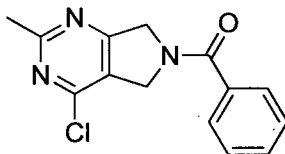
Prepared via Method C using **Intermediate 20** and 3-chlorobenzoic acid (CAS 535-80-8).

10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 - 2.41 (m, 3 H) 4.42 - 4.66 (m, 4 H) 7.43 - 7.72 (m, 4 H) 12.59 (br. s., 1 H).

MS ES+ 290

Intermediate 24

15 **6-Benzoyl-4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine**



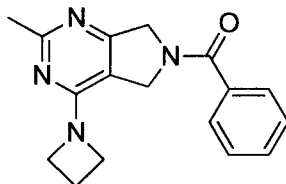
A solution of 6-benzoyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol (**Intermediate 21**, 130 mg, 0.51 mmol), triphenylphosphine (200 mg, 0.76 mmol), and carbon tetrachloride (0.15 mL, 1.53 mmol) in THF (20 mL) was heated under reflux for 4 hours.

20 The reaction mixture was cooled to RT and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-80 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.61 - 2.83 (m, 3 H) 4.68 - 5.17 (m, 4 H) 7.39 - 7.74 (m, 5 H).

25

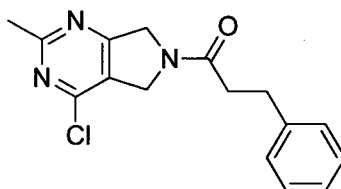
MS ES+ 274

Example 64**1-{6-Benzoyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**

A solution of 6-benzoyl-4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine
(**Intermediate 24**, 100 mg, 0.37 mmol), potassium carbonate (151 mg, 1.10 mmol), and
azetidine (30 μ L, 0.44 mmol) in THF (2 mL) was heated under microwave irradiation at
100 $^{\circ}$ C for 1 hour. The reaction mixture was partitioned between EtOAc and water. The
organic layer was dried (phase separator) and concentrated *in vacuo*. The crude product
was purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in
petrol to afford the title compound.

^1H NMR (400 MHz, CDCl_3) δ ppm 2.27 - 2.58 (m, 5 H) 4.00 - 4.39 (m, 4 H) 4.46 - 5.05
(m, 4 H) 7.36 - 7.61 (m, 5 H).

MS ES+ 295

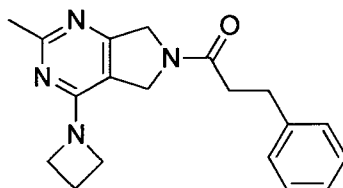
Intermediate 25**1-{4-Chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}-3-phenylpropan-1-one**

Prepared in a similar manner to **Intermediate 24** using **Intermediate 22**.

^1H NMR (400 MHz, CDCl_3) δ ppm 2.64 - 2.79 (m, 5H), 3.02 - 3.13 (m, 2H), 4.63 - 4.72
(m, 2H), 4.77 - 4.85 (m, 2H), 7.17 - 7.35 (m, 5H)

Example 65

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-phenylpropan-1-one



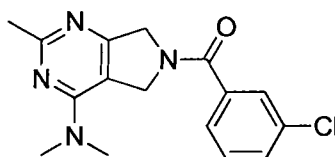
Prepared in a similar manner to **Example 64** using **Intermediate 25** and azetidine (CAS
5 503-29-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.22 - 2.43 (m, 5H), 2.62 - 2.71 (m, 2H), 2.82 -
2.92 (m, 2H), 4.09 - 4.25 (m, 4H), 4.32 - 4.56 (m, 2H), 4.58 - 4.81 (m, 2H), 7.14 - 7.33 (m,
4H), 7.51 - 7.66 (m, 1H).

10 MS ES+ 323

Example 66

6-[(3-Chlorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine

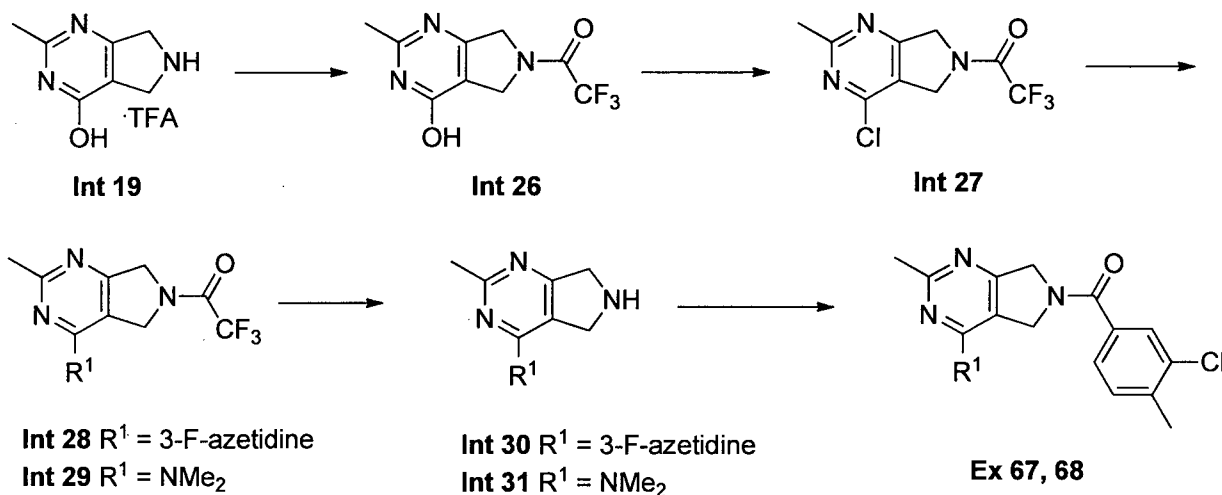


Triflic anhydride (78 μL, 0.41 mmol) was added dropwise to a solution of 6-[(3-
chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol (**Intermediate**
23, 100 mg, 0.35 mmol) and triethylamine (58 μL, 0.41 mmol) in DCM under nitrogen at
0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and partitioned between
20 DCM and water. The organic layer was dried (phase separator) and concentrated *in vacuo*
to give 6-[(3-chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl
trifluoromethanesulfonate (140 mg). The residue was taken up in DCM, followed by the
addition of dimethylamine hydrochloride (40 mg, 0.50 mmol) and triethylamine (69 μL,
0.50 mmol). The reaction mixture was stirred at RT for 30 minutes and concentrated *in*
25 *vacuo*. The crude product was purified by column chromatography on basic silica, eluting
with 0-30 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.28-2.41 (m, 3H), 2.95-3.19 (m, 6H), 4.49-4.59 (m, 2H), 4.98-5.10 (m, 2H), 7.45-7.62 (m, 3H), 7.63-7.68 (m, 1H).

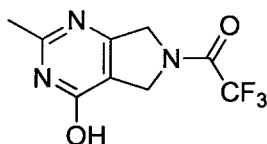
MS ES+ 317

5 **Scheme 5**



Intermediate 26

2,2,2-Trifluoro-1-{4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}ethan-1-one



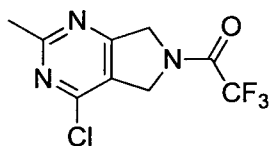
To a solution of 2-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-ol 2,2,2-trifluoroacetate (**Intermediate 19**, 16.4 g, 61.7 mmol) and triethylamine (21.5 mL, 154 mmol) in DCM (200 mL) at 0 °C was added trifluoroacetic anhydride (9.6 mL, 67.9 mmol) dropwise. The reaction was allowed to warm to RT and stirred for 3 hours. The reaction mixture was concentrated *in vacuo*. The residue was triturated from EtOAc to give the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 - 2.39 (m, 3 H) 4.51 - 4.86 (m, 4 H) 9.38 (br. s., 1 H).

MS ES+ 248

Intermediate 27

1-{4-Chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}-2,2,2-trifluoroethan-1-one



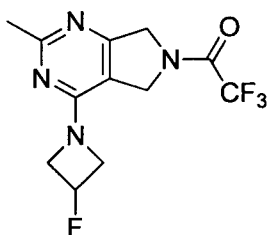
5 Phosphorus oxychloride (3.07 g, 20.04 mmol) was added to 2,2,2-trifluoro-1-{4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}ethan-1-one (**Intermediate 26**, 1.65 g, 6.68 mmol) in toluene (50 mL) at 0 °C under nitrogen. The reaction mixture was heated under reflux for 3 hours and quenched with ice cold water (500 mL) with vigorous stirring. The mixture was neutralised by addition of solid sodium bicarbonate and extracted with
10 EtOAc. The combined organic layers were washed with water and brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 10-12 % EtOAc in hexane to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.78 (s, 3H) 4.90 - 5.16 (m, 4H).

15 MS ES+ 266

Intermediate 28

2,2,2-Trifluoro-1-[4-(3-fluoroazetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]ethan-1-one



20 Triethylamine (171 mg, 1.70 mmol) and 3-fluoroazetidine hydrochloride (75 mg, 0.68 mmol) were added to 1-{4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}-2,2,2-trifluoroethan-1-one (**Intermediate 27**, 150 mg, 0.57 mmol) in DMSO (7 mL) at RT. The reaction mixture was heated to 120 °C overnight in a sealed tube and quenched with
25 water. The mixture was extracted with EtOAc and the combined organics dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on

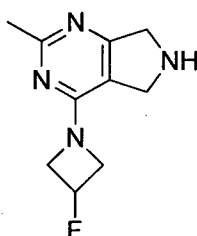
silica, eluting with 35 – 40 % EtOAc in hexane to afford the title compound which was taken directly to the next step.

MS ES+ 305

5

Intermediate 30

3-Fluoro-1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10 Aqueous ammonia (2 mL) was added to 2,2,2-trifluoro-1-[4-(3-fluoroazetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]ethan-1-one (**Intermediate 28**, 123 mg, 0.40 mmol) in MeOH (50 mL). The reaction mixture was heated to 70 °C for 2 hours in a sealed tube, diluted with water and extracted with EtOAc. The combined organics were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound which was taken to the next step without further purification.

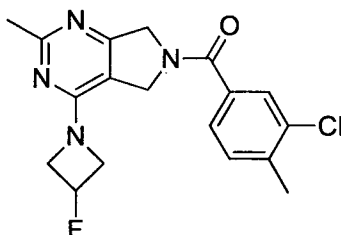
15

MS ES+ 209

Example 67

1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-3-fluoroazetidine

20



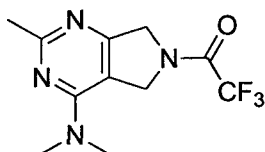
Prepared via Method E using **Intermediate 30** and 3-chloro-4-methylbenzoic acid (CAS 5162-82-3).

¹H NMR (400 MHz, CD₃CN) δ ppm 2.38 - 2.49 (m, 6H) 4.09 - 4.45 (m, 3H), 4.45 - 4.90 (m, 5H), 5.27 - 5.60 (m, 1H) 7.35 - 7.50 (m, 2H) 7.60 (s, 1H).

MS ES+ 361

5 **Intermediate 29**

1-[4-(Dimethylamino)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2,2,2-trifluoroethan-1-one

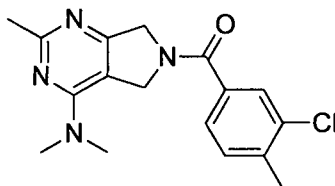


Prepared in a similar manner to Intermediate 28 using **Intermediate 27** and dimethylamine
10 hydrochloride (CAS 506-59-2).

MS ES+ 275

Example 68

15 **6-[(3-Chloro-4-methylphenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine**



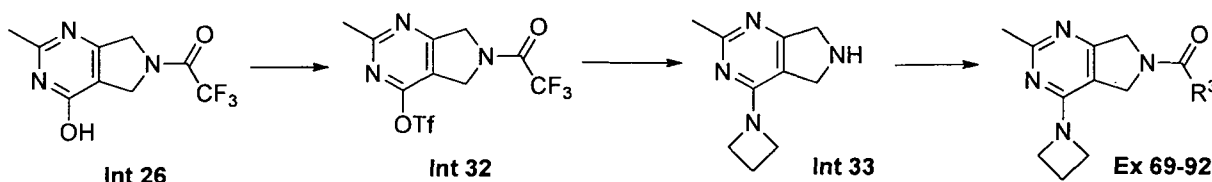
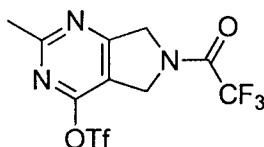
Prepared in a similar manner to **Example 68** using **Intermediate 29** and aqueous ammonia
then 3-chloro-4-methylbenzoic acid (CAS 5162-82-3).

20

¹H NMR (400 MHz, CD₃CN) δ ppm 2.38 - 2.44 (m, 6H), 3.04 - 3.20 (m, 2H) 4.53 - 4.62 (m, 2H) 4.97 - 5.09 (m, 2H) 7.40 - 7.45 (m, 2H) 7.59 (s, 1H)

MS ES+ 331

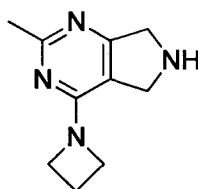
25 **Scheme 6**

**Intermediate 32****2-Methyl-6-(trifluoroacetyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl****trifluoromethanesulfonate**

To a solution of 2,2,2-trifluoro-1-{4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}ethan-1-one (**Intermediate 26**, 3 g, 12.14 mmol) and triethylamine (3.38 mL, 24.3 mmol) in DCM (40 mL) at 0 °C was added triflic anhydride (2.3 mL, 13.4 mmol) dropwise. The reaction was stirred at this temp for 1 h and then warmed to r.t. for 1 hour. Further triflic anhydride (1.1 mL, 6.4 mmol) added at 0 °C and the reaction stirred for about 1 hour. Water was added and the reaction partitioned between DCM and water. The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.71 (s, 3 H) 4.88 - 5.23 (m, 4 H).

MS ES+ 380

Intermediate 33**1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**

To a solution of 2-methyl-6-(trifluoroacetyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl trifluoromethanesulfonate (**Intermediate 32**, 9.2 g, 24.26 mmol) in THF (50 mL) at RT was added azetidine (6.93 g, 121 mmol) dropwise. The reaction was stirred at RT for 1 hour. The reaction was concentrated under reduced pressure. The crude material was

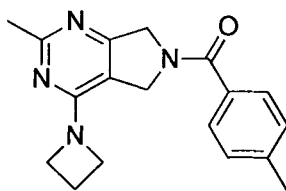
purified by column chromatography on basic silica, eluting with 0-10 % MeOH in EtOAc, to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 - 2.42 (m, 5 H) 3.75 - 4.20 (m, 8 H)

5 MS ES+ 191

Example 69

1-{2-Methyl-6-[(4-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10

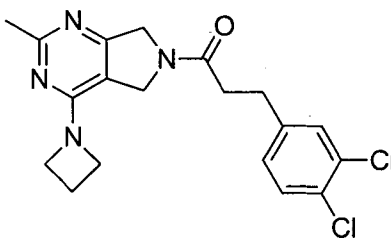
Prepared via Method B using **Intermediate 13** and 4-methylbenzoic acid (CAS 99-94-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.14 - 2.41 (m, 8 H) 3.93 - 4.29 (m, 4 H) 4.48 - 4.95 (m, 4 H) 7.18 - 7.34 (m, 2 H) 7.42 - 7.58 (m, 2 H).

15 MS ES+ 309

Example 70

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3,4-dichlorophenyl)propan-1-one



20

Prepared via Method C using **Intermediate 33** and 3,4-dichlorobenzenepropanoic acid (CAS 25173-68-6).

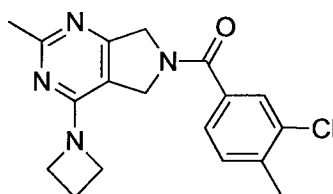
^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 2.24 - 2.40 (m, 5 H) 2.63 - 2.75 (m, 2 H) 2.83 - 2.92 (m, 2 H) 4.07 - 4.24 (m, 4 H) 4.29 - 4.84 (m, 4 H) 7.23 - 7.34 (m, 1 H) 7.46 - 7.63 (m, 2 H).

MS ES+ 391

5

Example 71

1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



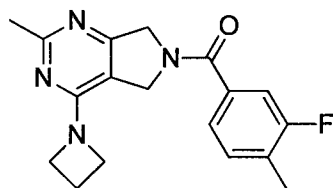
10 Prepared via Method A or C using **Intermediate 33** and 3-chloro-4-methylbenzoic acid (CAS 5162-82-3).

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 2.17 - 2.44 (m, 8 H) 4.00 - 4.30 (m, 4 H) 4.52 - 4.89 (m, 4 H) 7.40 - 7.49 (m, 1 H) 7.49 - 7.60 (m, 1 H) 7.60 - 7.70 (m, 1 H).

15 MS ES+ 343

Example 72

1-{6-[(3-Fluoro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



20

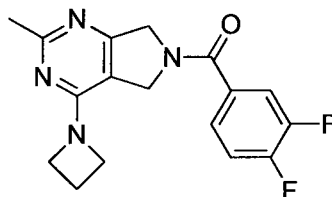
Prepared via Method B using **Intermediate 33** and 3-fluoro-4-methylbenzoic acid (CAS 350-28-7).

25 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 2.14 - 2.42 (m, 8 H) 3.93 - 4.36 (m, 4 H) 4.48 - 4.92 (m, 4 H) 7.26 - 7.50 (m, 3 H).

MS ES+ 327

Example 73

1-{6-[(3,4-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

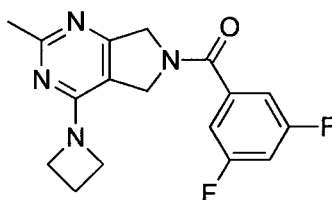


Prepared via Method A using **Intermediate 33** and 3,4-difluorobenzoic acid (CAS 455-86-7).

¹H NMR (400 MHz, CDCl₃): δ ppm 2.33 - 2.57 (m, 5H), 4.11 - 4.34 (m, 4H), 4.54 - 4.74 (m, 2H), 4.75 - 4.97 (m, 2H), 7.20 - 7.26 (m, 1H), 7.30 - 7.38 (m, 1H), 7.38 - 7.48 (m, 1H).
MS ES+ 331

Example 74

1-{6-[(3,5-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



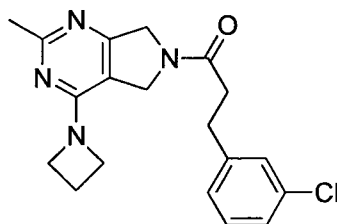
Prepared via Method A using **Intermediate 33** and 3,5-difluorobenzoic acid (CAS 455-40-3).

¹H NMR (400 MHz, CDCl₃) δ ppm 2.15 - 2.61 (m, 5 H) 4.04 - 4.38 (m, 4 H) 4.47 - 5.02 (m, 4 H) 6.81 - 6.99 (m, 1 H) 7.02 - 7.17 (m, 2 H).
MS ES+ 331

Example 75

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chlorophenyl)propan-1-one

106



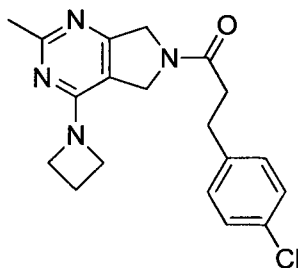
Prepared via Method A using **Intermediate 33** and 3-chlorobenzenepropanoic acid (CAS 21640-48-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 - 2.41 (m, 5 H) 2.63 - 2.73 (m, 2 H) 2.83 - 2.93 (m, 2 H) 4.08 - 4.25 (m, 4 H) 4.30 - 4.83 (m, 4 H) 7.13 - 7.41 (m, 4 H).

MS ES+ 357

Example 76

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-chlorophenyl)propan-1-one



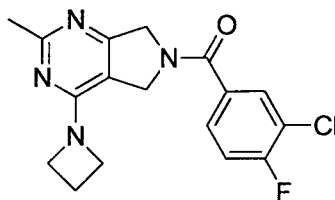
Prepared via Method A using **Intermediate 33** and 4-chlorobenzenepropanoic acid (CAS 2019-34-3).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.26 - 2.39 (m, 5H), 2.60 - 2.70 (m, 2H), 2.83 - 2.91 (m, 2H), 4.12 - 4.22 (m, 4H), 4.33 - 4.57 (m, 2H), 4.59 - 4.81 (m, 2H), 7.28 - 7.36 (m, 4H).

MS ES+ 357

Example 77

1-{6-[(3-Chloro-4-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



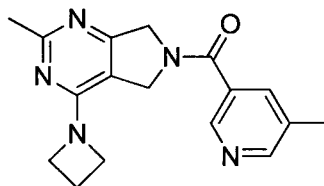
Prepared via Method C using **Intermediate 33** and 3-chloro-4-fluorobenzoic acid (CAS 403-16-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.11 - 2.43 (m, 5 H) 3.87 - 4.33 (m, 4 H) 4.43 - 4.95 (m, 4 H) 7.44 - 7.58 (m, 1 H) 7.64 - 7.74 (m, 1 H) 7.79 - 7.91 (m, 1 H).

MS ES+ 347

Example 78

3-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-5-methylpyridine



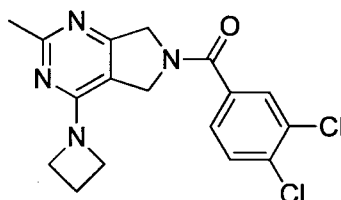
Prepared via Method B using **Intermediate 33** and 5-methyl-3-pyridinecarboxylic acid (CAS 3222-49-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.09 - 2.42 (m, 8 H) 3.92 - 4.34 (m, 4 H) 4.50 - 4.91 (m, 4 H) 7.86 (s, 1 H) 8.49 - 8.57 (m, 1 H) 8.57 - 8.69 (m, 1 H).

MS ES+ 310

Example 79

1-[[6-[(3,4-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



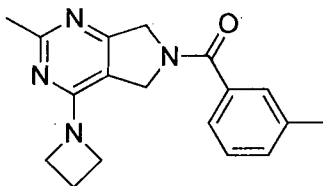
Prepared via Method B using **Intermediate 33** and 3,4-dichlorobenzoic acid (CAS 51-44-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.14 - 2.42 (m, 5 H) 3.91 - 4.31 (m, 4 H) 4.41 - 4.91 (m, 4 H) 7.51 - 7.68 (m, 1 H) 7.70 - 7.80 (m, 1 H) 7.80 - 7.96 (m, 1 H).

MS ES+ 363

Example 80

1-{2-Methyl-6-[(3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



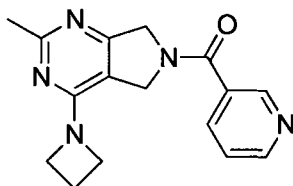
Prepared via Method B using **Intermediate 33** and 3-methylbenzoic acid (CAS 99-04-7).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.13 - 2.41 (m, 8H), 3.94 - 4.28 (m, 4H), 4.47 - 4.88 (m, 4H), 7.22 - 7.46 (m, 4H).

MS ES+ 309

Example 81

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyridine



Prepared via Method B using **Intermediate 33** and 3-pyridinecarboxylic acid (CAS 59-67-6).

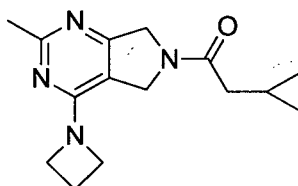
¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.13 - 2.42 (m, 5H), 3.92 - 4.15 (m, 2H), 4.13 - 4.32 (m, 2H), 4.50 - 4.66 (m, 2H), 4.77 - 4.91 (m, 2H), 7.76 - 7.94 (m, 1H), 8.46 - 8.56 (m, 1H), 8.57 - 8.70 (m, 1H).

MS ES+ 296

5

Example 82

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopropylethan-1-one



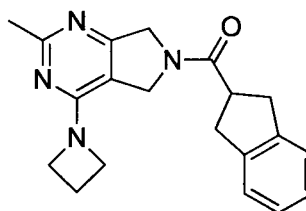
10 Prepared via Method B using **Intermediate 33** and 2-cyclopropylacetic acid (CAS 5239-82-7).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 0.07 - 0.18 (m, 2H), 0.40 - 0.53 (m, 2H), 0.88 - 1.10 (m, 1H), 2.34 (m, 7H), 4.02 - 4.83 (m, 8H).

15 MS ES+ 273

Example 83

1-{6-[(2,3-Dihydro-1H-inden-2-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



20

Prepared via Method B using **Intermediate 33** and 2-indanylcarboxylic acid (CAS 25177-85-9).

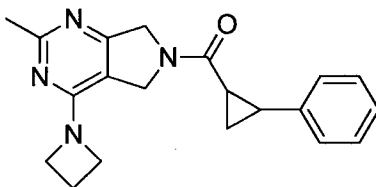
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.15 - 2.42 (m, 5 H) 2.99 - 3.26 (m, 4 H) 3.43 - 3.68 (m, 1 H) 4.08 - 4.29 (m, 4 H) 4.33 - 5.04 (m, 4 H) 7.05 - 7.29 (m, 4 H)

25

MS ES+ 335

Example 84

1-{2-Methyl-6-[(2-phenylcyclopropyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



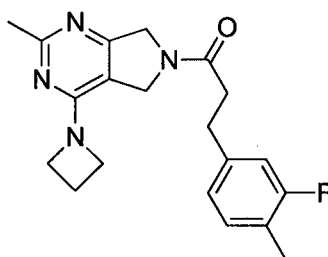
Prepared via Method B using **Intermediate 33** and 2-phenylcyclopropanecarboxylic acid (CAS 5685-38-1).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.22 - 1.51 (m, 2H), 2.10 - 2.46 (m, 7H), 4.05 - 4.44 (m, 5H), 4.54 - 5.12 (m, 3H), 7.08 - 7.36 (m, 5H).

MS ES+ 335

Example 85

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-fluoro-4-methylphenyl)propan-1-one



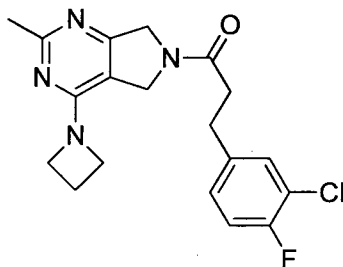
Prepared via Method A using **Intermediate 33** and 3-fluoro-4-methyl-benzenepropanoic acid (CAS 881189-62-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19 (s, 3 H) 2.25 - 2.43 (m, 5 H) 2.60 - 2.73 (m, 2 H) 2.73 - 2.89 (m, 2 H) 4.07 - 4.30 (m, 4 H) 4.32 - 4.90 (m, 4 H) 6.96 - 7.10 (m, 2 H) 7.10 - 7.25 (m, 1 H).

MS ES+ 355

Example 86

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chloro-4-fluorophenyl)propan-1-one



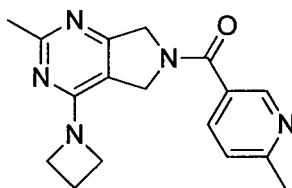
Prepared via Method A using **Intermediate 33** and 3-chloro-4-fluoro-benzenepropanoic acid (CAS 881190-93-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.14 - 2.41 (m, 5 H) 2.62 - 2.73 (m, 2 H) 2.77 - 2.93 (m, 2 H) 4.05 - 4.26 (m, 4 H) 4.26 - 4.86 (m, 4 H) 7.19 - 7.39 (m, 2 H) 7.46 - 7.56 (m, 1 H).

MS ES+ 375

Example 87

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-methylpyridine



Prepared via Method A using **Intermediate 33** and 6-methylpyridine-3-carboxylic acid (CAS 3222-47-7).

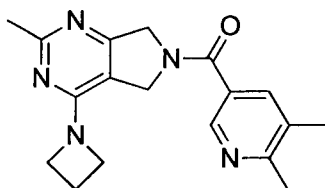
¹H NMR (400 MHz, CDCl₃) δ ppm 2.33 - 2.56 (m, 5H), 2.64 (s, 3H), 4.12 - 4.34 (m, 4H), 4.59 - 5.01 (m, 4H), 7.23 - 7.27 (m, 1H), 7.78 - 7.86 (m, 1H), 8.71 - 8.79 (m, 1H).

MS ES+ 310

Example 88

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2,3-dimethylpyridine

112



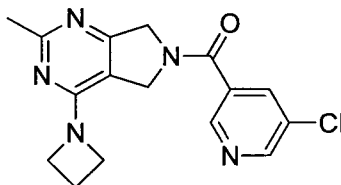
Prepared via Method A using **Intermediate 33** and 5,6-dimethylpyridine-3-carboxylic acid (CAS 757903-81-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.12 - 2.42 (m, 8 H) 2.48 (s, 3 H) 4.00 - 4.29 (m, 4 H) 4.52 - 4.95 (m, 4 H) 7.67 - 7.86 (m, 1 H) 8.44 - 8.60 (m, 1 H).

MS ES+ 324

Example 89

3-({[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-chloropyridine



Prepared via Method A using **Intermediate 33** and 5-chloro-3-pyridinecarboxylic acid (CAS 22620-27-5).

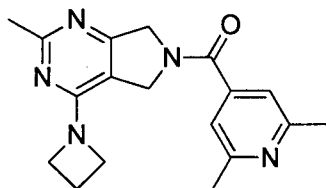
15

¹H NMR (400 MHz, CDCl₃): δ ppm 2.35 - 2.57 (m, 5H), 4.12 - 4.35 (m, 4H), 4.57 - 4.78 (m, 2H), 4.79 - 5.01 (m, 2H), 7.89 - 7.94 (m, 1H), 8.68 - 8.75 (m, 2H).

