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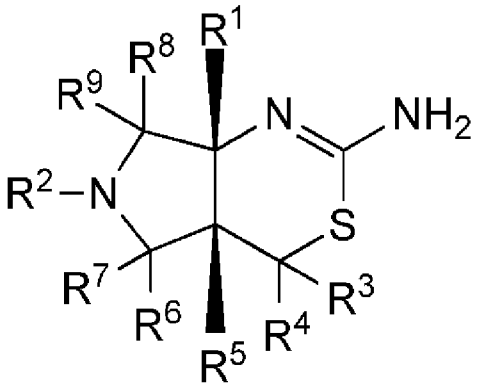
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(54) **Title**: HEXAHYDROPYRROLOTHIAZINE COMPOUNDS



(I)

(57) **Abstract**: A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1 to R^9 are as defined in the specification and which compound has an Aβ production inhibitory effect and may be useful as a prophylactic or therapeutic agent for a neurodegenerative disease caused by Aβ and typified by Alzheimer-type dementia (AD) or Down's syndrome.

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HEXAHYDROPYRROLOTHIAZINE COMPOUNDS

The present invention relates to an isothiourea derivative and pharmaceutical use thereof. More particularly, the present invention relates to an isothiourea derivative which has an amyloid-β (hereinafter referred to as Aβ) protein production inhibitory effect or a beta-site amyloid-β precursor protein cleavage enzyme 1 (hereinafter referred to as BACE1 or beta-secretase) inhibitory effect and which may be effective for treating a neurodegenerative disease caused by Aβ protein, in particular, Alzheimer's-type dementia (AD), Down's syndrome or the like, and to a pharmaceutical composition comprising the isothiourea derivative as an active ingredient.

Alzheimer's disease is characterized by degeneration and loss of neurons as well as formation of senile plaques and neurofibrillary tangles. Currently, only the symptoms of Alzheimer's disease are treated using a symptom-improving agent typified by an acetylcholinesterase inhibitor, and a fundamental remedy to inhibit progression of the disease has not yet been developed. It is necessary to develop a method for controlling the causative pathology in order to create a fundamental remedy for Alzheimer's disease.

It is believed that Aβ-proteins, as breakdown products of amyloid precursor proteins (hereinafter referred to as APP) are critical to the degeneration and loss of neurons and onset of symptoms of dementia. Aβ-proteins have, as main components, Aβ40 consisting of 40 amino acids and Aβ42 consisting of 42 amino acids wherein the two additional amino acids are present at the C-terminal. The Aβ40 and Aβ42 proteins are known to be highly prone to aggregation and to be the main components of the senile plaques linked to AD (Tanzi & Bertram, Cell 2005, 120: 545-555; Haass & Selkoe, Nat Rev Mol Cell Biol 2007, 8: 101-112).

Multiple mutations in the APP gene have been associated with early and late onset Alzheimer's disease. The homozygous expression of one such mutation, A673V at the BACE1 cleavage site, has been linked to early onset AD (EOAD) (Di Fede et al, Science 2009, 323, 1473-1477; Giaccone et al Acta Neuropathol. 2010, 120, 803-812). This mutation has, in cellular assays, been shown to significantly increase Aβ40 and Aβ42 production providing further support that genetic mutations in APP which increase its processing by BACE1 result in increased amyloid production and AD. Similarly, a K670N/M671L double mutant (Swedish mutation), which has previously been shown to be linked to early onset AD (Mullan et al Nat Genet. 1992 1(5), Aug, 345-347) produced even more pronounced increases in Aβ production than the A693V mutant.

A recent study of 1795 Icelanders (Jonsson et al, Nature 2012, 488, 2 August, 96-99) identified an APP mutation (A693T) which protects against Alzheimer's disease

and cognitive decline. This mutation is proximal to the BACE cleavage site (position two of Aβ) and was found to result in approximately 40% reduction of Aβ peptide production in an *in vitro* cellular assay which was attributed to the peptide being processed ~50% less efficiently with ~ 50% decrease in the rate of cleavage by BACE1. This (heterozygous) mutation was previously identified in a single individual (Peacock et al, Neurology, 1993, 43, 1254-1256) who lived to 65 years of age and showed no signs of dementia and no amyloid pathology upon autopsy. The implication of these findings is that reducing the production of amyloid-β could prevent or delay the onset of AD. Furthermore, analysis of non-AD populations with and without the A693T mutant revealed that A693T carriers showed better conservation of cognitive function (Jonsson et al, Nature 2012, 488, 2 August, 96-99). Three homozygotes carrying the A673T mutation were found within the set and none were found to have suffered from dementia, including one who had died at the age of 88. Thus, there is strong genetic evidence linking APP mutations to AD pathology, both as protective and pathogenic.

A study on the rate of clearance of Aβ from the CNS (Mawuenyeg et al Science 2010, 330, 24 December, 1774), reported that individuals with late onset AD (LOAD) had a 30% reduction versus controls. This data suggests that increasing the clearance of Aβ from the CNS or decreasing the formation of Aβ in the CNS by 30%, for example by inhibiting BACE1, may prevent or delay the onset of AD.

Accordingly, a compound that reduces production of Aβ40 and Aβ42 is predicted to be a disease progression inhibitor or prophylactic agent for Alzheimer's-type dementia (AD).

In addition to Alzheimer's-type dementia (AD), there are other amyloidogenic conditions such as Down's syndrome for which a compound that reduces production of Aβ40 and Aβ42 may be beneficial (Mann, Neurobiol. Aging, 1989, 10: 397-399; Mann et al., J. Neurol Sci. 1989, 92: 247-260). Early onset dementia and Alzheimer's type dementia (AD) are common outcomes in individuals with Down's syndrome and evidence suggests Aβ deposition may be a causative factor in cognitive impairment associated with Down's syndrome. Another common co-morbidity in Down's syndrome is diabetes, being seven times more likely in individuals with Down's syndrome than the general population, and this increased frequency may be attributed to a gene product of chromosome 21, the triplication of all or some of which is characteristic of Down's syndrome (trisomy 21). As the gene encoding BACE2 is on chromosome 21 (Webb and Murphy, Curr. Gerontol. Geratr. Res, 2012) and BACE2 and one of its substrates, Tmem27, have been linked to diabetes, BACE2 inhibitors may be useful for the treatment of diabetes (Esterhazy et al, Cell Metab., 2011, 14: 365-377). Accordingly, a dual BACE1/2 inhibitor may provide an effective treatment for amyloid pathology and diabetes in the general or Down's syndrome populations.

Examples of other neurodegenerative diseases that might be treatable or preventable with a compound that reduces progression of Aβ40 and Aβ42 include cerebrovascular amyloid angiopathy (CAA), mild cognitive impairment (MCI), memory loss, presenile dementia, senile dementia, hereditary cerebral hemorrhage with amyloidosis, and other degenerative dementias such as dementias of mixed vascular and degenerative origin, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, dementia associated with Parkinson's Disease (PD), and dementia associated with diffuse Lewy Body type of AD. Further conditions that might be treatable or preventable with a compound that reduces progression of Aβ40 and Aβ42 include Creutzfield-Jakob Disease (CJD), peripheral nerve injury, peripheral neuropathy, progressive supra-nuclear palsy, stroke, amyotrophic lateral sclerosis (ALS), autoimmune diseases, inflammation, arterial thrombosis, anxiety disorders, psychotic disorders, epilepsy, seizures, convulsions, stress disorders, vascular amyloidosis, pain, Gerstmann-Straeussler-Scheinker syndrome, scrapie, encephalopathy, spino cerebellar ataxia, Wilson's Disease, Graves Disease, Huntington's Disease, Whipple's Disease, Kostmann Disease, glaucoma, hereditary cerebral hemorrhage with amyloidosis, cerebral hemorrhage with amyloidosis, vascular amyloidosis, brain inflammation, fragile X syndrome, stroke, Tourette's syndrome, inclusion body myositis, stress disorders, depression, bipolar disorder and obsessive compulsive disorder.

Farah *et al.* (J. Neurosci. 13 April 2011, 31(15):5744-5754) have described how BACE1 inhibitors may also be useful in a therapeutic approach to accelerate regeneration and recovery after peripheral nerve damage.

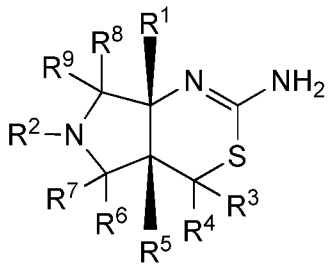
Aβ is produced by the cleavage of APP by beta-secretase (BACE1) and subsequently by gamma-secretase. For this reason, attempts have been made to create compounds which inhibit Aβ production. Examples of compounds having an Aβ or BACE 1 inhibitory effect are described for example in WO2011009897, WO2011063233, WO2011063272, WO2011090911, WO2011002409, WO2011005738, WO2009131975, WO2009022961, WO2009091016, WO2009097401 and WO2009097278. Several Aβ inhibitors have been investigated in clinical studies as potential treatments for AD. For example, the compound MK-8931 has been reported to reduce CSF Aβ40, Aβ42 and sAPPβ in AD patients (Forman et al., 11th International Conference on Alzheimer's & Parkinson's Diseases, Florence, Italy, 7th March 2013). Other examples include LY2811376 (J. Neurosci 2011, Vol. 31(46):16507-16516) and LY2886721 (May et al., 11th International Conference on Alzheimer's & Parkinson's Diseases, Florence, Italy, 7th March 2013).

The brain is protected by several barriers including the blood brain barrier (BBB) and transporters (Hitchcock and Pennington, J. Med. Chem. 2006, 29, 7559; Ueno, Curr. Med. Chem. 2007, 14, 1199; Gloor et al., Brain Res. Rev. 2001, 36, 258). Several

efflux transporters have been characterised which prevent compounds entering the brain. One of the best characterised and most prominent in preventing the CNS penetration of xenobiotics is P-glycoprotein (Pgp) (Kusuhara and Sugiyama, Drug Discovery Today, 2001, 6, 150; Mahar Doan et al., J. Pharm. Expt. Ther. 2002, 303, 1029; Lin, Drugs of Today 2004, 40, 5; Lin & Yamazaki, Clin Pharmacokinet. 2003, 42, 59; Schinkel, Adv. Drug Deliv. Rev. 1999, 36, 179). It has been shown that Pgp efflux is an important issue to overcome for BACE-1 inhibitors (Hussain et al., J. Neurochem. 2007, 100, 802) and difficulties have been encountered in identifying BACE-1 inhibitors which are not subjected to Pgp efflux (e.g. Hussain et al., J. Neurochem. 2007, 100, 802 – 80; Meredith et al., J. Pharm. Expt. Ther. 2008, 326, 502-513; and Iserloh et al., Bioorg. Med. Chem. Lett. 2008, 18, 418). Moreover, in some instances where Pgp efflux has been overcome high brain tissue binding has reduced efficacy (Malamas et al, Bioorg. Med. Chem. Lett. 2010, 20, 6597). Therefore, it would be desirable to identify new beta-secretase inhibitors that are not Pgp substrates and have a reasonable unbound fraction in brain tissue.

An object of the present invention is to provide compounds that have an Aβ production inhibitory effect or a BACE1 inhibitory effect and which may be useful as prophylactic or therapeutic agents for a neurodegenerative disease caused by Aβ and typified by Alzheimer-type dementia (AD) or Down's syndrome.

The invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a 5- to 10- membered carbocyclic group or a 5- to 10- membered heterocyclic group, either of which is optionally substituted with at least one substituent independently selected from a halogen atom, a cyano group, a nitro group, a hydroxyl group, a carbamoyl group which is optionally substituted with one or two C_{1-6} alkyl groups, a sulfonylamino group which is optionally substituted with one or two C_{1-6} alkyl groups, an aminosulfonyl group which is optionally substituted with one or two C_{1-6} alkyl groups, an amino group which is optionally substituted with one or two C_{1-6} alkyl groups which are each optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{2-6} alkenyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{2-6} alkynyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{1-6} alkoxy

group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{1-6} alkylthio group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, and a C_{1-6} alkyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α;

R^2 is a 5- to 6- membered heteroaryl group optionally substituted with at least one substituent independently selected from a halogen atom, a cyano group, a nitro group, a hydroxyl group, an amino group which is optionally substituted with one or two C_{1-6} alkyl groups, a C_{1-6} alkoxy group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, and a C_{1-6} alkyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α;

R^3 and R^4 each independently represent a hydrogen atom, a C_{3-6} cycloalkyl group or a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from Substituent Group α;

wherein each substituent selected from Substituent Group α is independently a halogen atom, a cyano group, a hydroxyl group, a C_{1-6} alkoxy group or an oxo group;

R^5 is a hydrogen atom or a fluorine atom;

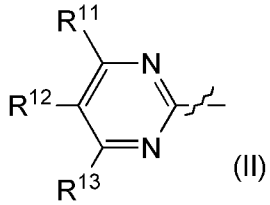
R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a trifluoromethyl group.

The isothiourea derivative of formula (I) or pharmaceutically acceptable salt thereof according to the present invention may be a solvate thereof. Examples of a solvate include a hydrate.

In one embodiment of the invention, R^2 is a 5- to 6- membered nitrogen-containing heteroaryl group optionally substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group and a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group.

In one embodiment of the invention, R^2 is a 5- to 6- membered nitrogen-containing heteroaryl group substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group.

In one embodiment of the invention, R^2 is a group of formula (II),



(II)

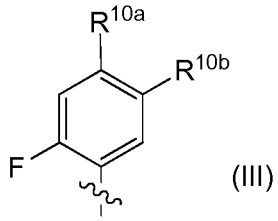
wherein R^{11}, R^{12} and R^{13} are independently a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group or a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group.

In one embodiment of the invention, R^1 is a phenyl group, a pyridinyl group or a thienyl group, any of which is optionally substituted with at least one substituent independently selected from a halogen atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, and an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

In one embodiment of the invention, R^1 is a phenyl group or thienyl group, either of which is optionally substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group or a C_{1-6} haloalkoxy group.

In one embodiment of the invention, R^1 is a phenyl group which is optionally substituted with at least one substituent independently selected from a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, and an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

In one embodiment of the invention, R^1 is a group of formula (III),



(III)

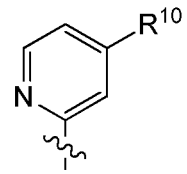
wherein R^{10a} is a hydrogen atom or a fluorine atom; and R^{10b} is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, or an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

In one embodiment of the invention, R^1 is a group of formula (III) wherein R^{10a} is a fluorine atom and R^{10b} is a hydrogen atom.

In one embodiment of the invention, R^1 is a group of formula (III), wherein R^{10a} is a hydrogen atom and R^{10b} is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, or an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

In one embodiment of the invention, R^1 is a pyridinyl group which is optionally substituted with at least one subsitituent independently selected from a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group and a C_{1-6} alkyl group.

In one embodiment of the invention, R^1 is a group of formula (IV),



(IV)

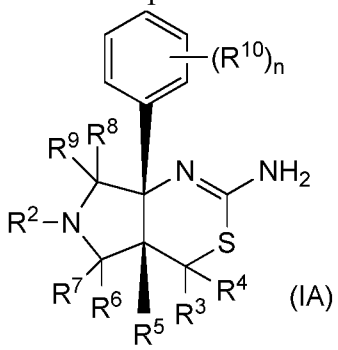
wherein R^{10} is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group or a C_{1-6} alkyl group.

In one embodiment of the invention, R^1 is a cyclohexyl group or cyclopentyl group, either of which is optionally substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group or a C_{1-6} haloalkoxy group.

In one embodiment of the invention, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently a hydrogen atom.

In one embodiment, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is a phenyl group or thienyl group, either of which is optionally substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group and a C_{1-6} haloalkoxy group; R^2 is a 5- to 6-membered nitrogen-containing heteroaryl group substituted with at least one substituent independently selected from a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkyl group and a C_{1-6} alkoxy group; and R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently a hydrogen atom.

In one aspect the present invention provides a compound of formula (IA)



(IA)

or a pharmaceutically acceptable salt thereof, wherein

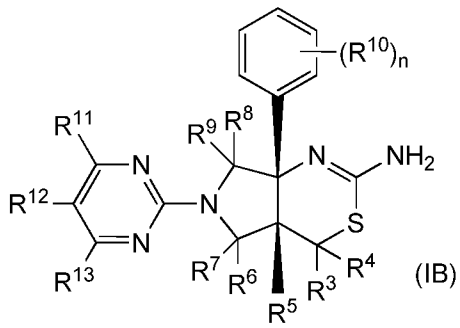
R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are defined as for formula (I);

n is 1 or 2; and each R^{10} is independently a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, or an amino group which is optionally

substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

In one embodiment, the invention provides a compound of formula (IA), or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently a fluorine atom.

In one aspect the present invention provides a compound of formula (IB)



(IB)

or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are defined as for Formula (I);

n is 1 or 2; each R^{10} is a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, or an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group; and

R^{11}, R^{12} and R^{13} are independently selected from a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group and a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group. In one aspect of this embodiment, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently a hydrogen atom.

In one embodiment, the present invention provides a compound of formula (IB), or a pharmaceutically acceptable salt thereof, wherein each R^{10} is fluorine; and R^{11}, R^{12} and R^{13} are independently selected from a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} hydroxyalkyl group and a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group.

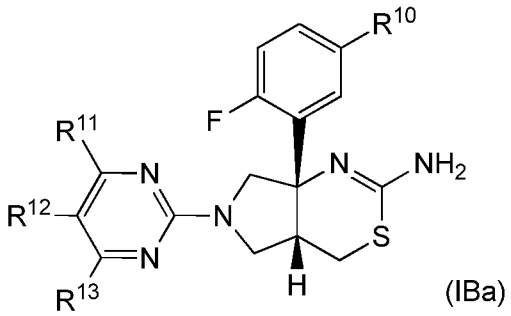
In one embodiment, the present invention provides a compound of formula (IB), or a pharmaceutically acceptable salt thereof, wherein

R^{11} is a C_{1-6} alkoxy group;

R^{12} is a fluorine atom or a C_{1-6} haloalkyl group;

R^{13} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} haloalkyl group or a C_{1-6} hydroxyalkyl group.

In one embodiment, the present invention provides a compound of formula (IBa),



(IBa)

or a pharmaceutically acceptable salt thereof, wherein

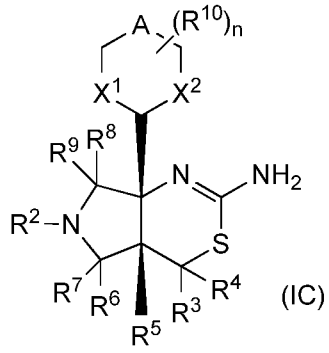
R^{10} is a hydrogen atom, a fluorine atom or a cyano group;

R^{11} is a methoxy group;

R^{12} is a hydrogen atom or a fluorine atom; and

R^{13} is a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a hydroxymethyl group.

In one aspect the present invention provides a compound of formula (IC)



(IC)

or a pharmaceutically acceptable salt thereof, wherein

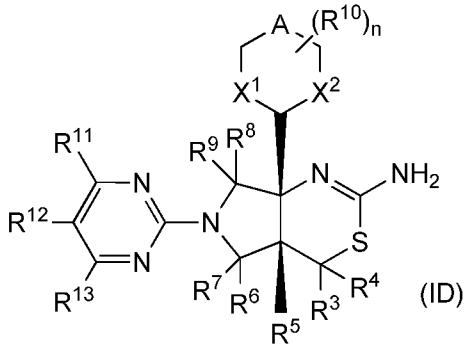
R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are defined as for formula (I);

n is 0, 1 or 2; each R^{10} is a fluorine atom; and

X^1 and X^2 are independently selected from a bond, methylene (-CH_2-) and ethylene (-CH_2CH_2)-; and

A is methylene (-CH_2-) or an oxygen atom.

In one aspect the present invention provides a compound of formula (ID)



(ID)

or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are defined as for Formula (I);

n is 0, 1 or 2; each R^{10} is fluorine;

A is methylene ($-CH_2-$) or an oxygen atom;

X^1 and X^2 are independently selected from a bond, methylene ($-CH_2-$) and ethylene ($-CH_2CH_2-$); and

R^{11}, R^{12} and R^{13} are independently selected from a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group and a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group.

In one embodiment the present invention provides a compound of formula (ID) wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9 are each independently a hydrogen atom.

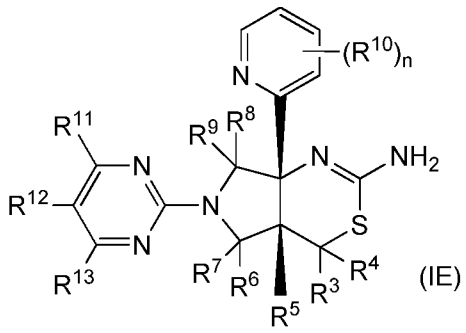
In one embodiment, the present invention provides a compound of formula (ID), or a pharmaceutically acceptable salt thereof, wherein

R^{11} is a C_{1-6} alkoxy group;

R^{12} is a fluorine atom or a C_{1-6} haloalkyl group;

R^{13} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} haloalkyl group or a C_{1-6} hydroxyalkyl group.

In one aspect the present invention provides a compound of formula (IE)



(IE)

or a pharmaceutically acceptable salt thereof, wherein

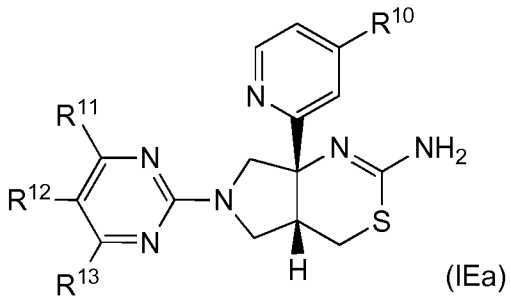
R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are defined as for formula (I);

n is 0 or 1; R^{10} is a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group or a C_{1-6} alkyl group.; and

R^{11}, R^{12} and R^{13} are independently selected from a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group and a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group.

In one embodiment the present invention provides a compound of formula (IE) wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9 are each independently a hydrogen atom.

In one embodiment the present invention provides a compound of formula (IEa), or a pharmaceutically acceptable salt thereof,



(IEa)

wherein

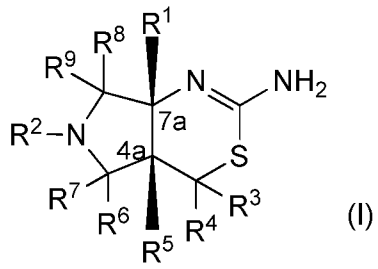
R^{10} is a hydrogen atom, a fluorine atom or a trifluoromethyl group;

R^{11} is a methoxy group;

R^{12} is a hydrogen atom or a fluorine atom; and

R^{13} is a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a hydroxymethyl group.

Those skilled in the art will recognise that the compounds of formula (I) comprise chiral centers located at the 7a and 4a positions as depicted below. For the avoidance of doubt, in the present invention the compounds of formula (I) may be present either in a stereochemically pure form or as a mixture with one or more of the other possible stereoisomers, for example in a racemic mixture or diastereomeric mixture.



(I)

In one embodiment, the present invention provides a compound of formula (I) selected from:-

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(5-fluoro-4-(fluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(4-(difluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(4-(difluoromethyl)-5-fluoro-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(4-(difluoromethoxy)-6-(difluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(2-((4aR,7aS)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methanol;

(4aR,7aS)-7a-(2-fluorophenyl)-6-(6-methoxy-4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluorophenyl)-6-(6-methoxypyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluorophenyl)-6-(6-methoxy-4-(methoxymethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluorophenyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2,4-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-7a-cyclohexyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-7a-cyclopentyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorobenzonitrile;

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(3-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-(dimethylamino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-(1,3-difluoropropan-2-yl)amino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(methylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine; and

(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine,

or a pharmaceutically acceptable salts thereof.

In another embodiment, the present invention provides a compound of formula (I) selected from:-

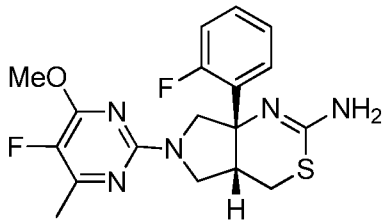
(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine; and

(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine,

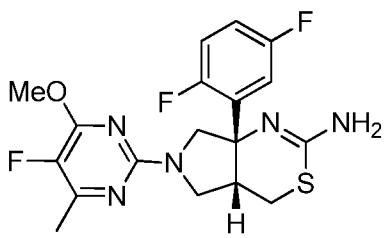
or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides the compound (4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



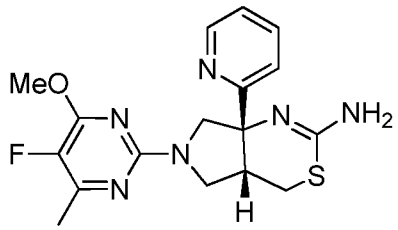
or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides the compound (4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides the compound (4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



or a pharmaceutically acceptable salt thereof.

As used herein, the term "C_{1-6}alkyl" refers to an alkyl group having 1 to 6 carbon atoms. Examples of the group include linear and branched alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 1-methylpropyl, 1,2-dimethylpropyl, 1-ethylpropyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1-methylbutyl, 2-methylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl and 3-methylpentyl.

As used herein, the term "C_{2-6}alkenyl" refers to an alkenyl group having 2 to 6 carbon atoms. Examples of the group include linear and branched alkenyl groups such as vinyl, allyl, 1-propenyl, isopropenyl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 2-buten-1-yl and 2-buten-2-yl.

As used herein, the term "C_{2-6}alkynyl" refers to an alkynyl group having 2 to 6 carbon atoms. Examples of the group include linear and branched alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, butynyl, pentynyl and hexynyl.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine or iodine.

As used herein, the term 'C_{1-6} haloalkyl' denotes a C_{1-6} alkyl group substituted with one to three halogen atoms wherein each halogen is independently selected from fluorine, chlorine, bromine and iodine. Examples of C_{1-6} haloalkyl groups include CF_3 (trifluoromethyl), CHF_2 (difluoromethyl), CH_2F (monofluoromethyl), CH_2CF_3, CH_2CHF_2 and CH_2CH_2F.

As used herein, the term 'C_{1-6} hydroxyalkyl' denotes a C_{1-6} alkyl group substituted with one to three hydroxyl groups. Examples of C_{1-6} hydroxyalkyl groups include -CH_2OH (hydroxymethyl).

Examples of a "C_{1-6}alkoxy" group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentoxy, isopentoxy, sec-pentoxy, t-pentoxy, n-hexyloxy, isohexyloxy, 1,2-dimethylpropoxy, 2-ethylpropoxy, 1-methyl-2-ethylpropoxy, 1-ethyl-2-methylpropoxy, 1,1,2-trimethylpropoxy, 1,1-dimethylbutoxy, 2,2-dimethylbutoxy, 2-ethylbutoxy, 1,3-dimethylbutoxy, 2-methylpentoxy, 3-methylpentoxy and hexyloxy.

Examples of a "C_{1-6}haloalkoxy" group include -$OCHF_2$ (difluoromethoxy).

Examples of a "C_{1-6} alkylthio" group include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, t-butylthio, n-pentylthio, isopentylthio, neopentylthio, n-hexylthio and 1-methylpropylthio.

Examples of an "amino"group optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group include amino (–NH_2), methylamino (–NHMe), ethylamino (–NHEt), dimethylamino (–NMe_2), diethylamino (–NEt_2) and bis(2-fluoroethyl)amino (–$NHCH(CH_2F)_2$.

Examples of a "carbamoyl"group which is optionally substituted with one or two C_{1-6} alkyl groups include –$CONH_2$, –$CONMe_2$ and –$CONEt_2$.

Examples of a "sulfonylamino"group which is optionally substituted with one or two C_{1-6} alkyl groups include methylsulfonylmethylamino (-$N(Me)SO_2Me$). ethylsulfonylmethylamino (-$N(Me)SO_2Et$) and ethylsulfonylethylamino (-$N(Et)SO_2Et$).

Examples of an "aminosulfonyl"group which is optionally substituted with one or two C_{1-6} alkyl groups include –SO_2NH_2, –SO_2NMe_2 and –SO_2NEt_2.

As used herein, the term "carbocyclic" denotes ring systems having 3 to 10 ring carbon atoms, including aryl rings, non-aromatic rings such as cycloalkyl rings and partially saturated rings, monocyclic rings and fused bicyclic rings including condensed, bridged and spirocyclic rings. The term "cycloalkyl" denotes saturated carbocyclic rings having 3 to 10 carbon atoms. The term "aryl" denotes aromatic carbocyclic rings having 6 to10 carbon atoms, including monocyclic aromatic rings and fused bicyclic rings wherein both rings are aromatic. The term carbocyclic includes fused bicyclic rings wherein one ring is non-aromatic and the other is aromatic, e.g. indanyl. Examples of "cycloalkyl" rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of "aryl" rings include phenyl and naphthyl.

As used herein, the term "heterocyclic" denotes ring systems having 5 to 10 ring atoms wherein at least one ring atom is selected from nitrogen, oxygen and sulphur, including heteroaryl rings, non-aromatic rings such as heterocycloalkyl rings and partially saturated rings, monocyclic rings and fused bicyclic rings including condensed, bridged and spirocyclic rings. The term heterocyclic also includes fused bicyclic rings containing at least one ring heteroatom wherein one ring is non-aromatic and the other is aromatic. The term "heteroaryl" denotes aromatic rings having 5 to10 ring atoms wherein at least one ring atom is selected from nitrogen, oxygen and sulphur, including monocyclic aromatic rings and fused bicyclic rings wherein both rings are aromatic. The term 'heterocycloalkyl' denotes saturated rings having 5 to 10 ring atoms wherein at least one ring atom is selected from nitrogen, oxygen and sulphur. Examples of 5 to 6-membered "heteroaryl" groups include furanyl, thienyl, pyrazolyl, imidazolyl,

triazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

In the context of the present specification, where it is stated that a group is optionally substituted, the group may be substituted or unsubstituted. Moreover, where it is stated that a group is optionally substituted with at least one substituent the group may for example be unsubstituted or substituted with 1, 2 or 3 substituents.

In the present invention, although crystal polymorphs of the compound of formula (I) may be present, the compound is similarly not limited thereto and may be present as a single crystal form or a mixture of single crystal forms. The compound may be an anhydride or a hydrate. Any of these forms are included in the scope of the present invention.

The present invention also includes isotopically-labelled compounds, which are identical to the compounds of formula (I), except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, phosphorous, chlorine, technetium and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{13}N, ^{15}O, ^{18}F, ^{32}P, ^{99m}Tc, ^{123}I and ^{131}I.

Compounds of the present invention and pharmaceutically acceptable derivatives (e.g. salts) of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically–labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and/or ^{14}C are incorporated, may be useful in drug and/or substrate tissue distribution assays due to their ease of preparation and detectability. ^{11}C, ^{15}O and ^{18}F isotopes may be useful in PET (positron emission tomography), and ^{99m}Tc, ^{123}I and ^{131}I isotopes may be useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Substitution with heavier isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be considered useful in some circumstances. Isotopically labelled compounds of formula (I) of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The isothiourea derivative of the formula (I) according to the present invention may be a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. Specific examples of the pharmaceutically acceptable salt include inorganic acid salts (such as sulfates, nitrates, perchlorates, phosphates, carbonates, bicarbonates,

hydrofluorides, hydrochlorides, hydrobromides and hydroiodides), organic carboxylates (such as acetates, oxalates, maleates, tartrates, fumarates, citrates, malonates, lactates and hippurates), organic sulfonates (such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and camphorsulfonates), amino acid salts (such as aspartates and glutamates), quaternary amine salts, alkali metal salts (such as sodium salts and potassium salts) and alkali earth metal salts (such as magnesium salts and calcium salts).

The compound of formula (I) according to the present invention may be converted to a pharmaceutically acceptable salt by a conventional method where necessary. The salt may be prepared by a method in which methods typically used in the field of organic synthetic chemistry and the like are appropriately combined. Specific examples of the method include neutralization titration of a free solution of the compound of the present invention with an acid solution.

The compound of formula (I) or a pharmaceutically acceptable salt thereof according to the present invention may be converted to a solvate by subjecting the compound to a solvate forming reaction known *per se* where necessary.

The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

The isothiourea derivative or pharmaceutically acceptable salt thereof according to the present invention has an Aβ production inhibitory effect and may be useful as a prophylactic or therapeutic agent for a neurodegenerative disease caused by Aβ and typified by Alzheimer-type dementia. The compounds of the invention may reduce both Aβ40 and Aβ42. Furthermore, the compounds of the present invention may have a BACE 1 and a BACE 2 inhibitory effect.

Thus, in another aspect, the present invention provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for inhibiting production of amyloid-β protein.

In a further aspect, the present invention provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for inhibiting beta-site amyloid-β precursor protein cleaving enzyme 1 (BACE 1).

In a further aspect, the present invention provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for treating or preventing a neurodegenerative disease.

In a further aspect, the present invention provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for treating or preventing Alzheimer-type dementia (AD).

In a further aspect, the present invention provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for treating Down's syndrome.

In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disease.

In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of Alzheimer-type dementia (AD).

In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Down's syndrome.

In another aspect, the invention provides a method of inhibiting production of amyloid-β protein involving administering to a human subject in need thereof a therapeutically or prophylactically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

In another aspect, the invention provides a method of treating or preventing Alzheimer-type dementia (AD) involving administering to a human subject in need thereof a therapeutically or prophylactically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method of treating Down's syndrome involving administering to a human subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In one aspect the present invention further provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for treating type 2 diabetes.

In a further aspect the present invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of type 2 diabetes.

In a yet furher aspect the present invention further provides a method of treating or preventing type 2 diabetes involving administering to a human subject in need thereof a therapeutically or prophylactically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, as active ingredient in association with a pharmaceutically acceptable carrier. The composition may be in any suitable form, depending on the

intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

The isothiourea derivative or pharmaceutically acceptable salt thereof according to the present invention may be formulated by a conventional method. Preferable examples of the dosage form include tablets, coated tablets such as film tablets and sugar-coated tablets, fine granules, granules, powders, capsules, syrups, troches, inhalants, suppositories, injections, ointments, eye drops, nasal drops, ear drops, cataplasms and lotions.

These solid preparations such as tablets, capsules, granules and powders may contain generally 0.01 to 100 wt%, and preferably 0.1 to 100 wt% of the fused isothiourea derivative or pharmaceutically acceptable salt thereof according to the present invention as an active ingredient.

The active ingredient is formulated by blending ingredients generally used as materials for a pharmaceutical preparation and adding an excipient, a disintegrant, a binder, a lubricant, a colorant and a corrective typically used, and adding a stabilizer, an emulsifier, an absorbefacient, a surfactant, a pH adjuster, a preservative and an antioxidant where necessary, for example, using a conventional method. Examples of such ingredients include animal and vegetable oils such as soybean oil, beef tallow and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; a silicone resin; silicone oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerol fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil and a polyoxyethylene-polyoxypropylene block copolymer; water-soluble polymers such as hydroxyethylcellulose, polyacrylic acid, a carboxyvinyl polymer, polyethylene glycol, polyvinylpyrrolidone and methylcellulose; lower alcohols such as ethanol and isopropanol; polyhydric alcohols such as glycerol, propylene glycol, dipropylene glycol and sorbitol; sugars such as glucose and sucrose; inorganic powders such as silicic anhydride, magnesium aluminum silicate and aluminum silicate; and purified water. Examples of the excipient used include lactose, corn starch, saccharose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. Examples of the binder used include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, a polypropylene glycol-polyoxyethylene block copolymer and meglumine. Examples of the disintegrant used include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin and carboxymethylcellulose calcium. Examples of the

lubricant used include magnesium stearate, talc, polyethylene glycol, silica and hydrogenated vegetable oil. Examples of the colorant used include those permitted to be added to pharmaceuticals. Examples of the corrective used include cocoa powder, menthol, empasm, mentha oil, borneol and cinnamon powder. Obviously, the ingredients are not limited to the above additive ingredients.

For example, an oral preparation is prepared by adding the fused isothiourea derivative or pharmaceutically acceptable salt thereof according to the present invention as an active ingredient, an excipient and, where necessary, a binder, a disintegrant, a lubricant, a colorant, a corrective and the like, and then forming the mixture into powder, fine granules, granules, tablets, coated tablets, capsules or the like by a conventional method. Obviously, tablets or granules may be appropriately coated, for example, sugar coated, where necessary.

For example, a syrup or an injection preparation is prepared by adding a pH adjuster, a solubilizer, an isotonizing agent and the like, and a solubilizing agent, a stabilizer and the like where necessary by a conventional method. The injection may be a previously prepared solution, or may be powder itself or powder containing a suitable additive, which is dissolved before use. The injection may contain usually 0.01 to 100 wt%, and preferably 0.1 to 100 wt% of the active ingredient. Further, a liquid preparation for oral administration such as a suspension or a syrup may contain usually 0.01 to 100 wt%, and preferably 0.1 to 100 wt% of the active ingredient.

For example, an external preparation may be prepared by any conventional method without specific limitations. As a base material, any of various materials usually used for a pharmaceutical, a quasi drug, a cosmetic or the like can be used. Examples of the base material include materials such as animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. A pH adjuster, an antioxidant, a chelator, a preservative and fungicide, a colorant, a flavor or the like can be added where necessary. Further, ingredients such as an ingredient having a differentiation inducing effect, a blood flow enhancer, a bactericide, an antiphlogistic, a cell activator, vitamin, amino acid, a humectant and a keratolytic agent can be blended where necessary.

The dose of the isothiourea derivative or pharmaceutically acceptable salt thereof according to the present invention may vary according to the degree of symptoms, age, sex, body weight, mode of administration, type of salt and specific type of disease, for example. Typically, the active ingredient is orally administered to an adult at about 30 μg to 10 g, preferably 100 μg to 5 g, and more preferably 100 μg to 1 g per day, or is administered to an adult by injection at about 30 μg to 1 g, preferably 100 μg to 500 mg, and more preferably 100 μg to 300 mg per day, in one or several doses, respectively.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example medicaments claimed to be useful as either disease modifying or symptomatic treatments of a neurodegenerative disease such as Alzheimer's disease. Thus, in a further aspect, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further active ingredient useful in treating a neurodegenerative disease. In one embodiment of the invention, the neurodegenerative disease is Alzheimer-type dementia (AD). Suitable examples of such further active ingredients may be symptomatic agents, for example those known to modify cholinergic transmission such as M1 and M3 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, M4 agonists or positive allosteric modulators (PAMs), acetylcholinesterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), nicotinic receptor agonists or allosteric modulators (such as α7 agonists or allosteric modulators or α4β2 agonists or allosteric modulators), PPAR agonists (such as PPARγ agonists), 5-HT_4 receptor agonists or partial agonists, histamine H3 antagonists, 5-HT_6 receptor antagonists or $5HT_{1A}$ receptor ligands and NMDA receptor antagonists or modulators (such as memantine), 5-HT_{2A} antagonists, 5-HT_7 antagonists, D1 agonists or PAMs, D4 agonists or PAMs, D5 agonists or PAMs, GABA-A α5 inverse agonists or negative allosteric modulators (NAMs), GABA-A α2/3 agonists or PAMs, mGluR2 modulators (PAMs or NAMs), mGluR3 PAMs, mGluR5 PAMs, PDE 1 inhibitors, PDE 2 inhibitors, PDE 4 inhibitors, PDE 5 inhibitors, PDE 9 inhibitors, PDE 10 inhibitors, GlyT1 inhibitors, DAAO inhibitors, ASC1 inhibitors, AMPA modulators, SIRT1 activators or inhibitors, AT4 antagonists, GalR1 antagonists, GalR3 ligands, adenosine A1 antagonists, adenosine A2a antagonists, α2A antagonists or agonists, selective and unselective norepinephrine reuptake inhibitors (SNRIs), or potential disease modifying agents such as gamma secretase inhibitors or modulators, alpha secretase activators or modulators, amyloid aggregation inhibitors, amyloid antibodies, tau aggregation inhibitors or tau phosphorylation/kinase inhibitors, tau dephosphorylation / phosphatase activators, mitogen-activated protein kinase kinase 4 (MKK4/MEK4/MAP2K4) inhibitors, c-Jun N-terminal kinase (JNK) inhibitors, casein kinase inhibitors, MK2 (mitogen activated protein kinase-activated protein kinase 2) inhibitors, MARK (microtubule affinity regulating kinase) inhibitors, CDK5 (cyclin dependent kinase 5) inhibitors, GSK-3 (glycogen synthase kinase-3) inhibitors and tau-tubulin kinase-1 (TTBK1) inhibitors. Further examples of such other therapeutic agents may be calcium channel blockers, HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins) and lipid lowering agents, NGF (nerve growth factor) mimics, antioxidants, GPR3 ligands, plasmin activators, neprilysin (NEP) activators, IDE (insulin degrading enzyme)

activators, melatonin MT1 and/or MT2 agonists, TLX/NR2E1 (tailless X receptor) ligands, GluR1 ligands, RAGE (receptor for advanced glycation end-products) antagonists, EGFR (epidermal growth factor receptor) inhibitors, FPRL-1 (formyl peptide-like receptor-1) ligands, GABA antagonists, and MICAL (molecule interacting with casL) inhibitors, e.g. oxoreductase inhibitors, CB1 antagonists/inverse agonists, non-steroidal anti-inflammatory drugs (NSAIDs), anti-inflammatory agents (for example agents that could be used to treat neuroinflammation either by enhancing or reducing neuroinflammation), amyloid precursor protein (APP) ligands, anti-amyloid vaccines and / or antibodies, agents that promote or enhance amyloid efflux and / or clearance, histone deacetylase (HDAC) inhbitors, EP2 antagonists, 11-beta HSD1 (hydroxysteroid dehydrogenase) inhibitors, liver X receptor (LXR) agonists or PAMs, lipoprotein receptor-related protein (LRP) mimics and / or ligands and/or enhancers and/or inhibitors, butyryl cholinesterase inhibitors, kynurinic acid antagonists and / or inhibitors of kynurenine aminotransferease (KAT), orphanin FQ / nociceptin (NOP) / opioid-like receptor 1 (ORL1) antagonists, excitatory amino acid transporter (EAAT) ligands (activators or inhibitors), and plasminogen activator inhibitor-1 (PAI-1) inhibitors, niacin and /or GPR109 agonists or PAMs in combination with cholesterol lowering agents and / or HMGCoA reductase inhibitors (statins), dimebolin or similar agents, antihistamines, metal binding / chelating agents, antibiotics, growth hormone secretagogues, cholesterol lowering agents, vitamin E, cholesterol absorption inhibitors, cholesterol efflux promoters and / or activators, and insulin upregulating agents.

In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one further active ingredient selected from:-

- cholinesterase inhibitors, e.g. donepezil, galantamine, rivastigamine, tetrahydroaminoacridine and pharmaceutically acceptable salts thereof,
- NMDA receptor antagonists e.g. memantine and pharmaceutically acceptable salts thereof, and any other compounds which elicit their effects by a similar mechanism of action,
- 5-HT_6 antagonists, e.g. SB-742457 and pharmaceutically acceptable salts thereof,
- HMGCoA reductase inhibitors e.g. lovastatin, rosuvastatin, atorvastatin, simvastatin, fluvastatin, pitavastatin, pravastatin and pharmaceutically acceptable salts thereof.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Consequently, the pharmaceutical product may, for example be a pharmaceutical composition comprising the first and further active ingredients in admixture.

Alternatively, the pharmaceutical product may for example comprise the first and further active ingredients in separate pharmaceutical preparations suitable for simultaneous, sequential or separate administration to a patient in need thereof.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention.

When a compound of formula (I) or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Thus, an additional aspect of the invention provides a method of preparing a pharmaceutical composition, involving admixing at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt therof, with one or more pharmaceutically acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

General Preparation Methods

General Methods for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to the present invention, are described herein below.

It will be appreciated by those skilled in the art that in some instances certain functional groups such as hydroxyl, carboxyl or amino groups in starting reagents or intermediate compounds may need to be protected by protecting groups. Thus the following Preparation Methods may involve at certain stages the incorporation of one or more protecting groups. The protection and deprotection of functional groups is, for example, described in 'Protective Groups in Organic Synthesis, 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999) and 'Protecting Groups', P.J. Kocienski, Georg Thieme Verlag (1994), hereby known as references 1 and 2. Many of the reaction schemes to make intermediates utilise chemistry that will be known to those skilled in the art and can be found in references such as 'Organic Chemistry', 2nd edition, J. Clayden, N. Greeves and S. Warren, Oxford University Press (2012) and 'March's Advanced Organic Chemistry', 6th edition, J. March, Wiley-VCH (2007), hereby known as references 3 and 4.

Unless otherwise stated, in the following Preparation Methods the choice of solvent for a particular reaction is not particularly limited in so far as it will not inhibit the reaction, is compatible with the reactants and will allow the starting material to be dissolved to a certain extent. Further, reaction temperatures and reaction time may be varied according to the starting material, the reagent used and the like.

