

H4 Antagonist Compounds

This application relates to novel compounds and their use as Histamine H4 receptor antagonists. Compounds described herein may be useful in the treatment or prevention of diseases in which H4 receptors are involved. The application is also directed to pharmaceutical compositions comprising these compounds and the manufacture and use of these compounds and compositions in the prevention or treatment of such diseases in which H4 receptors are involved.

10 BACKGROUND OF THE INVENTION

Histamine is a short-acting biogenic amine generated in mast cells where it is stored in cytosolic granules and released in response to various immunological and non-immunological stimuli. Histamine release from mast cells has been traditionally associated with mild to severe signs and symptoms that characterize hypersensitivity reactions, including erythema, urticaria, itching, tachycardia, hypotension, ventricular fibrillations, bronchospasm, and cardiac and respiratory arrest. To date, numerous additional sources have been identified, including basophils, neurons and cancer cells. In addition to modulating a wide range of physiological processes, histamine is implicated in pathological conditions including allergies and anaphylaxis, asthma and chronic inflammation, autoimmune, cardiovascular, neuropsychiatric and endocrine disorders as well as cancer.

Histamine exerts its pleiotropic actions mainly through binding to four types of G-protein-coupled receptors (GPCRs), designated as H1–H4 that are differentially expressed in various cell types and exhibit considerable variations among species. The H2 receptor is responsible for gastric acid secretion; the H3 receptor controls the release of histamine and other neuromodulators in the CNS and the H1 receptor is associated with wakefulness and inflammatory response.

30 Identified in 2000, the high affinity H4 receptor displays constitutive activity and is expressed mostly, but not exclusively on cells of the immune system including mast cells, monocytes, dendritic cells, eosinophils, basophils, neutrophils, and T cells. This discovery led to the attractive prospect of a new drug target with therapeutic potential

in acute and chronic inflammation, autoimmune disease, host defense and neuropathic pain.

The H4R shares only 40% homology with its nearest neighbour the H3R and neither
5 H2 nor H1 antagonists were shown to inhibit histamine induced eosinophil chemotaxis. Histamine has been shown to inhibit forskolin-induced cAMP responses in a pertussis toxin (PTx)-sensitive manner, suggesting that H4R signals via heterotrimeric Gai/o proteins. Transient expression of the H4R in heterologous cell systems (e.g. HEK293 cells) is a widely used method to measure H4 ligand signaling and binding to generate
10 estimates of functional potency and receptor affinity respectively.

The discovery of H4R antagonists using these techniques and their study in various animal disease models including asthma, chronic pruritus, dermatitis, rheumatoid arthritis, gastric ulcerogenesis and colitis has confirmed H4R antagonism leads to a
15 profound anti-inflammatory effect and has validated the therapeutic benefit for targeting this receptor. The first H4R antagonist phase 2a clinical trial in patients suffering from moderate-to-severe atopic dermatitis has already been conducted, further confirming H4 as a druggable target in patients

20 Notwithstanding a number of published H4R ligands, there remains a need to develop new H4R antagonists with good drug candidate quality. These antagonists should display excellent low nM potency and affinity with full selectivity against H1-H3 receptors. They should display no agonist activity due to risks associated with the induction of pro-inflammatory responses, and ideally display a similar pharmacological
25 profile across species to support PK/PD in various animal models of disease. They should be metabolically stable, with excellent PK, non-toxic and show excellent H4 specificity in broad safety panel profiling.

The human ether-a-go-go-related gene (hERG) encodes the pore-forming subunit of
30 the rapidly activating delayed rectifier potassium channel (IKr), which plays an important role in ventricular repolarisation and in determining the QT-interval of the electrocardiogram with QT-interval being the time taken for ventricular depolarisation and repolarisation. It is widely acknowledged that hERG is highly susceptible to inhibition by a wide range of structurally diverse compounds. When the channels ability

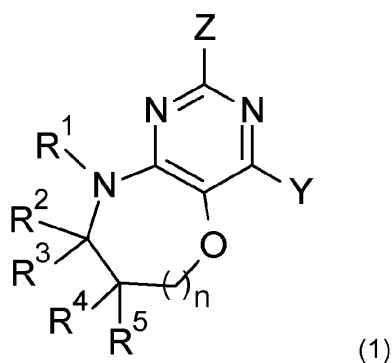
to conduct electrical current across the cell membrane is inhibited or compromised by application of drugs, it can result in a potentially fatal disorder called QT syndrome. A number of clinically successful drugs in the market have had the tendency to inhibit hERG, and create a concomitant risk of sudden death, as a side-effect, which has made hERG inhibition an important anti- target that must be avoided during drug development.

Compounds of the invention are antagonists of the H4 receptor. Certain compounds have a low hERG inhibition, making these particularly beneficial.

THE INVENTION

The present invention provides compounds having activity as H4 receptor antagonists. More particularly, the invention provides compounds that combine H4 receptor antagonism with low hERG activity.

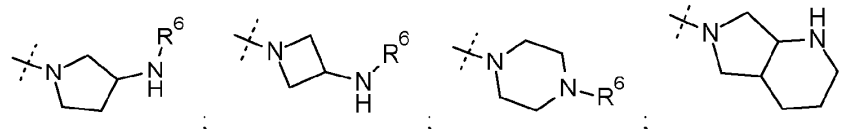
Accordingly, in one embodiment the invention provides a compound of the formula (1):



or a salt thereof, wherein;

Z is H, NH₂ or C₁₋₃ alkyl;

Y is selected from the group consisting of:



n is 0 or 1;

R¹ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

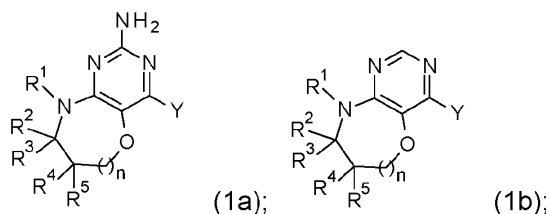
R² is H, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₆ cycloalkyl, or an optionally substituted 3 to 6-membered heterocyclcyl group, wherein the optional substituents are selected from OC₁₋₃ alkyl or 1 to 6 fluorine atoms, or R² is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R³ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R¹ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R² to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R⁴ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁵ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

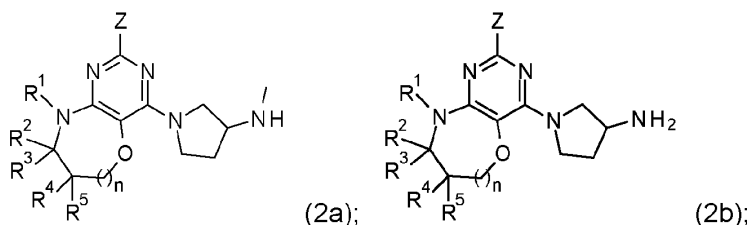
R⁵ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms; and R⁶ is H or methyl.

Particular compounds include compounds of formula (1a) and (1b):



or salts thereof, wherein Y, R¹, R², R³, R⁴, R⁵ and n are as defined above.

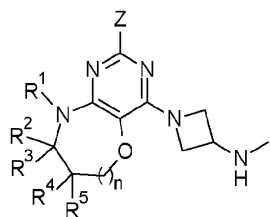
Particular compounds include compounds of formula (2a) and (2b):



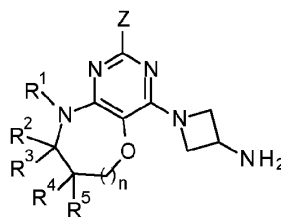
or salts thereof, wherein Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

5

Particular compounds include compounds of formula (2c) and (2d):



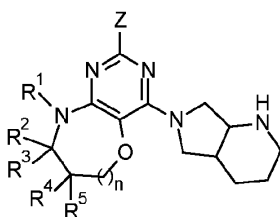
(2c);



(2d);

or salts thereof, wherein Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

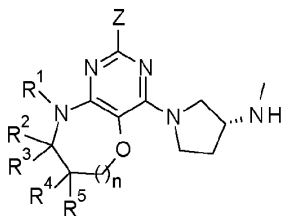
5 Particular compounds include a compound of formula (2e):



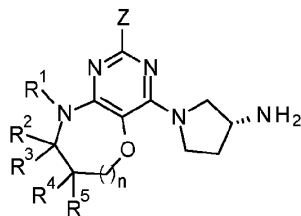
(2e);

or a salt thereof, wherein Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

10 Particular compounds include compounds of formula (3a) and (3b):



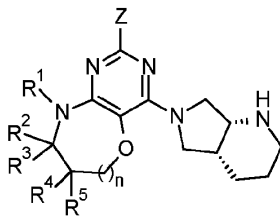
(3a);



(3b);

or salts thereof, wherein Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

Particular compounds include a compound of formula (3c):



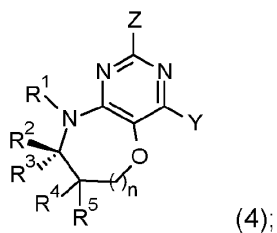
(3c);

or a salt thereof, wherein Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

15

6

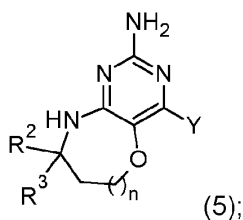
Particular compounds include a compound of formula (4):



or a salt thereof, wherein Y, Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

5

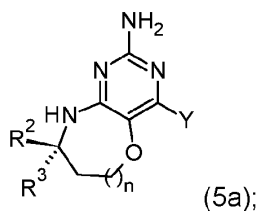
Particular compounds include a compound of formula (5):



or a salt thereof, wherein Y, R², R³ and n are as defined above.

10

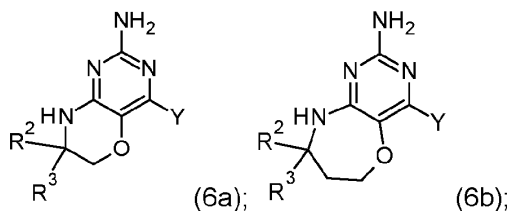
Particular compounds include a compound of formula (5a):



or a salt thereof, wherein Y, R², R³ and n are as defined above.

15

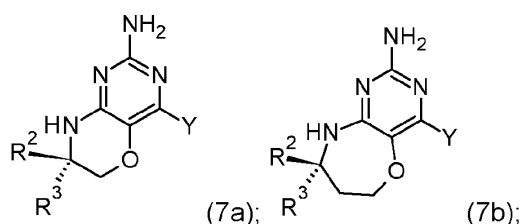
Particular compounds include a compound of formula (6a) and (6b):



or a salt thereof, wherein Y, R² and R³ are as defined above.

20

Particular compounds include a compound of formula (7a) and (7b):



or a salt thereof, wherein Y, R² and R³ are as defined above.

5

The compounds may be used as H₄ receptor antagonists. The compounds may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of inflammatory disorders including asthma, chronic pruritus, dermatitis, rheumatoid arthritis, gastric ulcerogenesis and colitis.

10

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to novel compounds. The invention also relates to the use of novel compounds as antagonists of the H₄ receptor. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as H₄ receptor antagonists or for the treatment of H₄ system dysfunction. The invention further relates to compounds, compositions and medicaments which are selective H₄ receptor antagonists.

15

The invention further relates to compounds, compositions and medicaments useful for the treatment of acute and chronic inflammation, autoimmune disease, host defense disorders and neuropathic pain.

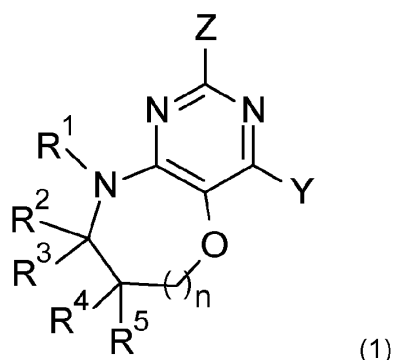
20

The invention further relates to compounds, compositions and medicaments useful for the treatment of inflammatory disorders including asthma, chronic pruritus, dermatitis, rheumatoid arthritis, gastric ulcerogenesis and colitis.

25

Compounds of the invention include compounds according to formula (1):

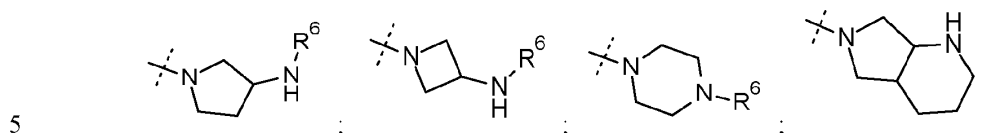
8



or a salt thereof, wherein;

Z is H, NH₂ or C₁₋₃ alkyl;

Y is selected from the group consisting of:



n is 0 or 1;

R¹ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

10 R² is H, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₆ cycloalkyl, or an optionally substituted 3 to 6-membered heterocyclyl group, wherein the optional substituents are selected from OC₁₋₃ alkyl or 1 to 6 fluorine atoms, or R² is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

15 R³ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R¹ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R² to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R⁴ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to

20 R⁵ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

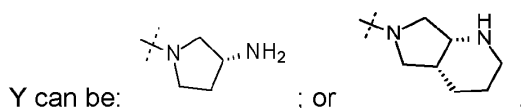
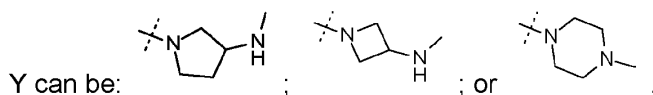
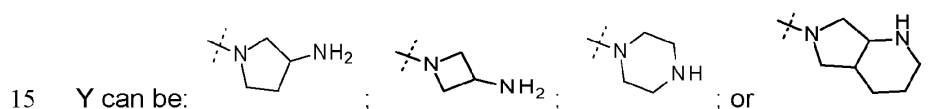
R⁵ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

and R⁶ is H or methyl.

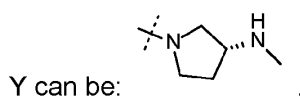
In the compounds herein, Z can be H. Z can be NH₂. Z can be C₁₋₃ alkyl. Z can be methyl.

5

In the compounds herein, Y can be an optionally substituted 3-aminopyrrolidine ring. Y can be an optionally substituted 3-aminoazetidine ring. Y can be an optionally substituted piperazine ring. Y can be an optionally substituted octahydro-1H-pyrrolo[3,4-b]pyridine ring system. Y can be 3-aminopyrrolidine. Y can be 3-aminoazetidine. Y can be piperazine. Y can be octahydro-1H-pyrrolo[3,4-b]pyridine. Y can be *N*-methylazetidin-3-amine. Y can be *N*-methylpyrrolidin-3-amine. Y can be *N*-methylpiperazine. Y can be (3*R*)-*N*-methylpyrrolidin-3-amine. Y can be (3*R*)-pyrrolidin-3-amine. Y can be (4*aR*,7*aR*)-octahydro-1*H*-pyrrolo[3,4-*b*]pyridine.



20



In the compounds herein, R¹ can be H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms. R¹ can be H or methyl. R¹ can be H. R¹ can be C₁₋₃ alkyl. R¹ can be joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R¹ can be methyl. R¹ can be joined to R³ to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R¹ can be joined to R³ to form a 5-

25

membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^1 can be joined to R^3 to form a 3 to 6-membered heterocycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^1 can be joined to R^3 to form a 5-membered heterocycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms.

5

In the compounds herein, R^2 can be H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl or an optionally substituted 3 to 6-membered heterocyclyl group, wherein the optional substituents are selected from OMe or 1 to 3 fluorine atoms, or R^2 is joined to R^3 to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be selected from the group consisting of H, methyl, ethyl, isopropyl, cyclopropyl, isobutyl, trifluoromethyl, CH_2OMe , $CH(CH_3)OMe$, $C(CH_3)_2OMe$ and oxetanyl. R^2 can be H. R^2 can be methyl. R^2 can be ethyl. R^2 can be isopropyl. R^2 can be cyclopropyl. R^2 can be isobutyl. R^2 can be trifluoromethyl. R^2 can be CH_2OMe . R^2 can be $CH(CH_3)OMe$. R^2 can be $C(CH_3)_2OMe$. R^2 can be oxetanyl. R^2 can be joined to R^3 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be joined to R^3 to form a 5-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be joined to R^3 to form a 4-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be joined to R^3 to form a 3 to 6-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be joined to R^3 to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^2 can be joined to R^3 to form a 4-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms.

In the compounds herein, R^3 can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^3 can be H. R^3 can be C_{1-3} alkyl. R^3 can be joined to R^1 to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^4 to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be methyl. R^3 can be joined to R^1 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^4 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^1 to form a 5-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 5-membered ring which is

30

optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 4-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^1 to form a 3 to 6-membered heterocycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 3 to 6-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^4 to form a 3 to 6-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^1 to form a heterocycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^4 to form a cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^1 to form a 5-membered heterocycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^2 to form a 4-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^3 can be joined to R^4 to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms.

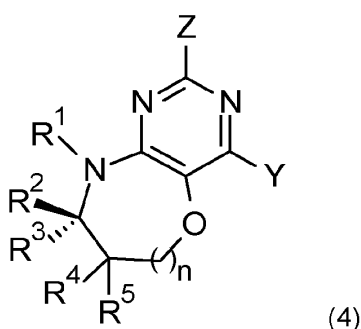
In the compounds herein, R^4 can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms, or can be joined to R^3 to form a ring which is optionally substituted with 1-6 fluorine atoms or can be joined to R^5 to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be selected from H, methyl, ethyl or isopropyl. R^4 can be H. R^4 can be C_{1-3} alkyl. R^4 can be methyl. R^4 can be ethyl. R^4 can be isopropyl. R^4 can be joined to R^3 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^5 to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^3 to form a 5-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^5 to form a 5-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^3 to form a cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^5 to form a cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^3 to form a 3 to 6-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^5 to form a 3 to 6-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^4 can be joined to R^3 to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R^4

can be joined to R⁵ to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms.

In the compounds herein, R⁵ can be H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or can be joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R⁵ can be H. R⁵ can be C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms. R⁵ can be C₁₋₃ alkyl. R⁵ can be joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms. R⁵ can be methyl. R⁵ can be joined to R⁴ to form a 3 to 6-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R⁵ can be joined to R⁴ to form a 5-membered ring which is optionally substituted with 1 to 6 fluorine atoms. R⁵ can be joined to R⁴ to form a cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms. R⁵ can be joined to R⁴ to form a 5-membered cycloalkyl ring which is optionally substituted with 1 to 6 fluorine atoms.

In the compounds herein, n can be 0. n can be 1.

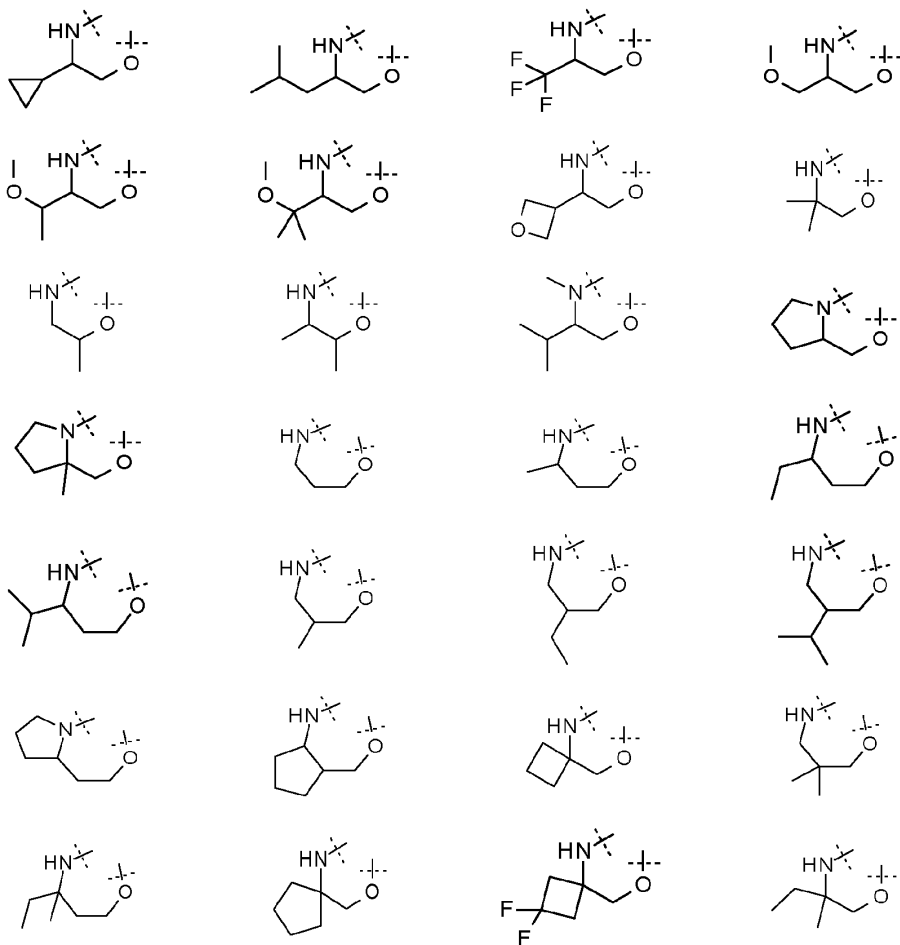
Compounds of the invention include compounds according to formula (4):



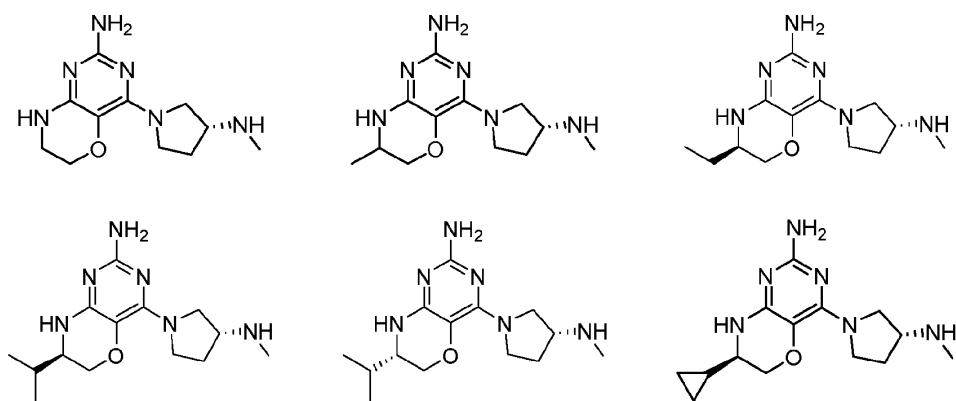
or a salt thereof, wherein Y, Z, R¹, R², R³, R⁴, R⁵ and n are as defined above.

The moiety comprising groups R¹, R², R³, R⁴ and R⁵ can be selected from the group consisting of:

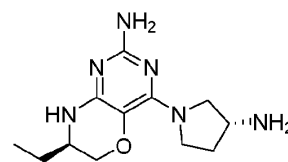
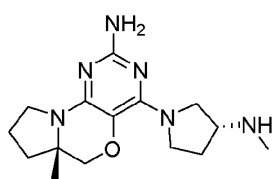
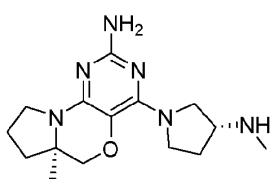
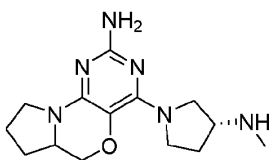
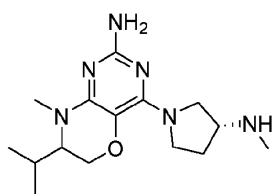
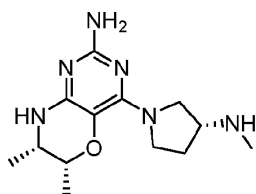
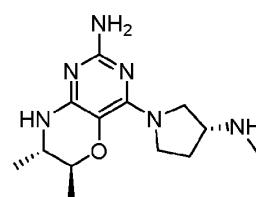
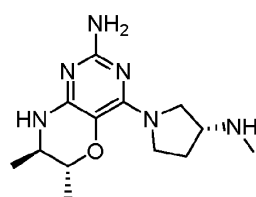
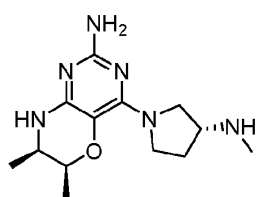
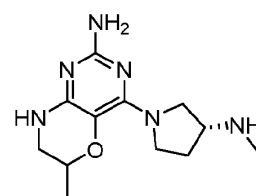
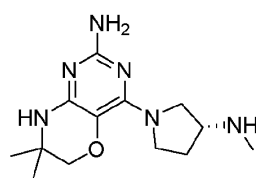
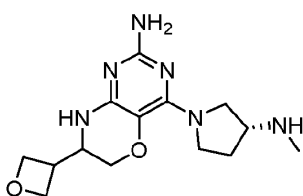
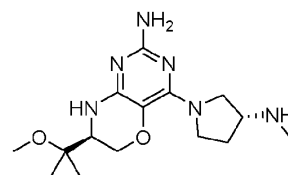
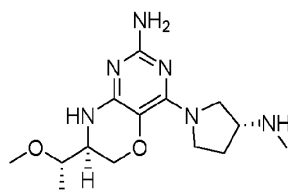
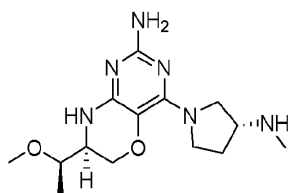
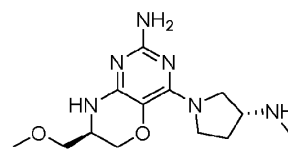
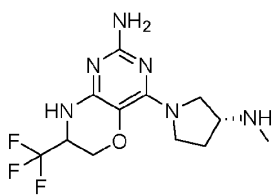
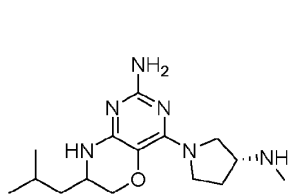




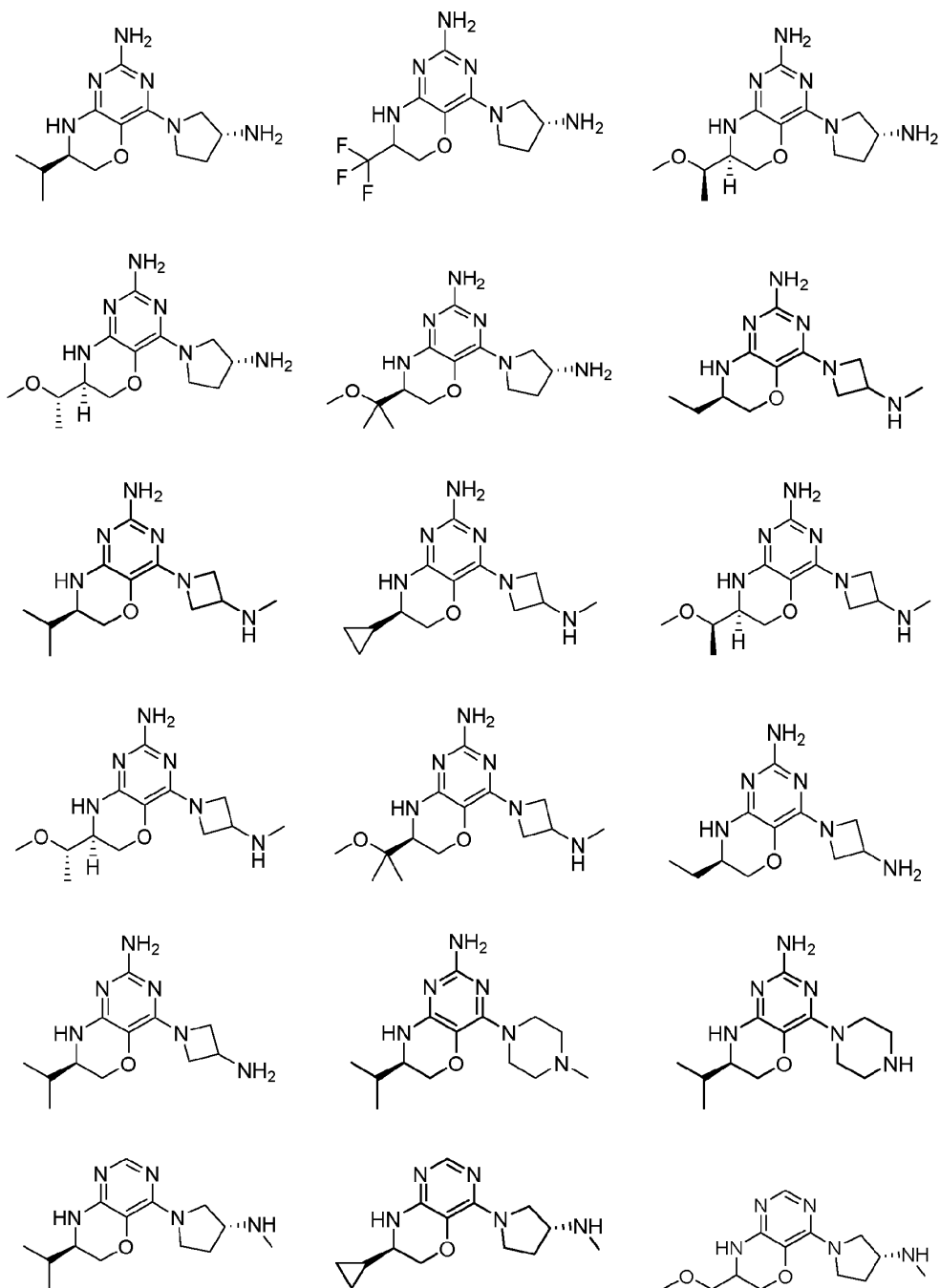
The compound can be selected from the group consisting of:



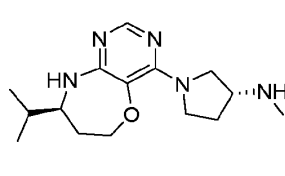
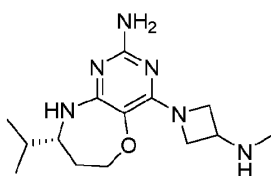
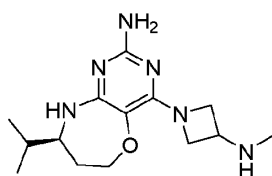
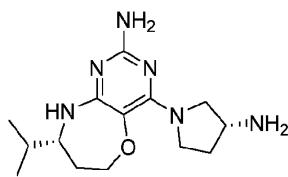
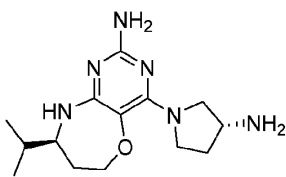
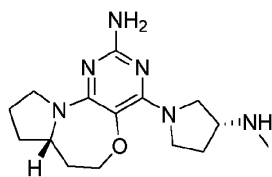
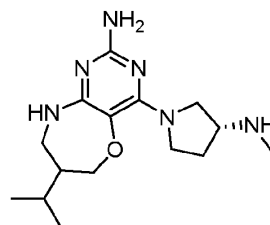
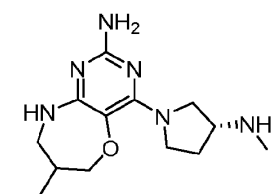
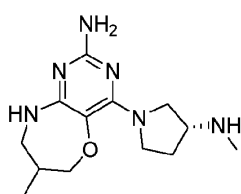
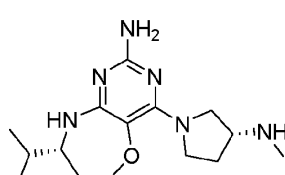
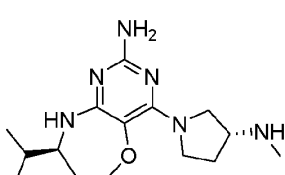
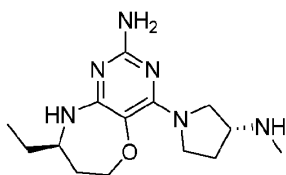
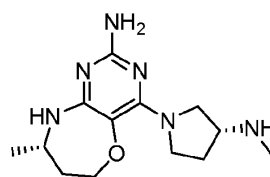
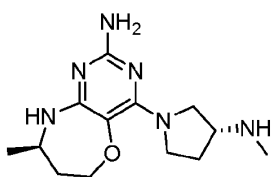
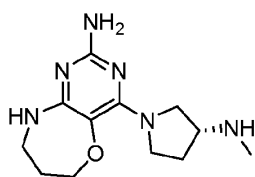
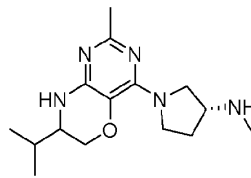
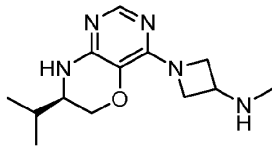
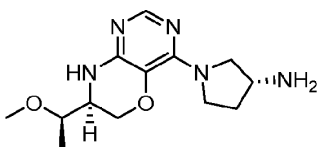
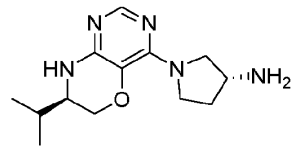
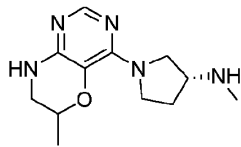
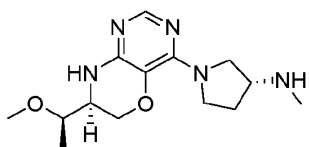
14

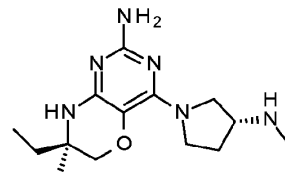
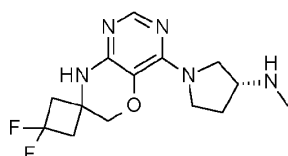
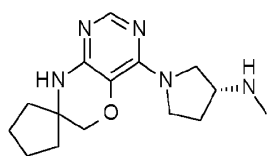
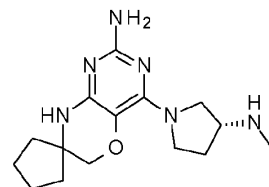
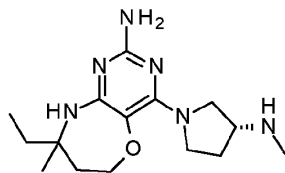
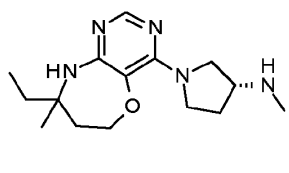
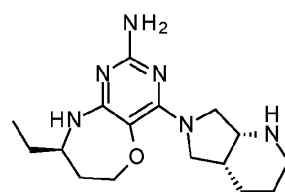
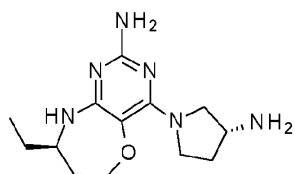
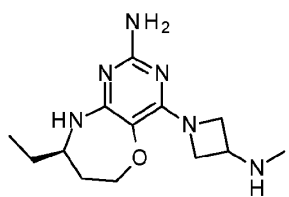
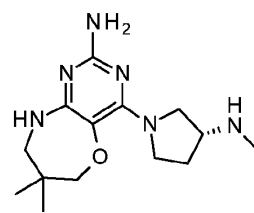
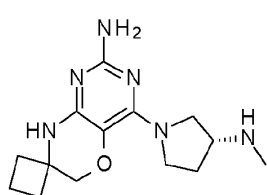
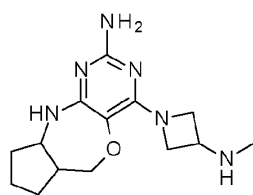
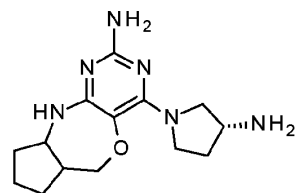
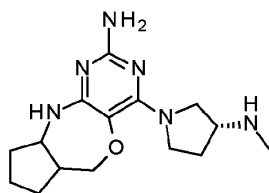
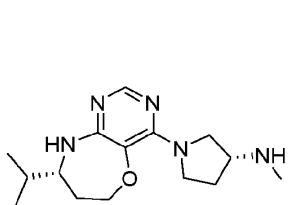


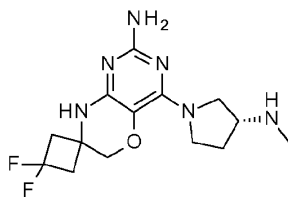
15



16







or a salt thereof.