MS ES+ 330

Example 90

4-({[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,6-dimethylpyridine



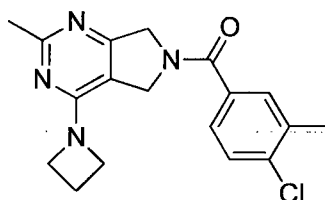
Prepared via Method A using **Intermediate 33** and 2,6-dimethylisonicotinic acid (CAS 54221-93-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.16 - 2.42 (m, 5 H) 2.48 (s, 6 H) 4.00 - 4.28 (m, 4 H) 4.46 - 4.87 (m, 4 H) 7.10 - 7.29 (m, 2 H).

MS ES+ 324

Example 91

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-
d]pyrimidin-4-yl}azetidine



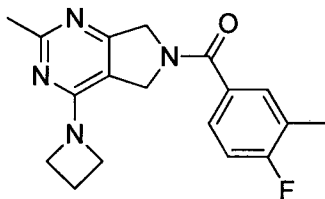
Prepared via Method A using **Intermediate 33** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.15 - 2.42 (m, 8 H) 3.93 - 4.31 (m, 4 H) 4.47 - 4.93 (m, 4 H) 7.37 - 7.57 (m, 2 H) 7.61 (s, 1 H).

MS ES+ 343

Example 92

1-{6-[(4-Fluoro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-
d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 33** and 4-fluoro-3-methylbenzoic acid (CAS 403-15-6).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.17 - 2.41 (m, 8 H) 4.02 - 4.28 (m, 4 H) 4.51 - 4.89 (m, 4 H) 7.15 - 7.28 (m, 1 H) 7.44 - 7.54 (m, 1 H) 7.54 - 7.63 (m, 1 H).

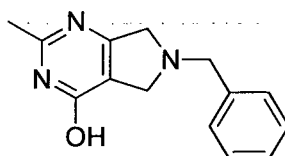
MS ES+ 327

5 **Scheme 7**



Intermediate 34

6-Benzyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol



10

To a solution of 2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol trifluoroacetate (**Intermediate 19**, 6.5 g, 24.51 mmol) and triethylamine (21.2 mL, 152 mmol) in DCM (150 mL) was added benzyl bromide (3.2 mL, 27.0 mmol). The reaction mixture was stirred at RT overnight, diluted with DCM and washed with water. The organic layer was dried (phase separator) and concentrated *in vacuo*. The aqueous was concentrated *in vacuo* and combined with the organics. The crude product was purified by column chromatography on silica, eluting with 0-15 % MeOH in EtOAc to afford the title compound.

15

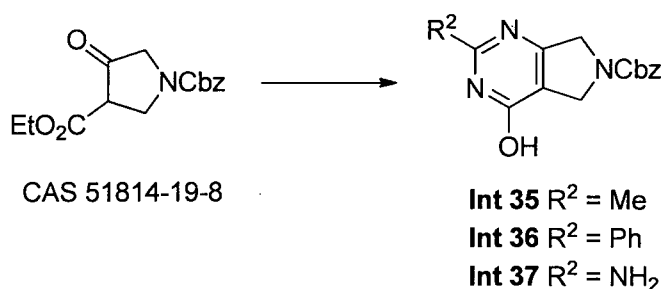
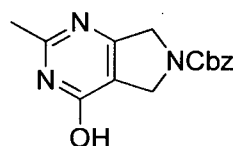
20 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.28 (s, 3 H) 3.62 - 3.77 (m, 4 H) 3.84 (s, 2 H) 7.18 - 7.43 (m, 5 H) 12.35 (br. s., 1 H).

MS ES+ 242

Scheme 8

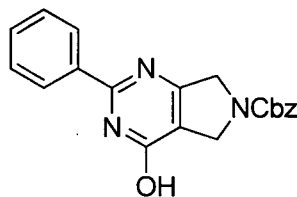
25

115

**Intermediate 35****Benzyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

Acetamidine hydrochloride (16.94 g, 179 mmol) was added to a solution of 1-benzyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 51814-19-8) (29 g, 100 mmol) and triethylamine (25 mL, 179 mmol) in *tert*-BuOH (250 mL). The mixture was heated at 80 °C for 24 hours under nitrogen. The mixture was concentrated *in vacuo* and partitioned between water and EtOAc. THF was added and the mixture filtered to give benzyl 4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (11.18 g). The organic phase from the filtrate was passed through a pad of silica, eluting with EtOAc, and the resulting solution concentrated *in vacuo*. The residue was suspended in ether and THF (4:1, 200 mL) and filtered to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6): δ ppm 2.32 (s, 3H), 4.33 - 4.54 (m, 4H), 5.14 (s, 2H), 7.29 - 7.45 (m, 5H), 12.57 (br s, 1H).
 MS ES+ 286

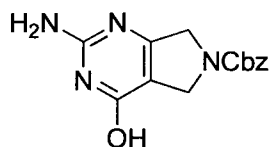
Intermediate 36**Benzyl 4-hydroxy-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

Prepared in a similar manner to **Intermediate 35** using benzamidine (CAS 618-39-3) and 1-benzyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 51814-19-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.24 - 4.55 (m, 4 H) 5.16 (s, 2 H) 7.23 - 7.47 (m, 3 H) 7.54 - 7.65 (m, 2 H) 7.65 - 7.76 (m, 1 H) 7.76 - 7.88 (m, 2 H) 8.10 - 8.22 (m, 2 H).
MS ES+ 348

Intermediate 37

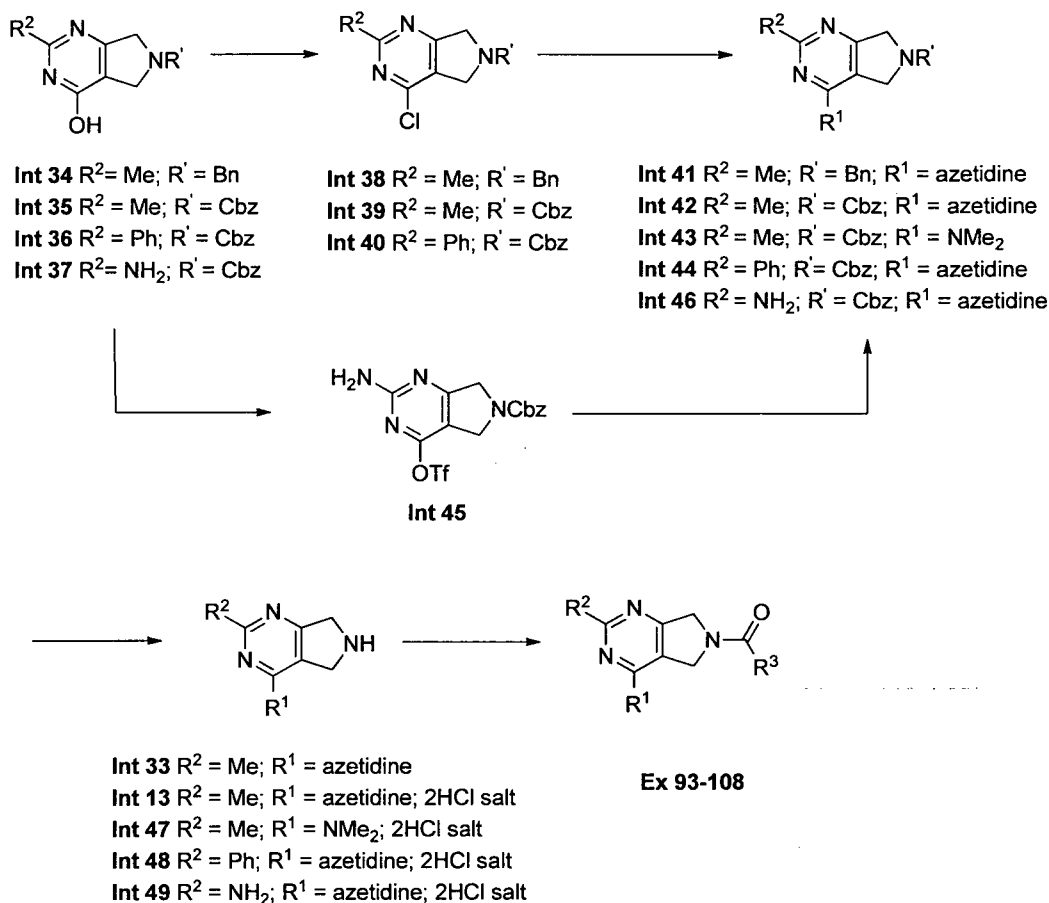
Benzyl 2-amino-4-hydroxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



Prepared in a similar manner to **Intermediate 35** using guanidine carbonate (CAS 100224-74-6) and 1-benzyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (CAS 51814-19-8).

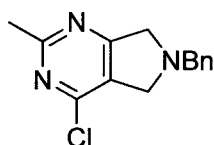
¹H NMR (400 MHz, DMSO-*d*₆) □ ppm 4.18 - 4.39 (m, 4 H) 5.13 (s, 2 H) 6.60 - 6.99 (m, 1 H) 7.24 - 7.49 (m, 5 H).
MS ES+ 287

Scheme 9



Intermediate 38

6-Benzyl-4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine



5

A suspension of 6-benzyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-ol (**Intermediate 34**, 5.91 g, 24.49 mmol), DMF (0.057 mL), and N,N-dimethylaniline (5.94 g, 49.0 mmol) in acetonitrile (15 mL) was heated under reflux until a solution had formed. The reaction mixture was cooled to RT, followed by dropwise addition of phosphoryl trichloride (9.13 mL, 98 mmol) over 10 minutes. The reaction mixture was heated under reflux for 30 minutes, cooled to RT and concentrated *in vacuo*. The residue was taken up in EtOAc, quenched with water and partitioned between EtOAc and sodium bicarbonate solution. The organic layer was dried (phase separator) and concentrated *in vacuo*. The

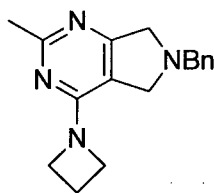
10

crude product was purified by column chromatography on silica, eluting with 0-80 % EtOAc in petrol then 0 – 10 % MeOH in EtOAc to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.51 - 2.89 (m, 3 H) 4.21 - 5.26 (m, 6 H) 7.37 - 7.93 (m, 5 H).
MS ES+ 260

Intermediate 41

1-{6-Benzyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10

A solution of 6-benzyl-4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine (**Intermediate 38**, 1.00 g, 3.85 mmol), potassium carbonate (1.60 g, 11.55 mmol), and azetidine (0.31 mL, 4.62 mmol) in THF (2 mL) was heated at 100 °C for 30 minutes under microwave irradiation. The reaction mixture was partitioned between EtOAc and water.
The organic layer was dried (phase separator) and concentrated *in vacuo* to afford the title compound.

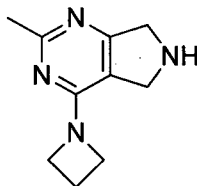
15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.14 - 2.40 (m, 5 H) 3.55 - 3.97 (m, 6 H) 3.99 - 4.15 (m, 4 H) 7.08 - 7.43 (m, 5 H).

20 MS ES+ 281

Intermediate 33

1-{2-Methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



25

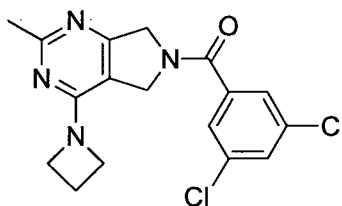
A solution of 1-{6-benzyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (**Intermediate 41**, 720 mg, 2.57 mmol), palladium hydroxide on carbon (20 % wt dry basis,

180 mg, 0.26 mmol), and ammonium formate (1.62 g, 25.7 mmol) in ethanol (10 mL) was heated to 70 °C for 3 hours. The reaction mixture was cooled to RT then filtered through a Celite cartridge, washing with ethanol. The filtrate was concentrated *in vacuo* and loaded onto a cation exchange cartridge. The cartridge was washed with methanol and eluting
5 with 2M ammonia in methanol solution then concentrated *in vacuo* to afford the title compound which was used directly in the next step.

MS ES+ 191

10 Example 93

1-{6-[(3,5-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 33** and 3,5-dichlorobenzoic acid (CAS 51-36-
15 5).

¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 - 2.59 (m, 5 H) 4.07 - 4.35 (m, 4 H) 4.50 - 4.99 (m, 4 H) 7.36 - 7.54 (m, 3 H).

MS ES+ 363

20 Intermediate 39

Benzyl 4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



Phosphorus oxychloride (0.63 mL, 6.71 mmol) was added to a solution of benzyl 4-
25 hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 35**, 957 mg, 3.35 mmol) in toluene (11 mL). The reaction was heated to reflux for 1 hour. The reaction mixture was cooled to RT and concentrated *in vacuo*. The crude product was

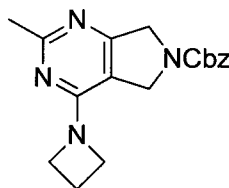
purified by column chromatography on silica, eluting with 0-50 % ethyl acetate/petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.63 (s, 3 H) 4.57 - 4.80 (m, 4 H) 5.17 (s, 2 H) 7.15 - 7.50 (m, 5 H).

MS ES+304

Intermediate 42

Benzyl 4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



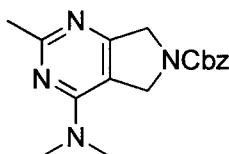
Azetidine (1.12 mL, 16.7 mmol) was added to a solution of benzyl 4-chloro-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 39**, 2.53 g, 8.33 mmol) and triethylamine (1.28 mL, 9.16 mmol) in DCM (28 mL) under nitrogen. The reaction was stirred at room temperature for 16 h. The reaction was partitioned between DCM and water and the layers separated. The organics were dried (phase separator) and concentrated *in vacuo*. The crude product was recrystallised from EtOAc to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.23 - 2.39 (m, 5H), 4.11 - 4.23 (m, 4H), 4.34 - 4.47 (m, 2H), 4.62 - 4.73 (m, 2H), 5.14 - 5.18 (m, 2H), 7.28 - 7.45 (m, 5H).

MS ES+ 325

Intermediate 43

Benzyl 4-(dimethylamino)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



Prepared in a similar manner to **Intermediate 42** using **Intermediate 39** and dimethylamine hydrochloride (CAS 506-59-2).

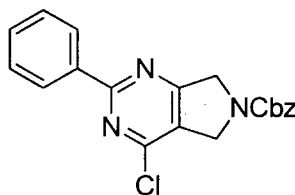
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.36 (s, 3 H) 3.04 - 3.18 (m, 6 H) 4.27 - 4.50 (m, 2 H) 4.81 - 4.99 (m, 2 H) 5.10 - 5.23 (m, 2 H) 7.26 - 7.48 (m, 5 H)

MS ES+ 313

5

Intermediate 40

Benzyl 4-chloro-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

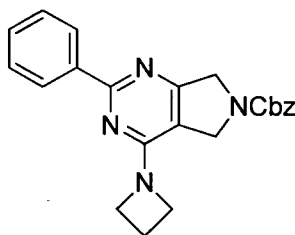


Prepared in a similar manner to **Intermediate 38** using **Intermediate 36**. The crude
10 material was used directly in the next step.

MS ES+ 366

Intermediate 44

15 **Benzyl 4-(azetidin-1-yl)-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



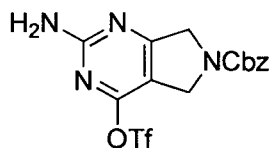
Prepared in a similar manner to **Intermediate 42** using **Intermediate 40** and azetidine
(CAS 503-29-7).

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.30 - 2.44 (m, 2H) 4.22 - 4.34 (m, 4H), 4.47 - 4.61 (m, 2H), 4.70 - 4.82 (m, 2H), 5.15 - 5.23 (m, 2H), 7.27 - 7.53 (m, 8H), 8.26 - 8.35 (m, 2H).

MS ES+ 387

Intermediate 45

Benzyl 2-amino-4-[(trifluoromethane)sulfonyloxy]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

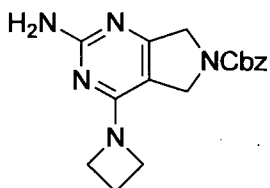


To a suspension of benzyl 2-amino-4-hydroxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 37**, 634 mg, 2.22 mmol) and triethylamine (0.46 mL, 3.32 mmol) in DCM (7 mL) was added triflic anhydride (0.56 mL, 3.32 mmol). The reaction was stirred at 0 °C for 4 hours. A further 0.5 equivalents triflic anhydride (0.19 mL, 1.11 mmol) was added and the reaction mixture stirred for a further 2 hours. The mixture was quenched with water and extracted into DCM. The organics were dried (phase separator) and concentrated *in vacuo* to afford the title compound, which was taken on to the next step without further purification, assuming quantitative yield.

MS ES+ 419

Intermediate 46

Benzyl 2-amino-4-(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



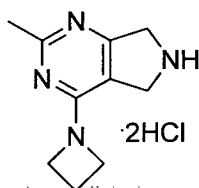
To a suspension of benzyl 2-amino-4-hydroxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 45**, 634 mg, 2.22 mmol) and triethylamine (0.46 mL, 3.32 mmol) in DCM (7 mL) was added triflic anhydride (0.56 mL, 3.32 mmol). The reaction was stirred at 0 °C for 4 hours. A further 0.5 equivalents triflic anhydride (0.19 mL, 1.11 mmol) was added and the reaction mixture stirred for a further 2 hours. The mixture was quenched with water and extracted into DCM. The organics were dried (phase separator) and concentrated *in vacuo*. The residue was taken up in DCM (7 mL) and azetidine (0.45 mL, 6.64 mmol) was added. The reaction was stirred at RT for 16 hours. The reaction was quenched with water and the layers separated. The organics were dried (phase separator) and concentrated *in vacuo*.

The crude product was purified by column chromatography on basic silica, eluting with 0-100% ethyl acetate/petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 - 2.38 (m, 2 H) 3.93 - 4.15 (m, 4 H) 4.18 - 4.35 (m, 2 H) 4.40 - 4.66 (m, 2 H) 5.07 - 5.22 (m, 2 H) 6.11 (s, 2 H) 7.10 - 7.56 (m, 5 H).
MS ES+ 326

Intermediate 13 (alternative method to Scheme 2)

1-{2-Methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



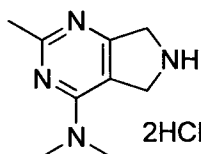
Palladium on carbon (10 wt %, dry basis, 1.73 g, 1.62 mmol) was added to a suspension of benzyl 4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 42**, 5.26 g, 16.22 mmol) and HCl (4.0 M in dioxane, 12.2 mL, 48.6 mmol) in ethanol under nitrogen. The reaction was stirred under an atmosphere of hydrogen at RT overnight. The suspension was filtered through diatomaceous earth and the filtrate concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.31 - 2.51 (m, 5H), 4.23 - 4.63 (m, 8H), 10.63 (br s, 2H).

MS ES+ 191

Intermediate 47

N,N,2-Trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine dihydrochloride



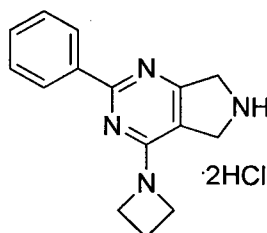
Prepared in a similar manner to **Intermediate 13** (alternative method above) using **Intermediate 43**.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.42 (s, 3 H) 3.17 (s, 6 H) 4.23 - 4.36 (m, 2 H) 4.68 - 4.85 (m, 2 H), 9.67 - 9.90 (m, 2H).

MS ES+ 179

5 **Intermediate 48**

1-{2-Phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



Prepared in a similar manner to **Intermediate 13** (alternative method above) using **Intermediate 44** and palladium hydroxide (20 wt %, dry basis) (CAS 63310-18-9) in place of Pd/C.

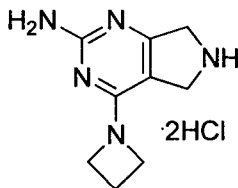
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 - 2.44 (m, 2 H) 4.22 - 4.68 (m, 8 H) 7.32 - 7.62 (m, 3 H) 8.25 - 8.39 (m, 2 H) 10.08 (br. s, 2 H).

MS ES+ 253

15

Intermediate 49

4-(Azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine dihydrochloride

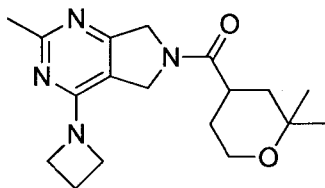


Prepared in a similar manner to **Intermediate 13** (alternative method above) using **Intermediate 46** and palladium hydroxide (20 wt %, dry basis) (CAS 63310-18-9) in place of Pd/C. The crude material was taken directly on to the next step.

MS ES+ 192

25 **Example 94**

1-{6-[(2,2-Dimethyloxan-4-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



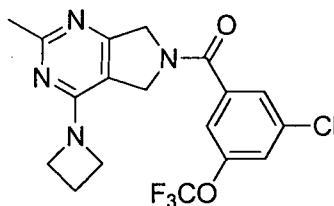
Prepared via Method A using **Intermediate 33** and 2,2-dimethyltetrahydropyran-4-carboxylic acid (CAS 52916-16-2).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.10 - 1.18 (m, 3H), 1.19 - 1.26 (m, 3H), 1.31 - 1.66 (m, 4H), 2.26 - 2.39 (m, 5H), 2.83 - 2.99 (m, 1H), 3.57 - 3.68 (m, 2H), 4.09 - 4.26 (m, 4H), 4.27 - 4.39 (m, 1H), 4.55 - 4.76 (m, 2H), 4.83 - 5.00 (m, 1H).

MS ES+ 331

Example 95

1-(6-{[3-Chloro-5-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



Prepared via Method A using **Intermediate 33** and 3-chloro-5-trifluoromethoxybenzoic acid (CAS 433926-46-6).

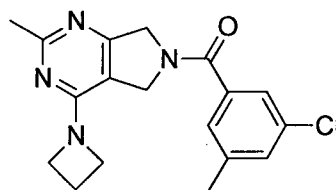
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.20 - 2.42 (m, 5 H) 4.05 - 4.08 (m, 2 H) 4.18 - 4.27 (m, 2 H) 4.55 - 4.57 (m, 2 H) 4.81 - 4.84 (m, 2 H) 7.64 - 7.67 (m, 1 H) 7.72 - 7.76 (m, 2 H).

MS ES+ 413

Example 96

1-{6-[(3-Chloro-5-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

126



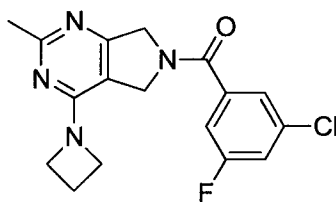
Prepared via Method C using **Intermediate 33** and 3-chloro-5-methylbenzoic acid (CAS 56961-33-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.16 - 2.41 (m, 8 H) 4.05 - 4.09 (m, 2 H) 4.17 - 4.25 (m, 2 H) 4.54 - 4.55 (m, 2 H) 4.79 - 4.83 (m, 2 H) 7.33 - 7.50 (m, 3 H).

MS ES+ 343

Example 97

1-{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



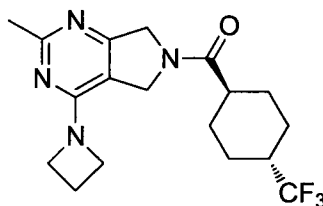
Prepared via Method C using **Intermediate 33** and 3-chloro-5-fluorobenzoic acid (CAS 25026-64-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.19-2.41 (m, 5H), 4.07 (s, 2H), 4.12-4.28 (m, 2H), 4.55 (s, 2H), 4.74-4.88 (m, 2H), 7.53 (s, 2H), 7.56-7.65 (m, 1H).

MS ES+ 347

Example 98

1-(2-Methyl-6-[(1R,4R)-4-(trifluoromethyl)cyclohexyl]pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



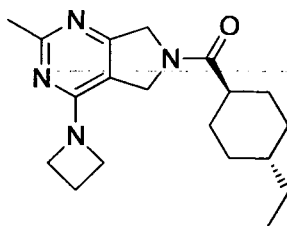
Prepared via Method A using **Intermediate 33** and trans-4-(trifluoromethyl)cyclohexanecarboxylic acid (CAS 133261-33-3).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 1.20 - 1.55 (m, 4H), 1.68 - 1.97 (m, 4H), 2.11 - 2.24 (m, 1H), 2.25 - 2.41 (m, 5H), 2.53 - 2.70 (m, 1H), 3.77 - 4.25 (m, 4H), 4.30 - 4.62 (m, 2H), 4.63 - 4.90 (m, 2H).

MS ES+ 369

Example 99

1-(2-Methyl-6-{[(1S,4R)-4-ethylcyclohexyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine



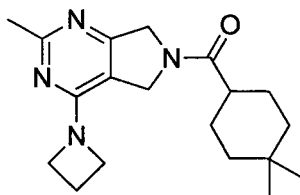
Prepared via Method A using **Intermediate 33** and trans-4-ethylcyclohexane-1-carboxylic acid (CAS 6833-47-2).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 0.81 - 0.90 (m, 3H), 0.91 - 1.03 (m, 2H), 1.05 - 1.27 (m, 3H), 1.28 - 1.45 (m, 2H), 1.59 - 1.83 (m, 4H), 2.12 - 2.47 (m, 6H), 4.08 - 4.26 (m, 4H), 4.30 - 4.61 (m, 2H), 4.61 - 4.89 (m, 2H).

MS ES+ 329

Example 100

1-{6-[(4,4-Dimethylcyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



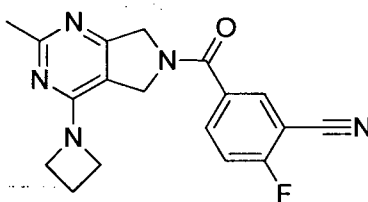
Prepared via Method A using **Intermediate 33** and 4,4-dimethyl-1-cyclohexanecarboxylic acid (CAS 25186-27-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.86 - 0.96 (m, 6 H) 1.17 - 1.32 (m, 2 H) 1.36 - 1.44 (m, 2 H) 1.46 - 1.62 (m, 4 H) 2.26 - 2.44 (m, 6 H) 4.11 - 4.25 (m, 4 H) 4.32 (m, 1 H) 4.57 - 4.65 (m, 2 H) 4.87 (m, 1 H).

5 MS ES+ 329

Example 101

5-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-fluorobenzonitrile



10

Prepared via Method C using **Intermediate 33** and 3-cyano-4-fluorobenzoic acid (CAS 171050-06-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.15 - 2.42 (m, 5 H) 3.98 - 4.29 (m, 4 H) 4.52 - 4.90 (m, 4 H) 7.54 - 7.71 (m, 1 H) 7.95 - 8.09 (m, 1 H) 8.13 - 8.28 (m, 1 H).

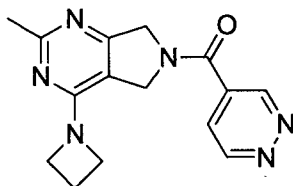
15

MS ES+ 338

Example 102

4-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]pyridazine

20



Prepared via Method A using **Intermediate 33** and 4-pyridazinecarboxylic acid (CAS 50681-25-9).

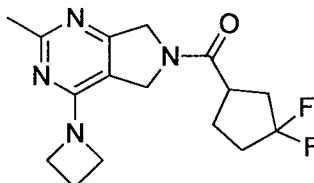
¹H NMR (400 MHz, CD₂Cl₂): δ ppm 2.19 - 2.44 (m, 5H), 3.97 - 4.27 (m, 4H), 4.45 - 4.63 (m, 2H), 4.63 - 4.89 (m, 2H), 7.44 - 7.55 (m, 1H), 9.16 - 9.31 (m, 2H).

25

MS ES+ 297

Example 103

1-{6-[(3,3-Difluorocyclopentyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



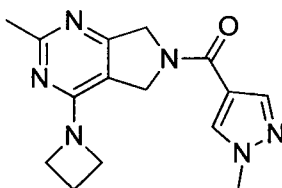
Prepared via Method A using **Intermediate 33** and 3,3-difluoro-cyclopentanecarboxylic acid (CAS 1260897-05-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.75 - 2.43 (m, 12 H) 4.07 - 4.27 (m, 4 H) 4.32 - 4.76 (m, 4 H).

MS ES+ 323

Example 104

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole



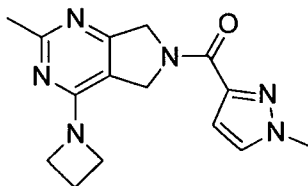
Prepared via Method A using **Intermediate 33** and 1-methyl-1H-pyrazole-4-carboxylic acid (CAS 5952-92-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.26 - 2.42 (m, 5H), 3.85 - 3.93 (m, 3H), 4.13 - 5.12 (m, 8H), 7.89 (s, 1H), 8.18 - 8.37 (m, 1H).

MS ES+ 299

Example 105

3-[[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-1-methyl-1H-pyrazole



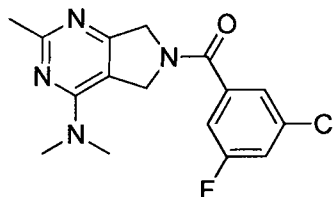
Prepared via Method A using **Intermediate 33** and 1-methyl-1H-pyrazole-3-carboxylic acid (CAS 25016-20-0).

¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 2.28 - 2.41 (m, 5H), 3.92 - 3.98 (m, 3H), 4.12 - 4.27 (m, 4H), 4.53 - 4.85 (m, 2H), 4.93 - 5.25 (m, 2H), 6.68 - 6.74 (m, 1H), 7.77 - 7.83 (m, 1H).