As will be understood by those skilled in the art, when preparing certain compounds of formula (I) it may be appropriate to modify the following Preparation Methods by alternating the sequence of reaction steps and/or incorporating additional steps to vary substituent groups on intermediate compounds. Moreover, it will also be recognised that compounds of formula (I) prepared according to the General Preparation Methods may subsequently be converted to other compounds of formula (I) using known chemistry.

In the reaction schemes accompanying the General Preparation Methods the groups equivalent to R^3, R^4, R^5, R^6, R^7, R^8 and R^9 in formula (I) are, for simplicity and clarity, depicted as hydrogen atoms. It will be understood by those skilled in the art that analogous chemistry may be used to prepare alternate compounds of formula (I) according to the present invention wherein any one or more of R^3 to R^9 are other than hydrogen.

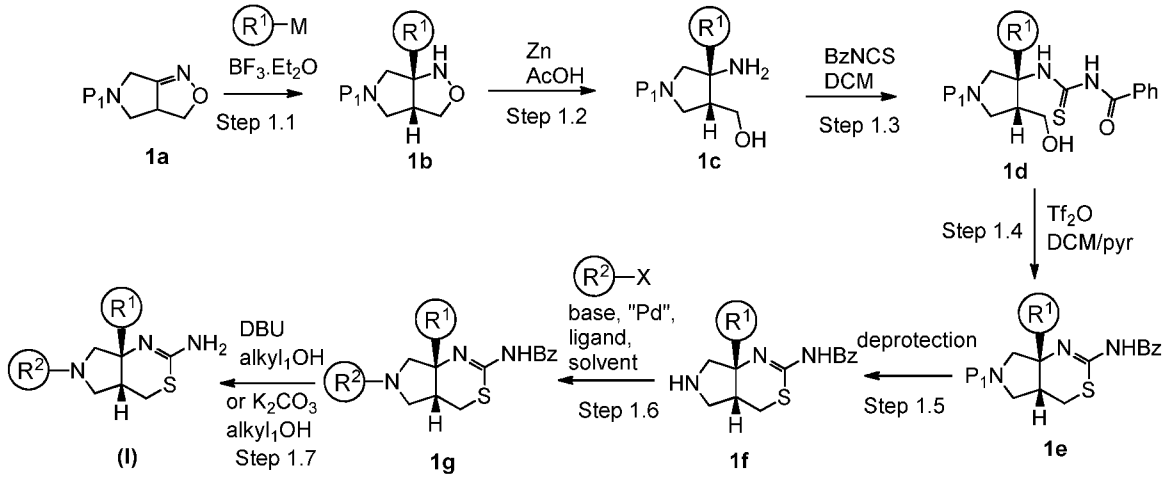
Abbreviations used in the General Preparation Methods and Intermediate Compound Preparation Methods include:- *t*-butoxycarbonyl (Boc); 1,8-Diazabicycloundec-7-ene (DBU); dichloromethane (DCM); 2,4,-dimethoxybenzyl (DMPM); N,N-Dimethylacetamide (DMA); N,N-Dimethylformamide (DMF); N, N-diisopropylethylamine (DIPEA); 4-methoxybenzyl (MPM); N-Methyl-2-pyrrolidone (NMP); mesyl (Ms); tetrahydrofuran (THF); triethylamine (TEA); trifluoroacetic acid (TFA); triflyl (Tf); Teoc (2-trimethylsilylethyl carbamate); tosyl (Ts). A further list of abbreviations can be found in the experimental section.

General Preparation Method 1

Compounds of formula (I) according to the present invention, wherein R^1 and R^2 are defined as before, can be prepared as outlined in Scheme 1 from intermediates such as **1a**. In Scheme 1, P_1 denotes a suitable protecting group (e.g. Boc, Cbz, Teoc, 2,4,-dimethoxybenzyl (DMPM), 4-methoxybenzyl (MPM) etc.) and $alkyl_1$ denotes a suitable alkyl group (e.g. a C_{1-6} alkyl group such Me, Et, Pr, Bu, *i*-Pr, *i*-Bu or *t*-Bu).

Suitable conditions for the preparation of **1b** from **1a** include addition of an organometallic reagent (R^1M) to **1a** in a suitable solvent, such as THF, PhMe, Et_2O and the like, in the presence or absence of a Lewis Acid, for example BF_3OEt_2. Suitable organometallic reagents include organolithium and Grignard reagents. The reaction temperature may for example be in the range -78°C to room temperature, preferably less than 0°C. The reaction time will vary based on the reagents used but those skilled in the art will be able to monitor the progress of the reaction and thereby judge the optimal reaction time.

Scheme 1



Suitable conditions to prepare **1c** from **1b** include Zn in acetic acid or mixed solvent systems which include acetic acid in addition to organic solvents that do not interfere with the reaction, for example THF. The reaction temperature may for example be in the range 0°C to solvent reflux, typically 0°C to room temperature. The reaction time may typically vary from 0.5 hours to 24 hours.

Suitable conditions to convert **1c** to **1d** include reaction with benzoylisothiocyanate in a suitable solvent such as DCM. The reaction temperature may for example be in the range -78°C to room temperature. The reaction time may vary from 5 minutes to 24 hours.

Suitable conditions to convert **1d** to **1e** include reaction with triflic anhydride in a suitable solvent, such as DCM, in the presence of a base, such as pyridine. The reaction temperature may for example be in the range -78°C to room temperature, typically -20°C to 0°C. The reaction time may vary from 5 minutes to 24 hours. Suitable conditions to convert **1e** to **1f** include those described in reference 1. Specifically when a) P_1 = Boc **1e** may be converted to **1f** by treating with an acid e.g. TFA or HCl in ether or dioxane; b) when P_1 = Cbz **1e** may be converted to **1f** by hydrogenation in the presence of a palladium catalyst in a suitable solvent; c) when P_1 = 4-methoxybenzyl (MPM) or 2,4-dimethoxybenzyl (DMPM) **1e** may be converted to **1f** by treatment with acid and / or hydrogenation in the presence of a palladium catalyst; d) when P_1 = Teoc **1e** may be converted to **1f** by treatment with fluoride in a suitable solvent.

Suitable conditions to convert **1f** to **1g** include transition metal (e.g. Pd) catalysed coupling reactions, suitable conditions include those described by Buchwald (for example Chemical Science, 2011, 2(1), 27-50; Chemical Science, 2011, 2(1), 57-68). Particular conditions include $Pd(OAc)_2$ as palladium source or precatalyst, NaO*t*-Bu as a base, *t*-BuDavePhos as ligand for palladium, dioxane as solvent and reaction

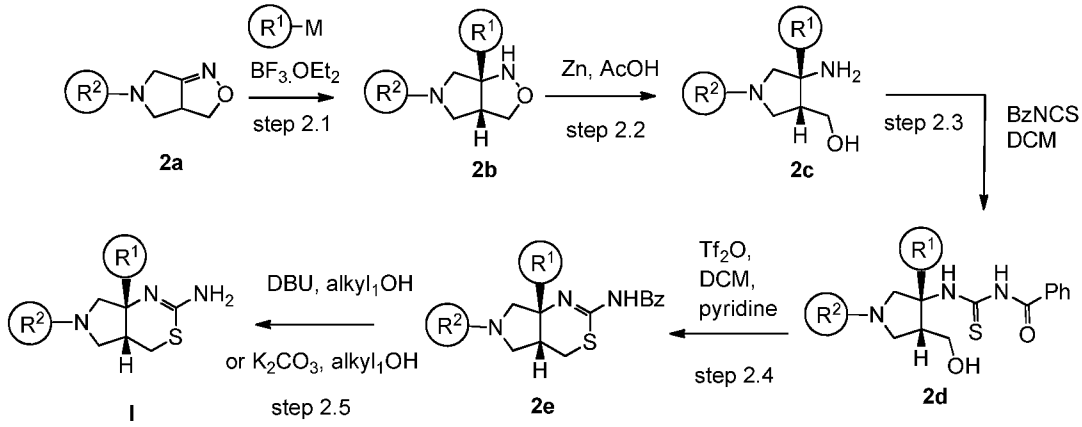
temperature 120°C. The reaction temperature may for example be in the range room temperature to solvent reflux, and the reaction time from 5 minutes to 1 week. Alternatively the same transformation may be effected by treating **1f** with a base such a triethylamine and the like in a solvent, such as acetonitrile or NMP. The reaction can be performed under microwave conditions in the range 80°C to 150°C, and reaction time from 0.5 to 24 hours.

Suitable conditions for the conversion of **1g** to compound (I) include treatment of **1g** with a base, such as DBU in a suitable solvent, such as an alkyl alcohol, such as methanol ($alkyl_1$ = Me). This reaction can be performed under the same conditions as those described in Synth. Commun. 2002, 32 (2), 265-272, for example. The reaction can be performed using 1 equivalent to a large excess of base. The reaction temperature is usually room temperature to solvent reflux temperature. The reaction time is usually 0.5 to 24 hours. Alternatively the same transformation may be effected by treating **1g** with a base such as K_2CO_3 in an alcoholic solvent, such as methanol ($alkyl_1$ = Me), ethanol ($alkyl_1$ = Et) or 1-propanol ($alkyl_1$ = Pr). The reaction can be performed using 1 equivalent to a large excess of base. The reaction temperature may for example be in the range 50°C to 100°C, and the reaction time from 0.5 to 24 hours.

General Preparation Method 2

Compounds of formula (I) according to the present invention, wherein R^1 and R^2 are as defined before, can be prepared from intermediates such as **2a**. In Scheme 2, $alkyl_1$ denotes a suitable alkyl group (e.g. a C_{1-6} alkyl group such Me, Et, Pr, Bu, *i*-Pr, *i*-Bu or *t*-Bu). Those skilled in the art will appreciate that the steps and conditions of Scheme 2 are generally analogous to those shown in Scheme 1, the principal difference being that R^2 is preinstalled prior to R^1.

Scheme 2



General Preparation Method 3

General Preparation Method 3 may be used to prepare compounds of formula (I) according to the present invention wherein R^2 is a pyrimidinyl group of formula (II) as described herein above, from intermediates such as **1f** (Scheme 3). In Scheme 3, W^1 denotes a suitable alkyl group (e.g. a C_{1-6} alkyl group such Me, Et, Pr, Bu, *i*-Pr, *i*-Bu, *t*-Bu) or a suitable aryl group (e.g. Ph or substituted-Ph) and R^{11}, R^{12} and R^{13} are as defined herein above in formula (II).

Pyrrolidine derivative **1f** can be prepared as described in General Preparation Method 1 and can be converted to the corresponding guanidine **3a** (Step 3.1) by reaction with reagents such as 1-pyrazolecarboxamidine (1H-pyrazole-1-carboximidamide). The reaction temperature may for example be in the range 0°C to solvent reflux temperature, typically room temperature. The reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours. The reaction solvent is not limited as long as it does not interfere with the reaction. Suitable solvents include DMF, DMA, NMP and the like. Those skilled in the art will appreciate that the reaction may require a non-nucleophilic bases, for example TEA, DIPEA or diisopropylamine as 1-pyrazolecarboxamidine is generally used as a hydrochloride salt. Those skilled in the art will appreciate that alternative reagents may be used in place of 1-pyrazolecarboxamidine and that such reagents may deliver a protected guanidine analogue of **3a**. Those skilled in the art will be able to select appropriate reagents and be able to effect the deprotection, if required at the appropriate stage.

Compound **3a** can be condensed with either diketone derivatives **3f** or with beta-ketoester derivatives **3g** to give compounds such as **3b** or **3c**, respectively, as depicted in Step 3.2 and Step 3.4. The reaction temperature may for example be in the range 0°C to solvent reflux temperature, typically reflux. The reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours. Compounds **3f** and **3g** are commercially available or can be prepared by those skilled in the art.

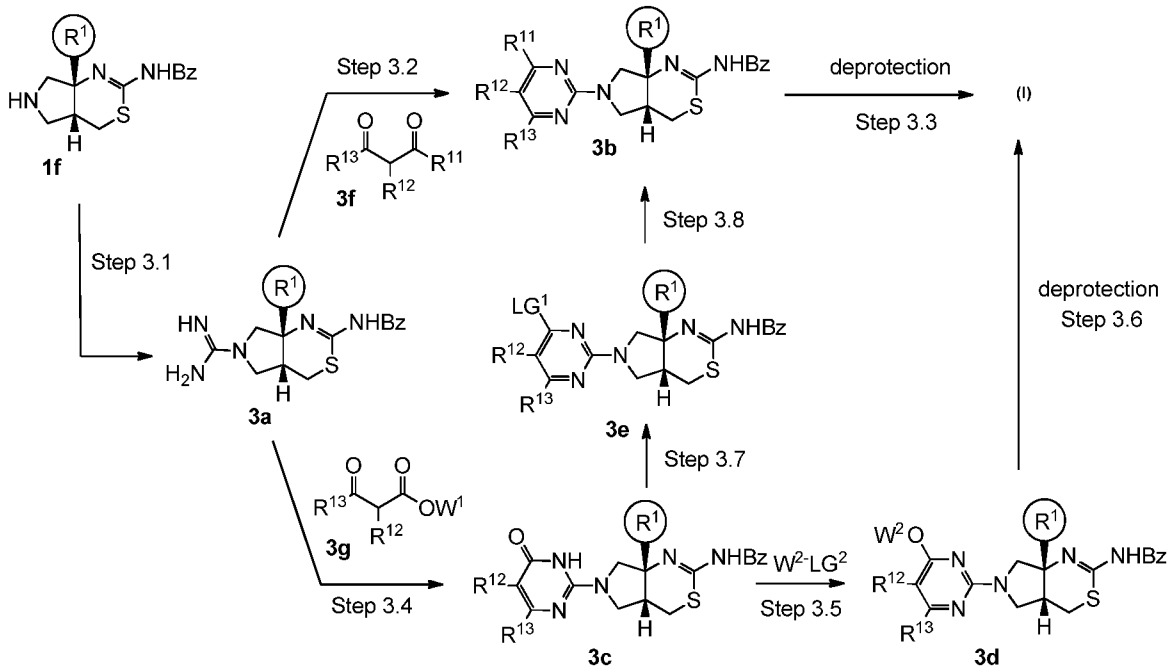
Compounds such as **3c** can be further functionalised by alkylation to give derivatives **3d** under standard conditions as depicted in Step 3.5, whereby LG^2 is a leaving group such as halogen (Cl, Br, I) or OTf, OMs, OTs or the like and W^2 is for example a C_{1-6} alkyl.

Alternatively **3c** may be converted to **3e** (Step 3.7) wherein LG^1 is a leaving group such as halogen (Cl, Br, I), for example by treatment with $POCl_3$, or LG^1 is OTf, OTs or OMs. Compound **3e** can then be reacted with nucleophiles (Step 3.8) to give **3b**. Examples of nucleophiles include alcohols, amines and carbon nucleophiles such as boronic acids and stannanes and the like. Those skilled in the art will appreciate that

when a carbon nucleophile is used then a transition metal catalyst will be required, for example a Pd catalyst.

Both compounds **3b** and **3d** can be deprotected (Step 3.3 and 3.6) using the same conditions as described in General Preparation Method 1, Step 1.7, to give Compound (I) wherein R_2 is a pyrimidinyl group of formula (II).

Scheme 3



Intermediate Compound Preparation Methods

Intermediate compounds **1a, 1b, 1c, 2a**, **2b** and **2c** may for example be prepared using chemistry according or analogous to that described in the following methods.

Preparation of Intermediate Compound **1a**

Intermediate **1a** can be prepared as shown in Scheme 4. In Scheme 4, P_1 and $alkyl_1$ are as defined in Scheme 1; $W^1$is as defined in Scheme 3, $alkyl_2$ is a suitable alkyl group (e.g. a C_{1-6} alkyl group such Me, Et, Pr, Bu, *i*-Pr, *i*-Bu or *t*-Bu) and LG is a suitable leaving group (e.g. halogen (Cl, Br, I), OTf, OMs OSu or OTs). Additionally, where there are two $alkyl_2$ groups present in a compound these groups may form a ring.

Conditions to form the protected derivatives incorporating P_1 include the use of Boc_2O (where LG = CO_2tBu), CbzCl (where LG = Cl), CbzOSu (N-benzyloxycarbonyloxysuccinimide where LG = OSu and HOSu = N-hydroxysuccinimide) and TeocCl (where LG = Cl). Conditions to form these protected intermediates include those described in Reference 1. Where P_1 is MPM or DMPM the protecting groups can be added as described in Reference 1, p. 581, or by reductive alkylation using 4-methoxybenzaldehyde or 2,4-dimethoxybenzaldehyde.

The steps depicted in Scheme 4 involve chemistry that will be known to those skilled in the art. Further details can be found in references 3 and 4. Additional information on how certain reaction steps in Scheme 4 may conveniently be performed are provided herein below.

Compounds **4f** are either comercially available or may be prepared by incorporation of a protecting group P_1 as outlined above. **4f** can be reacted with allyl bromide, **4e**, as in Step 4.4 to give compounds such as **4d**. The reaction temperature may for example be in the range -20°C to 0°C and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours. The reaction solvent is not limited as long as it does not interfere with the reaction. Suitable solvents include DMF, DMA, NMP and the like.

Compounds such as **4d** can then undergo reduction to the aldehyde **4j** (Step 4.7), using a suitable reagent and solvent such as DIBAL and DCM. The reaction temperature may for example be in the range -78°C to 0°C and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours.

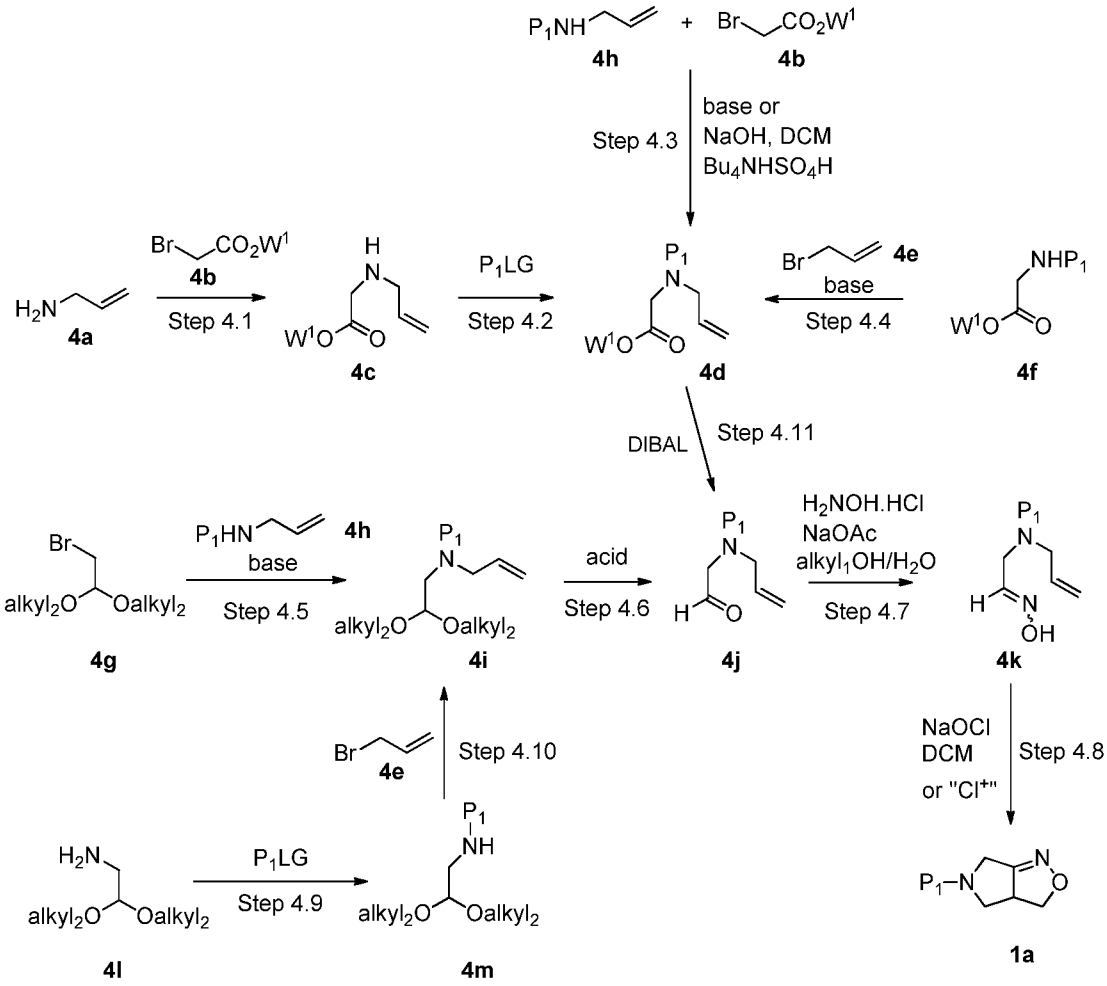
Hydroxyimine formation (Step 4.7) can then be carried out using hydroxylamine hydrochloride in a suitable alcoholic solvent. The reaction temperature may for example be in the range room temperature to solvent reflux, typically reflux and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours to give **4k**. Cyclisation of **4k** using NaOCl as in Step 4.8 affords intermediate **1a**.

Alternatively, intermediate **4c** can be prepared via a different synthetic sequence. N-alkylation of allylamine **4a** with bromoacetate **4b** (step 4.1) can give access to N-allylglycine derivative **4c** followed by subsequent protection with P_1LG (step 4.2). Suitable conditions to convert **4a** to **4c** can be accomplished in a suitable solvent such as diethyl ether, tetrahydrofuran, or the like. This reaction can be performed under the same conditions as those described in Carbohydrate Research **2005**, *340*, 2457–2468 for example. The reaction temperature may for example be in the range 0°C to room temperature, and the reaction time from 1h to 1 week. Suitable conditions to convert **4c** to **4d** include those described in reference 1.

Aldehyde **4j** may also be prepared from compound **4l** which is first protected with P_1LG (step 4.9). The resulting compound **4m** can undergo alkylation with allyl bromide **4e** to afford **4i** (step 4.10), which may also be accessed from bromoacetal **4g**. The acetal **4i** can be converted into aldehyde **4j** (step 4.10). Suitable conditions to convert **4i** to **4j** include those described in reference 1. Suitable conditions to convert **4m** to **4i** include use of base such as sodium hydride, cesium carbonate, or the like in a suitable solvent such as dimethylformamide, terahydrofuran, or the like. The reaction temperature may for example be in the range 0°C to room temperature, and the reaction time from 1h to 1 week. Suitable conditions to convert **4i** to **4j** include use of acid

such as formic acid, hydrogen chloride, or the like. The reaction temperature may for example be in the 0°C to room temperature, and the reaction time from 1h to 1 week.

Scheme 4



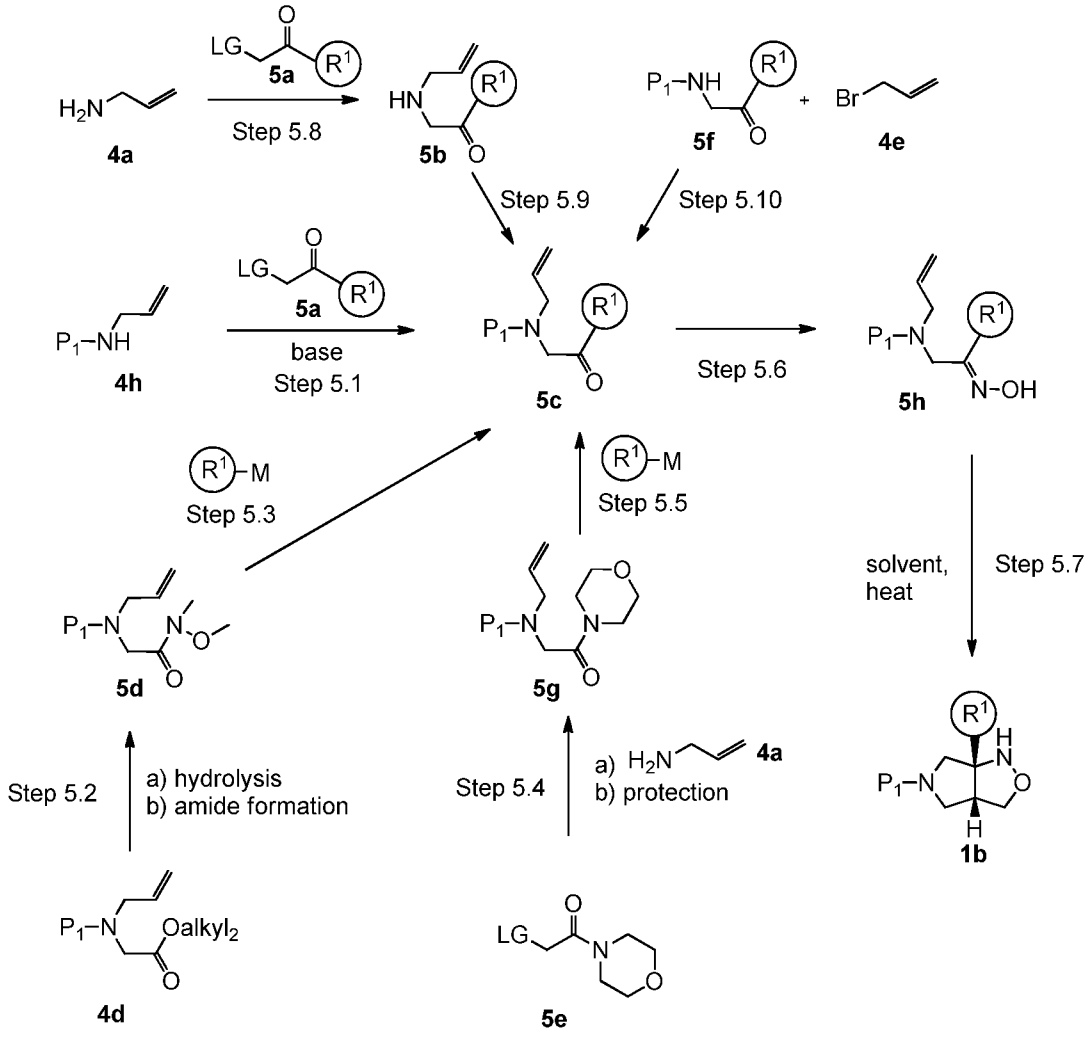
Preparation of Intermediate Compound **1b**

As an alternative to being prepared from intermediate **1a** as described in Scheme 1, intermediate **1b** may be prepared as outlined in Scheme 5. In Scheme 5, P_1 and $alkyl_1$ are as defined for Scheme 1 and LG is a suitable leaving group, (e.g. halogen (Cl, Br, I) or OTf, OTs, OMs and the like).

The steps depicted in Scheme 5 will be known to those skilled in the art. Further details can be found in references 3 and 4. General conditions for the reaction of Weinreb amides such as **5d** with organometallic reagents can be found in Tetrahedron Lett. 1981, 22, 3815. Compound **1b** wherein P_1 is DMPM can be prepared as described in WO2009019016. Additional information on how certain reaction steps in Scheme 5 may conveniently be performed are provided herein below.

In one instance protected allyl amine, **4h**, can be reacted with derivatives of **5a** (Step 5.1), both of which are either commercially available or can be synthesised usually in one step. A suitable non-nucleophilic base, for example TEA, DIPEA or diisopropylamine, is required as well as a suitable solvent such as DCM. This reaction affords the ketone derivative **5c** and the reaction temperature may for example be in the range room temperature to solvent reflux, typically room temperature and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours.

Oxime formation (Step 5.6) can then be carried out using hydroxylamine hydrochloride in a suitable alcoholic solvent, e.g. in buffered or basic consitions. The reaction temperature may for example be in the range room temperature to solvent reflux, typically reflux and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours to give **5h**.



Cyclisation as in Step 5.7 is then achieved by heating **5h** in a suitable solvent at reflux for between 1 -12 hours to give derivative **1b**. This route can convieniently be

used when R^1 is 2,4-difluorophenyl group (e.g. as in Example 17 of the experimental section).

Alternatively, compound **5c** can be prepared from either compound **4d** or commercialy available compound **5e** in a three steps sequence, as depicted in Scheme 5.

Scheme 5

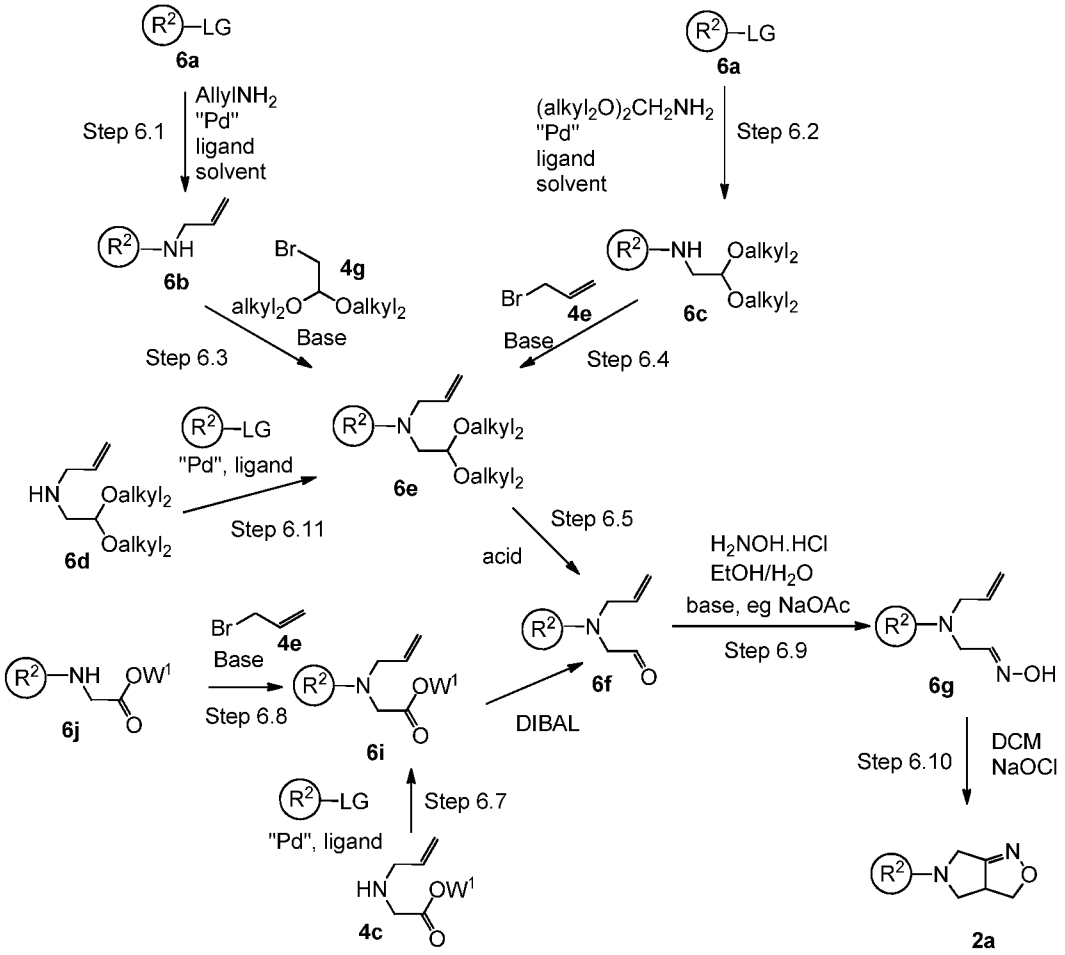
Preparation of Intermediate **2a**

Intermediate **2a**, can be prepared as shown in Scheme 6. In Scheme 6, W^1 is as defined for Scheme 3 and $alkyl_2$ and LG are as defined for Scheme 4. The reactions and conditions depicted in Scheme 6 will be known to those skilled in the art. Further details can be found in references 3 and 4. Additional information on how certain reaction steps in Scheme 6 may conveniently be performed are provided herein below.

In one instance allyl amine **6b** can be reacted with compounds **4g** (Step 6.1). Suitable conditions include use of base such as sodium hydride, cesium carbonate, or the like in a suitable solvent such as dimethylformamide, tetrahydrofuran, or the like. The reaction temperature may for example be in the range 0°C to reflux, and the reaction time from 1h to 1 week. The resulting acetal **6e** could be converted into the aldehyde **6f** and then to oxime **6g** when treated with hydroxylamine hydrochloride in a suitable alcoholic solvent (step 6.9), e.g. in buffered conditions. The reaction temperature may for example be in the range room temperature to solvent reflux and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours. 1,3-Dipolar cycloaddition reaction as in Step 6.10 is then achieved by conversion of **6g** to a nitrile oxide derivative which reacst with the olefin moiety in the same molecule to afford the cyclic compound **2a**. Suitable conditions include the use of N-chlorosuccinimide and sodium hypochlorite in a suitable solvent such as dichloromethane, chloroform, or the like. The reaction temperature may for example be in the range 0°C to solvent reflux temperature, and the reaction time from 1h to 48 hours. This reaction can be performed under analogous conditions as those described as Org. Lett. **2007,** *9*, 753-756, Tetrahedron: Asymmetry **1994** *5*, 1019-1028 and Tetrahedron **1998,** *54*, 5869-5882.

Allyl amines of formula **6b** may be prepared in one step from either allylamine or allylbromide following procedure as those described in Angew.Chem. Int. Ed.. **2011,** *50*, 5678-5681, JOC **2005,** *70*, 5164-5173 and Tet. Lett. **1998,** *39*3131-3141. A general method of preparing compounds **6b** wherein $R^2$is a pyrimidine, for example compound **9d**, is described in Scheme 9. Compounds **4g** are either commercially available or can be prepared by known chemistry.

Scheme 6



Preparation of Intermediate 2b

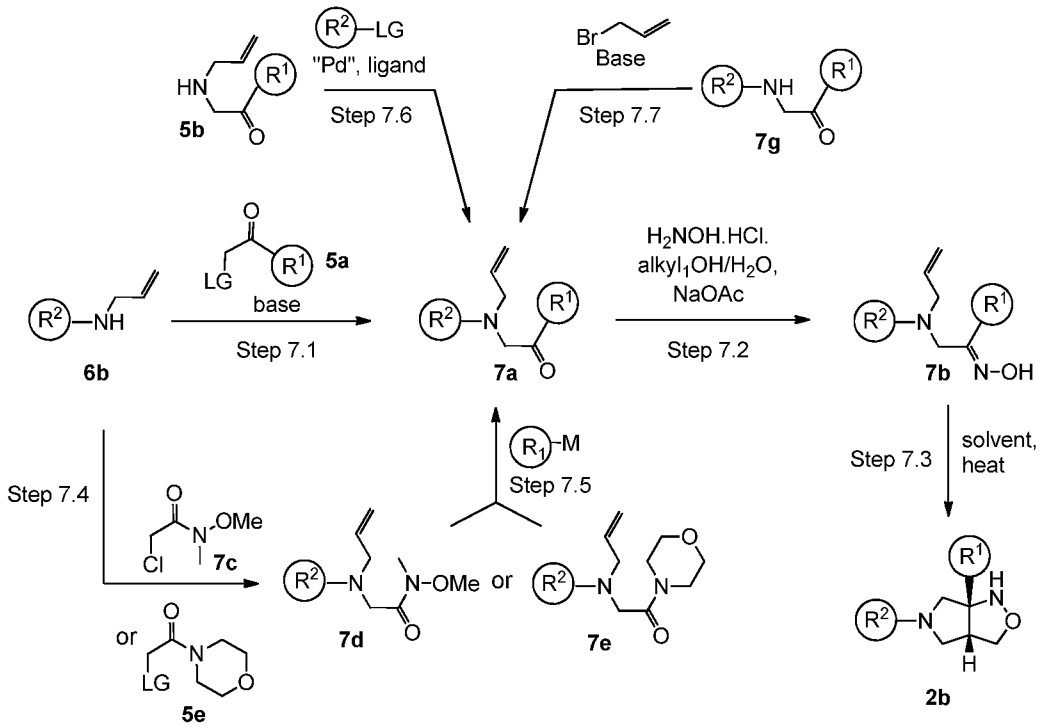
As an alternative to being prepared from intermediate **2a** as described in General Preparation Method 2, intermediate **2b** may be prepared as outlined in Scheme 7. In Scheme 7, $alkyl_1$ is as defined for Scheme 1 and LG is as defined for Scheme 4. The reactions and conditions depicted in Scheme 7 will be known to those skilled in the art. Further details can be found in references 3 and 4. Additional information on how certain reaction steps in Scheme 7 may conveniently be performed are provided herein below.

In one instance allyl amine **6b** can be reacted with derivatives of **5a** (Step 7.1) Suitable conditions include use of base such as sodium hydride, or the like in a suitable solvent such as dimethylformamide, terahydrofuran, or the like. The reaction temperature may for example be in the range 0°C to reflux, and the reaction time from 1h to 48h. The resulting ketone **7a** can be converted to oxime **7b** when treated with hydroxylamine hydrochloride in a suitable alcoholic solvent (step 7.2), e.g. in buffered conditions. The reaction temperature may for example be in the range room temperature

to solvent reflux, typically reflux and the reaction time may vary from 5 minutes to 24 hours, typically 1 - 12 hours. This reaction can be performed under the same conditions as those described as J. Med. Chem. **2002**, *45*, 3794-3804 and J. Med. Chem. **2000**, *43*, 3808-3812. 1,3-Dipolar cycloaddition reaction as in Step 7.3 is then achieved by heating the compound **7b** under reflux in a toluene solvent, for example. This reaction can be performed under analogous conditions as those described as J. Org. Chem. **1993**, *58*, 4538-4546 and Tetrahedron Letters, **1988** *29*, 5313-5316.

Alternatively, intermediate **7a** can be prepared via a different synthetic sequence. N-alkylation of allylamine **6b** with either 2-chloro-N-methoxy-N-methylacetamide **7c** can give the Weinreb amide derivative **7d** or reaction with reagent of type **5e** can give morpholinoethanone compound **7e** (Step 7.4), in the presence of a base such as sodium hydride, or the like in a suitable solvent such as dimethylformamide, terahydrofuran, or the like. Subsequently both compounds **7d** and **7e** can be converted into compound **7a** when treated with a suitable organometallic reagent (R^1-M) (Step7.5).

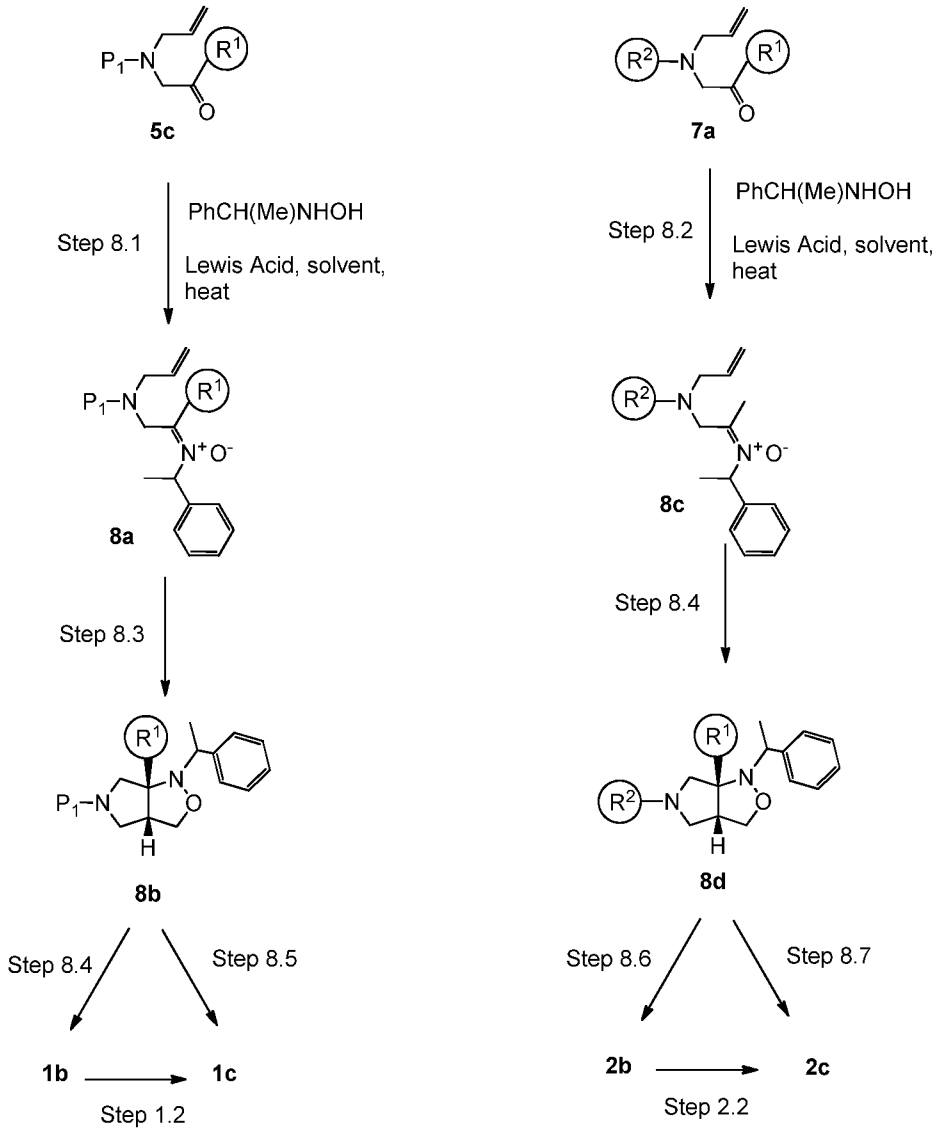
Scheme 7



Alternate Preparations of Intermediates **1b**/**1c** and **2b**/**2c**

Those skilled in the art will appreciate the routes depicted in Schemes 5 and 7, for the preparation of intermediates **1b** and **2b**, can be modified by replacement of hydroxylamine by a hydroxylamine derivative containing a chiral centre. An example of a hydroxylamine derivative containing a chiral centre is N-(α-methylbenzyl)hydroxylamine.

Scheme 8



Reaction of ketone derivatives **5c** or **7a** with N-(α -methylbenzyl)hydroxylamine result in intermediate nitrones **8a** and **8c** respectively which may or may not be possible to isolate (Scheme 8). Intramolecular cycloaddition of these nitrones results in cyclic hydroxylamines **8b** and **8d** respectively. Those skilled in the art will appreciate that utilising a hydroxylamine derivative with a chiral centre results in diastereomeric products, e.g. **8b** and **8d** and that the diastereomers may not be formed in equal amounts, hence the selection of the chiral centre in the starting hydroxylamine derivative, e.g. N-(α -methylbenzyl)hydroxylamine, may be used not only to deliver a diastereomeric product but also to influence the diastereomeric ratio. Examples of suitable Lewis acids include Ti(OEt)4. Examples of solvents THF. The

reaction temperature may be in the range room temperature to solvent reflux, typically 50°C to 100°C. The reaction time may vary from 1 hour to 1 week.

Those skilled in the art will appreciate that compounds **8b** and **8d** can be converted to derivatives such as **1c** (Scheme1) and **2c** (Scheme 2) respectively by reduction of the N-O bond, for example by treatment with Zn in AcOH or hydrogenation in the presence of a Pd catalyst, and removal of the α -methylbenzyl group, for example by hydrogenation in the presence of a Pd catalyst. Those skilled in the art will appreciate that it may be possible to reduce the N-O bond and remove the α -methylbenzyl group in a single step if desired.