The compound can be selected from the group consisting of:

(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

7-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Cyclopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

7-isobutyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-(Methoxymethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-((*R*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-((*S*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-7-(2-Methoxypropan-2-yl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((R)-3-(Methylamino)pyrrolidin-1-yl)-7-(oxetan-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(R)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

6-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6S,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6R,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6S,7S)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6R,7S)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

7-Isopropyl-8-methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((R)-3-(Methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine;

(R)-6a-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine;

(S)-6a-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine;

(R)-4-((R)-3-Aminopyrrolidin-1-yl)-7-ethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(R)-4-((R)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((R)-3-Aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-((R)-1-methoxyethyl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-((S)-1-methoxyethyl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-(2-methoxypropan-2-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-7-Ethyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-7-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-7-Cyclopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-7-((R)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-7-((S)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-7-(2-Methoxypropan-2-yl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-4-(3-Aminoazetidin-1-yl)-7-ethyl-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-4-(3-Aminoazetidin-1-yl)-7-isopropyl-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine

(R)-7-Isopropyl-4-(4-methylpiperazin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-7-Isopropyl-4-(piperazin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(R)-1-((R)-7-Isopropyl-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(R)-1-((R)-7-Cyclopropyl-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(3*R*)-1-(7-(Methoxymethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(3*R*)-*N*-Methyl-1-(6-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-((*R*)-7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-(7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylazetidin-3-amine;

(3*R*)-1-(7-Isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

7-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-6,7,7*a*,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-2-amine;

(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-1-((*S*)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-1-((*R*)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;

4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;

4-[(3*R*)-3-aminopyrrolidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;

4-[3-(methylamino)azetidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;

4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;

7,7-dimethyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

8-ethyl-4-[3-(methylamino)azetidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

4-[(3*R*)-3-aminopyrrolidin-1-yl]-8-ethyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

8-ethyl-4-[(4*aR*,7*aR*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(3*R*)-1-(8-ethyl-8-methyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;

8-ethyl-8-methyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclopentane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;

(3*R*)-*N*-methyl-1-(6'*H*,8'*H*-spiro[cyclopentane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-4'-yl)pyrrolidin-3-amine;

(3*R*)-1-(3,3-difluoro-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-4'-yl)-*N*-methylpyrrolidin-3-amine;

7-ethyl-7-methyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

3,3-difluoro-4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;

or a salt thereof.

The compound can be a salt of any compound described above. The compound can be a dihydrochloride salt. The compound can be a hydrochloride salt. The compound can be a ditrifluoroacetic acid salt. The compound can be a trifluoroacetic acid salt.

5

The compound can be selected from the group consisting of:

(*R*)-7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-7-Cyclopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine ditrifluoroacetic acid salt;

(*S*)-7-((*R*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*S*)-7-((*S*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(6*S*,7*R*)-6,7-Dimethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(6*R*,7*R*)-6,7-Dimethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(6*S*,7*S*)-6,7-Dimethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(6*R*,7*S*)-6,7-Dimethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-((*R*)-1-methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-((*S*)-1-methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-7-Ethyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine ditrifluoroacetic acid salt;

(*R*)-7-Cyclopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine ditrifluoroacetic acid salt;

(*S*)-7-((*R*)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt;

(*R*)-4-(3-Aminoazetidin-1-yl)-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine ditrifluoroacetic acid salt;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine hydrochloride salt;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine hydrochloride salt;

(*R*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*S*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*R*)-8-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*S*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*R*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

7-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*S*)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*R*)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine ditrifluoroacetic acid salt;

(*R*)-1-((*S*)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine trifluoroacetic acid salt; and

(*R*)-1-((*R*)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine trifluoroacetic acid salt.

Specific examples of compounds include those having low hERG activity.

Specific examples of compounds having low hERG activity may include compounds
5 selected from the group consisting of:

(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

- (*R*)-7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 5 4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-7-(Methoxymethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*S*)-7-((*R*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 10 (*S*)-7-(2-Methoxypropan-2-yl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 15 6-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine;
- (*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 20 4-((*R*)-3-Aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-7-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- 25 (*S*)-7-((*R*)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-7-Isopropyl-4-(piperazin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
- (*R*)-1-((*R*)-7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;
- 30 (*R*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
- (*S*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(S)-4-((R)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-
b][1,4]oxazepin-2-amine;

(S)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-
b][1,4]oxazepin-2-amine;

5 or a salt thereof.

Definitions

In this application, the following definitions apply, unless indicated otherwise.

10 The term “treatment”, in relation to the uses of any of the compounds described herein,
including those of the formula (1), formula (1a), formula (1b), formula (2a), formula
(2b), formula (2c), formula (2d), formula (2e), formula (3a), formula (3b), formula (3c)
and formula (4), is used to describe any form of intervention where a compound is
administered to a subject suffering from, or at risk of suffering from, or potentially at
15 risk of suffering from the disease or disorder in question. Thus, the term “treatment”
covers both preventative (prophylactic) treatment and treatment where measurable or
detectable symptoms of the disease or disorder are being displayed.

The term “effective therapeutic amount” (for example in relation to methods of
20 treatment of a disease or condition) refers to an amount of the compound which is
effective to produce a desired therapeutic effect. For example, if the condition is pain,
then the effective therapeutic amount is an amount sufficient to provide a desired level
of pain relief. The desired level of pain relief may be, for example, complete removal
of the pain or a reduction in the severity of the pain.

25 The term “alkyl” as in “C₁₋₃ alkyl”, “cycloalkyl” as in “C₃₋₆ cycloalkyl”, “heterocycloalkyl”
and “heterocyclyl” as in “3 to 6-membered heterocyclyl group” are all used in their
conventional sense (e.g. as defined in the IUPAC Gold Book), unless indicated
otherwise.

30 To the extent that any of the compounds described have chiral centres, the present
invention extends to all optical isomers of such compounds, whether in the form of
racemates or resolved enantiomers. The invention described herein relates to all

crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said compounds are included herein. In the case of pharmaceutical uses, the salt should be seen as
5 being a pharmaceutically acceptable salt.

Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with
10 one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

15

Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

20 Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and p-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic,
25 citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and ($\pm$)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic),
30 malonic, ($\pm$)-DL-mandelic, metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyrogutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g. (+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent).

5 Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulfoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known

10 and standard techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and

15 dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

The term "pharmaceutical composition" in the context of this invention means a

20 composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents, adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents,

25 antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections,

30 including liposome preparations.

The compounds of the invention may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^1H , ^2H (D), and ^3H (T).

Similarly, references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and ^{16}O and ^{18}O . In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group
5 or an alkoxy group such as a methoxy group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a trideuteromethoxy group). The isotopes may be
10 radioactive or non-radioactive.

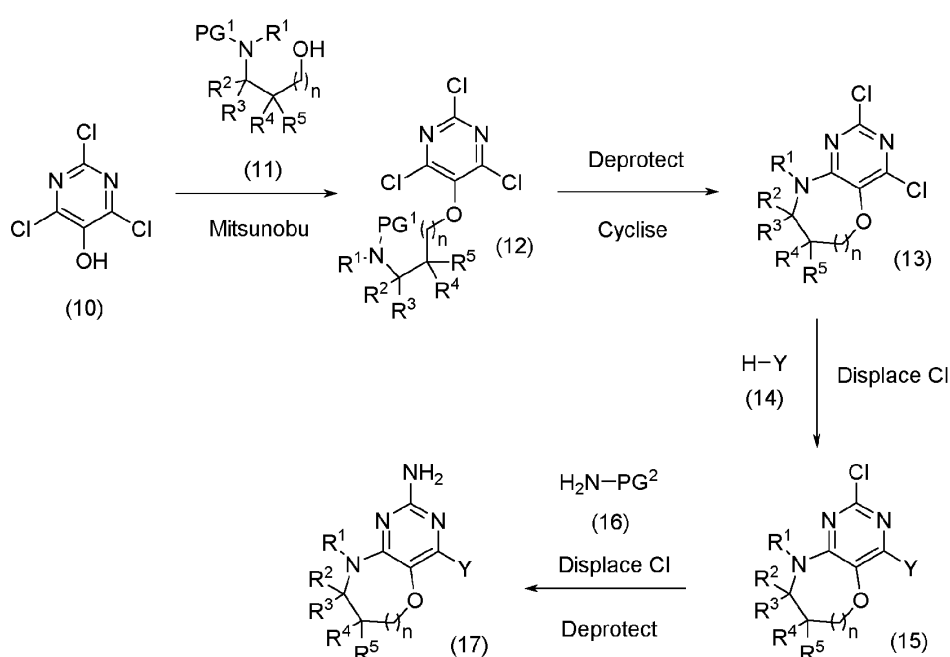
Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the
15 art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

20 The magnitude of an effective dose of a compound will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. The selection of appropriate dosages is within the ability of one of ordinary skill in this art, without undue burden. In general, the daily dose range
25 may be from about 10 μg to about 30 mg per kg body weight of a human and non-human animal, preferably from about 50 μg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 50 μg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 μg to about 30 mg per kg of body weight of a human and non-human animal, for example
30 from about 100 μg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 μg to about 1 mg per kg of body weight of a human and non-human animal.

Methods for the Preparation of Compounds of the Formula (1)

Compounds of the formula (1) can be prepared in accordance with synthetic methods well known to the skilled person and as described herein. Accordingly, in one embodiment, the invention provides a process for the preparation of a compound as defined in formula (1) above, which process comprises:

(A) When it is required to prepare a compound of formula (1) wherein Z is NH₂. The sequence of reactions as illustrated in Scheme 1 below:



Scheme 1

10

Thus, 2,4,6-trichloropyrimidin-5-ol (10), which is easily accessible via dealkylation of commercially available 2,4,6-trichloro-5-methoxypyrimidine, is reacted with a protected amino alcohol of formula (11), wherein R¹, R², R³, R⁴, R⁵ and n are as defined above and PG¹ represents a suitable amino protecting group such as Boc, Cbz, Fmoc, Teoc or Bn, under Mitsunobu conditions to afford a substituted trichloropyrimidine of formula (12), wherein R¹, R², R³, R⁴, R⁵ and n are as defined in above and PG¹ represents a suitable amino protecting group such as Boc, Cbz, Fmoc,

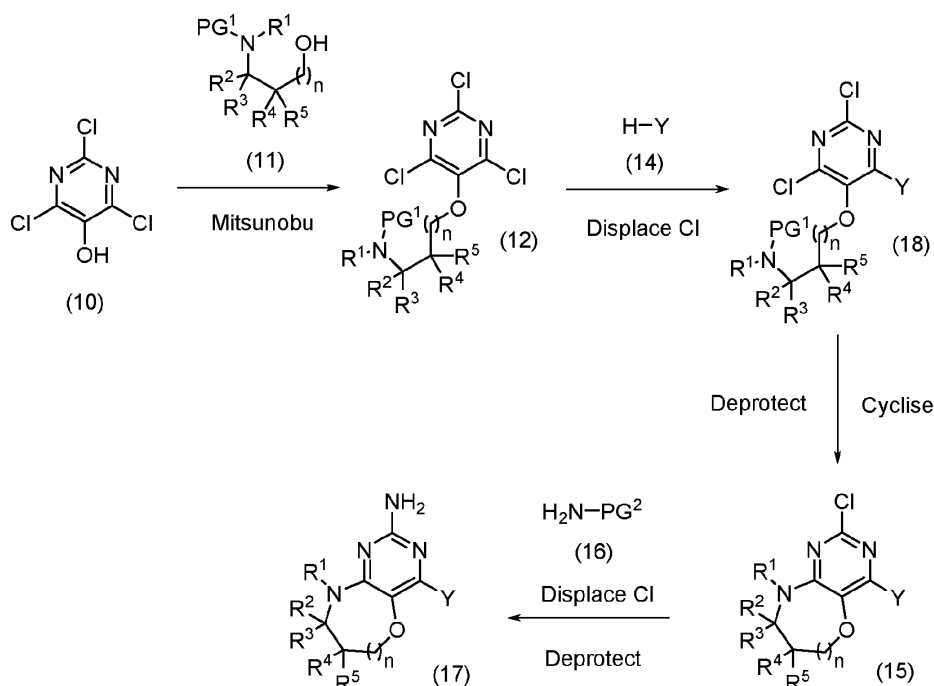
15

Teoc or Bn. Typically, the Mitsunobu reaction is carried out using a trisubstituted phosphine reagent such as Ph_3P or Bu_3P in the presence of an azodicarboxylate species such as DEAD, DIAD or TMAD in a solvent such as THF, toluene, MeCN or DCM at about 0 °C to about room temperature, or occasionally with moderate heating at about 50 °C to 100 °C.

Once formed, the amino function of the substituted trichloropyrimidine of formula (12) can be deprotected using conditions pertinent to the nature of the protecting group PG^1 , and well understood by the skilled person, and the resulting product then cyclised via an intramolecular $\text{S}_{\text{N}}\text{Ar}$ displacement reaction or via an intramolecular transition metal catalysed coupling reaction to form a compound of formula (13), wherein R^1 , R^2 , R^3 , R^4 , R^5 and n are as defined above. The $\text{S}_{\text{N}}\text{Ar}$ displacement reaction is typically carried out in the presence of a tertiary amine base such as TEA or DIPEA, or an inorganic base such as K_2CO_3 , Cs_2CO_3 , Na_2CO_3 or NaHCO_3 , or a strong base such as KO^tBu , NaH or LiHMDS , in a suitable solvent such as 1,4-dioxane, THF, DMF, acetone, DCM, MeCN, H_2O , EtOH, IPA, DMSO or NMP, or a combination of suitable solvents, at a temperature between about room temperature to about 200 °C, using conventional heating or optionally by heating with microwave irradiation, in an open vessel or optionally in a sealed vessel, optionally at a pressure greater than atmospheric pressure. The transition metal catalyzed coupling reaction is typically carried out in the presence of an alkoxide base such as NaO^tBu or KO^tBu , an inorganic base such as K_3PO_4 , K_2CO_3 , Cs_2CO_3 or NaOCN , or a tertiary amine base such as TEA or DIPEA, or a combination of suitable bases, in a suitable solvent such as 1,4-dioxane, THF, DME, $^t\text{BuOH}$ or toluene, or a combination of suitable solvents, in the presence of a sub-stoichiometric quantity of a transition metal catalyst such as $\text{Pd}(\text{OAc})_2$ (CAS: 3375-31-3), $\text{Pd}_2(\text{dba})_3$ (CAS: 51364-51-3), $\text{Pd}(\text{dppf})\text{Cl}_2$ (CAS: 72287-26-4), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (CAS: 13965-03-2) or $\text{Pd}(\text{PPh}_3)_4$ (CAS: 14221-01-3), optionally in the presence of a sub-stoichiometric quantity of a phosphine ligand such as Ph_3P , Bu_3P , $^t\text{Bu}_3\text{P}$, XPhos (CAS: 564483-18-7), Xantphos (CAS: 161265-03-8), $^t\text{BuBrettPhos}$ (CAS: 1160861-53-9) or BINAP (CAS: 76189-55-4, 76189-56-5), at a temperature between about room temperature to about 200 °C, using conventional heating or optionally by heating with microwave irradiation, in an open vessel or optionally in a sealed vessel, optionally at a pressure greater than atmospheric pressure.

Once formed, the compound of formula (13) can be reacted with an amine of formula (14), wherein Y is as defined above, using a S_NAr displacement reaction or a transition metal catalysed coupling reaction analogous to those described above to displace the 4-chloro substituent in the compound of formula (13) and form a compound of formula (15), wherein R¹, R², R³, R⁴, R⁵, n and Y are as defined above. Once formed, the 2-chloro substituent in the compound of formula (15) can be displaced with a suitably protected NH₃ equivalent (16), wherein PG² represents a protecting group or groups such as Boc, Cbz, (Boc)₂, Ac, Bz, Bn, Bn₂, PMB or DMB using another transition metal catalysed coupling reaction analogous to those described above. Finally, the protecting group or groups PG² can be removed using conditions pertinent to the nature of the protecting group PG², and well understood by the skilled person, to afford the desired compound of formula (17), wherein R¹, R², R³, R⁴, R⁵, n and Y are as defined above.

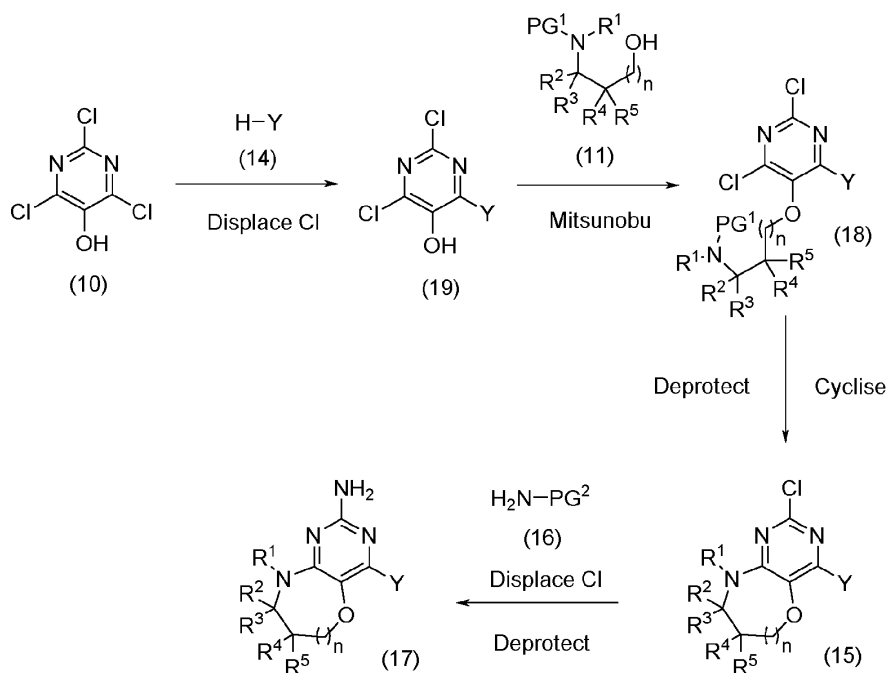
It will be understood by the skilled person that the order of steps as laid out in Scheme 1 may be completed in a different sequence to that shown, without affecting the overall success of the synthesis of the desired compound of formula (17). For example in Scheme 2 below, displacement of the 4-chloro substituent in the substituted trichloropyrimidine of formula (12) by reaction with an amine of formula (14) using a S_NAr displacement reaction or a transition metal catalysed coupling reaction as described above, can be conducted at Step 2 to form a substituted amino dichloropyrimidine of formula (18), wherein R¹, R², R³, R⁴, R⁵, n and Y are as defined above and PG¹ represents a suitable amino protecting group such as Boc, Cbz, Fmoc, Teoc or Bn. Once formed, the amino function of the substituted amino dichloropyrimidine of formula (18) can be deprotected using conditions pertinent to the nature of the protecting group PG¹, and well understood by the skilled person, and the resulting product then cyclised via an intramolecular S_NAr displacement reaction or via an intramolecular transition metal catalysed coupling reaction as described above to form a compound of formula (15). The synthesis of the desired compound of formula (17) from the compound of formula (15) then follows as described for Scheme 1.



Scheme 2

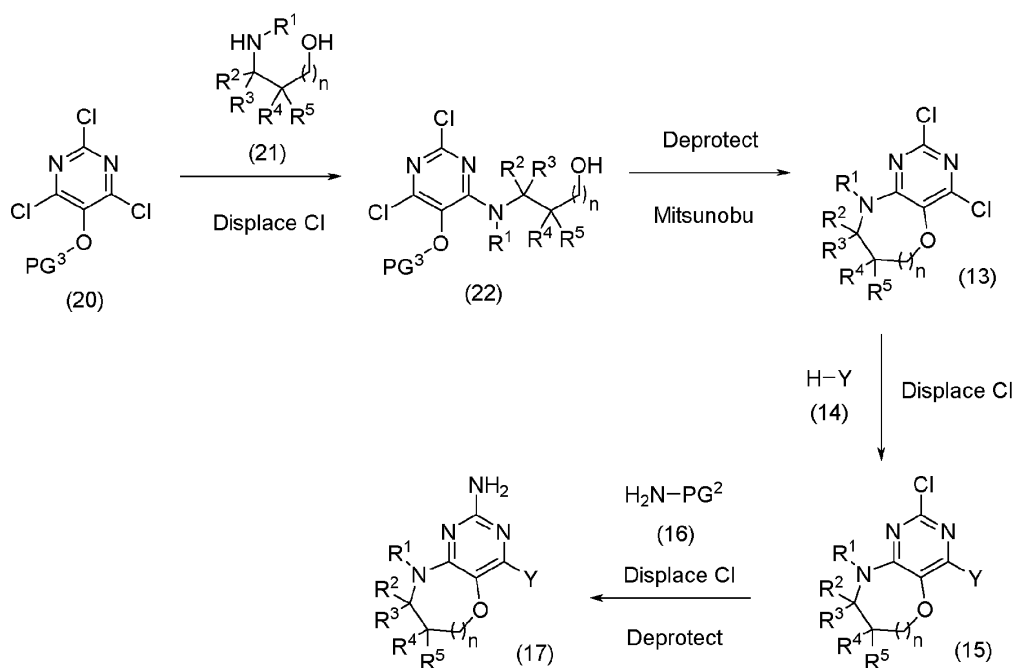
Alternatively, as set out in Scheme 3 below, displacement of the 4-chloro substituent with an amine of formula (14) can take place directly on 2,4,6-trichloropyrimidin-5-ol (10) in Step 1 of the sequence, using a S_NAr displacement reaction or a transition metal catalysed coupling reaction analogous to those described above, to form a 4-amino-2,6-dichloropyrimidin-5-ol analogue of formula (19), wherein Y is as defined above. Once formed, the 4-amino-2,6-dichloropyrimidin-5-ol analogue of formula (19) may then undergo reaction with a protected amino alcohol of formula (11) in Step 2, using Mitsunobu conditions analogous to those described above, to form the substituted amino dichloropyrimidine of formula (18). The synthesis of the desired compound of formula (17) from the substituted amino dichloropyrimidine of formula (18) then follows as described for Scheme 2.

35



Scheme 3

Scheme 4 below shows yet another variation, where a protected 2,4,6-trichloropyrimidin-5-ol of formula (20), wherein PG³ represents a suitable phenolic OH protecting group such as Me or PMB, is reacted with an amino alcohol of formula (21), wherein R¹, R², R³, R⁴, R⁵ and n are as defined above, to displace the 4-chloro substituent in protected 2,4,6-trichloropyrimidin-5-ol of formula (20) using a S_NAr displacement reaction or a transition metal catalysed coupling reaction analogous to those described above to form a protected 4-amino-2,6-dichloropyrimidin-5-ol of formula (22). Removal of the protecting group PG³ in protected 4-amino-2,6-dichloropyrimidin-5-ol of formula (22) via conditions appropriate to the nature of PG³, and well understood by the skilled person, then allows an intramolecular Mitsunobu reaction analogous to those described above to be conducted to form a compound of formula (13). The synthesis of the desired compound of formula (17) from the compound of formula (13) then follows as described for Scheme 1.

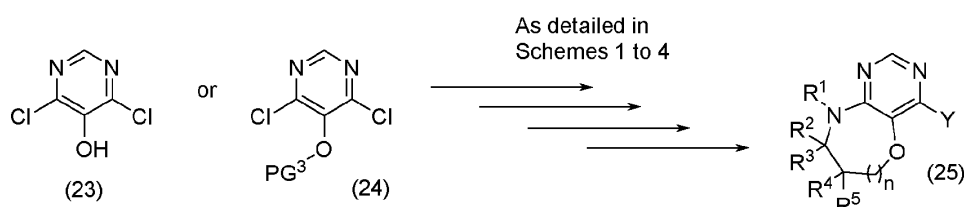


Scheme 4

The skilled person will understand that the reaction steps depicted in Schemes 1 to 4 may be combined in different ways as required to successfully prepare the desired compound of formula (17). It will also be obvious that there may be additional steps involving functional group modification, protection or deprotection introduced into the overall synthetic sequence. For example: carboxylic acid or ester groups may be reduced to alcohols, and the resulting alcohol then protected with a silyl-based protecting group; amide groups, nitriles or nitro groups may be reduced to amines, and the resulting amine then protected with a carbamate-based protecting group; primary or secondary amines may be further substituted using an alkylation reaction; Boc protecting groups may be reduced to methyl groups.

(B) When it is required to prepare a compound of formula (1) wherein Z is H: The sequence of reactions illustrated previously in Schemes 1 to 4 above, but starting either from 4,6-dichloropyrimidin-5-ol (23) or a protected 4,6-dichloropyrimidin-5-ol of formula (24), wherein PG^3 represents a suitable phenolic OH protecting group such

as Me or PMB, to give the desired compound of formula (25), wherein R^1 , R^2 , R^3 , R^4 , R^5 , n and Y are as defined above:

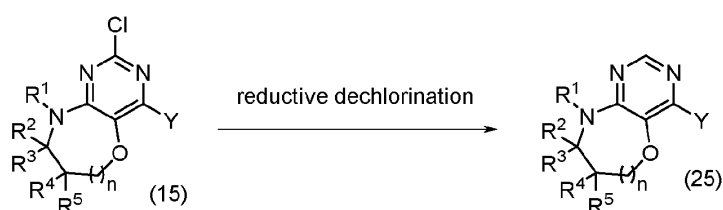


5

Alternatively, the 2-chloro substituent in a compound of formula (15) can be removed to give the desired compound of formula (25) using reductive conditions, such as treatment with H_2 gas, in a solvent such as MeOH or EtOH, in the presence of a transition metal catalyst such as palladium on carbon or palladium hydroxide on carbon, optionally in the presence of a tertiary amine base such as Et_3N or DIPEA, optionally at a pressure greater than atmospheric pressure. Alternatively, reductive dichlorination can be conducted using ammonium formate, in a solvent such as MeOH or EtOH, in the presence of a transition metal catalyst such as palladium on carbon or palladium hydroxide on carbon, at a temperature of between about room temperature to about the boiling temperature of the solvent that is used:

10

15



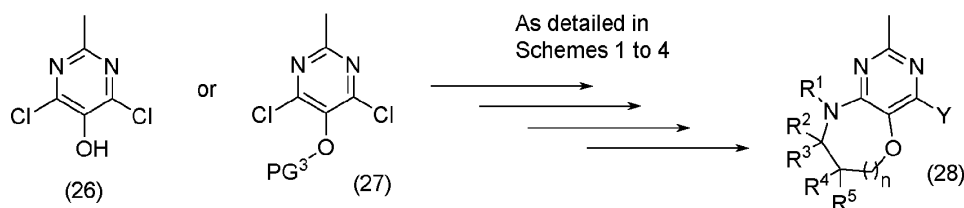
(C) When it is required to prepare a compound of formula (1) wherein Z is methyl:

20

The sequence of reactions illustrated previously in Schemes 1 to 4 above, but starting either from 4,6-dichloro-2-methylpyrimidin-5-ol (26) or a protected 4,6-dichloro-2-methylpyrimidin-5-ol of formula (27), wherein PG^3 represents a suitable phenolic OH protecting group such as Me or PMB, to give the desired compound of formula (28), wherein R^1 , R^2 , R^3 , R^4 , R^5 , n and Y are as defined above:

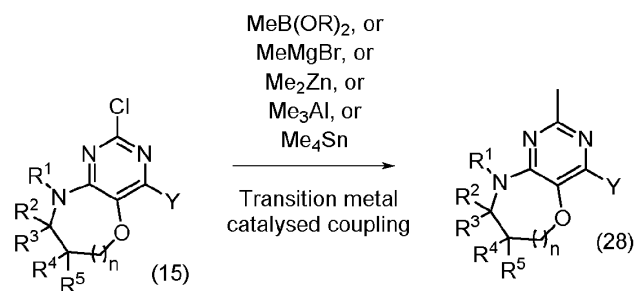
25

38



Alternatively, the 2-chloro substituent in a compound of formula (15) can be replaced with a methyl group using a transition metal catalysed coupling reaction, such as treatment with MeB(OH)₂, MeBPin (CAS: 94242-85-0) or trimethylboroxine (CAS: 823-96-1), in the presence of a palladium catalyst such as Pd(PPh₃)₄ (CAS: 14221-01-3), PdCl₂(dppe) (CAS: 19978-61-1), Pd(dppf)Cl₂ (CAS: 72287-26-4) or Pd₂(dba)₃ (CAS: 51364-51-3), optionally in the presence of a phosphine ligand such as P(Cy)₃, in the presence of an inorganic base such as K₂CO₃ or Cs₂CO₃, in a suitable solvent such as 1,4-dioxane, H₂O, THF or DME, or a mixture of suitable solvents, at a temperature between about room temperature to about 200 °C, using conventional heating or optionally by heating with microwave irradiation, in an open vessel or optionally in a sealed vessel, optionally at a pressure greater than atmospheric pressure. Alternatively, other methods well known to the skilled person can be used such as MeMgBr or MeMgCl in combination with a nickel catalyst such as Ni(dppf)Cl₂ (CAS: 67292-34-6), in a solvent such as THF, Et₂O, DME or 1,4-dioxane at elevated temperatures; Me₂Zn in combination with a palladium catalyst such as PdCl₂(dppe) (CAS: 19978-61-1) or Pd(dppf)Cl₂ (CAS: 72287-26-4), in a solvent such as toluene or 1,4-dioxane at elevated temperatures; Me₃Al in combination with a palladium catalyst such as Pd(PPh₃)₄ (CAS: 14221-01-3), in a solvent such as THF, hexane or heptane at elevated temperatures; or Me₄Sn in combination with a palladium catalyst such as Pd(PPh₃)₄ (CAS: 14221-01-3), in a solvent such as THF or DMF at elevated temperatures.