MS ES+ 299

Example 106

6-[(3-Chloro-5-fluorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine



Prepared via Method D using **Intermediate 47** and 3-chloro-5-fluorobenzoyl chloride (CAS 886496-62-4).

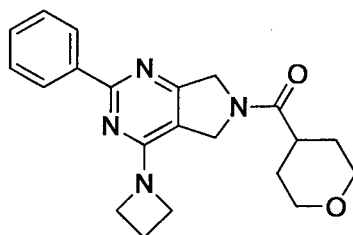
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.30 - 2.40 (m, 3 H) 2.98 - 3.19 (m, 6 H) 4.56 (m, 2 H) 5.01 - 5.10 (m, 2 H) 7.46 - 7.56 (m, 2 H) 7.57 - 7.64 (m, 1 H).

MS ES+ 335

Example 107

1-{6-[(Oxan-4-yl)carbonyl]-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

131



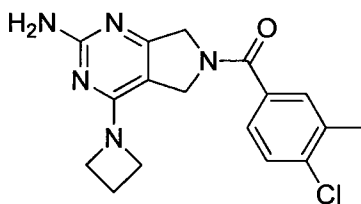
Prepared via Method C using **Intermediate 48** and tetrahydro-2H-pyran-4-carboxylic acid (CAS 5337-03-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.54 - 1.74 (m, 4 H) 2.30 - 2.45 (m, 2 H) 2.75 - 2.91 (m, 1 H) 3.36 - 3.48 (m, 2 H) 3.84 - 3.95 (m, 2 H) 4.22 - 4.38 (m, 4 H) 4.42 - 5.03 (m, 4 H) 7.43 - 7.52 (m, 3 H) 8.27 - 8.37 (m, 2 H).

MS ES+ 364

10 **Example 108**

4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine



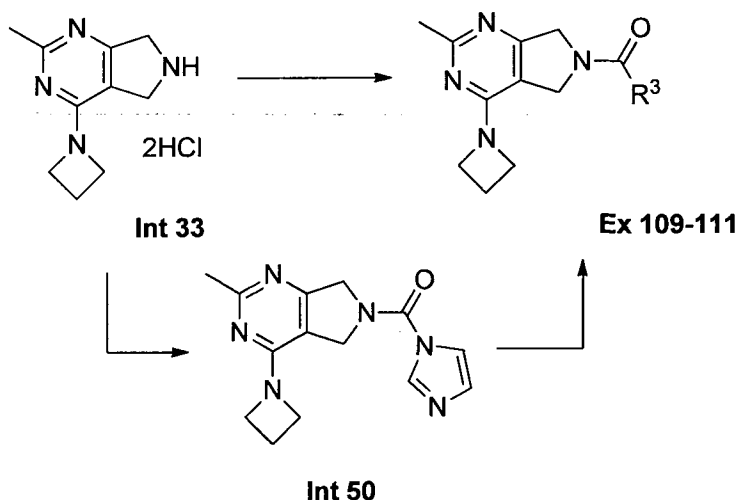
Prepared via Method C using **Intermediate 49** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.13 - 2.43 (m, 5 H) 3.90 - 4.20 (m, 4 H) 4.33 - 4.76 (m, 4 H) 6.01 - 6.26 (m, 2 H) 7.41 - 7.54 (m, 2 H) 7.59 (s, 1 H).

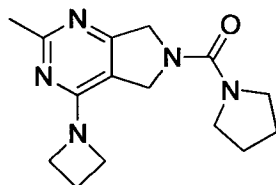
MS ES+ 344

Scheme 10

132

**Example 109**

1-{{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyrrolidine}



Pyrrolidine-1-carbonyl chloride (56 mg, 0.42 mmol) was added to a solution of 1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride (**Intermediate 33**, 100 mg, 0.38 mmol) and triethylamine (0.16 mL, 1.14 mmol) in DCM. The reaction mixture was stirred at room temperature for 2 hours. The mixture was partitioned between DCM and water. The organic phase was dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on basic silica, eluting with 0-50 % EtOAc in petrol to afford the title compound.

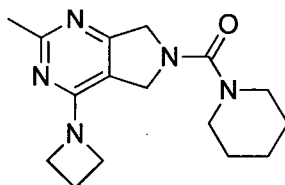
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.65 - 1.91 (m, 4 H) 2.19 - 2.40 (m, 5 H) 3.32 - 3.42 (m, 4 H) 4.06 - 4.28 (m, 4 H) 4.33 - 4.48 (m, 2 H) 4.59 - 4.73 (m, 2 H).

MS ES+ 288

Example 110

1-{{[4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}piperidine}

133



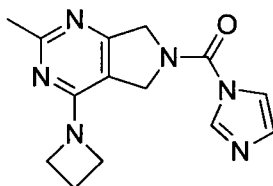
Prepared in a similar fashion to **Example 109** using **Intermediate 33** and piperidine-1-carbonyl chloride (CAS 13939-69-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 - 1.62 (m, 6 H) 2.26 - 2.38 (m, 5 H) 3.14 - 3.25 (m, 4 H) 4.09 - 4.23 (m, 4 H) 4.41 (s, 2 H) 4.67 (s, 2 H).

MS ES+ 302

Intermediate 50

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-1H-imidazole



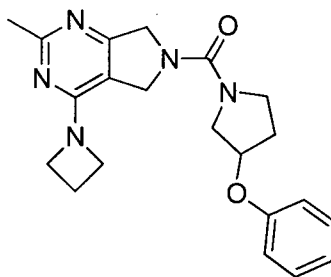
Carbonyl diimidazole (670 mg, 4.13 mmol) was added to a solution of triethylamine (1.20 mL, 8.61 mmol) and 1-{2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride (**Intermediate 33**, 906 mg, 3.44 mmol) in DCM (11.5 mL). The reaction was stirred at room temperature for 1 hour. The reaction was diluted with DCM and washed with water. The organics were dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on basic silica, eluting with 0-100 % ethyl acetate/petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.22 - 2.43 (m, 5 H) 3.93 - 4.37 (m, 4 H) 4.46 - 5.19 (m, 4 H) 7.07 (s, 1 H) 7.72 (s, 1 H) 8.26 (s, 1 H).

MS ES+ 285

Example 111

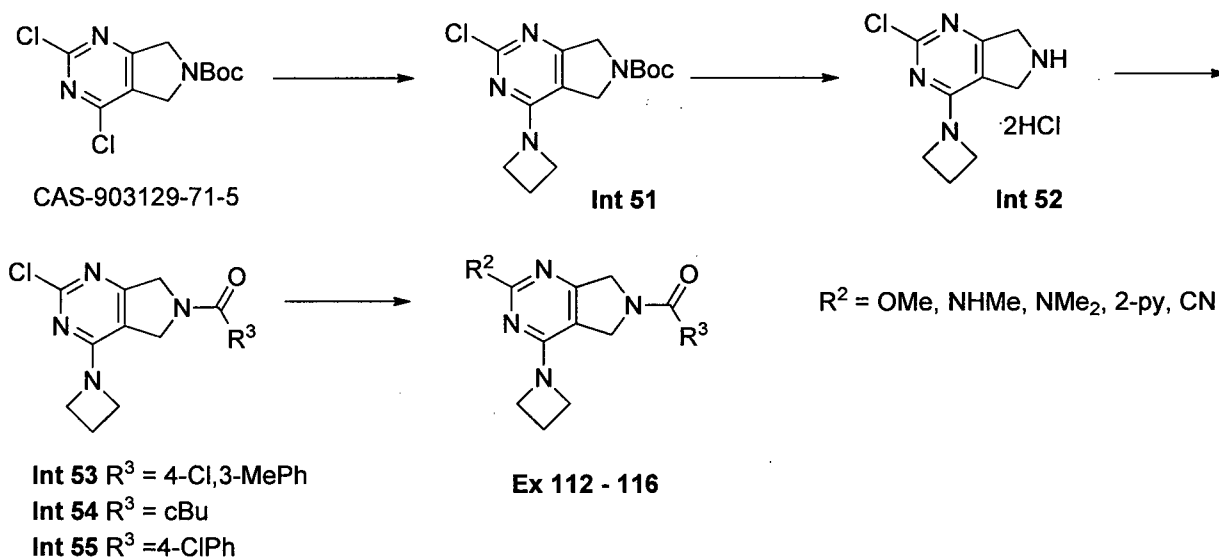
1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-phenoxypyrrolidine



A solution of 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-1H-imidazole (**Intermediate 50**, 100 mg, 0.35 mmol), 3-phenoxypropan-1-ol (69 mg, 0.42 mmol) and DBU (0.17 mL, 1.13 mmol) in acetonitrile (1.2 mL) was heated under microwave irradiation at 100 °C for 0.5 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC eluting with acetonitrile / water (with 0.1 % ammonia) to afford the title compound.

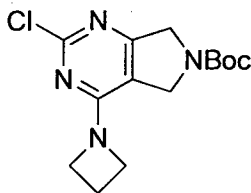
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.02 - 2.15 (m, 2 H) 2.26 - 2.40 (m, 5 H) 3.46 - 3.62 (m, 3 H) 3.72 - 3.82 (m, 1 H) 4.15 - 4.19 (m, 4 H) 4.29 - 4.40 (m, 1 H) 4.50 - 4.65 (m, 2 H) 4.77 - 4.81 (m, 1 H) 5.01 - 5.05 (m, 1 H) 6.88 - 7.02 (m, 3 H) 7.28 - 7.32 (m, 2 H).
MS ES+ 380

Scheme 11



Intermediate 51

***tert*-Butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



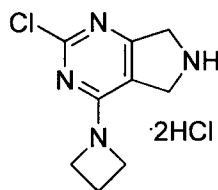
To a suspension of *tert*-butyl 2,4-dichloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (888 mg, 3.06 mmol) in *iso*-PrOH (6 mL) under nitrogen was added N,N-diisopropylethylamine (1.1 mL, 6.12 mmol) and azetidine (0.25 mL, 3.67 mmol). The reaction mixture was stirred for 16 hours and concentrated *in vacuo*. The crude product was purified by column chromatography on basic silica, eluting with 0-100 % DCM in petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 (s, 9H), 2.27 - 2.40 (m, 2H), 4.11 - 4.38 (m, 6H), 4.55 - 4.62 (m, 2H).

MS ES+ 311

Intermediate 52

1-{2-Chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



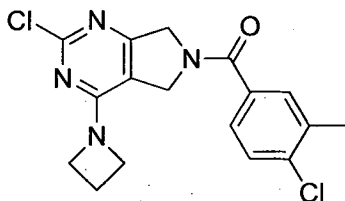
To a suspension of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 51**, 746 mg, 2.40 mmol) in methanol (8 mL) under nitrogen was added HCl (4.0 M in dioxane, 3 mL, 12.00 mmol). The solution was stirred for 3 hours, followed by the addition of HCl (4.0 in dioxane, 1.5 mL, 6.00 mmol). The reaction mixture was stirred for a further 3 hours and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.35 (m, 2H), 3.96 - 4.62 (m, 8H), 10.20 - 10.43 (m, 2H).

MS ES+ 211

Intermediate 53

1-{2-Chloro-6-[(4-chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



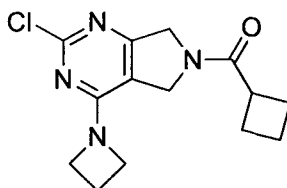
Prepared via Method C using **Intermediate 52** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.44 (m, 5 H) 4.03 - 4.44 (m, 4 H) 4.48 - 4.68 (m, 2 H) 4.77 - 4.91 (m, 2 H) 7.38 - 7.56 (m, 2 H) 7.61 (s, 1 H).

MS ES+ 363

Intermediate 54

1-{2-Chloro-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



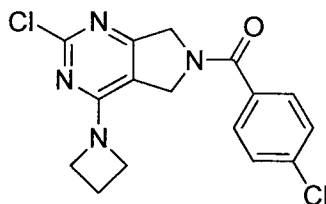
Prepared via Method D using **Intermediate 52** and cyclobutanecarbonyl chloride (CAS 5006-22-4).

¹H NMR (400 MHz, CD₃OD) δ ppm 1.78 - 1.96 (m, 1 H) 1.98 - 2.14 (m, 1 H) 2.15 - 2.37 (m, 4 H) 2.38 - 2.52 (m, 2 H) 3.34 - 3.51 (m, 1 H) 4.17 - 4.43 (m, 4 H) 4.43 - 4.81 (m, 4 H).

MS ES+ 293

Intermediate 55

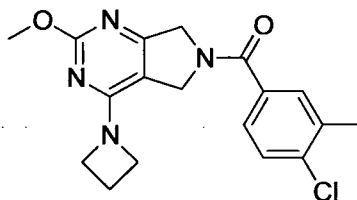
1-[2-Chloro-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



Prepared via Method D using **Intermediate 52** and 4-chlorobenzoyl chloride (CAS 122-01-0).

5 **Example 112**

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



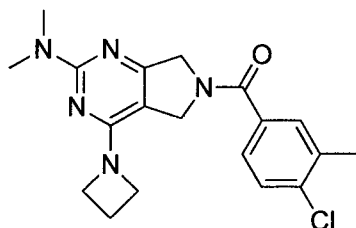
Sodium (6.33 mg, 0.275 mmol) was added to methanol (1 mL) and stirred at RT for 15
 10 minutes, followed by the addition of 1-{2-chloro-6-[(4-chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (**Intermediate 53**, 100 mg, 0.28 mmol). The reaction was heated to 130 °C for 1 hour. The reaction was concentrated *in vacuo* and 4-chloro-3-methylbenzoic acid (83 mg, 0.49 mmol), triethylamine (0.20 mL, 1.46 mmol) and 1-propanephosphonic acid cyclic anhydride (50 % in EtOAc, 0.29 mL, 0.49 mmol)
 15 were added. The reaction mixture was stirred at room temperature for 2 hours in DCM and partitioned between DCM and water. The layers were separated and the organic layer dried (phase separator). The crude product was purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 - 2.43 (m, 5 H) 3.68 - 3.84 (m, 3 H) 4.01 - 4.29 (m, 4 H) 4.49 - 4.84 (m, 4 H) 7.37 - 7.55 (m, 2 H) 7.57 - 7.68 (m, 1 H).

MS ES+ 359

Example 113

25 **4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine**



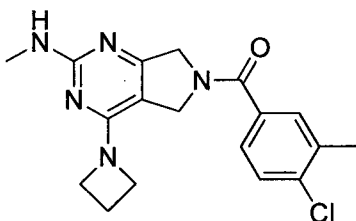
Dimethylamine (2.0 M in THF, 1.38 mL, 2.75 mmol) was added to a solution of 1-(2-chloro-6-[(4chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine (**Intermediate 53**, 100 mg, 0.28 mmol) in EtOH (1 mL) under nitrogen. The reaction mixture was heated under microwave irradiation at 130 °C for 1 hour. The mixture was concentrated *in vacuo* and partitioned between DCM and water. The layers were separated and the aqueous re-extracted. The combined organics were dried (phase separator) and concentrated. The crude product was purified by column chromatography on basic silica, eluting with 0-70 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 - 2.26 (m, 1 H), 2.33 (s, 1 H), 2.97 - 3.08 (m, 3 H), 3.31 (s, 6 H), 3.94 - 4.04 (m, 2 H), 4.10 - 4.19 (m, 2 H), 4.44 (s, 2 H), 4.63 - 4.75 (m, 2 H), 7.42 - 7.52 (m, 2 H), 7.57 - 7.64 (m, 1 H).

MS ES+ 372

Example 114

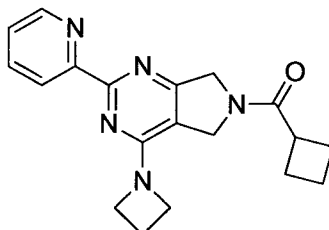
4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine



Prepared in a similar manner to **Example 113** using **Intermediate 53** and methylamine (2M in THF) (CAS 74-89-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 - 2.43 (m, 5 H) 2.74 - 2.88 (m, 3 H) 4.09 - 4.42 (m, 4 H) 4.56 - 4.79 (m, 4 H) 7.41 - 7.57 (m, 2 H) 7.57 - 7.64 (m, 1 H) 7.68 (br. s, 1 H).

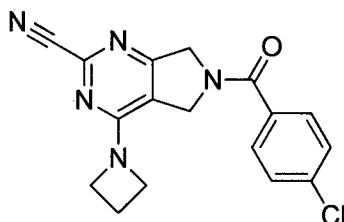
MS ES+ 358

Example 115**2-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine**

Chloro(pyridin-2-yl)zinc (0.5 M in THF, 0.79 mL, 0.40 mmol) was added to a degassed solution of 1-{2-chloro-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (**Intermediate 54**, 58 mg, 0.20 mmol), palladium(II) acetate (2 mg, 10 μ mol), and dicyclohexyl[2-(2,6-dimethoxyphenyl)phenyl]phosphane (8 mg, 0.020 mmol) in toluene (0.7 mL) under nitrogen in a dry flask. The reaction was heated to reflux for 3 hours and quenched with water. EtOAc was added and the layers separated. The organics were then washed with brine, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.71 - 1.87 (m, 1H), 1.89 - 2.04 (m, 1 H), 2.11 - 2.30 (m, 4H), 2.31 - 2.45 (m, 2H), 3.36 - 3.47 (m, 1H), 4.18 - 4.90 (m, 8H), 7.41 - 7.55 (m, 1H), 7.83 - 7.97 (m, 1H), 8.20 - 8.35 (m, 1H), 8.63 - 8.75 (m, 1H).

MS ES+ 336

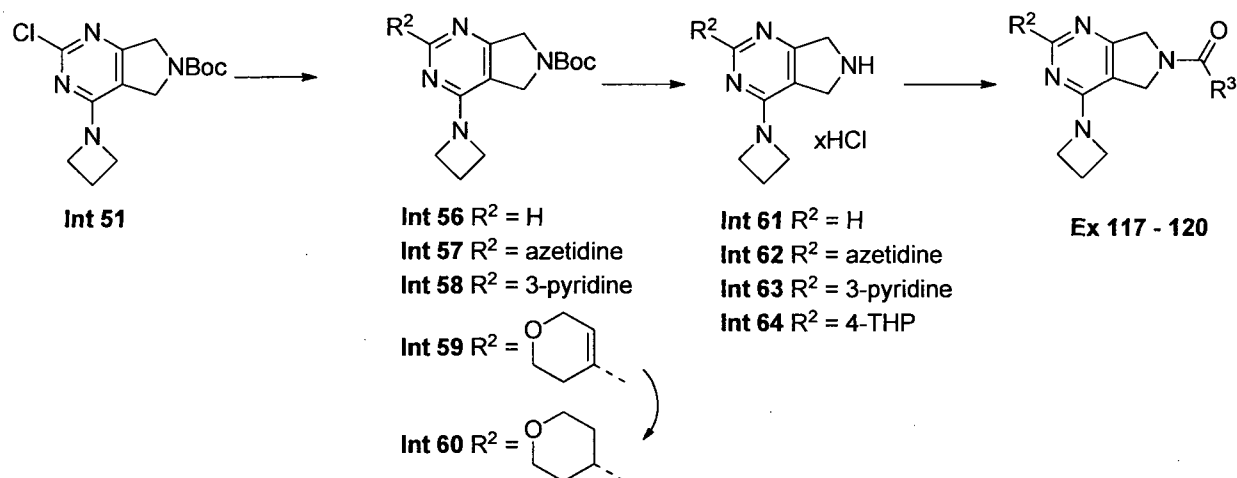
Example 116**4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonitrile**

A suspension of 1-[2-chloro-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine (**Intermediate 55**, 800 mg, 2.29 mmol), dicyanozinc (161 mg, 1.38 mmol) and tetrakis(triphenylphosphine) palladium (265 mg, 0.23 mmol) in DMF (7.6 mL) was heated under microwave irradiation at 140 °C for 30 minutes. The reaction was poured into water and extracted twice with EtOAc. The organics were combined, washed twice with brine, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.21 - 2.47 (m, 2 H) 4.12 - 4.25 (m, 4 H) 4.62 - 4.72 (m, 2 H) 4.87 - 5.02 (m, 2 H) 7.47 - 7.60 (m, 2 H) 7.61 - 7.73 (m, 2 H).

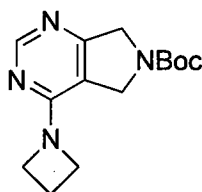
MS ES+ 340

Scheme 12



Intermediate 56

tert-Butyl 4-(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



To a solution of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 93**, 150 mg, 0.483 mmol) and HCl (4.0 M in dioxane, 0.5 mL,

2.00 mmol) in EtOH (20 mL) and THF (5 mL) was added palladium on carbon (10 wt %, dry basis, 51 mg, 0.05 mmol). The reaction mixture was stirred under an atmosphere of hydrogen for 5 hours, followed by the addition of further palladium on carbon (10 wt %, dry basis, 51 mg, 0.05 mmol). The reaction mixture was stirred under an atmosphere of hydrogen for 17 hours. Palladium on carbon (10 wt %, dry basis, 100 mg, 0.09 mmol) was added and the reaction mixture stirred under an atmosphere of hydrogen for a further 25 hours. The reaction was filtered through a Celite cartridge and concentrated *in vacuo* to afford the title compound which was taken on directly to the next step.

10 MS ES+ 277

Intermediate 61

1-{5H,6H,7H-Pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



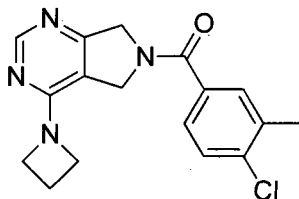
15 To a solution of *tert*-butyl 4-(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 56**, 133 mg, 0.48 mmol) in MeOH (1.6 mL) under nitrogen was added HCl (4.0 M in dioxane, 0.6 mL, 2.41 mmol). The reaction was stirred at RT for 4 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound which was taken directly on to the next step.

20

MS ES+ 177

Example 117

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



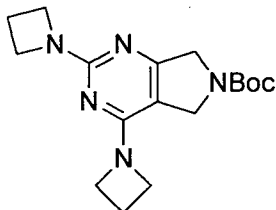
Prepared via Method C using **Intermediate 56** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.21 - 2.44 (m, 5 H) 4.03 - 4.32 (m, 4 H) 4.53 - 4.92 (m, 4 H) 7.41 - 7.55 (m, 2 H) 7.57 - 7.67 (m, 1 H) 8.29 - 8.42 (m, 1 H).

MS ES+ 329

Intermediate 57

***tert*-Butyl 2,4-bis(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

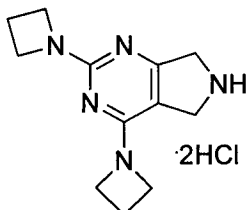


A solution of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 51**, 50 mg, 0.16 mmol) and azetidine (43 μL, 0.64 mmol) in EtOH (0.5 mL) was heated under microwave irradiation at 120 °C for 1 hour. The mixture was concentrated *in vacuo* to afford the title compound which was taken on directly to the next step.

MS ES+ 332

Intermediate 62

1-[2-(Azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine dihydrochloride

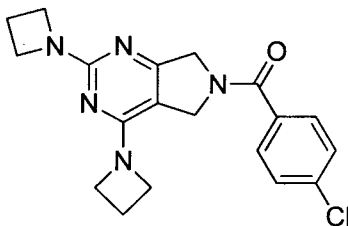


Prepared in a similar fashion to **Intermediate 61** using **Intermediate 57**. The crude material was taken on directly to the next step.

MS ES+ 232

Example 118

1-[4-(Azetidin-1-yl)-6-[(4-chlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]azetidine



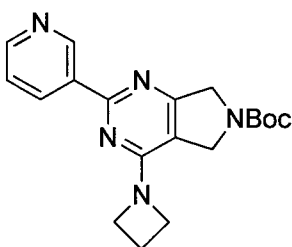
Prepared via Method D using **Intermediate 62** and 4-chlorobenzoyl chloride (CAS 122-01-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.05 - 2.39 (m, 4H), 3.80 - 4.06 (m, 6H), 4.08 - 4.22 (m, 2H), 4.33 - 4.50 (m, 2H), 4.56 - 4.80 (m, 2H), 7.38 - 7.77 (m, 4H).

MS ES+ 370

Intermediate 58

tert-Butyl 4-(azetidin-1-yl)-2-(pyridin-3-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



To a degassed mixture of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 51**, 100 mg, 0.32 mmol), pyridin-3-ylboronic acid (48 mg, 0.39 mmol), tetrakis(triphenylphosphine) palladium (19 mg, 0.016 mmol) and potassium carbonate (133 mg, 0.97 mmol) was added dioxane (0.7 mL) and water (0.7 mL). The reaction mixture was heated under microwave irradiation at 100 °C for 30 minutes. The reaction was partitioned between EtOAc and water and the layers separated. The organics were washed with brine, dried (phase separator) and concentrated *in vacuo*. The

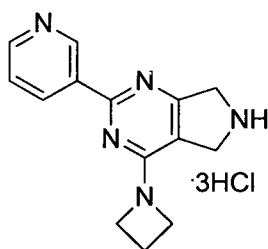
crude product was purified by column chromatography on basic silica, eluting with 0-40 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, CD₂Cl₂) δ ppm 1.54 (s, 9H), 2.41 - 2.57 (m, 2H), 4.26 - 4.40 (m, 4H),
5 4.50 - 4.56 (m, 2H), 4.64 - 4.74 (m, 2H), 7.35 - 7.42 (m, 1H), 8.60 - 8.72 (m, 2H), 9.56 (br.
s., 1H).

MS ES+ 354

Intermediate 63

10 **3-[4-(Azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine
trihydrochloride**



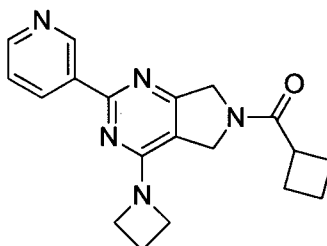
Prepared in a similar manner to **Intermediate 61** using **Intermediate 58**. The crude material was taken directly on to the next step.

15

MS ES+ 254

Example 119

20 **3-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-
yl]pyridine**



Prepared via Method C using **Intermediate 63** and cyclobutanecarboxylic acid (CAS 3721-95-7).

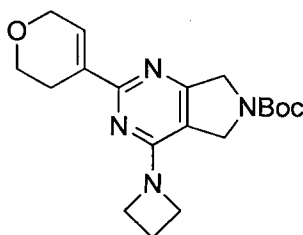
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 - 2.44 (m, 8H), 3.35 - 3.49 (m, 1H), 4.24 - 4.38 (m, 4H), 4.42 - 4.90 (m, 4H), 7.44 - 7.55 (m, 1H), 8.51 - 8.61 (m, 1H), 8.63 - 8.72 (m, 1H), 9.43 (s, 1H).

MS ES+ 336

5

Intermediate 59

***tert*-Butyl 4-(azetidin-1-yl)-2-(3,6-dihydro-2H-pyran-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



10 To a degassed mixture of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 51**, 100 mg, 0.32 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (81 mg, 0.39 mmol), tetrakis(triphenylphosphine) palladium (19 mg, 0.016 mmol) and potassium carbonate (133 mg, 0.97 mmol) was added dioxane (0.7 mL) and water (0.7 mL) under nitrogen. The
15 reaction was heated at 120 °C for 45 minutes under microwave irradiation. The reaction was partitioned between EtOAc and water and the layers separated. The organics were washed with brine, dried (phase separator) and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-90 % EtOAc in petrol to afford the title compound.

20

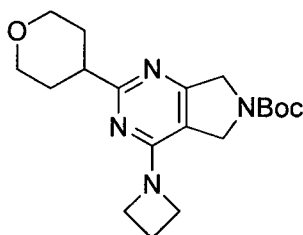
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.45 (s, 9 H) 2.21 - 2.39 (m, 2 H) 2.44 - 2.48 (m, 2 H) 3.65 - 4.75 (m, 12 H) 7.02 (br. s., 1 H)

MS ES+ 359

25 Intermediate 60

***tert*-Butyl 4-(azetidin-1-yl)-2-(oxan-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

146



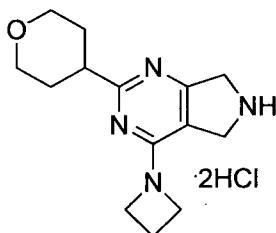
Palladium on carbon (10 wt %, dry basis, 42 mg, 0.04 mmol) was added to a solution of *tert*-butyl 4-(azetidin-1-yl)-2-(3,6-dihydro-2H-pyran-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 59**, 140 mg, 0.39 mmol) in EtOH (4 mL). The reaction mixture was stirred under an atmosphere of hydrogen for 3.5 hours, filtered through a Celite cartridge and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, CD₂Cl₂) δ ppm 1.13 - 1.23 (m, 9 H) 1.75 - 1.95 (m, 4 H) 2.25 - 2.48 (m, 2 H) 2.68 - 2.91 (m, 1 H) 3.38 - 3.53 (m, 2 H) 3.88 - 4.09 (m, 2 H) 4.10 - 4.28 (m, 4 H) 4.32 - 4.47 (m, 2 H) 4.51 - 4.68 (m, 2 H).

MS ES+ 361

Intermediate 64

1-[2-(Oxan-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine dihydrochloride



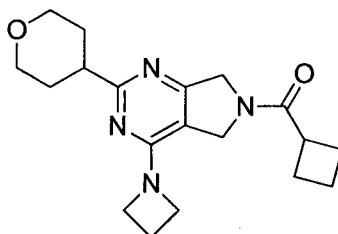
Prepared in a similar manner to **Intermediate 61** using **Intermediate 60**. The crude material was taken directly on to the next step.