Preparation of intermediates where R^2 is a Pyrimidinyl Group

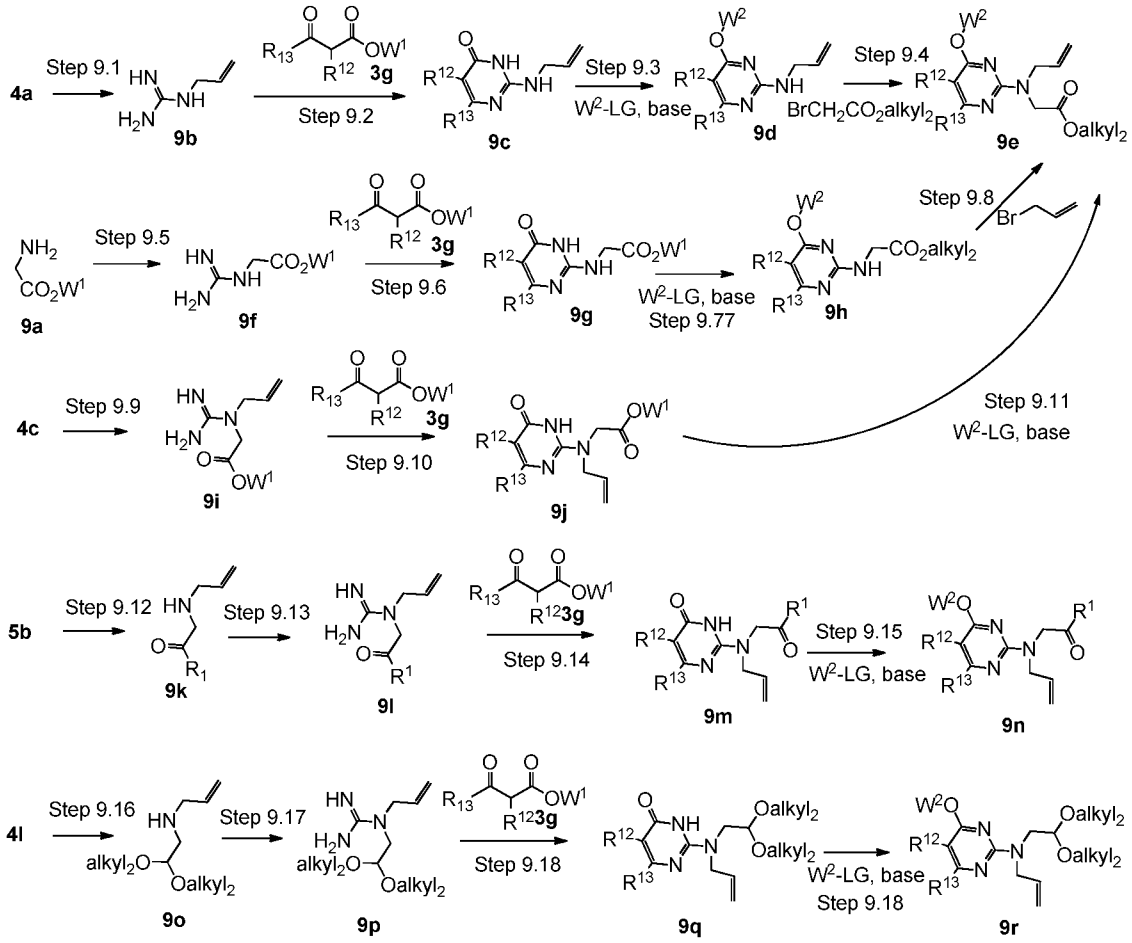
Scheme 9 depicts several routes for preparing intermediate compounds that may be used in preparing Compounds of formula (I), wherein R^2 is a pyrimidiyl group. In Scheme 9, R^1 is as defined for formula (I), R^{12}, R^{13} are as defined for formula (II), W^1 is as defined for Scheme 3, $alkyl_2$ is as defined for Scheme 4 and W^2 is, for example, a C_{1-6} alkyl group. The reactions and conditions depicted in Scheme 9 will be known to those skilled in the art. Further details can be found in references 3 and 4.

Allyl amine **4a** may be converted to the corresponding guanidine **9b** (as described in Scheme 9) which may then be condensed with a beta-ketoester derivative **3g** to give pyrimidone derivative **9c**. Selective O-alkylation may be achieved to give **9d** which may then undergo further alkylation to give **9e**. Compound **9e** may then be transformed to Compound (I) via a similar sequence to that shown in Schemes 5, 6, 7 and 8.

Similarly, the beta-ketoester derivative maybe replaced by a 1,3-diketone derivative such as **3f** (Scheme 3). If **3f** is used in place of **3g** then similar reactions may be undertaken as those depicted in Scheme 3 and the resultant product maybe transformed to Compound (I) using similar reactions to those depicted in Schemes 5, 6, 7 and 8.

Alternative starting materials to **4a** include, but are not limited to, **9a**, **4c**, **5b** and **4l** which are depicted in Scheme 9. The transformation of these starting materials may be accomplished as shown in Scheme 9 employing reaction conditions known to those skilled in the art. Compounds **9n** and **9r** may be transformed to Compound (I) using similar sequences to those described in Schemes 6, 7 and 8.

Scheme 9



The reactions and conditions depicted in Scheme 9 will generally be familiar to those skilled in the art and further details on how to perform these reactions may be found in references 3 and 4.

Compound Examples

The present invention will be described more specifically below with reference to the following Examples. However, the present invention is not limited thereto. The abbreviations used in Examples are conventional abbreviations known to a person skilled in the art. Some abbreviations are shown below:

AIBN: Azobisisobutyronitrile; BOC & Boc: tert-butoxycarbonyl; br: broad; Bn: benzyl; Bu: butyl; BuLi: n-butyl lithium; d: doublet; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene, DCM: dichloromethane; dd: doublet of doublets; DIBAL: disobutylaluminium hydride; DMF (N,N-dimethylformamide); DMAP (4-N,N-dimethylaminopyridine); DMSO (dimethylsulfoxide); EDC & EDAC: (N-3(-dimethylaminopropyl)N'ethylcarbodiimide hydrochloride); Et: ethyl; Et2O: diethyl ether; EtOAc: ethyl acetate; EtOH: ethanol; h, hr, hrs: hours; HCl: hydrochloric acid;

HPLC: high performance liquid chromatography; LCMS, LC/MS & LC-MS: liquid chromatography / mass spectrometry; m: multiplet; Me: methyl; MeCN: acetonitrile; MeOH: methanol; MS: mass spectrometry; MDAP: mass directed auto purification; min & mins: minutes; NaOH: sodium hydroxide; NBS: *N*-Bromosuccinimide; NMP: N-methylpyrrolidinone or 1-methyl-2-pyrrolidinone; NMR: nuclear magnetic resonance; Ph: phenyl; $PhCH_3$ & PhMe: toluene; Pr: propyl; Rt: retention time; RT, rt & r.t.: room temperature; s: singlet; SCX: strong cation exchange:- Isolute Flash SCX-2, Biotage; t: triplet; TBAF: tetrabutylammonium fluoride; TEA: triethylamine; THF: tetrahydrofuran; TFA: Trifluoroacetic acid; tlc: thin layer chromatography; UV (ultraviolet).

^{1}H NMR spectra were recorded on a Bruker AM series spectrometer operating at a (reported) frequency of 400 MHz. Chemical shifts in proton nuclear magnetic resonance spectra are recorded in δ units (ppm) relative to tetramethylsilane and coupling constants (J) are recorded in Hertz (Hz).

Chemical names were generated from chemical structures using ChemBioDraw Ultra 11.0 and 12.0 or ELN, both from Cambridgesoft.

It will be appreciated by those skilled in the art that where compounds are denoted as hydrochloride salts the exact stoichiometry has not been determined. Therefore, designation as a mono hydrochloride salt may mean that the compound is a mono hydrochloride, a dihydrochloride, a trihydrochloride or that the stoichiometry of the hydrochloride to compound may may be anywhere from 0 – 3.

Analytical Methods

Method A

Waters UPLC-MS analytical

A1 Short_5_95:

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7μm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min – held for 0.50min). Unless otherwise stated, this method was used for all quoted LCMS analysis.

A2 Short_20_95:

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7μm, 0.6mL per min, 40°C, gradient 20-95% MeCN in water (0.1% formic acid) over 1.50min – held for 0.50min).

A3 UPLC long_5_95:

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7μm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 3.00min – held for 1.00min).

A4 UPLC long_20_95:
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7μm, 0.6mL per min, 40°C, gradient 20-95% MeCN in water (0.1% formic acid) over 3.00min – held for 1.00min).

Method B
Agilent LCMS analytical
B1 FAST ANALYTICAL:
LCMS (Agilent ZORBAX Eclipse XDB-C18, 4.6 x 150mm, 5.0μm, 1.5mL per min, gradient 5-95% MeCN in water (0.1% formic acid) over 5.00min – held for 3.00min).

B2 TLC run No. 2:
LCMS (Agilent ZORBAX Eclipse XDB-C18, 4.6 x 150mm, 5.0μm, 1.5mL per min, gradient 0-100% MeCN in water (0.1% formic acid) over 2.00min – held for 2.00min).

Method C
Gilson/ Thermo Finnegan analytical
C1 AGILENT.GCT method (i.e. short run):
HPLC-MS (Phenomenex Gemini C18, 250 x 4.60mm, 5μm, 1.5mL per min, gradient 20-100% MeCN in water (0.1% acetic acid) over 6.00min – held for 3.00min).

C2 ORIGINAL.GCT method (i.e. long run):
HPLC-MS (Phenomenex Gemini C18, 250 x 4.60mm, 5μm, 1.0mL per min, gradient 20-100% MeCN in water (0.1% acetic acid) over 15.4min – held for 7.20min).

Purification

Method D
Gilson large scale reverse phase preparatory HPLC
MANUAL2.GCT method:
reverse phase HPLC (Phenomenex Luna C18, 250 x 50mm, 10μm, 80mL per min, gradient 20% to 95% (over 25min) then 95% (10min) MeCN in H2O [0.1% acetic acid]).

Method E
Agilent large scale reverse phase preparatory HPLC
PREP4.M method:
reverse phase HPLC (Phenomenex Luna C18, 250 x 50mm, 10μm, 80mL per min, gradient 35% to 100% (over 20min) then 100% (5min) MeCN in H2O [0.1% acetic acid]).

Method F

Waters reverse phase preparatory HPLC

F1 Buffered:

reverse phase HPLC (XBridge Prep C18, 19 x 150mm, 5μm, 20mL per min, gradient xx% to xx% (over 12min) then 95% (3min) MeCN in water [0.1% formic acid]).

F2 Non-buffered:

reverse phase HPLC (ACE 5 AQ, 21.2 x 150mm, 5μm, 20mL per min, gradient xx% to xx% (over 12min) then 95% (3min) MeCN in water).

Method G

Biotage Isolera

G1 purified by column chromatography (normal phase, (10g/25g/50g/100g/340g), Biotage SNAP cartridge KP-Sil, (12mL/25mL/50mL/100mL) per min, gradient xx% to xx% EtOAc in n-hexane / MeOH in DCM). Unless otherwise stated, this method was used for all quoted silica gel chromatography purification.

G2 purified by column chromatography (normal phase, (11g/28g/55g/110g/375g), Biotage SNAP cartridge KP-NH, (12mL/25mL/50mL/100mL) per min, gradient xx% to xx% EtOAc in n-hexane / MeOH in DCM).

Method H

Shimadzu Chiral HPLC

H1 Analytical

A 5μL sample of (Sample name/number) solution (containing 1.2mg (Sample name/number) in 1.2mL DCM) was subjected to chromatographic separation on the following 4 ChiralPAK® (i.d 4.6 mm x length 250 mm) chiral columns: IA (#1), IB (#2), IC (#3), and ID (#4).

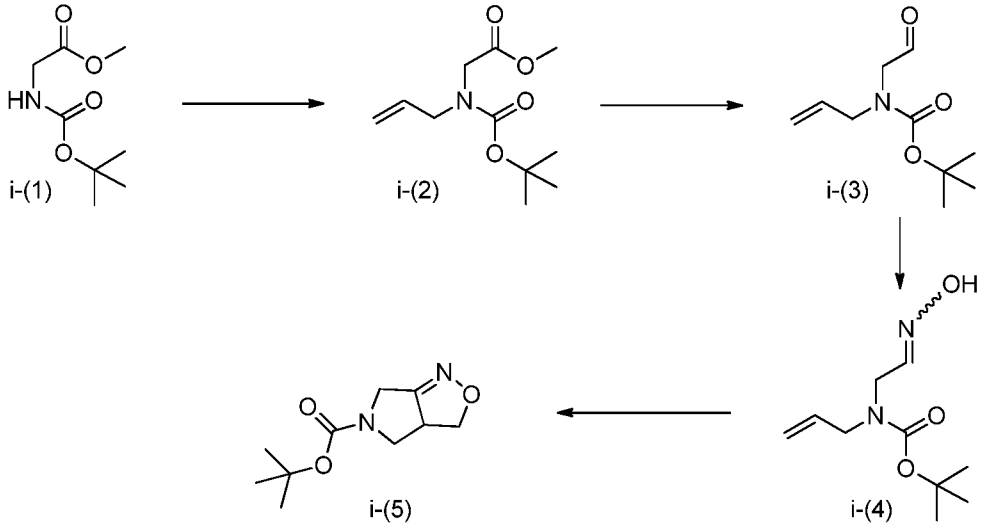
Four mobile phase isocratic conditions were examined: (DCM or 10% DCM/hexane):EtOH (80:20/85:15/90:10/95:5). Oven Temp: 30°C. Flow rate: 1.0 mL/min

H2 Preparative

A sample of (Sample name/number) (x mg) was dissolved in DCM (x mL), loaded into a vial (3.8 mL capacity) and subjected to chromatographic separation using preparative (column type) (i.d. 20 mm; length 250 mm) and (Solvent mixture) (v/v) as

eluent. injection volume: 1500µL. Flow rate: 18.0 mL/min. Oven temperature: 30°C. Collection: manual or automated

Preparation of common intermediate i-(5): *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate.



Preparation of methyl 2-(allyl(*tert*-butoxycarbonyl)amino)acetate i-(2)

To a solution of BOC-Gly-OMe i-(1) (100 g) in N,N-dimethylformamide (900 ml) at -10°C under nitrogen was added allyl bromide (69 ml) followed by 60% sodium hydride (31.7 g). The sodium hydride was added portionwise over forty minutes and the temperature rose from -10°C to -3°C then remained at -2°C. The reaction mixture was then stirred at -2°C to around 0°C for three hours. The reaction was quenched very cautiously with aqueous saturated ammonium chloride (500 ml) diluted with water (500 ml) and extracted with ethyl acetate (1000 ml and 500 ml). The combined organic layer was washed with water (3 x 500 ml) then dried ($MgSO_4$) and evaporated to afford the crude title compound (132.4 g;assumed 100%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (d, 9 H) 3.73 (s, 3 H) 3.79 - 4.06 (m, 4 H) 5.03 - 5.27 (m, 2 H) 5.68 - 5.89 (m, 1 H)

Preparation of *tert*-butyl allyl(2-oxoethyl)carbamate i-(3)

To a solution of crude methyl 2-(allyl(*tert*-butoxycarbonyl)amino)acetate i-(2) (132.4 g) in dichloromethane (2.1 L) at -78°C was added DIBAL-H (1M in dichloromethane; 750 ml) keeping the internal temperature below -70°C. Once the reaction appeared to be going no further by tlc, the reaction mixture was quenched quickly with aqueous sodium hydroxide (2M; 1.8 L, diluted with water (2.7 L) and dichloromethane (900 ml) and the organic layer removed and washed with

water/saturated aqueous sodium chloride (4.5 L). The organic layer was dried (Na_2SO_4) and evaporated to afford the title compound (112.0 g) as a pale yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.35 - 1.55 (m, 9 H) 3.76 - 4.08 (m, 4 H) 4.97 - 5.26 (m, 2 H) 5.62 - 5.96 (m, 1 H) 9.56 (br. s., 1 H)

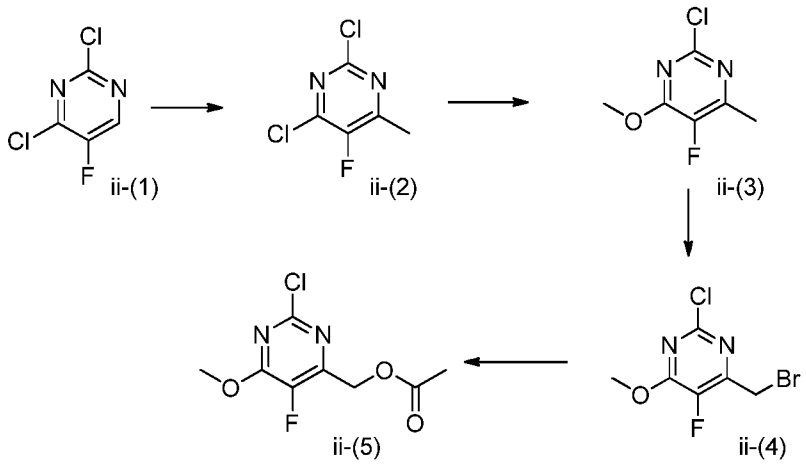
Preparation of *tert*-butyl allyl(2-(hydroxyimino)ethyl)carbamate i-(4)

To a solution of crude *tert*-butyl allyl(2-oxoethyl)carbamate i-(3) (112 g) in dichloromethane (800 ml) and methanol (400 ml) was added sodium acetate (130 g) and hydroxylamine hydrochloride (110 g) and the mixture stirred at room temperature for eighteen hours. The reaction mixture was poured into water (2000 ml), the organic layer removed and the aqueous extracted with dichloromethane (1000 ml). The combined organic layer was dried (Na_2SO_4) and evaporated to afford the title compound (118.83 g) as a pale yellow oil (mixture of isomers).
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.37 - 1.56 (m, 9 H) 3.75 - 4.28 (m, 4 H) 4.97 - 5.28 (m, 2 H) 5.59 - 5.99 (m, 1 H), 6.74 & 7.38 (2 x br s, 1 H in total).

Preparation of *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate i-(5)

To a solution of crude *tert*-butyl allyl(2-(hydroxyimino)ethyl)carbamate i-(4) (118.8 g) in dichloromethane (1200 ml) was added dropwise over sixty minutes, 15% aqueous sodium hypochlorite (450 ml). The reaction was allowed to stir for one hour. The reaction mixture was poured into water (1200 ml) and dichloromethane (400 ml) and the organic layer removed, the aqueous was extracted with dichloromethane (800 ml) and the combined organic layer washed with aqueous saturated sodium chloride. The organic layer was dried (Na_2SO_4) and evaporated to afford a yellow oily solid (113.4 g), which was then purified by silica gel column chromatography with eluant 5 to 30% ethyl acetate / hexane. The residue was stirred in hexane (300 ml) and seeded to give a crystalline solid which was refrigerated overnight then filtered off and washed with fresh cold hexane to afford the title compound (61.67 g) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9 H) 3.05 - 3.24 (m, 1 H) 3.80 - 4.31 (m, 5 H) 4.50 - 4.73 (m, 1 H)

Preparation of common intermediates ii-(3) and ii-(5): 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine and (2-chloro-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate



Preparation of 2,4-dichloro-5-fluoro-6-methylpyrimidine ii-(2)

To a solution of 1.0M methylmagnesium bromide in tetrahydrofuran (270 ml) at 0°C under nitrogen was added 2,4-dichloro-5-fluoropyrimidine (30 g) in 1,2-dimethoxyethane (90 ml) dropwise maintaining the temperature below 15°C. The resulting solution was stirred at ~15°C for one hour then cooled to 0°C. A solution of triethylamine (25 ml) in dry tetrahydrofuran (40 ml) was added maintaining the temperature at ~5°C, followed by a solution of iodine (45.6 g) in dry tetrahydrofuran (140 ml) maintaining the temperature below 15°C. The reaction was quenched with water (400 ml) maintaining the temperature below 25°C and treated with 5N aqueous hydrochloric acid solution (30 ml). The mixture was extracted with diethyl ether (2 x 500 ml) and the combined organic layer was washed with 2% w/w aqueous sodium metabisulfite (400 ml) and water (400 ml) then dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (gradient from 0 to 5% ethyl acetate / hexane) to afford the title compound (16.8 g) as an orange oil which was used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.57 (d, *J*=2.81 Hz, 3 H)

Preparation of 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine ii-(3)

To a solution of 2,4-dichloro-5-fluoro-6-methylpyrimidine (16.8 g;crude material) in dry tetrahydrofuran (170 ml) at 0°C under nitrogen was added dropwise 25%w/w sodium methoxide in methanol (21 ml equivalent to ~5g). After ten minutes at 0°C, the reaction mixture was poured into water (500 ml) and extracted with diethyl ether (250 ml). The organic layer was washed with water then dried ($MgSO_4$) and evaporated and the residue purified by preparative HPLC. The pure fractions were

combined, aqueous saturated sodium bicarbonate added and the aqueous extracted with diethyl ether. The organic layer was washed with water and then dried ($MgSO_4$) and carefully evaporated to afford the title compound (5.68 g) as a white crystalline solid.
LCMS (Method A2): Rt 1.11 min, m/z 177/179 $[M+H]^+$.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (d, *J*=2.93 Hz, 3 H) 4.08 (s, 3 H)

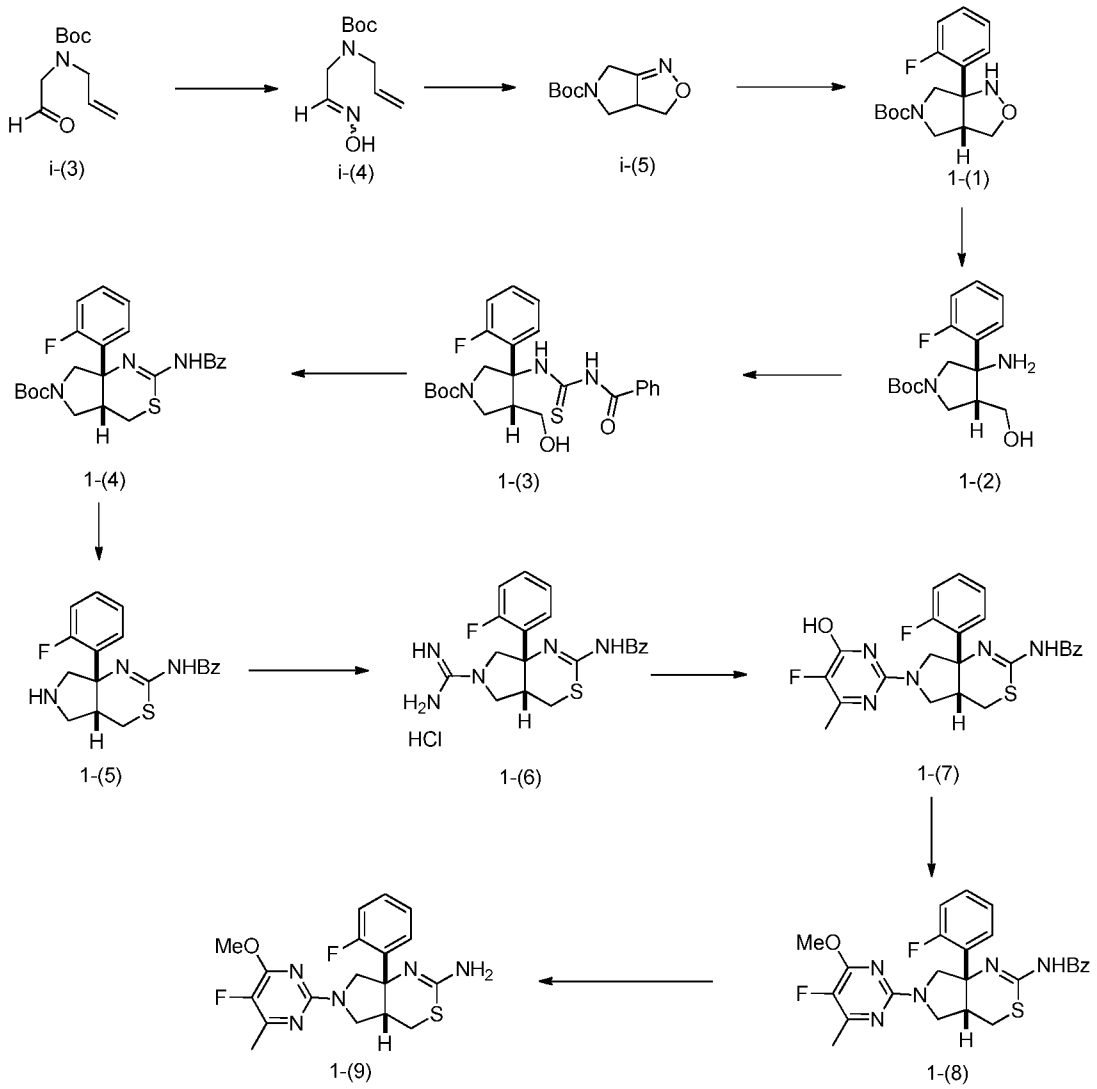
Preparation of 4-(bromomethyl)-2-chloro-5-fluoro-6-methoxypyrimidine ii-(4)

To a solution of 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine (2 g) in carbon tetrachloride (24 ml) was added AIBN (0.2 g) and NBS (6 g) and the reaction mixture stirred under reflux for twenty six hours then allowed to cool overnight. The reaction mixture was poured into cold water and extracted with dichloromethane (2 x 100 ml); the combined organic layer was washed with water and brine then dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether / hexane and a white solid filtered off and the filtrate evaporated to give the title compound (2.61 g) which contained an approximately 1:3 mixture of 4-(bromomethyl)-2-chloro-5-fluoro-6-methoxypyrimidine : 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine.

Preparation of (2-chloro-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate ii-(5)

A 1:3 mixture of 4-(bromomethyl)-2-chloro-5-fluoro-6-methoxypyrimidine : 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine (2.61 g) was dissolved in dry acetonitrile (10 ml) and sodium acetate (0.3 g) added. The reaction mixture was heated at 90°C for seventeen hours then the reaction mixture was cooled and poured into cold water and extracted with dichloromethane (100 ml). The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by silica gel column chromatography (gradient from 0 to 10% ethyl acetate / hexane) to afford the title compound (0.455 g) as an oil.
LCMS: Rt 1.34 min, m/z 235 $[M+H]^+$.
As reported in WO 2009/131975, page 182.

Example 1: (±)-(4aR*,7aS*)-6-(5-Fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 1-(9)



i-(4) Synthesis of tert-butyl allyl(2-(hydroxyimino)ethyl)carbamate

To *tert*-butyl allyl(2-oxoethyl)carbamate i-(3) (41.62 g, synthesized according to the procedure of S. Schleich & G. Helmchen, *Eur. J. Org. Chem*, **1999**, 2515, and used without purification, purity approx. 75%) in ethanol (400 mL) and water (100 mL) was added hydroxylamine hydrochloride (13.87 g) followed by sodium acetate (20.81 g) and the reaction mixture was allowed to stir at room temperature for 20 h. Water (200 mL) and brine (200 mL) were then added, and the mixture was extracted with ethyl acetate (2 x 300 mL). The combined organic portions were dried over $MgSO_4$ and evaporated to afford i-(4) (44.6 g, approx. purity 75%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.48 (s, 9 H), 3.71 – 4.25 (m, 4 H), 5.08 – 5.23 (m, 2 H), 5.70 – 5.86 (m, 1 H), 6.75 & 7.40 (2 x br s, 1 H in total).

i-(5) Synthesis of *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate

To a refluxing solution of tert-butyl allyl(2-(hydroxyimino)ethyl)carbamate, i-(4), (40.01 g, approx purity 75%) in dichloromethane (700 mL) was added sodium hypochlorite (100 mL, 15% available chlorine solution in water) dropwise over 2 h. The reaction mixture was stirred at reflux for 18 h, and then a further 50 mL of the above sodium hypochlorite solution was added dropwise over 15 mins. After stirring at reflux for a further 7 h, the mixture was cooled and water (200 mL) was added, followed by sodium bisulfite (100 g). The biphasic mixture was stirred vigorously for 30 min, the layers separated and the aqueous layer further extracted with dichloromethane (2 x 200 mL). The combined organic portions were then concentrated and the residue was purified by silica gel column chromatography (gradient from 0% to 25% EtOAc in Hexanes) to obtain the title compound (20.51 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (s, 9 H), 3.08 – 3.22 (m, 1 H), 3.84 – 4.25 (m, 5 H), 4.56 – 4.68 (m, 1 H).

1-(1) Synthesis of (±)- (3aR*,6aS*)-tert-butyl 6a-(2-fluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

A solution of 1-bromo-2-fluorobenzene (20.9 mL) in THF (50 mL) and toluene (250 mL) was cooled to -78°C. *n*-Butyl lithium (121 mL, 1.6N in hexanes) was then added dropwise over 18 min keeping the internal temperature below -75°C. After stirring for 1h at -78°C, boron trifluoride etherate (24.2 mL, 191.288 mmol) was added dropwise over 5 min keeping the internal temperature below -75°C. *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, i-(5), (20.3 g) was then added dropwise over 15 min as a solution in 100 mL THF, keeping the internal temperature below -72°C. After stirring at -78°C for a further 3h, the reaction was quenched by the addition of sat. aq. NH_4Cl (200 mL) and allowed to warm slowly to room temperature and stir overnight. Brine (200 mL) was then added and the mixture was extracted with EtOAc (3 x 400 mL). The combined organic portions were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography (gradient from 0% to 25% EtOAc in Hexanes) to obtain the title compound (9.37 g).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (s, 9 H) 3.26 - 3.39 (m, 1 H) 3.53 - 3.83 (m, 5 H), 4.45 (t, *J*=8.4 Hz, 1 H) 7.08 (ddd, *J*=11.8, 8.1, 1.1 Hz, 1 H) 7.17 (td, *J*=7.6, 1.2 Hz, 1 H) 7.25 - 7.35 (m, 1 H) 7.88 (t, *J*=7.4 Hz, 1 H)

1-(2) Synthesis of (±)-(3S*,4R*)-tert-butyl 3-amino-3-(2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a solution of (±)-(3aR*,6aS*)-tert-butyl 6a-(2-fluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate, obtained in preparation example 1-(1), (9.37 g) in acetic acid (80 mL) was added zinc powder (5 g) portionwise over 5 mins. The reaction mixture was stirred at room temperature for 18 h and then filtered through celite, washing with EtOAc (400 mL). The mixture was then evaporated and $NaHCO_3$ (sat., aq., 100 mL) was added carefully. The mixture was then extracted with EtOAc (3 x 200 mL), dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (gradient from 0% to 5% MeOH in EtOAc:DCM 1:1) to obtain the title compound (7.24 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 2.19 (br s, 3 H) 2.78 – 2.88 (m, 1 H) 3.46 - 3.69 (m, 3 H) 3.85 (d, *J*=4.8 Hz, 2 H) 3.88 - 4.04 (m, 1 H) 7.11 (ddd, *J*=12.6, 8.2, 1.2 Hz, 1 H) 7.18 (td, *J*=7.6, 1.2 Hz, 1 H) 7.29 - 7.36 (m, 1 H) 7.47 (td, *J*=8.1, 1.5 Hz, 1 H).

1-(3) Synthesis of (±)-(3S*,4R*)-tert-butyl 3-(3-benzoylthioureido)-3-(2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

(±)-(3S*,4R*)-tert-Butyl 3-amino-3-(2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate, obtained in preparation example 1-(2), (7.24 g) was dissolved in DCM (100 mL) and benzoyl isothiocyanate (4.0 mL) was added dropwise over 10 min. After stirring for 18 h, the reaction mixture was concentrated to *ca*. 20 mL and purified by silica gel column chromatography (gradient from 0% to 50% EtOAc in hexanes) to obtain the title compound (8.72 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.51 (s, 9 H) 3.04 – 3.15 (m, 1 H) 3.38 - 3.59 (m, 2 H) 3.86 – 3.95 (m, 1 H) 4.01 - 4.21 (m, 2 H) 4.52 – 4.65 (m, 1 H) 7.06 (dd, *J*=11.9, 8.6 Hz, 1 H) 7.11 - 7.22 (m, 1 H) 7.22 - 7.38 (m, 1 H) 7.53 (t, *J*=7.6 Hz, 3 H) 7.64 (t, *J*=7.5 Hz, 1 H) 7.80 - 7.91 (m, 2 H), 8.86 (s, 1 H), 11.76 – 11.90 (m, 1 H).

1-(4) Synthesis of (±)-(4aR*,7aS*)-tert-butyl 2-benzamido-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

(±)-(3S*,4R*)-tert-Butyl 3-(3-benzoylthioureido)-3-(2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate, obtained in preparation example 1-(3), (8.72 g) was dissolved in DCM (70 mL) and pyridine (7.0 mL) was added. After cooling to -10°C, triflic anhydride (5.0 mL) was added dropwise over 30 min, and the reaction mixture was allowed to stir at -10°C for 2 hours. $NaHCO_3$ (sat. aq., 100 mL) was then added cautiously and the mixture was extracted with DCM (2 x 150 mL). The combined organic portions were dried over $MgSO_4$, concentrated, and purified by silica gel

column chromatography (gradient from 0% to 40% EtOAc in hexanes) to obtain the title compound (5.76 g).
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 2.84 – 2.99 (m, 1 H) 3.05 - 3.17 (m, 1 H) 3.38 – 3.49 (m, 1 H) 3.67 - 3.88 (m, 3 H) 4.06 - 4.23 (m, 1 H) 7.11 - 7.59 (m, 7 H) 8.14 – 8.28 (m, 2 H).

1-(5) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-(4aR*,7aS*)-tert-Butyl 2-benzamido-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate, obtained in preparation example 1-(4), (5.40 g) was dissolved in DCM (20 mL) and trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 h, concentrated, and $NaHCO_3$ (sat. aq., 50 mL) was added. The mixture was then extracted with EtOAc (3 x 75 mL). The combined organic portions were dried over $MgSO_4$ and concentrated to afford the title compound (5.18 g, purity approx. 90%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.83 (dd, *J*=13.7, 3.5 Hz, 1 H) 3.07 (dd, *J*=13.7, 3.3 Hz, 1 H) 3.34 - 3.51 (m, 2 H) 3.54 - 3.70 (m, 2 H) 4.02 (d, *J*=11.2 Hz, 1 H) 7.09 - 7.16 (m, 1 H) 7.17 - 7.23 (m, 1 H) 7.28 - 7.41 (m, 2 H) 7.46 (t, *J*=7.5 Hz, 2 H) 7.56 (t, *J*=7.3 Hz, 1 H) 8.01 (d, *J*=7.5 Hz, 2 H)

1-(6) Synthesis of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride salt

(±)-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, obtained in preparation example 1-(5), (2.66 g) was dissolved in DMF (20 mL). 1H-Pyrazole-1-carboxamidine hydrochloride (1.12 g) was added followed by diisopropylamine (1.12 mL) dropwise. The reaction mixture was stirred for 3 h at room temperature and concentrated. Diethyl ether (100 mL) was added and the mixture was stirred vigorously overnight. The supernatant was poured off, and the tacky solid was dissolved in DCM (50 mL). Hexane (100 mL) was added, and the mixture was concentrated to ca. 100 mL. The mixture was then filtered to afford the title compound as a white powder (3.16g, purity approx. 90%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.81 (dd, *J*=13.8, 3.6 Hz, 1 H) 2.94 - 3.04 (m, 1 H) 3.31 - 3.53 (m, 2 H) 3.86 (d, *J*=9.4 Hz, 2 H) 4.28 (d, *J*=10.4 Hz, 1 H) 7.03 - 7.49 (m, 7 H) 8.02 (d, *J*=7.2 Hz, 2 H).

1-(7) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-N-((4aR*,7aS*)-6-Carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride salt, obtained in preparation example 1-(6), (3.12 g) was dissolved in ethanol (30 mL) and ethyl 2-fluoroacetate (0.95 mL) was added, followed by sodium ethoxide (4.78 g of a 21% w/w solution in ethanol). The reaction mixture was heated to 60°C and stirred for 1 h. The mixture was then diluted with brine (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic portions were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (gradient from 0% to 60% EtOAc in DCM) to obtain the title compound (1.88 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.19 (d, *J*=3.4 Hz, 3 H) 2.90 - 3.00 (m, 1 H) 3.13 (dd, *J*=13.5, 3.5 Hz, 1 H) 3.48 – 3.59 (m, 1 H) 3.85 - 4.03 (m, 3 H) 4.32 (d, *J*=11.5 Hz, 1 H) 7.08 - 7.25 (m, 2 H) 7.34 - 7.47 (m, 4 H) 7.48 - 7.55 (m, 1 H) 8.09 (d, *J*=6.5 Hz, 2 H)

1-(8) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-N-((4aR*,7aS*)-6-(5-Fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide obtained in preparation example 1-(7) (650 mg) was dissolved in DMF (3 mL) and potassium carbonate (280 mg) was added, followed by the dropwise addition of methyl iodide (192 mg) as a solution in DMF (2 mL). After stirring at room temperature for 1 h, water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic portions were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (gradient from 15% to 20% EtOAc in hexanes) to obtain the title compound (497 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.29 (d, *J*=2.8 Hz, 3 H) 2.98 (d, *J*=12.8 Hz, 1 H) 3.11 – 3.25 (m, 1 H) 3.48 – 3.64 (m, 1 H) 3.91 - 4.06 (m, 3 H), 3.97 (s, 3 H), 4.31 (d, *J*=12.0 Hz, 1 H) 7.10 - 7.25 (m, 2 H) 7.33 - 7.55 (m, 5 H) 8.11 – 8.25 (m, 2 H)

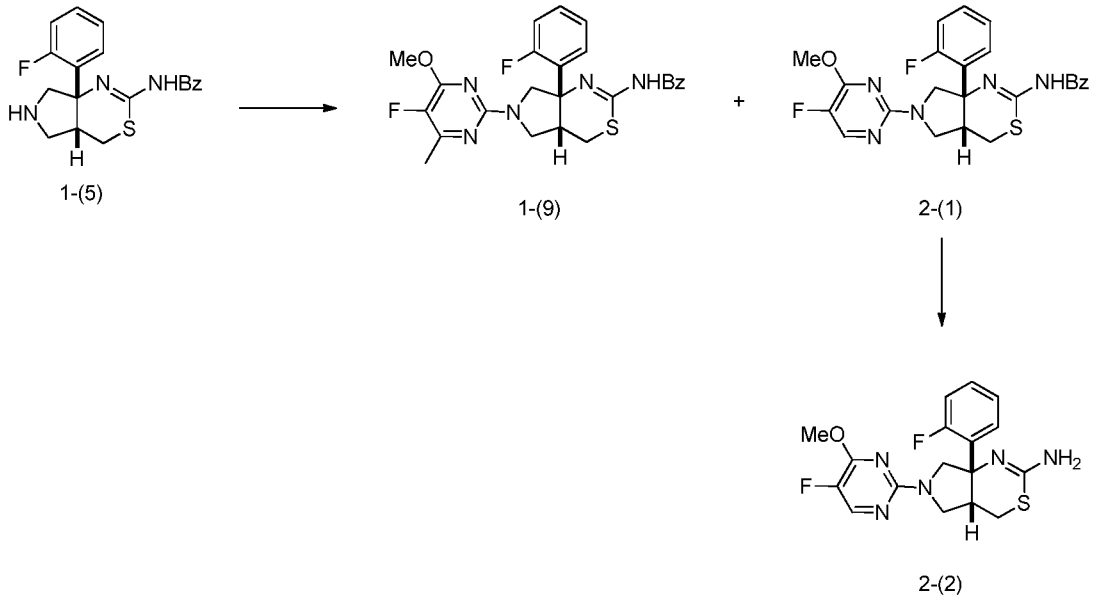
1-(9) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 1)

(±)-N-((4aR*,7aS*)-6-(5-Fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, obtained in preparation example 1-(8), (960 mg) was dissolved in methanol (10 mL) and 1,8-diazabicycloundec-7-ene (1.0 mL) was added. The reaction mixture was heated to reflux and stirred for 90 min, concentrated, and purified by silica gel column

chromatography (Method G2, gradient from 0% to 30% EtOAc in hexanes) to obtain the title compound (690 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.29 (d, *J*=2.9 Hz, 3 H) 2.94 (dd, *J*=13.0, 5.2 Hz, 1 H) 3.02 (dd, *J*=13.0, 4.0 Hz, 1 H) 3.14 - 3.23 (m, 1 H) 3.69 - 3.79 (m, 2 H) 3.81 (dd, *J*=11.2, 2.4 Hz, 1 H) 3.95 (s, 3H) 4.34 (d, *J*=11.1 Hz, 1 H) 4.42 (br. s., 2 H) 7.05 (ddd, *J*=12.6, 8.1, 1.1 Hz, 1 H) 7.09 - 7.15 (m, 1 H) 7.23 - 7.30 (m, 1 H) 7.32 - 7.38 (m, 1 H).

Example 2: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



2-(1) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (alternative route) and synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, obtained in preparation example 1-(5), (231 mg) in degassed 1,4-dioxane (2 mL), was added 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine, as obtained in preparation ii-(3), (173 mg, approx. purity 75%, remainder 2-chloro-5-fluoro-4-methoxypyrimidine), diacetoxypalladium (15 mg), 2-Di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl (23 mg) and sodium *tert*-butoxide (94 mg). The reaction mixture was irradiated in a microwave reactor for 20mins at 125°C with cooling. The reaction mixture was then cooled, diluted with water, and extracted with EtOAc (3 x 40 mL). The combined organic portions were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography silica, gradient from 0% to 20% EtOAc in hexanes) to obtain firstly (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-

methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 1-(9), (32 mg), data as above, and secondly (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 2-(1), (12 mg).

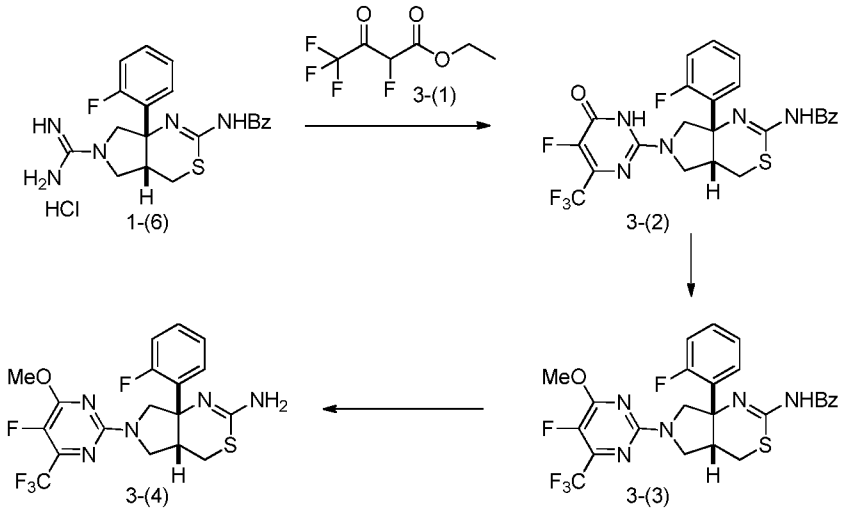
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 3.00 (dd, *J*=13.7, 4.3 Hz, 1 H) 3.19 (dd, *J*=13.6, 3.9 Hz, 1 H) 3.52 – 3.62 (m., 1 H) 3.92 - 4.08 (m, 6 H), 4.34 (d, *J*=12.0 Hz, 1 H) 7.11 - 7.28 (m, 2 H) 7.35 - 7.60 (m, 5 H) 7.98 (d, *J*=3.1 Hz, 1 H) 8.17 (d, *J*=6.8 Hz, 2 H)

2-(2) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 2)

To a solution of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (12 mg) in methanol (1 ml) was added 1,8-diazabicycloundec-7-ene (15 mg). The reaction mixture was heated to reflux and stirred for 2 h, concentrated, and purified by silica gel column chromatography (Method G2, gradient from 0% to 40% EtOAc in hexanes) to obtain the title compound (7.6 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.93 - 3.02 (m, 1 H) 3.02 - 3.12 (m, 1 H) 3.20 – 3.32 (m, 1 H) 3.73 – 4.10 (m, 6 H), 4.36 (d, *J*=11.2 Hz, 1 H) 7.08 (dd, *J*=12.6, 8.1 Hz, 1 H) 7.12 - 7.21 (m, 1 H) 7.25 - 7.44 (m, 2 H) 7.98 (d, *J*=3.2 Hz, 1 H).

Example 3: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



3-(1) Synthesis of ethyl 2,4,4,4-tetrafluoro-3-oxobutanoate

To a solution of ethyltrifluoroacetate (13.4 g) in dry tetrahydrofuran (25 mL) was added 60% sodium hydride (1.89 g) and the mixture heated to 50°C. Ethyl fluoroacetate (5 g) was then added dropwise over fifteen minutes and the reaction mixture stirred at 50°C for two hours, then cooled and poured into ice (25 g)/concentrated sulfuric acid (2.5 mL). The aqueous layer was extracted with ethyl acetate (100 mL) and the organic layer washed with water (50 mL) and aqueous saturated sodium chloride (50 mL) then dried (Na_2SO_4) and evaporated. The residue was dissolved in dichloromethane, applied to a 340 g SNAP KP-Si column and purified on the Biotage Isolera 4 eluting with 5 to 35% ethyl acetate / hexane over 10 column volumes to afford the title compound (6.2 g) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.38 (t, 3 H) 4.41 (q, *J*=7.09 Hz, 2 H) 5.06 (d, 1 H).

3-(2) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, prepared as described in preparation example 1-(6), (0.402 g) in ethanol (5 mL) was added ethyl 2,4,4,4-tetrafluoro-3-oxobutanoate (0.7 g) followed by sodium ethoxide (1.2 mL, 21% in ethanol) and the mixture refluxed for four hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with aqueous saturated sodium bicarbonate solution (25 mL) and water (25 mL) then dried ($MgSO_4$) and evaporated.The residue was dissolved in dichloromethane and applied to a 25g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 100% ethyl acetate / hexane over 10 column volumes to afford the title compound (0.195 g) as an off-white solid.

LCMS: Rt 1.66 min, m/z 536 [M+H]+.

3-(3) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-6-(5-fluoro-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.186 g) in N,N-dimethylformamide (2 mL) was added potassium carbonate (0.072 g) followed by a solution of methyl iodide (0.02 mL) in N,N-dimethylformamide (2 mL) and the mixture stirred at room temperature for ninety minutes. The reaction mixture was diluted with ethyl acetate (50 mL), washed with

water (2 x 25 mL) then dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane and applied to a 10 g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 30% ethyl acetate / hexane over 10 column volumes to afford the title compound (0.06 g) as a white solid.

LCMS: Rt 1.95 min, m/z 550 $[M+H]^+$.