39



(E) converting one compound of the formula (1) to another compound of the formula (1):

5

Additionally, one compound of the formula (1) can be converted into another compound of the formula (1) by methods well known to the skilled person. Examples of synthetic procedures for converting one functional group into another functional group are set out in standard texts such as *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 7th Edition, Michael B. Smith, John Wiley, 2013, (ISBN: 978-0-470-46259-1), *Organic Syntheses*, Online Edition, www.orgsyn.org, (ISSN 2333-3553) and *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2).

10

15

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Greene's Protective Groups in Organic Synthesis*, Fifth Edition, Editor: Peter G. M. Wuts, John Wiley, 2014, (ISBN: 9781118057483).

20

Compounds made by the foregoing methods may be isolated and purified by any of a variety of methods well known to those skilled in the art and examples of such methods include recrystallisation and chromatographic techniques such as column chromatography (e.g. flash chromatography) under normal or reversed-phase conditions, HPLC and SFC.

25

Pharmaceutical formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

- 5 Accordingly, in another embodiment of the invention, there is provided a pharmaceutical composition comprising at least one compound of the formula (1) as defined above together with at least one pharmaceutically acceptable excipient.

The composition may be a tablet composition.

10

The composition may be a capsule composition.

- The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents
15 such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring
20 agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

- The term “pharmaceutically acceptable” as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical
25 judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

30

Pharmaceutical compositions containing compounds of the formula (1) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

- 5 Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.
- 10 Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl
- 15 methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate
- 20 buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release

25 tablets) over a prolonged period of time or with a specific region of the GI tract.

- The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or
- 30 combination of such excipients. Preferably, the compositions comprise from approximately 20% (w/w) to approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient.

Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

- 5 Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the
10 tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

- Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if
15 freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

- The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack.
20

- The compounds of the formula (1) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient.
25 Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

- 30 For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

- The active compound will be administered to a patient in need thereof (for example a
35 human or animal patient) in an amount sufficient to achieve the desired therapeutic

effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

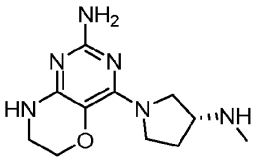
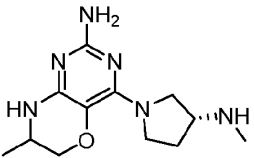
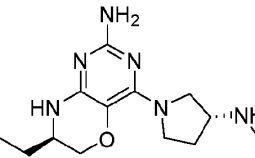
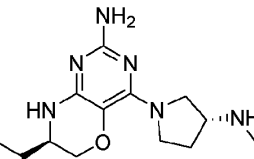
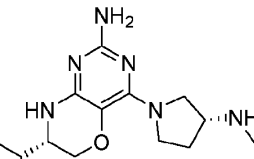
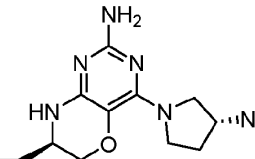
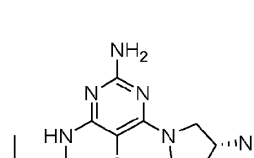
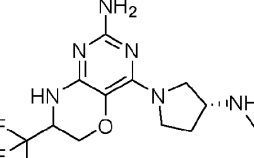
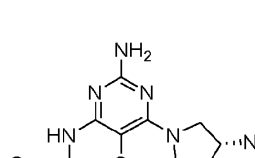
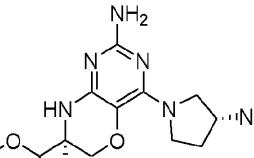
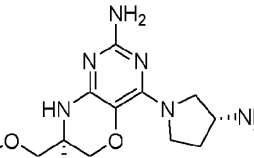
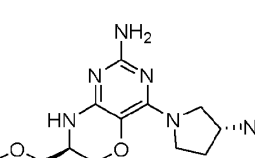
EXAMPLES

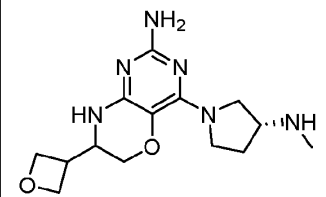
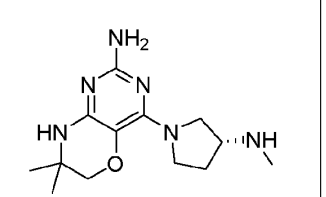
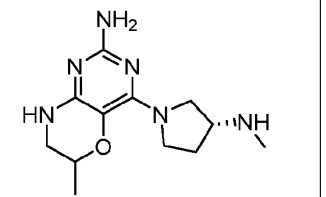
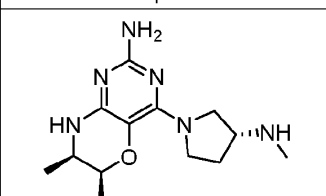
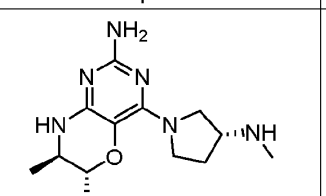
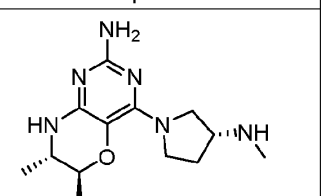
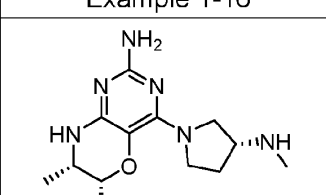
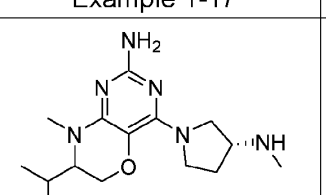
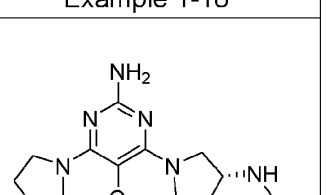
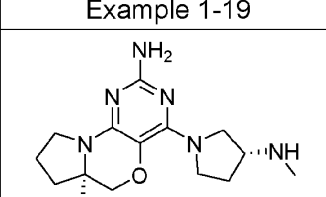
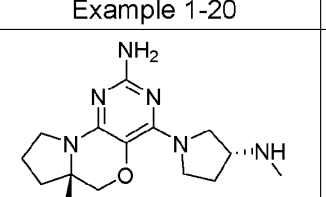
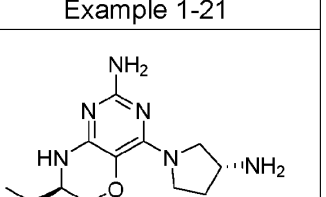
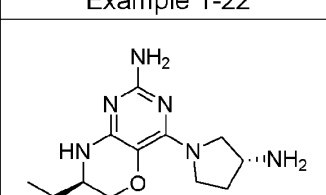
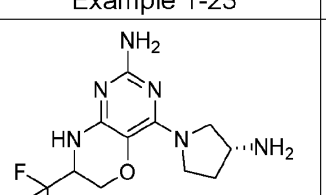
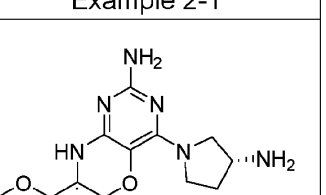
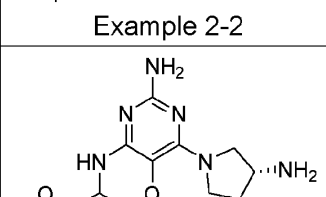
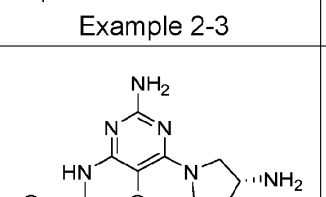
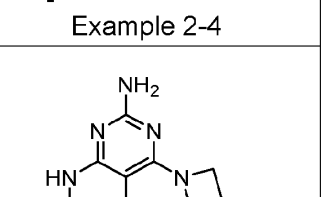
- 5 The invention will now be illustrated, but not limited, by reference to the following examples.

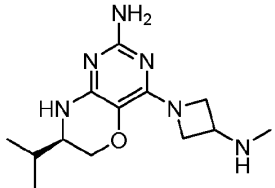
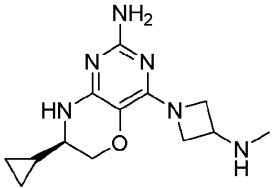
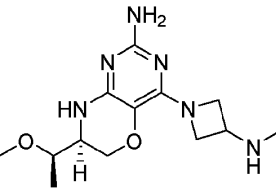
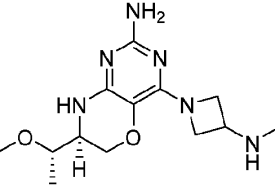
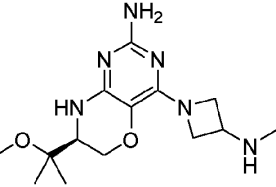
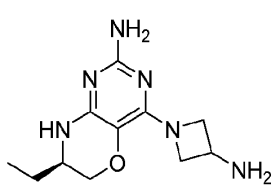
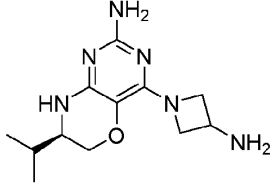
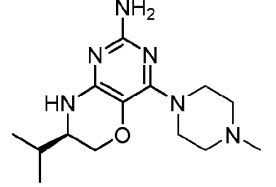
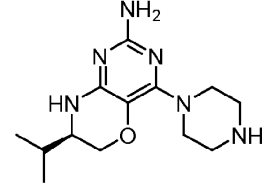
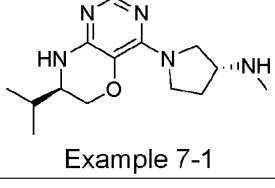
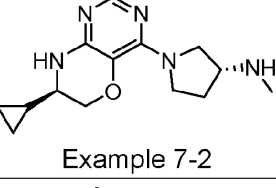
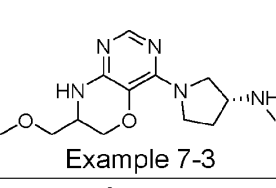
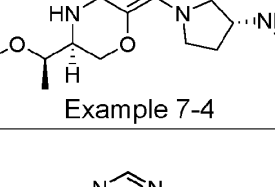
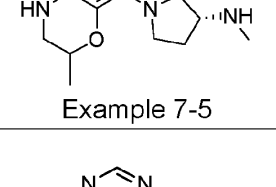
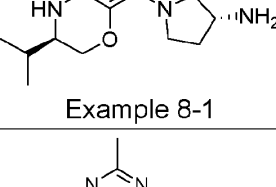
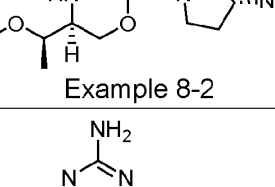
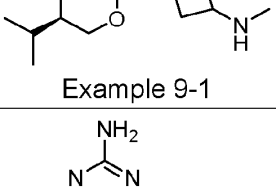
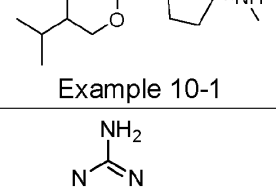
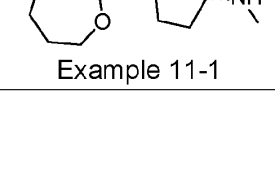
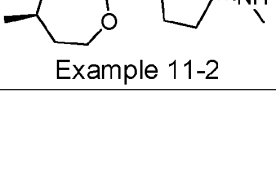
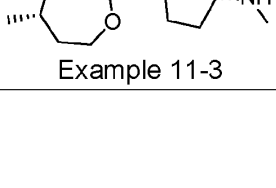
EXAMPLES 1-1 TO 17-15

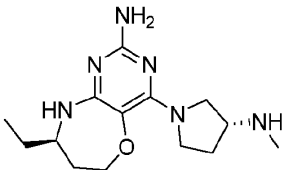
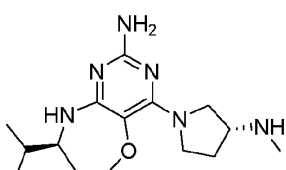
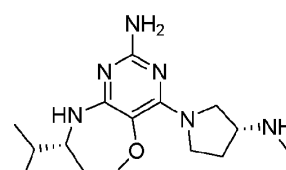
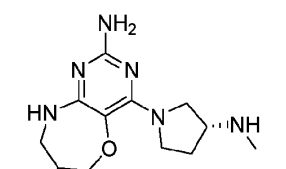
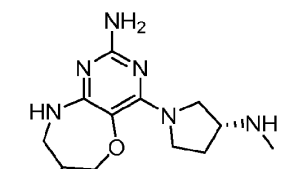
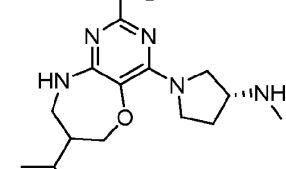
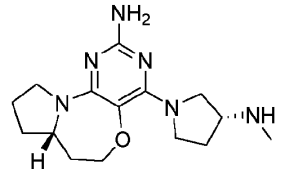
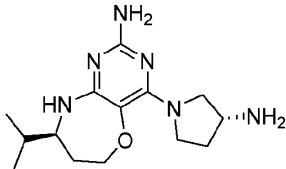
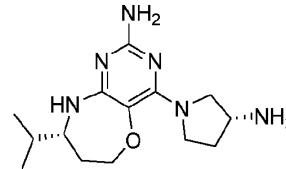
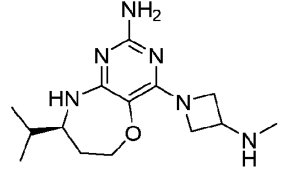
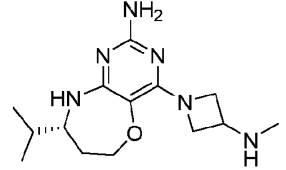
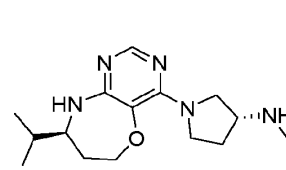
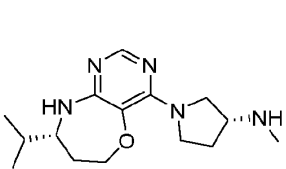
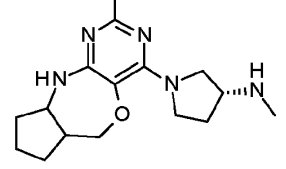
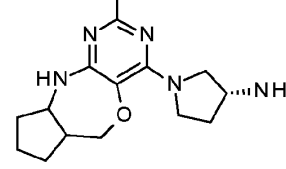
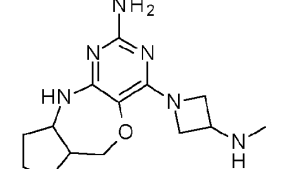
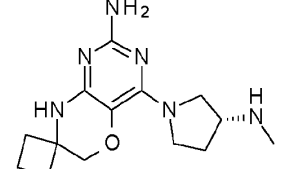
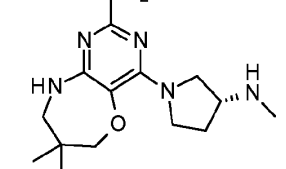
The compounds of Examples 1-1 to 17-15 shown in **Table 1** below have been prepared. NMR and LCMS properties and the methods used to prepare them are set
 10 out in **Table 3**. Starting materials are listed in **Table 2**.

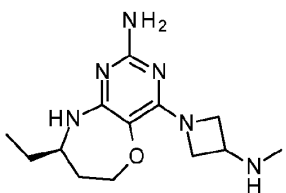
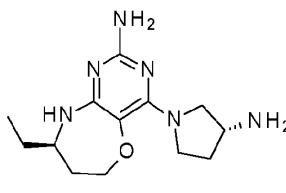
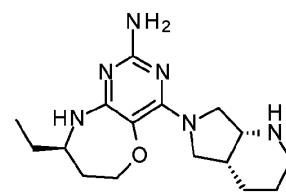
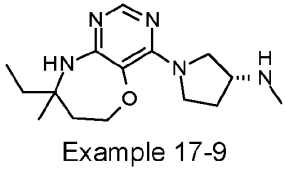
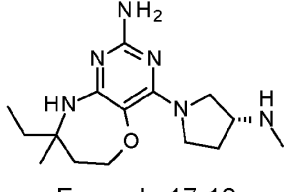
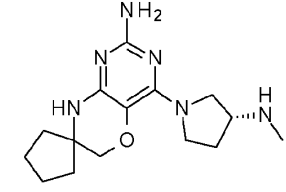
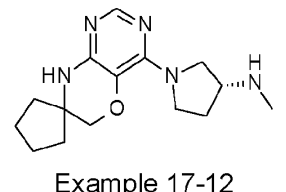
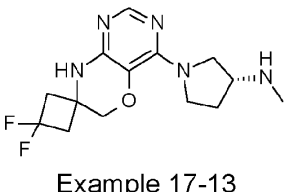
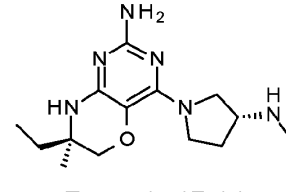
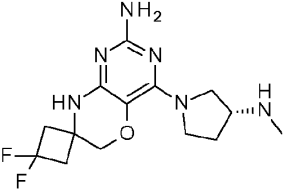
Table 1 – Example compounds

 Example 1-1	 Example 1-2	 Example 1-3
 Example 1-4	 Example 1-5	 Example 1-6
 Example 1-7	 Example 1-8	 Example 1-9
 Example 1-10	 Example 1-11	 Example 1-12

 Example 1-13	 Example 1-14	 Example 1-15
 Example 1-16	 Example 1-17	 Example 1-18
 Example 1-19	 Example 1-20	 Example 1-21
 Example 1-22	 Example 1-23	 Example 2-1
 Example 2-2	 Example 2-3	 Example 2-4
 Example 2-5	 Example 2-6	 Example 3-1

 Example 3-2	 Example 3-3	 Example 3-4
 Example 3-5	 Example 3-6	 Example 4-1
 Example 4-2	 Example 5-1	 Example 6-1
 Example 7-1	 Example 7-2	 Example 7-3
 Example 7-4	 Example 7-5	 Example 8-1
 Example 8-2	 Example 9-1	 Example 10-1
 Example 11-1	 Example 11-2	 Example 11-3

 Example 11-4	 Example 11-5	 Example 11-6
 Example 11-7	 Example 11-8	 Example 11-9
 Example 11-10	 Example 12-1	 Example 12-2
 Example 13-1	 Example 13-2	 Example 14-1
 Example 14-2	 Example 17-1	 Example 17-2
 Example 17-3	 Example 17-4	 Example 17-5

 Example 17-6	 Example 17-7	 Example 17-8
 Example 17-9	 Example 17-10	 Example 17-11
 Example 17-12	 Example 17-13	 Example 17-14
 Example 17-15		

General procedures

- Where no preparative routes are included, the relevant intermediate is commercially available. Commercial reagents were utilized without further purification. Final compounds and intermediates are named using ChemDraw Professional, Version 17.0.0.206 (121). Room temperature (RT) refers to approximately 20-27°C. ¹H NMR spectra were recorded at 400 or 500 MHz on either a Bruker, Varian or Jeol instrument. Chemical shift values are expressed in parts per million (ppm), i.e. (δ)-values relative to the following solvents: chloroform-*d* = 7.26 ppm, DMSO-*d*₆ = 2.50 ppm, methanol-*d*₄ = 3.31 ppm. The following abbreviations are used for the multiplicity of the NMR signals: s=singlet, br=broad, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling

- constants are listed as *J* values, measured in Hz. NMR and mass spectroscopy results were corrected to account for background peaks. Chromatography refers to column chromatography performed using 60 – 120 mesh or 40 – 633 μm , 60 Å silica gel and executed under nitrogen pressure (flash chromatography) conditions. PL-HCO₃ MP
- 5 SPE refers to StratoSpheres HCO₃⁻ bound macroporous polystyrene Solid Phase Extraction cartridges available from Polymer Laboratories. Microwave-mediated reactions were performed in Biotage Initiator or CEM Discover microwave reactors.

LCMS Analysis

- 10 LCMS analysis of compounds was performed under electrospray conditions using the instruments and methods given in the tables below:

System	Instrument Name	LC Detector	Mass Detector
1	Agilent 1100	Photo Diode Array	ZQ-2000
2	Waters Acquity UPLC	Photo Diode Array	SQ detector
3	Waters Acquity H Class	Photo Diode Array	SQ Detector
4	Shimadzu Nexera	Photo Diode Array	LCMS-2020
5	Waters Acquity H Class	Photo Diode Array	QDa Mass Detector

Method Name	Solvent System	Column used	Gradient	UV Range	Mass Range	Column Temp. °C	Flow Rate ml/min
A	(A) 5 mM ammonium acetate + 0.1% formic acid in water	Waters BEH C-18 2.1 x 50 mm, 1.7 µm or equivalent	98:2 at 0.01 min up to 0.50 min, 10:90 at 5.00 min, 5:95 at 6.00 min up to 7.00 min, 98:2 at 7.01 min up to 8.00 min	200 - 400 nm	60-1000 amu	Ambient	0.45
	(B) 0.1% formic acid in acetonitrile						
B	(A) 2 mM ammonium acetate + 0.1% formic acid in water	Waters BEH C-18 2.1 x 50 mm, 1.7 µm or equivalent	98:2 at 0.01 min up to 0.30 min (0.55 ml/min), 50:50 at 0.60 min (0.55 ml/min), 25:75 at 1.10 min (0.55 ml/min), 0:100 at 2.00 min up to 2.70 min (0.60 ml/min), 98:2 at 2.71 min up to 3.00 min (0.55 ml/min)	200 - 400 nm	100-1200 amu	Ambient	0.55-0.60
	(B) 0.1% formic acid in acetonitrile						
C	(A) 5 mM ammonium bicarbonate in water	Waters X-Bridge C-18 4.6 x 50 mm, 3.5 µm or equivalent	95:5 at 0.01 min, 10:90 at 5.0 min, 5:95 at 5.80 min up to 7.20 min, 95:5 at 7.21 min up to 10.0 min	200-400 nm	60-1000 amu	Ambient	1.00
	(B) acetonitrile						
D	(A) 10 mM ammonium formate in water, pH 3.8	Phenomenex Kinetex C-18 4.6 x 50 mm, 5 µm	95:5 at 0.01 min up to 0.50 min, 95:5 to 0:100 between 0.50 min and 2.50 min and 0:100 between 2.50 min and 3.50 min	190-320 nm	100-750 amu	30	2.2
	(B) acetonitrile						
E	(A) 10 mM ammonium bicarbonate in water, pH 10	Phenomenex Gemini-NX C-18 4.6 x 50 mm, 5 µm	95:5 at 0.01 min up to 0.50 min, 95:5 to 0:100 between 0.50 min and 2.50 min and 0:100 between 2.50 min and 3.50 min	190-320 nm	100-750 amu	30	2.2
	(B) acetonitrile						

[illegible]

LCMS data in the experimental section and Tables 2 and 3 are given in the format: **(Instrument system, Method)**: Mass ion, retention time, UV detection wavelength.

Compound Purification

- 5 Final purification of compounds was performed by reversed-phase column chromatography, preparative reversed-phase HPLC, chiral HPLC or chiral SFC using the instruments and methods detailed below where data is given in the following format: Purification technique: [phase (column description, column length × internal diameter, particle size), solvent flow-rate, gradient - given as % of mobile phase B in mobile phase A (over time), mobile phase (A), mobile phase (B)].

10

Reversed-phase column chromatography

Teledyne Isco instruments using pre-packaged disposable Silica-Based C18 (17%) / Silicycle / 40 - 63 µm, 60 Å stationary phase columns with an eluent flow rate range of 15 to 200 mL/min and UV detection (254 and 280 nm).

15

Preparative HPLC purification:

Shimadzu LC-20AP binary system with SPD-20A UV detector

Waters 2767 with PDA detector and mass triggered with a Waters ZQ equipped with an electrospray ion source operated in a positive ion mode

20

Chiral HPLC purification:

Shimadzu LC-20AP binary system with SPD-20A UV detector

Chiral SFC purification:

25

Waters SFC 200

Purification Method A

- 30 Prep HPLC: [Reversed-phase (BEH C-18, 50 × 30 mm, 5 µm), 40 mL / min, gradient 5 % (over 0.5 min), 5 % – 25 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 5 % (over 0.5 min), mobile phase (A): 10 mM ammonium carbonate in water, pH 10, (B): 100 % acetonitrile].

Purification Method B

- 35 Prep HPLC: [Reversed-phase (BEH C-18, 50 × 30 mm, 5 µm), 40 mL / min, gradient 10 % (over 0.5 min), 10 % – 30 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 10 % (over 0.5 min), mobile phase (A): 10 mM ammonium carbonate in water, pH 10, (B): 100 % acetonitrile].

Purification Method C

- 40 Prep HPLC: [Reversed-phase (BEH C-18, 50 × 30 mm, 5 µm), 40 mL / min, gradient 10 % (over 0.5 min), 10 % – 30 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 10 % (over 0.5 min), mobile phase (A): 10 mM ammonium bicarbonate in water, pH 10, (B): 100 % acetonitrile].

Purification Method D

- 45 Prep HPLC: [Reversed-phase (BEH C-18, 50 × 30 mm, 5 µm), 40 mL / min, gradient 22 % (over 0.5 min), 22 % – 42 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 22 % (over 0.5 min), mobile phase (A): 10 mM ammonium carbonate in water, pH 10, (B): 100 % acetonitrile].

Purification Method E

Prep HPLC: [Reversed-phase (Gemini-NX 30 x 150 mm, 5 µm), 40 mL / min, gradient 10 % (over 0.5 min), 10 % – 100 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 10 % (over 0.5 min), mobile phase (A): 10 mM ammonium bicarbonate in water, pH 10, (B): 100 % acetonitrile].

Purification Method F

Prep HPLC: [Reversed-phase (X-BRIDGE C-18, 250 x 19 mm, 5 µm), 11 mL / min, gradient 10 % – 32 % (over 30 min), 32 % (over 4 min), 100 % (over 2 min), 100 % – 10 % (over 6 min), mobile phase (A): 5 mM ammonium bicarbonate + 0.1 % ammonia in water, (B): 100 % acetonitrile].

Purification Method G

Prep HPLC: [Reversed-phase (BEH C-18, 150 x 30 mm, 5 µm), 40 mL / min, gradient 80 % (over 0.5 min), 80 % – 100 % (over 6.4 min), 100 % (over 1.6 min), 100 % – 80 % (over 0.5 min), mobile phase (A): 10 mM ammonium bicarbonate in water, pH 10, (B): 100 % acetonitrile].

Abbreviations used throughout this document

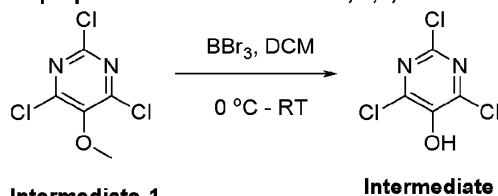
Ac	=	acetate
aq.	=	aqueous
Bn	=	benzyl
Bz	=	benzoyl
Boc	=	<i>tert</i> -butoxycarbonyl
ⁿ BuOH	=	<i>n</i> -butanol
^t BuOH	=	<i>t</i> -butanol
Bu ₃ P	=	tri <i>n</i> -butylphosphine
^t Bu ₃ P	=	tri <i>tert</i> -butylphosphine
Cbz	=	benzyloxycarbonyl
COMU	=	(1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
DCM	=	dichloromethane
DEAD	=	diethyl azodicarboxylate
DIAD	=	diisopropylazodicarboxylate
DIC	=	<i>N,N</i> -diisopropylcarbodiimide
DIPEA	=	<i>N,N</i> -diisopropylethylamine
DMA	=	<i>N,N</i> -dimethylacetamide
DMAP	=	4-(dimethylamino)pyridine
DMB	=	3,4-dimethoxybenzyl
DME	=	dimethoxyethane
DMF	=	<i>N,N</i> -dimethylformamide
DMSO	=	dimethylsulfoxide
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ES	=	electro spray ionization
Et ₃ N	=	triethylamine
Et ₂ O	=	diethylether
EtOAc	=	ethyl acetate
EtOH	=	ethanol
Fmoc	=	fluorenylmethyloxycarbonyl
h	=	hour(s)
HATU	=	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
H ₂ O	=	water
HCl	=	hydrogen chloride, hydrochloric acid
HOBt	=	hydroxybenzotriazole
HPLC	=	high performance liquid chromatography
IPA	=	propan-2-ol
LC	=	liquid chromatography
MeCN	=	acetonitrile
MeOH	=	methanol
min(s)	=	minute(s)
MS	=	mass spectrometry

	nm	=	nanometre(s)
	NMP	=	<i>N</i> -methyl-2-pyrrolidone
	NMR	=	nuclear magnetic resonance
	P(Cy) ₃	=	tricyclohexylphosphine
5	PMB	=	4-methoxybenzyl
	PPh ₃ , Ph ₃ P	=	triphenylphosphine
	PTSA	=	<i>para</i> -toluenesulfonic acid
	PyBOP	=	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
10	RP-flash	=	reversed-phased flash chromatography
	RP-HPLC	=	reversed-phased high performance liquid chromatography
	RT	=	room temperature
	sat.	=	saturated
	SFC	=	supercritical fluid chromatography
15	SNAr	=	nucleophilic aromatic substitution
	TBAF	=	tetrabutylammonium fluoride
	TEA	=	triethylamine
	Teoc	=	β-(trimethylsilyl)ethoxycarbonyl
	TFA	=	trifluoroacetic acid
20	TFAA	=	trifluoroacetic anhydride
	THF	=	tetrahydrofuran
	TMAD	=	<i>N,N,N',N'</i> -tetramethylazodicarboxamide
	T3P	=	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide

25

Synthesis of Intermediates:**Route 1**

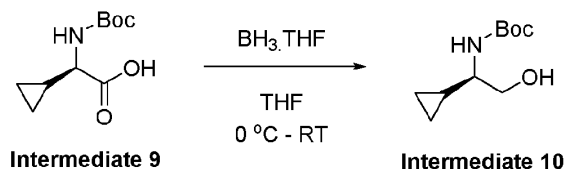
Typical procedure for the preparation of Intermediate 2, 2,4,6-trichloropyrimidin-5-ol



30

Under an atmosphere of nitrogen, a solution of 2,4,6-trichloro-5-methoxypyrimidine (**Intermediate 1**) (2.60 g, 12.2 mmol) in DCM (121 mL) was cooled to 0 °C and treated with boron tribromide (neat, 4.05 mL, 42.6 mmol) dropwise. After stirring for 18 h at room temperature, the reaction mixture was cooled below 0 °C, carefully quenched with methanol (20 mL), then diluted with water (120 mL) and the phases were separated. The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in-vacuo* to give a pale tan solid (2.27 g). The crude material was purified by flash chromatography on silica gel (80 g cartridge) using 0 % to 20 % EtOAc in DCM to afford 2,4,6-trichloropyrimidin-5-ol (**Intermediate 2**) (1.67 g, 62 %) as a white solid. The data for **Intermediate 2** are in Table 2.

40

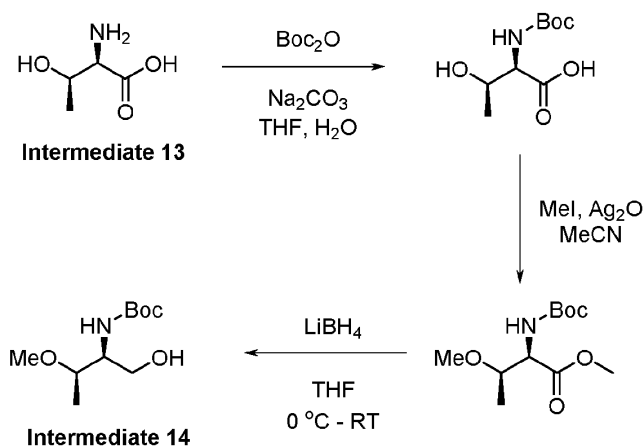
Route 2Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of Intermediate 10, *tert*-butyl (*R*)-(1-cyclopropyl-2-hydroxyethyl)carbamate

45

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-cyclopropylacetic acid (**Intermediate 9**) (2 g, 0.009 mol) was dissolved in THF (20.0 mL) and cooled to 0 °C. Borane THF complex solution in THF (1.0 M, 32 mL, 0.032 mol) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of methanol, then the solvent was removed *in-vacuo* and the residue was partitioned between H₂O (50 mL) and EtOAc (30 mL) and the phases were separated. The aqueous layer was further extracted with EtOAc (2 x 50 mL), and the combined organic layers were washed with aq. sat. NaHCO₃ solution. The organic layer was dried (Na₂SO₄) and the solvent was removed *in-vacuo* to give the crude product, which was purified by column chromatography (Normal-Phase 60-120 mesh silica gel, 0 to 30 % EtOAc in hexanes) to give *tert*-butyl (*R*)-(1-cyclopropyl-2-hydroxyethyl)carbamate (**Intermediate 10**) (1.8 g, 96 %) as a colourless gum. The data for **Intermediate 10** are in Table 2.