MS ES+ 261

Example 120

1-[6-Cyclobutanecarbonyl-2-(oxan-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

147

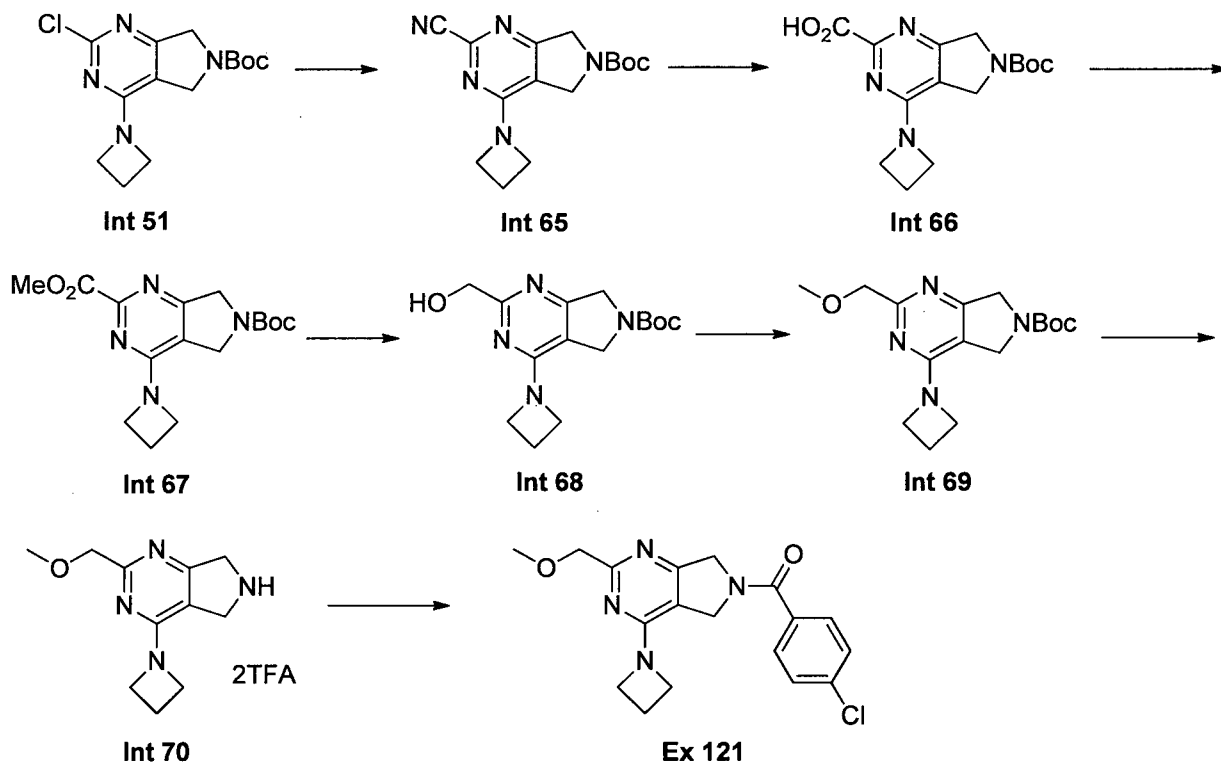


Prepared via Method D using **Intermediate 64** and cyclobutanecarbonyl chloride (CAS 5006-22-4).

- ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.66 - 1.85 (m, 5H), 1.86 - 2.02 (m, 1H), 2.09 - 2.26 (m, 4H), 2.27 - 2.40 (m, 2H), 2.72 - 2.86 (m, 1H), 3.35 - 3.47 (m, 3H), 3.84 - 3.96 (m, 2H), 4.09 - 4.27 (m, 4H), 4.31 - 4.76 (m, 4H).

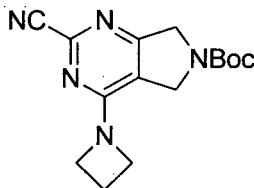
MS ES+ 343

Scheme 13



Intermediate 65

***tert*-Butyl 4-(azetidin-1-yl)-2-cyano-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



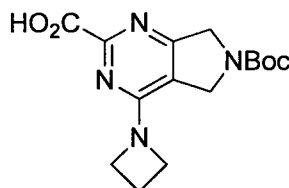
A suspension of *tert*-butyl 4-(azetidin-1-yl)-2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 51**, 250 mg, 0.80 mmol), tetrakis(triphenylphosphine) palladium (93 mg, 0.080 mmol) and dicyanozinc (57 mg, 0.48 mmol) in DMF (2.5 mL) was heated under microwave irradiation at 140 °C for 1 hour. The reaction was poured into water and extracted twice with EtOAc. The organics were combined washed twice with brine, dried (phase separator) and concentrated *in vacuo*. The resulting red residue was purified by column chromatography on basic silica, eluting with 0-50 % EtOAc in petrol to afford the title compound.

¹H NMR (300 MHz, CD₃OD) δ ppm 1.51 (s, 9 H) 2.34 - 2.56 (m, 2 H) 4.18 - 4.50 (m, 6 H) 4.65 - 4.78 (m, 2 H).

MS ES+ 302

Intermediate 66

4-(Azetidin-1-yl)-6-[(*tert*-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carboxylic acid



A suspension of *tert*-butyl 4-(azetidin-1-yl)-2-cyano-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 65**, 180 mg, 0.60 mmol) and NaOH (96 mg, 2.39 mmol) in MeOH (1.5 mL) and water (0.5 mL) was heated to 65 °C for 4 hours. The reaction was cooled to RT and acidified with aq. 2N HCl. The reaction was concentrated *in vacuo*. The resulting residue was taken up in MeOH and the salts were filtered off. The filtrate was

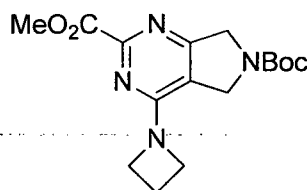
concentrated *in vacuo* yielding the title compound which was taken on directly to the next step.

¹H NMR (300 MHz, CD₃OD) δ ppm 1.40 - 1.57 (m, 9 H) 2.34 - 2.53 (m, 2 H) 4.20 - 4.42 (m, 4 H) 4.44 - 4.53 (m, 2 H) 4.65 - 4.76 (m, 2 H).

MS ES+ 321

Intermediate 67

6-*tert*-Butyl 2-methyl 4-(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2,6-dicarboxylate



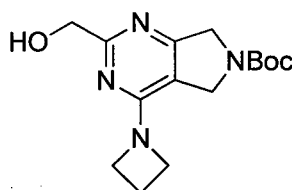
To a solution of 4-(azetidin-1-yl)-6-[(*tert*-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carboxylic acid (**Intermediate 66**, 192 mg, 0.60 mmol) in DCM (3 mL) and methanol (1 mL) at 0 °C was added TMS-diazomethane (2M in hexanes, 0.90 ml, 1.80 mmol) in a dropwise fashion. The reaction was stirred at 0 °C for 15 minutes. The reaction was concentrated *in vacuo* and the resulting residue purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

¹H NMR (300 MHz, CD₃OD) δ ppm 1.51 (s, 9 H) 2.35 - 2.52 (m, 2 H) 3.93 (s, 3 H) 4.24 - 4.42 (m, 4 H) 4.44 - 4.53 (m, 2 H) 4.66 - 4.78 (m, 2 H).

MS ES+ 335

Intermediate 68

tert-Butyl 4-(azetidin-1-yl)-2-(hydroxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

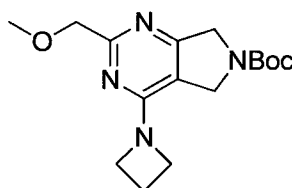


To a solution of 6-*tert*-butyl 2-methyl 4-(azetidin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2,6-dicarboxylate (**Intermediate 67**, 30 mg, 0.090 mmol) in DCM (0.7 mL) and methanol (2 mL) was added sodium borohydride (20 mg, 0.54 mmol). The reaction was stirred at room temperature for 1 hour. Further sodium borohydride (20 mg, 0.54 mmol) was added and the reaction stirred for a further hour. Further 6-*tert*-butyl 2-methyl 4-(azetidin-1-yl)-5H-pyrrolo[3,4-d]pyrimidine-2,6(7H)-dicarboxylate (30 mg, 0.090 mmol) and sodium borohydride (20 mg, 0.54 mmol) were added and the reaction stirred at room temperature for 2 hours. The reaction was quenched with water and extracted with EtOAc. The organics were washed with brine, dried (phase separator) and concentrated *in vacuo* yielding the title compound which was taken on directly to the next step.

¹H NMR (300 MHz, CD₃OD) δ ppm 1.47 (s, 9 H) 2.31 - 2.48 (m, 2 H) 4.18 - 4.49 (m, 8 H) 4.57 - 4.67 (m, 2 H)

Intermediate 69

tert-Butyl 4-(azetidin-1-yl)-2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



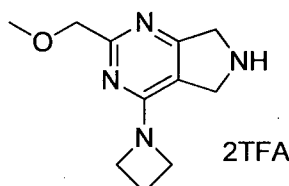
To a solution of *tert*-butyl 4-(azetidin-1-yl)-2-(hydroxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 68**, 44 mg, 0.14 mmol) in DMF (1 mL) was added NaH (9 mg, 0.22 mmol) followed by MeI (0.02 mL, 0.29 mmol) and the reaction was stirred at room temperature for 1 hr. The reaction mixture was poured into water and extracted with EtOAc. The organics were washed with brine, dried (phase separator) and concentrated *in vacuo*. The resulting residue was purified by column chromatography on basic silica, eluting with 0-100% EtOAc in petrol to afford the title compound.

¹H NMR (300 MHz, CD₃OD) δ ppm 1.53 (s, 9 H) 2.36 - 2.53 (m, 2 H) 3.45 (s, 3 H) 4.22 - 4.36 (m, 4 H) 4.37 - 4.48 (m, 4 H) 4.61 - 4.72 (m, 2 H)

MS ES+ = 321

Intermediate 70

1-[2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;
bis(trifluoroacetic acid)

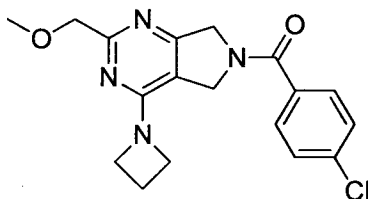


To a solution of *tert*-Butyl 4-(azetidin-1-yl)-2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 69**, 44 mg, 0.14 mmol) in DCM (2 mL) was added TFA (0.05 mL, 0.69 mmol). The reaction was stirred at room temperature with the
further addition of TFA (0.05 mL, 0.69 mmol) after 1 hour and 24 hours. The reaction was
stirred for a further 8 hours then concentrated *in vacuo* yielding the title compound which
was taken on directly to the next step.

MS ES+ 221

Example 121

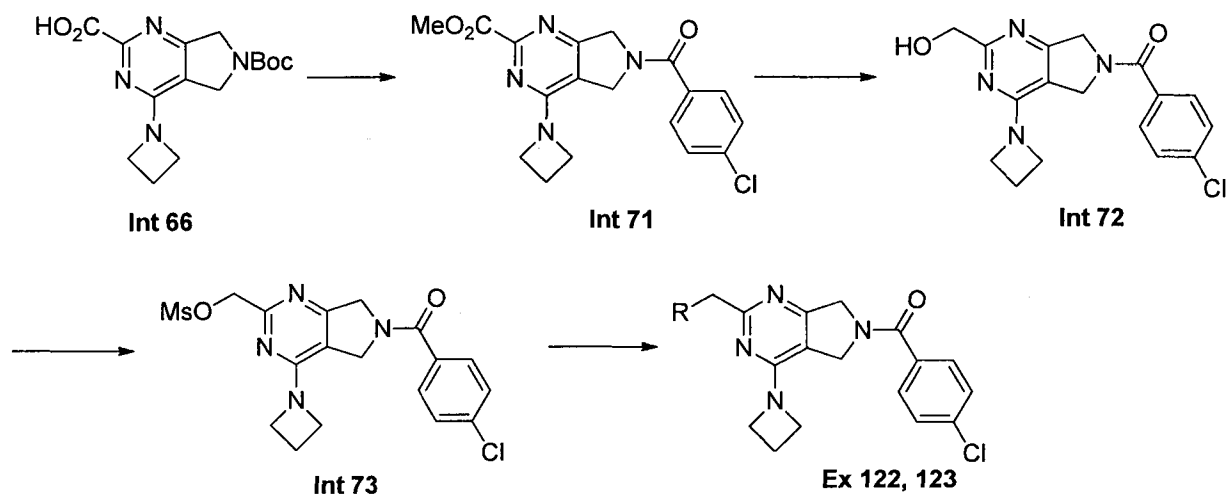
1-[6-(4-Chlorobenzoyl)-2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



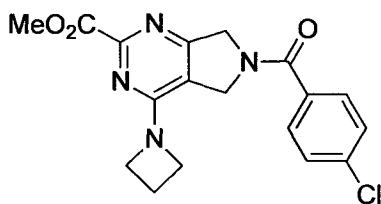
Prepared via Method D using **Intermediate 70** and 4-chlorobenzoyl chloride (CAS 122-01-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.21 - 2.45 (m, 2 H) 3.34 (s, 3 H) 4.02 - 4.35 (m, 6 H) 4.54 - 4.92 (m, 4 H) 7.53 - 7.55 (m, 2 H) 7.65 - 7.67 (m, 2 H)

MS ES+ 359

Scheme 14**Intermediate 71**

Methyl 4-(azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carboxylate



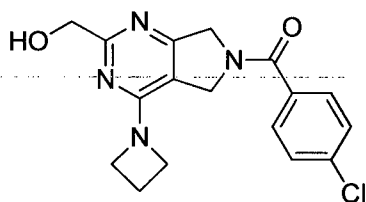
A solution of 4-(azetidin-1-yl)-6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carboxylic acid (**Intermediate 66**, 1.02 g, 3.18 mmol) in DCM (9 mL) and methanol (3 mL) under an atmosphere of nitrogen was cooled to 0 °C. TMS-diazomethane (1.59 mL, 3.18 mmol) was added and the reaction allowed to warm to room temperature over 18 hours. The reaction was acidified via the addition of AcOH and was then concentrated *in vacuo*. The resulting residue was taken up in DCM (9 mL) and methanol (3 mL) at 0 °C under an atmosphere of nitrogen and treated with TMS-diazomethane (1.59 mL, 3.18 mmol). The reaction was stirred at 0 °C for 1 hour then concentrated *in vacuo*. The resulting residue was loaded onto a cation exchange cartridge, washed with methanol and eluted with 2M ammonia in methanol solution then concentrated *in vacuo*. The resulting residue was diluted with DCM (9 mL) and treated with triethylamine (0.89 mL, 6.37 mmol) followed by 4-chlorobenzoyl chloride (0.41 mL, 3.18 mmol). The reaction was stirred at room temperature for 0.5 hours. The reaction was concentrated *in vacuo*. The resulting residue was partitioned between EtOAc and water. The organics were dried (MgSO₄),

filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

¹H NMR (300 MHz, CD₃OD) δ ppm 2.33 - 2.59 (m, 2 H) 3.89 - 3.99 (m, 3 H) 4.20 - 4.49 (m, 4 H) 4.61 - 5.11 (m, 4 H) 7.45 - 7.58 (m, 2 H) 7.60 - 7.69 (m, 2 H)
MS ES+ 373

Intermediate 72

[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methanol

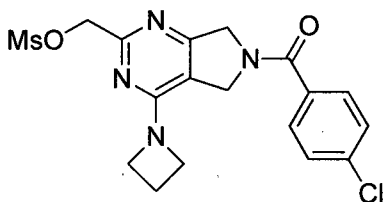


A solution of methyl 4-(azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carboxylate (**Intermediate 71**, 280 mg, 0.75 mmol) in MeOH (1 mL) and DCM (3 mL) was treated with NaBH₄ (170 mg, 4.51 mmol) and stirred at room temperature for 1.5 hours. The reaction was quenched with water and concentrated *in vacuo*. The resulting residue was partitioned between DCM and water. The organics were dried (phase separator) and concentrated *in vacuo* to afford the title compound which was taken directly onto the next step.

MS ES+ 345

Intermediate 73

[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl methanesulfonate

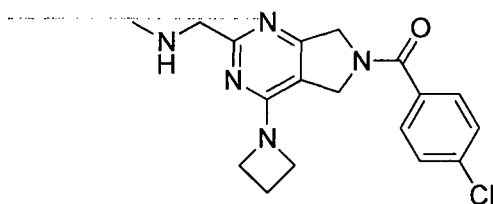


To a solution of [4-(azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methanol (**Intermediate 72**, 148 mg, 0.43 mmol) and triethylamine (0.12 mL, 0.86 mmol) in DCM (3 mL) at 0 °C was added methanesulfonyl chloride (0.04 mL, 0.52 mmol). The reaction was stirred at 0 °C for 1 hour. The reaction was diluted with DCM, washed with water, dried (phase separator) and concentrated *in vacuo* to afford the title compound which was taken directly onto the next step.

MS ES+ 423

Example 122

{[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}(methyl)amine



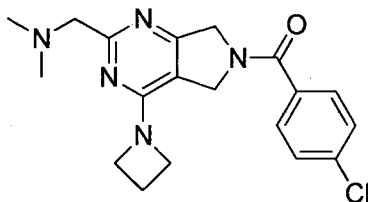
To a solution of [4-(azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl methanesulfonate (**Intermediate 73**, 90 mg, 0.21 mmol) in THF (1 mL) was added methylamine (2M in THF, 2.13 mL, 4.26 mmol) and the reaction stirred at RT for 18 hours. The reaction was concentrated *in vacuo* and the resulting residue was purified by reverse phase preparative HPLC eluted with acetonitrile / water (with 0.1% ammonia) to afford the title compound

¹H NMR (300 MHz, CDCl₃) δ ppm 2.27 - 2.57 (m, 5 H) 3.69 - 3.87 (m, 2 H) 4.09 - 4.37 (m, 4 H) 4.53 - 5.04 (m, 4 H) 7.37 - 7.47 (m, 2 H) 7.49 - 7.60 (m, 2 H)

MS ES+ 358

Example 123

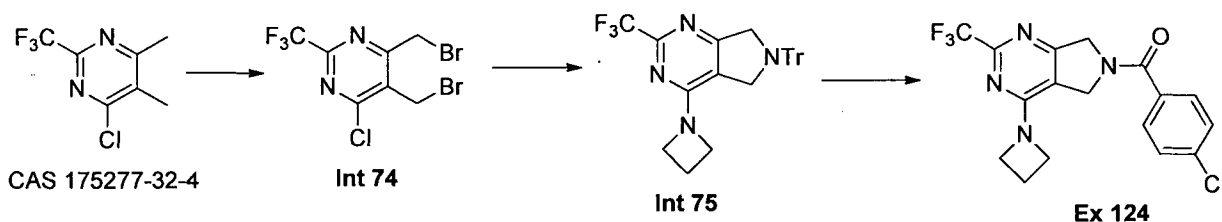
{[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}dimethylamine



To a solution of (4-(azetidin-1-yl)-6-(4-chlorobenzoyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)methyl methanesulfonate (90 mg, 0.21 mmol) in THF (1 mL) was added dimethylamine (2M in THF, 2.13 mL, 4.26 mmol) and the reaction stirred at RT for 18 hours. The reaction was concentrated *in vacuo* and the resulting residue was purified by reverse phase preparative HPLC eluted with acetonitrile / water (with 0.1% ammonia) to afford the title compound.

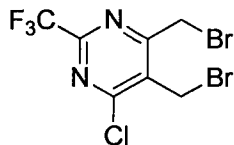
¹H NMR (300 MHz, CDCl₃) δ ppm 2.27 - 2.56 (m, 8 H) 3.47 - 3.60 (m, 2 H) 4.08 - 4.41 (m, 4 H) 4.55 - 5.04 (m, 4 H) 7.35 - 7.48 (m, 2 H) 7.48 - 7.58 (m, 2 H)
MS ES+ 372

Scheme 15



Intermediate 74

4,5-Bis(bromomethyl)-6-chloro-2-(trifluoromethyl)pyrimidine



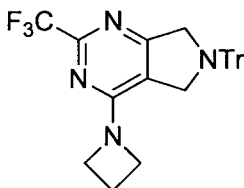
N-Bromosuccinimide (5.1 g, 28.5 mmol) was added to a suspension of 4-chloro-5,6-dimethyl-2-(trifluoromethyl)pyrimidine (3 g, 14.25 mmol) and benzoyl peroxide (0.46 g, 1.43 mmol) in carbon tetrachloride (48 mL) under nitrogen. The reaction was heated under reflux for 21 hours. Further N-bromosuccinimide (5.1 g, 28.5 mmol) and benzoyl peroxide (0.46 g, 1.43 mmol) were added and the reaction heated under reflux for a further 4 hours.

The reaction was concentrated *in vacuo*, partitioned between DCM and water and the solid was removed by filtration. The organics were dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-100 % DCM in petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.91 (s, 2H), 4.94 (s, 2H)

Intermediate 75

1-[2-(Trifluoromethyl)-6-(triphenylmethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

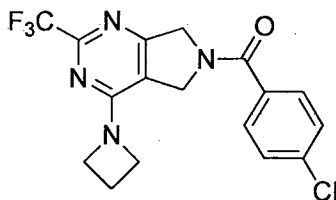


N,N-diisopropylethylamine (0.209 mL, 1.194 mmol) was added to a solution of 4,5-bis(bromomethyl)-6-chloro-2-(trifluoromethyl)pyrimidine (**Intermediate 74**, 200 mg, 0.54 mmol) and triphenylmethanamine (155 mg, 0.60 mmol) in DMF (2 mL) at RT. The mixture was stirred under nitrogen at RT for 2 hours. Further N,N-diisopropylethylamine (0.10 mL, 0.60 mmol) was added to the reaction, followed by azetidine (47 mg, 0.81 mmol). After standing for 1 hour the mixture was diluted with EtOAc and washed with saturated sodium carbonate solution, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography on basic silica, eluting with 20-50 % EtOAc in petrol and then again with 10-30 % EtOAc in petrol and then 5-10 % EtOAc in petrol to afford the title compound which was taken directly on to the next step.

MS ES+ 487

Example 124

1-{6-[(4-Chlorophenyl)carbonyl]-2-(trifluoromethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

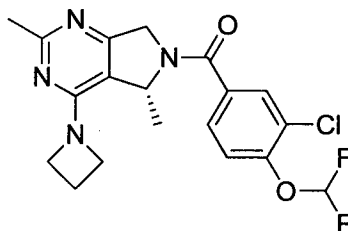


HCl (4.0 M in dioxane, 0.14 mL, 0.58 mmol) was added to a solution of 1-[2-(trifluoromethyl)-6-(triphenylmethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine (**Intermediate 75**, 56 mg, 0.12 mmol) in DCM (2 mL) at RT. The mixture was stirred and left to stand for 5 minutes, followed by the addition of N,N-diisopropylethylamine (0.20 mL, 1.15 mmol) and dropwise addition of a solution of 4-chlorobenzoyl chloride (30 mg, 0.17 mmol) in DCM (0.5 mL). After 5 minutes, the mixture was diluted with DCM and washed with saturated sodium carbonate solution, dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography on basic silica, eluting with 20-50 % EtOAc in petrol to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.37 - 2.58 (m, 2H), 4.17 - 4.49 (m, 4H), 4.63 - 4.80 (m, 2H), 4.84 - 5.06 (m, 2H), 7.41 - 7.48 (m, 2H), 7.49 - 7.55 (m, 2H),
MS ES+ 383

Example 125

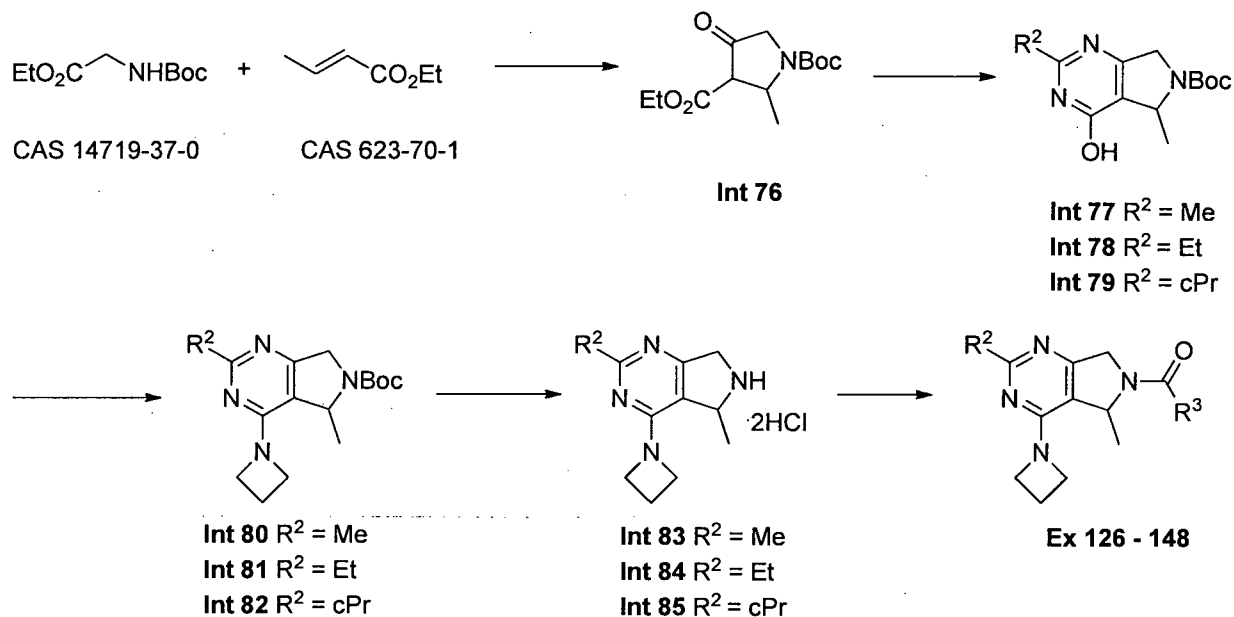
1-[(5R)-6-[3-Chloro-4-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



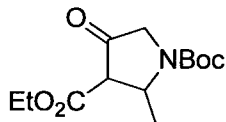
Prepared via Method C using **Intermediate 92** and 3-chloro-4-(difluoromethoxy)benzoic acid (CAS 1192829-74-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.50 (m, 3 H) 2.22 - 2.42 (m, 5 H) 4.00 - 4.38 (m, 5 H) 4.51 - 4.90 (m, 1 H) 5.20 - 5.54 (m, 1 H) 7.17 - 7.61 (m, 2 H) 7.62 - 7.73 (m, 1 H) 7.78 - 7.93 (m, 1 H)

MS ES+ 409

Scheme 16

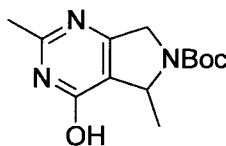
5

Intermediate 76**1-*tert*-Butyl 3-ethyl 2-methyl-4-oxopyrrolidine-1,3-dicarboxylate**

Potassium *tert*-butoxide (1.0 M in THF, 48.4 ml, 48.4 mmol) was added to a solution of
 10 ethyl 2-((*tert*-butoxycarbonyl)amino)acetate (8.20 g, 40.4 mmol) and (E)-ethyl but-2-
 enoate (6.91 g, 60.5 mmol) in THF (135 ml) under nitrogen. The reaction was stirred at RT
 for 18 hours. The reaction mixture was acidified to pH 6 via the addition of aqueous citric
 acid then partitioned between EtOAc and water. The organic layer was dried (phase
 separator) and concentrated *in vacuo*. The material was purified by column
 15 chromatography on silica, eluting with 0 – 20 % EtOAc in petrol to give the title
 compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.35 (m, 6 H) 1.36 - 1.50 (m, 9 H) 3.97 -
 4.23 (m, 5 H) 4.42 - 4.57 (m, 1 H).

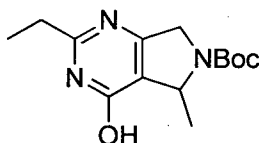
20 MS ES- 270

Intermediate 77***tert*-Butyl 4-hydroxy-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

5 Triethylamine (34.5 mL, 247 mmol) was added to a suspension of acetamidine hydrochloride (13.50 g, 143 mmol) and 1-*tert*-butyl 3-ethyl 2-methyl-4-oxopyrrolidine-1,3-dicarboxylate (**Intermediate 76**, 30.0 g, 95 mmol) in *tert*-BuOH (317 mL) under nitrogen. The reaction mixture was heated under reflux overnight, cooled to RT and concentrated *in vacuo*. The residue was triturated with EtOAc to a white solid. The filtrate
10 was concentrated to approximately half its volume and left standing to give further precipitate, which was combined with the first crop to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 - 1.59 (m, 12 H) 2.30 (s, 3 H) 4.20 - 4.47 (m, 2 H) 4.66 - 4.89 (m, 1 H) 12.51 (br. s., 1 H).

15 MS ES+ 266

Intermediate 78***tert*-Butyl 2-ethyl-4-hydroxy-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

20

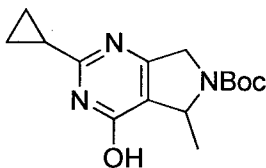
Prepared in a similar manner to **Intermediate 77** using **Intermediate 76** and propionamidine hydrochloride (CAS 3599-89-1).

25 ¹H NMR (300 MHz, CDCl₃) δ ppm 1.30 - 1.40 (m, 3H) 1.42 - 1.58 (m, 12H) 2.68 - 2.80 (m, 2H), 4.40 - 4.62 (m, 2H), 4.91 - 5.10 (m, 1H).