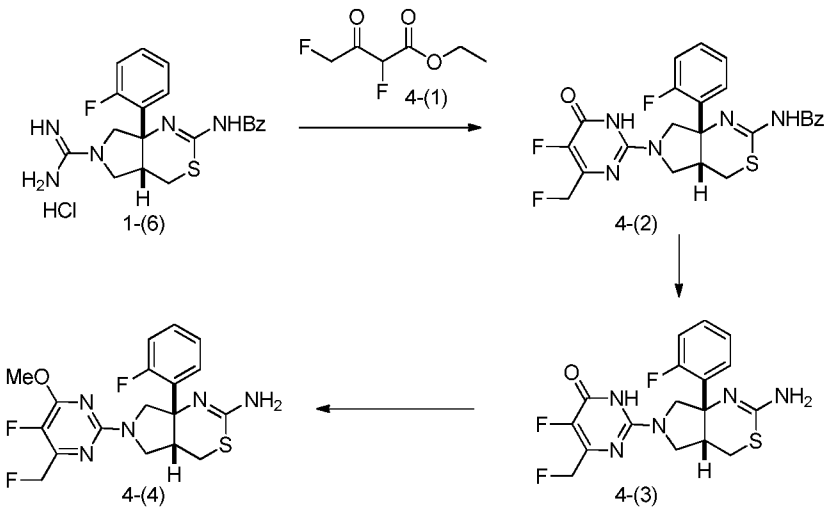
3-(4) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 3)

To a solution of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.056 g) in methanol (0.5 mL) was added DBU (0.05 mL) and the reaction mixture stirred at 80°C for three hours then cooled and diluted with ethyl acetate (40 mL). The organic layer was washed with water (3 x 20 mL) then dried ($MgSO_4$) and evaporated. The residue was purified by SCX (1 g) to afford the title compound (0.041 g) as a white solid.

LCMS: Rt 1.36 min, m/z 446 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 - 2.95 (m, 1 H) 2.98 - 3.23 (m, 2 H) 3.79 (m, 3 H) 3.91 - 4.18 (m, 4 H) 6.15 (br. s., 2 H) 7.11 - 7.29 (m, 2 H) 7.36 (dd, J=7.70, 4.28 Hz, 2 H).

Example 4: (±)-(4aR*,7aS*)-6-(5-fluoro-4-(fluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



4-(1) Synthesis of ethyl 2,4-difluoro-3-oxobutanoate

To a mixture of 60% sodium hydride (1.89 g) in dry diethyl ether (100 ml) at room temperature was added dropwise ethyl fluoroacetate (10 g) and then the reaction mixture stirred at 40°C for four hours then cooled and poured into ice (25 g)/concentrated sulfuric acid (2.5 ml). The aqueous layer was extracted with diethyl ether (2 x 100 ml) and the combined organic layer dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (gradient from 10 to 30% ethyl acetate / hexane) to afford the title compound (3.8 g) as a very pale yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 3 H) 4.24 (q, 2 H) 5.32 (d, *J*=46.34 Hz, 2 H) 5.94 (d, *J*=46.09 Hz, 1 H).

4-(2) Synthesis of rac-N-((4aR*,7aS*)-6-(5-fluoro-4-(fluoromethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a mixture of rac-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, prepared as described in preparation example 1-(6), (assumed 0.305 g) in ethanol (5 ml) was added ethyl 2,4-difluoro-3-oxobutanoate (0.26 g) followed by sodium ethoxide (0.525ml, 21% in ethanol) and the mixture refluxed for one hour. The reaction mixture was diluted with ethyl acetate (50 ml), washed with aqueous saturated sodium bicarbonate solution (25 ml) and water (25ml) then dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (gradient from 0 to 100% ethyl acetate / hexane) to afford the title compound (0.24 g) as a pale yellow solid. LCMS: Rt 1.45 min, m/z 500 $[M+H]^+$.

4-(3) Synthesis of rac-2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-(fluoromethyl)pyrimidin-4(3H)-one

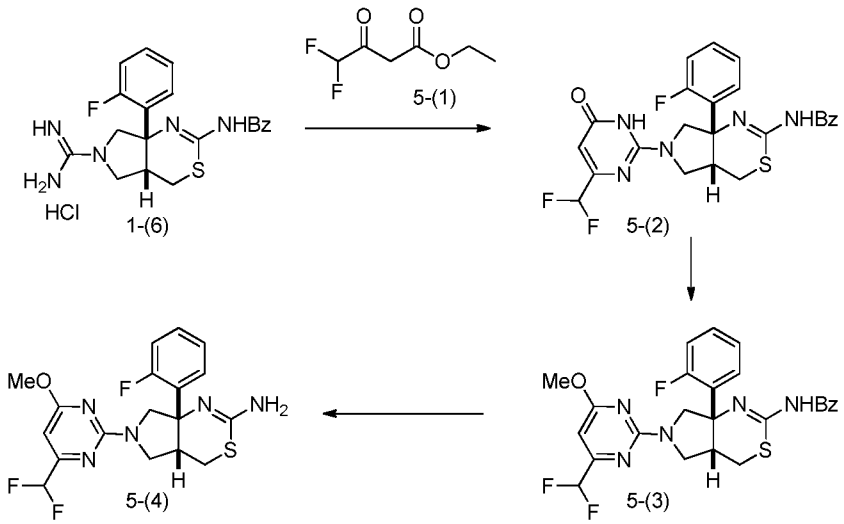
To a solution of rac-N-((4aR*,7aS*)-6-(5-fluoro-4-(fluoromethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.23 g) in methanol (4 ml) was added potassium carbonate (0.127 g) and the mixture heated at 60°C for three hours then cooled, loaded onto an SCX column (10 g) and purified to afford the title compound (0.157 g) as a pale yellow solid.
LCMS: Rt 0.88 min, m/z 396 $[M+H]^+$.

4-(4) Synthesis of rac-(4aR*,7aS*)-6-(5-fluoro-4-(fluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 4)

To a solution of rac-2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-(fluoromethyl)pyrimidin-4(3H)-one (0.15 g) in N'N-dimethylformamide (2 ml) was added potassium carbonate (0.105 g) followed by a solution of methyl iodide (0.03 ml) in N,N-dimethylformamide(2 ml) and the mixture stirred at room temperature for two hours then diluted with ethyl acetate (40 ml). The organic layer was washed with water (3 x 30ml) then dried ($MgSO_4$) and evaporated. The residue was purified by preparative HPLC and isolated by SCX (5 g) to afford the title compound (0.092 g) as a white foam. LCMS: Rt 1.15 min, m/z 410 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.80 - 2.93 (m, 1 H) 2.98 - 3.16 (m, 2 H) 3.51 - 3.82 (m, 3 H) 3.87 - 4.01 (m, 3 H) 4.02 - 4.15 (m, 1 H) 5.20 - 5.31 (m, 1 H) 5.33 - 5.47 (m, 1 H) 6.11 (s, 2 H) 7.13 - 7.27 (m, 2 H) 7.29 - 7.44 (m, 2 H)

Example 5: (±)-(4aR*,7aS*)-6-(4-(difluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



5-(2) Synthesis of (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Obtained as a pale yellow solid (0.39 g) following an analogous procedure to that used to prepare compound 1-(7) as described in Example 1, starting from (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride (0.61 g), prepared

as described in preparation example 1-(6), and ethyl 4,4-difluoro-3-oxobutanoate (0.52 g)

LCMS: Rt 1.50 min, m/z 500[M+H]+.

5-(3) Synthesis of (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.1 g), obtained in example 5-(2), the title compound (0.076g) was synthesised following an analogous procedure to that used to prepare compound 1-(8) as described in Example 1.

LCMS: Rt 1.86 min, m/z 514 [M+H]+.

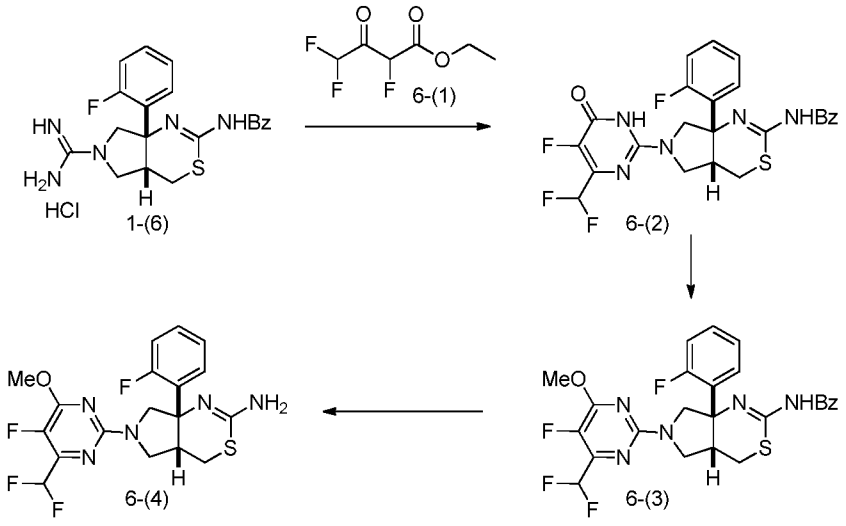
5-(4) Synthesis of (±)-(4aR*,7aS*)-6-(4-(difluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 5)

Starting from (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.07 g), obtained in example 5-(3), the title compound (0.056 g) was synthesized following an analogous procedure to that used to prepare compound 1-(9) as described in Example 1.

LCMS: Rt 1.19 min, m/z 410 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.77 - 2.96 (m, 1 H) 2.97 - 3.21 (m, 2 H) 3.54 - 3.98 (m, 6 H) 4.02 - 4.20 (m, 1 H) 6.12 (br. s., 2 H) 6.25 (s, 1 H) 6.44 - 6.85 (m, 1 H) 7.13 - 7.27 (m, 2 H) 7.28 - 7.44 (m, 2 H)

Example 6: (±)-(4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



6-(1) Synthesis of ethyl 2,4,4-trifluoro-3-oxobutanoate

To a solution of ethyl 2,2-difluoroacetate (11.7 g) in dry tetrahydrofuran (25 ml) was added 60% sodium hydride (1.89 g) and the mixture heated to 50°C. Ethyl fluoroacetate (5 g) was then added dropwise over fifteen minutes and the reaction mixture stirred at 50°C for two hours, then cooled and poured into ice (25 g)/concentrated sulfuric acid (2.5 ml). The aqueous layer was extracted with ethyl acetate (100 ml) and the organic layer washed with water (50 ml) and aqueous saturated sodium chloride (50 ml) then dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (gradient from 5 to 40% ethyl acetate / hexane) to afford the title compound (9 g) as a colourless oil.

6-(2) Synthesis of (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride (0.61 g), prepared as described in preparation example 1-(6), and ethyl 2,4,4-trifluoro-3-oxobutanoate (0.6 g) the title compound (0.5 g) was synthesised following an analogous procedure to that used to prepare compound 1-(7) as described in Example 1.
LCMS: Rt 1.55 min, m/z 518 [M+H]+.

6-(3) Synthesis of (±)- N-((4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.1 g), obtained in example 6-(2), the title compound (0.054 g) was synthesised following an analogous procedure to that used to prepare compound 1-(8) as described in Example 1.
LCMS: Rt 1.86 min, m/z 532 [M+H]+.

6-(4) Synthesis of (±)-(4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 6)

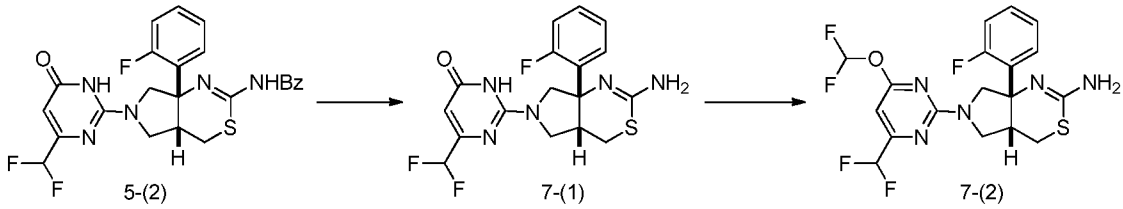
Starting from (±)- N-((4aR*,7aS*)-6-(4-(difluoromethyl)-5-fluoro-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-

d][1,3]thiazin-2-yl)benzamide (0.047 g), obtained in example 6-(3), the title compound (0.031 g) was synthesised following an analogous procedure to that used to prepare compound 1-(9) as described in Example 1.

LCMS: Rt 1.18 min, m/z 428 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.79 - 2.94 (m, 1 H) 2.96 - 3.21 (m, 2 H) 3.50 - 3.85 (m, 3 H) 3.87 - 4.23 (m, 4 H) 6.13 (br. s., 2 H) 6.67 - 7.09 (m, 1 H) 7.12 - 7.29 (m, 2 H) 7.30 - 7.45 (m, 2 H)

Example 7: (±)-(4aR*,7aS*)-6-(4-(difluoromethoxy)-6-(difluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



7-(1) Synthesis of rac-2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-6-(difluoromethyl)pyrimidin-4(3H)-one

To a solution of rac-N-((4aR*,7aS*)-6-(4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.17 g), obtained in example 5-(2), in methanol (4 ml) was added potassium carbonate (0.094g) and the mixture heated at 60°C for three hours then cooled, loaded onto an SCX column (5 g) and purified to afford the title compound (0.126g) as a white solid.

LCMS: Rt 0.94 min, m/z 396 $[M+H]^+$.

7-(2) Synthesis of rac-(4aR*,7aS*)-6-(4-(difluoromethoxy)-6-(difluoromethyl)pyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 7)

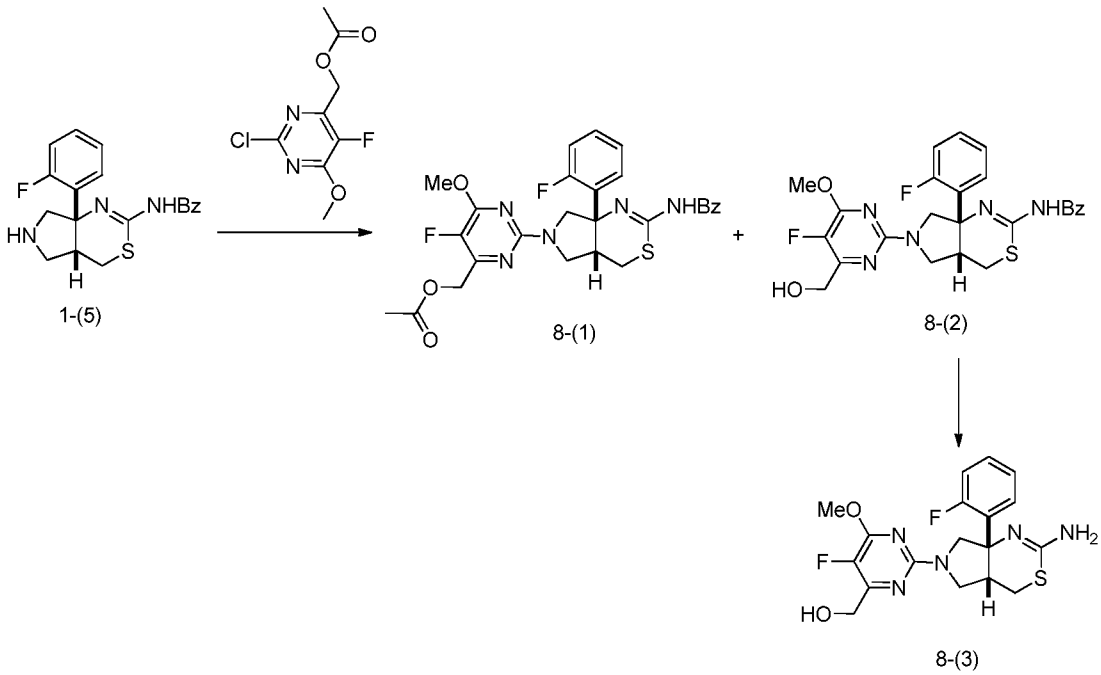
To a suspension of rac-2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-6-(difluoromethyl)pyrimidin-4(3H)-one (0.12 g), obtained in example 7-(1), in acetonitrile (3 ml) was added sodium carbonate (0.064 g) followed by 2-(fluorosulfonyl)difluoroacetic acid (0.038 ml) and the mixture stirred at room temperature for fifteen minutes then 2-(fluorosulfonyl)difluoroacetic acid (0.038 ml) added and stirred at room temperature for a further fifteen minutes.The reaction mixture was loaded onto an SCX column (5 g) and partially purified, then

purified by preparative HPLC and isolated by SCX (5 g) to afford the title compound (0.028 g) as a white solid.

LCMS: Rt 1.24 min, m/z 446 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.80 - 2.96 (m, 1 H) 2.99 - 3.11 (m, 1 H) 3.11 - 3.22 (m, 1 H) 3.63 (t, *J*=10.33 Hz, 1 H) 3.71 - 3.88 (m, 2 H) 4.06 - 4.19 (m, 1 H) 6.15 (br. s, 2 H) 6.50 (d, *J*=3.18 Hz, 1 H) 6.73 (td, *J*=54.41, 11.25 Hz, 1 H) 7.15 - 7.29 (m, 2 H) 7.31 - 7.44 (m, 2 H) 7.85 (td, *J*=72.01, 4.77 Hz, 1 H)

Example 8: (±)-(2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methanol



8-(2) Synthesis of rac-(2-((4aR*,7aS*)-2-benzamido-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate

A mixture of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.53 g) obtained in example 1-(5), (2-chloro-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate (0.455g) obtained in example ii-(5), 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl (0.028 g), palladium (II) acetate (0.017 g) and sodium tert-butoxide (0.315 g) in anhydrous toluene (5ml) was stirred at 100°C for twenty hours. The reaction mixture was diluted with ethyl acetate (100 ml) and washed with water (2 x 20 ml) then dried ($MgSO_4$) and evaporated to a brown foam (0.85 g) that contained rac-(2-((4aR*,7aS*)-2-benzamido-

7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate and rac-N-((4aR*,7aS*)-6-(5-fluoro-4-(hydroxymethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide and was used in the next step with purification.

LCMS: Rt 1.79 min, m/z 554 $[M+H]^+$.

LCMS: Rt 1.64 min, m/z 512 $[M+H]^+$.

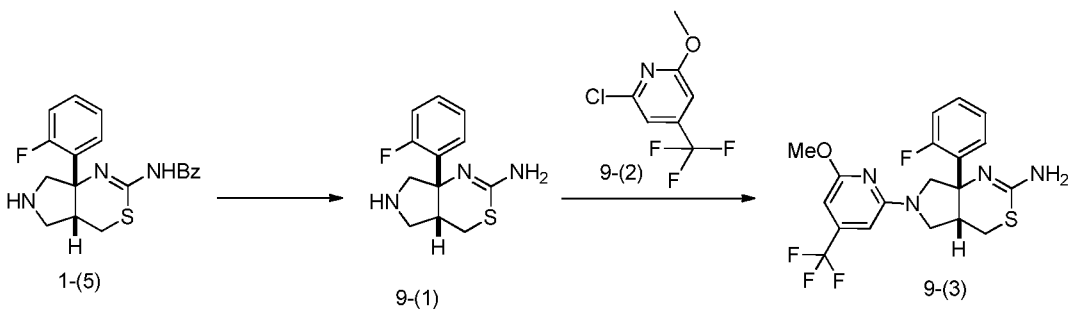
8-(3) Synthesis of rac-(2-((4aR*,7aS*)-2-amino-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methanol (Example 8)

A mixture of rac-(2-((4aR*,7aS*)-2-benzamido-7a-(2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methoxypyrimidin-4-yl)methyl acetate, rac-N-((4aR*,7aS*)-6-(5-fluoro-4-(hydroxymethyl)-6-methoxypyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (crude material; 0.85 g) and potassium carbonate (0.62 g) in methanol (10 ml) was heated at 60°C for three hours. Allowed to cool and the reaction mixture loaded onto an SCX column (20 g) to afford partial purification. The residue was purified by preparative HPLC and isolated by SCX (5 g) and trituration from diethyl ether to afford the title compound (0.13g) as a white solid.

LCMS: Rt 1.03 min, m/z 408 $[M+H]^+$.

^{1}H-NMR (400 MHz, MeOD) δ (ppm): 3.05 - 3.26 (m, 2 H) 3.27 – 3.35 (m, 1 H) 3.78 (t, *J*=6.85 Hz, 2 H) 3.91 - 4.09 (m, 4 H) 4.32 - 4.47 (m, 1 H) 4.56 (d, *J*=2.20 Hz, 2 H) 7.10 - 7.27 (m, 2 H) 7.30 - 7.46 (m, 2 H)

Example 9: (±)-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxy-4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



9-(1) Synthesis of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a solution of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.3 g) obtained in 1-(5) in methanol (6 ml) was added potassium carbonate (0.23 g) and the mixture heated at 60°C for three hours, cooled and the reaction mixture loaded onto an SCX column (10 g) and purified to afford the title compound (0.218 g) as a white foam.

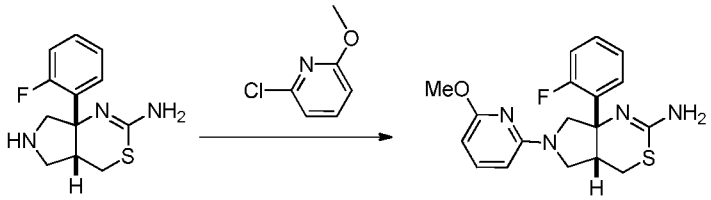
9-(2) Synthesis of 2-chloro-6-methoxy-4-(trifluoromethyl)pyridine

To a solution of 2,6-dichloro-4-(trifluoromethyl)pyridine (2.0 g) in dry methanol (40 ml) was added a solution of sodium hydroxide (1.85 g) in dry methanol (7ml) and the reaction mixture stirred at 50°C under nitrogen for two hours then allowed to cool. The reaction mixture was extracted with pentane (2 x 100 ml), and the extract combined and evaporated to afford the title compound (1.69 g) as a colourless oil.
LCMS: Rt 1.75 min, m/z 212/214 $[M+H]^+$.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.00 (s, 3 H) 6.89 (s, 1 H) 7.12 (s, 1 H)

9-(3) Synthesis of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxy-4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 9)

A mixture of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (0.1 g), 2-chloro-6-methoxy-4-(trifluoromethyl)pyridine (0.17 g) and triethylamine (0.083 ml) in anhydrous acetonitrile (1 ml) was stirred at 120°C for thirty minutes under microwave conditions. The reaction mixture was evaporated, purified by preparative HPLC and isolated by SCX (10 g) to afford the title compound (0.031 g) as a pale pink solid.
LCMS: Rt 1.31 min, m/z 427 $[M+H]^+$.
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.88 (dd, *J*=13.20, 3.91 Hz, 1 H) 3.03 (dd, *J*=13.20, 4.40 Hz, 1 H) 3.07 - 3.20 (m, 1 H) 3.41 - 3.79 (m, 3 H) 3.84 (s, 3 H) 4.03 - 4.20 (m, 1 H) 6.00 - 6.28 (m, 4 H) 7.14 - 7.28 (m, 2 H) 7.30 - 7.44 (m, 2 H)

Example 10: (±)-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxypyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



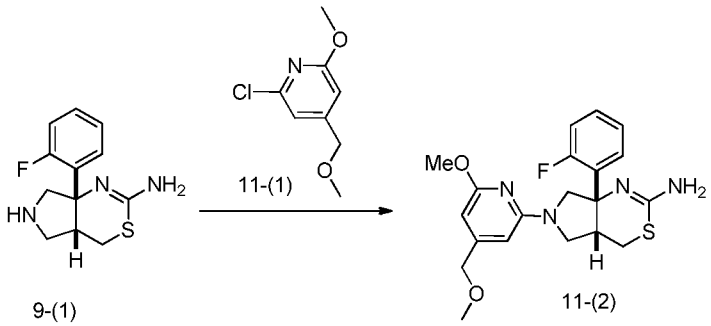
9-(1) 10-(1)

Starting from rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (0.08 g), obtained in example 9-(1), and 2-chloro-6-methoxypyridine (0.091 g), rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxypyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (0.01 g) was synthesised following an analogous procedure to that used to prepare compound 9-(3) as described in Example 9.

LCMS: Rt 1.19 min, m/z 359 $[M+H]^+$.

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 2.82 - 2.95 (m, 1 H) 2.97 - 3.12 (m, 2 H) 3.45 - 3.69 (m, 3 H) 3.77 (s, 3 H) 4.02 - 4.07 (m, 1 H) 5.88 - 5.98 (m, 2 H) 6.07 (br. s, 2 H) 7.14 - 7.41 (m, 5 H)

Example 11: (±)-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxy-4-(methoxymethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



9-(1) 11-(1) 11-(2)

11-(1) Synthesis of 2-chloro-6-methoxy-4-(methoxymethyl)pyridine

To a solution of 2-chloro-6-methoxyisonicotinic acid (2.5 g) in dry tetrahydrofuran (50 ml) at 0°C under nitrogen was added dropwise a solution of borane-tetrahydrofuran complex (1.0M solution in tetrahydrofuran; 40 ml) over fifteen minutes. After the addition was complete, the cooling bath was removed and the mixture allowed to warm to room temperature. After three hours, the mixture was cooled to 0°C and borane-tetrahydrofuran complex (1.0M solution in tetrahydrofuran; 40 ml) was added

over fifteen minutes. After the addition was complete, the cooling bath was removed and the mixture allowed to warm to room temperature and stirred for seventeen hours. The reaction mixture was cooled to 0°C, quenched with 1.0M aqueous sodium hydroxide solution (30 ml), diluted with saturated aqueous ammonium chloride solution (50 ml) and extracted with diethyl ether (2 x 100 ml), the combined organic layer washed with brine then dried (Na_2SO_4) and evaporated. The residue was triturated with hexane and filtered to afford (2-chloro-6-methoxypyridin-4-yl)methanol (2.0 g) as a white solid.

LCMS: Rt 1.16 min, m/z 174/176 $[M+H]^+$.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.96 (t, 1 H) 3.94 (s, 3 H) 4.67 (d, *J*=3.67 Hz, 2 H) 6.65 (d, *J*=0.86 Hz, 1 H) 6.91 (s, 1 H)

To a solution of (2-chloro-6-methoxypyridin-4-yl)methanol (0.25 g) in dry DMF (1.25 ml) at room temperature was added potassium carbonate (0.6 g) and methyl iodide (0.18 ml) and the reaction mixture stirred overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and washed with water (3 x 10 ml) then dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (gradient from 0 to 20% ethyl acetate / hexane) to afford the title compound (0.112 g) as a colourless oil.

LCMS: Rt 1.52 min, m/z 188/190 $[M+H]^+$.

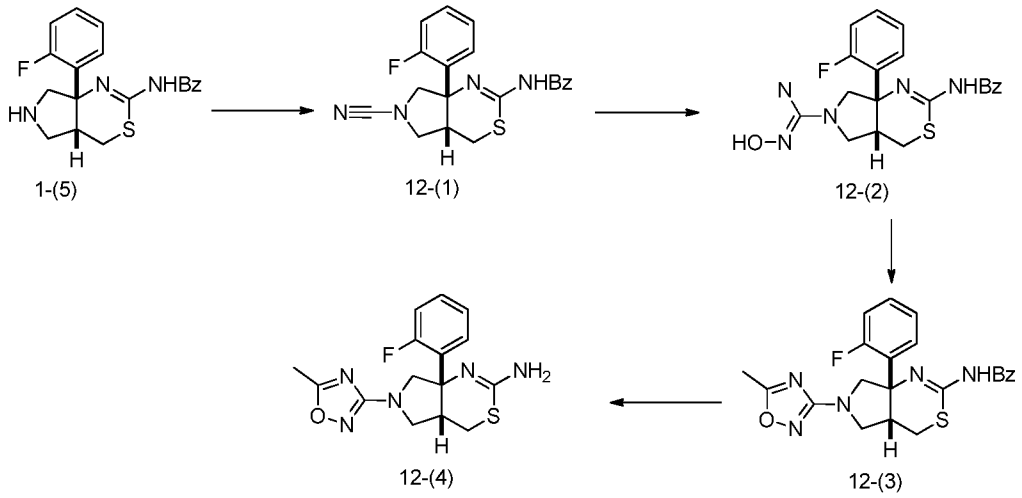
11-(2) Synthesis of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(6-methoxypyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 11)

A mixture of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (0.1 g) obtained in 9-(1), 2-chloro-6-methoxy-4-(methoxymethyl)pyridine (0.11 g) and triethylamine (0.083 ml) in anhydrous NMP (1 ml) was stirred at 120°C for thirty minutes under microwave conditions. The reaction mixture was diluted with DMF (1 ml) and partially purified by preparative HPLC. The residue was then purified by silica gel column chromatography (Method G2, gradient from 0% to 50% ethyl acetate / hexane) to afford the title compound (0.014 g) as a white solid.

LCMS: Rt 1.13 min, m/z 402 $[M+H]^+$.

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 2.88 (d, *J*=12.32 Hz, 1 H) 2.95 - 3.13 (m, 2 H) 3.28 (s, 3 H) 3.44 - 3.70 (m, 3 H) 3.76 (s, 3 H) 3.97 - 4.13 (m, 1 H) 4.29 (s, 2 H) 5.88 (s, 2 H) 6.05 (br. s., 2 H) 7.13 - 7.26 (m, 2 H) 7.29 - 7.41 (m, 2 H)

Example 12: (±)-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



12-(1) Synthesis of rac-N-((4aR*,7aS*)-6-cyano-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.2 g), obtained in 1-(5), in dichloromethane (1 ml) at 0°C was added DIPEA (0.11 ml) and cyanogen bromide (0.066 g) and the reaction stirred for thirty minutes. The reaction mixture was diluted with ethyl acetate (40 ml) and washed with water (2 x 20 ml) then dried $MgSO_4$ and evaporated to afford the title compound (0.22 g) as a pale yellow foam.
LCMS: Rt 1.48 min, m/z 381 $[M+H]^+$.

12-(2) Synthesis of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-6-((E)-N'-hydroxycarbamimidoyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of rac-N-((4aR*,7aS*)-6-cyano-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.214 g) in ethanol (2 ml) was added triethylamine (0.083 ml) and hydroxylamine hydrochloride (0.041 g) and the reaction mixture stirred at 80°C for thirty minutes, then evaporated to dryness and used crude in the next step.
LCMS: Rt 1.12 min, m/z 414 $[M+H]^+$.

12-(3) Synthesis of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-6-((E)-N'-hydroxycarbamimidoyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-

yl)benzamide (crude mixture) in pyridine (2 ml) was added acetic anhydride (0.06 ml) and the reaction mixture stirred at 80°C for two hours. The reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (gradient from 0 to 50% ethyl acetate / hexane) to afford the title compound (0.039 g) as a white foam.

LCMS: Rt 1.53 min, m/z 438 $[M+H]^+$.

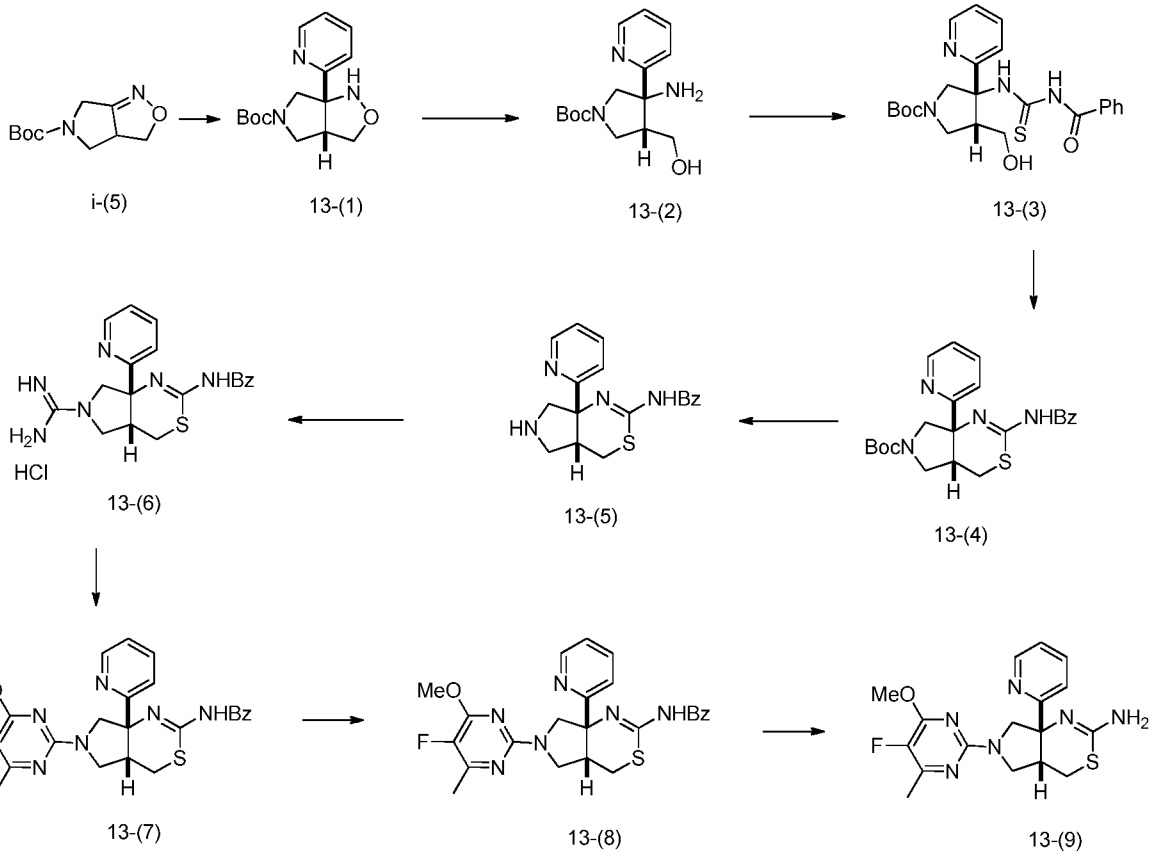
12-(4) Synthesis of rac-(4aR*,7aS*)-7a-(2-fluorophenyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 12)

To a solution of rac-N-((4aR*,7aS*)-7a-(2-fluorophenyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.035 g) in methanol (0.5 ml) was added potassium carbonate (0.022 g) and the mixture heated at 60°C for four and a half hours, cooled and the reaction mixture loaded onto an SCX column (1 g) and purified to afford the title compound (0.024 g) as a white solid.

LCMS: Rt 0.91 min, m/z 334 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.43 (s, 3 H) 2.77 - 2.92 (m, 1 H) 2.95 - 3.12 (m, 2 H) 3.41 - 3.62 (m, 3 H) 4.00 (d, *J*=9.78 Hz, 1 H) 6.12 (s, 2 H) 7.10 - 7.25 (m, 2 H) 7.29 - 7.42 (m, 2 H)

Example 13: (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



13-(1) Synthesis of (±)-(3aR*,6aR*)-tert-butyl 6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

2-bromopyridine (0.674 ml, 7.067 mmol) was dissolved in THF (5mL) at RT under N_2 before the resultant solution was cooled to -78°C. After reaching this temperature *n*-BuLi (2.83 ml, 7.067 mmol) was added and the resultant solution stirred for 30 minutes. After this time *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, i-(5), (1 g, 4.712 mmol) as a solution in THF (2 mL), which had previously been cooled to -78°C, was added dropwise. After 30 minutes there was no isoxazole starting material remaining and so the reaction was quenched with sat. NH_4Cl (aq) and the reaction mixture allowed to warm to room temperature. EtOAc was added and the layers separated, the aqueous was washed a further two times with EtOAc. The organics were combined, dried over $MgSO_4$, filtered and solvent removed in vacuo to give crude material as a brown oil. This was purified by column chromatography (normal phase, 50g, Biotage SNAP cartridge KP-Sil, 50mL per min, 100% EtOAc) to give afford the title compound (547 mg, 1.877 mmol, 39.8 % yield) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.48 (s, 9 H) 3.61 - 3.74 (m, 2 H) 3.83 - 3.95 (m, 2 H) 3.97 - 4.07 (m, 1 H) 4.43 - 4.60 (m, 2 H) 7.78 - 7.88 (m, 1 H) 8.38 (td, *J*=7.80, 1.47 Hz, 1 H) 8.49 (br. d, *J*=8.40 Hz, 1 H) 8.86 (dd, *J*=5.75, 1.10 Hz, 1 H).

13-(2) Synthesis of **(±)**-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate

(±)-(3aR*,6aR*)-tert-butyl 6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate, 13-(1), (1.422 g, 4.881 mmol) was dissolved in THF (35 ml, 427.151 mmol) before acetic acid (2.79 ml, 48.808 mmol) was added at RT under nitrogen. Zinc dust (2.81 g, 42.951 mmol) was then added and the resultant solution stirred at RT overnight. Reaction mixture was filtered through celite and washed with EtOAc before solvent was removed in vacuo. The residue was redissolved in EtOAc and washed with sat. $NaHCO_3$ (aq). The solution was again filtered through celite to remove the salts before the layers were separated and the aqueous extracted with EtOAc (x2). The organic fractions were combined, dried over $MgSO_4$, filtered and solvent removed in vacuo to afford the title compound (1.243 g, 4.11 mmol, 84 % yield) as a yellow foam.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 0.90min, ES^+: 294.60 $[MH]^+$.

13-(3) Synthesis of **(±)**-(3R*,4R*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate

To a solution of **(±)**-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate, 13-(2), (1.206 g, 4.111 mmol) in dichloromethane (20 ml) at -15°C was added a solution of benzoyl isothiocyanate (0.553 ml, 4.111 mmol) in dichloromethane (6.0 ml) and the reaction mixture stirred at -15°C for ninety minutes. Solvent was removed in vacuo and the residue redissolved in dichloromethane and applied to a 20g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 100% ethyl acetate / hexane over 10CV + 5% methanol / ethyl acetate over 10CV toafford the title compound (1.427 g, 3.13 mmol, 76 % yield) as a yellow foam.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.44min, ES^+: 457.61 $[MH]^+$.

13-(4) Synthesis of **(±)**-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

To a solution (±)-(3R*,4R*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate, 13-(3), (46 mg, .101 mmol) in DCM (1.601 mL, 24.882 mmol) and pyridine (0.033 mL, .403 mmol) at -40 °C was added dropwise Trifluoromethanesulphonic acid anhydride (0.047 mL, .277 mmol) and the reaction mixture stirred for 1 h at this temperature. The reaction mixture was quenched with sat. $NaHCO_3$ (aq) at -40°C before the reaction mixture was allowed to warm to RT. The layers were separated and the aqueous further extracted with DCM (x2). The combined organics were then washed with brine before being dried over $MgSO_4$, filtered and solvent removed in vacuo to afford the title compound (44 mg, 0.100 mmol, 100 % yield) as a yellow oil.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.60min, ES^+: 439.63 $[MH]^+$.

13-(5) Synthesis of (±)-N-((4aR*,7aR*)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

A solution of (±)-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate, 13-(4), (202 mg, .461 mmol) in DCM (0.8 mL, 12.433 mmol) and TFA (0.4 mL, 5.192 mmol) was stirred at room temperature for two hours. The reaction mixture was evaporated to dryness and the residue was purified by SCX (10g) to afford the title compound (66 mg, 0.195 mmol, 42.3 % yield) as a brown solid.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.01 min, 100%, ES^+: 339.57 $[MH]^+$.

13-(6) Synthesis of (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

To a solution of (±)-N-((4aR*,7aR*)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 13-(5), (66 mg, .195 mmol) in DMF (1mL, 12.915 mmol) was added 1H-pyrazole-1-carboximidamide hydrochloride (38.6 mg, .263 mmol) followed by N-ethyl-N-isopropylpropan-2-amine (0.051 mL, .293 mmol) added dropwise and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and material used crude in next step.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.01 min, 100%, ES^+: 381.58 $[MH]^+$.

13-(7) Synthesis of (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Assumed 100% on the previous step (based on 0.194 mmol): To a solution of (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, 13-(6), (81 mg, .194 mmol) in EtOH (1792 µl, 30.696 mmol) was added Ethyl 2-fluoroacetoacetate (48.7 µl, .389 mmol), then sodium ethoxide (33.5 µl, .427 mmol) (21% w/w solution in EtOH). The reaction was stirred at reflux for 1 h. The reaction mixture was diluted with EtOAc and sat. $NaHCO_3$ (aq), and H_2O (to avoid emulsion). The two layers were separated and the aqueous phase extracted with EtOAc (x2), the combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (normal phase, 10g, Biotage SNAP cartridge KP-Sil, 12mL per min, gradient 0% to 100% EtOAc in n-hexane over 20 CV then 5CV at 100%) to afford the title compound (33 mg, 0.071 mmol, 36.6 % yield) as a beige solid.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.21 min, ES^+: 465.62 $[MH]^+$.

13-(8) Synthesis of (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 13-(7), (33 mg, .071 mmol) in N,N-dimethylformamide(1 ml) was added K_2CO_3 (19.64 mg, .142 mmol) followed by methyl iodide (4 µl) and the mixture stirred at room temperature for 90 minutes. Reaction mixture was quenched with sat. NH_4Cl (aq) then diluted with ethyl acetate and water. The layers were separated and the aqueous further extracted with EtOAC (x2). The organic layers were combined, dried ($MgSO_4$), filtered and solvent removed in vacuo to give crude material as a yellow oil. This was was purified by column chromatography (normal phase, 10g, Biotage SNAP cartridge KP-Sil, 12mL per min, gradient 0% to 100% EtOAc in n-hexane over 30CV) to afford the title compound (22 mg, 0.046 mmol, 64.7 % yield) as a white solid.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.64min, 100%, ES^+: 479.64 $[MH]^+$.

13-(9) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

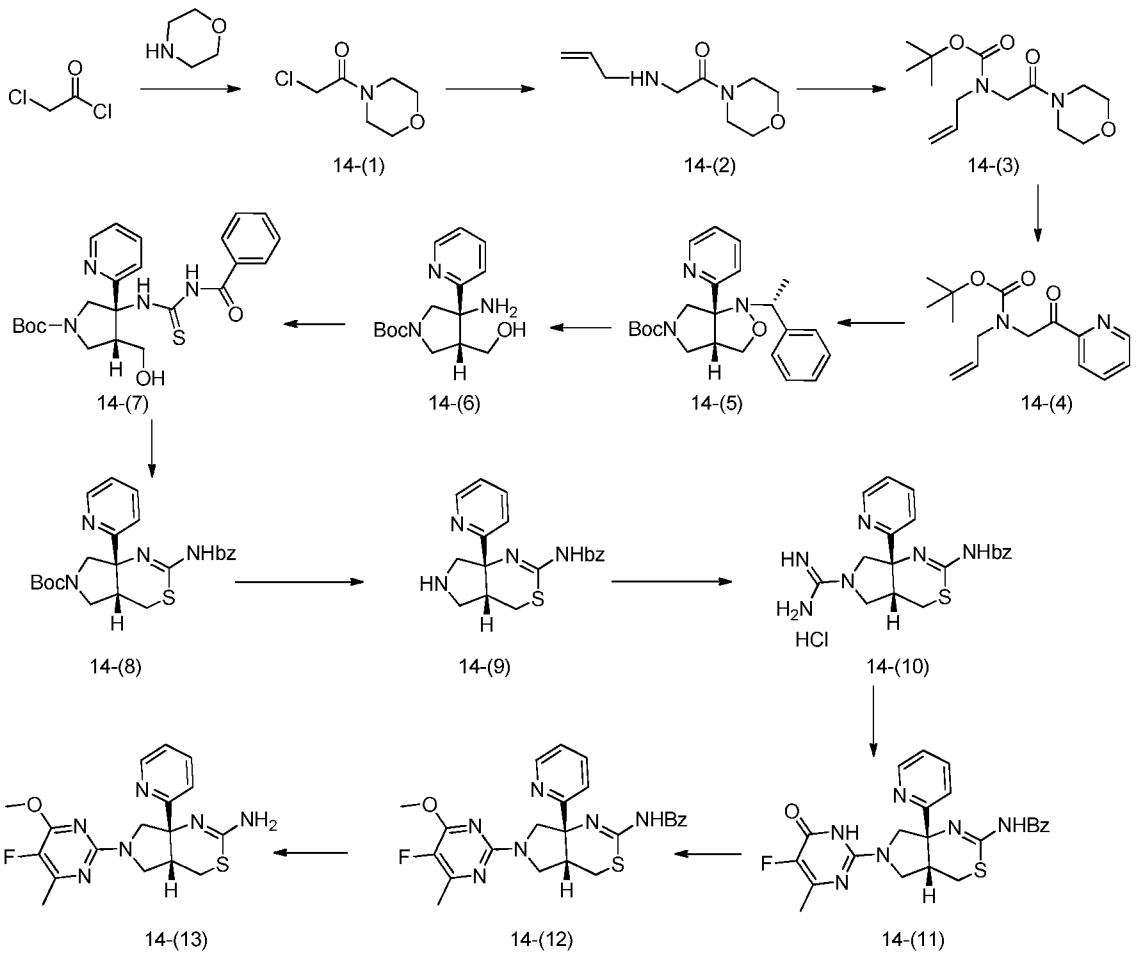
(±)-N-((4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 13-

(8), (22 mg, .046 mmol) was dissolved in MeOH (1 ml, 24.718 mmol) at RT under nitrogen before K_2CO_3 (12.71 mg, .092 mmol) was added and the resultant solution heated to 60 °C for 3 h. Solution was loaded on to a SCX (1 g) cartridge, impurities eluted with MeOH before the product was washed off using 2M NH_3/MeOH. Solvent was removed in vacuo to afford the title compound (16 mg, 0.043 mmol, 93 % yield) as a beige solid.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.09 min, 100%, ES^+: 375.57 $[MH]^+$.