Route 3

Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of **Intermediate 14**, *tert*-butyl ((2*S*,3*R*)-1-hydroxy-3-methoxybutan-2-yl)carbamate



To a stirred solution of *D*-allothreonine (3.0 g, 25.2 mmol) in THF (41 mL) and H₂O (41 mL) was added a solution of sodium carbonate (5.60 g, 52.8 mmol) in H₂O (13 mL) and the resulting mixture was stirred for 5 minutes before adding di-*tert*-butyl dicarbonate (6.59 g, 30.2 mmol). The mixture was stirred at room temperature overnight, then water (15 mL) was added and the mixture was extracted with diethylether (2 x 10 mL). The aqueous layer was acidified with 1 M aqueous HCl to pH 4 and extracted with EtOAc (3 x 25 mL). The combined EtOAc layers were dried (Na₂SO₄) and concentrated *in-vacuo* to give (*tert*-butoxycarbonyl)-*D*-allothreonine (5.10 g, 92 %) as a white solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 1.23 – 1.36 (m, 3H), 1.45 (s, 9H), 4.06 – 4.24 (m, 1H), 4.30 – 4.41 (m, 1H), 5.58 (d, *J* = 7.4 Hz, 1H), 6.16 (br. s, 2H).

To a stirred solution of (*tert*-butoxycarbonyl)-*D*-allothreonine (5.10 g, 23.3 mmol) in dry acetonitrile (320 mL) was added Ag₂O (26.95 g, 116.0 mmol) and methyl iodide (14.5 mL, 233.0 mmol) at room temperature and the resulting mixture was stirred in the dark for 4 days. The mixture was filtered through Celite and washed several times with DCM. The filtrate was concentrated *in-vacuo* to give the crude product, which was purified by flash chromatography (0 – 100 % EtOAc in hexanes, 80 g SiO₂ cartridge) to give methyl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-*D*-allothreoninate as a colorless liquid (3.80 g, 66 %). ¹H NMR (400 MHz, Chloroform-*d*) δ 1.20 (d, *J* = 6.5 Hz, 3H), 1.45 (s, 9H), 3.36 (s, 3H), 3.59 – 3.67 (m, 1H), 3.76 (s, 3H), 4.39 – 4.46 (m, 1H), 5.24 – 5.30 (m, 1H).

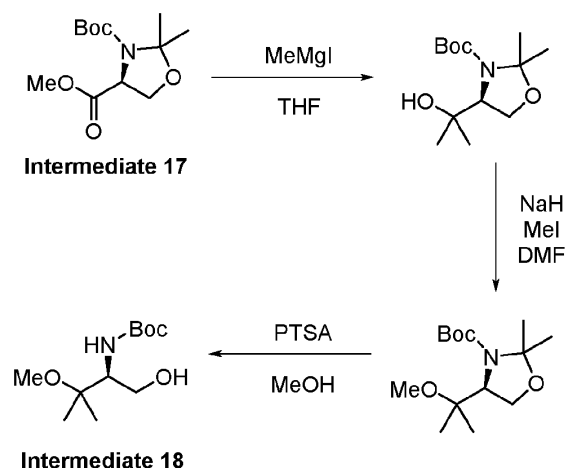
To a stirred solution of methyl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-*D*-allothreoninate (3.80 g, 15.4 mmol) in THF (30 mL) under nitrogen was added LiBH₄ solution in THF (2.0 M, 11.5 mL, 23.1 mmol) at 0 °C and the mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with sat. aq. NH₄Cl solution (15 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in-vacuo*. The residue was purified by flash chromatography (0 – 100 % EtOAc in hexanes, 80 g SiO₂ cartridge) to

give *tert*-butyl ((2*S*,3*R*)-1-hydroxy-3-methoxybutan-2-yl)carbamate, (**Intermediate 14**) (3.10 g, 92 %) as a colorless liquid.

The data for **Intermediate 14** are in Table 2.

5 Route 4

Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of **Intermediate 18**, *tert*-butyl (S)-(1-hydroxy-3-methoxy-3-methylbutan-2-yl)carbamate



10

A solution of methyl iodide (3.6 mL, 57.8 mmol) in dry Et₂O (39 mL) was added slowly to Mg filings (1.17 g, 48.2 mmol) in dry Et₂O (10 mL). After complete consumption of the Mg, a solution of 3-(*tert*-butyl) 4-methyl (S)-2,2-dimethyloxazolidine-3,4-dicarboxylate (**Intermediate 17**) (5 g, 19.3 mmol) in dry Et₂O (20 mL) was added dropwise at such a rate that the solution started to reflux. After complete addition, the reaction mixture was stirred for a further 10 min, before saturated aq. NH₄Cl solution (70 mL) was added carefully. The layers were separated, and the aqueous layer was extracted with Et₂O (2 x 70 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to give *tert*-butyl (S)-4-(2-hydroxypropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (4.62 g, 92 %) as a colorless oil, which was used directly in the next step without any purification.

15

20

¹H NMR (400 MHz, Chloroform-*d*) δ 1.16 (s, 3H), 1.17 (s, 3H), 1.49 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 3.72 – 3.82 (m, 1H), 3.92 – 4.02 (m, 2H), 5.25 (s, 1H).

25

To a solution of *tert*-butyl (S)-4-(2-hydroxypropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (5.12 g, 19.7 mmol) in DMF (19.0 mL), cooled to 0 °C, were added NaH (60 % dispersion in mineral oil, 1.02 g, 25.6 mmol) and methyl iodide (2.46 mL, 39.5 mmol) and the reaction mixture was stirred at room temperature for 2 h. MeOH (2.0 mL) was added to quench the reaction, then the mixture was diluted with DCM (50.0 mL) and washed twice with water. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 100 %) in hexanes to provide *tert*-butyl (S)-4-(2-methoxypropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (4.9 g, 91 %) as a colorless oil, which crystallized on standing.

30

¹H NMR (400 MHz, Chloroform-*d*) δ 1.13 (s, 3H), 1.19 (s, 3H), 1.48 (s, 9H), 1.49 (s, 3H), 1.61 (s, 3H), 3.21 (s, 3H), 3.83 – 3.89 (m, 1H), 3.90 – 4.11 (m, 1H), 4.12 – 4.18 (m, 1H).

35

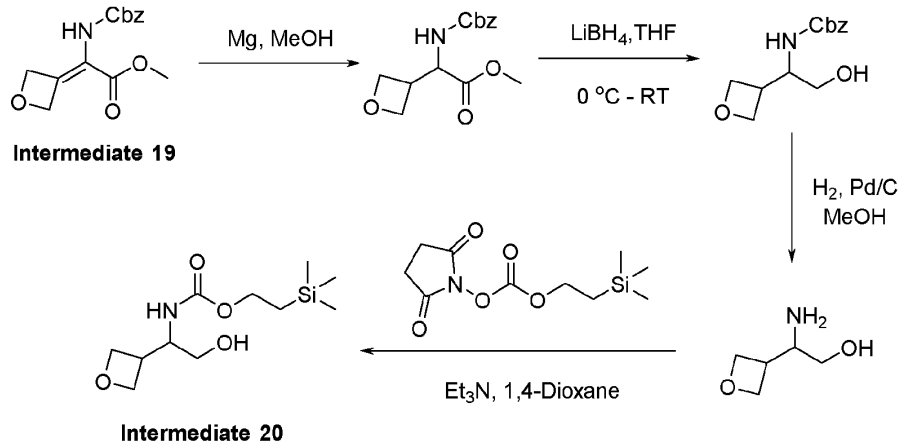
To a stirred solution of *tert*-butyl (S)-4-(2-methoxypropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (3.60 g, 13.2 mmol) in MeOH (55.0 mL) was added PTSA (250 mg, 1.32 mmol) and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. aq. NaHCO₃ (10 mL). The solvent was removed under reduced pressure and H₂O (15 mL) was added. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure to give *tert*-butyl (S)-(1-hydroxy-3-methoxy-3-methylbutan-2-yl)carbamate (**Intermediate 18**) (3.0 g, 98 %) as a white solid.

40

The data for **Intermediate 18** are in Table 2.

Route 5

Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of Intermediate 20, 2-(trimethylsilyl)ethyl (2-hydroxy-1-(oxetan-3-yl)ethyl)carbamate



5

A 500-mL flask under N₂ was charged with methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-ylidene)acetate (**Intermediate 19**) (4.06 g, 14.6 mmol) and MeOH (240 mL). Mg turnings (3.56 g, 146 mmol) were then added, and the mixture was stirred at room temperature for 3 h (Warning: copious evolution of H₂ was observed). The resulting mixture was cooled to 0 °C and sat. aq. NH₄Cl (85 mL) was slowly and carefully added. The mixture was concentrated under reduced pressure until most of the MeOH had been removed, and the residue was extracted with DCM (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (dry injection, 80 g SiO₂, 0:100 to 90:10, EtOAc:hexanes) to afford methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-yl)acetate (2.41 g, 59 %) as a colorless solid.

10

15

¹H NMR (400 MHz, DMSO-*d*₆) δ 3.20 – 3.37 (m, 1H), 3.62 (s, 3H), 4.35 (t, *J* = 6.3 Hz, 1H), 4.38 – 4.48 (m, 2H), 4.50 – 4.62 (m, 2H), 5.05 (s, 2H), 7.27 – 7.41 (m, 5H), 7.86 (d, *J* = 8.0 Hz, 1H).

20

A 100-mL flask under N₂ was charged with methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-yl)acetate (2.35 g, 8.41 mmol) and anhydrous THF (35 mL). The resulting solution was cooled to 0 °C, then LiBH₄ solution in THF (2 M, 8.4 mL, 16.8 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min, then it was further stirred at room temperature for 2 h. The resulting mixture was cooled to 0 °C, carefully quenched by the addition of water (20 mL), and further stirred at room temperature for 30 min. EtOAc (40 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The organic phases were combined, dried over MgSO₄, and concentrated under reduced pressure to afford benzyl (2-hydroxy-1-(oxetan-3-yl)ethyl)carbamate (1.90 g, 90 %) as a colorless solid.

25

30

¹H NMR (500 MHz, DMSO-*d*₆) δ 3.04 – 3.13 (m, 1H), 3.20 – 3.27 (m, 1H), 3.30 – 3.36 (m, 1H), 3.78 – 3.85 (m, 1H), 4.33 – 4.41 (m, 2H), 4.48 – 4.57 (m, 2H), 4.65 (t, *J* = 5.6 Hz, 1H), 5.03 (s, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.29 – 7.33 (m, 1H), 7.33 – 7.39 (m, 4H).

35

A 100-mL flask was charged with 10 % Pd/C (178 mg, 0.167 mmol Pd) then the flask was purged with N₂. A solution of benzyl (2-hydroxy-1-(oxetan-3-yl)ethyl)carbamate (1.68 g, 6.69 mmol) in MeOH (34 mL) was then added. The atmosphere was replaced with H₂ by four evacuation/H₂ cycles, and the suspension was stirred under H₂ (1 atm) at room temperature for 5 h. The atmosphere in the flask was replaced with N₂, the suspension was filtered over Celite, and the solid residue was washed several times with MeOH. The filtrate was concentrated under reduced pressure to afford 2-amino-2-(oxetan-3-yl)ethan-1-ol (784 mg, 100 %) as a colorless oil.

40

¹H NMR (400 MHz, Chloroform-*d*) δ 2.90 – 3.00 (m, 1H), 3.18 – 3.29 (m, 2H), 3.50 – 3.56 (m, 1H), 4.47 (t, *J* = 6.2 Hz, 1H), 4.58 (t, *J* = 6.2 Hz, 1H), 4.73 – 4.83 (m, 2H). Three exchangeable protons not observed.

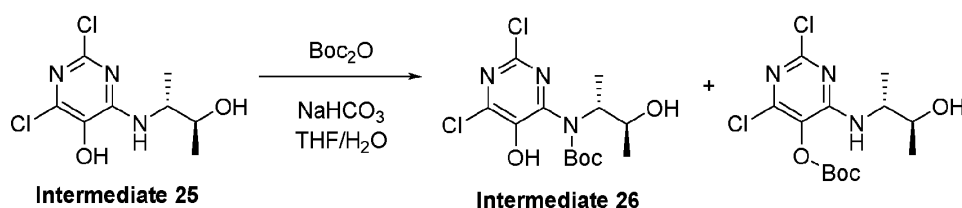
A 200-mL flask under N₂ was charged with 2-amino-2-(oxetan-3-yl)ethan-1-ol (784 mg, 6.69 mmol) and 1,4-dioxane (57 mL). Et₃N (1.4 mL, 10.0 mmol) was then added, followed by a solution of 2,5-

dioxopyrrolidin-1-yl (2-(trimethylsilyl)ethyl) carbonate (CAS: 78269-85-9) (1.77 g, 6.82 mmol) in 1,4-dioxane (10 mL). A thick suspension immediately formed, which was stirred at room temperature for 16 h. The resulting clear solution was concentrated under reduced pressure and the residue was dissolved in a mixture of EtOAc (75 mL) and sat. aq. NH_4Cl (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 25 mL). The organic phases were combined, washed with brine (25 mL), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography (dry injection, 40 g SiO_2 , 50:50 to 100:0, EtOAc:hexanes) to afford 2-(trimethylsilyl)ethyl (2-hydroxy-1-(oxetan-3-yl)ethyl)carbamate (**Intermediate 20**) (1.68 g, 96 %) as a colorless oil.

The data for **Intermediate 20** are in Table 2.

Route 6

Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of **Intermediate 26**, *tert*-butyl (2,6-dichloro-5-hydroxypyrimidin-4-yl)((2*R*,3*S*)-3-hydroxybutan-2-yl)carbamate

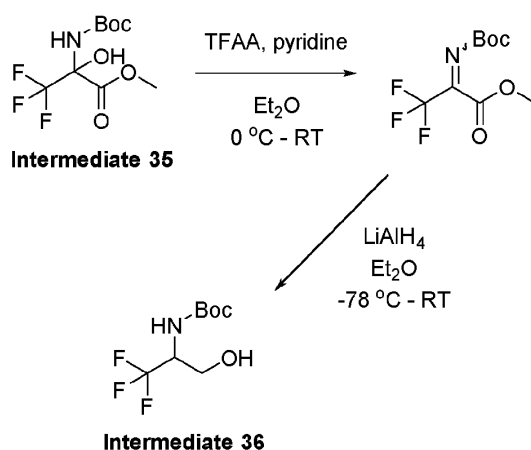


To a solution of 2,4-dichloro-6-(((2*R*,3*S*)-3-hydroxybutan-2-yl)amino)pyrimidin-5-ol (**Intermediate 25**) (1.02 g, 4.05 mmol) in a mixture of THF (40 mL) and water (20 mL) were added di-*tert*-butyl dicarbonate (927 mg, 4.25 mmol) and NaHCO_3 (714 mg, 8.5 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure and the residue was directly purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 100 %) in hexanes then using a gradient of MeOH (0 – 15 %) in DCM to provide *tert*-butyl (2,6-dichloro-5-hydroxypyrimidin-4-yl)((2*R*,3*S*)-3-hydroxybutan-2-yl)carbamate (**Intermediate 26**) (155 mg, 11 %) as a colorless oil and *tert*-butyl (2,4-dichloro-6-(((2*R*,3*S*)-3-hydroxybutan-2-yl)amino)pyrimidin-5-yl) carbonate (350 mg, 25 %) as a pale yellow oil. The undesired O-Boc product can be separately converted to the desired N-Boc product by stirring with NaHCO_3 in THF/ H_2O .

The data for **Intermediate 26** are in Table 2.

Route 7

Typical procedure for the preparation of protected amino alcohols, as exemplified by the preparation of **Intermediate 36**, *tert*-butyl (1,1,1-trifluoro-3-hydroxypropan-2-yl)carbamate



A 100-mL flask under N₂ was charged with methyl 2-((*tert*-butoxycarbonyl)amino)-3,3,3-trifluoro-2-hydroxypropanoate (**Intermediate 35**) (2.71 g, 9.92 mmol) and anhydrous Et₂O (50 mL). The resulting mixture was cooled to 0 °C, then TFAA (1.40 mL, 9.92 mmol) and pyridine (1.60 mL, 19.8 mmol) were added. The mixture was stirred for 1 h at 0 °C, and it was stirred for a further 16 h at room temperature.

The resulting suspension was filtered, and the solids were washed with Et₂O (2 x 25 mL). The filtrate was washed with water (25 mL), dried over MgSO₄, and concentrated under reduced pressure to give the crude methyl 2-((*tert*-butoxycarbonyl)imino)-3,3,3-trifluoropropanoate (2.51 g, 99 %) as a clear oil that was used in the next step without further purification.

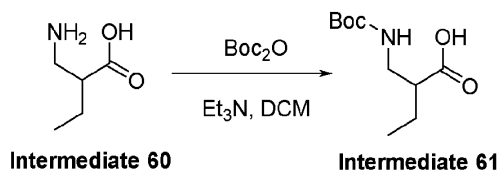
¹H NMR (500 MHz, Chloroform-*d*) δ 1.58 (s, 9H), 3.95 (s, 3H).

An oven-dried 100-mL flask under N₂ was charged with methyl 2-((*tert*-butoxycarbonyl)imino)-3,3,3-trifluoropropanoate (2.51 g, 9.84 mmol) and anhydrous Et₂O (30 mL). The resulting solution was cooled to -78 °C, then LiAlH₄ solution in THF (2 M, 9.84 mL, 19.7 mmol) was slowly added. The mixture was then stirred for 16 h while being slowly warmed to room temperature. The resulting solution was cooled to 0 °C, and carefully quenched by the successive addition of water (0.75 mL), aq. NaOH (3.8 M, 0.75 mL) and water (2.3 mL). The resulting suspension was warmed to room temperature, and MgSO₄ was added. The suspension was filtered, and the solids were washed with THF (4 x 20 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 5:95 to 70:30, EtOAc:hexanes) to give *tert*-butyl (1,1,1-trifluoro-3-hydroxypropan-2-yl)carbamate (**Intermediate 36**) (1.38 g, 61 %) as a colorless solid.

The data for **Intermediate 36** are in Table 2.

Route 8

Typical procedure for the preparation of protected amino acids, as exemplified by the preparation of **Intermediate 61**, 2-(((*tert*-butoxycarbonyl)amino)methyl)butanoic acid



2-(Aminomethyl)butanoic acid (**Intermediate 60**) (1.5 g, 9.8 mmol) was dissolved in DCM (5.0 mL), and TEA (379 mg, 14.7 mmol) was added dropwise at 0 °C. Di-*tert*-butyl dicarbonate (512 mg, 11.7 mmol) was then added and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in-vacuo* and the residue was partitioned between H₂O (100 mL) and DCM (60 mL). The aqueous layer was washed with 1 M citric acid solution and then further extracted with DCM (2 x 60 mL). All the organic layers were combined, dried (Na₂SO₄) and the solvent was removed *in-vacuo* to give the crude product, which was purified by column chromatography on silica using 16 % EtOAc in hexane to give 2-(((*tert*-butoxycarbonyl)amino)methyl)butanoic acid (**Intermediate 61**) (2.4 g, 86 %) as a colorless gum.

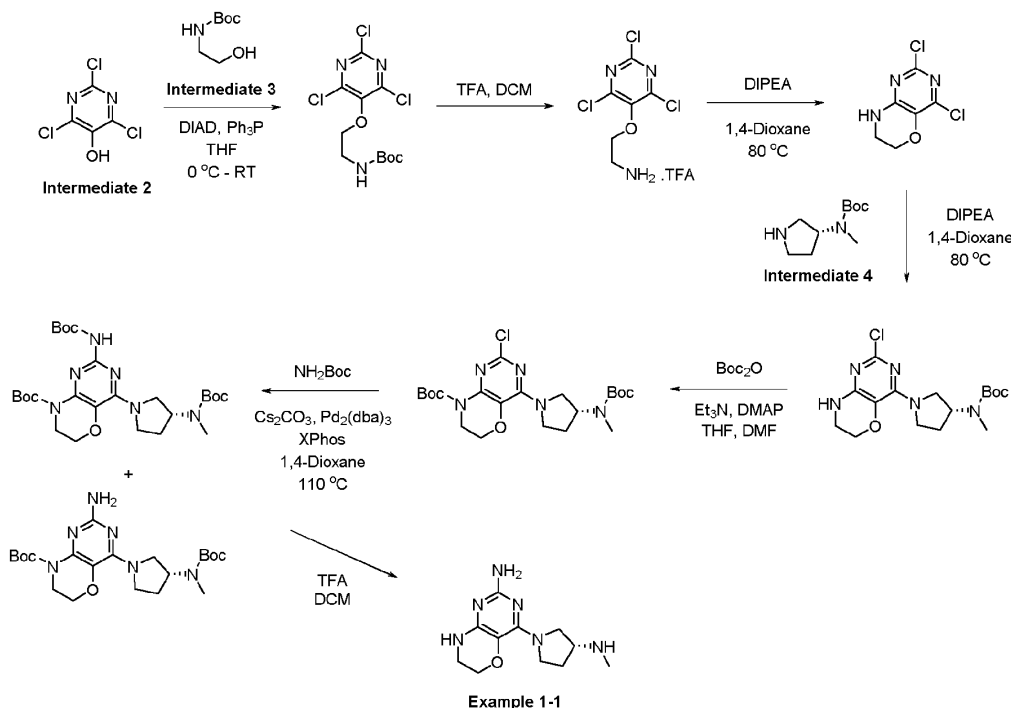
The data for **Intermediate 61** are in Table 2.

General Synthetic Procedures:

Route A

Typical procedure for the preparation of fused pyrimidines, as exemplified by the preparation of Example 1-1, (*R*)-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine

59



- To a solution of 2,4,6-trichloropyrimidin-5-ol (**Intermediate 2**) (384 mg, 1.926 mmol) and *tert*-butyl (2-hydroxyethyl)carbamate (**Intermediate 3**) 621 mg, 3.851 mmol) in THF (11.0 mL), cooled to 0°C, were added DIAD (0.57 mL, 2.888 mmol) and PPh₃ (758 mg, 2.888 mmol) and the reaction mixture was stirred for 2 h. The THF was then removed under reduced pressure and silica was added. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 60 %) in hexanes to provide *tert*-butyl (2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)carbamate (633 mg, 96 %) as a white solid.
- ¹H NMR (500 MHz, Chloroform-*d*) δ 1.45 (s, 9H), 3.56 (q, *J* = 5.5 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 5.05 (s, 1H).

- To a solution of *tert*-butyl (2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)carbamate (633 mg, 1.848 mmol) in DCM (5.10 mL) was added TFA (5.10 mL) and the reaction mixture was stirred at room temperature for 10 min. The mixture was then concentrated *in-vacuo* to dryness to give 2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethan-1-amine trifluoroacetic acid salt (675 mg, >100 %) as a colourless oil which was used directly in the next step without any purification.
- LCMS (System 1, Method D):** *m/z* 242/244 (*M*+*H*)⁺ (*ES*⁺), at 0.54 min, 190-320 nm.

- To a solution of 2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethan-1-amine trifluoroacetic acid salt (659 mg, 1.848 mmol) in 1,4-dioxane (5.00 mL) was added DIPEA (0.97 mL, 5.545 mmol) and the reaction mixture was heated at 80 °C for 18 h. The mixture was then diluted with water and extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 100 %) in hexanes to provide 2,4-dichloro-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazine (279 mg, 73 %) as a white solid.
- LCMS (System 1, Method D):** *m/z* 206/208 (*M*+*H*)⁺ (*ES*⁺), at 1.87 min, 190-320 nm.

- To a solution of 2,4-dichloro-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazine (279 mg, 1.354 mmol) in 1,4-dioxane (2.90 mL) were added *tert*-butyl (*R*)-methyl(pyrrolidin-3-yl)carbamate (**Intermediate 4**) (271 mg, 1.354 mmol) and DIPEA (0.47 mL, 2.708 mmol) and the mixture was heated at 80 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of EtOAc (0 – 100 %)

in hexanes to provide *tert*-butyl (*R*)-(1-(2-chloro-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (218 mg, 44 %) as a white solid.

LCMS (System 1, Method D): *m/z* 370/372 (*M*+*H*)⁺ (*ES*⁺), at 2.40 min, 190-320 nm.

- 5 To a solution of *tert*-butyl (*R*)-(1-(2-chloro-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (127 mg, 0.343 mmol) in a mixture of THF (0.83 mL) and DMF (0.22 mL) were added di-*tert*-butyl dicarbonate (112 mg, 0.515 mmol), Et₃N (0.102 mL, 0.755 mmol) and DMAP (21 mg, 0.172 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure, and the residue was diluted with DCM and silica was added.
- 10 The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 40 %) in hexanes to provide *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (113 mg, 70 %) as a colorless oil.

LCMS (System 1, Method D): *m/z* 470/472 (*M*+*H*)⁺ (*ES*⁺), at 2.75 min, 190-320 nm.

- 15 To a degassed solution of *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (114 mg, 0.243 mmol) and *tert*-butyl carbamate (28 mg, 0.243 mmol) in 1,4-dioxane (2.40 mL) were added Cs₂CO₃ (198 mg, 0.606 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (22.2 mg, 0.024 mmol) and XPhos (CAS: 564483-18-7) (23.1 mg, 0.049 mmol) and the reaction mixture was heated at 110 °C for 18 h. After
- 20 cooling to room temperature, the mixture was filtered through a pad of Celite, washing the residue with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography using a gradient of EtOAc (0 – 100 %) in hexanes then a gradient of MeOH (0 – 30 %) in DCM to provide *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (62 mg, 46 %) as a
- 25 pale yellow oil and *tert*-butyl (*R*)-2-amino-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (54 mg, 49 %) as a yellow oil.

LCMS (System 1, Method D): *m/z* 551 (*M*+*H*)⁺ (*ES*⁺), at 2.11 min, 190-320 nm.

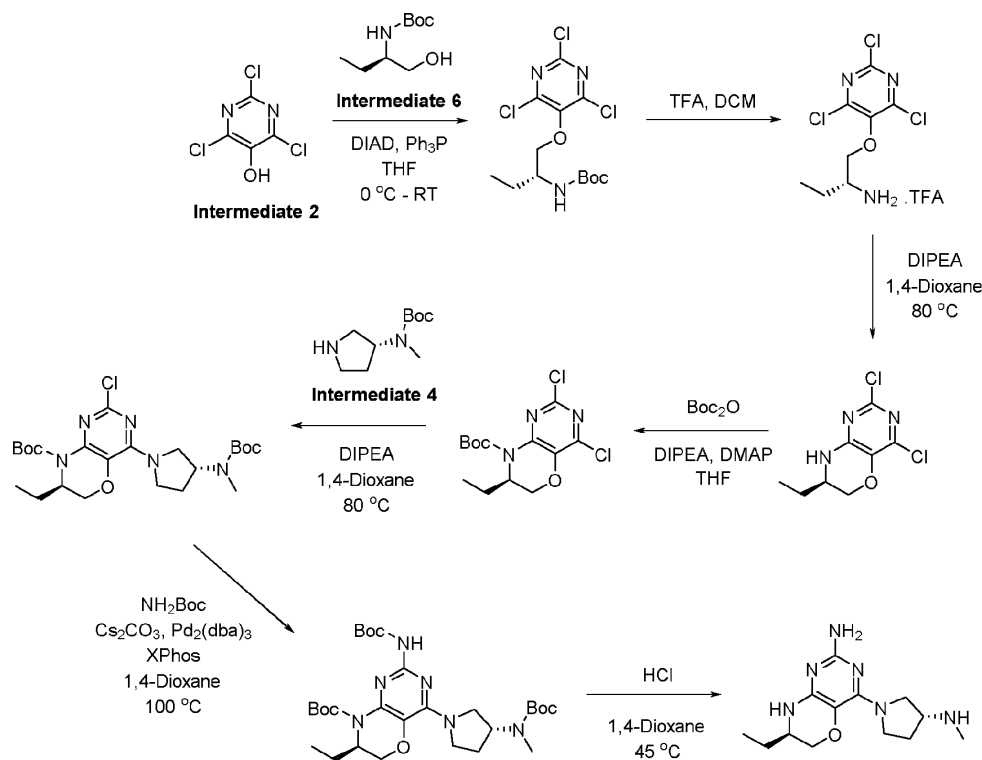
LCMS (System 1, Method D): *m/z* 451 (*M*+*H*)⁺ (*ES*⁺), at 1.96 min, 190-320 nm.

- 30 To a solution of *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (62 mg, 0.113 mmol) and *tert*-butyl (*R*)-2-amino-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (54 mg, 0.120 mmol) in DCM (1.10 mL) was added TFA (0.8 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was then
- 35 concentrated to dryness and the residue purified using purification method A to provide (*R*)-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine, **Example 1-1** (42 mg, 73 %) as a white solid.

The data for **Example 1-1** are in Table 3.

- 40 **Route B**
Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of Example 1-3, (*R*)-7-ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt

61

**Example 1-3**

A 100-mL flask under N₂ was charged with *tert*-butyl (*R*)-1-(1-hydroxybutan-2-yl)carbamate (**Intermediate 6**) (2.55 g, 13.5 mmol), 2,4,6-trichloropyrimidin-5-ol (**Intermediate 2**) (1.50 g, 7.50 mmol) and anhydrous THF (30 mL). The resulting solution was cooled to 0 °C, then Ph₃P (3.15 g, 12.0 mmol) was added. Once the Ph₃P had completely dissolved, DIAD (2.36 mL, 12.0 mmol) was then added dropwise over ca. 5 min. The reaction mixture was stirred at 0 °C for 10 min, then it was warmed to room temperature, and stirred for a further 16 h. The mixture was concentrated to dryness, and the residue was purified by column chromatography (dry injection, 80 g SiO₂, 0:100 to 50:50, EtOAc:hexanes) to afford *tert*-butyl (*R*)-1-((2,4,6-trichloropyrimidin-5-yl)oxy)butan-2-yl)carbamate (1.78 g, 64 %) as a colorless solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.38 (s, 9H), 1.40 – 1.51 (m, 1H), 1.59 – 1.69 (m, 1H), 3.61 – 3.70 (m, 1H), 3.97 – 4.11 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H).

A 100-mL flask was charged with *tert*-butyl (*R*)-1-((2,4,6-trichloropyrimidin-5-yl)oxy)butan-2-yl)carbamate (1.78 g, 4.80 mmol) and DCM (20 mL). TFA (10.0 mL, 135 mmol) was then added and the resulting solution was stirred at room temperature for 10 min. The mixture was co-evaporated with toluene under reduced pressure to afford crude (*R*)-1-((2,4,6-trichloropyrimidin-5-yl)oxy)butan-2-amine trifluoroacetic acid salt as a colorless oil. The product was used in the next step without further purification.

LCMS (System 1, Method E): *m/z* 234/236 (M-Cl)⁺ (ES⁺), at 2.05 min, 190-320 nm.

A 20-mL sealable tube under N₂ was charged with crude (*R*)-1-((2,4,6-trichloropyrimidin-5-yl)oxy)butan-2-amine trifluoroacetic acid salt (ca. 4.80 mmol) and 1,4-dioxane (13.5 mL). DIPEA (2.5 mL, 14.4 mmol) was then added, the tube was sealed, and the resulting solution was stirred at 80 °C for 16 h. The mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 80:20, EtOAc:hexanes) to afford (*R*)-2,4-dichloro-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazine (1.01 g, 90 % over 2 steps) as a colorless oil.

LCMS (System 1, Method D): *m/z* 234/236 (M+H)⁺ (ES⁺), at 2.18 min, 190-320 nm.

A 50-mL flask was charged with (*R*)-2,4-dichloro-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazine (1.01 g, 4.31 mmol) and THF (21.5 mL). DIPEA (1.5 mL, 8.6 mmol) was then added, followed by di-*tert*-butyl dicarbonate (1.70 g, 7.77 mmol) and DMAP (53 mg, 0.43 mmol). The resulting solution was stirred at room temperature for 16 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 30:70, EtOAc:hexanes) to afford *tert*-butyl (*R*)-2,4-dichloro-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (1.36 g, 94 %) as a colorless solid.

LCMS (System 1, Method D): *m/z* 278/280 (*M*-56+*H*)⁺ (*ES*⁺), at 2.68 min, 190-320 nm.

A 20-mL sealable tube under N₂ was charged with *tert*-butyl (*R*)-2,4-dichloro-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (680 mg, 2.03 mmol), *tert*-butyl (*R*)-methyl(pyrrolidin-3-yl)carbamate (**Intermediate 4**) (448 mg, 2.24 mmol) and anhydrous 1,4-dioxane (5.8 mL). DIPEA (0.71 mL, 4.1 mmol) was added, the tube was then sealed, and the mixture was stirred at 80 °C for 16 h. The resulting mixture was cooled to room temperature, then it was diluted with DCM (30 mL) to dissolve the solids that had precipitated. The resulting solution was concentrated under reduced pressure over silica gel, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 50:50, EtOAc:hexanes) to afford *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (878 mg, 87 %) as a colorless solid.

LCMS (System 1, Method D): *m/z* 442/444 (*M*-56+*H*)⁺ (*ES*⁺), at 2.90 min, 190-320 nm.