MS ES+ 280

Intermediate 79

***tert*-Butyl 2-cyclopropyl-4-hydroxy-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



Prepared in a similar manner to **Intermediate 77** using **Intermediate 76** and
 5 cyclopropylcarbamidine hydrochloride (CAS 57297-29-7).

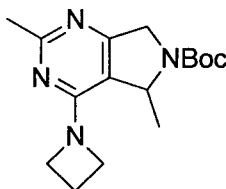
^1H NMR (300 MHz, CDCl_3) δ ppm 1.08 - 1.35 (m, 4H) 1.37 - 1.60 (m, 12H), 1.79 - 2.01
 (m, 1H) 4.03 - 4.55 (m, 2H) 4.90 - 5.07 (m, 1H).

MS ES+ 292

10

Intermediate 80

***tert*-Butyl 4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



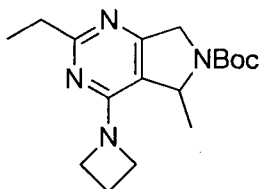
15 Triflic anhydride (5.6 mL, 33.1 mmol) was added dropwise to a suspension of *tert*-butyl 4-hydroxy-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 77**, 7.98 g, 30.1 mmol) and triethylamine (5.0 mL, 36.1 mmol) in DCM (100 mL) under nitrogen. The reaction was stirred at 0 °C for 45 minutes then poured into a solution of N,N-diisopropylethylamine (15.8 mL, 90 mmol) and azetidine (3.0 mL, 45.1 mmol) in
 20 DCM (100 mL) at 0 °C. This was stirred at 0 °C for 30 minutes and partitioned between DCM and water. The organic layer were dried (phase separator) and concentrated *in vacuo*. Purification was performed by column chromatography on silica, eluting with 0-25 % EtOAc in petrol to afford the title compound.

25 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.22 - 1.34 (m, 3 H) 1.37 - 1.57 (m, 9 H) 2.24 - 2.42 (m, 5 H) 3.97 - 4.47 (m, 6 H) 4.83 - 5.11 (m, 1 H)

MS ES+ 305

Intermediate 81

***tert*-Butyl 4-(azetidin-1-yl)-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



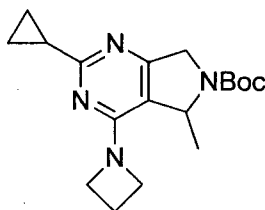
Prepared in a similar manner to **Intermediate 80** using **Intermediate 78**.

¹H NMR (300 MHz, CDCl₃) δ ppm 1.21 - 1.40 (m, 6H) 1.40 - 1.55 (m, 9H) 2.31 - 2.46 (m, 2H) 2.68 - 2.80 (m, 2H) 4.06 - 4.60 (m, 6H) 4.90 - 5.17 (m, 1H)

MS ES+ 319

Intermediate 82

***tert*-Butyl 4-(azetidin-1-yl)-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



Prepared in a similar manner to **Intermediate 80** using **Intermediate 79**.

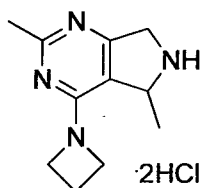
¹H NMR (300 MHz, CDCl₃) δ ppm 0.88 - 1.10 (m, 4H) 1.30 - 1.40 (m, 3H) 1.40 - 1.55 (m, 9H) 1.96 - 2.09 (m, 1H) 2.30 - 2.45 (m, 2H) 3.95 - 4.10 (m, 2H) 4.17 - 4.58 (m, 4H) 4.87 - 5.11 (m, 1H)

MS ES+ 331

Intermediate 83

1-{2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride

162

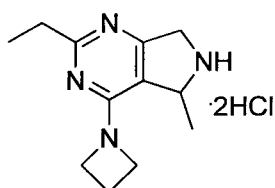


Prepared in a similar manner to **Intermediate 13** using **Intermediate 80**.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.41 - 1.57 (m, 3 H) 2.33 - 2.49 (m, 5 H) 4.16 -
5 4.46 (m, 5 H) 4.51 - 4.71 (m, 1 H) 4.95 - 5.19 (m, 1 H) 9.98 (br. s, 1 H) 10.65 (br. s, 1 H).
MS ES+ 205

Intermediate 84

1-{2-Ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine
10 dihydrochloride

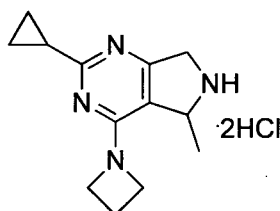


Prepared in a similar manner to **Intermediate 13** using **Intermediate 81**.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 - 1.56 (m, 6H), 2.34 - 2.48 (m, 2H), 2.70 -
15 3.43 (m, 3H), 4.22 - 4.46 (m, 4H), 4.55 - 4.75 (m, 1H), 4.98 - 5.15 (m, 1H), 10.04 (br. s.,
1H), 10.76 (br. s., 1H),
MS ES+ 219

Intermediate 85

20 1-{2-Cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine
dihydrochloride



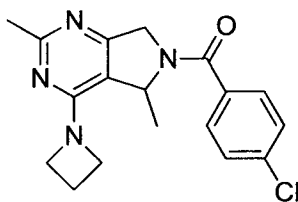
Prepared in a similar manner to **Intermediate 13** using **Intermediate 82**.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.76 - 1.24 (m, 4 H) 1.35 - 1.58 (m, 3 H) 2.02 - 2.19 (m, 1 H) 2.23 - 2.45 (m, 2 H) 4.01 - 4.68 (m, 6 H) 4.87 - 5.15 (m, 1 H) 9.88 (br. s, 1 H) 10.53 (br. s, 1 H)

5 MS ES+ 231

Example 126

1-{6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10

Prepared via Method A using **Intermediate 83** and 4-chlorobenzoic acid (CAS 74-11-3).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 - 1.43 (m, 3H), 2.24 - 2.41 (m, 5H), 4.00 - 4.17 (m, 2H), 4.18 - 4.32 (m, 2H), 4.48 - 4.84 (m, 2H), 5.19 - 5.53 (m, 1H), 7.52 - 7.57 (m, 2H), 7.60 - 7.66 (m, 2H).

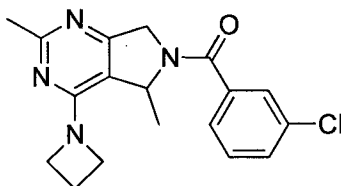
15

MS ES+ 343

Example 127

1-{6-[(3-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

20



Prepared via Method A using **Intermediate 83** and 3-chlorobenzoic acid (CAS 535-80-8).

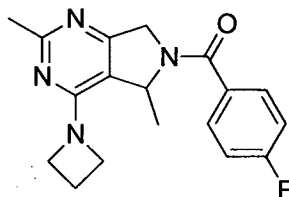
^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.96 - 1.45 (m, 3H), 2.24 - 2.42 (m, 5H), 4.03 - 4.16 (m, 2H), 4.18 - 4.30 (m, 2H), 4.49 - 4.84 (m, 2H), 5.18 - 5.52 (m, 1H), 7.47 - 7.61 (m, 2H), 7.63 - 7.68 (m, 1H).

25

MS ES+ 343

Example 128

1-{6-[(4-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



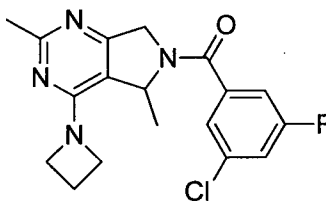
Prepared via Method A using **Intermediate 83** and 4-fluorobenzoic acid (CAS 456-22-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.44 (m, 3H), 2.21 - 2.44 (m, 5H), 4.02 - 4.16 (m, 2H), 4.17 - 4.63 (m, 3H), 4.75 - 4.87 (m, 1H), 5.20 - 5.55 (m, 1H), 7.26 - 7.35 (m, 2H), 7.63 - 7.72 (m, 2H).

MS ES+ 327

Example 129

1-{6-[(3-chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



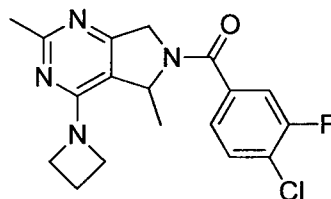
Prepared via Method A using **Intermediate 83** and 3-chloro-5-fluorobenzoic acid (CAS 25026-64-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.48 (m, 3 H) 2.20 - 2.44 (m, 5 H) 3.89 - 4.40 (m, 5 H) 4.46 - 4.87 (m, 1 H) 5.15 - 5.54 (m, 1 H) 7.31 - 7.74 (m, 3 H).

MS ES+ 361

Example 130

1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 83** and 4-chloro-3-fluorobenzoic acid (CAS
5 403-17-8).

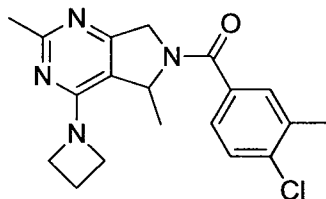
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.49 (m, 3 H) 2.18 - 2.43 (m, 5 H) 3.94 -
4.87 (m, 6 H) 5.15 - 5.57 (m, 1 H) 7.33 - 7.56 (m, 1 H) 7.59 - 7.80 (m, 2 H).

MS ES+ 361

10

Example 131

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



15 Prepared via Method A using **Intermediate 83** and 4-chloro-3-methylbenzoic acid (CAS
7697-29-2).

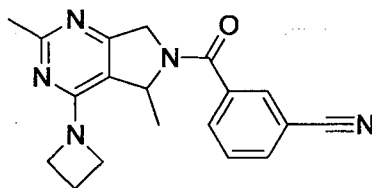
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.87 - 1.48 (m, 3 H) 2.18 - 2.43 (m, 8 H) 3.93 -
4.35 (m, 5 H) 4.46 - 4.88 (m, 1 H) 5.17 - 5.55 (m, 1 H) 7.35 - 7.55 (m, 2 H) 7.60 (s, 1 H).

20 MS ES+ 357

Example 132

3-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile

166



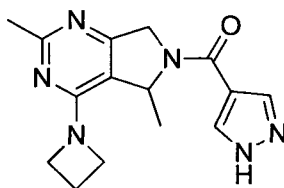
Prepared via Method A using **Intermediate 83** and 3-cyanobenzoic acid (CAS 1877-72-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.95 - 1.46 (m, 3H), 2.24 - 2.42 (m, 5H), 4.01 -
 4.17 (m, 2H), 4.18 - 4.32 (m, 2H), 4.50 - 4.87 (m, 2H), 5.17 - 5.53 (m, 1H), 7.66 - 7.73 (m,
 1H), 7.88 - 8.01 (m, 2H), 8.06 - 8.13 (m, 1H),

MS ES+ 334

Example 133

4-{{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-
 1H-pyrazole



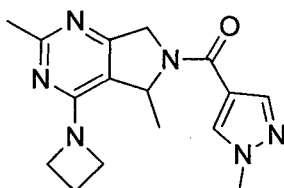
Prepared via Method C using **Intermediate 83** and 1H-pyrazole-4-carboxylic acid (CAS 37718-11-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15 - 1.42 (m, 3 H) 2.22 - 2.43 (m, 5 H) 3.92 -
 4.34 (m, 4 H) 4.65 - 5.08 (m, 2 H) 5.37 - 5.65 (m, 1 H) 7.68 - 8.48 (m, 2 H) 13.29 (br. s., 1
 H).

MS ES+ 299

Example 134

4-{{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-
 1-methyl-1H-pyrazole



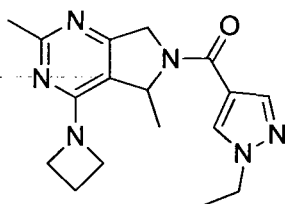
Prepared via Method C using **Intermediate 83** and 1-methyl-1H-pyrazole-4-carboxylic acid (CAS 5952-92-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.22 - 1.40 (m, 3H), 2.28 - 2.44 (m, 5H), 3.89 (s, 3H), 4.05 - 4.28 (m, 4H), 4.43 - 4.95 (m, 2H), 5.39 - 5.58 (m, 1H), 7.84 - 7.90 (m, 1H), 8.22 - 8.32 (m, 1H).

MS ES+ 313

Example 135

4-**{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-ethyl-1H-pyrazole**



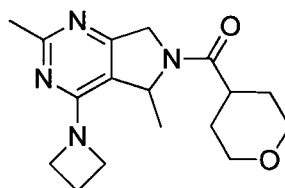
Prepared via Method C using **Intermediate 83** and 1-ethyl-1H-pyrazole-4-carboxylic acid (CAS 400858-54-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.31 - 1.45 (m, 6H), 2.29 - 2.43 (m, 5H), 4.06 - 4.26 (m, 6H), 4.43 - 4.95 (m, 2H), 5.38 - 5.58 (m, 1H), 7.85 - 7.93 (m, 1H), 8.26 - 8.35 (m, 1H).

MS ES+ 327

Example 136

1-**{2,5-Dimethyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**



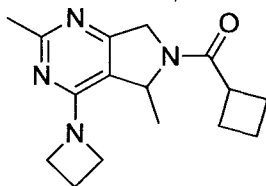
Prepared via Method A using **Intermediate 83** and tetrahydro-2H-pyran-4-carboxylic acid (CAS 5337-03-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.21 - 1.38 (m, 3H), 1.50 - 1.81 (m, 4H), 2.25 - 2.41 (m, 5H), 2.64 - 2.91 (m, 1H), 3.35 - 3.47 (m, 2H), 3.81 - 3.95 (m, 2H), 4.02 - 4.30 (m, 4H), 4.43 - 4.76 (m, 2H), 5.16 - 5.38 (m, 1H).

5 MS ES+ 317

Example 137

1-{6-Cyclobutanecarbonyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10

Prepared via Method A using **Intermediate 83** and cyclobutanecarboxylic acid (CAS 3721-95-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 - 1.33 (m, 3 H) 1.70 - 2.43 (m, 11 H) 3.97 - 4.30 (m, 5 H) 4.41 - 4.53 (m, 2 H) 5.06 - 5.26 (m, 1 H).

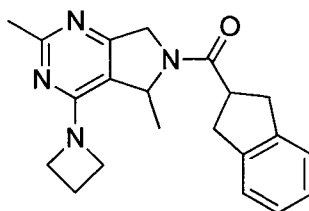
15

MS ES+ 287

Example 138

1-{6-[(2,3-Dihydro-1H-inden-2-yl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

20



Prepared via Method C using **Intermediate 83** and 2-indanylcarboxylic acid (CAS 25177-85-9).

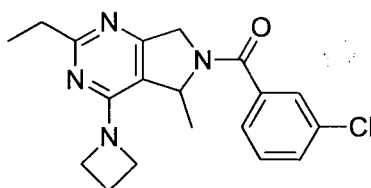
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.26 - 1.41 (m, 3H), 2.27 - 2.42 (m, 5H), 3.00 - 3.28 (m, 4H), 3.51 - 3.75 (m, 1H), 4.06 - 4.35 (m, 4H), 4.51 - 4.81 (m, 2H), 5.22 - 5.45 (m, 1H), 7.10 - 7.17 (m, 2H), 7.18 - 7.25 (m, 2H).

MS ES+ 349

5

Example 139

1-{6-[(3-Chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10 Prepared via Method D using **Intermediate 84** and 3-chlorobenzoyl chloride (CAS).

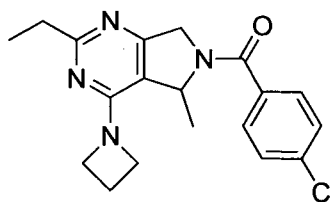
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.11 - 1.54 (m, 6H), 2.21 - 2.43 (m, 2H), 2.56 - 2.71 (m, 2H), 3.89 - 4.95 (m, 6H), 5.14 - 5.58 (m, 1H), 7.35 - 7.79 (m, 4H).

MS ES+ 357

15

Example 140

1-{6-[(4-Chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



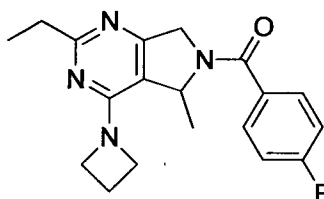
20 Prepared via Method D using **Intermediate 84** and 4-chlorobenzoyl chloride (CAS 122-01-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.10 - 1.50 (m, 6H), 2.23 - 2.43 (m, 2H), 2.57 - 2.73 (m, 2H), 3.92 - 4.93 (m, 6H), 5.10 - 5.60 (m, 1H), 7.42 - 7.72 (m, 4H).

25 MS ES+ 357

Example 141

1-{2-Ethyl-6-[(4-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



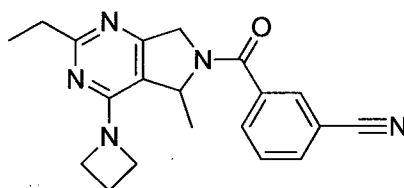
- 5 Prepared via Method D using **Intermediate 84** and 4-fluorobenzoyl chloride (CAS 403-43-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.95 - 1.48 (m, 6H), 2.25 - 2.42 (m, 2H), 2.57 - 2.71 (m, 2H), 4.04 - 4.18 (m, 2H), 4.18 - 4.27 (m, 2H), 4.28 - 4.87 (m, 2H), 5.19 - 5.56 (m, 1H), 7.25 - 7.36 (m, 2H), 7.63 - 7.72 (m, 2H).

MS ES+ 341

Example 142

3-{[4-(Azetidin-1-yl)-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile



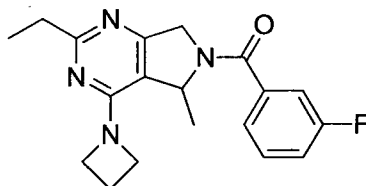
Prepared via Method D using **Intermediate 84** and 3-cyanobenzoyl chloride (CAS 1711-11-1).

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.50 (m, 6H), 2.21 - 2.44 (m, 2H), 2.57 - 2.71 (m, 2H), 4.03 - 4.28 (m, 4H), 4.29 - 4.88 (m, 2H), 5.16 - 5.55 (m, 1H), 7.65 - 7.74 (m, 1H), 7.88 - 8.01 (m, 2H), 8.06 - 8.12 (m, 1H).

MS ES+ 328

25 **Example 143**

1-{2-Ethyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



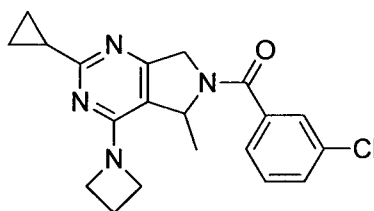
Prepared via Method D using **Intermediate 84** and 3-fluorobenzoyl chloride (CAS 1711-07-5).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.95 - 1.49 (m, 6H), 2.20 - 2.43 (m, 2H), 2.56 - 2.72 (m, 2H), 4.01 - 4.28 (m, 4H), 4.28 - 4.88 (m, 2H), 5.18 - 5.54 (m, 1H), 7.28 - 7.39 (m, 1H), 7.40 - 7.60 (m, 3H).

MS ES+ 341

Example 144

1-{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method D using **Intermediate 85** and 3-chlorobenzoyl chloride (CAS 618-46-2).

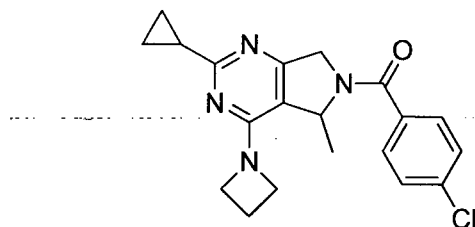
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.82 - 0.96 (m, 4H), 0.96 - 1.43 (m, 3H), 1.88 - 2.02 (m, 1H), 2.22 - 2.42 (m, 2H), 4.00 - 4.15 (m, 2H), 4.16 - 4.81 (m, 4H), 5.14 - 5.50 (m, 1H), 7.45 - 7.60 (m, 3H), 7.61 - 7.67 (m, 1H).

MS ES+ 369

Example 145

1-{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

172



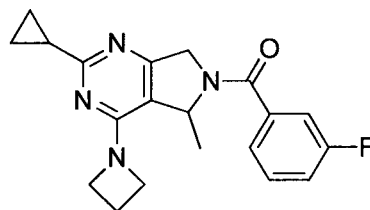
Prepared via Method D using **Intermediate 85** and 4-chlorobenzoyl chloride (CAS 122-01-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 - 0.94 (m, 4H), 0.95 - 1.43 (m, 3H), 1.84 - 2.03 (m, 1H), 2.19 - 2.43 (m, 2H), 4.00 - 4.15 (m, 2H), 4.16 - 4.81 (m, 4H), 5.15 - 5.53 (m, 1H), 7.50 - 7.58 (m, 2H), 7.59 - 7.66 (m, 2H).

MS ES+ 369

Example 146

1-{2-Cyclopropyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method D using **Intermediate 85** and 3-fluorobenzoyl chloride (CAS 1711-07-5).

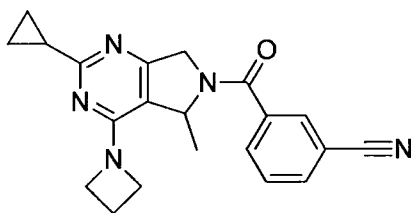
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 - 0.94 (m, 4H), 0.95 - 1.43 (m, 3H), 1.80 - 2.03 (m, 1H), 2.21 - 2.43 (m, 2H), 4.01 - 4.15 (m, 2H), 4.16 - 4.82 (m, 4H), 5.14 - 5.51 (m, 1H), 7.30 - 7.39 (m, 1H), 7.39 - 7.49 (m, 2H), 7.49 - 7.57 (m, 1H).

MS ES+ 353

Example 147

3-[[4-(Azetidin-1-yl)-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]benzonitrile

173



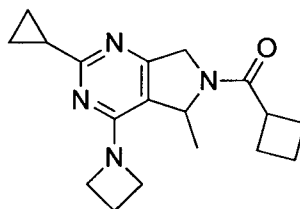
Prepared via Method D using **Intermediate 85** and 3-cyanobenzoyl chloride (CAS 1711-11-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 0.94 (m, 4H), 0.94 - 1.46 (m, 3H), 1.87 - 2.03 (m, 1H), 2.19 - 2.41 (m, 2H), 4.00 - 4.25 (m, 4H), 4.25 - 4.84 (m, 2H), 5.10 - 5.51 (m, 1H), 7.63 - 7.74 (m, 1H), 7.85 - 8.01 (m, 2H), 8.04 - 8.12 (m, 1H).

MS ES+ 360

Example 148

1-{6-Cyclobutanecarbonyl-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

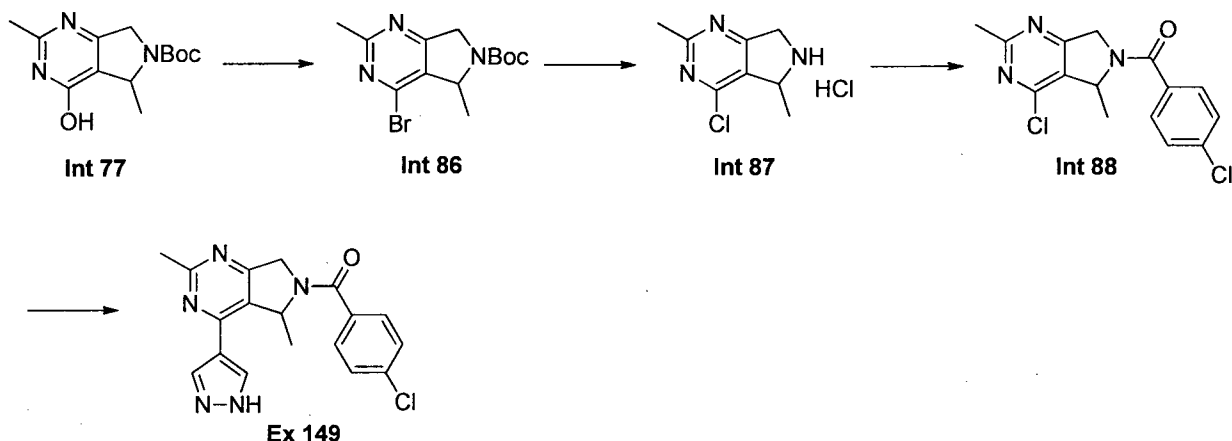


Prepared via Method D using **Intermediate 85** and cyclobutanecarbonyl chloride (CAS 5006-22-4).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.76 - 0.98 (m, 4 H) 1.15 - 1.34 (m, 3 H) 1.65 - 1.87 (m, 1 H) 1.87 - 2.03 (m, 2 H) 2.04 - 2.42 (m, 6 H) 3.96 - 4.26 (m, 5 H) 4.38 - 4.53 (m, 2 H) 5.05 - 5.26 (m, 1 H).

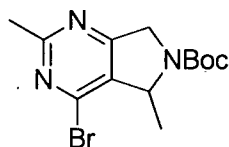
MS ES+ 313

Scheme 17



Intermediate 86

***tert*-Butyl 4-bromo-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



5

Triflic anhydride (1.78 mL, 10.55 mmol) was added dropwise to a solution of triethylamine (1.16 mL, 8.29 mmol) and *tert*-butyl 4-hydroxy-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 77**, 2.00 g, 7.54 mmol) in DCM (30 mL) at 0 °C. The reaction was stirred at 0 °C for 2 hours. The mixture was diluted with water. The phases were separated and the aqueous extracted with DCM. The combined organics were concentrated *in vacuo*. The residue was taken up in toluene (75 mL) and tetrabutylammonium bromide was added. The reaction was heated to reflux for 30 minutes. The reaction was then concentrated *in vacuo* and the residue partitioned between DCM and water. The phases were separated and the aqueous phase further extracted with DCM. The combined organics were concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-30 % ethyl acetate/petrol to afford the title compound.

10

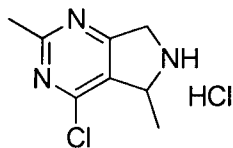
15

¹H NMR (400 MHz, CD₂Cl₂) δ ppm 1.37 - 1.60 (m, 12 H) 2.67 (s, 3 H) 4.42 - 4.77 (m, 2 H) 4.89 - 5.24 (m, 1 H).

MS ES+ 328

Intermediate 87

20

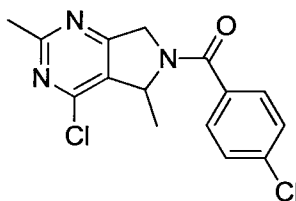
4-Chloro-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine hydrochloride

Hydrogen chloride (4 M in dioxane, 3.81 mL, 15.23 mmol) was added to a solution of *tert*-butyl 4-bromo-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

- 5 (Intermediate 86, 1 g, 3.05 mmol) in DCM (10 mL). The reaction was stirred at RT for 4 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound which was taken on directly to the next step.

Intermediate 88

- 10 **4-Chloro-6-(4-chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine**



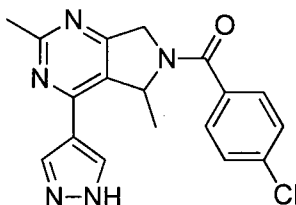
Prepared via Method C using **Intermediate 87** and 4-chlorobenzoic acid (CAS 74-11-3).

- ¹H NMR (DMSO-*d*₆) δ ppm 1.12 - 1.65 (m, 3H), 2.56 - 2.70 (m, 3H), 4.56 - 5.16 (m, 2H),
15 5.24 - 5.59 (m, 1H), 7.53 - 7.61 (m, 2H), 7.63 - 7.70 (m, 2H).

MS ES+ 322

Example 149

- 20 **4-[6-(4-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]-1H-pyrazole**



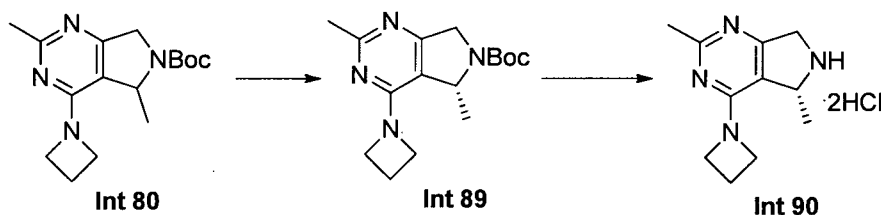
PdCl₂(dppf) (10 mg, 0.013 mmol) was added to a degassed mixture of 4-chloro-6-(4-chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine (**Intermediate 88**, 43 mg, 0.13 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (26 mg,

0.13 mmol) and tripotassium phosphate (85 mg, 0.40 mmol) in dioxane (0.5 mL) and water (0.13 mL) in a sealed tube. The reaction was heated to 100 °C for 3 hours. The mixture was partitioned between DCM and water. The phases were separated and the aqueous phase extracted with DCM. The combined organics were filtered through a pad of
5 diatomaceous earth and concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC eluted with acetonitrile/water (with 0.1 % ammonia) to afford the title compound.

¹H NMR (400 MHz, CD₃CN) δ ppm 1.17 - 1.56 (m, 3 H), 2.57 - 2.74 (m, 3 H), 4.44 - 4.98
10 (m, 1 H), 5.67 - 6.18 (m, 1 H), 6.50 - 6.63 (m, 1 H), 7.43 - 7.63 (m, 4 H), 7.72 - 7.96 (m, 1 H), 8.67 - 8.73 (m, 1 H).