^{1}H NMR (600 MHz, DMSO-*d6*) δ ppm 2.22 (d, *J*=16.73 Hz, 3 H) 2.51 - 2.53 (m, 1 H) 2.84 - 3.02 (m, 2 H) 3.58 - 3.66 (m, 1 H) 3.67 - 3.75 (m, 1 H) 3.77 - 3.81 (m, 1 H) 3.90 (d, *J*=42.26 Hz, 3 H) 3.98 - 4.07 (m, 1 H) 6.04 (br. s, 2 H) 7.28 (ddd, *J*=7.63, 4.70, 1.17 Hz, 1 H) 7.43 (d, *J*=7.92 Hz, 1 H) 7.81 (td, *J*=7.92, 1.76 Hz, 1 H) 8.56 (d, *J*=4.99 Hz, 1 H).

Example 14: (4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



14-(1) Synthesis of 2-chloro-1-morpholinoethanone

To a solution of chloroacetyl chloride (25 ml) in dry dichloromethane (125 ml) at -10°C was added dropwise a solution of morpholine (30 ml) and triethylamine (47.5 ml) in dry dichloromethane (125 ml) over approximately two hours keeping the internal temperature below 20°C. After addition, the reaction mixture was stirred for one hour then the reaction mixture was washed with 0.5N aqueous hydrochloric acid (200 ml) and water (2 x 200 ml). The combined aqueous was back extracted with dichloromethane (2 x 150 ml); the organic layers were combined, dried ($MgSO_4$) and evaporated to afford the title compound (46.69 g) as a brown oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.49 - 3.57 (m, 2 H) 3.58 - 3.66 (m, 2 H) 3.71 (dt, *J*=9.84, 4.86 Hz, 4 H) 4.06 (s, 2 H)

14-(2) Synthesis of 2-(allylamino)-1-morpholinoethanone

To a solution of 2-chloro-1-morpholinoethanone (10 g) in dry acetonitrile (400 ml) at 0°C under nitrogen was added potassium carbonate (67 g) followed by allylamine (23 ml) and the reaction mixture stirred for approximately four hours. The reaction mixture was filtered then evaporated to afford the title compound (11.6 g) as an orange oily solid which was used in the next step without purification.

14-(3) Synthesis of tert-butyl allyl(2-morpholino-2-oxoethyl)carbamate

To a solution of 2-(allylamino)-1-morpholinoethanone (11.24 g) in dry 1,4-dioxane (200 ml) at 0°C under nitrogen was added triethylamine (17 ml) followed by BOC_2O (14 g), the ice bath removed and the reaction mixture stirred for one hour. The reaction mixture was diluted with dichloromethane (200 ml) and washed with water (200 ml) and the organic layer dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (gradient from 0% to 100% ethyl acetate / hexane) to afford the title compound (11.84 g) as a very pale yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (s, 9 H) 3.30 - 3.79 (m, 8 H) 3.85 - 4.10 (m, 4 H) 5.14 (d, *J*=11.00 Hz, 2 H) 5.69 - 5.92 (m, 1 H)

14-(4) Synthesis of tert-butyl allyl(2-oxo-2-(pyridin-2-yl)ethyl)carbamate

To a solution of 2-bromopyridine (5.5 g) in dry tetrahydrofuran (55 ml) at -78°C under nitrogen was added dropwise butyl lithium (17.5 ml;1.6N in hexanes) keeping the internal temperature below -70°C. Stirred at -78°C for thirty minutes then added a solution of tert-butyl allyl(2-morpholino-2-oxoethyl)carbamate (6.6 g) in dry tetrahydrofuran (50 ml) keeping the internal temperature below -70°C. The reaction mixture was stirred for seven hours, stored in the freezer at ~ -20°C for two days then

poured into saturated aqueous ammonium chloride (100 ml), diluted with ethyl acetate (100 ml) and extracted. The organic layer was washed with brine then dried ($MgSO_4$) and evaporated and the residue was purified by silica gel column chromatography (gradient from 0% to 20% ethyl acetate / hexane) to afford the title compound (2.986 g) as a pale yellow oil.

LCMS: Rt 1.62 min, m/z 277 $[M+H]^+$.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 1.29 - 1.56 (m, 9 H) 3.86 - 4.10 (m, 2 H) 4.76 - 4.98 (m, 2 H) 5.07 - 5.23 (m, 2 H) 5.76 - 5.93 (m, 1 H) 7.40 - 7.56 (m, 1 H) 7.78 - 7.91 (m, 1 H) 8.04 (t, *J*=7.63 Hz, 1 H) 8.66 (dd, *J*=11.44, 4.40 Hz, 1 H)

14-(5) Synthesis of (3aR,6aR)-tert-butyl 1-((R)-1-phenylethyl)-6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a solution of tert-butyl allyl(2-oxo-2-(pyridin-2-yl)ethyl)carbamate (2.98g) and (R)-N-(1-phenylethyl)hydroxylamine (2 g) in dry tetrahydrofuran (60 ml) was added ethyl orthotitanate (5 g). The reaction was split over four sealed tubes and heated to 70°C for one hour then to 80°C for ninety six hours. The reaction mixtures were cooled, combined and then stirred vigorously in ethyl acetate (50 ml) and water (50 ml) for fifteen minutes. The solid formed was filtered off and washed thoroughly with ethyl acetate and the layers separated, the organic layer was dried ($MgSO_4$) and evaporated. The diastereoisomers were separated by three purifications by silica gel column chromatography (gradient from 0% to 2% methanol/dichloromethane) to afford the title compound (3.143 g; approximately 16 : 1 (3aR,6aR)-tert-butyl 1-((R)-1-phenylethyl)-6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate : (3aS,6aS)-tert-butyl 1-((R)-1-phenylethyl)-6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate) as a pale yellow foam.

LCMS: Rt 1.74 min, m/z 396 $[M+H]^+$.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 1.23 (d, *J*=6.46 Hz, 3 H) 1.44 (br. s., 9 H) 3.28 (br. s., 1 H) 3.33 - 3.66 (m, 4 H) 3.87 - 4.31 (m, 3 H) 6.93 - 7.36 (m, 6 H) 7.51 (d, *J*=7.92 Hz, 1 H) 7.67 - 7.86 (m, 1 H) 8.28 - 8.49 (m, 1 H)

14-(6) Synthesis of (3R,4R)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate

To a solution of (3aR,6aR)-tert-butyl 1-((R)-1-phenylethyl)-6a-(pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (2.63 g) in 10% aqueous methanol (30 ml) was added ammonium formate (1.7 g) and 10% palladium on carbon (0.26 g) and the mixture stirred at 65°C for twenty three hours. Ammonium formate (1.7 g) and 10% palladium on carbon (0.26g) were added and the mixture stirred at 65°C for a further two hours then ammonium formate (1.7 g) was added and the mixture stirred

at 65°C for a further three and a half hours then ammonium formate (1.7 g) was added and the mixture stirred at 65°C for a further three and a half hours then ammonium formate (1.7 g) was added and the mixture stirred at 65°C for a further twenty four hours. The catalyst was filtered off washing thoroughly with methanol and evaporated. The residue was purified by silica gel column chromatography (gradient from 0% to 100% ethyl acetate / hexane then 5% methanol / ethyl acetate) to afford the title compound (0.87 g) as a colourless oil which was used in the next step without further purification.

14-(7) Synthesis of (3R,4R)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate

To a solution of (3R,4R)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate (0.87 g) in dichloromethane (15 ml) at -15°C was added benzoyl isothiocyanate (0.4 ml) in dichloromethane (5 ml) and the reaction mixture stirred at -15°C for ninety minutes then evaporated with a stream of nitrogen. The residue was purified by silica gel column chromatography (gradient from 0% to 100% ethyl acetate / hexane then 5% methanol/ethyl acetate) to afford the title compound (1 g) as a white foam.
LCMS: Rt 1.51 min, m/z 457 $[M+H]^+$.

14-(8) Synthesis of (4aR,7aR)-tert-butyl 2-benzamido-7a-(pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

To a solution of (3R,4R)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(pyridin-2-yl)pyrrolidine-1-carboxylate (1 g) in dichloromethane (11 ml) and pyridine (0.9 ml) at -40°C was added dropwise triflic anhydride (0.6 ml) and the reaction mixture stirred for one hour. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with aqueous saturated sodium bicarbonate (2 x 25 ml) and aqueous saturated sodium chloride (25 ml) then dried ($MgSO_4$) and evaporated to afford the title compound (0.813 g) as a yellow foam.
LCMS: Rt 1.67 min, m/z 439 $[M+H]^+$.

14-(9) Synthesis of N-((4aR,7aR)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (4aR,7aR)-tert-butyl 2-benzamido-7a-(pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (0.812 g) in dichloromethane (10 ml) at -0°C was added dropwise TFA (5 ml) and the reaction mixture stirred for four hours. The reaction mixture was evaporated and purified by SCX (10 g) to afford the title compound (0.571 g) as a pale brown solid.

LCMS: Rt 1.06 min, m/z 339 $[M+H]^+$.

14-(10) Synthesis of N-((4aR,7aR)-6-carbamimidoyl-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

To a solution of N-((4aR,7aR)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.571 g) in N,N-dimethylformamide (7 ml) was added 1H-pyrazole-1-carboximidamide hydrochloride (0.27 g) followed by diisopropylamine (0.33 ml) added dropwise and the reaction mixture stirred at room temperature for seventeen hours. The mixture was evaporated to dryness and used crude in the next step.
LCMS: Rt 1.05 min, m/z 381 $[M+H]^+$.

14-(11) Synthesis of N-((4aR,7aR)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a mixture of N-((4aR,7aR)-6-carbamimidoyl-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride (assumed 0.703 g) in ethanol (10 ml) was added ethyl 2-fluoro-3-oxobutanoate (0.57 g) followed by sodium ethoxide (1.26 ml, 21% in ethanol) and the mixture refluxed for two hours. The reaction mixture was diluted with ethyl acetate (100 ml), washed with water (50 ml) and brine (50 ml) then dried ($MgSO_4$) and evaporated (Note: the aqueous was back extracted several times with dichloromethane). The residue was purified by silica gel column chromatography (gradient from 0 to 100% ethyl acetate / hexane followed by 5% methanol / ethyl acetate) to afford the title compound (0.613 g) as a pale yellow solid.
LCMS: Rt 1.27 min, m/z 465 $[M+H]^+$.
^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 2.09 (d, *J*=2.93 Hz, 3 H) 2.93 (d, *J*=3.52 Hz, 1 H) 2.99 (d, *J*=3.52 Hz, 1 H) 3.32 - 3.46 (m, 1 H) 3.64 - 3.76 (m, 1 H) 3.81 (br. s., 1 H) 4.03 (m, *J*=7.00 Hz, 1 H) 4.15 (d, *J*=11.15 Hz, 1 H) 7.36 - 7.42 (m, 1 H) 7.42 - 7.49 (m, 2 H) 7.53 (d, *J*=7.92 Hz, 2 H) 7.86 - 7.95 (m, 1 H) 7.96 - 8.12 (m, 2 H) 8.65 (d, *J*=4.11 Hz, 1 H) 10.36 (br. s, 1 H) 11.49 (br. s, 1 H)

14-(12) Synthesis of N-((4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of N-((4aR,7aR)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.61 g) in N,N-dimethylformamide (20 ml) was added potassium carbonate (0.27 g) followed by methyl iodide (0.082 ml) in N,N-

dimethylformamide (5 ml) and the mixture stirred at room temperature for one hour. The reaction mixture was diluted with ethyl acetate (250 ml), washed with water (2 x 50 ml and 100 ml) then dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (gradient from 0 to 50% ethyl acetate / hexane) to afford the title compound (0.343 g) as a white foam.

LCMS: Rt 1.74 min, m/z 479 $[M+H]^+$.

^{1}H-NMR (600 MHz, DMSO) δ (ppm): 2.23 (br. s., 3 H) 2.88 - 2.99 (m, 1 H) 3.00 - 3.08 (m, 1 H) 3.35 - 3.53 (m, 1 H) 3.65 - 3.79 (m, 1 H) 3.82 - 4.00 (m, 4 H) 4.07 - 4.29 (m, 2 H) 7.35 - 7.41 (m, 1 H) 7.42 - 7.48 (m, 2 H) 7.48 - 7.55 (m, 1 H) 7.57 (d, *J*=7.92 Hz, 1 H) 7.87 - 7.96 (m, 1 H) 7.97 - 8.10 (m, 2 H) 8.63 - 8.69 (m, 1 H) 10.08 - 11.26 (m, 1 H)

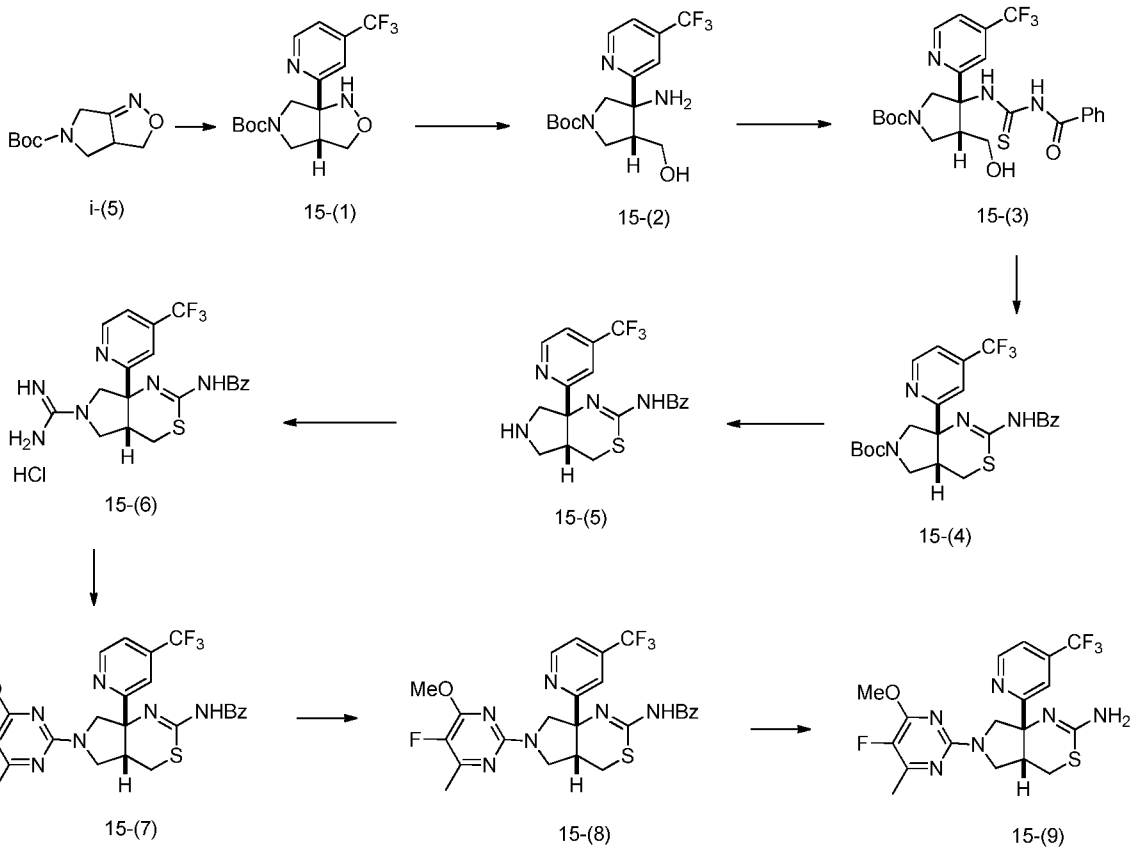
14-(13) Synthesis of (4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a solution of N-((4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.336 g) in methanol (10 ml) was added potassium carbonate (0.2 g) and the mixture heated at 60°C for three hours. Allowed to cool and the reaction mixture loaded onto an SCX column (10 g) and partially purified, then purified by silica gel column chromatography (Method G2, gradient from 0% to 50% ethyl acetate / hexane) to afford the title compound (0.175 g) as a white solid.

LCMS: Rt 1.11 min, m/z 375 $[M+H]^+$.

^{1}H-NMR (600 MHz, DMSO) δ (ppm): 2.21 (d, *J*=15.26 Hz, 3 H) 2.83 - 3.03 (m, 2 H) 3.07 - 3.22 (m, 1 H) 3.58 - 3.67 (m, 1 H) 3.67 - 3.82 (m, 2 H) 3.83 - 3.97 (m, 3 H) 3.97 - 4.09 (m, 1 H) 6.03 (br. s., 2 H) 7.21 - 7.33 (m, 1 H) 7.43 (d, *J*=7.92 Hz, 1 H) 7.81 (d, *J*=1.76 Hz, 1 H) 8.56 (d, *J*=3.81 Hz, 1 H)

Example 15: (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



15-(1) Synthesis of (±)-(3aR*,6aR*)-tert-butyl 6a-(4-(trifluoromethyl)pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a solution of 2-dimethylaminoethanol (2.84 ml, 28.3 mmol) in toluene (85 ml) at 0°C was added dropwise under nitrogen a 1M solution of ((trimethylsilyl)methyl)lithium in pentane (85 ml, 84.8 mmol), the solution became yellow at this point. After being stirred for 30 min at this temperature, a solution of 2-bromo-4-(trifluoromethyl)pyridine (3.50 ml, 28.3 mmol) in toluene (27 ml) was added dropwise. The resulting brown solution was stirred at 0°C for 30 min and was then cooled to -78°C. A premade solution of tert-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate (i-(5)) (2 g, 9.4 mmol) and $BF_3.OEt_2$ (2.4 ml, 18.84 mmol) in THF (18 ml) and toluene (18 ml) was added dopwise to the previous solution at -78°C. The mixture was left to warm to RT overnight and was then quenched with water. The organic layer was extracted with EtOAc (x3), the combined organic extracts were washed with brine, dried over MgSO4 and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (gradient from 0% to 50% EtOAc in Hexanes) to give the title compound as a brown oil (1.67 g).

LCMS: Rt 1.66 min, m/z= 360 $[M+H]^+$.

15-(2) Synthesis of (±)-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate

Obtained as a brown foam (671 mg) following analogous procedure to that prepared compound 1-(2) as described in Example 1, starting from (±)-(3aR*,6aR*)-tert-butyl 6a-(4-(trifluoromethyl)pyridin-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate 15-(1) (1.67 g).
LCMS: Rt 1.13 min, m/z 362 [M+H]+.

15-(3) Synthesis of (±)-(3R*,4R*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate

Obtained as a yellow foam (473 mg) following analogous procedure to that prepared compound 1-(3) as described in Example 1, starting from (±)-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate 15-(2) (671 mg).
LCMS: Rt 1.68 min, m/z 525 [M+H]+.

15-(4) Synthesis of (±)-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(4-(trifluoromethyl)pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

Obtained as a yellow foam (383 mg) following analogous procedure to that prepared compound 1-(4) as described in Example 1, starting from (±)-(3aR*,6aR*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate 15-(3) (473 mg).
LCMS: Rt 1.85 min, m/z 507 [M+H]+.

15-(5) Synthesis of (±)-(4aR*,7aR*)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Obtained as a brown oil (308 mg) following analogous procedure to that prepared compound 1-(5) as described in Example 1, starting from (±)-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(4-(trifluoromethyl)pyridin-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate 15-(4) (383 mg).
LCMS: Rt 1.28 min, m/z 407 [M+H]+.

15-(6) Synthesis of (±)-(4aR*,7aR*)-6-carbamimidoyl-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

Obtained (364 mg) following analogous procedure to that prepared compound 1-(6) as described in Example 1, starting from (±)-(4aR*,7aR*)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 15-(5) (308 mg).
LCMS: Rt 1.30 min, m/z 449 [M+H]+.

15-(7) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Obtained as a yellow solid (325 mg) following analogous procedure to that prepared compound 1-(7) as described in Example 1, starting from (±)-(4aR*,7aR*)-6-carbamimidoyl-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride 15-(6) (364 mg).
LCMS: Rt 1.50 min, m/z 533 [M+H]+.

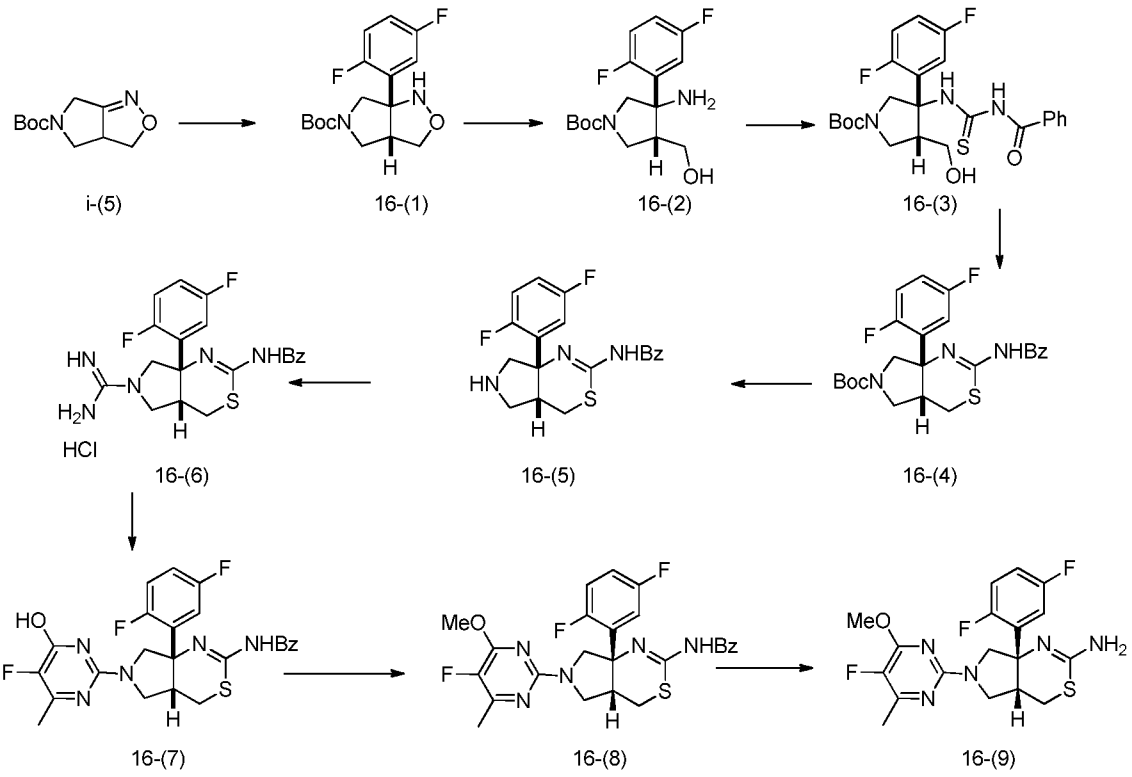
15-(8) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Obtained as a colorless foam (179 mg) following analogous procedure to that prepared compound 1-(8) as described in Example 1, starting from (±)-(4aR*,7aR*)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 15-(7) (325 mg).
LCMS: Rt 1.91 min, m/z 547 [M+H]+.

15-(9) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 15)

Obtained as a colorless solid (80 mg) following analogous procedure to that prepared compound 1-(9) as described in Example 1, starting from (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(4-(trifluoromethyl)pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 15-(8) (179 mg).
LCMS: Rt 1.32 min, m/z 443 $[M+H]^+$.
^{1}H NMR (600 MHz, CDCl3) δ ppm 2.30 (s, 3 H), 2.95 (dd, *J*=13.1, 4.0 Hz, 1 H), 3.14 (d, *J*=10.9 Hz, 1 H), 3.47-3.56 (m, 1 H), 3.81-4.05 (m, 6 H), 4.05-4.12 (m, 1 H), 7.42 (d, *J*=4.4 Hz, 1 H), 7.80 (s, 1 H), 8.76 (d, *J*=5.0 Hz, 1 H).

Example 16: (4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



16-(1) Synthesis of (±)-(3aR*,6aS*)-tert-butyl 6a-(2,5-difluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a solution of 1-bromo-2,5-difluorobenzene (3.64 g) in dry tetrahydrofuran (5 mL) and dry toluene (25 mL) at -78°C under nitrogen was added dropwise *n*-butyl lithium (7.55 mL;2.5 N in hexanes) keeping the internal temperature below -70°C. Stirred at -78°C for one hour then added a -78°C solution of tert-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, obtained as described in preparation example i-(5), (2 g) and boron trifluoride etherate (2.4 mL) in dry tetrahydrofuran (20 mL) keeping the internal temperature below -60°C. The mixture was then stirred at -78°C for two hours. The reaction was quenched with aqueous saturated ammonium chloride (100 mL), extracted with ethyl acetate (100 mL) then dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane and applied to a 100g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 30% ethyl acetate / hexane over 10 column volumes to afford the title compound (1.2 g) as a colourless oil. LCMS: Rt 1.55 min, m/z 327 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$-d) δ ppm 1.48 (s, 9 H) 3.30 (d, J=7.83 Hz, 1 H) 3.45 - 3.86 (m, 5 H) 4.48 (t, J=8.38 Hz, 1 H) 4.93 - 5.24 (m, 1 H) 6.86 - 7.12 (m, 2 H) 7.64 (m, 1 H)

16-(2) Synthesis of (±)-(3S*,4R*)-tert-butyl 3-amino-3-(2,5-difluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a solution of (±)-(3aR*,6aS*)-tert-butyl 6a-(2,5-difluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (1.15 g) in acetic acid (9 mL) was added zinc dust (0.576 g) and the reaction mixture stirred at room temperature for twenty four hours. The reaction mixture was filtered through celite washing thoroughly with ethyl acetate then evaporated. The residue was dissolved in ethyl acetate (100 mL) and washed with aqueous saturated sodium bicarbonate (2 x 50 mL) and aqueous saturated sodium chloride (50 mL) then dried ($MgSO_4$) and evaporated to afford the title compound (1.16 g) as a white foam.
LCMS: Rt 0.97 min, m/z 329 $[M+H]^+$.

16-(3) Synthesis of (±)-(3S*,4R*)-tert-butyl 3-(3-benzoylthioureido)-3-(2,5-difluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a solution of (±)-(3S*,4R*)-tert-butyl 3-amino-3-(2,5-difluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (1.157 g) in dichloromethane (15 mL) was added benzoyl isothiocyanate (0.61 mL) and the reaction mixture stirred at room temperature for twenty four hours and evaporated. The residue was dissolved in dichloromethane and applied to a 50 g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 30% ethyl acetate / hexane over 10 column volumes to afford the title compound (1.518 g) as a white foam.
LCMS: Rt 1.86 min, no mass ion.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (s, 9 H) 2.63 - 2.88 (m, 1 H) 3.43 (s, 2 H) 3.55 - 3.82 (m, 2 H) 4.07 - 4.35 (m, 1 H) 4.39 - 4.67 (m, 1 H) 5.19 (d, J=2.93 Hz, 1 H) 6.98 – 7.35 (m, 3 H) 7.42 - 7.75 (m, 3 H) 7.79 - 8.07 (m, 2 H) 11.27 (br. s., 1 H) 11.94 (d, J=9.66 Hz, 1 H)

16-(4) Synthesis of (±)-(4aR*,7aS*)-tert-butyl 2-benzamido-7a-(2,5-difluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

To a solution of (±)-(3S*,4R*)-tert-butyl 3-(3-benzoylthioureido)-3-(2,5-difluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (1.51 g) in dichloromethane (12 mL) and pyridine (1.2 mL) at -10°C was added dropwise triflic anhydride (0.83ml) and the reaction mixture stirred for two hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with aqueous saturated sodium bicarbonate (2 x 50 mL) and aqueous saturated sodium chloride (50 mL) then dried ($MgSO_4$) and evaporated and triturated with diethyl ether to afford the title compound (1.176 g) as a pale yellow solid.
LCMS: Rt 1.71 min, m/z 474 $[M+H]^+$.

16-(5) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

A solution of (±)-(4aR*,7aS*)-tert-butyl 2-benzamido-7a-(2,5-difluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (1.17 g) in dichloromethane (4 mL) and trifluoroacetic acid (2 mL) was stirred at room temperature for two hours. The reaction mixture was evaporated to dryness and the residue was purified by SCX (10 g) to afford the title compound (0.902 g) as a pale yellow foam.
LCMS: Rt 1.09 min, m/z 374 $[M+H]^+$.

16-(6) Synthesis of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2,5-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

To a solution of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.892 g) in N,N-dimethylformamide (7 mL) was added 1H-pyrazole-1-carboximidamide hydrochloride (0.361 g) followed by diisopropylamine (0.35 mL) added dropwise and the reaction mixture stirred at room temperature for four hours. 1H-pyrazole-1-carboximidamide hydrochloride (90 mg) and diisopropylamine (0.09 mL) was added and continued stirring for two hours then 1H-pyrazole-1-carboximidamide hydrochloride (0.18 g), diisopropylamine (0.2 mL) and N,N-dimethylformamide (3 mL) were added and continued stirring for seventeen hours. The precipitate formed was filtered off and the solid washed with diethyl ether and dried to afford the title compound (1.242 g) as a white solid which was used without further purification.
LCMS: Rt 1.14 min, m/z 416 $[M+H]^+$.

16-(7) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2,5-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride (1.242 g) in ethanol (10 mL) was added ethyl 2-fluoroacetoacetate (0.28 mL) followed by sodium ethoxide (1.68 mL, 21% in ethanol) and the mixture refluxed for four hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with aqueous saturated sodium bicarbonate solution (50 mL) and water (50 mL) then dried ($MgSO_4$) and evaporated to a red foam (1.06 g).The residue was dissolved in dichloromethane and applied to a 50g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 100% ethyl acetate / hexane over 10 column volumes to afford the title compound (0.707 g) as an off-white solid.

LCMS: Rt 1.36min, m/z 500 $[M+H]^+$.

16-(8) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.698 g) in N,N-dimethylformamide (3 mL) was added potassium carbonate (0.29 g) followed by a solution of methyl iodide (0.087 mL) in N,N-dimethylformamide (2 mL) and the mixture stirred at room temperature for forty minutes. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (3 x 50 mL) then dried ($MgSO_4$) and evaporated.The residue was dissolved in dichloromethane and applied to a 25g SNAP KP-Si column. Purified on the Biotage Isolera 4 eluting with 0 to 30% ethyl acetate / hexane over 10 column volumes to afford the title compound (0.488 g) as a white foam.
LCMS: Rt 1.77 min, m/z 514 $[M+H]^+$.

Separation of N-((4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide and N-((4aS,7aR)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide:

The isomers of (±)-N-((4aR*,7aS*)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide were separated by preparative chiral HPLC, Method H2, (IC column (#3), eluent (10% dichloromethane / hexane):EtOH 97:3 (v/v)) to afford the faster running enantiomer, N-((4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.207 g) as a white solid.
LCMS: Rt 1.77 min, m/z 514 [M+H]+.

16-(9) Synthesis of (4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 16)

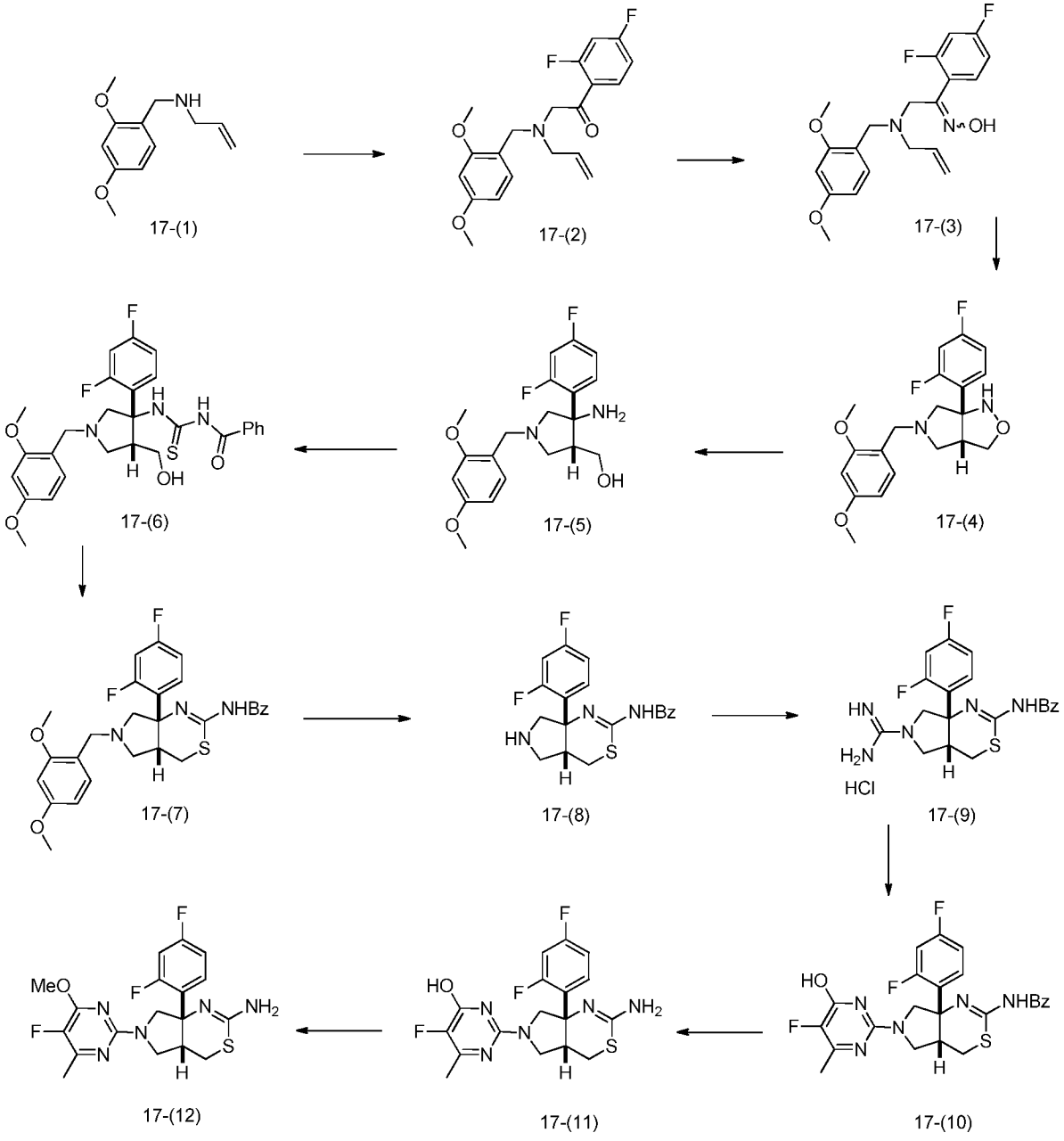
To a solution of N-((4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (0.2 g) in methanol (2 mL) was added DBU (0.2 mL) and the reaction mixture stirred at 80°C for two hours then evaporated. The residue was purified by

preparative HPLC, Method D, (1 injection in 1 mL DMF). The residue was isolated by SCX (2 g) to afford the title compound (0.096 g) as a white solid.

LCMS: Rt 1.21 min, m/z 410 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ ppm 2.30 (d, J=2.81 Hz, 3 H) 2.89 - 3.10 (m, 2 H) 3.14 - 3.29 (m, 1 H) 3.69 - 3.87 (m, 3 H) 3.96 (s, 3 H) 4.28 (d, J=11.25 Hz, 1 H) 4.45 (br. s., 2 H) 6.89 - 7.07 (m, 2 H) 7.11 (ddd, J=9.81, 6.45, 3.06 Hz, 1 H)

Example 17: (±)- (4aR*,7aS*)-7a-(2,4-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



17-(1) Synthesis of N-(2,4-dimethoxybenzyl)prop-2-en-1-amine

Allylamine (11.29 ml, 150.445 mmol) and 2,4-Dimethoxybenzaldehyde (20 g, 120.356 mmol) were dissolved in DCM (540 ml, 8392.539 mmol) at RT under nitrogen before acetic acid (8.61 ml, 150.445 mmol) was added and the resultant suspension stirred for 5 minutes. Sodium triacetoxyborohydride (44.6 g, 210.623 mmol) was then added and the resultant solution stirred at RT for 5h. The reaction mixture was concentrated before being redissolved in DCM and the organic layer washed with 2M NaOH (aq). The layers were separated and the aqueous extracted a further two times using DCM. The combined organics were washed with brine before being dried over magnesium sulfate, filtered and solvent removed in vacuo to give the title compound (27.54 g, 88 mmol, 72.9 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.44 (d, *J*=6.72 Hz, 2 H) 3.80 (s, 3 H) 3.86 (s, 3 H) 4.03 (s, 2 H) 5.31 - 5.41 (m, 2 H) 5.92 - 6.05 (m, 1 H) 6.42 - 6.49 (m, 2 H) 7.24 (d, *J*=8.93 Hz, 1 H).

17-(2) Synthesis of 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(2,4-difluorophenyl)ethanone

2-Bromo-1-(2,4-difluorophenyl)ethanone (10.62 g, 45.187 mmol) was dissolved in DCM (200 mL) at RT under nitrogen before N,N-diisopropylethylamine (11.84 ml, 67.78 mmol) was added. N-(2,4-dimethoxybenzyl)prop-2-en-1-amine, 17-(1), (11.71 g, 56.483 mmol) as a solution in DCM (20 mL) was then added to the reaction mixture and the resultant solution left to stir at RT under nitrogen for 2h. The reaction mixture was quenched with sat. NH_4Cl (aq), before being diluted with sat. $NaHCO_3$ (aq) and the layers separated. The aqueous layer was further extracted with DCM (x2) before the organic fractions were combined, dried over MgSO4, filtered and solvent removed in vacuo to afford crude material as a brown oil. Crude material was purified by column chromatography (normal phase, 340g, Biotage SNAP cartridge KP-Sil, 100mL per min, gradient 0% to 40% EtOAc in n-hexane) to afford the title compound (9.960 g, 27.6 mmol, 61.0 % yield) as an orange oil.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.13min, ES^+: 362.58 $[MH]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.36 (d, *J*=6.60 Hz, 2 H) 3.64 (s, 3 H) 3.80 (s, 3 H) 3.84 (s, 2 H) 3.86 (d, *J*=3.06 Hz, 2 H) 5.14 - 5.26 (m, 2H) 5.89 - 6.02 (m, 1 H) 6.40 (d, *J*=2.45 Hz, 1 H) 6.44 (dd, *J*=8.25, 2.38 Hz, 1 H) 6.83 (ddd, *J*=10.85, 8.65, 2.38 Hz, 1 H) 6.91 - 6.98 (m, 1 H) 7.19 (d, *J*=8.31 Hz, 1 H) 7.88 (td, *J*=8.44, 6.72 Hz, 1 H).

17-(3) Synthesis of 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(2,4-difluorophenyl)ethanone oxime

2-(Allyl(2,4-dimethoxybenzyl)amino)-1-(2,4-difluorophenyl)ethanone, 17-(2), (9.960 g, 27.561 mmol) was dissolved in ethanol (176 ml, 3008.688 mmol) before hydroxylamine hydrochloride (3.83 g, 55.122 mmol) and sodium acetate (4.52 g, 55.122 mmol) were added and the resultant solution heated to 90 °C for 4h. Solvent was removed in vacuo before the residue was redissolved in EtOAc and washed with sat. $NaHCO_3$ (aq). The layers were separated and the aqueous further extracted with EtOAc (x4). The combined organics were dried over $MgSO_4$, filtered and solvent removed in vacuo to give crude material as a dark orange oil. Crude material was purified by column chromatography (normal phase, 340g, Biotage SNAP cartridge KP-Sil, 100mL per min, gradient 0% to 60% EtOAc in n-hexane) to afford the title compound (6.52 g, 17.32 mmol, 62.9 % yield) as an orange oil.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.23min, 100% by ELSD, ES^+: 377.57 $[MH]^+$. desired product.

^1H NMR (400 MHz, METHANOL-*d*4) δ ppm 3.03 (dd, *J*=24.09, 7.21 Hz, 2 H) 3.36 - 3.54 (m, 4 H) 3.72 (d, *J*=0.98 Hz, 3 H) 3.76 (d, *J*=1.83 Hz, 3 H) 5.01 - 5.16 (m, 2 H) 5.67 - 5.85 (m, 1 H) 6.29 - 6.39 (m, 1 H) 6.42 - 6.47 (m, 1 H) 6.80 - 7.04 (m, 4 H).

17-(4) Synthesis of (±)- (3aR*,6aS*)-6a-(2,4-difluorophenyl)-5-(2,4-dimethoxybenzyl)hexahydro-1H-pyrrolo[3,4-c]isoxazole

2-(Allyl(2,4-dimethoxybenzyl)amino)-1-(2,4-difluorophenyl)ethanone oxime, 17-(3), (6.52 g, 17.322 mmol) was dissolved in toluene (129 ml, 1212.549 mmol) before the reaction mixture was heated at 120 °C. After 44h reaction showed progression of about 80%. Reaction mixture was allowed to cool before being concentrated in vacuo. The residue was then dissolved in DCM and purified by column chromatography (normal phase, 340g, Biotage SNAP cartridge KP-Sil, 50mL per min, gradient 0% to 80% EtOAc in n-hexane 20CV) to afford the title compound (3.169 g, 8.42 mmol, 48.6 % yield) as a dark orange oil.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.12min, ES^+: 377.57 $[MH]^+$.

17-(5) Synthesis of (±)-((3R*,4S*)-4-amino-4-(2,4-difluorophenyl)-1-(2,4-dimethoxybenzyl)pyrrolidin-3-yl)methanol

(±)-(3aR*,6aS*)-6a-(2,4-Difluorophenyl)-5-(2,4-dimethoxybenzyl)hexahydro-1H-pyrrolo[3,4-c]isoxazole, 17-(4), (1.921 g, 5.104 mmol) was dissolved in acetic acid

(26.5 ml, 462.088 mmol) at RT under nitrogen before zinc dust (3.34 g, 51.037 mmol) was added and the resultant solution stirred at RT for 19 h. The reaction mixture was filtered through celite washing thoroughly with ethyl acetate then evaporated. The residue was redissolved in ethyl acetate before sat. $NaHCO_3$ (aq) was added and the resultant solution stirred using a stirrer plate. The pH was adjusted to ~pH 9 using 1M NaOH (aq) before the layers were then separated. The aqueous layer was further extracted with EtOAc (x2) before the combined organics were washed with brine then dried ($MgSO_4$), filtered and evaporated to afford the title compound (1.773 g, 4.69 mmol, 92 % yield) as an orange oil.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.10min, 100% UV ES^+: 379.61 $[MH]^+$.

^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.68 - 2.81 (m, 1 H) 2.83 - 3.05 (m, 3 H) 3.07 - 3.22 (m, 1 H) 3.71 - 3.92 (m, 10 H) 6.41 - 6.53 (m, 2 H) 6.71- 6.93 (m, 2 H) 7.27 - 7.33 (m, 1 H) 7.45 - 7.60 (m, 1 H).

17-(6) Synthesis of (±)-N-(((3S*,4R*)-3-(2,4-difluorophenyl)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)pyrrolidin-3-yl)carbamothioyl)benzamide

(±)-((3R*,4S*)-4-Amino-4-(2,4-difluorophenyl)-1-(2,4-dimethoxybenzyl)pyrrolidin-3-yl)methanol, 17-(5), (1.733 g, 4.58 mmol) was dissolved in DCM (30 ml, 466.252 mmol) before benzoyl isothiocyanate (0.646 ml, 4.809 mmol) was added and the reaction mixture stirred at RT for 45 minutes. Solvent was evaporated after this time to give crude material as a beige foam, which was redissolved in DCM before being purified by column chromatography (normal phase, 50g, Biotage SNAP cartridge KP-Sil, 50mL per min, gradient 0% to 85% EtOAc in n-hexane 30CV) to afford the title compound (1.542 g, 2.85 mmol, 62.2 % yield) as a beige foam.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.46 min, ES^+: 542.66 $[MH]^+$.

^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.89 - 3.26 (m, 2 H) 3.59 - 4.05 (m, 13 H) 6.37 - 6.55 (m, 2 H) 6.69 - 6.81 (m, 1 H) 6.82 - 6.92 (m, 1 H) 7.47 - 7.57 (m, 2 H) 7.58 - 7.72 (m, 2 H) 7.86 (d, *J*=7.34 Hz, 2 H) 8.81 (s, 1 H).