A 20-mL sealable tube under N₂ was charged with *tert*-butyl carbamate (310 mg, 2.64 mmol), Cs₂CO₃ (1.15 g, 3.53 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (80.7 mg, 0.0882 mmol) and XPhos (CAS: 564483-18-7) (168 mg, 0.353 mmol). A solution of *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (878 mg, 1.76 mmol) in 1,4-dioxane (14 mL) was then added, and the resulting suspension was sparged with N₂ for 15 min. The tube was then sealed, and the mixture was stirred at 100 °C for 3 h. The mixture was concentrated under reduced pressure over silica gel, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 60:10, EtOAc:hexanes) to afford the still impure product as a yellow solid. The product was further purified by reversed-phase column chromatography (MeOH injection, 60 g C-18, 10:90 to 95:5, MeCN:10 mM ammonium bicarbonate in water, pH 10) to afford *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (630 mg, 62 %) as a colorless solid after lyophilization.

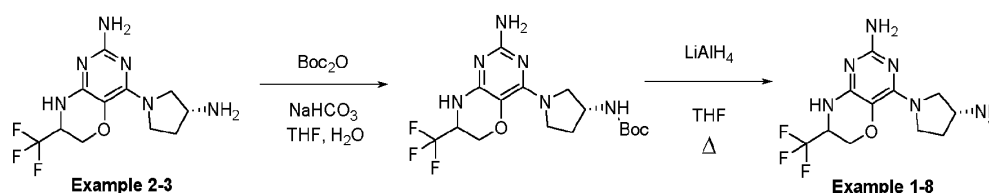
LCMS (System 1, Method D): *m/z* 579 (*M*+*H*)⁺ (*ES*⁺), at 2.20 min, 190-320 nm.

A 50-mL flask under N₂ was charged with *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-7-ethyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (630 mg, 1.09 mmol) and 1,4-dioxane (5.5 mL). Once the solids had dissolved, HCl solution in 1,4-dioxane (4 M, 5.5 mL, 22 mmol) was added, and the resulting mixture was stirred vigorously at 45 °C for 3 h. The resulting suspension was concentrated under reduced pressure, the residue was dissolved in water (10 mL) and lyophilized to dryness. The resulting yellow solid was purified by reversed-phase column chromatography (H₂O injection, 60 g C-18, isocratic 5:95, MeCN:H₂O) to afford (*R*)-7-ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt, **Example 1-3** (324 mg, 77 %) as a colorless solid after lyophilization.

The data for **Example 1-3** are in Table 3.

Route C

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of Example 1-8, 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine



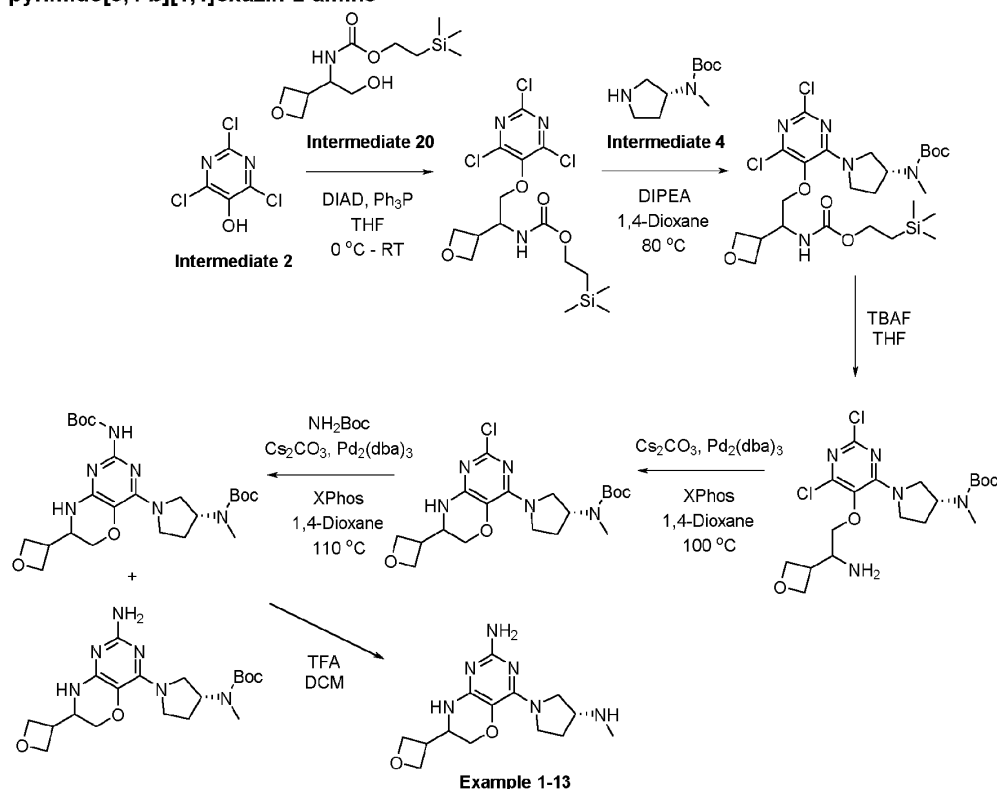
In a 5-mL flask was charged 4-((*R*)-3-aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine (**Example 2-3**) (20 mg, 0.0657 mmol). A solution of di-*tert*-butyl dicarbonate (15.1 mg, 0.0690 mmol) in THF (0.66 mL) was then added, followed by a solution of NaHCO₃ (11.6 mg) in water (0.33 mL). The resulting mixture was stirred at room temperature for 60 h. The mixture was diluted in EtOAc (10 mL) and brine (5 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 5 mL). The organic phases were combined, dried over Na₂SO₄, and concentrated to dryness to give *tert*-butyl ((3*R*)-1-(2-amino-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)carbamate (17.0 mg, 64 %) as a colorless solid. This product was used in the next step without further purification.

LCMS (System 1, Method D): *m/z* 405 (M+H)⁺ (ES⁺), at 1.79 min, 190-320 nm.

A 10-mL flask under N₂ was charged with *tert*-butyl ((3*R*)-1-(2-amino-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)carbamate (27.0 mg, 0.0668 mmol) and anhydrous THF (3.3 mL). The solution was cooled to 0 °C, then LiAlH₄ solution in THF (2 M, 0.17 mL, 0.34 mmol) was added dropwise. The resulting mixture was heated at reflux for 5 h, then it was cooled to 0 °C, and carefully quenched by the addition of Na₂SO₄·10H₂O (danger: exotherm and H₂ evolution). The resulting suspension was filtered, and the collected solid was washed several times with MeOH. The filtrate was filtered through a 0.45 µm filter and concentrated under reduced pressure. The residue was purified using purification method B to afford 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine, **Example 1-8** (14.0 mg, 66 %) as a colorless solid. The data for **Example 1-8** are in Table 3.

Route D

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of Example 1-13, 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine



A 50-mL flask under N₂ was charged with 2-(trimethylsilyl)ethyl 2-hydroxy-1-(oxetan-3-yl)ethylcarbamate (**Intermediate 20**) (1.05 g, 4.01 mmol), 2,4,6-trichloropyrimidin-5-ol (**Intermediate**

2) (0.500 g, 2.51 mmol) and anhydrous THF (12.5 mL). The resulting solution was cooled to 0 °C, then Ph₃P (986 mg, 3.76 mmol) was added. Once the Ph₃P had completely dissolved, DIAD (0.740 mL, 3.76 mmol) was then added dropwise over ca. 5 min. The reaction mixture was then stirred at 0 °C for 10 min, then it was warmed to room temperature, and stirred for a further 16 h. The mixture was concentrated to dryness, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 80:20, EtOAc:hexanes) to afford the crude product, which was further purified by reversed-phase column chromatography (DMSO injection, 12 g C-18, 5:95 to 95:5, MeCN:0.1 % formic acid in water) to give 2-(trimethylsilyl)ethyl (1-(oxetan-3-yl)-2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)carbamate (847 mg, 63 %).

10 **LCMS (System 1, Method D):** m/z 414/416 (M-CO+H)⁺ (ES⁺), at 2.20 min, 190-320 nm.

A 20-mL sealable tube under N₂ was charged with 2-(trimethylsilyl)ethyl (1-(oxetan-3-yl)-2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)carbamate (690 mg, 1.28 mmol), *tert*-butyl (*R*)-methyl(pyrrolidin-3-yl)carbamate (**Intermediate 4**) (256 mg, 1.28 mmol) and anhydrous 1,4-dioxane (6.4 mL). DIPEA (0.45 mL, 2.58 mmol) was then added, the tube was sealed, and the mixture was stirred at 80 °C for 18 h. The resulting solution was concentrated to dryness, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 90:10, EtOAc:hexanes) to afford *tert*-butyl ((3*R*)-1-(2,6-dichloro-5-(2-(oxetan-3-yl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)ethoxy)pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (730 mg, 94 %) as a colorless solid.

20 **LCMS (System 1, Method D):** m/z 578/580 (M-CO+H)⁺ (ES⁺), at 2.32 min, 190-320 nm.

A 10-mL flask under N₂ was charged with *tert*-butyl ((3*R*)-1-(2,6-dichloro-5-(2-(oxetan-3-yl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)ethoxy)pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (210 mg, 0.346 mmol) and anhydrous THF (3.5 mL). TBAF solution in THF (1 M, 0.865 mL, 0.865 mmol) was then added, and the resulting yellow solution was stirred at room temperature for 16 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (1 mL) and water (1 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL) and the combined organic phases were dried over MgSO₄ and concentrated to dryness. The residue was purified by column chromatography (dry injection, 12 g SiO₂, 0:100 to 10:90, MeOH:DCM) to afford the crude product, which was combined with product from a similar reaction conducted at ca. twice the scale and purified by reversed-phase column chromatography (MeOH injection, 12 g C-18, 5:95 to 70:30, MeCN:10 mM ammonium bicarbonate in water, pH 10) to afford *tert*-butyl ((3*R*)-1-(5-(2-amino-2-(oxetan-3-yl)ethoxy)-2,6-dichloropyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (142 mg, 26 %) as a colorless solid.

35 **LCMS (System 1, Method E):** m/z 326/328 (M-Cl-BOC+H)⁺ (ES⁺), at 1.97 min, 190-320 nm.

A 5-mL sealable tube under N₂ was charged with *tert*-butyl ((3*R*)-1-(5-(2-amino-2-(oxetan-3-yl)ethoxy)-2,6-dichloropyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (142 mg, 0.307 mmol), Cs₂CO₃ (200 mg, 0.614 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (14.1 mg, 0.0154 mmol) and XPhos (CAS: 564483-18-7) (29.3 mg, 0.0614 mmol). 1,4-Dioxane (3.0 mL) was then added, and the resulting suspension was sparged with N₂ for 15 min. The tube was then sealed, and the mixture was stirred at 100 °C for 3 h. The mixture was concentrated under reduced pressure over silica gel, and the residue was purified by column chromatography (dry injection, 40 g SiO₂, 0:100 to 90:10, EtOAc:hexanes) to give *tert*-butyl ((3*R*)-1-(2-chloro-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (70 mg, 54 %) as a colorless solid.

45 **LCMS (System 1, Method D):** m/z 426/428 (M+H)⁺ (ES⁺), at 2.00 min, 190-320 nm.

A 5-mL sealable tube under N₂ was charged with *tert*-butyl carbamate (28.9 mg, 0.247 mmol), Cs₂CO₃ (107 mg, 0.329 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (15.1 mg, 0.0164 mmol) and XPhos (CAS: 564483-18-7) (31.3 mg, 0.0657 mmol). A solution of *tert*-butyl ((3*R*)-1-(2-chloro-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (70.0 mg, 0.164 mmol) in 1,4-dioxane (1.6 mL) was then added, and the resulting suspension was sparged with N₂ for 15 min. The tube was then sealed, and the mixture was stirred at 110 °C for 11 h. The mixture was concentrated under reduced pressure over silica gel, and the residue was purified by reversed-phase column chromatography (DMSO injection, 30 g C-18, 5:95 to 90:10, MeCN:10 mM ammonium bicarbonate in water, pH 10) to give *tert*-butyl ((3*R*)-1-(2-((*tert*-butoxycarbonyl)amino)-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (15 mg, 18 %) as a colorless solid and *tert*-butyl ((3*R*)-1-(2-amino-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (15 mg, 22 %) as a colorless solid.

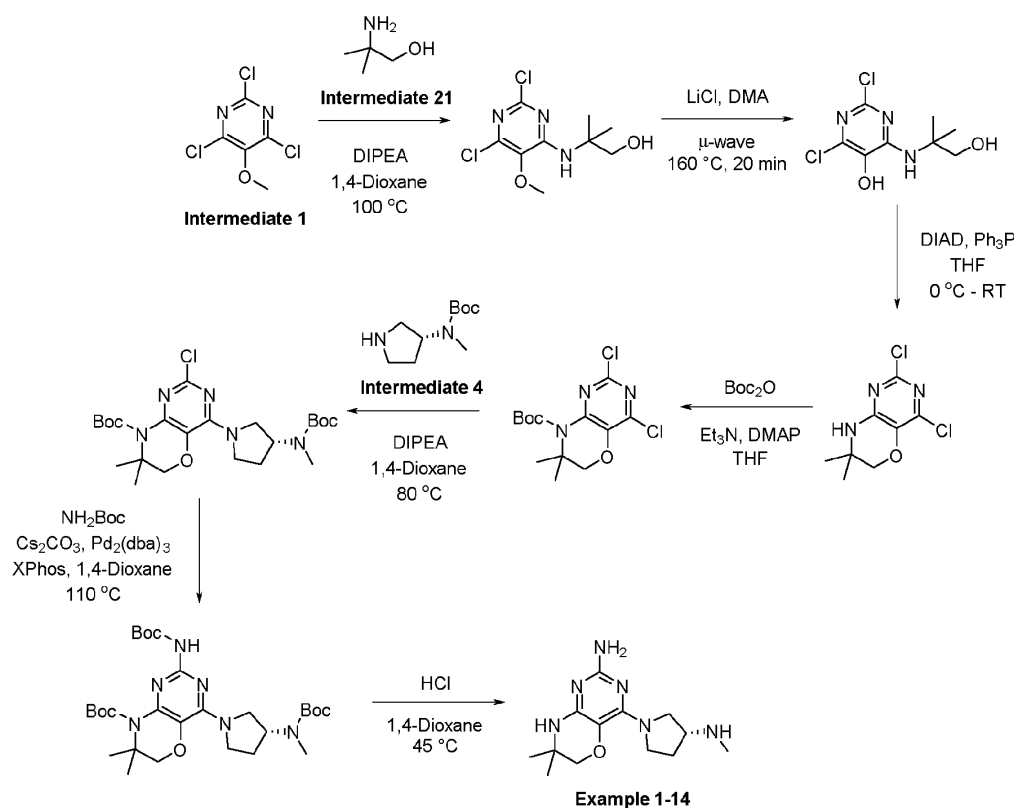
60 **LCMS (System 1, Method D):** m/z 507 (M+H)⁺ (ES⁺), at 2.06 min, 190-320 nm.

LCMS (System 1, Method D): m/z 407 (M+H)⁺ (ES⁺), at 1.83 min, 190-320 nm.

A 5-mL flask under N₂ was charged with a mixture of *tert*-butyl ((3*R*)-1-(2-((*tert*-butoxycarbonyl)amino)-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate and *tert*-butyl ((3*R*)-1-(2-amino-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (total 0.0620 mmol) and DCM (1.0 mL). TFA (0.2 mL) was then added, and the resulting solution was stirred at room temperature for 5 h. The solution was co-evaporated with toluene under reduced pressure, and the residue was purified using purification method C to afford 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7-(oxetan-3-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine, **Example 1-13** (13.6 mg, 72 %) as a colorless solid after lyophilization. The data for **Example 1-13** are in Table 3.

Route E

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of **Example 1-14**, (*R*)-7,7-dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine dihydrochloride salt



To a solution of 2,4,6-trichloro-5-methoxypyrimidine (**Intermediate 1**) (1.00 g, 4.68 mmol) in 1,4-dioxane (7.00 mL) were added 2-amino-2-methylpropan-1-ol (**Intermediate 21**) (0.47 mL, 4.92 mmol) and DIPEA (2.00 mL, 11.7 mmol) and the reaction mixture was heated at 100 °C for 3 h. After cooling to room temperature, the mixture was diluted with water and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 80 %) in hexanes to provide 2-((2,6-dichloro-5-methoxypyrimidin-4-yl)amino)-2-methylpropan-1-ol (891 mg, 72 %) as a colorless oil which crystallised to a white solid on standing.

LCMS (System 1, Method E): m/z 266/268 (M+H)⁺ (ES⁺), at 2.05 min, 190-320 nm.

To a solution of 2-((2,6-dichloro-5-methoxypyrimidin-4-yl)amino)-2-methylpropan-1-ol (800 mg, 3.01 mmol) in DMA (6.0 mL) was added LiCl (318 mg, 7.51 mmol) and the mixture was stirred at 160 °C under microwave heating for 20 min. After cooling to room temperature, the mixture was directly purified by reversed-phase column chromatography (C-18, isocratic 5:95, MeCN:0.1 % formic acid in water) to provide 2,4-dichloro-6-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-5-ol formic acid salt (130 mg, 17 %) as a brown oil.

LCMS (System 1, Method D): m/z 252/254 (M+H)⁺ (ES⁺), at 1.99 min, 190-320 nm.

To a solution of 2,4-dichloro-6-((1-hydroxy-2-methylpropan-2-yl)amino)pyrimidin-5-ol formic acid salt (200 mg, 0.793 mmol) in THF (4.7 mL) cooled to 0 °C, were added Ph₃P (416 mg, 1.59 mmol) and DIAD (0.313 mL, 1.59 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated to dryness to afford crude 2,4-dichloro-7,7-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine, which was used directly in the next step without any purification.

LCMS (System 1, Method D): m/z 234/236 (M+H)⁺ (ES⁺), at 1.87 min, 190-320 nm.

To a solution of the crude 2,4-dichloro-7,7-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine (0.793 mmol) in THF (7.9 mL) were added di-*tert*-butyl dicarbonate (537 mg, 2.46 mmol), Et₃N (0.33 mL, 2.46 mmol) and DMAP (48 mg, 0.396 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure and silica was added. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 50 %) in hexanes to provide *tert*-butyl 2,4-dichloro-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (30 mg, 11 % over 2 steps) as a colorless oil.

LCMS (System 1, Method D): m/z 278/280 (M-56+H)⁺ (ES⁺), at 2.26 min, 190-320 nm.

To a solution of *tert*-butyl 2,4-dichloro-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (30 mg, 0.089 mmol) in 1,4-dioxane (0.3 mL) were added *tert*-butyl (*R*)-methyl(pyrrolidin-3-yl)carbamate (**Intermediate 4**) (20 mg, 0.099 mmol) and DIPEA (0.031 mL, 0.18 mmol) and the mixture was heated to 80 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 60 %) in hexanes to provide *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (37 mg, 83 %) as a colorless oil.

LCMS (System 1, Method D): m/z 442/444 (M-56+H)⁺ (ES⁺), at 2.41 min, 190-320 nm.

To a degassed solution of *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (37 mg, 0.074 mmol) and *tert*-butyl carbamate (13 mg, 0.111 mmol) in 1,4-dioxane (0.74 mL) were added Cs₂CO₃ (61 mg, 0.186 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (6.8 mg, 0.00743 mmol) and XPhos (CAS: 564483-18-7) (7.1 mg, 0.0149 mmol) and the reaction mixture was heated to 110 °C for 2 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the residue washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue purified by silica gel chromatography using a gradient of EtOAc (0 – 100 %) in hexanes, and then by reversed-phase column chromatography (C-18, isocratic 5:95, MeCN:10 mM ammonium bicarbonate in water, pH 10) to provide *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (22 mg, 51 %) as a colorless oil.

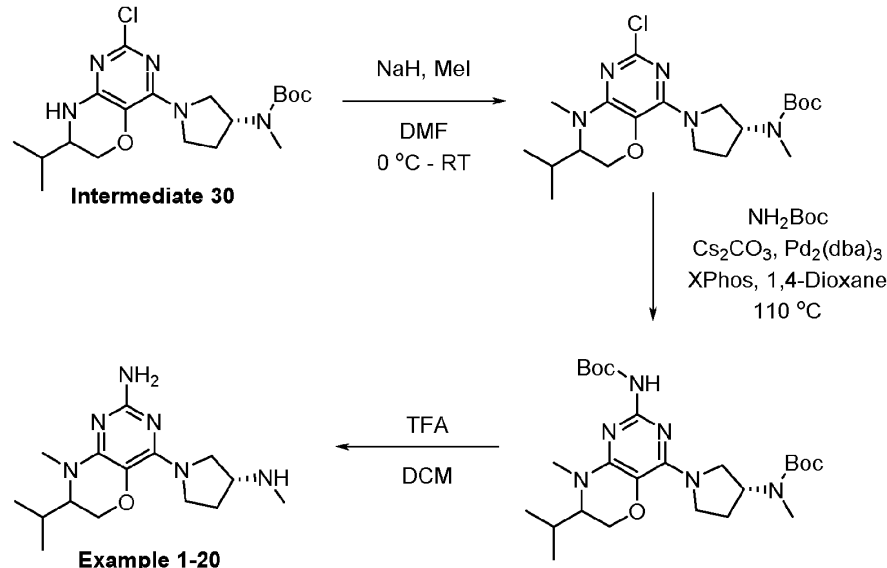
LCMS (System 1, Method D): m/z 579 (M+H)⁺ (ES⁺), at 2.29 min, 190-320 nm.

To a solution of *tert*-butyl (*R*)-4-(3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-7,7-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate (22 mg, 0.038 mmol) in 1,4-dioxane (0.48 mL) was added HCl solution in 1,4-dioxane (4M, 0.48 mL, 1.9 mmol) and the reaction mixture was heated to 45 °C for 3 h. After cooling to room temperature, the mixture was concentrated to dryness. The residue was diluted with water and purified by reversed-phase column chromatography (H₂O injection, 4 g C-18, isocratic 5:95, MeCN:H₂O) to afford (*R*)-7,7-dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt, **Example 1-14** (12 mg, 90 %) as a white solid.

The data for **Example 1-14** are in Table 3.

Route F

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of Example 1-20, 7-isopropyl-8-methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine



- 5 To a solution of *tert*-butyl ((3*R*)-1-(2-chloro-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (**Intermediate 30**) (100 mg, 0.243 mmol) in DMF (1.30 mL), cooled to 0 °C, were added NaH (60 % dispersion in mineral oil, 15 mg, 0.364 mmol) and iodomethane (0.018 mL, 0.291 mmol) and the reaction mixture was stirred at 0 °C for 30 min then warmed to room temperature and stirred for an additional 1 h. The mixture was then quenched with water and the aqueous layer was extracted with EtOAc (3 x 5.00 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 40 %) in hexanes to provide *tert*-butyl ((3*R*)-1-(2-chloro-7-isopropyl-8-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (68 mg, 66 %) as a pale yellow oil.
- 10
- 15 **LCMS (System 1, Method D):** *m/z* 426/428 (*M*+*H*)⁺ (*ES*⁺), at 2.83 min, 190-320 nm.

To a degassed solution of *tert*-butyl ((3*R*)-1-(2-chloro-7-isopropyl-8-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (68 mg, 0.16 mmol) and *tert*-butyl carbamate (19 mg, 0.16 mmol) in 1,4-dioxane (1.60 mL) were added Cs₂CO₃ (130 mg, 0.399 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (14.6 mg, 0.016 mmol) and XPhos (CAS: 564483-18-7) (15.2 mg, 0.032 mmol) and the reaction mixture was heated at 110 °C for 18 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography using a gradient of EtOAc (0 – 50 %) in hexanes to provide *tert*-butyl ((3*R*)-1-(2-((*tert*-butoxycarbonyl)amino)-7-isopropyl-8-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (43 mg, 53 %) as a pale yellow oil.

20

25 **LCMS (System 1, Method D):** *m/z* 507 (*M*+*H*)⁺ (*ES*⁺), at 2.17 min, 190-320 nm.

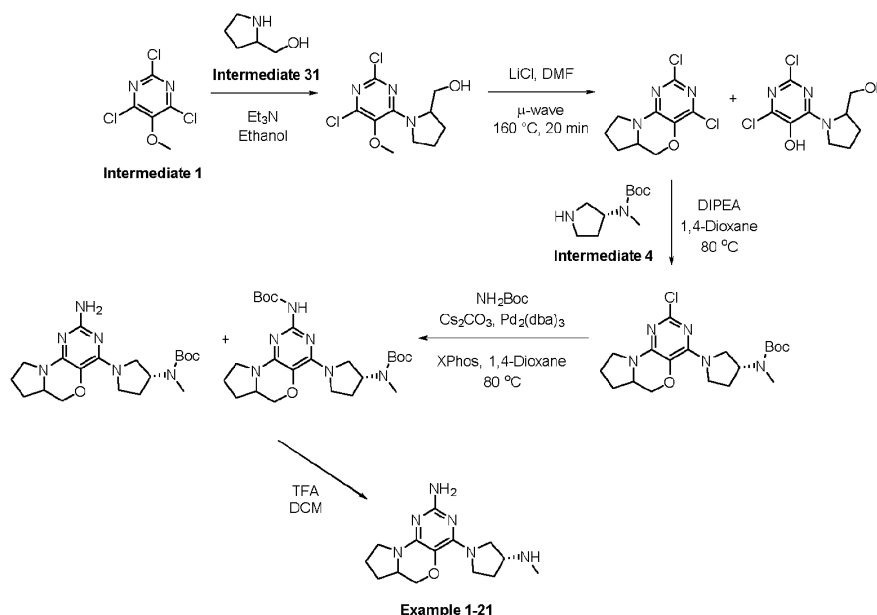
To a solution of *tert*-butyl ((3*R*)-1-(2-((*tert*-butoxycarbonyl)amino)-7-isopropyl-8-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (43 mg, 0.085 mmol) in DCM (0.50 mL) was added TFA (0.50 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was then concentrated to dryness and the residue was purified by purification method D to provide 7-isopropyl-8-methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine, **Example 1-20** (12 mg, 46 %) as a white solid.

30

35 The data for **Example 1-20** are in Table 3.

Route G

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of Example 1-21, 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6*a*,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine



To a solution of 2,4,6-trichloro-5-methoxypyrimidine (**Intermediate 1**) (320 mg, 1.5 mmol) in ethanol (10 mL) was added pyrrolidin-2-ylmethanol (**Intermediate 31**) (227 mg, 2.25 mmol) and TEA (0.42 mL, 3.0 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in DCM (10 mL). The DCM solution was washed with water (10 mL) and dried over Na₂SO₄ concentrated under reduced pressure. The residue was purified using flash chromatography with 0 – 60 % ethyl acetate in hexanes to give (1-(2,6-dichloro-5-methoxypyrimidin-4-yl)pyrrolidin-2-yl)methanol (400 mg, 96 %) as a white solid.

LCMS (System 1, Method D): m/z 278/280 (M+H)⁺ (ES⁺), at 2.13 min, 190-320 nm.

To a solution of (1-(2,6-dichloro-5-methoxypyrimidin-4-yl)pyrrolidin-2-yl)methanol (400 mg, 1.44 mmol) in DMF (5 mL) was added LiCl (152 mg, 3.6 mmol) and the mixture was stirred at 160 °C under microwave heating for 20 min. The reaction mixture was concentrated and the residue was purified by flash chromatography using 0 – 100 % ethyl acetate in hexanes to afford 2,4-dichloro-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazine (150 mg, 42 %) as white solid and 2,4-dichloro-6-(2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-5-ol (100 mg, 26 %) as a white solid.

2,4-Dichloro-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazine:

¹H NMR (500 MHz, Chloroform-*d*) δ 1.48 – 1.58 (m, 1H), 1.99 – 2.10 (m, 1H), 2.14 – 2.19 (m, 1H), 2.20 – 2.26 (m, 1H), 3.44 – 3.50 (m, 1H), 3.56 – 3.64 (m, 1H), 3.72 – 3.80 (m, 2H), 4.62 – 4.67 (m, 1H).

LCMS (System 1, Method D): m/z 246/248 (M+H)⁺ (ES⁺), at 2.20 min, 190-320 nm.

2,4-Dichloro-6-(2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-5-ol:

LCMS (System 1, Method D): m/z 264/266 (M+H)⁺ (ES⁺), at 1.97 min, 190-320 nm.

To a solution of 2,4-dichloro-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazine (200 mg, 0.813 mmol) and *tert*-butyl (*R*)-methyl(pyrrolidin-3-yl)carbamate (**Intermediate 4**) (0.163 g, 0.813 mmol) in 1,4-dioxane (4 mL) was added DIPEA (0.28 mL, 1.63 mmol) and the resulting mixture was stirred at 80 °C for 24 h. The reaction mixture was concentrated and the residue was purified by flash chromatography using 0 – 60 % ethyl acetate in hexanes to afford *tert*-butyl ((*3R*)-1-(2-chloro-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (252 mg, 75 %) as a white solid.

LCMS (System 1, Method D): m/z 410/412 (M+H)⁺ (ES⁺), at 2.64 min, 190-320 nm.

To a degassed solution of *tert*-butyl ((*3R*)-1-(2-chloro-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (150 mg, 0.366 mmol) and *tert*-butyl

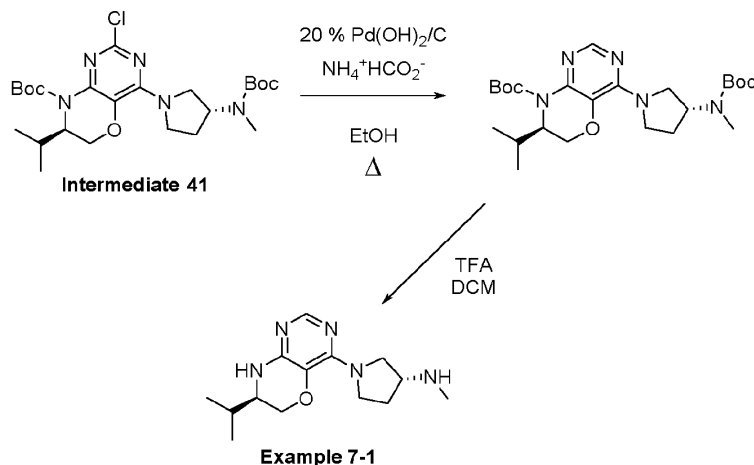
carbamate (42.9 mg, 0.366 mmol) in 1,4-dioxane (4 mL) was added Cs₂CO₃ (0.477 g, 1.46 mol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (21.0 mg, 0.0365 mmol) and XPhos (CAS: 564483-18-7) (34.9 mg, 0.0732 mmol). The solution was degassed with N₂ and stirred at 80 °C for 18 h. A mixture of *tert*-butyl ((3*R*)-1-(2-((*tert*-butoxycarbonyl)amino)-6*a*,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate and *tert*-butyl ((3*R*)-1-(2-amino-6*a*,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate was observed by LCMS. The reaction mixture was filtered over a bed of Celite under vacuum, washing the residue with ethyl acetate and the filtrate was concentrated to obtain a mixture of the two products as a yellow oil, which was used directly in the next step without any purification.

LCMS (System 1, Method D): *m/z* 491 (M+H)⁺ (ES⁺), at 2.11 min, 190-320 nm.
 LCMS (System 1, Method D): *m/z* 391 (M+H)⁺ (ES⁺), at 1.91 min, 190-320 nm.

The yellow oil from the step above was dissolved in DCM (2.0 mL) and TFA (2.0 mL) was added at RT. The mixture was stirred at RT for 1 h and then concentrated to dryness. The residue was purified using reversed-phase column chromatography (C-18, isocratic 5:95, MeCN:10 mM ammonium bicarbonate in water, pH 10) to afford 4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6*a*,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine, **Example 1-21** (21 mg, 20 % over two steps) as a white solid. The data for **Example 1-21** are in Table 3.

Route H

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of **Example 7-1**, (*R*)-1-((*R*)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine



25

A 25-mL flask was charged with 20 % Pd(OH)₂/C (15.1 mg, 10 mol % Pd). The atmosphere was replaced with N₂, then a solution of *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-isopropyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (**Intermediate 41**) (110 mg, 0.215 mmol) in EtOH (2.1 mL) was added followed by ammonium formate (135 mg, 2.15 mmol). The reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite and the residue was washed several times with MeOH. The filtrate was concentrated under reduced pressure to give *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-7-isopropyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate as a white solid (103 mg, 100 %), which was used directly in the next step without further purification.

LCMS (System 1, Method D): *m/z* 478 (M+H)⁺ (ES⁺), at 2.22 min, 190-320 nm.