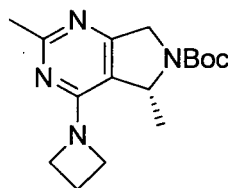
MS ES+ 354

Scheme 18



Intermediate 89

***tert*-Butyl (5R)-4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



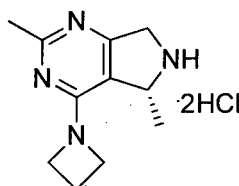
tert-Butyl 4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 80**) was dissolved to 50 mg/mL and was then purified by SFC to give the title compound. The column used was a Lux Cellulose-4 20 x 250 mm 5 μm. The organic eluant was 20 % heptane / IPA in a 50/50 ratio. No modifier was added and
25 the flow rate was 50 mL/min.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (dd, *J*=8.97, 6.19 Hz, 3 H) 1.45 (d, *J*=5.05 Hz, 9 H) 2.24 - 2.42 (m, 5 H) 3.95 - 4.43 (m, 6 H) 4.86 - 5.12 (m, 1 H).

MS ES+ 305

5 **Intermediate 90**

1-[(5R)-2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine dihydrochloride



HCl (4.0 M in dioxane, 5.0 mL, 19.9 mmol) was added to a solution of *tert*-butyl (5R)-4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate
10 (Intermediate 89, 1.97 g, 6.47 mmol) in DCM (22 mL) under nitrogen. The reaction was stirred at RT overnight and concentrated *in vacuo* to afford the title compound.

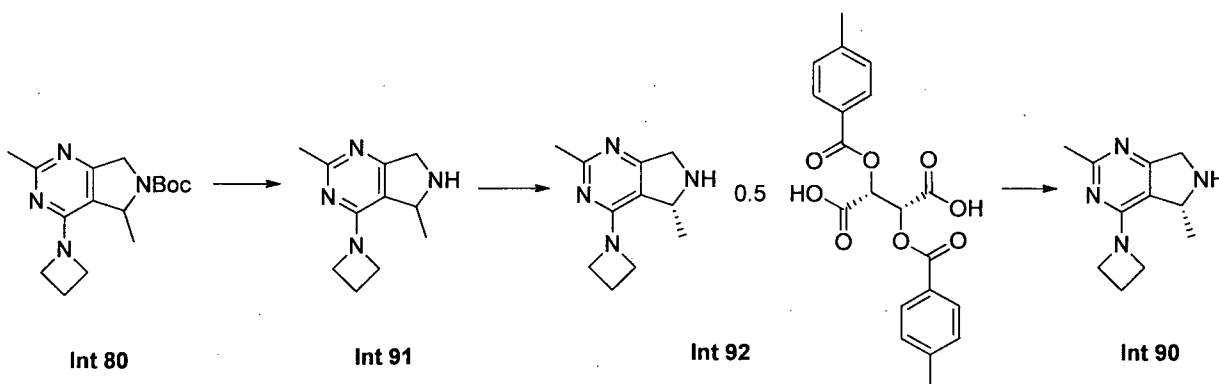
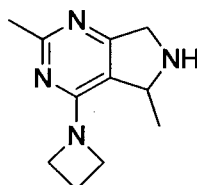
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.40 - 1.53 (m, 3 H) 2.31 - 2.49 (m, 5 H) 4.10 -
15 4.44 (m, 5 H) 4.49 - 4.74 (m, 1 H) 4.98 - 5.19 (m, 1 H) 9.61 - 10.10 (m, 1 H) 10.34 - 10.71 (m, 1 H).

MS ES+ 205

Alternatively, **Intermediate 90** (as the free base) can be prepared as described in the
20 following reaction scheme.

Scheme 19

178

**Intermediate 91****1-{2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine**

5

Hydrogen chloride (4 M in dioxane, 123 mL, 493 mmol) was added to a solution of *tert*-Butyl 4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 80**, 30 g, 99 mmol) in DCM (330 mL). The reaction was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo*. The crude product was, in four batches, loaded onto a cation exchange cartridge, washed with methanol and eluted with 2M ammonia/methanol solution then concentrated *in vacuo*. The filtrates were combined to afford the title compound.

10

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.13 (d, *J*=6.3 Hz, 3 H) 2.21 - 2.41 (m, 5 H) 3.70 - 3.95 (m, 2 H) 3.96 - 4.07 (m, 2 H) 4.10 - 4.22 (m, 2 H) 4.40 - 4.57 (m, 1 H)

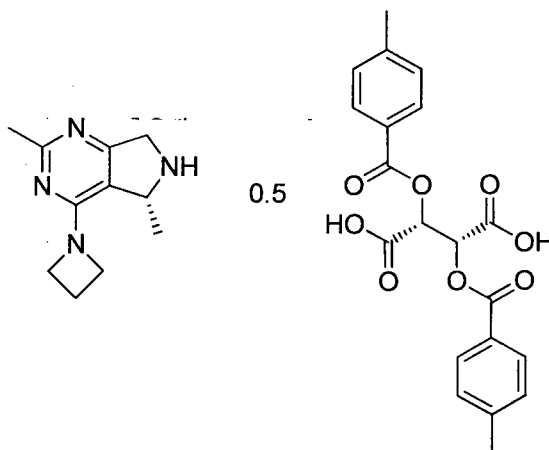
MS ES+ 205

15

Intermediate 92

1-[(5R)-2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine hemi((2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate)

20



1-{2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (**Intermediate 91**, 20 g, 98 mmol) was suspended in acetonitrile (325 mL) and warmed to 50 °C. The suspension was filtered. To the stirring, 50 °C-warmed filtrate was added a quarter of a solution of di-p-toluoyl-L-tartaric acid (9.46 g, 24.49 mmol) in acetonitrile (25 mL) over 5 minutes. The mixture was stirred at 50 °C for 10 minutes. The remainder of the acid solution was added. The mixture was stirred at 50 °C for a further 5 minutes. Seed crystals were then added. The mixture was allowed to slowly cool to RT and was then left to stand overnight with slow evaporation of the solvent via the application of a flow of nitrogen over the mixture. The resulting solid was filtered off and washed with a small volume of acetonitrile to afford the first crystallisation of the title compound. This was dissolved in boiling isopropanol (300 mL), seeded with a seed crystal and allowed to stand at RT for overnight. The crystals were collected by filtration and recrystallised again from 150 mL isopropanol to afford the title compound.

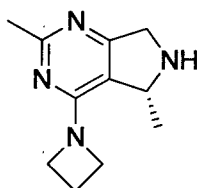
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.31 (m, 3 H) 2.22 - 2.43 (m, 8 H) 3.88 - 4.24 (m, 6 H) 4.59 - 4.79 (m, 1 H) 5.59 (s, 1 H) 7.28 (d, *J*=8.1 Hz, 2 H) 7.79 (d, *J*=8.1 Hz, 2 H).

MS ES+ 205

Intermediate 90 (as the free base)

1-[(5R)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

180



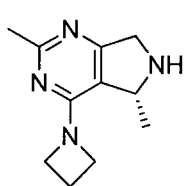
1-[(5R)-2,5-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine hemi((2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate) (**Intermediate 92**, 5 g, 6.29 mmol) was loaded onto a cation exchange cartridge, washed with methanol and eluted with 2 M ammonia/methanol solution then concentrated *in vacuo* to afford the title compound.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.12 (d, $J=6.6$ Hz, 3 H) 2.18 - 2.42 (m, 5 H) 3.68 - 3.95 (m, 2 H) 3.95 - 4.22 (m, 4 H) 4.36 - 4.54 (m, 1 H).

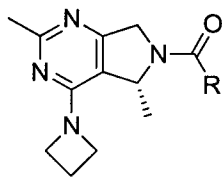
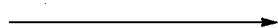
MS ES+ 205

10

Scheme 20



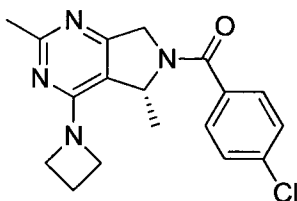
Int 90 2HCl salt
Int 92 free base



Ex 150 - 171

Example 150

1-[(5R)-6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



Prepared via method A or C using **Intermediate 90** or **Intermediate 92** and 4-chlorobenzoic acid (CAS 74-11-3).

20

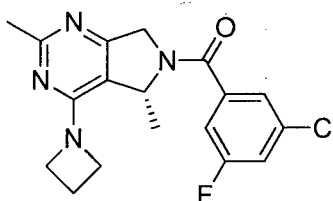
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.91 - 1.43 (m, 3 H), 2.20 - 2.43 (m, 5 H), 3.97 - 4.34 (m, 5 H), 4.46 - 4.86 (m, 1 H), 5.14 - 5.55 (m, 1 H), 7.47 - 7.58 (m, 2 H), 7.59 - 7.69 (m, 2 H).

MS ES+ 343

5

Example 151

1-[(5R)-6-[(3-Chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



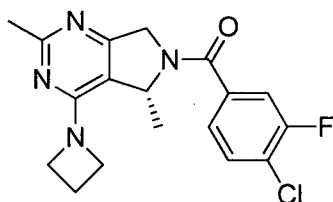
10 Prepared via Method A using **Intermediate 90** and 3-chloro-5-fluorobenzoic acid (CAS 25026-64-6).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.75 - 1.33 (m, 2H), 1.34 - 1.49 (m, 3H), 2.23 - 2.42 (m, 3H), 4.01 - 4.86 (m, 6H), 5.17 - 5.53 (m, 1H), 7.41 - 7.65 (m, 3H).

15 MS ES+ 361

Example 152

1-[(5R)-6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



20

Prepared via Method A or C using **Intermediate 90** or **Intermediate 92** and 4-chloro-3-fluorobenzoic acid (CAS 403-17-8).

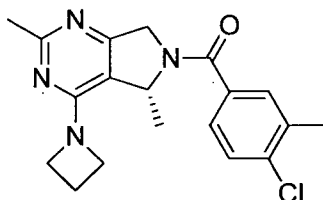
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.51 (m, 3 H) 2.20 - 2.44 (m, 5 H) 3.95 - 4.37 (m, 5 H) 4.46 - 4.89 (m, 1 H) 5.14 - 5.57 (m, 1 H) 7.38 - 7.54 (m, 1 H) 7.61 - 7.80 (m, 2 H).

25

MS ES+ 361

Example 153

1-[(5R)-6-[(4-Chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-
d]pyrimidin-4-yl]azetidine



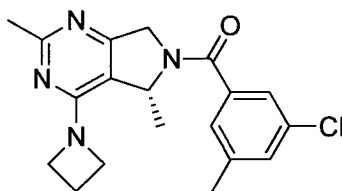
Prepared via Method A or C using **Intermediate 90** or **Intermediate 92** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.48 (m, 3H), 2.19 - 2.46 (m, 8H), 4.05 - 4.17 (m, 2H), 4.17 - 4.33 (m, 3H), 4.51 - 4.86 (m, 1H), 5.20 - 5.55 (m, 1H), 7.39 - 7.48 (m, 1H), 7.48 - 7.54 (m, 1H), 7.57 - 7.65 (m, 1H).

MS ES+ 357

Example 154

1-[(5R)-6-[(3-Chloro-5-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-
d]pyrimidin-4-yl]azetidine



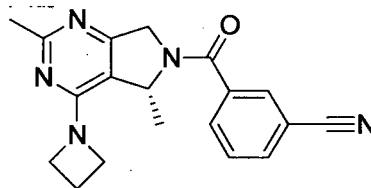
Prepared via Method A using **Intermediate 90** and 3-chloro-5-methylbenzoic acid (CAS).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.06 - 1.49 (m, 3H), 2.23 - 2.44 (m, 8H), 3.99 - 4.17 (m, 2H), 4.16 - 4.35 (m, 3H), 4.52 - 4.84 (m, 1H), 5.17 - 5.52 (m, 1H), 7.37 (s, 1H), 7.38 - 7.48 (m, 2H).

MS ES+ 357

Example 155

3-[[[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]benzonitrile



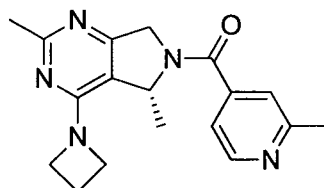
Prepared via Method A using **Intermediate 90** or **Intermediate 92** and 3-cyanobenzoic acid (CAS 1877-72-1).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.87 - 1.49 (m, 3 H) 2.18 - 2.44 (m, 5 H) 3.99 - 4.36 (m, 5 H) 4.50 - 4.91 (m, 1 H) 5.12 - 5.59 (m, 1 H) 7.58 - 7.77 (m, 1 H) 7.86 - 8.18 (m, 3 H).

MS ES+ 334

Example 156

4-[[[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-methylpyridine



Prepared via Method A using **Intermediate 90** and 2-methyl-4-pyridinecarboxylic acid (CAS 4021-11-8).

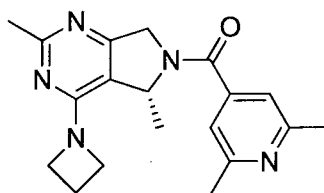
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.46 (m, 3H), 2.26 - 2.43 (m, 5H), 2.51 - 2.58 (m, 3H), 4.03 - 4.16 (m, 2H), 4.18 - 4.33 (m, 3H), 4.51 - 4.79 (m, 1H), 5.45-5.47 (m, 1H), 7.30 - 7.39 (m, 1H), 7.39 - 7.47 (m, 1H), 8.51 - 8.61 (m, 1H).

MS ES+ 324

Example 157

4-[[[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2,6-dimethylpyridine

184



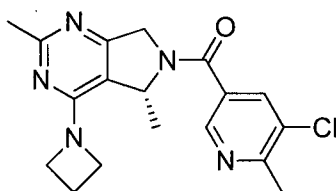
Prepared via Method A using **Intermediate 90** and 2,6-dimethyl-4-pyridinecarboxylic acid (CAS 54221-93-1).

¹H NMR (400 MHz, CD₃OD) δ ppm 1.12 - 1.59 (m, 3H), 2.44 (s, 3H), 2.45 - 2.54 (m, 2H), 2.59 (s, 6H), 4.19 - 4.31 (m, 2H), 4.31 - 4.43 (m, 2H), 4.54 - 4.66 (m, 1H), 4.74 - 4.75 (m, 1H), 5.56 - 5.67 (m, 1H), 7.22 - 7.33 (m, 2H).

MS ES+ 338

10 Example 158

5-[[[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-3-chloro-2-methylpyridine



Prepared via Method A or C using **Intermediate 90** or **Intermediate 92** and 5-chloro-6-methyl-3-pyridinecarboxylic acid (CAS 1256835-19-4).

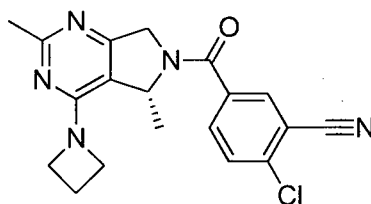
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.46 (m, 3H), 2.21 - 2.42 (m, 5H), 2.61 (s, 3H), 4.04 - 4.18 (m, 2H), 4.20-4.26 (m, 2H), 4.36-4.40 (m, 1H), 4.51 - 4.93 (m, 1H), 5.37 - 5.56 (m, 1H), 8.03 - 8.23 (m, 1H), 8.57 - 8.74 (m, 1H).

20 MS ES+ 358

Example 159

5-[[[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-chlorobenzonitrile

185



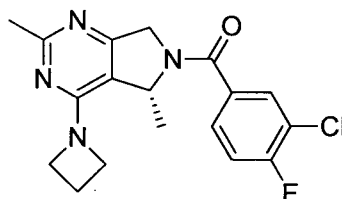
Prepared via Method C using **Intermediate 92** and 4-chloro-3-cyanobenzoic acid (CAS 117738-76-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.91 - 1.47 (m, 3H), 2.25 - 2.41 (m, 5H), 3.99 - 4.88 (m, 6H), 5.15 - 5.57 (m, 1H), 7.69 - 8.36 (m, 3H).

MS ES+ 368

Example 160

1-[(5R)-6-[(3-Chloro-4-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



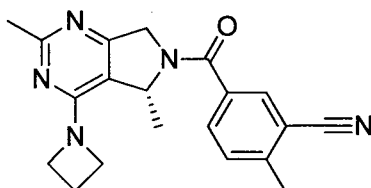
Prepared via Method A or C using **Intermediate 90** or **Intermediate 92** and 3-chloro-4-fluorobenzoic acid (CAS 403-16-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.79 - 1.56 (m, 3H), 2.20 - 2.42 (m, 5H), 3.94 - 4.93 (m, 6H), 5.13 - 5.60 (m, 1H), 7.31 - 7.98 (m, 3H).

MS ES+ 361

Example 161

5-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl-2-methylbenzonitrile



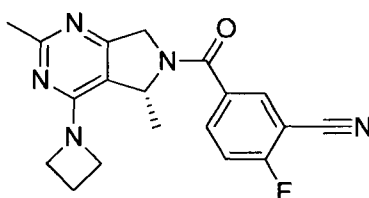
Prepared via Method C using **Intermediate 92** and 3-cyano-4-methylbenzoic acid (CAS 138642-93-0).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.90 - 1.46 (m, 3 H) 2.21 - 2.42 (m, 5 H) 2.55 (s, 3 H) 3.98 - 4.38 (m, 5 H) 4.49 - 4.91 (m, 1 H) 5.16 - 5.57 (m, 1 H) 7.42 - 7.66 (m, 1 H) 7.71 - 7.90 (m, 1 H) 7.97 - 8.10 (m, 1 H).

MS ES+ 348

Example 162

5-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile



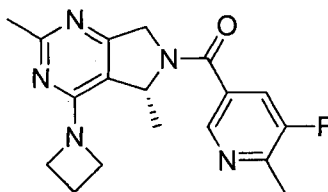
Prepared via Method C using **Intermediate 92** and 3-cyano-4-fluorobenzoic acid (CAS 171050-06-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.91 - 1.50 (m, 3H), 2.21 - 2.43 (m, 5H), 3.90 - 4.97 (m, 6H), 5.15 - 5.57 (m, 1H), 7.53 - 7.73 (m, 1H), 7.91 - 8.09 (m, 1H), 8.14 - 8.32 (m, 1H).

MS ES+ 352

Example 163

5-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-fluoro-2-methylpyridine



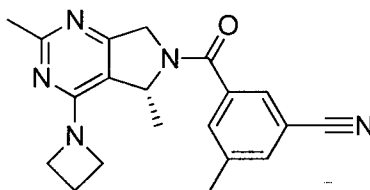
Prepared via Method C using **Intermediate 92** and 5-fluoro-6-methylpyridine-3-carboxylic acid (CAS 932705-78-7).

¹H NMR (400 MHz, CD₃OD) δ ppm 1.08 - 1.63 (m, 3 H) 2.35 - 2.53 (m, 5 H) 2.54 - 2.61 (m, 3 H) 4.16 - 4.44 (m, 4 H) 4.59 - 4.89 (m, 2 H) 5.27 - 5.74 (m, 1 H) 7.76 - 7.92 (m, 1 H) 8.54 (s, 1 H).

5 MS ES+ 342

Example 164

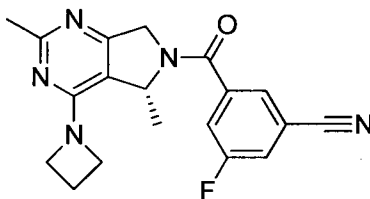
3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-methylbenzonitrile



10 Prepared via Method C using **Intermediate 92** and 3-methyl-5-cyanobenzoic acid (CAS 78621-81-5).

Example 165

15 3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-fluorobenzonitrile



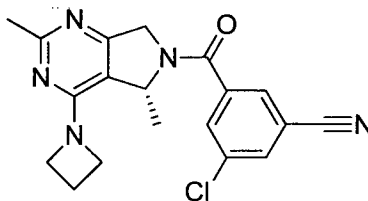
20 Prepared via Method C using **Intermediate 92** and 3-fluoro-5-cyanobenzoic acid (CAS 327056-74-6).

¹H NMR (400 MHz, CD₂Cl₂) δ ppm 1.09 - 1.63 (m, 3 H) 2.35 - 2.59 (m, 5 H) 4.13 - 4.43 (m, 4 H) 4.43 - 4.82 (m, 2 H) 5.55 - 5.74 (m, 1 H) 7.44 - 7.73 (m, 3 H).

MS ES+ 352

25 **Example 166**

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-chlorobenzonitrile



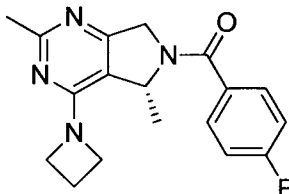
Prepared via Method C using **Intermediate 92** and 3-chloro-5-cyanobenzoic acid (CAS 327056-71-3).

¹H NMR (400 MHz, CD₃OD) δ ppm 1.05 - 1.60 (m, 3 H) 2.38 - 2.56 (m, 5 H) 4.20 - 4.45 (m, 4 H) 4.56 - 4.84 (m, 2 H) 5.18 - 5.72 (m, 1 H) 7.84 - 8.07 (m, 3 H).

MS ES+ 368

Example 167

1-[(5R)-6-(4-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



Prepared via Method C using **Intermediate 92** and 4-fluorobenzoic acid (CAS 456-22-4).

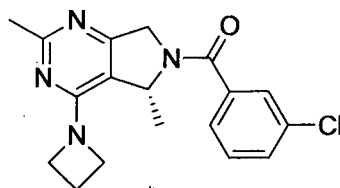
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.46 (m, 3 H) 2.23 - 2.42 (m, 5 H) 4.02 - 4.86 (m, 6 H) 5.20 - 5.56 (m, 1 H) 7.30 (m, 2 H) 7.68 (m, 2 H).

MS ES+ 327

Example 168

1-[(5R)-6-(3-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

189



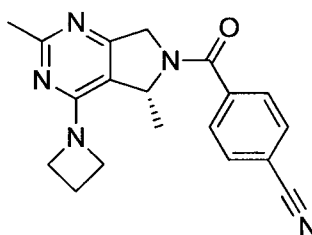
Prepared via Method C using **Intermediate 92** and 3-chlorobenzoic acid (CAS 535-80-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.46 (m, 3 H) 2.23 - 2.42 (m, 5 H) 4.02 - 4.86 (m, 6 H) 5.20 - 5.56 (m, 1 H) 7.30 (m, 2 H) 7.68 (m, 2 H).

MS ES+ 343

Example 169

4-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]benzonitrile



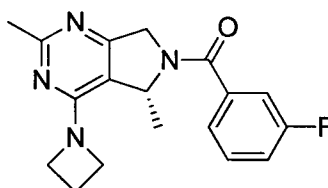
Prepared via Method C using **Intermediate 92** and 4-cyanobenzoic acid (CAS 619-65-8).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.91 - 1.50 (m, 3 H) 2.18 - 2.42 (m, 5 H) 3.95 - 4.80 (m, 6 H) 5.13 - 5.56 (m, 1 H) 7.64 - 7.85 (m, 2 H) 7.89 - 8.04 (m, 2 H).

MS ES+ 334

Example 170

1-[(5R)-6-(3-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

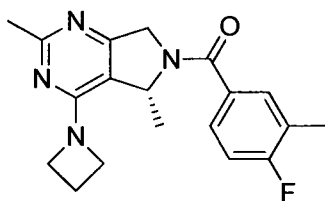


Prepared via Method C using **Intermediate 92** and 3-fluorobenzoic acid (CAS 455-38-9).

^1H NMR (400 MHz, CD_3OD) δ ppm 1.07 - 1.61 (m, 3 H) 2.34 - 2.56 (m, 5 H) 4.06 - 4.82 (m, 6 H) 5.27 - 5.72 (m, 1 H) 7.23 - 7.33 (m, 1 H) 7.34 - 7.48 (m, 2 H) 7.49 - 7.61 (m, 1 H).
MS ES+ 327

5 Example 171

1-[(5R)-6-(4-Fluoro-3-methylbenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

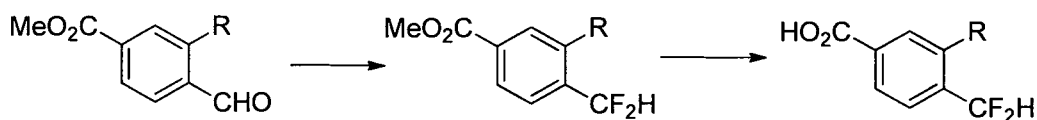


Prepared via Method C using **Intermediate 92** and 4-fluoro-3-methylbenzoic acid (CAS
10 403-15-6).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.92 - 1.45 (m, 3 H) 2.29 (s, 3 H) 2.32 - 2.41 (m, 5 H) 4.02 - 4.87 (m, 6 H) 5.17 - 5.57 (m, 1 H) 7.20 - 7.25 (m, 1 H) 7.42 - 7.52 (m, 1 H) 7.55 - 7.57 (m, 1 H).

15 MS ES+ 341

Scheme 21



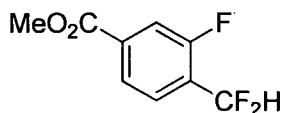
R = 3-F; CAS 74733-25-8
R = 3-Cl; CAS 74733-26-9

R = 3-F; **Int 93**
R = 3-Cl; **Int 94**

R = 3-F; **Int 95**
R = 3-Cl; **Int 96**

20 Intermediate 93

Methyl 4-(difluoromethyl)-3-fluorobenzoate



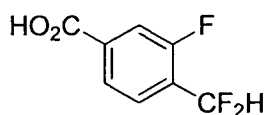
Diethylaminosulfur trifluoride (0.73 ml, 5.49 mmol) was added to an ice-cooled solution of methyl 3-fluoro-4-formylbenzoate (0.50 g, 2.75 mmol) in DCM (9 mL). The reaction was

stirred at 0 °C for 1 hour then at 25 °C for a further 1 hour. The reaction mixture was quenched with sat. NaHCO₃ (aq), the layers were separated, the organics washed with water, dried (phase separator) and concentrated in *vacuo*. The crude product was purified by flash column chromatography (silica, 0-100 % DCM / petrol) to afford the title compound.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.96 (s, 3 H) 6.76 - 7.08 (m, 1 H) 7.70 (s, 1 H) 7.76 - 7.85 (m, 1 H) 7.89 - 7.97 (m, 1 H).

Intermediate 95

4-(Difluoromethyl)-3-fluorobenzoic acid

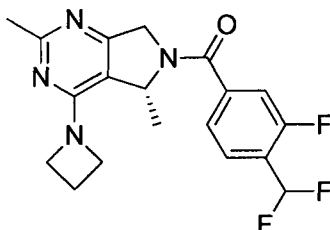


A solution of methyl 4-(difluoromethyl)-3-fluorobenzoate (**Intermediate 94**, 0.54 g, 2.65 mmol) in EtOH (2.7 mL) and 2 M sodium hydroxide (aq.) (5.3 mL, 10.58 mmol) was heated to reflux for 4 hours. The reaction was cooled to room temperature, concentrated in *vacuo*, diluted in water and acidified to pH 5 with 2N HCl (aq). The resulting precipitate was filtered, washed with water and dried to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.13 - 7.44 (m, 1 H) 7.74 - 7.84 (m, 2 H) 7.86 - 7.94 (m, 1 H) 13.18 - 13.80 (m, 1 H)

Example 172

1-[(5R)-6-[4-(Difluoromethyl)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



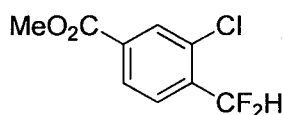
Prepared via Method C using **Intermediate 92** and **Intermediate 95**.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 - 1.47 (m, 3 H) 2.21 - 2.42 (m, 5 H) 4.01 - 4.84 (m, 6 H) 5.17 - 5.55 (m, 1 H) 7.27 (s, 1 H) 7.56 (s, 3 H).

MS ES+ 377

5 Intermediate 94

Methyl 3-chloro-4-(difluoromethyl)benzoate



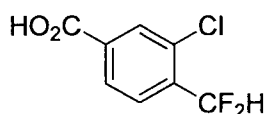
Prepared in a similar manner to **Intermediate 93** using methyl 3-chloro-4-formylbenzoate (CAS).

10

^1H NMR (400 MHz, CD_2Cl_2) δ ppm 3.92 (s, 3 H) 6.83 - 7.16 (m, 1 H) 7.75 (d, $J=8.1$ Hz, 1 H) 8.03 (d, $J=8.1$ Hz, 1 H) 8.07 - 8.14 (m, 1 H)

Intermediate 96

15 3-Chloro-4-(difluoromethyl)benzoic acid



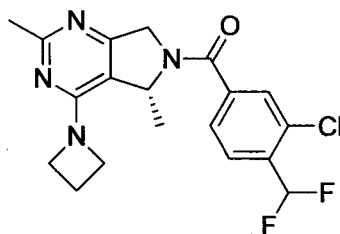
Prepared in a similar manner to **Intermediate 95** using **Intermediate 94**.

20

^1H NMR (400 MHz, CD_3OD) δ ppm 6.94 - 7.24 (m, 1 H), 7.79 (d, $J=8.1$ Hz, 1 H), 8.04 - 8.12 (m, 2 H)

Example 173

1-[(5R)-6-[3-Chloro-4-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



25

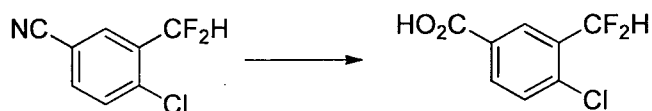
Prepared via Method C using **Intermediate 92** and **Intermediate 96**.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 - 1.50 (m, 3 H) 2.26 - 2.42 (m, 5 H) 4.00 - 4.84 (m, 6 H) 5.15 - 5.55 (m, 1 H) 7.09 - 7.45 (m, 1 H) 7.65 - 7.93 (m, 3 H)

MS ES+ 393

5

Scheme 22

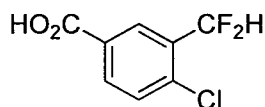


Int 97

CAS 1261850-38-7

Intermediate 97

10 4-Chloro-3-(difluoromethyl)benzoic acid



A solution of 4-chloro-3-(difluoromethyl)benzonitrile (479 mg, 2.55 mmol) in 2M sodium hydroxide (aq.) (6.6 mL, 13.19 mmol) was heated to reflux for 2 hours. The reaction mixture was cooled to RT then washed with DCM. The aqueous phase was acidified with 2M HCl (aq) then extracted with DCM. The organic layer was dried (phase separator) and concentrated *in vacuo* to afford the title compound.