17-(7) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,4-difluorophenyl)-6-(2,4-dimethoxybenzyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-(((3S*,4R*)-3-(2,4-difluorophenyl)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)pyrrolidin-3-yl)carbamothioyl)benzamide, 17-(6), (1.705 g, 3.148 mmol) in DCM (50 ml, 777.087 mmol) and pyridine (1.018 ml, 12.592

mmol) at -50 °C was added dropwise Trifluoromethanesulphonic acid anhydride (1.451 ml, 8.626 mmol) and the reaction mixture stirred for 1h at this temperature. The reaction mixture was quenched with sat. $NaHCO_3$ (aq) at -50°C before the reaction mixture was allowed to warm to RT. The layers were separated and the aqueous further extracted with DCM (x2). The combined organics were then washed with brine before being dried over $MgSO_4$, filtered and solvent removed in vacuo to give crude material as a bright yellow oil. Crude material was purified by column chromatography (normal phase, 50g, Biotage SNAP cartridge KP-Sil, 50mL per min, gradient 0% to 100% EtOAc in n-hexane over 35CV) to afford the title compound (1.115 g, 2.130 mmol, 67.6 % yield) as a beige foam.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.45min, ES^+: 524.66 $[MH]^+$.

17-(8) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,4-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-N-((4aR*,7aS*)-7a-(2,4-Difluorophenyl)-6-(2,4-dimethoxybenzyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 17-(7), (267 mg, .51 mmol) and DCM (2mL, 31.083 mmol) were added to a rbf at RT under nitrogen before trifluoroacetic acid (1 mL, 12.98 mmol) was added dropwise. The reaction mixture was then heated to 55°C overnight. Solvent was removed in vacuo after this time before the residue was redissolved in DCM. The reaction mixture was quenched with sat. $NaHCO_3$ (aq), before being basified to pH 9 using 1M NaOH (aq). The layers were separated and the aqueous extracted a further three times with DCM. The combined organics were dried over $MgSO_4$, filtered and solvent removed in vacuo to give crude material. Crude material was purified by column chromatography (normal phase, 10g, Biotage SNAP cartridge KP-Sil, 12mL per min, gradient 0% to 80% EtOAc in n-hexane) to afford the title compound (162 mg, 0.434 mmol, 85 % yield) as a beige foam.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.28min, ES^+: 374.55 $[MH]^+$.

17-(9) Synthesis of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2,4-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

To a solution (±)-N-((4aR*,7aS*)-7a-(2,4-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 17-(8), (162 mg, .434 mmol) in DMF (1 mL, 12.915 mmol) was added 1H-pyrazole-1-carboximidamide hydrochloride (86 mg, .586 mmol) followed by N-ethyl-N-isopropylpropan-2-amine (0.113 mL, .651

mmol) added dropwise and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to afford the title compound (196 mg, 0.434 mmol) and material used crude in next step.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.14min, ES^+: 416.55 $[MH]^+$.

17-(10) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2,4-difluorophenyl)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2,4-difluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, 17-(9), (196 mg, .434 mmol) in ethanol (4mL, 68.507 mmol) was added Ethyl 2-fluoroacetoacetate (0.109 mL, .867 mmol), then sodium ethoxide (0.356 mL, .954 mmol) (21% w/w solution in EtOH). The reaction was stirred at reflux for 1 h. The reaction mixture was diluted with EtOAc, sat. $NaHCO_3$ (aq), and H_2O (to avoid emulsion). The two layers were separated and the aqueous phase extracted with EtOAc (x2), the combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (normal phase, 10g, Biotage SNAP cartridge KP-Sil, 12mL per min, gradient 0% to 100% EtOAc in n-hexane over 20 CV then 8CV at 100%) to afford the title compound (130 mg, 0.260 mmol, 60.0 % yield) as a beige solid.
LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.39min, ES^+: 500.57 $[MH]^+$.
^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.19 (d, *J*=3.30 Hz, 3 H) 3.02 - 3.15 (m, 2 H) 3.52 (br. s., 2 H) 3.86 - 3.94 (m, 1 H) 3.94 - 4.03 (m, 1 H) 4.31 (d, *J*=11.49 Hz, 1 H) 6.76 - 7.10 (m, 2 H) 7.28 - 7.66 (m, 4 H) 8.13 (br. s., 2 H).

17-(11) Synthesis of (±)-2-((4aR*,7aS*)-2-amino-7a-(2,4-difluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methylpyrimidin-4-ol

(±)-N-((4aR*,7aS*)-7a-(2,4-Difluorophenyl)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 17-(10), (130 mg, .26 mmol) was dissolved in methanol (2.1 mL, 51.907 mmol) before DBU (0.157 mL, 1.041 mmol) was added and the solution was heated to reflux for 3 h. LCMS showed ~20% starting material after this time. A further 2.0 eq of DBU was added and heating continued for a further 1 h. Reaction mixture was allowed to cool before solvent was removed in vacuo and crude material purified by column

chromatography (normal phase, 10g, Biotage SNAP cartridge KP-NH, 12mL per min, gradient 0% to 100% 5CV EtOAc in n-hexane, 0-20% MeOH in EtOAc 5CV) to afford the title compound (150 mg, 0.152 mmol, 58.3 % yield) Residual DBU, 40% pure, as a yellow oil.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 0.88min, 100%, ES^+: 396.52 $[MH]^+$. Material was used as such in the next step.

^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.11 (d, *J*=2.93 Hz, 3 H) 2.69 - 2.80 (m, 1 H) 2.81 - 2.97 (m, 2 H) 3.50 - 3.64 (m, 3 H) 4.28 (d, *J*=11.25 Hz, 1H) 6.64 - 6.77 (m, 2 H) 7.22 - 7.31 (m, 1 H).

17-(12) Synthesis of (±)- (4aR*,7aS*)-7a-(2,4-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 17)

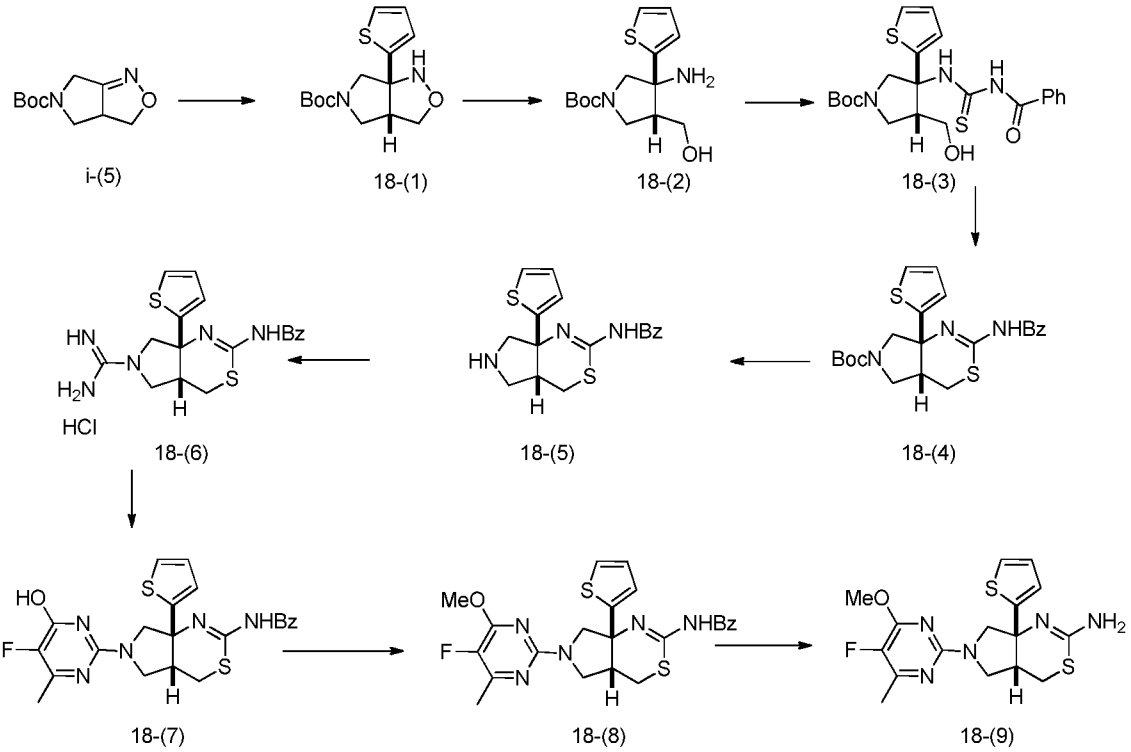
To a solution of (±)-2-((4aR*,7aS*)-2-amino-7a-(2,4-difluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methylpyrimidin-4-ol, 17-(11), (150 mg, .152 mmol) (contains DBU, 40% pure) in N,N-dimethylformamide(1 ml) was added potassium carbonate(42 mg) followed by methyl iodide (9.49 µl) in N,N-dimethylformamide(0.8 ml) and the mixture stirred at room temperature for two hours. LCMS showed 25% reaction progression after this time and so the reaction mixture was left stirring at RT. LCMS after 3 h indicated no change. A further 9.50 µL of MeI was added after this time and the solution left to stir at RT for a further 1h. LCMS indicated 40% reaction progression. Reaction mixture was left stirring over night. LCMS showed no change. A further 19.0 µL of MeI was added and the reaction left to stir for a further 2h. No starting material remaining. Reaction mixture was then diluted with ethyl acetate. The organic layer was washed with water (x3) then dried ($MgSO_4$) and evaporated to give crude material. This was purified by preparative HPLC using the Thermo Finnigan / Gilson system reverse phase HPLC (Phenomenex Luna C18, 250 x 50mm, 10µm, 80mL per min, gradient 20% to 95% (over 25min) then 95% (10min) MeCN in H_2O [0.1% acetic acid]) (1 injection in 2ml DMF). Only 1 fraction was found to be pure which was concentrated in vacuo, the residue dissolved in methanol and material isolated using a SCX (1 g) cartridge to afford the title compound (12 mg, 0.029 mmol, 19.0 % yield) as a white foam.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.19min, 100%, ES^+: 410.55 $[MH]^+$.

^1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.21 (s, 3 H) 2.80 - 2.93 (m, 1 H) 2.95 - 3.08 (m, 2 H) 3.51 - 3.62 (m, 1 H) 3.62 - 3.76 (m, 2 H) 3.89 (br. d, *J*=12.60 Hz, 3 H) 3.98 - 4.10

(m, 1 H) 6.13 (br. s, 2 H) 7.11 (td, *J*=8.44, 2.45 Hz, 1 H) 7.18 - 7.28 (m, 1 H) 7.29 - 7.42 (m, 1 H).

Example 18: (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



18-(1) Synthesis of (±)-(3aR*,6aR*)-tert-butyl 6a-(thiophen-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a solution of 2-bromothiophene (4.65 mL, 48.1 mmol) in dry THF (15 mL) and toluene (75 mL) at –78°C under nitrogen was added dropwise 1.6 M *n*-BuLi in hexanes (30 mL, 48.1 mmol). The reaction mixture was stirred at this temperature for 20 mins. $BF_3.OEt_2$ (6.1 mL, 48.1 mmol) was then added dropwise, followed by a solution of tert-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, prepared as described in preparation example i-(5), (6 g, 28.27 mmol) in THF (30 mL) over 25 min via canula. The mixture was stirred for 3h at –78°C and then quenched with sat. aq. NH_4Cl. (150 mL), and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as a brown oil (10.93 g). The residue was then purified by silica gel column chromatography (gradient from 10% to 50% EtOAc in Hexanes) to give the title compound as a yellow syrup (6.33 g, 76%).
LCMS: Rt 1.39 min, m/z= 297 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.47 (s, 9 H), 3.33 (tt, J=7.7, 4.1 Hz, 1 H), 3.52-3.63 (m, 1 H), 3.68-3.99 (m, 4 H), 4.18-4.45 (m, 1 H), 5.30 (br. s, 1 H), 7.01 (dd, J=4.9, 3.6 Hz, 1 H), 7.06 (dd, J=3.5, 1.2 Hz, 1 H), 7.24-7.28 (m, 1H).

18-(2) Synthesis of (±)-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(thiophen-2-yl)pyrrolidine-1-carboxylate

To a solution of (±)-(3aR*,6aR*)-tert-butyl 6a-(thiophen-2-yl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (6.33 g, 21.4 mmol) in THF (155 mL) was added zinc powder (12.3 g, 187.9 mmol) and AcOH (12.5 mL, 218.3 mmol). The reaction mixture was stirred at r.t. for 4h. Another portion of AcOH (10 mL) and Zn (10 g) were added. The reaction mixture was stirred for 19h at r.t., then filtered over celite, washed with EtOAc and the resulting solution was concentrated under reduced pressure. The residue was then basified with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc (x 2). The combined organic extracts were dried over Na_2SO_4, concentrated to give the crude amino alcohol (6.35 g) as a colorless foam, which was used without further purification in the next step.
LCMS: Rt 0.96 min, m/z= 299 $[M+H]^+$.

18-(3) Synthesis of (±)-(3R*,4R*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(thiophen-2-yl)pyrrolidine-1-carboxylate

Benzoyl isothiocyanate (3.72 mL, 27.7 mmol) was added dropwise to a solution (±)-(3R*,4R*)-tert-butyl 3-amino-4-(hydroxymethyl)-3-(thiophen-2-yl)pyrrolidine-1-carboxylate (6.35 g, 21.3 mmol) in DCM (37 mL). The reaction was stirred at r.t. for 2h and was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient from 20% to 60% EtOAc in Hexanes) to afford the title compound as a colorless foam (8.18 g, 83% over 2 steps).
LCMS: Rt 1.53 min, m/z =462 $[M+H]^+$.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 2.22-2.48 (m, 1 H), 2.67-2.84 (m, 1 H), 3.52-3.65 (m, 1 H), 3.73 (br. s., 1 H), 4.01 (m, 2 H), 4.21 (m, 1 H), 4.66-4.74 (m, 1 H), 6.96-7.01 (m, 1 H), 7.05 (d, J=3.3 Hz, 1 H), 7.26 (d, J=5.0 Hz, 1 H), 7.47-7.57 (m, 2 H), 7.64 (m, 1 H), 7.85 (m, 2 H), 8.91 (br. s., 1 H), 11.62-11.86 (m, 1 H).

18-(4) Synthesis of (±)-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(thiophen-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

To a solution (±)-(3R*,4R*)-tert-butyl 3-(3-benzoylthioureido)-4-(hydroxymethyl)-3-(thiophen-2-yl)pyrrolidine-1-carboxylate (5 g, 10.8 mmol) in dichloromethane (54 mL) was added pyridine (5.4 mL). The solution was cooled to –20°C and Tf_2O (2.7 ml, 16.2 mmol) was added dropwise over 30 min. The reaction was

left to warm to 0°C over 1h and was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (gradient from 20% to 50% EtOAc in Hexanes) to afford the title product as a colorless foam (4.35 g, 91%).

LCMS: Rt 1.71min, m/z 444 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9 H), 2.81-2.98 (m, 2 H), 3.29 (dd, J=12.9, 2.6 Hz, 1 H), 3.70-3.83 (m, 2 H), 3.84-3.96 (m, 2 H), 6.95-7.11 (m, 2 H), 7.30-7.34 (m, 1 H), 7.41-7.48 (m, 2 H), 7.53 (s, 1 H), 8.12 (br. s., 2 H), 12.55 (br. s, 1 H).

18-(5) Synthesis of (±)-N-((4aR*,7aR*)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-(4aR*,7aR*)-tert-butyl 2-benzamido-7a-(thiophen-2-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (4.35 g, 9.8 mmol) in dichloromethane (42 mL) was added TFA (21 mL). The reaction mixture was stirred for 1.5h at r.t. and was then concentrated under reduced pressure. The residue was purified by SCX to give the title product as a yellow foam (3.17 g, 94%).

LCMS: Rt 1.11 min, m/z 344 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.84 (dd, J=13.4, 4.2 Hz, 1 H), 2.95 (tt, J=8.4, 4.0 Hz, 1 H), 3.31-3.49 (m, 5 H), 7.02 (dd, J=5.1, 3.6 Hz, 1 H), 7.07 (d, J=2.6 Hz, 1 H), 7.30 (dd, J=5.1, 1.2 Hz, 1 H), 7.40-7.46 (m, 2 H), 7.48-7.54 (m, 1 H), 8.16 (d, J=7.2 Hz, 2 H).

18-(6) Synthesis of (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

To a solution of (±)-N-((4aR*,7aR*)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (3.17 g, 9.2 mmol) in DMF (19 mL) was added 1H-pyrazole-1-carboximidamide hydrochloride (1.34 g, 9.5 mmol), then diisopropylamine (1.38 mL, 9.7 mmol). The reaction mixture was stirred for 6h at r.t.. 1H-pyrazole-1-carboximidamide hydrochloride (700 mg) and diisopropylamine (0.7 mL) were added, and the reaction mixture left to stir at r.t. for 17h. The mixture was then concentrated under reduced pressure to give a viscous sticky oil which was used directly in the next step without further purification.

LCMS: Rt 1.15 min, m/z 386 $[M+H]^+$.

18-(7) Synthesis of (±)- N-((4aR*,7aR*)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of the crude (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride in EtOH (84 ml) was added ethyl 2-fluoroacetoacetate (2.32 mL, 18.5 mmol), then NaOEt (7.6 mL, 20.3 mmol, 21% w/w solution in EtOH). The reaction was stirred at r.t. for 2h and at reflux for 2h. The reaction mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous phase extracted with EtOAc (x2). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient from 60% to 100% EtOAc in Hexanes) to give the desired product as a colorless foam (3.27g, 75% over 2 steps).
LCMS: Rt 1.34 min, m/z 470 $[M+H]^+$.
^1H NMR (400 MHz, CDCl3) δ ppm 2.20 (d, J=3.3 Hz, 3 H), 2.96 (dd, J=13.6, 3.8 Hz, 1 H), 3.07 (m, J=8.5, 8.5, 4.2 Hz, 1 H), 3.35 (dd, J=13.5, 3.5 Hz, 1 H), 3.92-4.04 (m, 2 H), 4.07-4.16 (m, 1 H), 4.19 (d, J=11.6 Hz, 1 H), 7.01-7.05 (m, 1 H), 7.07 (d, J=2.8 Hz, 1 H), 7.33 (d, J=5.0 Hz, 1 H), 7.39-7.47 (m, 2 H), 7.48-7.56 (m, 1 H), 8.04 (d, J=7.2 Hz, 2 H), 11.25 (br. s, 1 H).

18-(8) Synthesis of (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (200 mg, 0.43 mmol) in DMF (0.5 ml) was added K_2CO_3 (88 mg, 0.64 mmol) followed by MeI (0.5 mL, 0.11 mmol, 0.2M in DMF) every 30 min (x4). The reaction mixture was stirred at r.t. for a further 40 min and was then quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated uder reduced pressure. The residue was purified by silica gel column chromatography (gradient from 30% to 100% EtOAc in Hexanes) to give the title compound as a colorless oil (96 mg).
LCMS: Rt 1.79 min, m/z 484 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (d, J=2.9 Hz, 3 H), 2.96 (dd, J=13.5, 4.1 Hz, 1 H), 3.07 (m, 1 H), 3.36 (dd, J=13.4, 3.7 Hz, 1 H), 3.95-4.02 (m, 5 H), 4.09 (d, J=12.1 Hz, 1 H), 4.22 (d, J=12.0 Hz, 1 H), 7.04 (dd, J=5.1, 3.6 Hz, 1 H), 7.11 (d, J=2.7 Hz, 1 H), 7.33 (dd, J=5.1, 1.2 Hz, 1 H), 7.39-7.45 (m, 2 H), 7.47-7.51 (m, 1 H), 8.12 (d, J=7.0 Hz, 2 H).

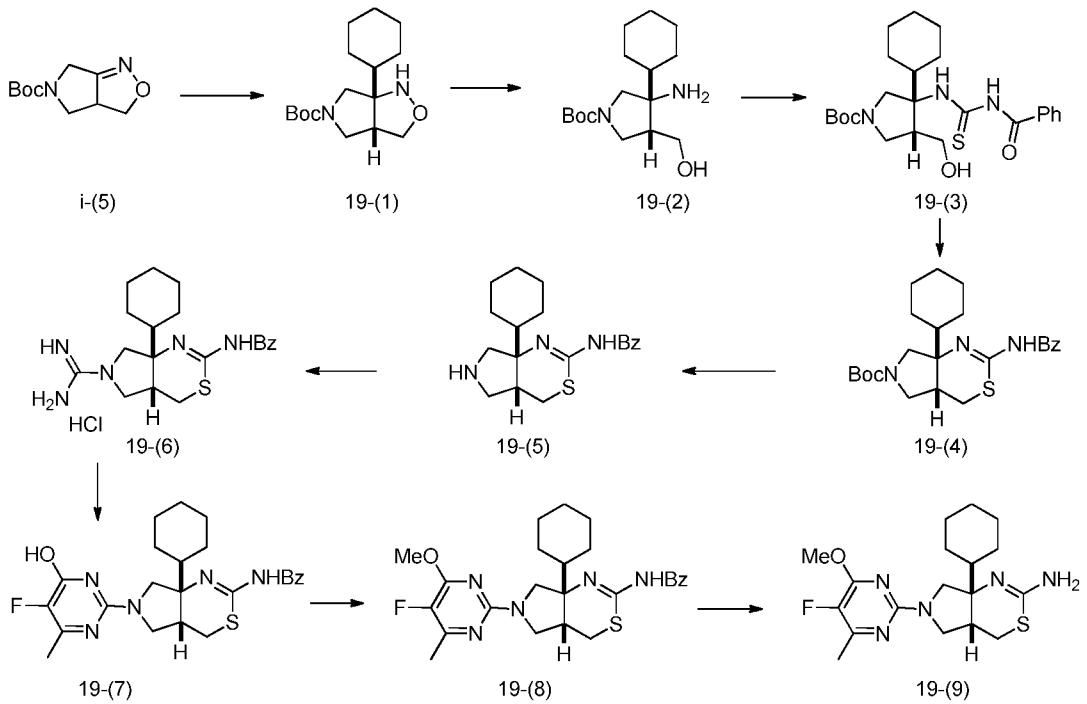
18-(9) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 18)

(±)-N-((4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(thiophen-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (89 mg, 0.18 mmol) was dissolved in MeOH (1.5 mL). DBU (61 µL, 0.40 mmol) was added, and the solution was heated to reflux for 20h and then concentrated under reduced pressure. H_2O was then added, and the solution was extracted with EtOAc (x 3). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by SCX and silica gel column chromatography (gradient from 0% to 9% MeOH in DCM) to afford the title compound as a colorless solid (16 mg).

LCMS: Rt 1.19 min, m/z 380 $[M+H]^+$.

^1H NMR (600 MHz, CDCl3) δ ppm 2.30 (d, J=2.6 Hz, 3 H), 2.83 (dq, J=8.4, 4.2 Hz, 1 H), 2.96 (dd, J=13.1, 4.5 Hz, 1 H), 3.26 (dd, J=13.1, 4.0 Hz, 1 H), 3.76-3.81 (m, 1 H), 3.83-3.89 (m, 1 H), 3.96 (s, 3 H), 4.00 (d, J=11.1 Hz, 1 H), 4.09 (d, J=11.1 Hz, 1 H), 4.25-4.52 (m, 2 H), 6.93-6.96 (m, 1 H), 7.00 (dd, J=5.0, 3.8 Hz, 1 H), 7.23 (dd, J=5.1, 1.0 Hz, 1 H).

Example 19: (±)-(4aR*,7aR*)-7a-cyclohexyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



19-(3) Synthesis of (±)-(3R*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-cyclohexyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate

A solution of *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, i-(5), (2.20 g) in THF (15 ml) and toluene (15 ml) was cooled to -78°C, and boron trifluoride etherate (1.5 mL) followed by cyclohexylmagnesium chloride (6 ml, 2N in diethyl ether) were added dropwise. After stirring for 1 h, ammonium chloride (sat., aq., 10 mL) was added and the reaction mixture was allowed to warm to room temperature. Water (50 mL) was added, and the mixture extracted with EtOAc (2 x 75 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to give an oil (3.45 g) presumed to contain 19-(1). The oil was dissolved in THF (40 mL) and acetic acid (5 mL) was added, followed by zinc powder (2.50 g). After stirring vigorously for 18 h, the mixture was filtered through celite, washing with EtOAc (150 mL). The filtrate was evaporated and $NaHCO_3$ (sat., aq., 50 mL) was added. The mixture was extracted with EtOAc (2 x 100 mL), dried over $MgSO_4$, and evaporated to afford an oil (2.78 g), presumed to contain 19-(2). The oil was dissolved in DCM (20 mL) before benzoyl isothiocyanate (0.20 mL) was added. After 10mins, the reaction mixture was concentrated to a volume of ~5 mL and purified by silica gel column chromatography (gradient from 0% to 50% EtOAc in hexanes) to afford the title compound, 19-(3) (374 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.96 – 1.99 (m, 9 H), 1.49 (s, 9 H), 2.69 – 2.93 (m, 2 H), 3.17 – 3.45 (m, 2 H), 3.54 – 3.67 (m, 1 H), 3.70 – 3.84 (m, 2 H), 3.88 – 4.02 (m, 2 H), 7.47 – 7.56 (m, 2 H), 7.58 – 7.66 (m, 1 H), 7.80 – 7.86 (m, 2 H), 8.84 (s, 1 H), 11.24 (br s, 1 H).

19-(4) Synthesis of (±)-(4aR*,7aR*)-*tert*-butyl 2-benzamido-7a-cyclohexyl-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

(±)-(3R*,4R*)-tert-Butyl 3-(3-benzoylthioureido)-3-cyclohexyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate, prepared in preparation example 19-(3), (202 mg) was dissolved in DCM (2mL) and pyridine (0.20 mL) was added. The solution was cooled to -10°C and trifluoromethanesulfonic anhydride (0.12 mL) added dropwise over 30mins. After stirring for 2 h, $NaHCO_3$ (sat., aq., 20 mL) was added, and the mixture extracted with DCM (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, evaporated and purified by silica gel column chromatography (gradient from 0% to 40% EtOAc in hexanes) to afford the title compound, 6-(4) (110 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 0.92 – 1.24 (m, 4 H), 1.39 (s, 9 H), 1.49 – 1.86 (m, 6 H), 1.91 – 2.02 (m, 1 H), 2.67 – 2.90 (m, 2 H), 3.21 – 3.67 (m, 5 H), 7.29 – 7.45 (m, 3 H), 8.11 (d, J 7.2 Hz, 2 H).

19-(5) Synthesis of (±)-N-((4aR*,7aR*)-7a-cyclohexyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-(4aR*,7aR*)-*tert*-butyl 2-benzamido-7a-cyclohexyl-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate, prepared in preparation example 19-(4), (110 mg) was dissolved in DCM (2 mL) and trifluoracetic acid (1 mL) was added. After stirring for 90 min, the reaction mixture was evaporated, $NaHCO_3$ (sat., aq., 20 mL) was added, and the mixture extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to afford the title compound, 6-(5) (71 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.06 - 1.36 (m, 5 H), 1.53 - 1.64 (m, 1 H), 1.66 - 1.98 (m, 5 H), 2.70 - 2.90 (m, 2 H), 3.02 - 3.17 (m, 2 H), 3.24 - 3.39 (m, 3 H), 7.37 - 7.45 (m, 2 H), 7.45 - 7.56 (m, 1 H), 8.16 (d, *J*=7.5 Hz, 2 H).

19-(8) Synthesis of (±)-N-((4aR*,7aR*)-7a-cyclohexyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

(±)-N-((4aR*,7aR*)-7a-cyclohexyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, obtained in preparation example 19-(5), (71 mg) was dissolved in DMF (1 mL). 1H-Pyrazole-1-carboxamidine hydrochloride (31.0 mg) was added, followed by diisopropylethylamine (30.0 mg) dropwise. After stirring at room temperature for 1 h, the reaction mixture was concentrated to dryness to obtain a solid presumed to contain 6-(6) as a hydrochloride salt. The solid was dissolved in ethanol (2 ml), before ethyl 2-fluoro-3-oxobutanoate (61.2 mg) was added, followed by sodium ethoxide (105 mg). The reaction mixture was stirred at room temperature for 2 h, and then heated to reflux. After a further hour the mixture was cooled, $NaHCO_3$ (sat., aq., 25 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, evaporated and purified by silica gel chromatography (0 to 80% EtOAc in DCM), collecting the spot at Rf 0.30 in EtOAc:DCM 2:1, to afford an impure sample of 6-(7) (50 mg). The crude pyrimidone was dissolved in DMF (0.5 mL), and K_2CO_3 (100 mg) was added, followed by methyl iodide (12.6 mg) as a solution in DMF (0.9 mL), portionwise over 1 h. $NaHCO_3$ (sat. aq., 10mL) was then added and the mixture was extracted with 3 x 15mL EtOAc. The combined organic portions were dried over $MgSO_4$, evaporated and purified by silica gel column chromatography (gradient from 0% to 40% EtOAc in hexanes) to afford the title compound, 19-(8) (24 mg).

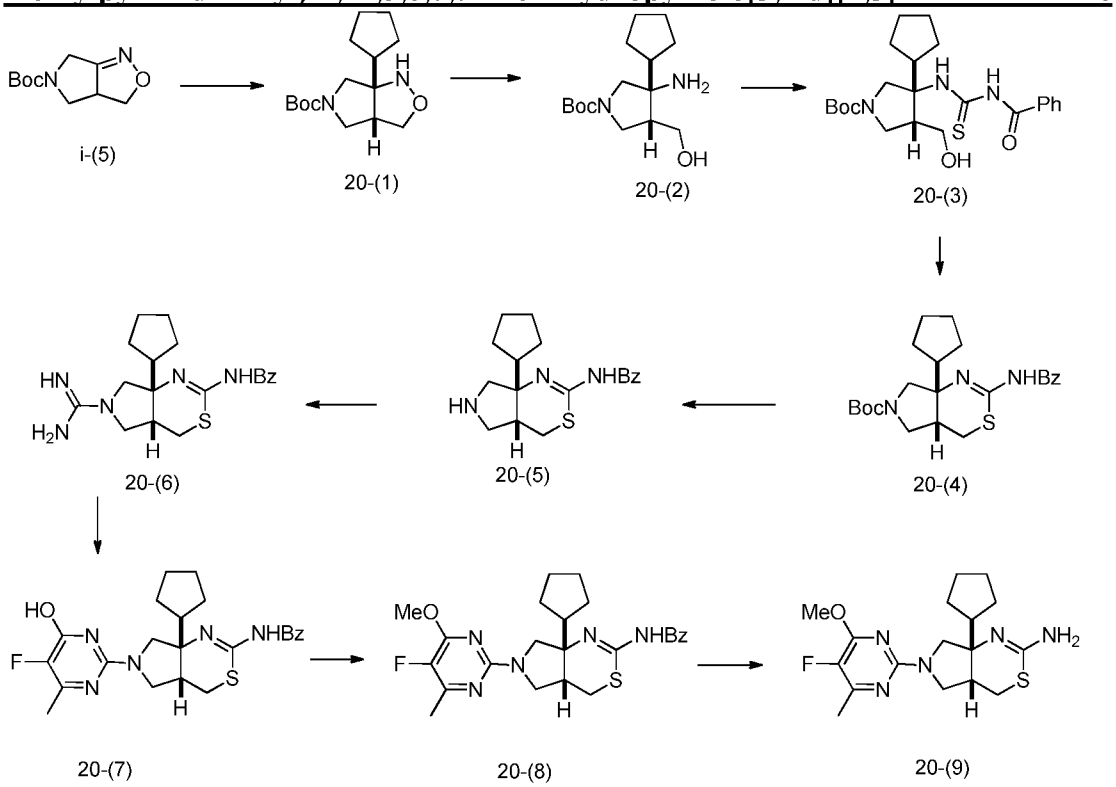
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.02 – 1.41 (m, 5 H), 1.50 – 2.37 (m, 9 H), 2.86 – 3.05 (m, 2 H), 3.37 – 3.46 (m, 1 H), 3.68 – 3.95 (m, 4 H), 3.98 (s, 3 H), 7.36 – 7.50 (m, 3 H), 8.18 (d, J 7.5 Hz, 2 H), 12.38 (br s, 1 H).

19-(9) Synthesis of (±)-(4aR*,7aR*)-7a-cyclohexyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 19)

(±)-N-((4aR*,7aR*)-7a-cyclohexyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, obtained in preparation example 19-(8), (24 mg) was dissolved in methanol (1 ml) before 1,8-diazabicycloundec-7-ene (30 mg) was added. The reaction mixture was heated to reflux and stirred for 5 h, then concentrated and purified by silica gel column chromatography (Method G2, gradient from 0% to 40% EtOAc in hexanes) to obtain the title compound, 6-(9) (14.6 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.01 - 1.31 (m, 4 H), 1.47 - 1.58 (m, 1 H), 1.63 - 1.88 (m, 5 H), 1.95 – 2.04 (m, 1 H), 2.30 (d, J=2.9 Hz, 3 H), 2.53 - 2.65 (m, 1 H), 2.95 (dd, *J*=12.9, 5.6 Hz, 1 H), 3.23 (dd, *J*=12.8, 4.3 Hz, 1 H), 3.50 - 3.63 (m, 2 H), 3.70 - 3.79 (m, 2 H), 3.97 (s, 3 H).

Example 20: (±)-(4aR*,7aR*)-7a-cyclopentyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



20-(3) Synthesis of (±)-(3R*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-cyclopentyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate

A solution of *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate i-(5) (4.13g) in THF (80 ml) was cooled to 0°C, and boron trifluoride etherate (2.6 mL) followed by cyclopentylmagnesium bromide (40 ml, 2N in diethyl ether) were added dropwise. After stirring for 3 h, ammonium chloride (sat., aq., 100 mL) was added and the reaction mixture was allowed to warm to room temperature. Water (100 mL) was added, and the mixture extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to give an oil (8.24 g). The oil was purified by silica gel chromatography, collecting fractions containing molecular weight 282 on LCMS analysis, to afford a crude sample presumed to contain 20-(1) (3.30 g). The oil was dissolved in THF (20 mL) and acetic acid (2 mL) was added, followed by zinc powder (1.00 g). After stirring vigorously for 16 h, the mixture was filtered through celite, washing with MeOH (100 mL). The filtrate was evaporated and $NaHCO_3$ (sat., aq., 50 mL) was added. The mixture was extracted with EtOAc (2 x 75 mL), dried over $MgSO_4$, and evaporated to afford an oil (3.29 g), presumed to contain 20-(2). The oil was dissolved in DCM (25 mL) before benzoyl isothiocyanate (1.5 mL) was added. After 18 h, the reaction mixture was added to $NaHCO_3$ (sat., aq., 100 mL) and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, evaporated and purified by silica gel column chromatography (gradient from 0% to 50% EtOAc in hexanes) to afford the title compound, 20-(3) (980 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.37 – 1.94 (m, 7 H), 1.50 (s, 9 H), 2.61 – 2.83 (m, 2 H), 3.29 – 4.04 (m, 7 H), 7.48 – 7.60 (m, 2 H), 7.60 – 7.70 (m, 1 H), 7.78 – 7.90 (m, 2 H), 8.86 (s, 1 H), 11.24 (br s, 1 H).

20-(4) Synthesis of (±)-(4aR*,7aR*)-*tert*-butyl 2-benzamido-7a-cyclopentyl-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

Synthesized from (±)-(3R*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-cyclopentyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate 20-(3) (725 mg) by an analogous procedure to that used in preparation example 19-(4), affording 359 mg. LCMS (method A2 Short_20_95): Rt 1.62 min, m/z 430 $[M+H]^+$.

20-(5) Synthesis of (±)-N-((4aR*,7aR*)-7a-cyclopentyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-(4aR*,7aR*)-*tert*-butyl 2-benzamido-7a-cyclopentyl-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate 20-(5) (359 mg) by a

procedure analogous to preparation example 19-(5) affording 272 mg of crude product, which was used without purification or analysis.

20-(8) Synthesis of (±)-N-((4aR*,7aR*)-7a-cyclopentyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aR*)-7a-cyclopentyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (272 mg, crude) by an analogous procedure to that used in preparation example 19-(8), affording 51 mg.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.40 - 1.68 (m, 4 H), 1.69 – 1.81 (m, 2 H), 1.82 - 1.99 (m, 2 H), 2.23 - 2.35 (m, 4 H), 2.73 - 2.89 (m, 1 H), 3.02 (dd, *J*=13.4, 5.1 Hz, 1 H), 3.40 (dd, *J*=13.4, 4.0 Hz, 1 H), 3.70 - 3.95 (m, 4 H), 3.99 (s, 3 H), 7.34 - 7.43 (m, 2 H), 7.43 - 7.52 (m, 1 H), 8.13 – 8.22 (m, 2 H)

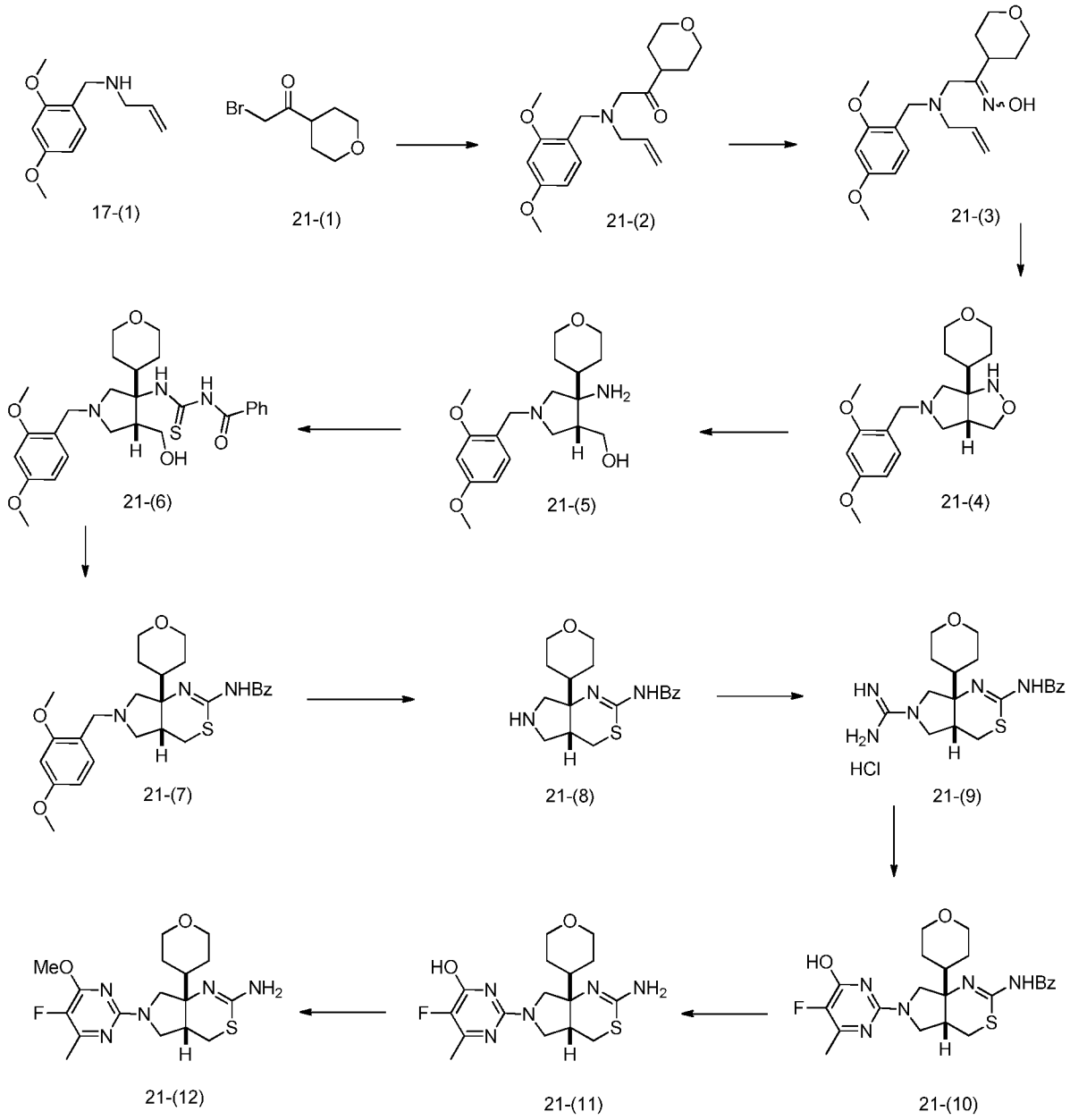
20-(9) Synthesis of (±)-(4aR*,7aR*)-7a-cyclopentyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 20)

Synthesized from (±)-N-((4aR*,7aR*)-7a-cyclopentyl-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 20-(8), (69 mg) by a procedure analogous to preparation example 19-(9), affording 51mg as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.26 - 1.37 (m, 2 H), 1.46 - 1.57 (m, 2 H), 1.57 - 1.66 (m, 2 H), 1.66 - 1.80 (m, 2 H), 2.06 - 2.16 (m, 1 H), 2.29 (d, *J*=2.9 Hz, 3 H), 2.34 – 2.41 (m, 1 H), 2.94 (dd, *J*=12.8, 6.8 Hz, 1 H), 3.16 (dd, *J*=12.8, 3.9 Hz, 1 H), 3.49 - 3.63 (m, 2 H), 3.71 - 3.82 (m, 2 H), 3.96 (s, 3 H), 4.27 (br. s., 2 H).

LCMS (method A2 Short_20_95): Rt 0.97 min, m/z 366 $[M+H]^+$.

Example 21: (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



21-(1) Synthesis of 2-bromo-1-(tetrahydro-2H-pyran-4-yl)ethanone

Tetrahydro-2H-pyran-4-carboxylic acid (3 g, 23.052 mmol) was dissolved in dry DCM (20 mL) and one drop of DMF added. The reaction mixture was cooled to 0°C before Oxalyl chloride (2.212 ml, 25.357 mmol) was added dropwise and the reaction mixture stirred at rt under nitrogen for 2 hours. Solvent was removed in vacuo after this time, before the residue was redissolved in DCM (20 mL) and the resulting solution was added dropwise to a solution of Trimethylsilyldiazomethane (20.75 ml, 41.493 mmol) (2M in hexane) at -10°C. The reaction mixture was stirred at rt overnight. The reaction mixture was cooled to -10°C again after this time before aqueous Hydrobromic acid

(2.4 ml, .00 mmol) (48% in water) was added dropwise. The reaction mixture was allowed to stir at rt for 1 h before being diluted with sat. $NaHCO_3$ (aq) and brine. The layers were separated and the aqueous extracted a further 2 times with DCM. The combined organics were dried over $MgSO_4$, filtered and solvent removed in vacuo to afford crude material as a brown oil. Crude material was purified by column chromatography (normal phase, 50g, Biotage SNAP cartridge KP-Sil, 50mL per min, gradient 0% to 60% EtOAc in n-hexane 10CV) to afford the title compound (3.413 g, 16.48 mmol, 71.5 % yield) as yellow crystals.

LCMS (Acquity UPLC C18, 2.1 x 50mm, 1.7mm, 0.6mL per min, 40°C, gradient 5-95% MeCN in water (0.1% formic acid) over 1.50min - held for 0.50min). Retention time 1.05min, ES^+: 207.40, 209.40 $[MH]^+$.

^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.69 - 1.87 (m, 4H) 2.94 - 3.04 (m, 1H) 3.46 (td, *J*=11.31, 3.06 Hz, 2H) 3.96 (s, 2H) 3.98 -4.05 (m, 2H).

21-(2) Synthesis of 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)ethanone

Starting from N-(2,4-dimethoxybenzyl)prop-2-en-1-amine, obtained in example 17-(1) and 2-bromo-1-(tetrahydro-2H-pyran-4-yl)ethanone, 21-(1), compound 21-(2) (2.33 g) was synthesised following an analogous procedure to that for preparing compound 17-(2) as described in Example 17.

LCMS Retention time 1.03min, m/z 334.61 $[MH]^+$.

^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.57 - 1.63 (m, 4 H) 2.73 - 2.86 (m, 1 H) 3.18 (br. s., 2 H) 3.28 (br. s., 2 H) 3.33 - 3.42 (m, 2 H) 3.65 (br. s., 2H) 3.80 (s, 3 H) 3.81 (s, 3 H) 3.93 - 3.99 (m, 2 H) 5.11 - 5.27 (m, 2 H) 5.81 - 6.00 (m, 1 H) 6.40 - 6.50 (m, 2 H) 7.22 (d, *J*=7.95 Hz, 1 H).

21-(3) Synthesis of 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)ethanone oxime

Starting from 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)ethanone, 21-(2), compound 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)ethanone oxime (2.083 g) was synthesised following an analogous procedure to that for preparing compound 17-(3) as described in Example 17.

LCMS Retention time 1.01-1.05 min, ES^+: 349.62 $[MH]^+$.

21-(4) Synthesis of **(±)**-(3aR*,6aR*)-5-(2,4-dimethoxybenzyl)-6a-(tetrahydro-2H-pyran-4-yl)hexahydro-1H-pyrrolo[3,4-c]isoxazole

Starting from 2-(allyl(2,4-dimethoxybenzyl)amino)-1-(tetrahydro-2H-pyran-4-yl)ethanone oxime, 21-(3), compound **(±)**-(3aR*,6aR*)-5-(2,4-dimethoxybenzyl)-6a-

(tetrahydro-2H-pyran-4-yl)hexahydro-1H-pyrrolo[3,4-c]isoxazole (1.085 g) was synthesised following an analogous procedure to that for preparing compound 17-(4) as described in Example 17.
LCMS Retention time 0.91min, ES^+: 349.62 $[MH]^+$.