To a solution of *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-7-isopropyl-6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (103 mg, 0.216 mmol) in DCM (1.00 mL) was added TFA (1.00 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was then concentrated to dryness and the residue was purified by purification method E to provide (*R*)-

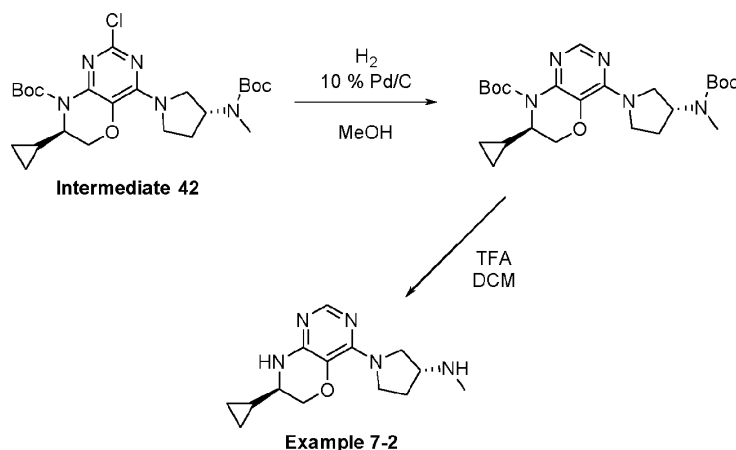
40

1-((*R*)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine,
Example 7-1 (43 mg, 72 %) as a white foam.

The data for **Example 7-1** are in Table 3.

5 Route I

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of
Example 7-2, (*R*)-1-((*R*)-7-cyclopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-
methylpyrrolidin-3-amine



10

To *tert*-butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-cyclopropyl-
6,7-dihydro-8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (**Intermediate 42**) (270 mg, 0.530 mmol) in
MeOH (20 mL) was added 10 % Pd/C catalyst (50 mg) and the resulting mixture was stirred at RT under
H₂ (1 atmosphere pressure) for 8 h. The reaction mixture was then filtered on a bed of Celite and the
residue washed with MeOH. The filtrate was concentrated under reduced pressure to afford *tert*-butyl
(*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-7-cyclopropyl-6,7-dihydro-8*H*-
pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (250 mg, 99 %) as a brown solid, which was forwarded to the
next step without purification.

20 **LCMS (System 4, Method C):** *m/z* 476 (M+H)⁺ (ES⁺), at 4.84 min, 228 nm

tert-Butyl (*R*)-4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-7-cyclopropyl-6,7-dihydro-
8*H*-pyrimido[5,4-*b*][1,4]oxazine-8-carboxylate (250 mg, 0.526 mmol) was dissolved in DCM (5.00 mL),
and TFA (5 mL) was added dropwise at 0 °C, and the resulting mixture was stirred for 2 h at room
temperature. The solvent was removed *in-vacuo* and the residue was triturated with hexanes (2 x 20
mL) and diethyl ether (2 x 10 mL) to give the crude product (150 mg), which was purified by purification
method F to afford (*R*)-1-((*R*)-7-cyclopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-
methylpyrrolidin-3-amine, **Example 7-2** (35 mg, 22 %) as a white solid.

The data for **Example 7-2** are in Table 3.

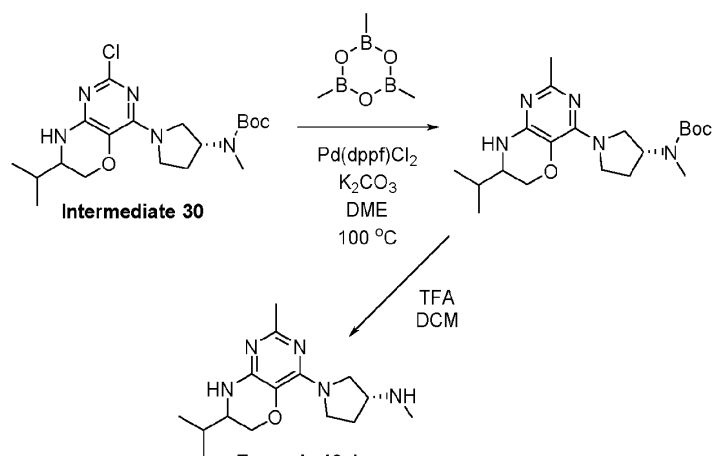
30

Route J

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of
Example 10-1, (3*R*)-1-(7-isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-
methylpyrrolidin-3-amine

35

71



A vial was charged with *tert*-butyl ((3*R*)-1-(2-chloro-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (**Intermediate 30**) (110 mg, 0.267 mmol), trimethylboroxine (CAS: 823-96-1) (0.15 mL, 1.07 mmol), K₂CO₃ (74 mg, 0.534 mmol) and DME (5.80 mL). Then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (CAS: 72287-26-4) (20 mg, 0.027 mmol) was added and the mixture was degassed with nitrogen for 15 min. The tube was sealed and the mixture was heated at 100 °C for 18 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography using a gradient of EtOAc (0 – 100 %) in hexanes to provide *tert*-butyl ((3*R*)-1-(7-isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (69 mg, 66 %) as a colorless oil.

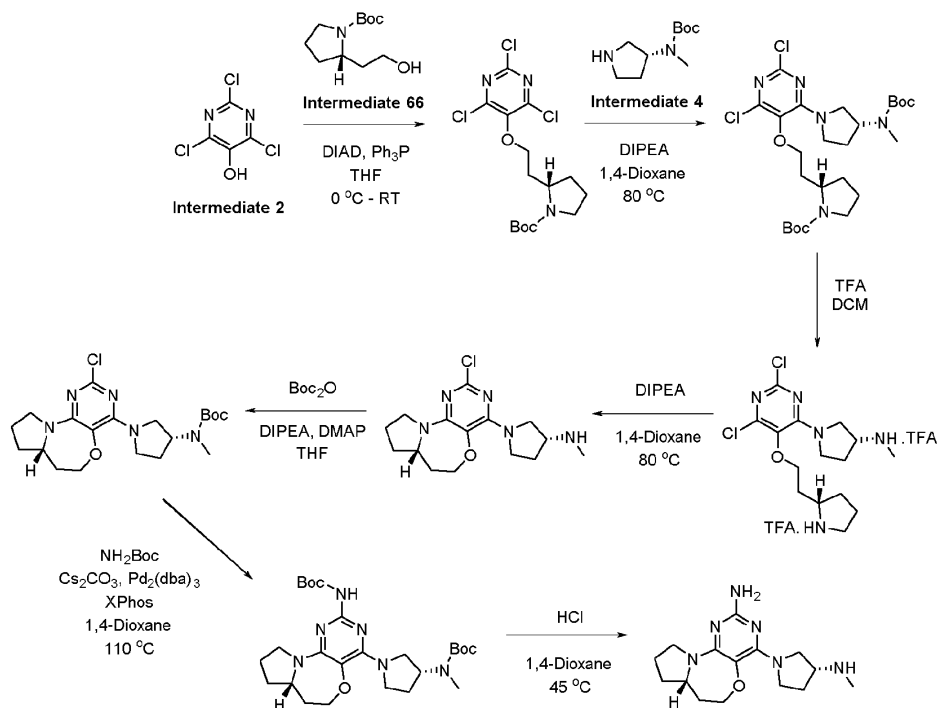
LCMS (System 1, Method D): *m/z* 392 (M+H)⁺ (ES⁺), at 2.02 min, 190-320 nm.

To a solution of *tert*-butyl ((3*R*)-1-(7-isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (61 mg, 0.156 mmol) in DCM (1.00 mL) was added TFA (1.00 mL) and the reaction mixture was stirred at room temperature for 1 h. After concentration to dryness, the residue was purified by purification method D to provide (3*R*)-1-(7-isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine, **Example 10-1** (35 mg, 77 %) as a white solid.

The data for **Example 10-1** are in Table 3.

Route K

Typical procedure for the preparation of fused pyrimidines as exemplified by the preparation of **Example 11-10**, (S)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,7*a*,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-2-amine



Example 11-10

To a solution of 2,4,6-trichloropyrimidin-5-ol (**Intermediate 2**) (550 mg, 2.76 mmol) and *tert*-butyl (*S*)-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (**Intermediate 66**) (1.19 g, 5.52 mmol) in THF (15.5 mL), cooled to 0 °C, were added Ph₃P (1.09 g, 4.14 mmol) and DIAD (0.815 mL, 4.14 mmol) and the reaction mixture was stirred at room temperature for 3 h. THF was then removed by concentration under reduced pressure and silica was added. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 50 %) in hexanes to provide *tert*-butyl (*S*)-2-(2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)pyrrolidine-1-carboxylate (844 mg, 77 %) as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 1.45 (s, 9H), 1.75 – 1.83 (m, 1H), 1.83 – 1.97 (m, 3H), 1.99 – 2.11 (m, 1H), 2.25 – 2.36 (m, 1H), 3.26 – 3.48 (m, 2H), 3.95 – 4.06 (m, 1H), 4.07 – 4.23 (m, 2H).

To a solution of *tert*-butyl (*S*)-2-(2-((2,4,6-trichloropyrimidin-5-yl)oxy)ethyl)pyrrolidine-1-carboxylate (820 mg, 2.07 mmol) and *tert*-butyl (*R*)-methylpyrrolidin-3-ylcarbamate (**Intermediate 4**) (414 mg, 2.07 mmol) in 1,4-dioxane (4.73 mL) was added DIPEA (1.08 mL, 6.2 mmol) and the reaction mixture was heated at 80 °C for 3 h. The mixture was then diluted with water and the aqueous layer was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 80 %) in hexanes to provide *tert*-butyl (*S*)-2-(2-((4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2,6-dichloropyrimidin-5-yl)oxy)ethyl)pyrrolidine-1-carboxylate (1.07 g, 92 %) as a colorless oil.

LCMS (System 1, Method D): *m/z* 560/562 (M+H)⁺ (ES⁺), at 2.39 min, 190-320 nm.

To a solution of *tert*-butyl (*S*)-2-(2-((4-((*R*)-3-((*tert*-butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2,6-dichloropyrimidin-5-yl)oxy)ethyl)pyrrolidine-1-carboxylate (1.07 g, 1.91 mmol) in DCM (8.00 mL) was added TFA (8.00 mL) and the reaction mixture was stirred at room temperature for 10 min. The mixture was then concentrated to dryness to provide the crude (*R*)-1-(2,6-dichloro-5-(2-((*S*)-pyrrolidin-2-yl)ethoxy)pyrimidin-4-yl)-*N*-methylpyrrolidin-3-amine ditrifluoroacetic acid salt as a yellow oil, which was used directly in the next step without any purification.

LCMS (System 1, Method D): *m/z* 360/362 (M+H)⁺ (ES⁺), at 1.35 min, 190-320 nm.

To a solution of the crude (*R*)-1-(2,6-dichloro-5-(2-((*S*)-pyrrolidin-2-yl)ethoxy)pyrimidin-4-yl)-*N*-methylpyrrolidin-3-amine ditrifluoroacetic acid salt (1.91 mmol) in 1,4-dioxane (5.1 mL) was added

DIPEA (1.33 mL, 7.64 mmol) and the reaction mixture was heated at 80 °C for 18 h. The mixture was then concentrated under reduced pressure and the residue was purified by silica gel chromatography (dry pack) using a gradient of MeOH (0 – 30 %) in DCM to provide (*R*)-1-((*S*)-2-chloro-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine (620 mg, 100 %) as a beige solid.

LCMS (System 1, Method D): *m/z* 324/326 (*M*+*H*)⁺ (*ES*⁺), at 1.86 min, 190-320 nm.

To a solution of (*R*)-1-((*S*)-2-chloro-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine (618 mg, 1.91 mmol) in THF (19.1 mL) were added di-*tert*-butyl dicarbonate (833 mg, 3.82 mmol), Et₃N (0.567 mL, 4.2 mmol) and DMAP (117 mg, 0.954 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure and silica was added. The residue was purified by silica gel chromatography (dry pack) using a gradient of EtOAc (0 – 70 %) in hexane to provide *tert*-butyl ((*R*)-1-((*S*)-2-chloro-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (480 mg, 59 %) as a colorless oil.

LCMS (System 1, Method D): *m/z* 424/426 (*M*+*H*)⁺ (*ES*⁺), at 2.27 min, 190-320 nm.

To a degassed solution of *tert*-butyl ((*R*)-1-((*S*)-2-chloro-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (480 mg, 1.13 mmol) and *tert*-butyl carbamate (199 mg, 1.7 mmol) in 1,4-dioxane (11.3 mL) were added Cs₂CO₃ (922 mg, 2.83 mmol), tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) (104 mg, 0.113 mmol) and XPhos (CAS: 564483-18-7) (216 mg, 0.453 mmol) and the reaction mixture was heated at 110 °C for 3 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the residue washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography using a gradient of EtOAc (0 – 100 %) in hexanes and then by reversed-phase column chromatography (C-18, isocratic 5:95, MeCN:10 mM ammonium bicarbonate in water, pH 10) to provide *tert*-butyl ((*R*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (291 mg, 51 %) as a beige solid.

LCMS (System 2, Method F): *m/z* 505 (*M*+*H*)⁺ (*ES*⁺), at 2.15 min, 254 nm.

To a solution of *tert*-butyl ((*R*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (291 mg, 0.577 mmol) in 1,4-dioxane (5.77 mL) was added HCl solution in 1,4-dioxane (4 M, 5.77 mL, 23.1 mmol) and the reaction mixture was heated at 45 °C for 3 h. After cooling to room temperature, the mixture was concentrated to dryness. The residue was diluted with water and purified by reversed-phase column chromatography (C-18, isocratic 5:95, MeCN:H₂O) and then re-purified by reverse-phase column chromatography (C-18, isocratic 5:95, MeCN:10 mM ammonium bicarbonate in water, pH 10) to provide (*S*)-4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-6,7,7a,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-2-amine, **Example 11-10** (85 mg, 48 %) as a white solid.

The data for **Example 11-10** are in Table 3.

Table 2 – Intermediates

Table 2				
Intermediate Number	Name	Synthetic Route	Intermediates Used	Characterising Data
1	2,4,6-Trichloro-5-methoxypyrimidine	-	-	Commercially available, CAS: 60703-46-0
2	2,4,6-Trichloropyrimidin-5-ol	1	1	LCMS (System 1, Method D): m/z 197/199 (M-H) ⁺ (ES ⁺), at 1.93 min, 190-320 nm
3	<i>tert</i> -Butyl (2-hydroxyethyl)carbamate	-	-	Commercially available, CAS: 26690-80-2
4	<i>tert</i> -Butyl (<i>R</i>)-methyl(pyrrolidin-3-yl)carbamate	-	-	Commercially available, CAS: 392338-15-7
5	<i>tert</i> -Butyl (1-hydroxypropan-2-yl)carbamate	-	-	Commercially available, CAS: 147252-84-4
6	<i>tert</i> -Butyl (<i>R</i>)-(1-hydroxybutan-2-yl)carbamate	-	-	Commercially available, CAS: 150736-71-3
7	<i>tert</i> -Butyl (<i>R</i>)-(1-hydroxy-3-methylbutan-2-yl)carbamate	-	-	Commercially available, CAS: 106391-87-1
8	<i>tert</i> -Butyl (<i>S</i>)-(1-hydroxy-3-methylbutan-2-yl)carbamate	-	-	Commercially available, CAS: 79069-14-0
9	(<i>R</i>)-2-((<i>tert</i> -butoxycarbonyl)amino)-2-cyclopropylacetic acid	-	-	Commercially available, CAS: 609768-49-2
10	<i>tert</i> -Butyl (<i>R</i>)-(1-cyclopropyl-2-hydroxyethyl)carbamate	2	9	LCMS (System 4, Method C): m/z 200 (M-H) ⁺ (ES ⁺), at 2.19 min, 202 nm
11	<i>tert</i> -Butyl (1-hydroxy-4-methylpentan-2-yl)carbamate	-	-	Commercially available, CAS: 142121-48-0
12	<i>tert</i> -Butyl (<i>S</i>)-(1-hydroxy-3-methoxypropan-2-yl)carbamate	-	-	Commercially available, CAS: 721927-59-9
13	<i>D</i> -Allothreonine	-	-	Commercially available, CAS: 24830-94-2
14	<i>tert</i> -Butyl ((2 <i>S</i> ,3 <i>R</i>)-1-hydroxy-3-methoxybutan-2-yl)carbamate	3	13	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 1.22 (d, <i>J</i> = 6.4 Hz, 3H), 1.46 (s, 9H), 3.34 (s, 3H), 3.51 – 3.56 (m, 1H), 3.59 – 3.65 (m, 2H), 3.93 – 3.98 (m, 1H), 5.33 – 5.40 (m, 1H). One exchangeable proton not observed.
15	(<i>tert</i> -Butoxycarbonyl)- <i>D</i> -threonine	-	-	Commercially available, CAS: 55674-67-4
16	<i>tert</i> -Butyl ((2 <i>S</i> ,3 <i>S</i>)-1-hydroxy-3-methoxybutan-2-yl)carbamate	3 Steps 2 and 3	15	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 1.17 (d, <i>J</i> = 6.2 Hz, 3H), 1.43 (s, 9H), 3.32 (s, 3H), 3.48 – 3.70 (m, 3H), 3.70 – 3.78 (m, 1H), 5.02 – 5.12 (m, 1H). One exchangeable proton not observed.
17	3-(<i>tert</i> -Butyl) 4-methyl (<i>S</i>)-2,2-dimethyloxazolidine-3,4-dicarboxylate	-	-	Commercially available, CAS: 108149-60-6
18	<i>tert</i> -Butyl (<i>S</i>)-(1-hydroxy-3-methoxy-3-methylbutan-2-yl)carbamate	4	17	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 1.22 (s, 3H), 1.27 (s, 3H), 1.45 (s, 9H), 3.18 – 3.23 (m, 1H), 3.21 (s, 3H), 3.51 – 3.56 (m, 1H), 3.62

Table 2				
Intermediate Number	Name	Synthetic Route	Intermediates Used	Characterising Data
				– 3.68 (m, 1H), 3.93 – 3.99 (m, 1H), 5.28 – 5.36 (m, 1H).
19	Methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-ylidene)acetate	-	-	Commercially available, CAS: 394653-39-5
20	2-(Trimethylsilyl)ethyl (2-hydroxy-1-(oxetan-3-yl)ethyl)carbamate	5	19	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 0.02 (s, 9H), 0.87 – 0.97 (m, 2H), 3.01 – 3.13 (m, 1H), 3.16 – 3.25 (m, 1H), 3.28 – 3.35 (m, 1H), 3.73 – 3.83 (m, 1H), 3.97 – 4.10 (m, 2H), 4.32 – 4.41 (m, 2H), 4.46 – 4.56 (m, 2H), 4.61 (t, <i>J</i> = 5.6 Hz, 1H), 6.87 (d, <i>J</i> = 8.9 Hz, 1H).
21	2-Amino-2-methylpropan-1-ol	-	-	Commercially available, CAS: 124-68-5
22	<i>tert</i> -Butyl (2-hydroxypropyl)carbamate	-	-	Commercially available, CAS: 95656-86-3
23	(2 <i>R</i> ,3 <i>R</i>)-3-Aminobutan-2-ol hydrochloride	-	-	Commercially available, CAS: 960008-54-2
24	(2 <i>S</i> ,3 <i>R</i>)-3-Aminobutan-2-ol hydrochloride	-	-	Commercially available, CAS: 1605313-24-3
25	2,4-Dichloro-6-(((2 <i>R</i> ,3 <i>S</i>)-3-hydroxybutan-2-yl)amino)pyrimidin-5-ol	E Steps 1 and 2	1 and 24	LCMS (System 1, Method D): <i>m/z</i> 252/254 (M+H) ⁺ (ES ⁺), at 1.67 min, 190-320 nm.
26	<i>tert</i> -Butyl (2,6-dichloro-5-hydroxypyrimidin-4-yl)((2 <i>R</i> ,3 <i>S</i>)-3-hydroxybutan-2-yl)carbamate	6	25	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 1.07 (d, <i>J</i> = 7.2 Hz, 3H), 1.24 (d, <i>J</i> = 6.5 Hz, 3H), 1.49 (s, 9H), 4.24 – 4.37 (m, 2H). Two exchangeable protons not observed.
27	(2 <i>R</i> ,3 <i>S</i>)-3-Aminobutan-2-ol hydrochloride	-	-	Commercially available, CAS: 126307-45-7
28	(2 <i>S</i> ,3 <i>S</i>)-3-Aminobutan-2-ol hydrochloride	-	-	Commercially available, CAS: 310450-42-1
29	<i>tert</i> -Butyl (1-hydroxy-3-methylbutan-2-yl)carbamate	-	-	Commercially available, CAS: 169556-48-3
30	<i>tert</i> -Butyl ((3 <i>R</i>)-1-(2-chloro-7-isopropyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate	A Steps 1 to 4	2, 29 and 4	LCMS (System 1, Method D): <i>m/z</i> 412/414 (M+H) ⁺ (ES ⁺), at 2.73 min, 190-320 nm.
31	Pyrrolidin-2-ylmethanol	-	-	Commercially available, CAS: 498-63-5
32	(<i>R</i>)-(2-Methylpyrrolidin-2-yl)methanol hydrochloride	-	-	Commercially available, CAS: 1523530-30-4
33	(<i>S</i>)-(2-Methylpyrrolidin-2-yl)methanol hydrochloride	-	-	Commercially available, CAS: 1523541-78-7
34	<i>tert</i> -Butyl (<i>R</i>)-pyrrolidin-3-ylcarbamate	-	-	Commercially available, CAS: 122536-77-0
35	Methyl 2-((<i>tert</i> -butoxycarbonyl)amino)-3,3,3-trifluoro-2-hydroxypropanoate	-	-	Commercially available, CAS: 126535-83-9

Table 2				
Intermediate Number	Name	Synthetic Route	Intermediates Used	Characterising Data
36	<i>tert</i> -Butyl (1,1,1-trifluoro-3-hydroxypropan-2-yl)carbamate	7	35	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.40 (s, 9H), 3.46 – 3.55 (m, 1H), 3.60 – 3.68 (m, 1H), 4.07 – 4.21 (m, 1H), 5.04 (t, <i>J</i> = 5.9 Hz, 1H), 7.40 (d, <i>J</i> = 9.2 Hz, 1H).
37	<i>tert</i> -Butyl azetidin-3-yl(methyl)carbamate hydrochloride	-	-	Commercially available, CAS: 943060-59-1
38	<i>tert</i> -Butyl azetidin-3-ylcarbamate hydrochloride	-	-	Commercially available, CAS: 217806-26-3
39	1-Methylpiperazine	-	-	Commercially available, CAS: 109-01-3
40	<i>tert</i> -Butyl piperazine-1-carboxylate	-	-	Commercially available, CAS: 57260-71-6
41	<i>tert</i> -Butyl (<i>R</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-isopropyl-6,7-dihydro-8 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazine-8-carboxylate	A Steps 1 to 5 No DMF was used in Step 5	2, 7 and 4	LCMS (System 1, Method D): <i>m/z</i> 456/458 (M-56+H) ⁺ (ES ⁺), at 2.97 min, 190-320 nm.
42	<i>tert</i> -Butyl (<i>R</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-cyclopropyl-6,7-dihydro-8 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazine-8-carboxylate	B Steps 1 to 5 DCM was used in Step 4	2, 10 and 4	LCMS (System 4, Method C): <i>m/z</i> 510/512 (M+H) ⁺ (ES ⁺), at 5.72 min, 258 nm
43	<i>tert</i> -Butyl (1-hydroxy-3-methoxypropan-2-yl)carbamate	-	-	Commercially available, CAS: 1334171-66-2
44	<i>tert</i> -Butyl 4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-(methoxymethyl)-6,7-dihydro-8 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazine-8-carboxylate	A Steps 1 to 5 No DMF or DMAP was used in Step 5	2, 43 and 4	LCMS (System 1, Method D): <i>m/z</i> 458/460 (M-56+H) ⁺ (ES ⁺), at 2.81 min, 190-320 nm.
45	<i>tert</i> -Butyl (<i>S</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-7-((<i>R</i>)-1-methoxyethyl)-6,7-dihydro-8 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazine-8-carboxylate	B Steps 1 to 5	2, 14 and 4	LCMS (System 1, Method D): <i>m/z</i> 472/474 (M-56+H) ⁺ (ES ⁺), at 2.83 min, 190-320 nm.
46	<i>tert</i> -Butyl 4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-6-	A	2, 22 and 4	LCMS (System 1, Method D): <i>m/z</i> 428/430 (M-56+H) ⁺ (ES ⁺), at 2.81 min, 190-320 nm.

Table 2				
Intermediate Number	Name	Synthetic Route	Intermediates Used	Characterising Data
	methyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate	Steps 1 to 5 No DMF was used in Step 5		
47	<i>tert</i> -Butyl (<i>R</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)amino)pyrrolidin-1-yl)-2-chloro-7-isopropyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate	Steps 1 to 5 No DMF was used in Step 5	2, 7 and 34	LCMS (System 1, Method D): m/z 442/444 (M-56+H) ⁺ (ES ⁺), at 2.81 min, 190-320 nm.
48	<i>tert</i> -Butyl (<i>S</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)amino)pyrrolidin-1-yl)-2-chloro-7-((<i>R</i>)-1-methoxyethyl)-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate	B Steps 1 to 5	2, 14 and 34	LCMS (System 1, Method D): m/z 458/460 (M-56+H) ⁺ (ES ⁺), at 2.69 min, 190-320 nm.
49	<i>tert</i> -Butyl (<i>R</i>)-4-(3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)azetidin-1-yl)-2-chloro-7-isopropyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazine-8-carboxylate	B Steps 1 to 5	2, 7 and 37	LCMS (System 1, Method D): m/z 442/444 (M-56+H) ⁺ (ES ⁺), at 2.88 min, 190-320 nm.
50	<i>tert</i> -Butyl (3-hydroxypropyl)carbamate	-	-	Commercially available, CAS: 58885-58-8
51	<i>tert</i> -Butyl (<i>R</i>)-(4-hydroxybutan-2-yl)carbamate	-	-	Commercially available, CAS: 167216-17-3
52	<i>tert</i> -Butyl (<i>S</i>)-(4-hydroxybutan-2-yl)carbamate	-	-	Commercially available, CAS: 106539-36-0
53	(<i>R</i>)-3-((<i>tert</i> -Butoxycarbonyl)amino)penta noic acid	-	-	Commercially available, CAS: 183990-60-5
54	<i>tert</i> -Butyl (<i>R</i>)-(1-hydroxypentan-3-yl)carbamate	2	53	LCMS (System 4, Method C): m/z 204 (M+H) ⁺ (ES ⁺), at 3.14 min, 202 nm
55	(<i>S</i>)-3-((<i>tert</i> -Butoxycarbonyl)amino)-4-methylpentanoic acid	-	-	Commercially available, CAS: 179412-79-4
56	<i>tert</i> -Butyl (<i>S</i>)-(1-hydroxy-4-methylpentan-3-yl)carbamate	2	55	LCMS (System 4, Method C): m/z 216 (M-H) ⁻ (ES ⁻), at 3.32 min, 202 nm
57	(<i>R</i>)-3-((<i>tert</i> -Butoxycarbonyl)amino)-4-methylpentanoic acid	-	-	Commercially available, CAS: 183990-64-9
58	<i>tert</i> -Butyl (<i>R</i>)-(1-hydroxy-4-methylpentan-3-yl)carbamate	2	57	LCMS (System 3, Method B): m/z 218 (M+H) ⁺ (ES ⁺), at 1.47 min, 202 nm
59	<i>tert</i> -Butyl (3-hydroxy-2-methylpropyl)carbamate	-	-	Commercially available, CAS: 480451-99-8

Table 2				
Intermediate Number	Name	Synthetic Route	Intermediates Used	Characterising Data
60	2-(Aminomethyl)butanoic acid	-	-	Commercially available, CAS: 4385-92-6
61	2-(((<i>tert</i> -Butoxycarbonyl)amino)methyl)butanoic acid	8	60	LCMS (System 4, Method C): m/z 216 (M-H) ⁻ (ES ⁻), at 1.74 min, 202 nm
62	<i>tert</i> -Butyl (2-(hydroxymethyl)butyl)carbamate	2	61	LCMS (System 4, Method C): m/z 204 (M+H) ⁺ (ES ⁺), at 3.12 min, 202 nm
63	2-(((<i>tert</i> -Butoxycarbonyl)amino)methyl)-3-methylbutanoic acid	-	-	Commercially available, CAS: 1233517-91-3
64	<i>tert</i> -Butyl (2-(hydroxymethyl)-3-methylbutyl)carbamate	2	63	LCMS (System 3, Method B): m/z 218 (M+H) ⁺ (ES ⁺), at 1.54 min, 202 nm
65	(<i>S</i>)-2-(1-(<i>tert</i> -Butoxycarbonyl)pyrrolidin-2-yl)acetic acid	-	-	Commercially available, CAS: 56502-01-3
66	<i>tert</i> -Butyl (<i>S</i>)-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate	2	65	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 1.45 (s, 9H), 1.57 – 1.63 (m, 1H), 1.64 – 1.72 (m, 1H), 1.82 – 1.92 (m, 2H), 1.92 – 2.02 (m, 1H), 3.26 – 3.36 (m, 2H), 3.50 – 3.66 (m, 2H), 4.11 – 4.18 (m, 1H), 4.39 (s, 1H). One exchangeable proton not observed.
67	<i>tert</i> -Butyl (<i>S</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-8-isopropyl-7,8-dihydropyrimido[5,4- <i>b</i>][1,4]oxazepine-9(6 <i>H</i>)-carboxylate	B Steps 1 to 5 DCM was used in Step 4	2, 56 and 4	LCMS (System 3, Method B): m/z 526/528 (M+H) ⁺ (ES ⁺), at 2.29 min, 202 nm
68	<i>tert</i> -Butyl (<i>R</i>)-4-((<i>R</i>)-3-((<i>tert</i> -butoxycarbonyl)(methyl)amino)pyrrolidin-1-yl)-2-chloro-8-isopropyl-7,8-dihydropyrimido[5,4- <i>b</i>][1,4]oxazepine-9(6 <i>H</i>)-carboxylate	B Steps 1 to 5 DCM was used in Step 4	2, 58 and 4	LCMS (System 3, Method B): m/z 470/472 (M-56+H) ⁺ (ES ⁺), at 2.19 min, 260 nm