15

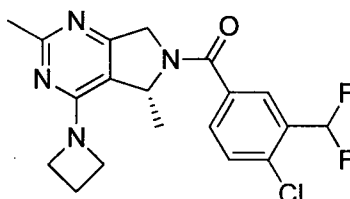
^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.09 - 7.45 (m, 1 H) 7.76 (d, $J=8.3$ Hz, 1 H) 8.09 (d, $J=8.3$ Hz, 1 H) 8.18 (s, 1 H) 13.49 (br. s, 1 H).

20

MS ES- 205

Example 174

1-[(5R)-6-[4-Chloro-3-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



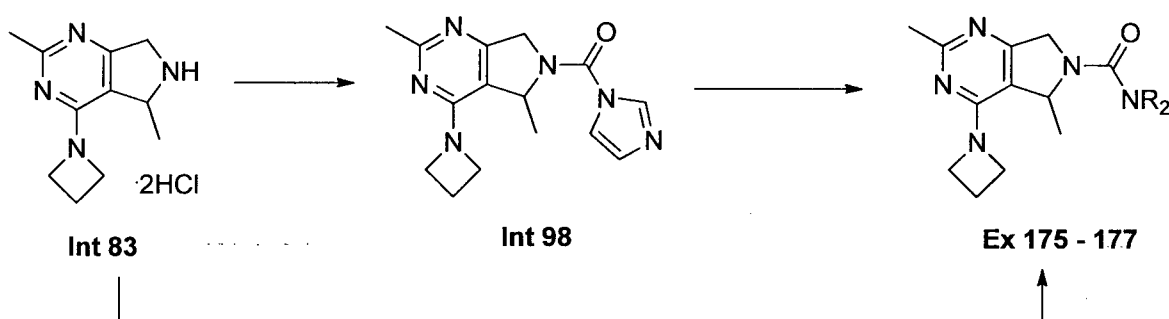
25

Prepared via Method C using **Intermediate 92** and **Intermediate 97**.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.92 - 1.47 (m, 3 H) 2.21 - 2.45 (m, 5 H) 4.00 - 4.86 (m, 6 H) 5.14 - 5.57 (m, 1 H) 7.09 - 7.43 (m, 1 H) 7.68 - 7.77 (m, 1 H) 7.81 - 7.84 (m, 1 H) 7.86 - 7.93 (m, 1 H).

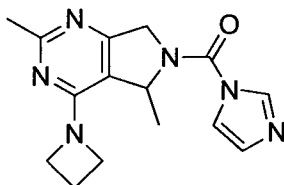
MS ES+ 393

Scheme 23



Intermediate 98

1-[[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-1H-imidazole



Carbonyl diimidazole (860 mg, 5.30 mmol) was added to a solution of 1-[[4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]azetidine dihydrochloride (**Intermediate 83**, 700 mg, 2.53 mmol) and triethylamine (0.88 mL, 6.31 mmol) in DCM (8 mL) under nitrogen. The reaction was stirred at RT for 4.5 hours. Water was added and the layers separated (phase separator). The organics were concentrated *in vacuo* and the crude product purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in petrol to afford the title compound.

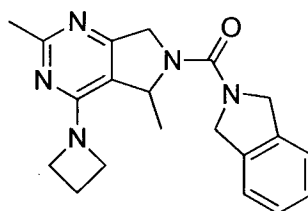
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.20 - 2.44 (m, 5 H) 3.97 - 4.34 (m, 4 H) 4.39 - 4.62 (m, 1 H) 4.79 - 5.18 (m, 1 H) 5.36 - 5.62 (m, 1 H) 7.07 (s, 1 H) 7.71 (s, 1 H) 8.26 (s, 1 H).

MS ES+ 335

5

Example 175

2- $\{[4-(\text{Azetidin-1-yl})-2,5\text{-dimethyl-}5\text{H},6\text{H},7\text{H-pyrrolo}[3,4\text{-d}]\text{pyrimidin-6-yl}]\text{carbonyl}\}$ -2,3-dihydro-1H-isoindole



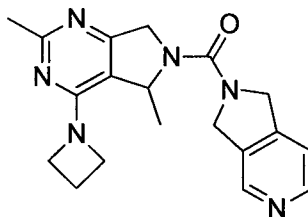
- 10 DBU (0.06 mL, 0.40 mmol) was added to a solution of 1- $\{[4-(\text{azetidin-1-yl})-2,5\text{-dimethyl-}5\text{H},6\text{H},7\text{H-pyrrolo}[3,4\text{-d}]\text{pyrimidin-6-yl}]\text{carbonyl}\}$ -1H-imidazole (**Intermediate 98**, 100 mg, 0.34 mmol) and 2,3-dihydro-1H-isoindole (48 mg, 0.40 mmol) in acetonitrile (1 mL) in a sealed tube. The reaction was heated to 50 °C for 48 hours, cooled to RT and partitioned between EtOAc and water. The organic layer was dried (phase separator) and
- 15 concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC eluting with acetonitrile / water (with 0.1 % ammonia) to afford the title compound.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.06 - 1.37 (m, 3H), 2.24 - 2.44 (m, 5H), 4.01 - 4.82 (m, 8H), 4.88 - 5.10 (m, 2H), 5.33 - 5.54 (m, 1H), 7.25 - 7.40 (m, 4H).

20 MS ES+ 350

Example 176

1-[2,5-Dimethyl-6- $\{[1\text{H},2\text{H},3\text{H-pyrrolo}[3,4\text{-c}]\text{pyridin-2-yl}\}]\text{carbonyl}\}$ -5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



25

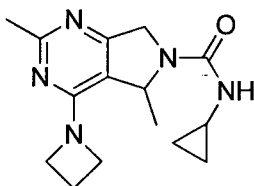
Prepared in a similar manner to **Example 175** using **Intermediate 98** and 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (CAS 496-13-9).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.21 - 1.30 (m, 2H), 2.27 - 2.44 (m, 5H), 4.05 - 4.16 (m, 2H), 4.17 - 4.30 (m, 2H), 4.44 - 4.56 (m, 1H), 4.57 - 4.77 (m, 3H), 4.98 - 5.13 (m, 2H), 5.38 - 5.52 (m, 1H), 7.36 - 7.47 (m, 1H), 8.44 - 8.51 (m, 1H), 8.55 - 8.62 (m, 1H).

MS ES+ 351

Example 177

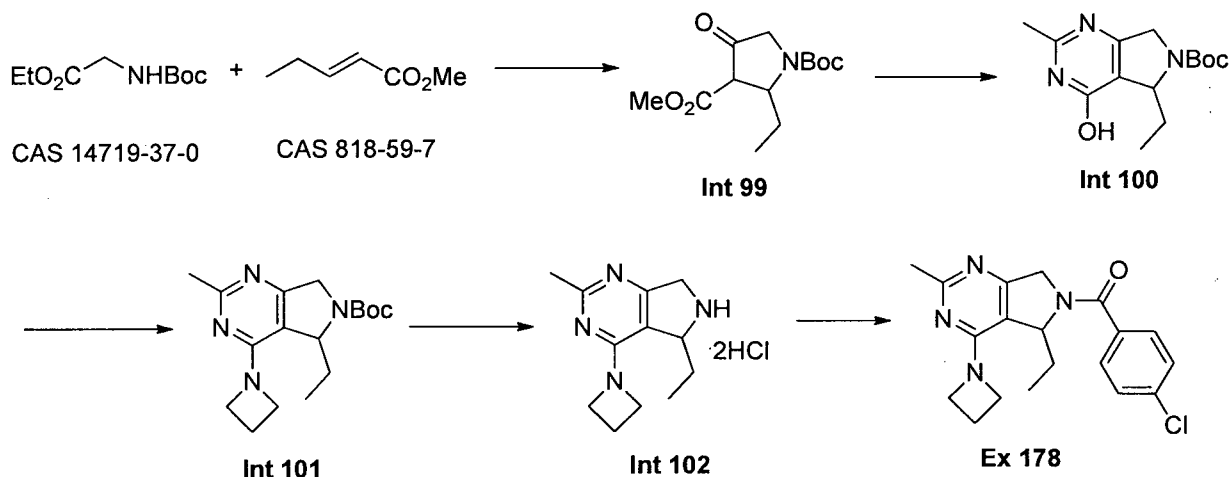
4-(Azetidin-1-yl)-N-cyclopropyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxamide



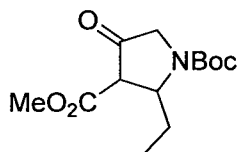
Cyclopropanecarboxylic acid (500 mg, 5.81 mmol), diphenylphosphoryl azide (1.25 mL, 5.81 mmol) and triethylamine (810 μL, 5.81 mmol) in toluene (4 mL) were heated to 80 °C for 2 hours. The reaction was cooled and 1-{2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride (**Intermediate 83**, 100 mg, 0.36 mmol) and N,N-diisopropylethylamine (1.01 mL, 5.81 mmol) were added. THF and DCM were added and the reaction mixture heated to 80 °C for 30 minutes. The reaction was cooled to RT and a solution of 1-{2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride (**Intermediate 83**, 100 mg, 0.36 mmol) in DCM (1 mL) and N,N-diisopropylethylamine (1.01 mL, 5.81 mmol) were added. The mixture was stirred at RT for 72 hours and was then partitioned between EtOAc and water. The layers were separated and the organics dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on basic silica, eluting with 0-100 % EtOAc in petrol and re-purified by reverse phase chromatography on C18 silica eluting with 0-40 % acetonitrile/water (with 0.05 % ammonia) to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.30 - 0.77 (m, 4H), 1.15 - 1.37 (m, 3 H), 2.21 - 2.44 (m, 5H), 3.99 - 4.36 (m, 7H), 5.02 - 5.18 (m, 1H), 6.38 - 6.49 (m, 1H).

MS ES+ 288

Scheme 24

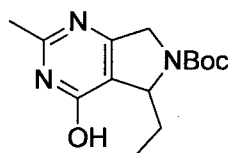
5

Intermediate 99**1-tert-Butyl 3-methyl 2-ethyl-4-oxopyrrolidine-1,3-dicarboxylate**

Potassium tert-butoxide (1.0 M in THF, 12.48 mL, 12.48 mmol) was added to a solution of ethyl 2-[[[(tert-butoxy)carbonyl]amino]acetate (2.49 g, 10.40 mmol) and ethyl (2Z)-pent-2-enoate (2.00 g, 15.60 mmol) in THF (35 mL) under nitrogen. The reaction was stirred at RT for 18 hours. The reaction mixture was acidified to pH 6 via the addition of aqueous citric acid then partitioned between EtOAc and water. The organic layer was washed with water, dried (phase separator) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-20 % EtOAc in petrol to afford the title compound, which was taken directly on to the next step.

MS ES- 284

Intermediate 100**tert-Butyl 5-ethyl-4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

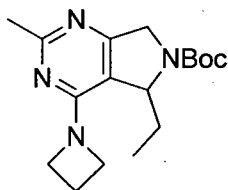


Triethylamine (1.54 mL, 11.03 mmol) was added to a suspension of acetimidamide hydrochloride (0.60 g, 6.36 mmol) and 1-*tert*-butyl 3-ethyl 2-ethyl-4-oxopyrrolidine-1,3-dicarboxylate (**Intermediate 99**, 1.21 g, 4.24 mmol) in *tert*-BuOH (14 mL) under nitrogen. The reaction was heated under reflux overnight. The reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was taken up in THF and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica, eluting with 0-15 % MeOH in DCM to afford the title compound which was taken directly to the next step.

MS ES+ 280

Intermediate 101

***tert*-Butyl 4-(azetidin-1-yl)-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**



Triflic anhydride (0.33 mL, 1.97 mmol) was added dropwise to a suspension of *tert*-butyl 5-ethyl-4-hydroxy-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 100**, 500 mg, 1.79 mmol) and triethylamine (0.3 mL, 2.15 mmol) in DCM (6 mL). The reaction was stirred at 0 °C for 30 minutes, and added to a mixture of N,N-diisopropylethylamine (0.94 mL, 5.37 mmol) and azetidine (0.18 mL, 2.68 mmol) in DCM (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and partitioned between DCM and water. The organic layer was dried (phase separator) and concentrated *in vacuo*. The crude product was loaded onto a cation exchange cartridge, washed with methanol and eluting with 2M ammonia/methanol solution and concentrated *in vacuo*. The crude product was purified by column chromatography on basic silica, eluting with 0-30 %

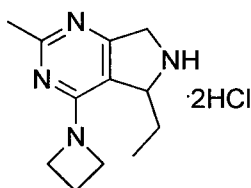
EtOAc in petrol, then 0-10% MeOH in EtOAc to afford the title compound which was taken directly on to the next step.

MS ES+ 319

5

Intermediate 102

1-{5-Ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride



10 HCl (4.0 M in dioxane, 0.12 mL, 0.47 mmol) was added to a solution of *tert*-butyl 4-(azetidin-1-yl)-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (**Intermediate 101**, 50 mg, 0.16 mmol) in DCM (0.5 mL) under nitrogen. The reaction was stirred at RT overnight and concentrated *in vacuo* to afford the title compound which was taken directly on to the next step.

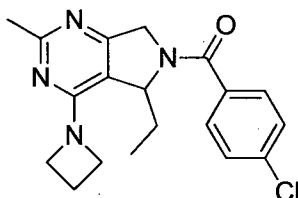
15

MS ES+ 219

Example 178

1-{6-[(4-Chlorophenyl)carbonyl]-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine

20



Prepared via Method A using **Intermediate 102** and 4-chlorobenzoic acid (CAS 74-11-3).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.35 - 0.76 (m, 3 H) 2.23 - 2.42 (m, 5 H) 3.96 - 4.34 (m, 5 H) 4.41 - 4.78 (m, 1 H) 5.34 - 5.69 (m, 1 H) 7.46 - 7.59 (m, 2 H) 7.59 - 7.68 (m, 2 H).

25

MS ES+ 357

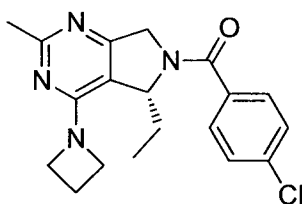
The racemate was purified by chiral SFC to give the single enantiomer (Example 179).

- 5 1-{6-[(4-Chlorophenyl)carbonyl]-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (**Example 178**) was dissolved to 10 mg/mL in ethanol and was then purified by SFC to give the title compound. The column used was a Chiralpak IC column 250 x 10mm.. The eluant was 34 % ethanol / 66 % CO₂. No modifier was added and the flow rate was 30 mL/min.

10

Example 179

1-[(5R)-6-(4-Chlorobenzoyl)-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine

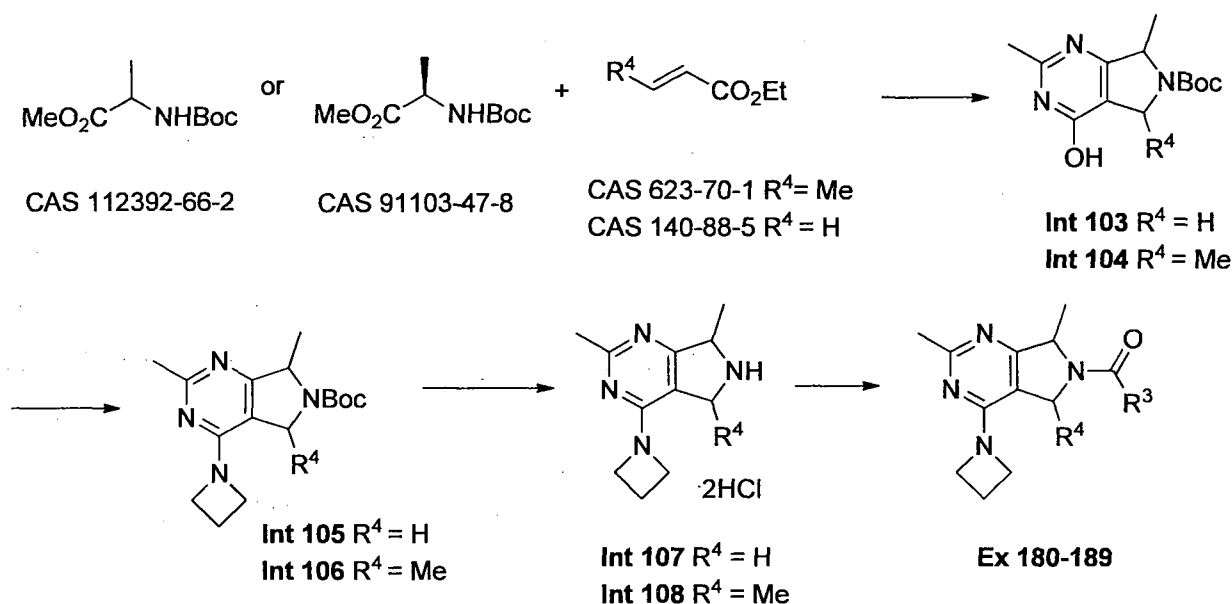
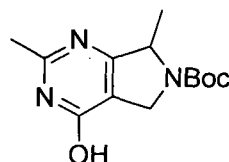


- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.30 - 0.77 (m, 3 H) 2.24 - 2.44 (m, 5 H) 3.96 - 4.34 (m, 5 H) 4.41 - 4.81 (m, 1 H) 5.32 - 5.68 (m, 1 H) 7.47 - 7.60 (m, 2 H) 7.60 - 7.71 (m, 2 H)

MS ES+ 357

20 **Scheme 25**

201

**Intermediate 103*****tert*-Butyl 4-hydroxy-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

5

Potassium *tert*-butoxide (1.0M in THF, 103 mL, 103 mmol) was added to a solution of methyl 2-{[(*tert*-butoxy)carbonyl]amino}propanoate (17.48 g, 86 mmol) and ethyl prop-2-enoate (13.73 mL, 129 mmol) in THF (20 mL) in an ice-water bath. The mixture was allowed to warm to RT and further ethyl prop-2-enoate (9.1 mL, 86 mmol) was added.

- 10 The mixture was stirred at RT for 18 hours and ammonium chloride (5.5 g, 103 mmol) was added. The mixture was stirred for approximately 5 minutes and filtered through silica, eluting with THF (approximately 800 mL). The filtrate was concentrated and the residue purified by column chromatography, eluting with 5-30 % EtOAc in petrol to give a mixture of 1-*tert*-butyl 3-ethyl 5-methyl-4-oxopyrrolidine-1,3-dicarboxylate and 1-*tert*-
- 15 butyl 3-methyl 5-methyl-4-oxopyrrolidine-1,3-dicarboxylate. The mixture was taken up in triethylamine (2.71 mL) and *tert*-BuOH (40 mL), followed by the addition of acetamidine hydrochloride (1.84 g, 19.46 mmol). The mixture was heated to 80 °C for 16 hours, followed by the addition of further acetamidine hydrochloride (0.92 g, 9.73 mmol) and triethylamine (1.36 mL, 9.73 mmol). The mixture was heated to 80 °C for 8 hours, cooled
- 20 and left to stand for 3 days. The reaction mixture was concentrated *in vacuo*, and the

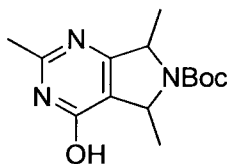
residue dissolved in DCM and washed with water. The organic phase was dried and concentrated *in vacuo* to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 - 1.57 (m, 12 H) 2.32 (s, 3 H) 4.11 - 4.44 (m, 2 H) 4.52 - 4.86 (m, 1 H) 12.52 (br. s., 1 H).

MS ES+ 266

Intermediate 104

***tert*-Butyl (7R)-4-hydroxy-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**



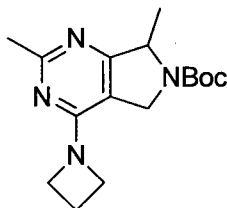
Prepared in a similar manner to **Intermediate 103** using methyl (R)-2-(tert-butoxycarbonylamino)propanoate (CAS 91103-47-8) and ethyl (2E)-but-2-enoate (CAS 6776-19-8)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.30 - 1.55 (m, 15 H) 2.31 (s, 3 H) 4.48 - 4.62 (m, 1 H) 4.65 - 4.83 (m, 1 H) 12.50 (br. s., 1 H).

MS ES+ 280

Intermediate 105

***tert*-Butyl 4-(azetidin-1-yl)-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**



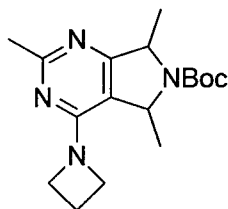
Prepared in a similar manner to **Intermediate 80** using **Intermediate 103**, triflic anhydride and then azetidine (CAS 503-29-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.30 - 1.40 (m, 3 H) 1.45 (s, 9 H) 2.20 - 2.41 (m, 5 H) 4.08 - 4.27 (m, 4 H) 4.43 - 4.65 (m, 3 H).

MS ES+ 305

5 **Intermediate 106**

tert-Butyl (7R)-4-(azetidin-1-yl)-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



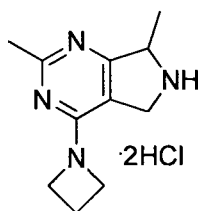
Prepared in a similar manner to **Intermediate 80** using **Intermediate 104**, triflic anhydride
10 and then azetidine (CAS 503-29-7).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 - 1.35 (m, 3H), 1.35 - 1.42 (m, 3H), 1.43 - 1.51 (m, 9H), 2.25 - 2.40 (m, 5H), 3.99 - 4.27 (m, 4H), 4.50 - 4.61 (m, 1H), 4.88 - 5.02 (m, 1H).

15 MS ES+ 319

Intermediate 107

1-{2,7-Dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride

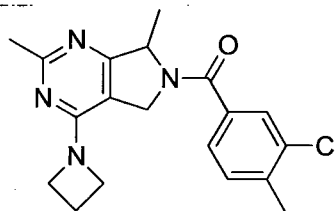


20 Prepared in a similar manner to **Intermediate 13** using **Intermediate 105**. The crude material was taken directly on to the next step.

MS ES+ 205

25 **Example 180**

1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 107** and 3-chloro-4-methylbenzoic acid CAS
5 5162-82-3.

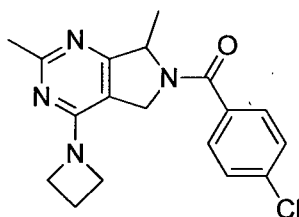
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.50 (m, 3 H) 2.18 - 2.43 (m, 8 H) 4.00 -
4.30 (m, 4 H) 4.51 - 5.07 (m, 3 H) 7.41 - 7.54 (m, 2 H) 7.62 (s, 1 H).

MS ES+ 357

10

Example 181

1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



15 Prepared via Method A using **Intermediate 107** and 4-chlorobenzoic acid (CAS 74-11-3).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.04 - 1.66 (m, 3H), 2.28 - 2.56 (m, 5H), 4.05 - 4.37
(m, 3H), 4.44 - 5.33 (m, 4H), 7.38 - 7.55 (m, 4H).

MS ES+ 343

20

The racemate was purified by chiral SFC to give the 2 enantiomers (Example 182 and
Example 183).

1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-
25 yl}azetidine (**Example 181**) was dissolved to 10 mg/mL in ethanol and was then purified

by SFC to give the title compound. The column used was a Chiralpak IC column 250 x 10mm.. The eluant was 34 % ethanol / 66 % CO₂. No modifier was added and the flow rate was 30 mL/min.

5 **Example 182 (Enantiomer 1)**

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 - 1.50 (m, 3H), 2.16 - 2.41 (m, 5H), 3.99 - 4.30 (m, 4H), 4.49 - 5.09 (m, 3H), 7.50 - 7.57 (m, 2H), 7.58 - 7.68 (m, 2H).

ME ES+ 343

10

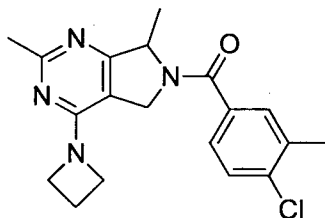
Example 183 (Enantiomer 2)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.96-1.46 (m, 3 H) 2.18 - 2.41 (m, 5 H) 3.99 - 4.29 (m, 4 H) 4.49 - 5.08 (m, 3 H) 7.49 - 7.58 (m, 2 H) 7.58 - 7.69 (m, 2 H).

15 MS ES+ 343

Example 184

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



20

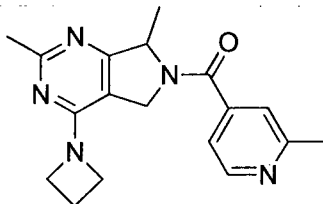
Prepared via Method A using **Intermediate 107** and 4-chloro-3-methylbenzoic acid (CAS 7697-29-2).

25 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.91 - 1.50 (m, 3H), 2.16 - 2.43 (m, 8H), 3.99 - 4.31 (m, 4H), 4.50 - 5.06 (m, 3H), 7.37 - 7.54 (m, 2H), 7.55 - 7.62 (m, 1H).

MS ES+ 357

Example 185

4-[[4-(Azetidin-1-yl)-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl]-2-methylpyridine

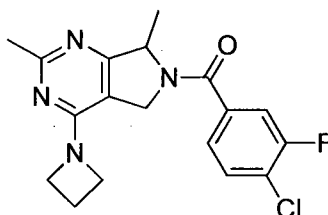


Prepared via Method A using **Intermediate 107** and 2-methyl-4-pyridinecarboxylic acid
(CAS 4021-11-8).

^1H NMR (400 MHz, CDCl_3) δ ppm 1.11 - 1.65 (m, 3H), 2.31 - 2.69 (m, 8H), 4.03 - 4.39 (m, 4H), 4.43 - 5.31 (m, 3H), 7.18 - 7.24 (m, 1H), 7.24 - 7.27 (m, 1H), 8.57 - 8.67 (m, 1H).
MS ES+ 324

Example 186

1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 107** and 4-chloro-3-fluorobenzoic acid (CAS 403-17-8).

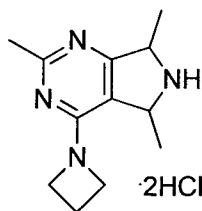
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.95 - 1.50 (m, 3H), 2.17 - 2.41 (m, 5H), 4.02 - 4.30 (m, 4H), 4.52 - 5.07 (m, 3H), 7.43 - 7.52 (m, 1H), 7.62 - 7.76 (m, 2H).

MS ES+ 361

Intermediate 108

1-{2,5,7-Trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine dihydrochloride

207

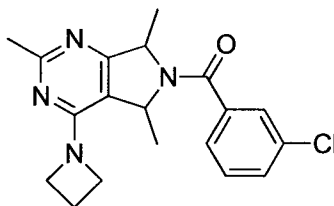


Prepared in a similar manner to **Intermediate 13** using **Intermediate 106**. The crude material was taken directly on to the next step.

5 MS ES+ 219

Example 187

1-{6-[(3-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



10

Prepared via Method A using **Intermediate 108** and 3-chlorobenzoic acid (CAS 535-80-8).

The crude product was purified by chiral SFC to give 1-{6-[(3-chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine as a single stereomer.

15

1-{6-[(3-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine was dissolved to 10 mg/mL in ethanol and was then purified by SFC to give the separate stereoisomers. The column used was a Chiralpak IC column 250 x 10mm.. The eluant was 34 % ethanol / 66 % CO₂. No modifier was added and the flow rate was 30 mL/min.

20

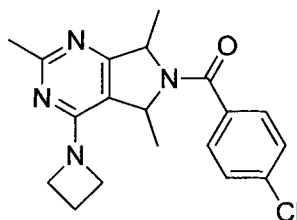
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.97 - 1.15 (m, 3H), 1.41 - 1.58 (m, 3H), 2.20 - 2.45 (m, 5H), 3.97 - 4.32 (m, 4H), 4.66 - 5.41 (m, 2H), 4.91 - 5.07 (m, 1H), 7.42 - 7.63 (m, 4H).

25

MS ES+ 357

Example 188

1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



Prepared via Method A using **Intermediate 108** and 4-chlorobenzoic acid (CAS 74-11-3).

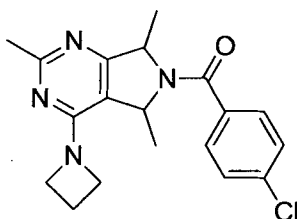
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.00 - 1.14 (m, 3H), 1.40 - 1.59 (m, 3H), 2.18 - 2.44 (m, 5H), 3.95 - 4.33 (m, 4H), 4.66 - 5.41 (m, 2H), 7.48 - 7.60 (m, 4H).

MS ES+ 357

10

Example 189

1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine



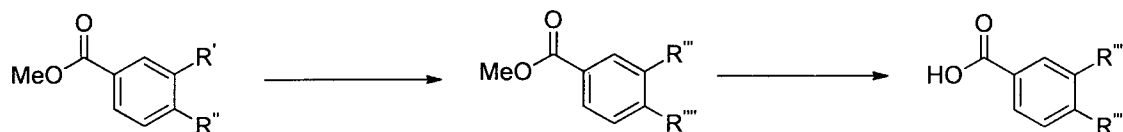
Example 188 was purified by chiral SFC to give 1-{6-[(4-chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine as a single stereoisomer.