21-(5) Synthesis of (±)-((3R*,4R*)-4-amino-1-(2,4-dimethoxybenzyl)-4-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanol

Starting from (±)-(3aR*,6aR*)-5-(2,4-dimethoxybenzyl)-6a-(tetrahydro-2H-pyran-4-yl)hexahydro-1H-pyrrolo[3,4-c]isoxazole, 21-(4), compound (±)-((3R*,4R*)-4-amino-1-(2,4-dimethoxybenzyl)-4-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanol (630 mg) was synthesised following an analogous procedure to that for preparing compound 17-(5) as described in Example 17.
LCMS Retention time 0.73min, ES^+: 351.63 $[MH]^+$.
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.43 - 1.54 (m, 3 H) 1.55 - 1.66 (m, 1 H) 1.73 (d, *J*=12.72 Hz, 1 H) 2.11 - 2.21 (m, 1 H) 2.45 - 2.54 (m, 3 H) 2.66 (br. s, 2 H) 2.66 (dd, *J*=9.35, 4.22 Hz, 1 H) 3.30 - 3.44 (m, 2 H) 3.56 (d, *J*=3.55 Hz, 2 H) 3.68 (d, *J*=5.99 Hz, 2 H) 3.81 (d, *J*=6.11 Hz, 6 H) 4.04 (d, *J*=12.35 Hz, 2 H) 6.41 - 6.51 (m, 2 H) 7.20 (d, *J*=8.07 Hz, 1 H).

21-(6) Synthesis of (±)-N-(((3R*,4R*)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)-3-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)carbamothioyl)benzamide

Starting from (±)-((3R*,4R*)-4-amino-1-(2,4-dimethoxybenzyl)-4-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanol, 21-(5), compound (±)-N-(((3R*,4R*)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)-3-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)carbamothioyl)benzamide (648 mg) was synthesised following an analogous procedure to that for preparing compound 17-(6) as described in Example 17.
LCMS Retention time 1.20 min, ES^+: 514.65 $[MH]^+$.
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.39 - 1.50 (m, 1 H) 1.53 - 1.63 (m, 3 H) 1.72 (d, *J*=12.47 Hz, 1 H) 2.42 (br. s, 1 H) 2.68 (br. s., 1 H) 2.81 (br. s., 1 H) 3.15 (br. s, 1 H) 3.28 (br. s., 1 H) 3.35 - 3.48 (m, 3 H) 3.53 - 3.69 (m, 3 H) 3.82 (s, 6 H) 3.84 - 3.93 (m, 2 H) 4.02 (d, J=10.76 Hz, 2 H) 6.41 - 6.52 (m, 2 H) 7.24 (br. s., 1 H) 7.52 (t, *J*=7.50 Hz, 2 H) 7.63 (t, *J*=7.34 Hz, 1 H) 7.82 - 7.87 (m, 2 H) 8.81 (s, 1 H).

21-(7) Synthesis of (±)-N-((4aR*,7aR*)-6-(2,4-dimethoxybenzyl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-(((3R*,4R*)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)-3-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)carbamothioyl)benzamide, 21-(6), compound (±)-N-((4aR*,7aR*)-6-(2,4-dimethoxybenzyl)-7a-(tetrahydro-2H-pyran-4-

yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (362 mg, 81% pure) was synthesised following an analogous procedure to that for preparing compound 17-(7) as described in Example 17.
LCMS Retention time 1.27min, ES^+: 496.66 $[MH]^+$.

21-(8) Synthesis of (±)-N-((4aR*,7aR*)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-((4aR*,7aR*)-6-(2,4-dimethoxybenzyl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 21-(7), compound (±)-N-((4aR*,7aR*)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (134 mg) was synthesised following an analogous procedure to that for preparing compound 17-(8) as described in Example 17.
LCMS Retention time 1.00min, ES^+: 346.57 $[MH]^+$.
^1H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.52 - 1.91 (m, 6 H) 2.65 - 2.78 (m, 1 H) 2.87 (dd, *J*=13.4, 4.7 Hz, 1 H) 3.02 - 3.18 (m, 2 H) 3.24 - 3.34 (m, 2H) 3.39 (tt, *J*=11.6, 2.5 Hz, 2 H) 4.02 - 4.12 (m, 2 H) 7.38 - 7.46 (m, 2 H) 7.46 - 7.53 (m, 1 H) 8.02 - 8.25 (m, 2 H).

21-(9) Synthesis of (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

Starting from (±)-N-((4aR*,7aR*)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 21-(8), compound (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride (164 mg) was synthesised following an analogous procedure to that for preparing compound 17-(9) as described in Example 17.
LCMS Retention time 0.98 min, ES^+: 388.61 $[MH]^+$.

21-(10) Synthesis of (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Starting from (±)-N-((4aR*,7aR*)-6-carbamimidoyl-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, 21-(10), compound (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (148 mg) was synthesised following an analogous procedure to that for preparing compound 17-(10) as described in Example 17.
LCMS Retention time 1.17 min, ES^+: 472.62 $[MH]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.62 - 1.74 (m, 3 H) 1.87 (d, *J*=14.9 Hz, 1 H) 1.96 (br. s, 1 H) 2.21 (d, *J*=3.4 Hz, 3 H) 2.89 (br. s, 1 H) 3.03 (dd, *J*=13.2, 3.3 Hz, 1 H) 3.34 - 3.47 (m, 3 H) 3.71 - 3.87 (m, 3 H) 3.88 - 3.98 (m, 1 H) 4.05 - 4.12 (m, 2 H) 7.36 - 7.45 (m, 2 H) 7.45 - 7.52 (m, 1 H) 8.10 (d, *J*=6.8 Hz, 2 H).

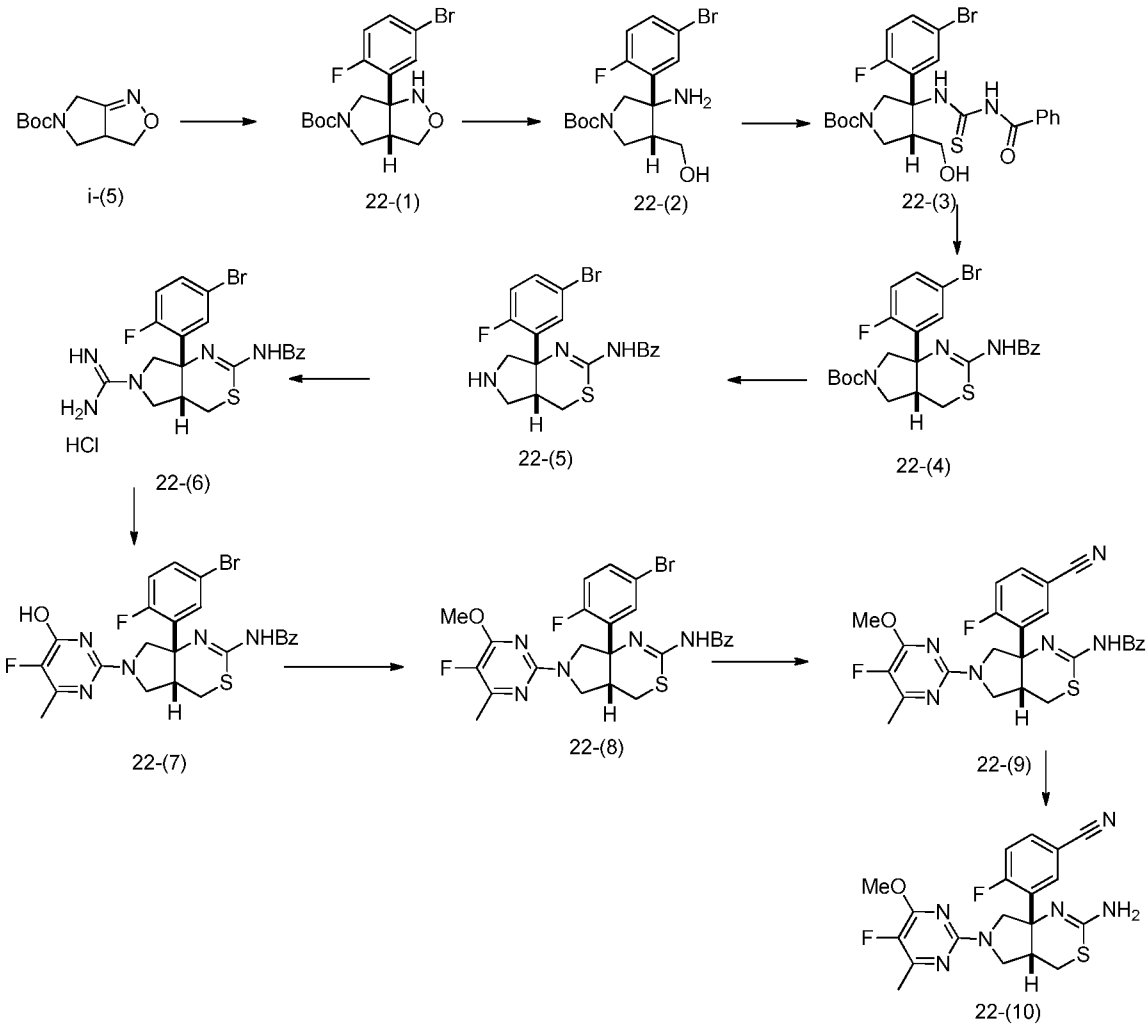
21-(11) Synthesis of (±)-2-((4aR*,7aR*)-2-amino-7a-(tetrahydro-2H-pyran-4-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methylpyrimidin-4-ol

Starting from (±)-N-((4aR*,7aR*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 21-(10), compound (±)-2-((4aR*,7aR*)-2-amino-7a-(tetrahydro-2H-pyran-4-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methylpyrimidin-4-ol (118 mg) was synthesised following an analogous procedure to that for preparing compound 17-(11) as described in Example 17.
LCMS Retention time 1.59min, 100%, ES^+: 482.63 $[MH]^+$.

21-(12) Synthesis of (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example 21)

Starting from (±)-2-((4aR*,7aR*)-2-amino-7a-(tetrahydro-2H-pyran-4-yl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-5-fluoro-6-methylpyrimidin-4-ol, 21-(11), compound (±)-(4aR*,7aR*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(tetrahydro-2H-pyran-4-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine) was synthesised following an analogous procedure to that for preparing compound 13-(9) as described in Example 13.
LCMS Retention time 1.04 min, 100%, ES^+: 382.58 $[MH]^+$.
^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1.24 (ddd, *J*=24.8, 12.7, 3.5 Hz, 1 H) 1.39 - 1.68 (m, 3 H) 1.73 (d, *J*=12.5 Hz, 1 H) 2.20 (d, *J*=2.8 Hz, 3 H) 2.39 - 2.48 (m, 1 H) 2.93 (dd, *J*=12.6, 5.3 Hz, 1 H) 3.17 (d, *J*=5.3 Hz, 1 H) 3.19 - 3.29 (m, 2 H) 3.38 - 3.47 (m, 2 H) 3.47 - 3.68 (m, 2 H) 3.83 - 3.89 (m, 2 H) 3.90 (s, 3H) 5.69 (br. s, 2 H).

Example 22: (±)-3-((4aR*,7aS*)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorobenzonitrile 22-(10)



22-(1) Synthesis of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(5-bromo-2-fluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a stirred solution of 4-bromo-1-fluoro-2-iodobenzene (10.96 g) in THF (30 mL) and toluene (150 mL) at -78°C was added *n*-butyl lithium (22.7 mL, 1.6 N in hexanes) over 20 mins. After stirring for 40 mins at -78°C, boron trifluoride etherate (4.60 mL) was added dropwise over 2 mins, followed by *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate (4.83 g) as a solution in THF (30 mL) over 5 mins. After stirring for a further 2 hrs at -78°C, the reaction mixture was quenched by the addition of NH_4Cl (sat., aq., 50 mL) and allowed to warm to room temperature. water (100 mL) was then added and the mixture extracted with EtOAc (3 x 150 mL). The combined organic portions were dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, 0 to 20% EtOAc in hexanes) to afford (±)-(3aR,6aS)-*tert*-butyl 6a-(5-bromo-2-fluorophenyl)tetrahydro-1H-pyrrolo[3,4-

c]isoxazole-5(3H)-carboxylate (5.71 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 3.22 - 3.33 (m, 1 H), 3.45 - 3.59 (m, 2 H), 3.60 - 3.80 (m, 3 H), 4.49 (t, *J*=8.4 Hz, 1 H), 6.96 (dd, *J*=11.0, 8.7 Hz, 1 H), 7.40 (ddd, *J*=8.6, 4.5, 2.7 Hz, 1 H), 8.06 (dd, *J*=7.0, 2.5 Hz, 1 H).

22-(2) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(5-bromo-2-fluorophenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (5.71 g) in THF (100 mL) was added acetic acid (5 mL) followed by powdered zinc (5.0 g) portionwise over 5 mins. After stirring at room temperature for 18 hrs, further portions of acetic acid (2.0 mL) and zinc (2.0 g) were added. After a further 24 hrs, the reaction mixture was filtered through celite®, washing with methanol (500 mL), and evaporated. $NaHCO_3$ (sat., aq., 250 mL) was then added, and the mixture was extracted with EtOAc (3 x 250 mL). The combined organic portions were dried over $MgSO_4$ and evaporated to afford (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (5.22 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.50 (s, 9 H), 2.75 – 2.88 (br. s., 1 H), 3.44 - 3.69 (m, 3 H), 3.76 - 4.02 (m, 3 H), 7.00 (dd, *J*=11.9, 8.7 Hz, 1 H), 7.43 (ddd, *J*=8.6, 4.2, 2.4 Hz, 1 H), 7.63 (dd, *J*=7.3, 2.3 Hz, 1 H).

22-(3) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (5.24 g) in DCM (50 mL) was added benzoyl isothiocyanate (2.20 mL) dropwise. After stirring at room temperature for 3 days, the reaction mixture was concentrated to *ca.* 10 mL and purified directly by flash column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to afford (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (6.99 g) as a foam.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.53 (m, 9 H), 2.98 – 3.14 (m, 1 H), 3.36 – 3.60 (m, 2 H), 4.05 (dd, *J*=11.7, 7.4 Hz, 1 H), 4.09 - 4.15 (m, 1 H), 4.58 (d, *J*=12.3 Hz, 1 H), 6.95 (dd, *J*=11.6, 8.7 Hz, 1 H), 7.42 (ddd, *J*=8.7, 4.2, 2.4 Hz, 1 H), 7.46 - 7.56 (m, 2 H), 7.56 - 7.69 (m, 2 H), 7.75 - 7.92 (m, 2 H), 8.87 (s, 1 H), 11.84 (br. s., 1 H).

22-(4) Synthesis of (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

Synthesized from (±)-(3S*,4*R)-*tert*-butyl 3-(3-benzoylthioureido)-3-(5-bromo-2-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate 22-(3) (3.85 g) by a procedure analogous to preparation example 1-(4), affording 3.20 g
LCMS (method A2 Short_20_95) RT 1.76min, m/z 534/536 $[M+H]^+$.

22-(5) Synthesis of (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (3.20 g) by a procedure analogous to preparation example 1-(5), affording 2.59 g.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.85 (dd, *J*=13.6, 3.9 Hz, 1 H), 3.13 – 3.23 (m, 1 H), 3.24 - 3.34 (m, 2 H), 3.41 - 3.54 (m, 2 H), 3.67 – 3.77 (m, 1 H), 7.03 (dd, *J*=11.7, 8.6 Hz, 1 H), 7.38 - 7.61 (m, 5 H), 8.10 (br. s., 2 H)

22-(6) Synthesis of (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-carbamimidoyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

Synthesized from (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 22-(5) (2.59 g) by a procedure analogous to preparation example 1-(6), affording 4.75 g (approx. purity 65%).
LCMS (method A2 Short_20_95) RT 1.02min, m/z 478/478 $[M+H]^+$.

22-(7) Synthesis of (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from crude (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-carbamimidoyl-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride 22-(6) (4.71 g, approx. purity 65%) by a procedure analogous to preparation example 1-(7), affording 2.31 g.
LCMS (method A2 Short_20_95) RT 1.34min, m/z 560/562 $[M+H]^+$.

22-(8) Synthesis of (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-

2-yl)benzamide 22-(7) (2.31 g) by a procedure analogous to preparation example 1-(8), affording 1.16 g.
LCMS (method A2 Short_20_95) RT 1.84min, m/z 574/576 $[M+H]^+$.

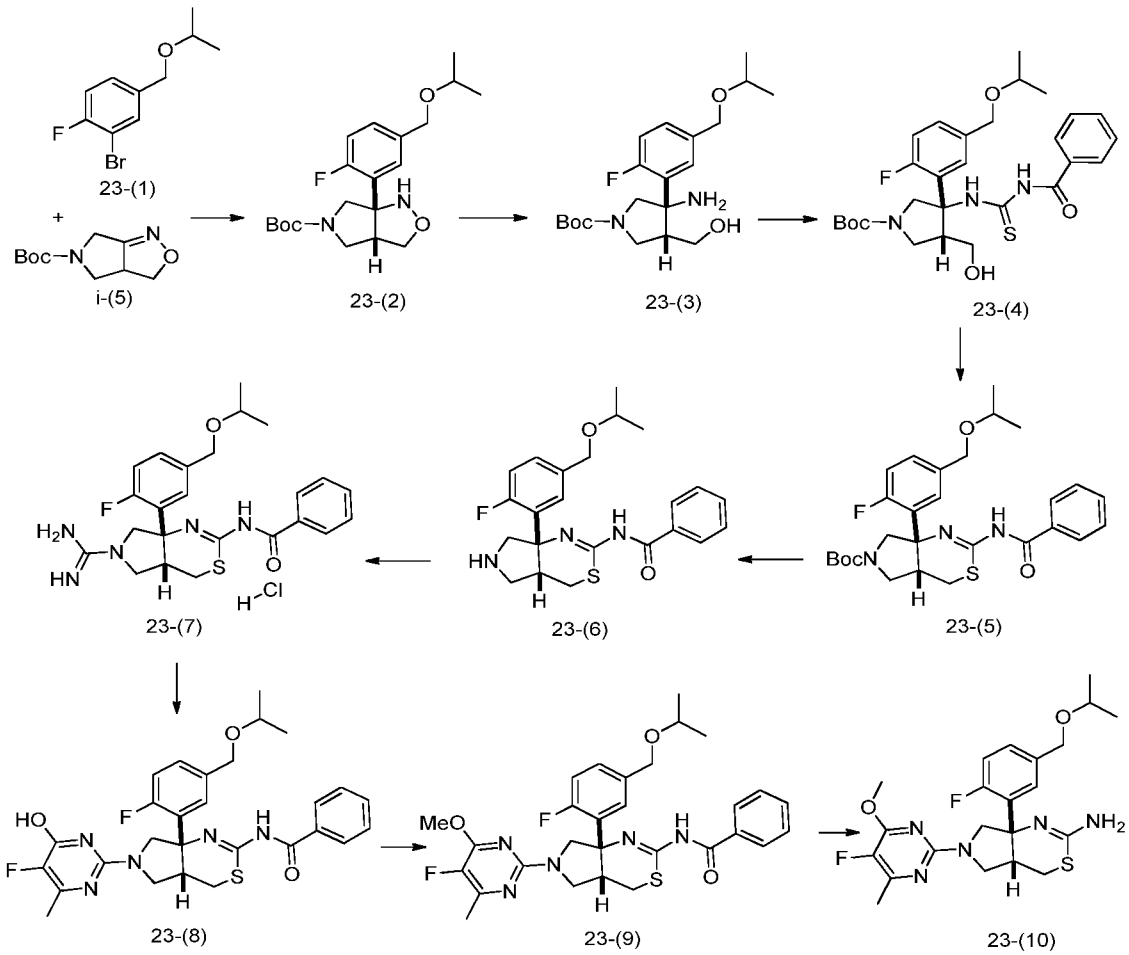
22-(9) Synthesis of (±)-N-((4aR*,7aS*)-7a-(5-cyano-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

To a solution of (±)-N-((4aR*,7aS*)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 22-(8) (70 mg) in NMP (1 mL) was added $Zn(CN)_2$ (50 mg) and tetrakis(triphenylphosphine)palladium(0) (10 mg). The solution was stirred under microwave irradiation for 1 hr at 120°C. The reaction mixture was then cooled, diluted with EtOAc (50 mL) and extracted with water (3 x 10 mL). The combined organic portions were dried over $MgSO_4$, evaporated, and purified by flash column chromatography (0 to 35% EtOAc in hexanes) to afford (±)-N-((4aR*,7aS*)-7a-(5-cyano-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 22-(9) (31 mg).
LCMS (method A2 Short_20_95) RT 1.64min, m/z 521 $[M+H]^+$

22-(10) Synthesis of (±)-3-((4aR*,7aS*)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorobenzonitrile

Synthesized from (±)-N-((4aR*,7aS*)-7a-(5-cyano-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 22-(9) (31 mg) by a procedure analogous to preparation example 1-(9), using aminosilica for purification, affording 10 mg.
^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 (d, *J*=2.9 Hz, 3 H), 2.98 – 3.03 (m, 2 H), 3.16 – 3.24 (m, 1 H), 3.74 - 3.91 (m, 3 H), 3.98 (s, 3 H), 4.29 (d, *J*=11.4 Hz, 1 H), 4.62 (br. s., 2 H), 7.20 (dd, *J*=11.6, 8.4 Hz, 1 H), 7.59 - 7.68 (m, 1 H), 7.70 - 7.81 (m, 1 H).
LCMS (method A2 Short_20_95) RT 0.97min, m/z 417 $[M+H]^+$

Example 23: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(3-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine, 23-(9)



23-(1) Synthesis of 2-bromo-1-fluoro-4-(isopropoxymethyl)benzene

Sodium hydride (0.60 g, 60% in mineral oil) was added portionwise over 10 mins to propan-2-ol (50 ml). After stirring for 15 mins, 2-bromo-4-(bromomethyl)-1-fluorobenzene (2.0 ml) was added dropwise over 10mins, and the reaction mixture was allowed to stir for 3 days. The mixture was then diluted with water (50 mL) and brine (100 mL), and extracted with EtOAc (2 x 150 mL). The combined organic portions were dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, 0 to 5% EtOAc in hexanes) to afford 2-bromo-1-fluoro-4-(isopropoxymethyl)benzene (2.96 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (d, *J*=6.1 Hz, 6 H), 3.69 (septet, *J*=6.1 Hz, 1 H), 4.46 (s, 2 H), 7.09 (t, *J*=8.4 Hz, 1 H), 7.18 - 7.32 (m, 1 H), 7.56 (dd, *J*=6.6, 2.1 Hz, 1 H)

23-(2) Synthesis of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-(isopropoxymethyl)phenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a stirred solution of 2-bromo-1-fluoro-4-(isopropoxymethyl)benzene, 23-(1), (827 mg) in THF (2 mL) and toluene (10 mL) at -78°C was added *n*-butyl lithium (2.0 mL, 1.6 N in hexanes) dropwise over 10 mins. After stirring for 20 mins at -78°C, boron trifluoride etherate (0.40 mL) was added dropwise, followed by *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, i-(5), (418 mg) as a solution in THF (3 mL). After stirring for a further 90 mins at -78°C, the reaction mixture was quenched by the addition of NH_4Cl (sat., aq., 10 mL) and allowed to warm to room temperature. Brine (20 mL) was then added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic portions were dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to afford (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-(isopropoxymethyl)phenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (372 mg) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (d, *J*=6.1 Hz, 6 H), 1.48 (s, 9 H), 3.26 – 3.35 (m, 1 H), 3.48 - 3.61 (m, 2 H), 3.61 - 3.82 (m, 4 H), 4.34 - 4.51 (m, 3 H), 5.12 (br. s., 1 H), 7.05 (dd, *J*=11.4, 8.4 Hz, 1 H) 7.24 - 7.35 (m, 1 H), 7.75 – 7.87 (m, 1 H)

23-(3) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-(isopropoxymethyl)phenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate, 23-(2), (1.20 g) in THF (10 mL) and acetic acid (1 mL) was added powdered zinc (1.0 g). After stirring at room temperature for 18 hrs, a further portion of zinc (1.0 g) and more acetic acid (1 mL) were added. After stirring for a further 24 hrs, the reaction mixture was filtered through celite®, washing with MeOH (100 mL) and evaporated. $NaHCO_3$ (sat., aq., 50 mL) was then added, and the mixture was extracted with EtOAc (2 x 75 mL). The combined organic portions were dried over $MgSO_4$ and evaporated to afford (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (1.14 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (d, *J*=6.1 Hz, 6 H), 1.49 (s, 9 H), 2.76 – 2.91 (m, 1 H), 3.45 - 3.64 (m, 3 H), 3.70 (septet, *J*= 6.1 Hz, 1 H), 3.84 (d, *J*=4.8 Hz, 2 H), 3.87 - 4.03 (m, 1 H), 4.48 (s, 2 H), 7.08 (dd, *J*=12.3, 8.3 Hz, 1 H), 7.28 – 7.46 (m, 2 H).

23-(4) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate, 23-(3), (1.14

g) in DCM (5 mL) was added benzoyl isothiocyanate (0.50 mL) dropwise. After stirring at room temperature for 2 hrs, the reaction mixture was concentrated to *ca*. 2 mL and purified directly by flash column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to afford (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (1.47 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (d, *J*=6.1 Hz, 6 H), 1.51 (br s, 9 H), 2.98 - 3.18 (m, 1 H), 3.30 - 3.59 (m, 2 H), 3.68 (septet, *J*=6.1 Hz, 1 H), 3.85 - 4.21 (m, 3 H), 4.44 - 4.57 (m, 3 H), 6.96 - 7.11 (m, 1 H), 7.28 - 7.36 (m, 1 H), 7.39 - 7.58 (m, 3 H), 7.58 - 7.68 (m, 1 H), 7.74 - 7.96 (m, 2 H), 8.84 (s, 1 H), 11.80 (br s, 1 H).

23-(5) Synthesis of (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

Synthesized from (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-(isopropoxymethyl)phenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate, 23-(4), (1.05 g) by a procedure analogous to preparation example 1-(4), affording 872 mg. LCMS (method A2 Short_20_95): Rt 1.78 min, m/z 528 $[M+H]^+$.

23-(6) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate, 23-(5), (248 mg) by a procedure analogous to preparation example 1-(5), affording 697mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.21 (d, *J*=6.1 Hz, 6 H), 2.84 (dd, *J*=13.6, 3.7 Hz, 1 H), 3.12 – 3.26 (m, 1 H), 3.31 - 3.43 (m, 2 H), 3.47 – 3.58 (m, 2 H), 3.68 (septet, *J*=6.1 Hz, 1 H), 3.76 – 3.88 (m, 1 H), 4.48 (s, 2 H), 7.11 (dd, *J*=12.2, 8.3 Hz, 1 H), 7.28 - 7.57 (m, 5 H), 7.98 - 8.22 (m, 2 H).

23-(7) Synthesis of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

Synthesized from (±)-N-((4aR*,7aS*)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 23-(6), (369 mg) by a procedure analagous to preparation example 1-(6), affording 680 mg, approx. purity 64%).
LCMS (method A2 Short_20_95) RT 1.06min, m/z 470 $[M+H]^+$.

23-(8) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride, 23-(7), (680 mg, approx. purity 64%), affording 141 mg.
LCMS (method A2 Short_20_95) RT 1.35min, m/z 554 $[M+H]^+$.

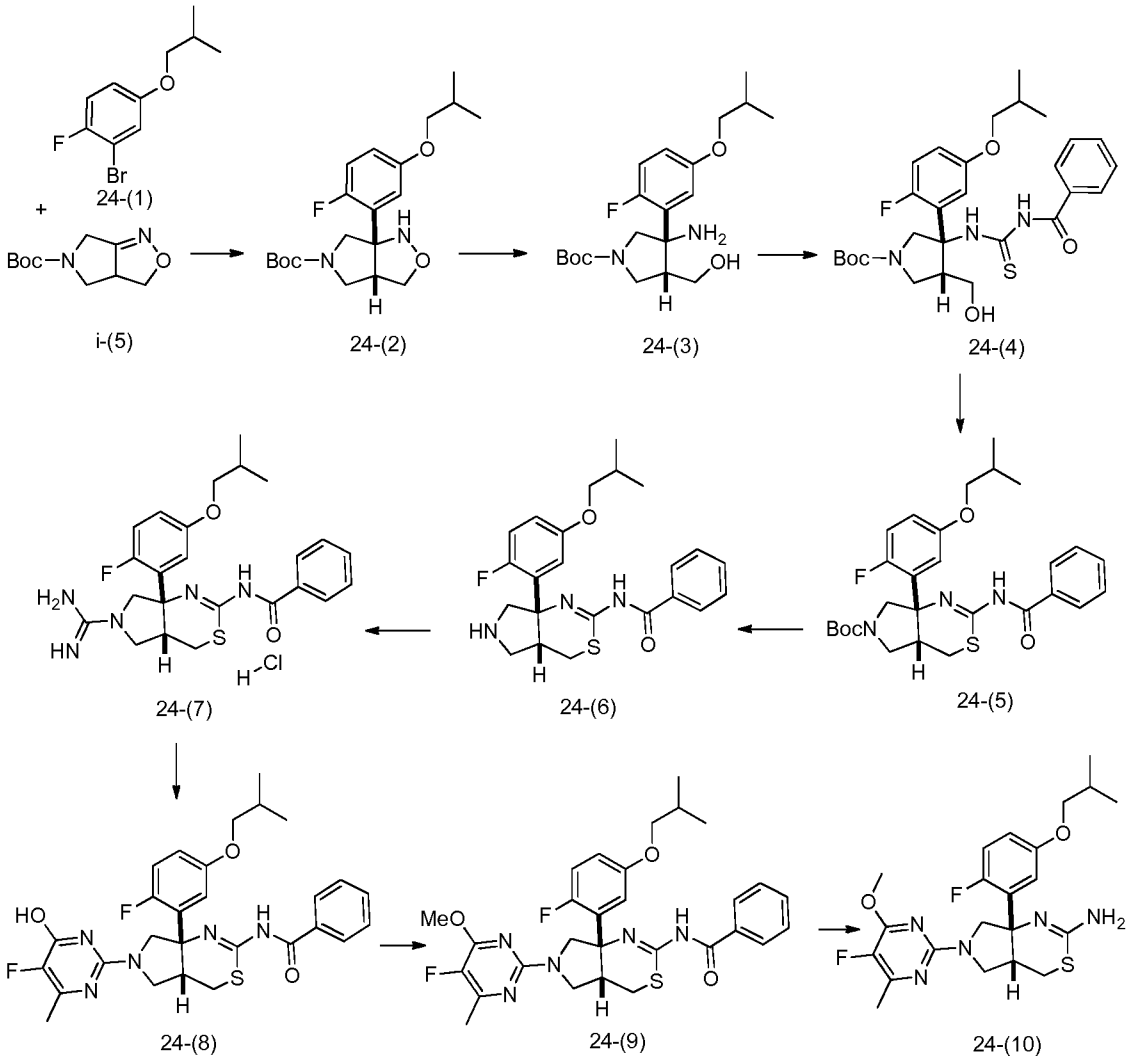
23-(9) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 23-(8), (141 mg) by a procedure analogous to preparation example 1-(8), affording 62 mg.
LCMS (method A2 Short_20_95) RT 1.85min, m/z 568 $[M+H]^+$.

23-(10) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Synthesized from (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide, 23-(9), (62 mg) by a procedure analogous to preparation example 1-(9), affording 46 mg.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (d, *J*=6.1 Hz, 6 H), 2.31 (d, *J*=2.8 Hz, 3 H), 2.95 (dd, *J*=13.0, 5.1 Hz, 1 H), 3.05 (dd, *J*=13.0, 3.9 Hz, 1 H), 3.17 - 3.28 (m, 1 H), 3.66 (septet, 6.1 Hz, 1 H), 3.72 - 3.87 (m, 3 H), 3.96 (s, 3 H), 4.32 (d, *J*=11.2 Hz, 1 H), 4.42 - 4.50 (m, 2 H), 7.04 (dd, *J*=12.2, 8.4 Hz, 1 H), 7.23 - 7.34 (m, 2 H)
LCMS (method A2 Short_20_95) RT 1.09min, m/z 448 $[M+H]^+$.

Example 24: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 24-(10)



24-(1) Synthesis of 2-bromo-1-fluoro-4-isobutoxybenzene

To a stirred solution of 3-bromo-4-fluorophenol (6.43 g) and cesium carbonate (15.00 g) in DMF (30 mL) was added 1-bromo-2-methylpropane (5.54 g). The reaction mixture was heated to 65°C, then after 22 hrs, was cooled, diluted with EtOAc (200 mL), and extracted with brine (3 x 50 mL). The organic portion was dried over $MgSO_4$, evaporated, purified by flash column chromatography (silica gel, 0 to 2% EtOAc in hexanes) to afford 2-bromo-1-fluoro-4-isobutoxybenzene (6.17 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.03 (d, *J*=6.7 Hz, 6 H), 2.08 (nonet, *J*=6.7 Hz, 1 H), 3.68 (d, *J*=6.6 Hz, 2 H), 6.80 (ddd, *J*=3.1, 3.7, 9.0 Hz, 1 H), 7.03 (dd, *J*=9.0, 8.3 Hz, 1 H), 7.08 (dd, *J*=5.6, 3.1 Hz, 1 H).

24-(2) Synthesis of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-isobutoxyphenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate

To a stirred solution of 2-bromo-1-fluoro-4-isobutoxybenzene 24-(1) (2.00 g) in THF (5 mL) and toluene (25 mL) at -78°C was added n-butyl lithium (5.0 mL, 1.6 N in hexanes) dropwise over 10 mins. After stirring for 20 mins at -78°C, boron trifluoride etherate (1.0 mL) was added dropwise over 2 mins, followed by *tert*-butyl 3a,4-dihydro-3H-pyrrolo[3,4-c]isoxazole-5(6H)-carboxylate, i-(5), (1.08 g) as a solution in THF (5 mL) dropwise over 5 mins. After stirring for a further 90 mins at -78°C, the reaction mixture was quenched by the addition of NH_4Cl (sat., aq., 10 mL) and allowed to warm to room temperature. Water (10 mL) was then added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic portions were dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, 0 to 20% EtOAc in hexanes) to afford (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-isobutoxyphenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (1.10 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 (d, *J*=6.7 Hz, 6 H), 1.48 (s, 9 H), 2.00 - 2.15 (m, 1 H), 3.25 - 3.39 (m, 1 H), 3.53 - 3.82 (m, 7 H), 4.40 – 4.49 (m, 1 H), 5.13 (br. s., 1 H), 6.76 (dt, *J*=8.8, 3.6 Hz, 1 H), 6.89 - 7.04 (m, 1 H), 7.35 - 7.49 (m, 1 H).

24-(3) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3aR*,6aS*)-*tert*-butyl 6a-(2-fluoro-5-isobutoxyphenyl)tetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate, 24-(2), (1.10 g) in THF (10 mL) and acetic acid (1 mL) was added powdered zinc (1.0 g). After stirring at room temperature for 18 hrs the reaction mixture was filtered through celite®, washing with MeOH (100 mL) and evaporated. $NaHCO_3$ (sat., aq., 50 mL) was then added, and the mixture was extracted with EtOAc (3 x 75 mL). The combined organic portions were dried over $MgSO_4$ and evaporated to afford (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (1.05 g).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 - 1.08 (m, 6 H), 1.49 (s, 9 H), 2.01 – 2.13 (m, 1 H), 2.75 – 2.87 (m, 1 H), 3.07 – 3.18 (m, 1 H), 3.46 – 4.04 (m, 7 H), 4.44 – 4.54 (m, 1 H), 6.75 – 6.81 (m, 1 H), 6.96 - 7.04 (m, 1 H), 7.11 - 7.26 (m, 1 H)

24-(4) Synthesis of (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

To a stirred solution of (±)-(3S*,4R*)-*tert*-butyl 3-amino-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate, 24-(3), (635 mg). in DCM (5 mL) was added benzoyl isothiocyanate (0.30 mL) dropwise. After stirring at

room temperature for 1 hr, the reaction mixture was concentrated to *ca.* 1 mL and purified directly by flash column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to afford (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (540 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.03 (d, *J*=6.6Hz, 6 H), 1.52 (s, 9 H), 1.96 - 2.14 (m, 1 H), 2.97 - 3.14 (m, 1 H), 3.33 - 3.61 (m, 2 H), 3.62 - 3.78 (m, 2 H), 3.82 - 3.96 (m, 1 H), 3.99 - 4.10 (m, 1 H), 4.10 - 4.18 (m, 1 H), 4.52 - 4.70 (m, 1 H), 6.79 (dt, *J*=8.8, 3.3 Hz, 1 H), 6.95 (dd, *J*=11.4, 9.0 Hz, 1 H), 7.02 – 7.08 (m, 1 H), 7.46 - 7.56 (m, 2 H), 7.57 - 7.66 (m, 1 H), 7.80 - 7.89 (m, 2 H), 8.88 (s, 1 H), 11.82 (br. s., 1 H).

24-(5) Synthesis of (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(2-fluoro-5-isobutoxyphenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate

Synthesized from (±)-(3S*,4R*)-*tert*-butyl 3-(3-benzoylthioureido)-3-(2-fluoro-5-isobutoxyphenyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate 24-(4) (380 mg) by a procedure analagous to preparation example 1-(4), affording 267 mg.
LCMS (method A2 Short_20_95) RT 1.91 min, m/z 528 $[M+H]^+$.

24-(6) Synthesis of (±)-N-((4aR*,7aS*)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Prepared from (±)-(4aR*,7aS*)-*tert*-butyl 2-benzamido-7a-(2-fluoro-5-isobutoxyphenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate 24-(5) (267 mg) by a procedure analogous to preparation example 1-(5), affording 245mg, approximate purity 88%.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.00 (d, *J*=6.7 Hz, 6 H), 1.97 - 2.13 (m, 1 H), 2.71 - 2.91 (m, 1 H), 3.06 – 3.16 (m, 1 H), 3.30 - 3.49 (m, 2 H), 3.54 – 3.71 (m, 4 H), 3.89 – 4.00 (m, 1 H), 6.81 (dd, *J*=6.3, 2.9 Hz, 2 H), 7.02 (t, *J*=10.6 Hz, 1 H), 7.33 - 7.48 (m, 2 H), 7.50 - 7.62 (m, 1 H), 8.01 (d, *J*=7.2 Hz, 2 H)

24-(7) Synthesis of (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride

Synthesized from (±)-N-((4aR*,7aS*)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 24-(6) (245 mg, approx. purity 88%) by a procedure analagous to preparation example 1-(6) affording 290mg, approx. purity 87%.
LCMS (method A2 Short_20_95) RT 1.20min, m/z 470 $[M+H]^+$.

24-(8) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aS*)-6-carbamimidoyl-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide hydrochloride 24-(7) (198 mg) by a procedure analogous to preparation example 1-(7).
LCMS (method A2 Short_20_95) RT 1.53min, m/z 554 $[M+H]^+$.

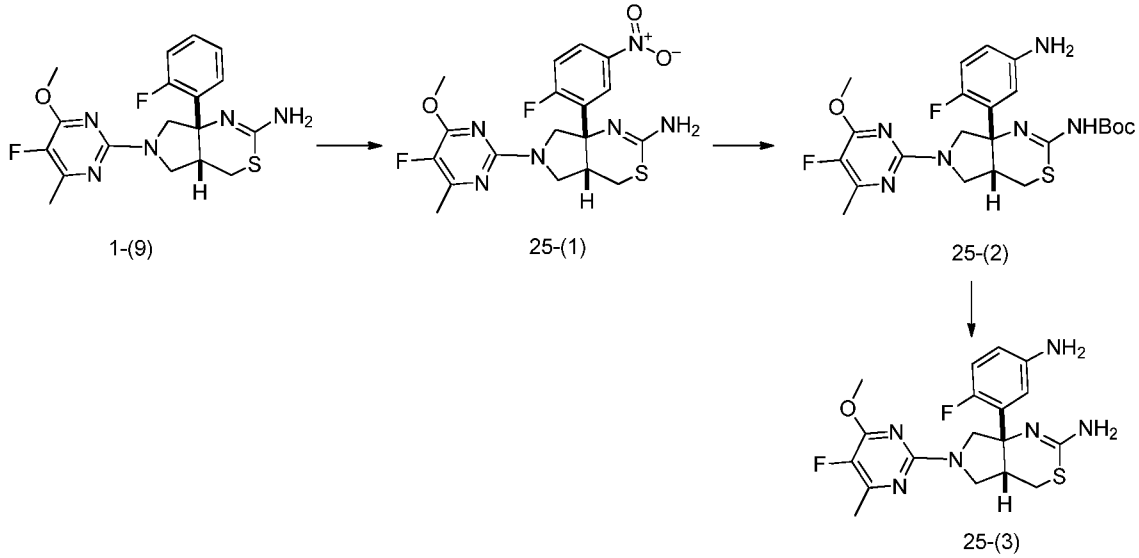
24-(9) Synthesis of (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide

Synthesized from (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-hydroxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropoxymethyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 24-(8) (198 mg) by a procedure analagous to preparation example 1-(8) affording 55 mg.
LCMS (method A2 Short_20_95) RT 1.99min, m/z 568 $[M+H]^+$.

24-(10) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Synthesized from (±)-N-((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-isobutoxyphenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 24-(9) (55 mg) by a procedure analagous to preparation example 1-(9) affording 31 mg.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 - 1.06 (m, 6 H), 1.99 - 2.12 (m, 1 H), 2.31 (d, *J*=2.8 Hz, 3 H), 2.87 - 3.01 (m, 1 H), 3.01 - 3.11 (m, 1 H), 3.17 - 3.29 (m, 1 H), 3.65 (d, *J*=6.5 Hz, 2 H), 3.69 - 3.82 (m, 3 H), 3.96 (s, 3 H), 4.32 (d, *J*=11.2 Hz, 1 H), 4.45 (br. s., 2 H), 6.76 (dt, *J*=8.8, 3.4 Hz, 1 H), 6.90 (dd, *J*=6.7, 3.2 Hz, 1 H), 6.96 (dd, *J*=11.7, 8.9 Hz, 1 H).
LCMS (method A2 Short_20_95) RT 1.25 min, m/z 464 $[M+H]^+$.

Example 25: (±)-(4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 25-(3)



25-(1) Synthesis of (±)- (4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-nitrophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a stirred solution of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 1-(9) (314 mg) in TFA (2mL) at 0°C was added sulfuric acid (0.2mL) dropwise, then fuming nitric acid (0.034 mL) dropwise. After stirring at 0°C for a further 3 h, the reaction mixture was poured onto 100g ice, which after melting was basified with NaOH (2N aq.) to pH 12 and extracted with EtOAc (3 x 100 mL). The combined organic portions were dried over $MgSO_4$ and evaporated to afford 25-(1) (365 mg, approx. purity 85%).

LCMS (method A2 Short_20_95) RT 1.00 min, m/z 437 $[M+H]^+$.

25-(2) Synthesis of (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate

To a solution of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-nitrophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 25-(1) (365 mg, approx. purity 85%) in DCM (2mL) was added N,N-diisopropylethylamine (0.372 mL) followed by di-*tert*-butyl dicarbonate (230 mg). After stirring for 3 days, $NaHCO_3$ (sat., aq., 25 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic portions were dried over

$MgSO_4$, evaporated, and purified by silica gel chromatography (0 to 35% EtOAc in hexanes) to afford 25-(2) (274 mg).

LCMS (method A2 Short_20_95) RT 1.60min, m/z 537 $[M+H]^+$.

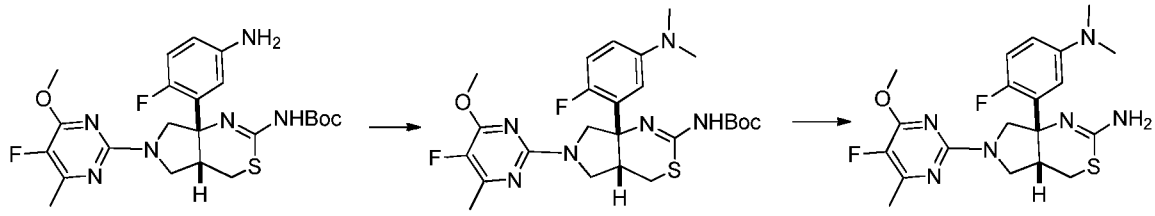
25-(3) Synthesis of (±)-(4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a solution of (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 25-(2) (14 mg) in DCM (1 mL) was added trifluoracetic acid (0.5ml). After stirring for 2 h, the reaction mixture was evaporated and $NaHCO_3$ (sat., aq., 5 mL) was added. The mixture was extracted with EtOAc (2 x 10mL) and the combined organic portions were dried over MgSO4 and evaporated to afford 25-(3) (10 mg).