Table 3 – Example compounds

Table 3					
Ex. No.	Name	Synthetic Route and Intermediate <i>s</i> Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method LCMS data
1-1	(<i>R</i>)-4-(3-(Methylamino)pyrrolidin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 1, 3 and 4	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.54 – 1.63 (m, 1H), 1.84 – 1.93 (m, 1H), 2.26 (s, 3H), 3.02 – 3.09 (m, 1H), 3.22 – 3.27 (m, 1H), 3.28 – 3.32 (m, 2H), 3.44 – 3.51 (m, 1H), 3.52 – 3.59 (m, 1H), 3.59 – 3.65 (m, 1H), 3.84 – 3.90 (m, 2H), 5.05 (s, 2H), 6.18 – 6.23 (m, 1H). One exchangeable proton not observed.	m/z 251 (M+H) ⁺ (ES ⁺), at 0.78 min, 254 nm
1-2	7-Methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 2, 5 and 4 Step 5 omitted	RP-flash (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.06 (d, <i>J</i> = 6.1 Hz, 3H), 1.54 – 1.63 (m, 1H), 1.83 – 1.93 (m, 1H), 2.26 (d, <i>J</i> = 1.2 Hz, 3H), 3.02 – 3.08 (m, 1H), 3.21 – 3.26 (m, 1H), 3.40 – 3.51 (m, 3H), 3.52 – 3.59 (m, 1H), 3.59 – 3.65 (m, 1H), 3.88 – 3.93 (m, 1H), 5.03 (s, 2H), 6.26 (s, 1H). One exchangeable proton not observed.	m/z 265 (M+H) ⁺ (ES ⁺), at 0.85 min, 254 nm
1-3	(<i>R</i>)-7-Ethyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine dihydrochloride salt	B 2, 6 and 4	RP-flash (neutral)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 0.93 (t, <i>J</i> = 7.5 Hz, 3H), 1.45 – 1.59 (m, 2H), 2.12 – 2.28 (m, 2H), 2.54 (t, <i>J</i> = 5.3 Hz, 3H), 3.41 – 3.47 (m, 1H), 3.67 – 3.77 (m, 2H), 3.79 – 3.84 (m, 1H), 3.85 – 4.09 (m, 2H), 3.93 – 3.98 (m, 2H), 7.37 (s, 2H), 8.21 (d, <i>J</i> = 2.9 Hz, 1H), 9.55 – 9.66 (m, 1H), 9.73 (s, 1H), 11.96 (s, 1H).	m/z 279 (M+H) ⁺ (ES ⁺), at 0.96 min, 254 nm
1-4	(<i>R</i>)-7-Isopropyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 2, 7 and 4 No DMF was used in Step 5 Step 6 heated for 3 hours to give only one product	RP-HPLC (basic)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 0.87 – 0.95 (m, 6H), 1.56 – 1.66 (m, 1H), 1.73 (h, <i>J</i> = 6.8 Hz, 1H), 1.85 – 1.94 (m, 1H), 2.27 (s, 3H), 3.05 – 3.13 (m, 2H), 3.22 – 3.29 (m, 1H), 3.43 – 3.51 (m, 1H), 3.52 – 3.58 (m, 1H), 3.58 – 3.65 (m, 1H), 3.79 (d, <i>J</i> = 4.0 Hz, 2H), 5.02 (s, 2H), 6.31 (d, <i>J</i> = 3.0 Hz, 1H). One exchangeable proton not observed.	m/z 293 (M+H) ⁺ (ES ⁺), at 3.04 min, 220 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
1-5	(S)-7-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	A	RP-HPLC	(500 MHz, DMSO-d ₆) δ 0.89 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 1.54 – 1.62 (m, 1H), 1.65 – 1.77 (m, 2H), 1.84 – 1.92 (m, 1H), 2.26 (d, J = 2.3 Hz, 3H), 3.01 – 3.06 (m, 1H), 3.07 – 3.11 (m, 1H), 3.21 – 3.26 (m, 1H), 3.44 – 3.51 (m, 1H), 3.52 – 3.58 (m, 1H), 3.58 – 3.64 (m, 1H), 3.79 (d, J = 4.1 Hz, 2H), 5.01 (s, 2H), 6.30 (d, J = 3.0 Hz, 1H).	System 2	m/z 293 (M+H) ⁺ (ES ⁺), at 1.11 min, 254 nm
		2, 8 and 4 No DMF was used in Step 5	(basic)		Method F	
1-6	(R)-7-Cyclopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine ditrifluoroacetic acid salt	B	RP-HPLC	(400 MHz, DMSO-d ₆) δ 0.28 – 0.42 (m, 2H), 0.42 – 0.59 (m, 2H), 0.84 – 0.96 (m, 1H), 2.00 – 2.14 (m, 1H), 2.17 – 2.31 (m, 1H), 2.62 (s, 3H), 2.86 – 2.95 (m, 1H), 3.64 – 4.09 (m, 7H), 7.13 (br. s, 2H), 7.89 (br. s, 1H), 8.91 (br. s, 3H).	System 4	m/z 291 (M+H) ⁺ (ES ⁺), at 2.33 min, 202 nm
		2, 10 and 4 DCM was used in Step 4 TFA/DCM was used in Step 7	(acidic)		Method C	
1-7	Isomer 2: 7-isobutyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	A	RP-HPLC	(500 MHz, DMSO-d ₆) δ 0.89 (d, J = 6.5 Hz, 6H), 1.17 – 1.24 (m, 1H), 1.34 – 1.42 (m, 1H), 1.66 – 1.78 (m, 2H), 1.93 – 2.01 (m, 1H), 2.36 (s, 3H), 3.21 – 3.28 (m, 1H), 3.37 – 3.43 (m, 2H), 3.45 – 3.52 (m, 1H), 3.56 – 3.68 (m, 3H), 3.83 – 3.88 (m, 1H), 5.07 (s, 2H), 6.31 – 6.35 (m, 1H), 6.52 (s, 1H).	System 2	m/z 307 (M+H) ⁺ (ES ⁺), at 1.28 min, 254 nm
		2, 11 and 4 No DMF was used in Step 5	(basic) The two diastereomers were separated		Method F	
1-8	4-((R)-3-(Methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	C Example 2-3	RP-HPLC (basic)	NMR (500 MHz, DMSO-d ₆) δ 1.58 – 1.67 (m, 1H), 1.85 – 1.95 (m, 1H), 2.27 (d, J = 2.7 Hz, 3H), 3.06 – 3.13 (m, 1H), 3.24 – 3.29 (m, 1H), 3.45 – 3.53 (m, 1H), 3.53 – 3.60 (m, 1H), 3.59 – 3.69 (m, 2H), 4.15 – 4.24 (m, 1H), 4.31 (d, J = 12.0 Hz, 1H), 5.24 (s, 2H), 7.04 (d, J = 6.0 Hz, 1H). One exchangeable proton not observed.	System 2 Method I	m/z 319 (M+H) ⁺ (ES ⁺), at 2.74 min, 220 nm

Table 3					
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method
1-9	(R)-7-(Methoxymethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	B 2, 12 and 4 TFA/DCM was used in Step 7	RP-flash (basic)	(500 MHz, DMSO-d ₆) δ 1.55 – 1.63 (m, 1H), 1.84 – 1.92 (m, 1H), 2.26 (s, 3H), 3.02 – 3.09 (m, 1H), 3.21 – 3.27 (m, 1H), 3.27 (s, 3H), 3.28 – 3.36 (m, 2H), 3.45 – 3.56 (m, 3H), 3.57 – 3.65 (m, 1H), 3.71 – 3.76 (m, 1H), 3.84 – 3.89 (m, 1H), 5.08 (s, 2H), 6.29 (d, J = 3.4 Hz, 1H). One exchangeable proton not observed.	m/z 295 (M+H) ⁺ (ES ⁺), at 1.56 min, 254 nm
1-10	(S)-7-((R)-1-Methoxyethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B 2, 14 and 4	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.14 (d, J = 6.2 Hz, 3H), 2.12 – 2.27 (m, 2H), 2.52 – 2.59 (m, 3H), 3.28 (s, 3H), 3.34 – 3.40 (m, 1H), 3.44 – 3.53 (m, 1H), 3.67 – 3.79 (m, 2H), 3.80 – 3.86 (m, 1H), 3.86 – 4.03 (m, 3H), 4.05 – 4.15 (m, 1H), 7.37 (br. s, 2H), 8.16 (br. s, 1H), 9.37 – 9.75 (m, 2H), 11.80 (br. s, 1H).	m/z 309 (M+H) ⁺ (ES ⁺), at 0.89 min, 254 nm
1-11	(S)-7-((S)-1-Methoxyethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B 2, 16 and 4	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.12 (d, J = 6.2 Hz, 3H), 2.09 – 2.18 (m, 1H), 2.18 – 2.28 (m, 1H), 2.56 (s, 3H), 3.30 (s, 3H), 3.47 – 3.55 (m, 1H), 3.64 – 3.80 (m, 2H), 3.80 – 4.10 (m, 5H), 7.29 (br. s, 2H), 7.85 (br. s, 1H), 9.19 – 9.59 (m, 2H), 11.66 (br. s, 1H). One proton obscured by water peak.	m/z 309 (M+H) ⁺ (ES ⁺), at 0.92 min, 254 nm
1-12	(S)-7-(2-Methoxypropan-2-yl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	B 2, 18 and 4 TFA/DCM was used in Step 7	RP-HPLC (basic)	(500 MHz, DMSO-d ₆) δ 1.07 (s, 3H), 1.11 (s, 3H), 1.57 – 1.65 (m, 1H), 1.85 – 1.93 (m, 1H), 2.27 (s, 3H), 3.05 – 3.11 (m, 1H), 3.14 (s, 3H), 3.23 – 3.28 (m, 1H), 3.43 – 3.50 (m, 1H), 3.53 – 3.58 (m, 1H), 3.58 – 3.64 (m, 1H), 3.68 – 3.73 (m, 1H), 3.96 – 4.01 (m, 1H), 5.07 (s, 2H), 6.04 (d, J = 3.8 Hz, 1H). Two protons obscured by water peak.	m/z 323 (M+H) ⁺ (ES ⁺), at 0.99 min, 254 nm
1-13	4-((R)-3-(Methylamino)pyrrolidin-1-yl)-7-(oxetan-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	D 2, 20 and 4	RP-HPLC (basic)	(500 MHz, DMSO-d ₆) δ 1.54 – 1.62 (m, 1H), 1.84 – 1.92 (m, 1H), 2.25 (s, 3H), 3.00 – 3.08 (m, 2H), 3.20 – 3.26 (m, 1H), 3.43 – 3.49 (m, 1H), 3.51 – 3.57 (m, 1H), 3.58 – 3.63 (m, 1H), 3.66 – 3.73 (m, 3H), 4.41 (t, J = 6.2 Hz, 1H), 4.48 (t, J = 6.1 Hz, 1H), 4.54 – 4.61 (m, 2H), 5.07 (s, 2H), 6.65 – 6.69 (m, 1H). One exchangeable proton not observed.	m/z 307 (M+H) ⁺ (ES ⁺), at 0.72 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
1-14	(R)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	E 1, 21 and 4	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.21 (s, 6H), 2.06 – 2.18 (m, 1H), 2.18 – 2.28 (m, 1H), 2.58 (s, 3H), 3.69 (s, 3H), 3.71 – 3.99 (m, 5H), 7.64 – 8.26 (m, 1H), 9.16 (br. s, 2H), 11.56 (br. s, 1H). Two exchangeable protons not observed.	System 2 Method G	m/z 279 (M+H) ⁺ (ES ⁺), at 0.94 min, 254 nm
1-15	6-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	A 2, 22 and 4 No DMF was used in Step 5	RP-flash (basic)	(500 MHz, DMSO-d ₆) δ 1.21 (d, J = 6.2 Hz, 3H), 1.54 – 1.64 (m, 1H), 1.72 (s, 1H), 1.83 – 1.93 (m, 1H), 2.26 (d, J = 2.3 Hz, 3H), 2.92 – 2.99 (m, 1H), 3.02 – 3.08 (m, 1H), 3.22 – 3.28 (m, 1H), 3.28 – 3.31 (m, 1H), 3.44 – 3.53 (m, 1H), 3.53 – 3.59 (m, 1H), 3.59 – 3.65 (m, 1H), 3.73 – 3.81 (m, 1H), 5.03 (s, 2H), 6.19 (d, J = 4.3 Hz, 1H).	System 2 Method F	m/z 265 (M+H) ⁺ (ES ⁺), at 0.84 min, 254 nm
1-16	(6S,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	E 1, 23 and 4	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.07 (d, J = 6.5 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H), 2.19 (d, J = 32.9 Hz, 2H), 2.57 (s, 3H), 3.57 – 3.64 (m, 1H), 3.65 – 3.81 (m, 2H), 3.82 – 4.01 (m, 4H), 7.89 – 8.25 (m, 2H), 9.17 – 9.61 (m, 3H), 11.97 (br. s, 1H).	System 2 Method G	m/z 279 (M+H) ⁺ (ES ⁺), at 0.91 min, 254 nm
1-17	(6R,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	E 26 and 4 Steps 3, 5, 6 and 7 only	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.15 (d, J = 6.5 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 2.11 – 2.28 (m, 2H), 2.53 – 2.59 (m, 3H), 3.23 – 3.31 (m, 1H), 3.53 – 3.61 (m, 1H), 3.67 – 3.82 (m, 2H), 3.83 – 4.05 (m, 3H), 7.33 (br. s, 2H), 7.96 (br. s, 1H), 9.32 (br. s, 1H), 9.56 (br. s, 1H), 11.77 (br. s, 1H).	System 2 Method F	m/z 279 (M+H) ⁺ (ES ⁺), at 0.97 min, 254 nm
1-18	(6S,7S)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	E 1, 27 and 4	RP-flash (neutral)	(400 MHz, DMSO-d ₆) δ 1.16 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 2.06 – 2.29 (m, 3H), 2.59 (s, 3H), 3.24 – 3.30 (m, 1H), 3.50 – 3.63 (m, 1H), 3.65 – 4.00 (m, 4H), 7.23 (br. s, 2H), 7.73 (br. s, 1H), 8.97 – 9.26 (m, 2H), 11.48 (br. s, 1H).	System 2 Method G	m/z 279 (M+H) ⁺ (ES ⁺), at 0.94 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
1-19	(6 <i>R</i> ,7 <i>S</i>)-6, 7-Dimethyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-7, 8-dihydro-6 <i>H</i> -pyrimido[5, 4- <i>b</i>][1, 4]oxazin-2-amine dihydrochloride salt	E 1, 28 and 4	RP-flash (neutral)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.07 (d, <i>J</i> = 6.5 Hz, 3H), 1.21 (d, <i>J</i> = 6.4 Hz, 3H), 2.10 – 2.28 (m, 2H), 2.57 (s, 3H), 3.57 – 3.65 (m, 1H), 3.67 – 3.81 (m, 2H), 3.83 – 4.01 (m, 4H), 7.03 – 7.43 (m, 2H), 7.89 – 8.27 (m, 1H), 9.13 – 9.53 (m, 2H), 11.93 (s, 1H).	System 2 Method G	<i>m/z</i> 279 (M+H) ⁺ (ES ⁺), at 0.94 min, 254 nm
1-20	7-Isopropyl-8-methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-7, 8-dihydro-6 <i>H</i> -pyrimido[5, 4- <i>b</i>][1, 4]oxazin-2-amine	F 30	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 0.89 (d, <i>J</i> = 6.8 Hz, 3H), 0.95 (d, <i>J</i> = 7.0 Hz, 3H), 1.52 – 1.63 (m, 1H), 1.82 – 1.94 (m, 1H), 1.95 – 2.04 (m, 1H), 2.25 (d, <i>J</i> = 4.9 Hz, 3H), 3.00 (s, 3H), 3.02 – 3.06 (m, 2H), 3.20 – 3.25 (m, 1H), 3.40 – 3.47 (m, 1H), 3.47 – 3.55 (m, 2H), 3.55 – 3.64 (m, 2H), 4.10 – 4.16 (m, 1H), 5.12 (s, 2H).	System 2 Method F	<i>m/z</i> 307 (M+H) ⁺ (ES ⁺), at 1.21 min, 254 nm
1-21	4-((<i>R</i>)-3-(Methylamino)pyrrolidin-1-yl)-6 <i>a</i> , 7, 8, 9-tetrahydro-6 <i>H</i> -pyrimido[5, 4- <i>b</i>]pyrrolo[1, 2- <i>d</i>][1, 4]oxazin-2-amine	G 1, 31 and 4	RP-flash (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.33 – 1.42 (m, 1H), 1.52 – 1.65 (m, 1H), 1.75 – 1.85 (m, 1H), 1.85 – 1.95 (m, 2H), 1.98 – 2.05 (m, 1H), 2.26 (d, <i>J</i> = 5.6 Hz, 3H), 3.00 – 3.09 (m, 2H), 3.20 – 3.28 (m, 1H), 3.40 – 3.47 (m, 2H), 3.49 – 3.57 (m, 2H), 3.57 – 3.63 (m, 1H), 3.64 – 3.68 (m, 1H), 4.27 – 4.32 (m, 1H), 5.17 (d, <i>J</i> = 2.8 Hz, 2H). One exchangeable proton not observed.	System 2 Method F	<i>m/z</i> 291 (M+H) ⁺ (ES ⁺), at 0.97 min, 254 nm
1-22	(<i>R</i>)-6 <i>a</i> -Methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6 <i>a</i> , 7, 8, 9-tetrahydro-6 <i>H</i> -pyrimido[5, 4- <i>b</i>]pyrrolo[1, 2- <i>d</i>][1, 4]oxazin-2-amine	G 1, 32 and 4	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.09 (s, 3H), 1.48 – 1.61 (m, 2H), 1.65 – 1.81 (m, 2H), 1.82 – 1.90 (m, 1H), 1.90 – 2.03 (m, 2H), 2.27 (s, 3H), 3.00 (d, <i>J</i> = 10.0 Hz, 1H), 3.02 – 3.10 (m, 1H), 3.25 – 3.31 (m, 2H), 3.45 – 3.52 (m, 1H), 3.55 (t, <i>J</i> = 7.0 Hz, 2H), 3.59 – 3.65 (m, 1H), 4.06 (d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H).	System 2 Method F	<i>m/z</i> 305 (M+H) ⁺ (ES ⁺), at 1.06 min, 254 nm
1-23	(<i>S</i>)-6 <i>a</i> -Methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6 <i>a</i> , 7, 8, 9-tetrahydro-6 <i>H</i> -pyrimido[5, 4- <i>b</i>]pyrrolo[1, 2- <i>d</i>][1, 4]oxazin-2-amine	G 1, 33 and 4	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.09 (s, 3H), 1.49 – 1.58 (m, 1H), 1.58 – 1.66 (m, 1H), 1.67 – 1.76 (m, 1H), 1.74 – 1.80 (m, 1H), 1.82 – 1.91 (m, 2H), 1.91 – 2.03 (m, 1H), 2.26 (s, 3H), 3.00 (d, <i>J</i> = 10.0 Hz, 1H), 3.04 – 3.10 (m, 1H), 3.22 – 3.35 (m, 2H), 3.42 – 3.53 (m, 2H), 3.59 – 3.64 (m, 1H), 3.65 – 3.71 (m, 1H), 4.06 (d, <i>J</i> = 9.9 Hz, 1H), 5.14 (s, 2H).	System 2 Method F	<i>m/z</i> 305 (M+H) ⁺ (ES ⁺), at 1.06 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
2-1	(R)-4-((R)-3-Aminopyrrolidin-1-yl)-7-ethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B 2, 6 and 34	RP-flash (neutral)	(400 MHz, DMSO-d ₆) δ 0.93 (t, J = 7.5 Hz, 3H), 1.46 – 1.58 (m, 2H), 1.99 – 2.11 (m, 1H), 2.13 – 2.25 (m, 1H), 3.42 – 3.50 (m, 1H), 3.67 – 3.99 (m, 7H), 7.31 (br. s, 2H), 8.13 (br. s, 1H), 8.47 (br. s, 3H), 11.83 (br. s, 1H).	System 2 Method G	m/z 265 (M+H) ⁺ (ES ⁺), at 0.87 min, 254 nm
2-2	(R)-4-((R)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	A 2, 7 and 34 No DMF was used in Step 5 Step 6 heated for 3 hours to give only one product HCl/1,4-Dioxane was used in Step 7	Solid isolated from deprotection step	(500 MHz, DMSO-d ₆) δ 0.88 – 0.99 (m, 6H), 1.75 – 1.84 (m, 1H), 2.01 – 2.10 (m, 1H), 2.13 – 2.23 (m, 1H), 3.24 – 3.31 (m, 1H), 3.68 – 4.00 (m, 7H), 7.37 (s, 2H), 8.20 (s, 1H), 8.52 (s, 3H). One exchangeable proton not observed.	System 2 Method G	m/z 279 (M+H) ⁺ (ES ⁺), at 0.97 min, 254 nm
2-3	4-((R)-3-Aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	A 2, 36 and 34 No DMF was used in Step 5	RP-flash (basic)	(500 MHz, DMSO-d ₆) δ 1.51 – 1.61 (m, 1H), 1.85 – 1.94 (m, 1H), 3.17 – 3.25 (m, 1H), 3.40 – 3.45 (m, 1H), 3.46 – 3.54 (m, 1H), 3.56 – 3.70 (m, 3H), 4.15 – 4.24 (m, 1H), 4.31 (d, J = 12.1 Hz, 1H), 5.24 (s, 2H), 7.04 (d, J = 6.0 Hz, 1H). Two exchangeable protons not observed.	System 2 Method F	m/z 305 (M+H) ⁺ (ES ⁺), at 0.87 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
2-4	(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-((R)-1-methoxyethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B 2, 14 and 34	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.13 (d, J = 6.2 Hz, 3H), 1.98 – 2.13 (m, 1H), 2.13 – 2.25 (m, 1H), 3.27 (s, 3H), 3.32 – 3.38 (m, 1H), 3.45 – 3.52 (m, 1H), 3.65 – 3.99 (m, 6H), 4.06 – 4.12 (m, 1H), 7.38 (br. s, 2H), 8.18 (br. s, 1H), 8.52 (br. s, 3H), 11.85 (br. s, 1H).	System 2 Method G	m/z 295 (M+H) ⁺ (ES ⁺), at 0.80 min, 254 nm
2-5	(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-((S)-1-methoxyethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B 2, 16 and 34	RP-flash (neutral)	(500 MHz, DMSO-d ₆) δ 1.12 (d, J = 6.2 Hz, 3H), 1.95 – 2.10 (m, 1H), 2.12 – 2.25 (m, 1H), 3.30 (s, 3H), 3.33 – 3.39 (m, 1H), 3.48 – 3.55 (m, 1H), 3.68 – 4.05 (m, 7H), 7.25 (br. s, 2H), 7.82 (br. s, 1H), 8.38 (br. s, 3H), 11.68 (br. s, 1H).	System 2 Method G	m/z 295 (M+H) ⁺ (ES ⁺), at 0.87 min, 254 nm
2-6	(S)-4-((R)-3-Aminopyrrolidin-1-yl)-7-(2-methoxypropan-2-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	B 2, 18 and 34 TFA/DCM was used in Step 7	RP-HPLC (basic)	(500 MHz, DMSO-d ₆) δ 1.07 (s, 3H), 1.11 (s, 3H), 1.46 – 1.54 (m, 1H), 1.81 – 1.89 (m, 1H), 3.10 – 3.14 (m, 1H), 3.14 (s, 3H), 3.30 – 3.34 (m, 1H), 3.34 – 3.41 (m, 1H), 3.43 – 3.49 (m, 1H), 3.55 – 3.60 (m, 1H), 3.60 – 3.65 (m, 1H), 3.68 – 3.74 (m, 1H), 3.96 – 4.01 (m, 1H), 5.05 (s, 2H), 6.02 (d, J = 3.8 Hz, 1H). Two exchangeable protons not observed.	System 2 Method F	m/z 309 (M+H) ⁺ (ES ⁺), at 0.91 min, 254 nm
3-1	(R)-7-Ethyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine ditrifluoroacetic acid salt	B 2, 6 and 37 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.90 (t, J = 7.4 Hz, 3H), 1.44 – 1.55 (m, 2H), 2.56 (s, 3H), 3.39 – 3.47 (m, 1H), 3.76 – 3.82 (m, 1H), 3.89 – 3.95 (m, 1H), 3.99 – 4.08 (m, 1H), 4.22 (s, 2H), 4.37 – 4.51 (m, 2H). Four exchangeable protons not observed.	System 4 Method C	m/z 265 (M+H) ⁺ (ES ⁺), at 2.21 min, 202 nm
3-2	(R)-7-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	A 2, 7 and 37	RP-HPLC (basic)	(400 MHz, DMSO-d ₆) δ 0.86 – 0.94 (m, 6H), 1.68 – 1.78 (m, 1H), 2.19 (s, 3H), 3.05 – 3.11 (m, 1H), 3.37 – 3.45 (m, 1H), 3.59 – 3.65 (m, 2H), 3.74 – 3.83 (m, 2H), 4.00 – 4.07 (m, 2H), 5.13 (s, 2H), 6.43 (d, J = 2.9 Hz, 1H). One exchangeable proton not observed.	System 2 Method F	m/z 279 (M+H) ⁺ (ES ⁺), at 0.98 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
3-3	(R)-7-Cyclopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine ditrifluoroacetic acid salt	B	RP-HPLC	(400 MHz, Methanol-d ₄) δ 0.32 – 0.40 (m, 1H), 0.40 – 0.48 (m, 1H), 0.54 – 0.70 (m, 2H), 0.87 – 0.98 (m, 1H), 2.73 (s, 3H), 2.80 – 2.88 (m, 1H), 3.87 – 3.95 (m, 1H), 4.09 – 4.19 (m, 2H), 4.28 – 4.42 (m, 2H), 4.54 – 4.68 (m, 2H). Four exchangeable protons not observed.	System 4	m/z 277 (M+H) ⁺ (ES ⁺), at 2.36 min, 301 nm
		2, 10 and 37	(acidic)		Method C	
3-4	(S)-7-((R)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine dihydrochloride salt	B	TFA salt neutralized using PL-HCO ₃ MP SPE and converted to HCl salt using 2 M aq. HCl	(500 MHz, DMSO-d ₆) δ 1.13 (d, J = 6.3 Hz, 3H), 2.51 (s, 3H), 3.27 (s, 3H), 3.32 – 3.39 (m, 1H), 3.44 – 3.52 (m, 1H), 3.78 – 3.86 (m, 1H), 3.99 – 4.11 (m, 2H), 4.25 – 4.59 (m, 4H), 7.36 (s, 2H), 8.29 (s, 1H), 9.92 (s, 2H). One exchangeable proton not observed.	System 2	m/z 295 (M+H) ⁺ (ES ⁺), at 0.82 min, 254 nm
		2, 14 and 37			Method G	
3-5	(S)-7-((S)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	B	RP-HPLC	(500 MHz, DMSO-d ₆) δ 1.07 (d, J = 6.2 Hz, 3H), 2.19 (s, 3H), 3.27 (s, 3H), 3.29 – 3.43 (m, 3H), 3.58 – 3.64 (m, 2H), 3.77 – 3.86 (m, 2H), 4.00 – 4.06 (m, 2H), 5.20 (s, 2H), 6.18 (d, J = 2.7 Hz, 1H). One exchangeable proton not observed.	System 2	m/z 295 (M+H) ⁺ (ES ⁺), at 0.85 min, 254 nm
		2, 16 and 37	(basic)		Method F	
3-6	(S)-7-(2-Methoxypropan-2-yl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	B	RP-HPLC	(500 MHz, DMSO-d ₆) δ 1.06 (s, 3H), 1.11 (s, 3H), 2.19 (s, 3H), 3.14 (s, 3H), 3.28 – 3.35 (m, 1H), 3.37 – 3.43 (m, 1H), 3.58 – 3.64 (m, 2H), 3.69 – 3.74 (m, 1H), 3.95 – 3.99 (m, 1H), 4.00 – 4.07 (m, 2H), 5.18 (s, 2H), 6.15 (d, J = 3.6 Hz, 1H). One exchangeable proton not observed.	System 2	m/z 309 (M+H) ⁺ (ES ⁺), at 0.90 min, 254 nm
		2, 18 and 37	(basic)		Method F	
4-1	(R)-4-(3-Aminoazetidin-1-yl)-7-ethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine ditrifluoroacetic acid salt	B	RP-HPLC	(400 MHz, DMSO-d ₆) δ 0.92 (t, J = 7.5 Hz, 3H), 1.44 – 1.57 (m, 2H), 3.76 – 3.84 (m, 1H), 3.91 – 3.98 (m, 1H), 4.03 – 4.22 (m, 3H), 4.36 – 4.51 (m, 2H), 7.15 (br. s, 2H), 7.99 (br. s, 1H), 8.42 (br. s, 3H), 11.99 (br. s, 1H). One proton obscured by water peak.	System 4	m/z 251 (M+H) ⁺ (ES ⁺), at 2.01 min, 202 nm
		2, 6 and 38	(acidic)		Method C	