1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine was dissolved to 10 mg/mL in ethanol and was then purified by SFC to give the separate stereoisomers. The column used was a Chiralpak AD column 250 x 10mm.. The eluant was 34 % ethanol / 66 % CO₂. No modifier was added and the flow rate was 30 mL/min.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.94 - 1.15 (m, 3H), 1.40 - 1.63 (m, 3H), 2.16 - 2.43 (m, 5H), 3.92 - 4.32 (m, 4H), 4.65 - 5.43 (m, 2H), 7.43 - 7.63 (m, 4H).

25

MS ES+ 357

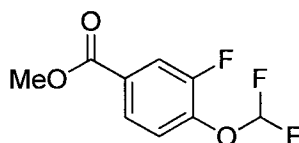
Scheme 26

CAS 403-01-0; R' = F, R'' = OH
CAS 166272-81-7; R' = OH, R'' = Cl

Int 109; R''' = F, R'''' = OCF₂H
Int 110; R''' = OCF₂H, R'''' = Cl

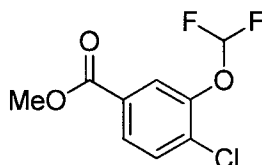
Int 111; R''' = F, R'''' = OCF₂H
Int 112; R''' = OCF₂H, R'''' = Cl

5

Intermediate 109**Methyl 4-(difluoromethoxy)-3-fluorobenzoate**

Sodium 2-chloro-2,2-difluoroacetate (1.18 g, 7.76 mmol) was added to a suspension of methyl 3-fluoro-4-hydroxybenzoate (1.1 g, 6.47 mmol) and potassium carbonate (1.07 g, 7.76 mmol) in DMF (20 mL). The reaction was heated to 125 °C for 5 hours. The reaction was allowed to cool to RT and was partitioned between EtOAc and brine. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with 0-20 % ethyl acetate/petrol to afford the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) □ ppm 3.87 (s, 3 H) 7.18 - 7.62 (m, 2 H) 7.81 - 7.94 (m, 2 H)

Intermediate 110**Methyl 4-chloro-3-(difluoromethoxy)benzoate**

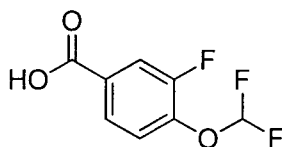
Prepared in a similar manner to **Intermediate 109** using methyl 4-chloro-3-hydroxybenzoate (CAS 166272-81-7).

20

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.89 (s, 3 H) 7.21 - 7.63 (m, 1 H) 7.74 - 7.89 (m, 3 H)

5 **Intermediate 111**

4-(Difluoromethoxy)-3-fluorobenzoic acid



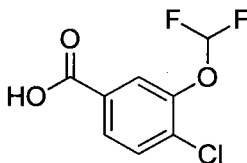
A mixture of methyl 4-(difluoromethoxy)-3-fluorobenzoate (**Intermediate 109**, 500 mg, 2.27 mmol) and LiOH (272 mg, 11.36 mmol) in THF (6 mL/water (1.5 mL) was stirred at
10 RT for 3 hours. The THF was removed *in vacuo* and the resultant aqueous phase extracted with EtOAc. The aqueous phase was acidified via the addition of 2N HCl (aq.) and was then extracted with EtOAc. The organic phase was dried (MgSO_4) and concentrated *in vacuo* to afford the title compound.

15 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.18 - 7.60 (m, 2 H) 7.78 - 7.92 (m, 2 H) 13.36 (br. s., 1 H)

MS ES- 205

Intermediate 112

20 **4-Chloro-3-(difluoromethoxy)benzoic acid**



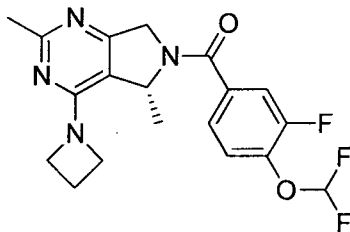
Prepared in a similar manner to **Intermediate 111** using **Intermediate 110**.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.19 - 7.64 (m, 1 H) 7.69 - 7.78 (m, 1 H) 7.79 -
25 7.87 (m, 2 H)

MS ES- 221

Example 190

1-[(5R)-6-[4-(Difluoromethoxy)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



Prepared via Method C using **Intermediate 92** and **Intermediate 111**.

5

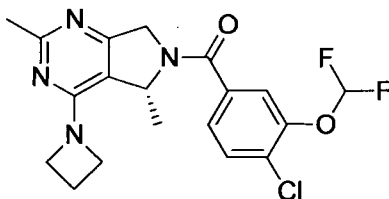
^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.95 - 1.48 (m, 3 H) 2.25 - 2.44 (m, 5 H) 4.02 - 4.37 (m, 5 H) 4.50 - 4.90 (m, 1 H) 5.17 - 5.53 (m, 1 H) 7.09 - 7.59 (m, 3 H) 7.63 - 7.81 (m, 1 H)

MS ES+ 393

10

Example 191

1-[(5R)-6-[4-Chloro-3-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine



15

Prepared via Method C using **Intermediate 92** and **Intermediate 112**.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 - 1.48 (m, 3 H) 2.22 - 2.44 (m, 5 H) 4.00 - 4.36 (m, 5 H) 4.50 - 4.87 (m, 1 H) 5.18 - 5.56 (m, 1 H) 7.18 - 7.66 (m, 3 H) 7.67 - 7.80 (m, 1 H)

20

MS ES+ 409

3. Biological Assay

In Vitro M4 & M2 Functional Assay

The functional activity of compounds at the M4 and M2 receptors was determined by measuring changes in the level of intracellular calcium ions caused by signaling cascades

25

mediated by the receptor. Intracellular calcium levels were measured using a calcium sensitive fluorescent dye, 'Calcium 5' (Molecular Devices). The changes in fluorescence were monitored by a fluorescent imager, FLiPR Tetra (Molecular devices). Increases in intracellular calcium were readily detected upon activation of both receptors by the muscarinic receptor agonist acetylcholine.

CHOK1 cells stably expressing human M4 or M2 receptor and co-expressing the accessory g-protein G α 16 were routinely grown as monolayers in Hams-F12 medium (Invitrogen) supplemented with 10% foetal bovine serum (FBS) (Hyclone), 500 μ g/mL Geneticin and 250 μ g/mL zeocin (both Invitrogen) in 5% CO₂ at 37 °C. Once confluent, cells were cryopreserved by freezing at -186 °C in freezing solution (90% FBS 10% DMSO) (Sigma-Aldrich Co.). Twenty-four hours prior to testing, cells were resuscitated and the freezing media was removed via centrifugation. Cells were then seeded in black-walled clear bottom 384-well plates (Corning) at a density of 15,000 cells/well in Hams F12 media supplemented with 10% FBS. On the day of assay, growth media was removed and replaced with 53 μ l of Calcium 5 dye solution (Molecular Devices) in assay buffer (HBSS, 20mM HEPES, 0.1% BSA, 1mM Probenecid pH 7.4 (Sigma-Aldrich Co.)) per well (each vial of Calcium 5 resuspended in 27 mL of assay buffer). Cells were then incubated for 45 minutes at 37 °C, 5% CO₂ in the case of M4 cells, or incubated for 45 minutes at ambient temperature, 5% CO₂ in the case of M2 cells. Compound was serially diluted in DMSO (log/half log) before being diluted 1:20 with assay buffer. Seven (7) μ l of compound diluted in assay buffer was then added to cells and fluorescence intensity measured for 7 minutes using the FLiPR Tetra imager. Ten (10) μ l of acetylcholine, diluted in assay buffer at 7 x EC₂₀, was then added to cells and fluorescence intensity measured for 5 minutes using the FLiPR Tetra imager.

EC₅₀ values were determined in the presence of an EC₂₀ amount of acetylcholine to determine positive allosteric modulator (PAM) activity for each compound. EC₅₀ values were calculated from ten point half log scale dose-response studies and represent the concentration of compound required to prevent 50% inhibition of its own maximal response. Curves were generated using the average of duplicate wells for each data point and analyzed using non-linear regression of four parameter dose response. Percentage

Relative efficacy (RE) to an EC₁₀₀ concentration of acetylcholine was reported for all compounds. The results are set out in the tables following in which the term “No Response” means that there was no significant response of calcium flux in the assay indicative of PAM activity.

5

Results

Table 1

Compound of Example No.	M4 EC₅₀ (μM) / M4 RE (%)	Compound of Example No.	M4 EC₅₀ (μM) / M4 RE (%)
1	0.56 / 86	2	0.80 / 47
3	0.88 / 74	4	0.69 / 65
5	0.21 / 91	6	0.27 / 80
7	2.84 / 73	8	2.10 / 54
9	1.43 / 75	10	2.34 / 61
11	2.19 / 76	12	1.34 / 74
13	0.12 / 77	14	0.28 / 76
15	2.05 / 81	16	1.59 / 67
17	0.73 / 68	18	0.28 / 78
19	0.40 / 69	20	0.42 / 83
21	1.02 / 65	22	1.26 / 68
23	0.09 / 58	24	0.73 / 61
25	2.61 / 61	26	0.56 / 60
27	0.18 / 77	28	0.52 / 73
29	1.57 / 60	30	0.54 / 76
31	0.48 / 80	32	0.43 / 61
33	1.01 / 82	34	0.86 / 61
35	0.24 / 74	36	2.92 / 45
37	0.78 / 75	38	1.09 / 74
39	0.97 / 70	40	0.41 / 41
41	0.90 / 77	42	0.35 / 77

Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)	Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)
43	0.99 / 72	44	0.30 / 82
45	1.19 / 88	46	0.45 / 71
47	0.42 / 75	48	0.88 / 77
49	1.10 / 76	50	2.55 / 43
51	3.38 / 54	52	0.31 / 79
53	2.44 / 70	54	1.76 / 53
55	0.27 / 60	56	0.26 / 61
57	0.07 / 71	58	0.12 / 58
59	0.21 / 67	60	0.15 / 65
61	0.23 / 71	62	0.26 / 84
63	2.38 / 64	64	1.43 / 70
65	1.06 / 57	66	1.35 / 82
67	0.83 / 52	68	0.30 / 69
69	2.05 / 49	70	0.20 / 62
71	0.12 / 72	72	0.52 / 68
73	1.95 / 70	74	2.78 / 69
75	0.55 / 72	76	1.09 / 46
77	0.29 / 79	78	1.79 / 70
79	0.16 / 81	80	1.30 / 56
81	1.83 / 55	82	1.91 / 70
83	0.89 / 46	84	0.84 / 44
85	0.99 / 49	86	0.25 / 62
87	1.49 / 54	88	1.20 / 77
89	0.36 / 80	90	0.26 / 85
91	0.20 / 79	92	0.26 / 76
93	0.11 / 78	94	2.59 / 53
95	0.21 / 77	96	0.16 / 96
97	0.18 / 95	98	0.92 / 60
99	0.17 / 50	100	2.19 / 51

Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)	Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)
101	0.45 / 75	102	0.87 / 74
103	2.32 / 69	104	0.43 / 87
105	1.91 / 58	106	0.94 / 79
107	1.31 / 59	108	0.18 / 74
109	1.96 / 55	110	2.10 / 47
111	1.61 / 28	112	0.14 / 81
113	0.14 / 73	114	0.19 / 70
115	1.22 / 53	116	0.10 / 87
117	0.13 / 83	118	0.37 / 73
119	1.61 / 57	120	1.43 / 54
121	0.36 / 86	122	0.17 / 90
123	0.37 / 92	124	0.28 / 46
125	0.23 / 83	126	0.24 / 86
127	0.39 / 78	128	0.47 / 81
129	0.20 / 89	130	0.25 / 82
131	0.20 / 84	132	0.36 / 85
133	2.94 / 53	134	0.44 / 79
135	2.42 / 60	136	1.22 / 87
137	1.42 / 74	138	0.39 / 75
139	0.12 / 81	140	0.55 / 81
141	0.44 / 81	142	0.67 / 82
143	1.00 / 76	144	0.21 / 84
145	0.21 / 78	146	0.30 / 77
147	0.20 / 77	148	1.63 / 69
149	2.11 / 58	150	0.16 / 90
151	0.07 / 89	152	0.11 / 88
153	0.06 / 89	154	0.05 / 83
155	0.12 / 82	156	0.12 / 88
157	0.30 / 90	158	0.18 / 84

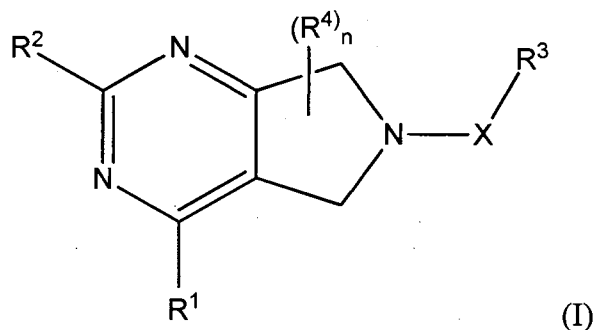
Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)	Compound of Example No.	M4 EC ₅₀ (μM) / M4 RE (%)
159	0.14 / 86	160	0.04 / 85
161	0.13 / 81	162	0.12 / 80
163	0.43 / 86	164	0.05 / 87
165	0.09 / 87	166	0.13 / 85
167	0.29 / 86	168	0.10 / 89
169	0.94 / 77	170	0.18 / 85
171	0.06 / 87	172	0.28 / 87
173	0.15 / 88	174	0.22 / 81
175	0.52 / 69	176	2.19 / 63
177	2.14 / 72	178	0.36 / 77
179	0.36 / 88	180	0.47 / 55
181	0.64 / 65	182	1.65 / 66
183	2.89 / 66	184	0.65 / 64
185	2.39 / 75	186	1.69 / 70
187	0.92 / 69	188	2.03 / 70
189	1.95 / 78	190	0.43 / 83
191	0.62 / 73		

Table 2

Compound of Example No.	M2 EC₅₀ (μM) / M2 RE @ 10 μM (%)	Compound of Example No.	M2 EC₅₀ (μM) / M2 RE @ 10 μM (%)
71	>10 / 15	70	>10 / 4
68	>10 / 10	96	>10 / 16
150	>10 / 24	151	>10 / 9
155	>10 / 22	156	>10 / 33
144	>10 / 31	138	>10 / 24
172	>10 / 18		

CLAIMS

1. A compound of formula



5 wherein

R^1 represents $-NR^5R^6$ or a C₅-C₆ heteroaryl group;

R^2 represents a hydrogen atom or a group selected from cyano, $-NR^7R^8$, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, C₃-C₈ heterocyclyl, C₆-C₁₀ aryl and C₅-C₁₀ heteroaryl, wherein each of the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl and heteroaryl groups may be optionally substituted by at least one substituent independently selected from halogen, hydroxyl, $-NR^9R^{10}$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulphinyl, C₁-C₆ alkylsulphonyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkoxycarbonyl, $-CONR^{11}R^{12}$, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy and C₃-C₆ cycloalkylmethyl;

R^3 represents a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by at least one substituent independently selected from halogen, cyano, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyloxy,

C₁-C₆ alkoxy carbonyl, -NR¹³R¹⁴, -CONR¹⁵R¹⁶, C₃-C₆ cycloalkyl, phenoxy, phenyl(C₁-C₆alkyl)oxy and sulphonamido;

n is 0, 1, 2 or 3;

each R⁴ independently represents a C₁-C₆ alkyl group;

5 X represents C(O), C(O)NH or CO(CHR¹⁷)_y(CHR¹⁸)_z, wherein the latter two groups are oriented such that the NH or (CHR¹⁷)_y(CHR¹⁸)_z moieties are attached to the R³ substituent group;

y is 0 or 1 and z is 0 or 1 provided that y + z is at least 1;

R⁵ and R⁶ each independently represent a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or

10 R⁵ and R⁶ may together with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by at least one substituent independently selected from halogen and C₁-C₆ alkyl;

R⁷ and R⁸ each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R⁷ and R⁸ may together with the nitrogen atom to which they
15 are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R⁹ and R¹⁰ each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R⁹ and R¹⁰ may together with the nitrogen atom to which they
20 are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R¹¹ and R¹² each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R¹¹ and R¹² may together with the nitrogen atom to which
25 they are attached form a 4- to 7-membered saturated heterocyclic ring optionally

substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R¹³ and R¹⁴ each independently represent a hydrogen atom, or a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxycarbonyl or C₁-C₆ alkylsulphonyl group, or R¹³ and R¹⁴ may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy;

R¹⁵ and R¹⁶ each independently represent a hydrogen atom, or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or R¹⁵ and R¹⁶ may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl, C₁-C₆ alkyl and C₁-C₆ alkoxy; and

R¹⁷ and R¹⁸ each independently represent a hydrogen atom or C₁-C₆ alkyl group, or R¹⁷ and R¹⁸ may together with the carbon atoms to which they are attached form a cyclopropyl ring;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R¹ represents -NR⁵R⁶.

3. A compound according to claim 1 or claim 2, wherein R⁵ and R⁶ each independently represent a methyl group, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form an azetidiny ring optionally substituted by at least one substituent independently selected from fluorine and methyl.

4. A compound according to any one of the preceding claims, wherein R² represents a hydrogen atom or a group selected from cyano, -NR⁷R⁸, C₁-C₂ alkyl, C₁-C₂ alkoxy,

cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl, wherein each of the alkyl, alkoxy, cyclopropyl, tetrahydropyranyl, phenyl and pyridinyl groups may be optionally substituted by at least one substituent independently selected from fluorine, chlorine, $-NR^9R^{10}$ and C_1 - C_2 alkoxy.

5

5. A compound according to any one of the preceding claims, wherein R^3 represents a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom independently selected from nitrogen, oxygen and sulphur selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, bicyclo[2.2.1]heptyl, oxazolyl, pyrazolyl, phenyl, pyridinyl, pyridazinyl, 2,3-dihydroindenyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl and 2,3-dihydroisoindolyl, all optionally substituted.

10

6. A compound according to any one of claims 1 to 4, wherein R^3 represents a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom independently selected from nitrogen, oxygen and sulphur that is optionally substituted by at least one substituent independently selected from halogen, cyano, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy and phenoxy.

15

20

7. A compound according to any one of the preceding claims, wherein n is 0 or 1.

8. A compound according to any one of the preceding claims, wherein X represents $C(O)$.

9. A compound according to any one of the preceding claims, wherein R^7 and R^8 each independently represent a hydrogen atom or a methyl group, or R^7 and R^8 may together with the nitrogen atom to which they are attached form an azetidinyl ring.

25

10. A compound according to any one of the preceding claims, wherein R^9 and R^{10} each independently represent a hydrogen atom or a methyl group.

30

11. A compound selected from the group consisting of:

1-[6-(4-Chloro-2-methylbenzoyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-{6-[(3-Chloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-3-yl)propan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(pyridin-4-yl)propan-1-one;

1-{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclobutylethan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopentylethan-1-one;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-ethylpyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methoxypyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-(trifluoromethyl)pyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile;

1-{6-[(3,5-Dichloro-4-methoxyphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-fluoro-3-methylphenyl)propan-1-one;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-(trifluoromethyl)pyridine;

1-(6-{[3-Chloro-5-(trifluoromethyl)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-3-chloro-2-methylpyridine;

5 1-{6-[(4-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-(2-Methyl-6-{[4-(trifluoromethyl)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

10 1-{6-[(3-Fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-(2-Methyl-6-{[3-(trifluoromethyl)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(2-Methyl-6-{[4-(trifluoromethoxy)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

15 1-(6-{[3-Chloro-4-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[3-Fluoro-4-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

20 1-(6-{[4-Fluoro-3-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(2-Methyl-6-{[3-methyl-5-(trifluoromethoxy)phenyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[4-(Difluoromethoxy)-3,5-dimethylphenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

25 1-(6-{[4-(Difluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(6-{[3-(Difluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

30 5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-2-ethylbenzonitrile;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopropylpropan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-cyclopentylpropan-1-one;

1-{2-Methyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-{2-Methyl-6-[(oxan-3-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

10 1-{6-[(2,2-Dimethylcyclopropyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-Cyclobutanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-Cyclopentanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

15 1-{6-Cyclohexanecarbonyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[6-({Bicyclo[2.2.1]heptan-2-yl}carbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

20 1-{6-[(4,4-Difluorocyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{2-Methyl-6-[(4-methylcyclohexyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

25 1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-fluorobenzonitrile;

30 4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-chlorobenzonitrile;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-chlorobenzonitrile;

3-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl}carbonyl}-5-chlorobenzonitrile;

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-1-methyl-1,2-dihydropyridin-2-one;

5 2-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-5-chloropyridine;

2-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-5-fluoropyridine;

10 1-{{2-Methyl-6-(3-methylcyclobutanecarbonyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-(3-Fluorocyclobutanecarbonyl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

(2R)-1-{{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine;

15 (2S)-1-{{6-[(3-Chlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-2-methylazetidine;

1-{{6-[(4-Chlorophenyl)carbonyl]-2-ethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-{{2-Cyclopropyl-6-[(3,4-dichlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

30 6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-cyclopropyl-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

5-{{4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl}-2-methyl-1,3-oxazole;

1-{6-Benzoyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-phenylpropan-1-one;
6-[(3-Chlorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;
5 1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}-3-fluoroazetidine;
6-[(3-Chloro-4-methylphenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;
10 1-{2-Methyl-6-[(4-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3,4-dichlorophenyl)propan-1-one;
1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
15 1-{6-[(3-Fluoro-4-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
1-{6-[(3,4-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
20 1-{6-[(3,5-Difluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chlorophenyl)propan-1-one;
1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(4-chlorophenyl)propan-1-one;
25 1-{6-[(3-Chloro-4-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;
3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-methylpyridine;
30 1-{6-[(3,4-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{2-Methyl-6-[(3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyridine;

5 1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-cyclopropylethan-1-one;

1-{6-[(2,3-Dihydro-1H-inden-2-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 1-{2-Methyl-6-[(2-phenylcyclopropyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-fluoro-4-methylphenyl)propan-1-one;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-(3-chloro-4-fluorophenyl)propan-1-one;

15 5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,3-dimethylpyridine;

20 3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-5-chloropyridine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,6-dimethylpyridine;

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-[(4-Fluoro-3-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3,5-Dichlorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

30 1-{6-[(2,2-Dimethyloxan-4-yl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-(6-{[3-Chloro-5-(trifluoromethoxy)phenyl]carbonyl}-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-{6-[(3-Chloro-5-methylphenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chloro-5-fluorophenyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-(2-Methyl-6-{[(1R,4R)-4-(trifluoromethyl)cyclohexyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

1-(2-Methyl-6-{[(1S,4R)-4-ethylcyclohexyl]carbonyl}-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl)azetidine;

10 1-{6-[(4,4-Dimethylcyclohexyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyridazine;

15 1-{6-[(3,3-Difluorocyclopentyl)carbonyl]-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole;

3-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole;

20 6-[(3-Chloro-5-fluorophenyl)carbonyl]-N,N,2-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-amine;

1-{6-[(Oxan-4-yl)carbonyl]-2-phenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

1-{[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}pyrrolidine;

30 1-{[4-(azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}piperidine;

1-[4-(Azetidin-1-yl)-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-phenoxy-pyrrolidine;

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N,N-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

5 4-(Azetidin-1-yl)-6-[(4-chloro-3-methylphenyl)carbonyl]-N-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-amine;

2-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine;

10 4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonitrile;

1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[4-(Azetidin-1-yl)-6-[(4-chlorophenyl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]azetidine;

15 3-[4-(Azetidin-1-yl)-6-cyclobutanecarbonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]pyridine;

1-[6-Cyclobutanecarbonyl-2-(oxan-4-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

20 1-[6-(4-Chlorobenzoyl)-2-(methoxymethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

{[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}(methyl)amine;

{[4-(Azetidin-1-yl)-6-(4-chlorobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]methyl}dimethylamine;

25 1-{6-[(4-Chlorophenyl)carbonyl]-2-(trifluoromethyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[(5R)-6-[3-Chloro-4-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

30 1-{6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-{6-[(4-chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

10 3-{[4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

4-{[4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1H-pyrazole;

4-{[4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-methyl-1H-pyrazole;

15 4-{[4-(azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-1-ethyl-1H-pyrazole;

1-{2,5-dimethyl-6-[(oxan-4-yl)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

20 1-{6-cyclobutanecarbonyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(2,3-dihydro-1H-inden-2-yl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-[(4-chlorophenyl)carbonyl]-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{2-ethyl-6-[(4-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

30 3-{[4-(azetidin-1-yl)-2-ethyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

1-{2-ethyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(3-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

5 1-{2-Cyclopropyl-6-[(3-fluorophenyl)carbonyl]-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

3-{[4-(Azetidin-1-yl)-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

10 1-{6-Cyclobutanecarbonyl-2-cyclopropyl-5-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-[6-(4-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]-1H-pyrazole;

1-[(5R)-6-[(4-Chlorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

15 1-[(5R)-6-[(3-Chloro-5-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

20 1-[(5R)-6-[(4-Chloro-3-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[(3-Chloro-5-methylphenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

3-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}benzonitrile;

25 4-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

4-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,6-dimethylpyridine;

30 5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-3-chloro-2-methylpyridine;

5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-chlorobenzonitrile;

1-[(5R)-6-[(3-Chloro-4-fluorophenyl)carbonyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylbenzonitrile;

5-5-{[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-fluorobenzonitrile;

5-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-3-fluoro-2-methylpyridine;

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-methylbenzonitrile;

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-fluorobenzonitrile;

3-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]-5-chlorobenzonitrile;

15-1-[(5R)-6-(4-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-(3-Chlorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

4-[(5R)-4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carbonyl]benzonitrile;

1-[(5R)-6-(3-Fluorobenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-(4-Fluoro-3-methylbenzoyl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

25-1-[(5R)-6-[4-(Difluoromethyl)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

1-[(5R)-6-[3-Chloro-4-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

30-1-[(5R)-6-[4-Chloro-3-(difluoromethyl)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

2-{[4-(Azetidin-1-yl)-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2,3-dihydro-1H-isoinidole;

1-[2,5-Dimethyl-6-({1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}carbonyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

4-(Azetidin-1-yl)-N-cyclopropyl-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxamide;

5 1-{6-[(4-Chlorophenyl)carbonyl]-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-[(5R)-6-(4-Chlorobenzoyl)-5-ethyl-2-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

10 1-{6-[(3-Chloro-4-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

15 1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (Enantiomer 1 substantially as hereinbefore described and with reference to Example 182);

1-{6-[(4-Chlorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (Enantiomer 2 substantially as hereinbefore described and with reference to Example 183);

20 1-{6-[(4-Chloro-3-methylphenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

4-{[4-(Azetidin-1-yl)-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}-2-methylpyridine;

1-{6-[(4-Chloro-3-fluorophenyl)carbonyl]-2,7-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

25 1-{6-[(3-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine;

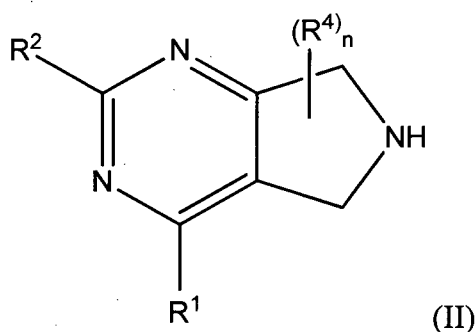
30 1-{6-[(4-Chlorophenyl)carbonyl]-2,5,7-trimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl}azetidine (a stereoisomer substantially as hereinbefore described and with reference to Example 189);

1-[(5R)-6-[4-(Difluoromethoxy)-3-fluorobenzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine; and

1-[(5R)-6-[4-Chloro-3-(difluoromethoxy)benzoyl]-2,5-dimethyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-4-yl]azetidine;

5 and pharmaceutically acceptable salts thereof.

12. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof which comprises reacting a compound of formula



10 wherein n , R^1 , R^2 and R^4 are as defined in formula (I), with a compound of formula (III), R^3 -X- L^1 , wherein L^1 represents a leaving group and X and R^3 are as defined in formula (I);

and optionally thereafter carrying out one or more of the following procedures:

- 15
- removing any protecting groups
 - converting a compound of formula (I) into another compound of formula (I)
 - forming a pharmaceutically acceptable salt.

13. A pharmaceutical composition comprising a compound of formula (I) or a
20 pharmaceutically acceptable salt thereof according to any one of claims 1 to 11 in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

14. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to
25 any one of claims 1 to 11 for use in treating a disease or condition whose development or symptoms are linked to M4 muscarinic receptor activity.

15. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11 for use in treating schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive disorders or pain.

5

16. An intermediate of formula (II) as defined in claim 12.

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2017/036899

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/519 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2004/094363 A1 (LILLY CO ELI [US]; ALLEN JENNIFER REBECCA [US]; HITCHCOCK STEPHEN ANDR) 4 November 2004 (2004-11-04) claims 1,10,15; examples 1-17 -----	1-16
A	WO 01/83472 A1 (ACADIA PHARM INC [US]; ANDERSSON CARL MAGNUS A [DK]; FRIBERG BO LENNAR) 8 November 2001 (2001-11-08) page 1, line 4 - line 10; claim 1 -----	1-16
X	WO 2008/101665 A1 (NOVARTIS AG [CH]; BRITT SHAWN D [US]; FU JIPING [US]; PARKER DAVID THO) 28 August 2008 (2008-08-28) page 361 -----	16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 December 2017

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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