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (d, *J*=2.8 Hz, 3 H), 2.98 (dd, *J*=13.3, 4.3 Hz, 1 H), 3.15 (dd, *J*=13.3, 3.7 Hz, 1 H), 3.39 – 3.51 (m, 1 H), 3.60 – 3.71 (m, 1 H), 3.76 (t, *J*=10.1 Hz, 1 H), 3.88 (dd, *J*=10.8, 8.4 Hz, 1 H), 3.95 (s, 3 H), 4.01 – 4.12 (m, 1 H), 4.22 (d, *J*=11.7 Hz, 1 H), 6.51 - 6.69 (m, 2 H), 6.87 (dd, *J*=12.1, 8.6 Hz, 1 H).

LCMS (method A2 Short_20_95) RT 1.60min, m/z 537 $[M+H]^+$.

Example 26: (±)-(4aR*,7aS*)-7a-(5-(dimethylamino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 26-(2)



26-(1) Synthesis of (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-(dimethylamino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate

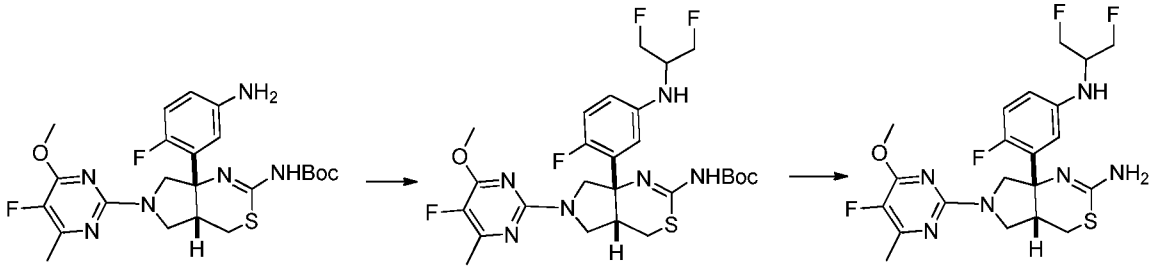
To a solution of (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 25-(2) (35 mg) in methanol was added acetic acid (0.2mL), formaldehyde (6.20 µL, 37% aq. solution) and sodium cyanoborohydride (10 mg). After stirring for 1 h, the reaction mixture was poured onto $NaHCO_3$ (sat., aq., 20

mL). The mixture was extracted with EtOAc (2 x 25 mL) and the combined organic portions were dried over $MgSO_4$, evaporated and purified by silica gel chromatography (0 to 50% EtOAc in hexanes) to afford 26-(1) (9 mg)
LCMS (method A2 Short_20_95) RT 1.53min, m/z 535 $[M+H]^+$.

26-(2) Synthesis of (±)-(4aR*,7aS*)-7a-(5-(dimethylamino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Synthesized from (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-(dimethylamino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 26-(1) (11 mg) by a procedure analogous to preparation example 25-(3), affording 9 mg.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (d, *J*=2.8 Hz, 3 H), 2.87 (s, 6 H), 2.96 (dd, *J*=13.0, 4.5 Hz, 1 H), 3.05 – 3.15 (m, 1 H), 3.20 – 3.39 (m, 1 H), 3.66 - 3.86 (m, 3 H), 3.94 (s, 3 H), 4.32 (d, *J*=11.1 Hz, 1 H), 6.59 (dt, *J*=8.9, 3.4 Hz, 1 H), 6.70 (dd, *J*=6.8, 3.1 Hz, 1 H), 6.93 (dd, *J*=11.9, 8.9 Hz, 1 H)

Example 27: (±)-(4aR*,7aS*)-7a-(5-((1,3-difluoropropan-2-yl)amino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 27-(2)



25-(2) 27-(1) 27-(2)

27-(1) Synthesis of (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-((1,3-difluoropropan-2-yl)amino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate

1,3-Difluoropropan-2-one (7 mg) was added to (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 25-(2) (25 mg), and after 5 mins, methanol (1 ml) and acetic acid (0.2 ml) were added, followed by 2-Picoline borane complex (10 mg). After stirring for 2 h, the reaction mixture was poured onto $NaHCO_3$ (sat., aq., 10 mL). The mixture was extracted with EtOAc (2 x 20

mL) and the combined organic portions were dried over $MgSO_4$, evaporated and purified by silica gel chromatography (0 to 30% EtOAc in hexanes) to afford 27-(1) (17 mg).

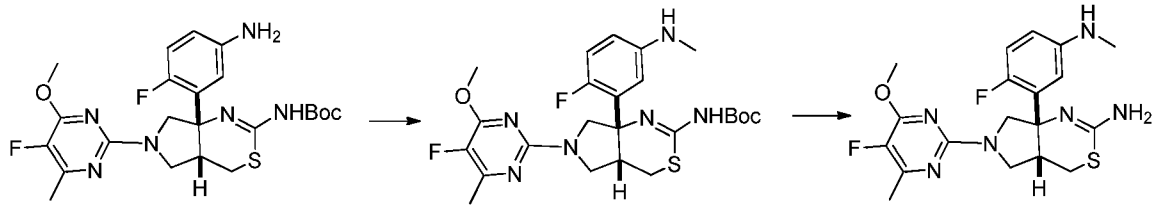
LCMS (method A2 Short_20_95) RT 1.61min, m/z 585 $[M+H]^+$.

27-(2) Synthesis of (±)-(4aR*,7aS*)-7a-(5-(1,3-difluoropropan-2-yl)amino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Prepared from (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-((1,3-difluoropropan-2-yl)amino)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate by a procedure analogous to preparation example 25-(3) affording 12 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (d, *J*=2.8 Hz, 3 H), 2.98 (dd, *J*=13.2, 4.4 Hz, 1 H), 3.13 (dd, *J*=13.1, 3.7 Hz, 1 H), 3.36 – 3.48 (m, 1 H), 3.68 - 4.02 (m, 7 H), 4.23 (d, *J*=11.6 Hz, 1 H), 4.41 - 4.70 (m, 4 H), 6.56 (dt, *J*=8.7, 3.3 Hz, 1 H), 6.63 (dd, *J*=6.7, 3.0 Hz, 1 H), 6.93 (dd, *J*=11.9, 8.7 Hz, 1 H).

Example 28: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(methylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 28-(2)



28-(1) Synthesis of (±)-*tert*-butyl ((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(methylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate

Prepared from (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 25-(2) (25 mg) and 37% aq. Formaldehyde by a procedure analogous to preparation example 27-(1) affording 6 mg.

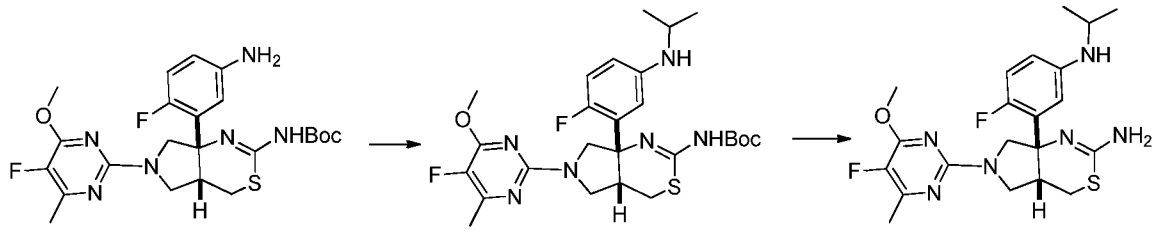
LCMS (method A2 Short_20_95) RT 1.40min, m/z 520 $[M+H]^+$.

28-(2) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(methylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Prepared from (±)-*tert*-butyl ((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(methylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate by a procedure analogous to preparation example 25-(3) affording 2 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33 (d, *J*=2.4 Hz, 3 H), 2.80 (s, 3 H), 3.06 (dd, *J*=13.6, 4.1 Hz, 1 H), 3.27 (dd, *J*=13.2, 4.0 Hz, 1 H), 3.64 – 3.74 (m, 1 H), 3.80 (t, *J*=10.1 Hz, 1 H), 3.93 - 4.04 (m, 4 H), 4.16 - 4.23 (m, 1 H), 4.27 - 4.43 (m, 1 H), 6.46 - 6.60 (m, 2 H), 6.88 - 7.01 (m, 1 H).

Example 29: (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 29-(2)



25-(2) 29-(1) 29-(2)

29-(1) Synthesis of (±)-*tert*-butyl ((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate

Synthesized from (±)-*tert*-butyl ((4aR*,7aS*)-7a-(5-amino-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate 25-(2) (37 mg) by a procedure analogous to preparation example 27-(1) affording 21mg.

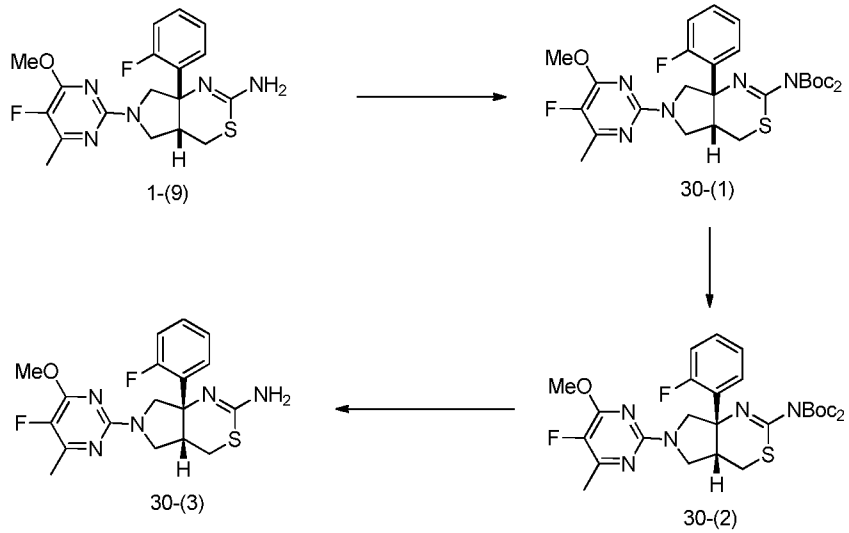
LCMS (method A2 Short_20_95) RT 1.47min, m/z 549 $[M+H]^+$.

29-(2) Synthesis of (±)-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

Prepared from (±)-*tert*-butyl ((4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluoro-5-(isopropylamino)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)carbamate by a procedure analogous to preparation example 25-(3) affording 19 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (d, *J*=6.1 Hz, 6 H), 2.30 (d, *J*=2.8 Hz, 3 H), 2.98 (dd, *J*=13.2, 4.3 Hz, 1 H), 3.17 (dd, *J*=13.3, 3.6 Hz, 1 H), 3.42 – 3.59 (m, 2 H), 3.75 (t, *J*=10.0 Hz, 1 H), 3.81 - 3.91 (m, 1 H), 3.95 (s, 3 H), 4.01 - 4.13 (m, 2 H), 4.23 (d, *J*=11.7 Hz, 1 H), 6.40 - 6.54 (m, 2 H), 6.89 (dd, *J*=12.0, 8.6 Hz, 1 H).

Example 30: (4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine



30-(1) Synthesis of (±)-N,N-di-tert-butyloxycarbonyl-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a stirred solution of (4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (58 mg) and N,N-diisopropylethylamine (40 mg) in DCM (2 mL) was added di-*tert*-butyl dicarbonate (50 mg), followed by 4-(dimethylamino)pyridine (0.2 mg). After stirring at room temperature for 16 h, a further portion of di-*tert*-butyl dicarbonate (50 mg) was added. After stirring for a further hour, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient from 0% to 20% EtOAc in hexanes) to obtain the title compound (62 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 18 H), 2.29 (d, *J*= 1.8 Hz, 3 H), 2.93 (dd, *J*=13.4, 3.6 Hz, 1 H), 3.13 (dd, *J*=13.3, 3.1 Hz, 1 H), 3.33 – 3.42 (m, 1 H), 3.84 (t, *J*=10.4 Hz, 1 H), 3.88 - 4.09 (m, 5 H), 4.40 (d, *J*=11.6 Hz, 1 H), 7.03 - 7.20 (m, 2 H), 7.28 - 7.37 (m, 1 H), 7.53 (t, *J*=7.7 Hz, 1 H)

30-(2) Separation of N,N-di-tert-butyloxycarbonyl-(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine and N,N-di-tert-butyloxycarbonyl-(4aS,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

The isomers of (±)-N,N-di-tert-butyloxycarbonyl-(4aR*,7aS*)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (62 mg) were separated by preparative chiral HPLC, Method H2, (IC column (#5), eluent (10% dichloromethane / hexane):EtOH 95:5 (v/v)) to afford the faster running enantiomer, N,N-di-tert-butyloxycarbonyl-(4aS,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (29 mg) as a white solid, NMR data as for racemic mixture 30-(1). This was followed by the slower running enantiomer, N,N-di-tert-butyloxycarbonyl-(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 1-(14) (30 mg) as a white solid, NMR data as for racemic mixture 30-(1).

30-(3) Synthesis of (4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine

To a solution of N,N-di-tert-butyloxycarbonyl-(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine 30-(2) (30 mg) in DCM (2 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred at RT for 2 hrs. The mixture was then concentrated and $NaHCO_3$ (sat. aq., 10 mL) was added. The mixture was then extracted with EtOAc (2 x 20 mL), and the combined organic extracts were dried over $MgSO_4$ and evaporated to afford (4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (22 mg) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.31 (d, *J*=2.3 Hz, 3 H), 2.97 (dd, *J*=13.1, 5.1 Hz, 1 H), 3.05 (dd, *J*=13.1, 3.8 Hz, 1 H), 3.20 – 3.30 (m, 1 H), 3.70 - 3.85 (m, 2 H), 3.85 – 3.92 (m, 1 H), 3.96 (s, 3 H), 4.34 (d, *J*=11.4 Hz, 1 H), 7.07 (dd, *J*=12.5, 8.2 Hz, 1 H), 7.12 - 7.21 (m, 1 H), 7.23 - 7.33 (m, 1 H), 7.37 (t, *J*=8.0 Hz, 1 H).

Biological Data – *in vitro* analysis

***In vitro* cellular assay:**

Quantification of Aβ peptide in culture of neurons from rat fetus brain

(1) Rat primary neuronal culture

Primary neuronal cultures were prepared from the cerebral cortex of embryonic day 18 Wistar rats (Charles River, UK). Specifically, the embryos were aseptically removed from pregnant rats following CO_2 overdose. The brain was isolated from the embryo and immersed in HBSS (Sigma Aldrich #H9269) containing 10mM HEPES (Gibco #15630-056). The cerebral cortex was collected from the isolated brain under a stereoscopic microscope. The cerebral cortex fragments collected were enzymatically treated in an enzyme solution containing 0.05% trypsin-EDTA solution (GIBCO, #25300) at 37°C for 20 minutes to disperse the cells. The cells were then washed twice and then gently resuspended in Neurobasal medium (Gibco #21103) supplemented with 1x B27 supplement (GIBCO #17504-044), 2 mM L-glutamine (GIBCO #25030), 1x N2 (GIBCO #17502-048), 100U/ml Pen/Strep (GIBCO 15140-122) and 5% heat inactivated FCS (PAA #A15-551). The cell dispersion was filtered through a 40-μm nylon mesh (BD Falcon #352340) to remove the remaining cell mass, and thus a neuronal cell suspension was obtained. The neuronal cell suspension was diluted with the medium above and then plated in a volume of 100 μL /well at an initial cell density of 3.25×10^5 cells/ml in poly- D-lysine coated 96-well culture plate (Greiner #655940). The plated cells were cultured in the culture plate at 37°C in 5% CO_2-95% air for 24hrs. The total amount of the medium was replaced with 'assay Neurobasal medium' (as above excluding heat inactivated FCS), and then the cells were cultured for a further five days.

(2) Addition of compound

The drug was added to the culture plate on Day 6 of culture as follows. 8 point compound serial dilutions were generated in DMSO at a concentration of x1000 that of the final assay concentration (FAC). Compound solutions were then prepared by adding 300μl of 'Assay Neurobasal media' (as described in above section) to lμl of DMSO compound stock. The total amount of the medium was removed from each of the cell plate wells, and 140μL/well of fresh culture medium was added to cells, and subsequently a further 60μl of compound solution was then added to the cells. The final DMSO concentration was 0.1%.

(3) Sampling

The cells were cultured for either 1 day after addition of the compound for ABx-40. 150µl of sample medium was collected and used as the ELISA sample.

(4) Evaluation of cell survival

Cell survival was evaluated using an Alamar assay according to the following procedure. After collecting the sample to be used in the ELISA assay, 50µl of 20% Alamar blue solution (Invitrogen #DAL1100) in assay Neurobasal media, was added to 50µl of remaining sample within each well. Cells were then incubated at 37°C in 5% CO_2-95% air for 45 minutes.

Measurement of fluorescence intensity for each well was carried out at 540/590nm using a Pherastar plus plate reader (BMG labtech). Upon measurement, wells having no cells plated and containing only the medium and Alamar solution were set as background (bkg).

(5) Aβ ELISA

Human/Rat β Amyloid (42) ELISA Kit Wako (#290-62601) and Human/Rat β Amyloid (40) ELISA Kit Wako (#294-62501) from Wako Pure Chemical Industries, Ltd. were used for Aβ ELISA. Aβ ELISA was carried out according to the protocols recommended by the manufacturers, described in the documents accompanying the kits. The results were shown as percentage of the control groups and IC50 values for each compound were determined using four parameter logistic fit model using the XLFIT5 software package (IDBS).

As measured by the above *in vitro* assay, compound Examples gave the IC_{50} values (Aβ40) recorded in Table 1.

Table 1

Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	14	16	22
2	48	17	22
3	172	18	59
4	36	19	144
5	54	20	173
6	47	21	541
7	158	22	5
8	10	23	11
9	147	24	165
10	51	25	8
11	6	26	60
12	265	27	1
13	34	28	13
14	12	29	17
15	31	30	5

n = 1 [except Ex. 1 (n = 3) and Ex. 26, 27, 29 (n = 2)].

MDR1-MDCK Permeability Assay (Bi-directional; pH 7.4/pH 7.4)

A compounds potential for CNS penetration may be assessed *in vitro* by determining whether a compound can be subjected to Pgp efflux, i.e. by conducting an *in vitro* Pgp assay.

Protocol Summary

MDCK cells are an epithelial cell line of canine kidney origin. These cells can be transfected to stably express active P-glycoprotein (MDR1-MDCK) and are ideal for studying drug efflux. Test compound was added to either the apical or basolateral side of a confluent monolayer of MDR1-MDCK cells and permeability was measured by monitoring the appearance of the test compound on the opposite side of the membrane using LC-MS/MS. From this an apparent permeability (P_{app}) coefficient and efflux ratio was measured/calculated.

Objective

To measure the permeability of test compound in the apical to basolateral (A-B) and basolateral to apical (B-A) direction across MDR1-MDCK cells. A ratio of B-A and A-B permeabilities was calculated (efflux ratio) to show whether the compound undergoes P-glycoprotein efflux.

Compounds were provided as a 200 µL solution of 10 mM test compound in DMSO.

Experimental Procedure

MDR1-MDCK cells obtained from the NIH (Rockville, MD, USA) were used. Following culture to confluency, the monolayers were prepared by rinsing both basolateral and apical surfaces twice with pH 7.4 buffer at 37°C. Cells were then incubated with pH 7.4 buffer in both apical and basolateral compartments for 40 min to stabilise physiological parameters.

Buffer at pH 7.4 was then removed from the apical compartment and replaced with test compound dosing solutions. The solutions were prepared by diluting 10 mM test compound in DMSO with buffer to give a final test compound concentration of 10 µM (final DMSO concentration adjusted to 1%). The fluorescent integrity marker Lucifer yellow was also included in the dosing solution. The apical compartment inserts were then placed into 'companion' plates containing fresh buffer at pH 7.4. Analytical standards were made from dosing solutions.

For basolateral to apical (B-A) experiments the experiment was initiated by replacing buffer in the inserts then placing them in companion plates containing dosing solutions. Incubations were carried out in an atmosphere of 5% CO_2 with a relative humidity of 95% at 37°C for 60 minutes.

After the incubation period, the companion plate was removed and apical and basolateral samples diluted for analysis by LC-MS/MS. Test compound permeability was assessed in duplicate. On each plate compounds of known permeability characteristics were run as controls.

Test and control compounds were quantified by LC-MS/MS cassette analysis using a 5-point calibration with appropriate dilution of the samples. General analytical conditions were used. The starting concentration (C_0) was determined from the dosing solution and the experimental recovery calculated from C_0 and both apical and basolateral compartment concentrations.

The integrity of the monolayers throughout the experiment was checked by monitoring Lucifer yellow permeation using fluorimetric analysis. Lucifer yellow permeation is low if monolayers have not been damaged. If a Lucifer yellow P_{app} value was above QC limits in one individual test compound well, then an n=1 result was reported. If Lucifer yellow P_{app} values were above QC limits in both replicate wells for a test compound, the compound was re-tested. If on repeat, high Lucifer yellow permeation was observed in both wells then toxicity or inherent fluorescence of the test compound was assumed. No further experiments were performed in this instance.

Data Analysis

The permeability coefficient for each compound (P_{app}) was calculated from the following equation:

$$P_{app} = (dQ \div dt) \div (C_0 \times A)$$

Where dQ/dt is the rate of permeation of the drug across the cells, C_0 is the donor compartment concentration at time zero and A is the area of the cell monolayer. C_0 was obtained from analysis of the dosing solution at the start of the experiment.

In addition, an efflux ratio (ER) was calculated from mean A-B and B-A data. This is derived from:

$$ER = ((P_{app} (B - A)) \div ((P_{app} (A - B))$$

Two control compounds were screened alongside the test compounds, propranolol (highly permeable) and prazosin (a substrate for P-glycoprotein).

Data are shown in Table 2:

Table 2:

Example	**Pgp ER**
1	7.4
13	17.3
14	7.0
30	1.5

The data in Table 2 demonstrate that the example compounds tested have low Pgp efflux.

Biological Data – *in vivo* analysis

The *in vitro* data presented above demonstrate that compounds according to the present invention lower Aβ production in a cellular assay and display low Pgp efflux. The following *in vivo* assays and results demonstrate that they reduce Aβ40 in animal models and have desirable brain:blood (Br:Bl) and brain:plasma (Br:Pl) ratios.

Measurement of Compound Concentrations in Blood and Plasma

Compound concentrations in blood or plasma and brain may be measured to calculate a brain:blood (Br:Bl) or brain:plasma (Br:Pl) ratio. This method has been used historically and has been widely accepted as a method of determining CNS penetration (Summerfield et al., J Pharmacol. Expt. Ther. 2007, 322, 205). Literature has been published to suggest that it is important to consider the free concentrations *in vivo* and that when no efflux occurs from the brain the free plasma concentration should be the same or equivalent to the free brain concentration (Kalvass and Maurer, Biopharmaceutics & Drug Disposition 2002, 23, 327; Mauer et al, Drug Metab. Disposition 2005, 33, 175; Trainor Expert Opin. Drug Discov. 2007, 2, 51). Thus, a compound that can freely penetrate the CNS and is not subjected to active efflux, for example by Pgp or another transporter, should demonstrate a free brain:free plasma (Br_{fr} : Pl_{fr}) or an unbound brain:unbound plasma (Br_u : Pl_u) of approximately 1:1. Free or unbound concentrations can be calculated by multiplying the total brain or total plasma concentration by the fraction unbound in brain tissue or plasma, which can be measured by the assay described herein below. It has also been proposed that drug concentrations in cerebrospinal fluid (CSF) are equivalent to free brain concentrations for compounds which are not actively effluxed from the brain (He et al., Xenobiotica 2009, 39, 687). Thus another method of determining CNS penetration would be to assess the CSF:free plasma (CSF : Pl_{fr}) or CSF :unbound plasma (CSF : Pl_u). If the free drug in plasma is able to permeate into the CNS and is not actively influxed or effluxed then the CSF:Pl_{fr} or CSF:Pl_u should be approximately 1:1.

Rat in vivo CNS penetration

Male Sprague Dawley rats were acquired from Charles River UK Ltd. (Margate, UK) and housed according to UK Home Office guidelines. Drugs were made up to the appropriate concentrations in 0.5% methyl cellulose. Animals were dosed orally (2mL/kg) by gavage at the doses outlined below.

At the specified time point post-dosing, the animals were administered an i.p. injection of sodium pentobarbitone (approximately 330mg/kg for terminal anaesthesia).

Using a guillotine, the animals were decapitated and trunk blood collected into 15ml Falcon tubes containing 100 IU heparin. Blood was vortexed followed by centrifugation at 6000rpm, 4°C for 5 minutes. Plasma was collected for DMPK and ELISA assays and stored at -80°C until use. Brains were dissected out and divided along the midline, weighed and stored at -80°C until further use.

Method for Analysis of Plasma, Brain and CSF Samples

Preparation of Acetonitrile Working Solutions

Test compound was prepared as a 1 mg free base/mL solution in DMSO, vortexed and sonicated for 5 min. The 1 mg/mL DMSO solution was diluted to 30 and 100 µg/mL acetonitrile stocks, by adding 30 µL to 970 µL acetonitrile and 100 µL to 900 µL acetonitrile, respectively. The 30 and 100 µg/mL acetonitrile stocks were then serially diluted 1:9 (v/v) (100 µL stock into 900 µL acetonitrile) to give the following solutions: 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 and 100 µg/mL acetonitrile.

Preparation of Plasma Standards, Blanks and Samples

Control male Sprague Dawley rat plasma and the study plasma samples were stored at -80˚C until the day of analysis when they were thawed at room temperature. Control plasma and study samples were centrifuged (2,000 x g, 10 min, 4^0C) and the control plasma aliquoted (90 µL) into Micronics tubes for preparation of standards and blank samples. Study samples were aliquoted (100 µL) into Micronics tubes.

An aliquot (10 µL) of the appropriate acetonitrile stock was added to the control plasma (to give a final volume of 100 µL) to give the required calibration standards covering the range 1 - 10,000 ng/mL. Double blank and blank samples were prepared by adding 10 µL of acetonitrile to 90 µL of blank plasma.

Preparation of Brain Standards, Blanks and Samples

Control male Sprague Dawley rat brain and the study brain samples were weighed after collection and stored at -80˚C until the day of analysis when they were thawed at room temperature. Once thawed brains were diluted with water (4 mL per gram of tissue) and homogenised using a mechanical homogeniser. An aliquot (100 µL) of each study sample was taken into Micronics tubes ready for analysis and sufficient aliquots (90 µL) of control brain homogenate prepared for preparation of standards and blanks.

An aliquot (10 µL) of the appropriate acetonitrile stocks was added to the control brain homogenate (to give a final volume of 100 µL) to give the required calibration standards covering the range 1.5 – 15,000 ng/g. Double blank and blank samples were prepared by adding 10 µL of acetonitrile to 90 µL of blank brain homogenate.

Extraction of Plasma and Brain Samples, Standards and Blanks

Each plasma and brain homogenate sample, standard and blank (100 µL) was extracted with an aliquot (300 µL) of acetonitrile (containing 0.1% formic acid and

internal standard). Double blanks were extracted with an aliquot (300 µL) of acetonitrile containing 0.1% formic acid). All samples, standards and blanks were then vortex mixed and centrifuged (2000 x g, 15 min, 4°C). An aliquot (50 µL) of the resulting supernatant was then taken into a 2 mL 96-deep well plate and diluted with acetonitrile:water (50:50 v/v) (150 µL) ready for analysis by a specific LC/MS/MS method.

Preparation of CSF Samples, Standards and Blanks

Control male Sprague Dawley rat CSF and the study CSF samples were stored at -80˚C until the day of analysis when they were thawed at room temperature. An aliquot (50 µL) of each study sample was taken into Micronics tubes ready for analysis and sufficient aliquots (45 µL) of control CSF prepared for preparation of standards and blanks.

An aliquot (5 µL) of the appropriate acetonitrile stocks was added to the control CSF (to give a final volume of 50 µL) to give the required calibration standards covering the range 1 - 3,000 ng/mL. Double blank and blank samples were prepared by adding 5 µL of acetonitrile to 45 µL of blank CSF.

Extraction of CSF Samples, Standards and Blanks

Each CSF sample, standard and blank (50 µL) was extracted with an aliquot (150 µL) of acetonitrile (containing 0.1% formic acid and internal standard). Double blanks were extracted with an aliquot (150 µL) of acetonitrile containing 0.1% formic acid. All samples were then vortex mixed and an aliquot (50 µL) of each was then further diluted in 150 µL of acetonitrile:water (50/50 v/v) in a 2 mL 96-deep well block ready for LC-MS/MS analysis.

All samples were then analysed using a Waters Acquity UPLC coupled to a Waters Xevo TQ mass spectrometer.

LC Conditions:

Column: Acquity UPLC BEH C18, 1.7 um, 2.1 x 50 mm, maintained at 40˚C

Mobile Phase: A = Water containing 0.1% formic acid

B = Acetonitrile containing 0.1% formic acid

Gradient:

Time (min)	B (%)
0	5
1.2	95
1.5	95
1.7	5
2.0	5

Flow rate: 0.6 mL/min; injection volume 5 µL; autosampler temperature 6°C
LC flow was diverted to waste for the first 0.3 min of each injection
MS/MS transitions were optimised automatically by Waters QuanOptimise software.

Data Analysis

Compound to internal standard peak area ratios were calculated by TargetLynx v4.1 software and the data for calibration curves fitted appropriately. Concentrations of test compound were then quantified automatically in TargetLynx v4.1 and exported to Microsoft Excel 2003.

Amyloid detection

DEA/ NaCl Extraction of Aβ peptides from rat brain:

100ml of chilled 0.2% diethyl amine (DEA) in 50 mM NaCl (pH 10) was freshly prepared and 1ml/25mg brain tissue was added to each hemisphere (i.e. 40x brain volume). The brains were immediately homogenized using a Polytron PT 1200 for 1.5 minutes and samples left to incubate on ice for one hour after homogenisation. 3ml of the homogenate was transferred to a polyallomer tube (Beckman #362333) and spun at 133000 x g (55,000rpm) for 45 min at 4° C. The supernatant was then neutralised to pH 8-8.3 by adding 1/10 volume 0.5M Tris/HCl, pH 6.8. The samples can be used fresh or snap frozen on dry-ice and stored at -80°C until required for analysis.

Human/ Rat βAmyloid (40) ELISA (Wako Kit)

The Wako Aβ40 ELISA kit (Code No. 294-62501) uses the monoclonal antibody BNT77, raised against epitope Aβ(11-28) and the monoclonal antibody BA27, which specifically detects the C-terminal portion of Aβ40. This kit is used for the quantitative determination of human or rat Aβ(1-40) and also N-terminally truncated Aβ40 species (Aβ(x-40)) in biological matrices such as tissue culture medium, tissue homogenate, CSF and plasma.

For analysis, plasma and brain samples are diluted 1:1 with the standard diluent contained in the kit and CSF samples are diluted 1:8 with the standard diluent contained in the kit. The assay is carried out according to the manufacturers instructions and samples are analysed in duplicate. Data is analysed using Microsoft Excel 2003 and statistical analysis is carried out using Genstat 9th Edition.

Results

Compounds were administered at a dose of 60mg/kg p.o. and plasma and brain samples were collected at 3 hours post-dose and the concentrations were measured. The

results, including percentage Aβ40 reductions (%↓) as measured in Plasma (%↓ Pl), Brain (%↓ Br) and CSF (%↓ CSF) are shown in Table 3.

Table 3:

Ex.	[Pl] nM	[1][Pl_u] nM	[Br] nM	[2][Br_u] nM	[CSF] nM	Br_{tot}: Pl_{tot}	Br_u: Pl_u	CSF: Pl_u	%↓ Pl	%↓ Br	%↓ CSF
1	517	8	962	8	6	1.8	0.9	0.8	46	0*	47
14	526	15	324	13	6	0.7	0.9	0.4	53	4	28

1. Calculated by multiplying the [Pl] by Pl Fu value recorded in Table 4.
2. Calculated by multiplying the [Br] by Br Fu value recorded in Table 4 below.
* Recorded value greater than vehicle therefore no reduction reported.

The results of this assay demonstrate that compound examples 1 and 14 can reduce CSF Aβ after oral administration. The efficacy is achieved with low circulating plasma (total and free) concentrations. This is advantageous and indicates that the compound examples would be efficacious at low concentrations and thus less likely to cause unwanted peripherally mediated side effects than compounds requiring higher plasma concentrations to achieve comparable efficacy.

Whilst the compound examples displayed no statistically significant Aβ reduction in rat brain it is known in the art that a lack of Aβ reduction in rat brain may be attributable to a compound having low metabolic stability in rat, to a different rate of amyloid turnover in rat compared to higher species, or to a combination of both. Data presented below demonstrate that compound example 1 of the present invention has a lower metabolic stability in rat microsomes than human microsomes (Table 5) and a moderate-high clearance in vivo in rat (Table 6). Therefore, it is predicted that in a different species, for example human or monkey, the compound examples would reduce Aβ in the brain.

Method For Determination of Plasma Protein Binding (PPB) and Brain Tissue Binding (BTB)

Compounds were grouped into cassettes of up to n=4 compounds based on molecular weights differing by a minimum of 5-Da for the purpose of cassetting compounds for incubation. Compounds were dissolved singly in DMSO to give 10 mM stock solutions before further dilution 100-fold in acetonitrile to give combined solutions containing 100 μM of each compound.

Naive male Sprague Dawley rat plasma and brains stored at -80 °C were thawed at room temperature. Plasma was centrifuged (2000 × g, 10 minutes, 4 °C) to remove any precipitate. Brains were weighed and diluted with 2 mL of Phosphate Buffered Saline (PBS) (pH 7.4) per gram of tissue and homogenised using a Polytron homogeniser. An aliquot of each 100 μM combined compound solution was then added

to plasma and brain homogenate and vortex mixed to give a final compound concentration of 1 μM per compound in matrix.

A Rapid Equilibrium Dialysis (RED) base plate was filled with the appropriate number of 8-kDa molecular weight cut-off disposable inserts (n=3 per cassette) (Thermo Scientific). Matrix containing compounds was then added into the matrix chamber of the inserts (200 μL) and an aliquot (350 μL) of PBS added to the buffer chambers. The plate was covered with a gas permeable seal (Thermo Scientific) and incubated at 37 ˚C (with 5% CO_2 and 95% humidity) for 6 hours with 200 rpm agitation. At the end of the incubation, the seal was removed and an equal aliquot taken from the matrix and PBS chambers and dispensed into Micronics tubes. Plasma and brain was then matrix matched with an equal volume of drug-free PBS and the PBS samples with an equal volume of the corresponding drug-free matrix, to give equal final compositions and volumes.

Samples are vortex mixed and extracted by protein precipitation with a 1:3 aliquot of acetonitrile containing 0.1% formic acid and internal standard. Samples are then vortex mixed and centrifuged (2000 × g, 15 minutes, 4 °C) and an aliquot of the supernatant removed into a 96-deep well plate and diluted with an equal volume of water ready for analysis by LC/MS/MS.

LC/MS/MS analysis was conducted on a Waters Acquity UPLC and Xevo TQ MS (Massachusetts, US). Compound and internal standard were analyzed using specific MRM transitions. Peak area response ratios of parent compound to internal standard were determined using Waters TargetLynx v4.1 (Massachusetts, US).

Plasma protein binding was calculated using the following equations:

$$\text{Plasma fu} = \text{PBS response ratio} / \text{Plasma response ratio}$$
$$\% \text{ Binding} = (1 - \text{Plasma fu}) \times 100$$

Brain tissue binding was calculated using the following equations:

$$\text{Apparent fu} = \text{PBS response ratio} / \text{Brain response ratio}$$
$$\text{Brain fu} = (1/D) / [((1 / \text{Apparent fu}) - 1) + (1/D)]$$
$$\% \text{ Binding} = (1 - \text{Brain fu}) \times 100$$

D = Brain homogenate dilution (i.e. ‘3’ for a 2mL:1g dilution): (Kalvass JC. and Maurer TS. (2002) Influence of nonspecific brain and plasma binding on CNS exposure: Implications for rational drug discovery. Biopharm. Drug Dispos. 23, 327).

Table 4

Compound	Rat PPB (%)	Rat Plasma fu (Pl Fu)	Rat BTB (%)	Rat Brain fu (Br Fu)
Ex. 1	98.4	0.016	99.2	0.008
Ex. 14	97.2	0.028	96.1	0.039

Determination of rat and human in vitro microsomal stability

Pooled human liver microsomes (pooled male and female) and pooled rat liver microsomes (male Sprague-Dawley rats) are used. Supplies are stored frozen at -80°C prior to use.

Liver microsomes (final protein concentration 0.5 mg/ml), 0.1 M phosphate buffer pH7.4 (including 0.25% DMSO) and test compound (1 µM), are pre-incubated at 37°C prior to the addition of NADPH (1mM) to initiate the reaction. A control incubation is included for each compound tested where 0.1 M phosphate buffer pH 7.4 is added instead of NADPH. Two standard marker compounds are incubated with each experiment for each species.

Each compound is incubated for 0, 5, 15, 30 and 45 minutes. The control incubation (minus NADPH) is incubated for 45 minutes only The reactions are stopped by the addition of 2 volumes of methanol containing internal standard at the appropriate time points. The incubation plates are centrifuged at 2500 rpm for 20 minutes at 4 °C to precipitate the protein.

Following protein precipitation, the supernatants are combined into cassettes and analysed using LC-MS/MS.

The gradient of the line is determined from a plot of ln peak area ratio (compound peak area/internal standard peak area) against time. Subsequently, half-life (t1/2) and intrinsic clearance are calculated using the equations below:

k (Elimination rate constant) =- gradient

t½ (mins) = 0.693/k

V (µL) = incubation volume µl per mg microsomal protein.

Clint (µL/min/mg) = V*0.693/ t½

The Clint values for the two standard marker compounds must be in the acceptable range to validate the experiment.

Table 5

Compound	Human Clint (uL/min/mg protein)	Rat Clint (uL/min/mg protein)
Ex. 1	40	175
Ex. 14	29	119

Determination of Rat Metabolic Stability

Compounds were formulated in 5:5:90% (v/v/v) DMSO: 1M HCl: MilliQ water at 1 mg/mL and dosed intravenous bolus into the tail vein at 1 mL/kg to n=3 male Sprague Dawley rats (1 mg/kg) which had been surgically prepared to cannulate the jugular vein (JV). Serial blood samples were collected from the JV cannula at intervals from 2 minutes to up 24 hours into tubes containing sodium heparin as anticoagulant and immediately stored at –20 °C or below.

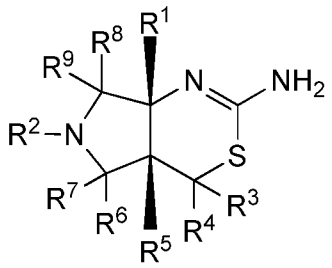
Blood samples were then thawed and vortex mixed, and a calibration line prepared in control rat blood by spiking known amounts of each compound into blood to cover the range 2 – 4000 ng/mL. Samples, standards and blanks were then extracted by protein precipitation with acetonitrile containing internal standard, vortex mixed and centrifuged. The resulting supernatant was analysed by LC/MS/MS to quantify concentrations of compound in blood. Non-compartmental analysis of the concentration data was conducted in WinNonlin v5.3 to determine the intravenous pharmacokinetics of each compound.

Table 6

Compound	CLb (mL/min/Kg)	Vd (L/Kg)	t½ (h)
Ex. 1	53.3	2.62	1.4

CLAIMS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a 5- to 10- membered carbocyclic group or a 5- to 10- membered heterocyclic group, either of which is optionally substituted with at least one substituent independently selected from a halogen atom, a cyano group, a nitro group, a hydroxyl group, a carbamoyl group which is optionally substituted with one or two C_{1-6} alkyl groups, a sulfonylamino group which is optionally substituted with one or two C_{1-6} alkyl groups, an aminosulfonyl group which is optionally substituted with one or two C_{1-6} alkyl groups, an amino group which is optionally substituted with one or two C_{1-6} alkyl groups which are each optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{2-6} alkenyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{2-6} alkynyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{1-6} alkoxy group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, a C_{1-6} alkylthio group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, and a C_{1-6} alkyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α;

R^2 is a 5- to 6- membered heteroaryl group optionally substituted with at least one substituent independently selected from a halogen atom, a cyano group, a nitro group, a hydroxyl group, an amino group which is optionally substituted with one or two C_{1-6} alkyl groups, a C_{1-6} alkoxy group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α, and a C_{1-6} alkyl group which is optionally substituted with 1 to 3 substituents selected from Substituent Group α;

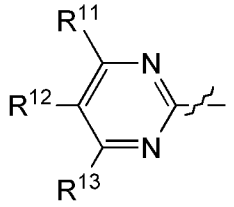
R^3 and R^4 each independently represent a hydrogen atom, a C_{3-6} cycloalkyl group or a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from Substituent Group α;

wherein each substituent selected from Substituent Group α is independently a halogen atom, a cyano group, a hydroxyl group, a C_{1-6} alkoxy group or an oxo group;

R^5 is a hydrogen atom or a fluorine atom;

R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a trifluoromethyl group.

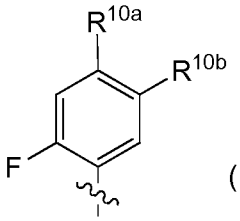
2. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is a group of formula (II),



(II)

wherein R^{11}, R^{12} and R^{13} are independently a hydrogen atom, a halogen atom, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} haloalkoxy group, a C_{1-6} hydroxyalkyl group or a C_{1-6} alkyl group optionally substituted with a C_{1-6} alkoxy group.

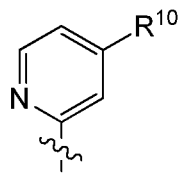
3. A compound as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is a group of formula (III),



(III)

wherein R^{10a} is a hydrogen atom or a fluorine atom; and R^{10b} is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which is optionally substituted with a C_{1-6} alkoxy group, or an amino group which is optionally substituted with one or two substituents independently selected from a C_{1-6} alkyl group and a C_{1-6} haloalkyl group.

4. A compound as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is a group of formula (IV),

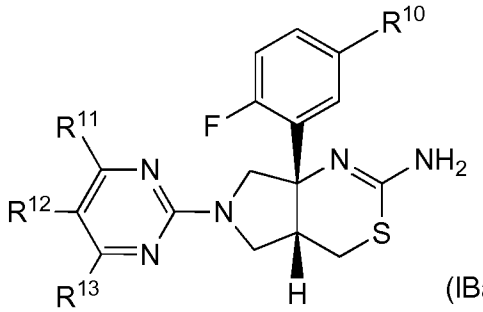


(IV)

wherein R^{10} is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a C_{1-6} haloalkyl group or a C_{1-6} alkyl group.

5. A compound as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently a hydrogen atom.

6. A compound as claimed in claim 1 of formula (IBa), or a pharmaceutically acceptable salt thereof,



(IBa)

wherein

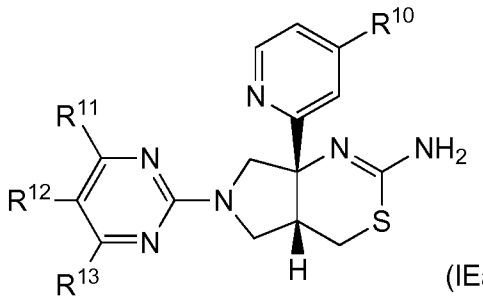
R^{10} is a hydrogen atom, a fluorine atom or a cyano group;

R^{11} is a methoxy group;

R^{12} is a hydrogen atom or a fluorine atom; and

R^{13} is a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a hydroxymethyl group.

7. A compound as claimed in claim 1 of formula (IEa), or a pharmaceutically acceptable salt thereof,



(IEa)

wherein

R^{10} is a hydrogen atom, a fluorine atom or a trifluoromethyl group;

R^{11} is a methoxy group;

R^{12} is a hydrogen atom or a fluorine atom; and

R^{13} is a hydrogen atom, a methyl group, a monofluoromethyl group, a difluoromethyl group or a hydroxymethyl group.

8. A compound as claimed in claim 1 which is selected from:-
(4aR,7aS)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
(4aR,7aS)-7a-(2,5-difluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine; and
(4aR,7aR)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-7a-(pyridin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine,
or a pharmaceutically acceptable salt thereof.

9. A compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in therapy.

10. A compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for inhibiting beta-site amyloid-β precursor protein cleaving enzyme 1 (BACE1).

11. A compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for treating or preventing Alzheimer-type dementia (AD).

12. A compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for treating Down's syndrome.

13. Use of a compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of Alzheimer-type dementia (AD).

14. Use of a compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Down's syndrome.

15. A pharmaceutical composition comprising the compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, as an active ingredient in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065352

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 A61K31/542 A61P25/28
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 A61K

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X,P	& EP 2 511 269 A1 (SHIONOGI & CO [JP]) 17 October 2012 (2012-10-17) claims 1-3, 8-17	1-15

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A	WO 2011/005738 A1 (LILLY CO ELI [US]; AUDIA JAMES EDMUND [US]; MERGOTT DUSTIN JAMES [US];) 13 January 2011 (2011-01-13) the whole document	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"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	Date of mailing of the international search report
22 August 2013	03/09/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065352

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/065352

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