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
4-2	(<i>R</i>)-4-(3-Aminoazetidin-1-yl)-7-isopropyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 2, 7 and 38 No DMF was used in Step 5	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 0.87 – 0.95 (m, 6H), 1.69 – 1.77 (m, 1H), 3.06 – 3.11 (m, 1H), 3.50 – 3.56 (m, 2H), 3.59 – 3.66 (m, 1H), 3.74 – 3.82 (m, 2H), 4.03 – 4.08 (m, 2H), 5.13 (s, 2H), 6.41 (d, <i>J</i> = 2.8 Hz, 1H). Two exchangeable protons not observed.	System 2 Method G	<i>m/z</i> 265 (M+H) ⁺ (ES ⁺), at 0.88 min, 254 nm
5-1	(<i>R</i>)-7-Isopropyl-4-(4-methylpiperazin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 2, 7 and 39 No DMF was used in Step 5	RP-HPLC (basic)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 0.87 – 0.94 (m, 6H), 1.69 – 1.78 (m, 1H), 2.16 (s, 3H), 2.27 – 2.34 (m, 4H), 3.08 – 3.13 (m, 1H), 3.36 – 3.47 (m, 4H), 3.80 – 3.87 (m, 2H), 5.15 (s, 2H), 6.57 (d, <i>J</i> = 3.1 Hz, 1H).	System 2 Method F	<i>m/z</i> 293 (M+H) ⁺ (ES ⁺), at 1.11 min, 254 nm
6-1	(<i>R</i>)-7-Isopropyl-4-(piperazin-1-yl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-2-amine	A 2, 7 and 40 No DMF was used in Step 5	RP-HPLC (basic)	(400 MHz, DMSO- <i>d</i> ₆) δ 0.87 – 0.95 (m, 6H), 1.68 – 1.79 (m, 1H), 2.65 – 2.74 (m, 4H), 3.06 – 3.13 (m, 1H), 3.32 – 3.36 (m, 4H), 3.79 – 3.87 (m, 2H), 5.13 (s, 2H), 6.53 (d, <i>J</i> = 3.0 Hz, 1H). One exchangeable proton not observed.	System 2 Method I	<i>m/z</i> 279 (M+H) ⁺ (ES ⁺), at 2.80 min, 220 nm
7-1	(<i>R</i>)-1-((<i>R</i>)-7-Isopropyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)- <i>N</i> -methylpyrrolidin-3-amine	H 41	RP-HPLC (basic)	(500 MHz, Chloroform- <i>d</i>) δ 0.96 – 1.05 (m, 6H), 1.71 – 1.85 (m, 2H), 2.04 – 2.12 (m, 1H), 2.47 (s, 3H), 3.21 – 3.29 (m, 2H), 3.49 – 3.54 (m, 1H), 3.67 – 3.75 (m, 1H), 3.78 – 3.89 (m, 3H), 4.06 – 4.11 (m, 1H), 4.94 (s, 1H), 7.81 (s, 1H). One exchangeable proton not observed.	System 2 Method G	<i>m/z</i> 278 (M+H) ⁺ (ES ⁺), at 1.09 min, 254 nm
7-2	(<i>R</i>)-1-((<i>R</i>)-7-Cyclopropyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)- <i>N</i> -methylpyrrolidin-3-amine	I 42	RP-HPLC (basic)	(400 MHz, DMSO- <i>d</i> ₆) δ 0.25 – 0.36 (m, 2H), 0.36 – 0.51 (m, 2H), 0.79 – 0.90 (m, 1H), 1.57 – 1.70 (m, 1H), 1.85 – 1.97 (m, 1H), 2.26 (s, 3H), 2.74 – 2.82 (m, 1H), 3.04 – 3.13 (m, 1H), 3.30 – 3.36 (m, 1H), 3.50 – 3.63 (m, 2H), 3.63 – 3.70 (m, 1H), 3.81 – 3.91 (m, 1H), 3.94 – 4.04 (m, 1H), 6.89	System 4 Method C	<i>m/z</i> 276 (M+H) ⁺ (ES ⁺), at 2.39 min, 202 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
				(s, 1H), 7.61 (s, 1H). One exchangeable proton not observed.		
7-3	(3 <i>R</i>)-1-(7-(Methoxymethyl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)- <i>N</i> -methylpyrrolidin-3-amine	H 44	RP-flash (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.60 – 1.67 (m, 1H), 1.74 (br. s, 1H), 1.87 – 1.95 (m, 1H), 2.26 (s, 3H), 3.06 – 3.12 (m, 1H), 3.28 (s, 3H), 3.32 – 3.36 (m, 3H), 3.51 – 3.58 (m, 1H), 3.58 – 3.64 (m, 2H), 3.64 – 3.69 (m, 1H), 3.84 – 3.89 (m, 1H), 3.93 – 3.99 (m, 1H), 6.80 – 6.85 (m, 1H), 7.61 (s, 1H).	System 2 Method F	m/z 280 (M+H) ⁺ (ES ⁺), at 0.86 min, 254 nm
7-4	(<i>R</i>)-1-((<i>S</i>)-7-((<i>R</i>)-1-Methoxyethyl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)- <i>N</i> -methylpyrrolidin-3-amine hydrochloride salt	H 45 HCl/1,4-Dioxane was used in Step 2	RP-flash (neutral)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.15 (d, <i>J</i> = 6.2 Hz, 3H), 2.14 – 2.22 (m, 1H), 2.22 – 2.30 (m, 1H), 2.58 (t, <i>J</i> = 5.4 Hz, 3H), 3.29 (s, 3H), 3.37 – 3.43 (m, 1H), 3.56 – 3.61 (m, 1H), 3.71 – 3.83 (m, 2H), 3.90 – 4.01 (m, 4H), 4.17 – 4.23 (m, 1H), 8.06 (s, 1H), 8.35 (s, 1H), 9.27 (s, 1H), 9.39 (s, 1H).	System 2 Method G	m/z 294 (M+H) ⁺ (ES ⁺), at 0.92 min, 254 nm
7-5	(3 <i>R</i>)- <i>N</i> -Methyl-1-(6-methyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)pyrrolidin-3-amine	H 46	RP-HPLC (basic)	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 1.32 – 1.37 (m, 3H), 1.70 – 1.81 (m, 1H), 2.03 – 2.13 (m, 1H), 2.47 (d, <i>J</i> = 1.8 Hz, 3H), 3.19 – 3.24 (m, 1H), 3.24 – 3.29 (m, 1H), 3.43 – 3.49 (m, 1H), 3.50 – 3.56 (m, 1H), 3.69 – 3.76 (m, 1H), 3.79 – 3.91 (m, 2H), 4.00 – 4.08 (m, 1H), 4.75 (s, 1H), 7.82 (d, <i>J</i> = 0.8 Hz, 1H). One exchangeable proton not observed.	System 2 Method G	m/z 250 (M+H) ⁺ (ES ⁺), at 0.88 min, 254 nm
8-1	(<i>R</i>)-1-((<i>R</i>)-7-Isopropyl-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-yl)pyrrolidin-3-amine	H 47	RP-HPLC (basic)	(500 MHz, Chloroform- <i>d</i>) δ 0.97 – 1.04 (m, 6H), 1.64 – 1.73 (m, 1H), 1.75 – 1.86 (m, 1H), 2.03 – 2.12 (m, 1H), 3.21 – 3.27 (m, 1H), 3.40 – 3.46 (m, 1H), 3.57 – 3.63 (m, 1H), 3.68 – 3.75 (m, 1H), 3.80 – 3.90 (m, 3H), 4.06 – 4.11 (m, 1H), 4.90 (s, 1H), 7.81 (s, 1H). Two exchangeable protons not observed.	System 2 Method G	m/z 264 (M+H) ⁺ (ES ⁺), at 1.00 min, 254 nm
8-2	(<i>R</i>)-1-((<i>S</i>)-7-((<i>R</i>)-1-Methoxyethyl)-7,8-dihydro-6 <i>H</i> -pyrimido[5,4- <i>b</i>][1,4]oxazin-4-	H 48	RP-flash (neutral)	(500 MHz, DMSO- <i>d</i> ₆) δ 1.15 (d, <i>J</i> = 6.2 Hz, 3H), 2.07 – 2.14 (m, 1H), 2.18 – 2.27 (m, 1H), 3.29 (s, 3H), 3.36 – 3.44 (m, 1H), 3.58 – 3.65 (m, 1H), 3.75 – 3.83 (m, 1H), 3.83 – 3.89 (m, 1H), 3.89 – 4.01 (m, 4H), 4.17 – 4.23 (m, 1H), 8.11 (s, 1H), 8.58 (br. s, 4H).	System 2 Method G	m/z 280 (M+H) ⁺ (ES ⁺), at 0.83 min, 254 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
	y)pyrrolidin-3-amine hydrochloride salt	HCl/1,4-Dioxane was used in Step 2				
9-1	(R)-1-(7-Isopropyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)-N-methylazetidin-3-amine	H 49	RP-HPLC (basic)	(500 MHz, Chloroform- <i>d</i>) δ 0.99 – 1.05 (m, 6H), 1.86 – 1.94 (m, 1H), 2.81 (s, 3H), 3.39 – 3.44 (m, 1H), 3.99 – 4.06 (m, 1H), 4.07 – 4.12 (m, 1H), 4.13 – 4.21 (m, 1H), 4.53 – 4.61 (m, 2H), 4.61 – 4.70 (m, 2H), 7.94 (s, 1H), 8.45 (s, 1H). One exchangeable proton not observed.	System 2 Method G	m/z 264 (M+H) ⁺ (ES ⁺), at 1.02 min, 254 nm
10-1	(3R)-1-(7-Isopropyl-2-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-4-yl)-N-methylpyrrolidin-3-amine	J 30	RP-HPLC (basic)	(500 MHz, DMSO- <i>d</i> ₆) δ 0.88 – 0.95 (m, 6H), 1.57 – 1.65 (m, 1H), 1.69 – 1.79 (m, 1H), 1.85 – 1.93 (m, 1H), 2.11 (s, 3H), 2.26 (s, 3H), 3.04 – 3.10 (m, 1H), 3.12 – 3.16 (m, 1H), 3.27 – 3.32 (m, 1H), 3.48 – 3.55 (m, 1H), 3.56 – 3.61 (m, 1H), 3.61 – 3.67 (m, 1H), 3.82 – 3.90 (m, 2H), 6.75 (s, 1H). One exchangeable proton not observed.	System 2 Method F	m/z 292 (M+H) ⁺ (ES ⁺), at 1.15 min, 254 nm
11-1	(R)-4-(3-(Methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine	A 2, 50 and 4 No DMF was used in Step 5	RP-HPLC (basic)	(400 MHz, DMSO- <i>d</i> ₆) δ 1.56 – 1.68 (m, 1H), 1.79 – 1.87 (m, 2H), 1.87 – 1.95 (m, 1H), 2.27 (s, 3H), 3.04 – 3.10 (m, 2H), 3.20 – 3.27 (m, 2H), 3.42 – 3.51 (m, 1H), 3.51 – 3.57 (m, 1H), 3.57 – 3.63 (m, 1H), 3.80 (t, <i>J</i> = 5.8 Hz, 2H), 5.20 (s, 2H), 5.52 (s, 1H). One exchangeable proton not observed.	System 2 Method F	m/z 265 (M+H) ⁺ (ES ⁺), at 0.78 min, 254 nm
11-2	(R)-8-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 51 and 4 DCM was used in Step 4	RP-HPLC (acidic)	(400 MHz, DMSO- <i>d</i> ₆) δ 1.25 (d, <i>J</i> = 6.6 Hz, 3H), 1.81 – 1.94 (m, 1H), 1.97 – 2.13 (m, 2H), 2.19 – 2.30 (m, 1H), 2.63 (s, 3H), 3.62 – 3.97 (m, 7H), 4.04 – 4.14 (m, 1H), 6.82 (br. s, 1H), 7.26 (br. s, 2H), 8.83 – 9.16 (m, 2H), 11.61 (br. s, 1H).	System 4 Method C	m/z 279 (M+H) ⁺ (ES ⁺), at 2.09 min, 202 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
		TFA/DCM was used in Step 7				
11-3	(S)-8-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	2, 52 and 4 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 1.25 (d, J = 6.6 Hz, 3H), 1.82 – 1.94 (m, 1H), 1.97 – 2.16 (m, 2H), 2.16 – 2.29 (m, 1H), 2.63 (s, 3H), 3.60 – 3.98 (m, 7H), 4.02 – 4.14 (m, 1H), 6.71 (s, 1H), 7.18 (s, 2H), 8.67 – 8.92 (m, 2H). One exchangeable proton not observed.	System 4 Method C	m/z 279 (M+H) ⁺ (ES ⁺), at 2.29 min, 297 nm
11-4	(R)-8-Ethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	2, 54 and 4 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, Methanol-d ₄) δ 1.04 (t, J = 7.4 Hz, 3H), 1.60 – 1.80 (m, 2H), 1.91 – 2.03 (m, 1H), 2.10 – 2.23 (m, 2H), 2.35 – 2.48 (m, 1H), 2.78 (s, 3H), 3.66 – 3.75 (m, 1H), 3.80 – 3.90 (m, 2H), 3.91 – 4.00 (m, 2H), 4.00 – 4.10 (m, 2H), 4.15 – 4.24 (m, 1H). Six exchangeable protons not observed.	System 3 Method A	m/z 293 (M+H) ⁺ (ES ⁺), at 2.03 min, 310 nm
11-5	(S)-8-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	2, 56 and 4 DCM was used in Step 4	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.94 (t, J = 6.8 Hz, 6H), 1.85 – 2.03 (m, 3H), 2.05 – 2.15 (m, 1H), 2.18 – 2.30 (m, 1H), 2.63 (s, 3H), 3.50 – 3.58 (m, 1H), 3.60 – 3.93 (m, 5H), 3.93 – 4.04 (m, 1H), 4.05 – 4.15 (m, 1H), 6.67 (br. s, 1H), 7.28 (br. s, 2H), 8.83 – 9.13 (m, 2H), 11.61 (br. s, 1H).	System 4 Method C	m/z 307 (M+H) ⁺ (ES ⁺), at 2.57 min, 202 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
		TFA/DCM was used in Step 7				
11-6	(<i>R</i>)-8-Isopropyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4- <i>b</i>][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 58 and 4 DCM was used in Step 4	RP-HPLC (acidic)	(400 MHz, DMSO- <i>d</i> ₆) δ 0.94 (t, <i>J</i> = 6.6 Hz, 6H), 1.84 – 2.03 (m, 3H), 2.06 – 2.16 (m, 1H), 2.17 – 2.29 (m, 1H), 2.62 (s, 3H), 3.53 – 3.62 (m, 1H), 3.64 – 3.93 (m, 5H), 3.95 – 4.04 (m, 1H), 4.05 – 4.14 (m, 1H), 6.65 (s, 1H), 7.30 (s, 2H), 8.89 (d, <i>J</i> = 46.1 Hz, 2H), 11.46 (s, 1H).	System 3 Method A	<i>m/z</i> 307 (M+H) ⁺ (ES ⁺), at 2.16 min, 310 nm
11-7	7-Methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4- <i>b</i>][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 59 and 4 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, Methanol- <i>d</i> ₄) δ 1.00 (d, <i>J</i> = 6.9 Hz, 3H), 2.13 – 2.25 (m, 1H), 2.30 – 2.46 (m, 2H), 2.78 (s, 3H), 3.22 – 3.29 (m, 1H), 3.46 – 3.55 (m, 1H), 3.62 – 3.70 (m, 1H), 3.78 – 3.91 (m, 2H), 3.91 – 4.08 (m, 3H), 4.18 – 4.26 (m, 1H). Six exchangeable protons not observed.	System 4 Method C	<i>m/z</i> 279 (M+H) ⁺ (ES ⁺), at 2.23 min, 202 nm
11-8	7-Ethyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4- <i>b</i>][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 62 and 4 Step 3 conducted at RT DCM was used in Step 4	RP-HPLC (acidic)	(400 MHz, Methanol- <i>d</i> ₄) δ 0.97 (t, <i>J</i> = 7.5 Hz, 3H), 1.33 – 1.51 (m, 2H), 2.07 – 2.28 (m, 2H), 2.32 – 2.48 (m, 1H), 2.77 (s, 3H), 3.32 – 3.41 (m, 1H), 3.47 – 3.61 (m, 1H), 3.71 – 4.13 (m, 6H), 4.16 – 4.33 (m, 1H). Six exchangeable protons not observed.	System 4 Method C	<i>m/z</i> 293 (M+H) ⁺ (ES ⁺), at 2.28 min, 202 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
		TFA/DCM was used in Step 7				
11-9	7-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	2, 64 and 4 Steps 3 and 5 conducted at RT DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.81 – 0.95 (m, 6H), 1.56 – 1.69 (m, 1H), 1.93 – 2.04 (m, 1H), 2.04 – 2.16 (m, 1H), 2.16 – 2.29 (m, 1H), 2.63 (s, 3H), 3.42 – 3.48 (m, 2H), 3.61 – 3.70 (m, 1H), 3.72 – 3.94 (m, 5H), 4.07 – 4.15 (m, 1H), 7.21 (s, 3H), 8.61 – 9.28 (m, 2H), 11.87 (s, 1H).	System 4 Method C	m/z 307 (M+H) ⁺ (ES ⁺), at 2.61 min, 202 nm
11-10	(S)-4-((R)-3-(Methylamino)pyrrolidin-1-yl)-6,7,7a,8,9,10-hexahydropyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazepin-2-amine	K 2, 66 and 4	RP-flash (neutral) then RP-flash (basic)	(500 MHz, DMSO-d ₆) δ 1.48 – 1.57 (m, 1H), 1.59 – 1.67 (m, 1H), 1.67 – 1.75 (m, 1H), 1.76 – 1.84 (m, 1H), 1.84 – 1.94 (m, 2H), 1.96 – 2.03 (m, 1H), 2.04 – 2.11 (m, 1H), 2.26 (s, 3H), 3.04 – 3.10 (m, 1H), 3.23 – 3.28 (m, 1H), 3.35 – 3.42 (m, 2H), 3.44 – 3.54 (m, 2H), 3.55 – 3.60 (m, 1H), 3.77 – 3.84 (m, 1H), 3.84 – 3.90 (m, 2H), 5.21 (s, 2H). One exchangeable proton not observed.	System 2 Method F	m/z 305 (M+H) ⁺ (ES ⁺), at 1.03 min, 254 nm
12-1	(S)-4-((R)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 56 and 34 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.94 (t, J = 6.8 Hz, 6H), 1.82 – 2.06 (m, 4H), 2.10 – 2.26 (m, 1H), 3.63 – 3.92 (m, 6H), 3.94 – 4.03 (m, 1H), 4.04 – 4.14 (m, 1H), 6.65 (br. s, 1H), 7.31 (br. s, 2H), 8.14 (br. s, 3H), 11.44 (br. s, 1H).	System 3 Method A	m/z 293 (M+H) ⁺ (ES ⁺), at 2.21 min, 225 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
12-2	(R)-4-((R)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 58 and 34 DCM was used in Step 4	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.94 (t, J = 6.5 Hz, 6H), 1.83 – 2.08 (m, 4H), 2.11 – 2.28 (m, 1H), 3.52 – 3.62 (m, 1H), 3.64 – 3.92 (m, 5H), 3.93 – 4.03 (m, 1H), 4.04 – 4.14 (m, 1H), 6.60 (br. s, 1H), 7.28 (br. s, 2H), 8.10 (br. s, 3H), 11.35 (br. s, 1H).	System 3 Method A	m/z 293 (M+H) ⁺ (ES ⁺), at 2.29 min, 202 nm
13-1	(S)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 56 and 37 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.93 (t, J = 6.2 Hz, 6H), 1.82 – 2.05 (m, 3H), 2.59 (s, 3H), 3.46 – 3.58 (m, 1H), 3.89 – 4.00 (m, 1H), 4.00 – 4.13 (m, 2H), 4.14 – 4.60 (m, 4H), 6.70 (br. s, 1H), 7.27 (br. s, 2H), 9.29 (br. s, 2H). One exchangeable proton not observed.	System 3 Method A	m/z 293 (M+H) ⁺ (ES ⁺), at 1.94 min, 254 nm
13-2	(R)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt	B 2, 58 and 37 DCM was used in Step 4 TFA/DCM was used in Step 7	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.93 (t, J = 5.9 Hz, 6H), 1.84 – 2.05 (m, 3H), 2.59 (s, 3H), 3.46 – 3.55 (m, 1H), 3.81 – 4.60 (m, 4H), 3.89 – 3.99 (m, 1H), 4.00 – 4.13 (m, 2H), 6.63 (br. s, 1H), 7.30 (br. s, 2H), 9.16 (br. s, 2H). One exchangeable proton not observed.	System 3 Method A	m/z 293 (M+H) ⁺ (ES ⁺), at 2.09 min, 202 nm
14-1	(R)-1-((S)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-4-yl)-N-methylpyrrolidin-3-amine trifluoroacetic acid salt	H 67	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.87 – 0.99 (m, 6H), 1.79 – 1.90 (m, 1H), 1.91 – 2.11 (m, 3H), 2.19 – 2.31 (m, 1H), 2.63 (s, 3H), 3.29 – 3.38 (m, 1H), 3.61 – 3.70 (m, 1H), 3.71 – 3.86 (m, 4H), 3.94 – 4.04 (m, 1H), 4.12 – 4.22 (m, 1H), 6.43 (br. s, 1H), 7.89 (s, 1H), 8.73 – 8.96 (m, 2H).	System 3 Method B	m/z 292 (M+H) ⁺ (ES ⁺), at 1.24 min, 240 nm
14-2	(R)-1-((R)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-4-yl)-N-dioxane was	H 68	RP-HPLC (acidic)	(400 MHz, DMSO-d ₆) δ 0.88 – 1.00 (m, 6H), 1.87 – 2.00 (m, 2H), 2.01 – 2.19 (m, 2H), 2.20 – 2.31 (m, 1H), 2.64 (s, 3H), 3.49 – 3.60 (m, 1H), 3.65 – 3.76 (m, 1H), 3.76 – 3.86 (m, 3H), 3.87 – 3.96 (m, 1H), 4.06 – 4.16 (m, 1H), 4.16 –	System 3 Method A	m/z 292 (M+H) ⁺ (ES ⁺), at 2.13 min, 241 nm

Table 3					
Ex. No.	Name	Synthetic Route and Intermediate Used	Isolation or Purification Method *	¹ H NMR	LCMS data
	methylpyrrolidin-3-amine trifluoroacetic acid salt			4.24 (m, 1H), 7.20 (s, 1H), 8.09 (s, 1H), 8.68 – 9.07 (m, 2H).	
17-1	4-((R)-3-(methylamino)pyrrolidin-1-yl)-6a,7,8,9,9a,10-hexahydro-6H-cyclopenta[e]pyrimido[5,4-b][1,4]oxazepin-2-amine ditrifluoroacetic acid salt				m/z 305 (M+H) ⁺ (ES ⁺), at 1.20 min, 226 nm
17-2	4-((R)-3-aminopyrrolidin-1-yl)-6a,7,8,9,9a,10-hexahydro-6H-cyclopenta[e]pyrimido[5,4-b][1,4]oxazepin-2-amine				m/z 291 (M+H) ⁺ (ES ⁺), at 1.18 min, 226 nm
17-3	4-(3-(methylamino)azetidin-1-yl)-6a,7,8,9,9a,10-hexahydro-6H-cyclopenta[e]pyrimido[5,4-b][1,4]oxazepin-2-amine				m/z 291 (M+H) ⁺ (ES ⁺), 1.21 min, at 225 nm
17-4	(R)-4'-(3-(methylamino)pyrrolidin-1-yl)-6'H,8'H-spiro[cyclobutane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine				m/z 291 (M+H) ⁺ (ES ⁺), at 1.16 min, 226 nm
17-5	(R)-7,7-dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine				m/z 293 (M+H) ⁺ (ES ⁺), at 1.17 min, 229 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate _s Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
17-6	(<i>R</i>)-8-ethyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine				System 5 Method J	m/z 279 (M+H) ⁺ (ES ⁺), at 1.17 min, 225 nm
17-7	(<i>R</i>)-4-((<i>R</i>)-3-aminopyrrolidin-1-yl)-8-ethyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine dihydrochloride salt				System 5 Method J	m/z 279 (M+H) ⁺ (ES ⁺), at 1.15 min, 226 nm
17-8	(<i>R</i>)-8-ethyl-4-((4a <i>R</i> ,7a <i>R</i>)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine				System 5 Method J	m/z 319 (M+H) ⁺ (ES ⁺), at 1.19 min, 229 nm
17-9	(3 <i>R</i>)-1-(8-ethyl-8-methyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-4-yl)-N-methylpyrrolidin-3-amine				System 5 Method J	m/z 292 (M+H) ⁺ (ES ⁺), at 1.22 min, 235 nm
17-10	8-ethyl-8-methyl-4-((<i>R</i>)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]oxazepin-2-amine				System 5 Method J	m/z 307 (M+H) ⁺ (ES ⁺), at 1.20 min, 226 nm

Table 3						
Ex. No.	Name	Synthetic Route and Intermediate S Used	Isolation or Purification Method *	¹ H NMR	LCMS System and Method	LCMS data
17-11	(R)-4'-(3-(methylamino)pyrrolidin-1-yl)-6'H,8'H-spiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2-amine				System 5 Method J	m/z 305 (M+H) ⁺ (ES ⁺), at 1.21 min, 228 nm
17-12	(R)-N-methyl-1-(6'H,8'H-spiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-4'-yl)pyrrolidin-3-amine				System 5 Method J	m/z 290 (M+H) ⁺ (ES ⁺), at 1.22 min, 234 nm
17-13	(R)-1-(3,3-difluoro-6'H,8'H-spiro[cyclobutane-1,7'-pyrimido[5,4-b][1,4]oxazin]-4'-yl)-N-methylpyrrolidin-3-amine				System 5 Method J	m/z 312 (M+H) ⁺ (ES ⁺), at 1.20 min, 232 nm
17-14	(R)-7-ethyl-7-methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine				System 5 Method J	m/z 293 (M+H) ⁺ (ES ⁺), at 1.19 min, 225 nm
17-15	(R)-3,3-difluoro-4'-(3-(methylamino)pyrrolidin-1-yl)-6'H,8'H-spiro[cyclobutane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2-amine				System 5 Method J	m/z 327 (M+H) ⁺ (ES ⁺), at 1.19 min, 225 nm

* For the purification methods: basic=using high pH aqueous eluent (with (NH₄)₂CO₃ or NH₄HCO₃); acidic=using low pH aqueous eluent (with HCO₂H or TFA); neutral=using water.

BIOLOGICAL ACTIVITY**H4 Antagonist Functional cAMP Gi Assay**

HEKf cells were infected overnight using baculovirus expressing the human H4 receptor, then centrifuged at 1,200 rpm for 5 min, frozen in cell freezing medium (Sigma) and stored at -150 °C. On the day of assay, the cells were thawed and resuspended in HBSS with 500 nM IBMX to achieve a density of 1,500 cells/well. H4 ligands were prepared in DMSO and stamped by LabCytE ECHO acoustic dispensing at 25 nL in low volume plates. 10 µL/well cells were plated in the presence of 1 µM forskolin, subjected to centrifugation at 1,200 rpm for 1 min and incubated for 30 min prior to addition of Cisbio cAMP detection reagents to a total volume 20 µL/well. For the antagonist assay, cells were pre-incubated with H4 antagonist ligands for 30 min prior to addition of EC₈₀ concentration of histamine and a further 30 min incubation. Following detection reagent addition and shaking at room temperature for 60 min, cAMP accumulation was measured using HTRF on a PheraStar plate reader. EC₅₀ values were generated using a 4-parameter logistical fit equation to quantify agonist potencies. Functional antagonist affinity values were generated using the Cheng-Prusoff equation to calculate a pK_b value using the antagonist assay data.

H4 Antagonist Functional Dynamic Mass Redistribution Assay

HEKf cells were infected using baculovirus expressing the human H4 receptor, plated into fibronectin-coated EPIC plates at a density of 10,000 cells/well and incubated overnight at 37 °C. The medium on cells was changed to 30 µL HBSS with 20 mM HEPES per well and 30 nL DMSO were added per well by LabCytE ECHO acoustic dispensing. Following 2 h equilibration at room temperature, 30 nL of H4 ligands prepared in DMSO were stamped by LabCytE ECHO acoustic dispensing into seeded EPIC plates and cellular dynamic mass redistribution was monitored using a Corning EPIC plate reader. Following 45 min measurement, 30 nL/well of histamine EC₈₀ was added and monitored to obtain antagonist assay data. Maximum baseline-corrected responses in pm were used to generate concentration response curves. EC₅₀ values were generated using a 4-parameter logistical fit equation to quantify agonist potencies. Functional antagonist affinity values were generated using the Cheng-Prusoff equation to calculate a pK_b value using the antagonist assay data.

hERG Assay

hERG assay data was determined by Metrion Biosciences, Cambridge, UK, using the experimental protocols detailed below:

A Chinese Hamster Ovary (CHO) cell line stably expressing the human ether-á-go-go related gene was grown and passaged under standard culture conditions. Cells were prepared for assays using dissociation protocols designed to optimise cell health, yield, and seal and assay quality. Test samples were provided as 10 mM stock solutions in 100 % DMSO. All sample handling and serial dilutions were performed using glass containers and glass-lined plates. A top working concentration of 30 µM was prepared from the 10 mM sample stock solution using a 1:333-fold dilution into external recording solution (0.3 % DMSO v/v). In the single-concentration assay, test samples were screened at 30 µM

against a minimum of three separate cells. In the pIC₅₀ assay, test samples were screened at 1, 3, 10 and 30 μ M against a minimum of three separate cells. Each four-point concentration-response curve was constructed using cumulative double sample additions of each concentration to the same cell.

- 5 All experiments were performed on the QPatch gigaseal automated patch clamp platform. The composition of external and internal recording solutions for the QPatch experiments is shown in **Table A** below. All solutions were filtered (0.2 μ m) prior to each experiment.

Constituent	Intracellular Solution (mM)	Extracellular Solution (mM)
NaCl	-	140
KCl	70	2
KF	60	-
HEPES	10	10
MgCl ₂	-	1
CaCl ₂	-	2
Glucose	-	5
EGTA	5	-
MgATP	5	-
pH	7.2 (KOH)	7.4 (NaOH)

- 10 **Table A:** The composition of external and internal solutions (in mM) used in the hERG study

All recordings were made in the conventional whole-cell configuration and performed at room temperature (~ 21 °C) using standard single hole chips (Rchip 1.5 - 4 M Ω). Series resistance (4 - 15 M Ω) was compensated by > 80 %. Currents were elicited from a holding potential of -90 mV using the industry standard "+40 / -40" voltage protocol as shown in **Figure A** below; this was applied at a stimulus frequency of 0.1 Hz.

- 15

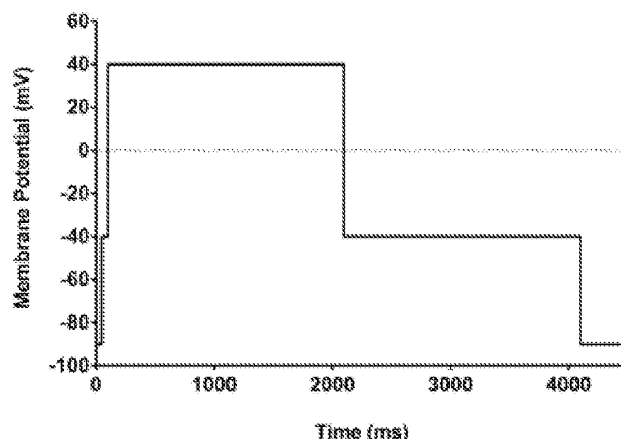


Figure A: Schematic of the QPatch voltage protocol used for the hERG assay.

On achieving the whole-cell configuration, vehicle (0.3 % DMSO v/v in external recording solution) was applied to each cell in two bolus additions with a two-minute recording period between each addition to allow stable recordings to be achieved. Following the vehicle period, either:

- i) For the single concentration assay – a single concentration of test sample was applied at 30 μ M as five bolus additions per test concentration at two-minute intervals; or
- ii) For the pIC₅₀ assay – four concentrations of test sample were applied from 1 μ M to 30 μ M as two bolus additions per test concentration at two-minute intervals;

and then the effects on hERG tail current amplitude were measured during the four-minute recording period. For each sweep of the voltage protocol, membrane current and the passive properties of the individual cells were recorded by the QPatch assay software (version 5.0). Peak outward tail current amplitude elicited during the test pulse to -40 mV was measured relative to the instantaneous leak current measured during the initial pre-pulse step to -40 mV. For QC purposes, the minimum current amplitude for the assay is > 200 pA peak outward current, measured at the end of the vehicle period. The QPatch analysis software calculates the mean peak current for the last three sweeps at the end of each concentration application period and the data is exported to Excel and interrogated using a bioinformatics suite developed running in Pipeline Pilot (Biovia, USA). The template calculates percent inhibition for each test concentration application period as the reduction in mean peak current or charge relative to the value measured at the end of the control (i.e. vehicle) period. The percent inhibition values from each cell are used to construct concentration-response curves employing a four-parameter logistic fit with 0 and 100 % inhibition levels fixed at very low and very high concentrations, respectively, and a free Hill slope factor. The IC₅₀ (50 % inhibitory concentration) and Hill coefficient are then determined, but only data from cells with Hill slopes within $0.5 > n_H < 2.0$ are included. The IC₅₀ data reported below represents the mean of at least three separate cells ($N \geq 3$). By convention, a test sample that fails to

achieve > 40 % block at the top concentration will yield an ambiguous IC₅₀ value due to a poor or unconstrained fit. In this instance an arbitrary IC₅₀ value is returned that is 0.5 log unit above the highest concentration tested. For example, if a sample fails to demonstrate a mean inhibition of > 40 % block at a top concentration of 30 µM then an IC₅₀ value of 100 µM is reported, i.e. pIC₅₀ ≤ 4.0.

5

The vast majority of examples have been prepared as single enantiomers or single diastereomers. Some compounds however, have been prepared as racemates or mixtures of diastereomers, and occasionally those racemates or diastereomers have been separated into single isomers using the techniques of reversed-phased HPLC, chiral HPLC or chiral SFC. For these particular compounds, isomer assignment (Isomer 1, Isomer 2) is based on the retention time of the compound using the separation technique that was performed in the final isomer separation step. By implication, this could be reversed-phased HPLC, chiral HPLC or chiral SFC retention time, and this will vary from compound to compound.

10

Table 4 – H4 and hERG Activity

Table 4				
	H4 Antagonist Activity		hERG Activity	
Ex.No.	Human H4 cAMP fpK_b	Human H4 DMR fpK_b	hERG pIC₅₀	hERG % inhibition at 30 µM
Thiopramide ¹	7.2	6.5	-	-
JNJ-7777120 ²	8.0	8.5	5.4	-
JNJ-39758979 ³	8.1	8.5	≤ 4.0	-
Toreforant ⁴	7.7	7.9	5.5	89
PF-3893787 ⁵	9.1	9.1	5.1	67
Compound 61 ⁶	9.0	9.1	5.2	-
Compound 48 ⁷	8.1	9.0	4.5	55
1-1	6.3	-	-	25
1-2	7.9	-	-	-
1-3	9.0	-	-	18
1-4	9.1	-	≤ 4.0	20
1-5	7.6	-	-	68
1-6	9.2	-	-	-
1-7	7.7	-	-	-
1-8	8.0	-	-	19
1-9	8.0	-	-	12
1-10	8.2	-	-	12
1-11	7.8	-	-	-
1-12	8.7	-	-	8.3
1-13	7.5	-	-	-
1-14	8.2	-	-	11
1-15	6.4	-	-	1.5
1-16	7.5	-	-	-
1-17	7.1	-	-	-
1-18	6.5	-	-	-
1-19	7.1	-	-	-
1-20	7.0	-	-	-

Table 4				
Ex.No.	H4 Antagonist Activity		hERG Activity	
	Human H4 cAMP fpK_b	Human H4 DMR fpK_b	hERG pIC₅₀	hERG % inhibition at 30 μM
1-21	7.9	-	-	8.5
1-22	6.6	-	-	45
1-23	7.4	-	-	-
2-1	8.5	-	-	-
2-2	9.2	-	≤ 4.0	-
2-3	8.0	-	-	28
2-4	7.3	-	-	-
2-5	7.1	-	-	-
2-6	7.7	-	-	-
3-1	8.7	-	-	-
3-2	8.9	-	≤ 4.0	26
3-3	8.1	-	-	-
3-4	7.9	-	-	12
3-5	7.7	-	-	-
3-6	7.6	-	-	-
4-1	7.1	-	-	-
4-2	7.2	-	-	-
5-1	8.5	-	-	44
6-1	8.4	-	-	13
7-1	9.2	-	-	31
7-2	8.5	-	-	-
7-3	6.5	-	-	48
7-4	7.5	-	-	-
7-5	6.6	-	-	-
8-1	8.3	-	-	21
8-2	6.2	-	-	-
9-1	8.4	-	-	18
10-1	6.4	-	-	-
11-1	6.7	-	-	-
11-2	8.6	8.3	-	13
11-3	7.5	8.0	-	-
11-4	9.2	8.9	≤ 4.0	39
11-5	9.4	-	≤ 4.0	21
11-6	7.9	-	-	-
11-7	6.6	-	-	-
11-8	7.5	-	-	-
11-9	7.2	7.3	-	-
11-10	6.1	-	-	-
12-1	9.2	8.6	≤ 4.0	-
12-2	7.4	-	-	-
13-1	9.0	8.8	≤ 4.0	15
13-2	7.8	-	-	-
14-1	8.5	9.1	-	41
14-2	7.0	-	-	-
17-1	-	7.9	-	29

Table 4				
Ex.No.	H4 Antagonist Activity		hERG Activity	
	Human H4 cAMP fpK_b	Human H4 DMR fpK_b	hERG pIC₅₀	hERG % inhibition at 30 μM
17-2	-	7.7	-	-
17-3	-	7.5	-	42
17-4	-	8.7	-	-
17-5	-	6.7	-	-
17-6	-	8.0	-	-
17-7	-	8.0	-	-
17-8	-	7.8	-	-
17-9	-	7.4	-	-
17-10	-	8.0	-	-
17-11	-	8.1	-	-
17-12	-	8.1	-	-
17-13	-	8.4	-	-
17-14	-	8.1	-	-
17-15	-	8.1	-	-

¹ Changlu Liu *et al*, J Pharmacol Exp Ther., 299, (2001), 121-130.

² Jennifer D. Venable *et al*, J. Med. Chem., 48, (2005), 8289-8298.

³ Brad M. Savall *et al*, J. Med. Chem., 57, (2014), 2429-2439.

5 ⁴ Robin L Thurmond *et al*, Ann Pharmacol Pharm., 2, (2017), 1-11.

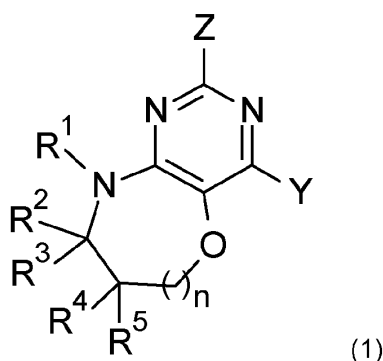
⁵ Charles E. Mowbray *et al*, Bioorg. Med. Chem. Lett., 21, (2011), 6596-6602.

⁶ Rogier A. Smits *et al*, Bioorg. Med. Chem. Lett., 23, (2013), 2663-2670.

⁷ Chan-Hee Park *et al*, J. Med. Chem., 61, (2018), 2949-2961.

Claims

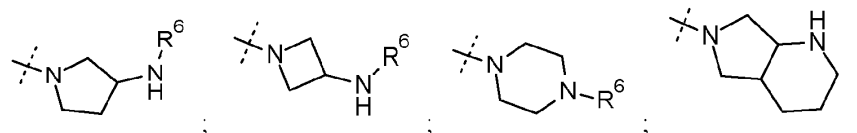
1. A compound of the formula (1):



or a salt thereof, wherein;

Z is H, NH₂ or C₁₋₃ alkyl;

Y is selected from the group consisting of:



n is 0 or 1;

R¹ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R² is H, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₆ cycloalkyl, or an optionally substituted 3 to 6-membered heterocyclyl group, wherein the optional substituents are selected from OC₁₋₃ alkyl or 1 to 6 fluorine atoms, or R² is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

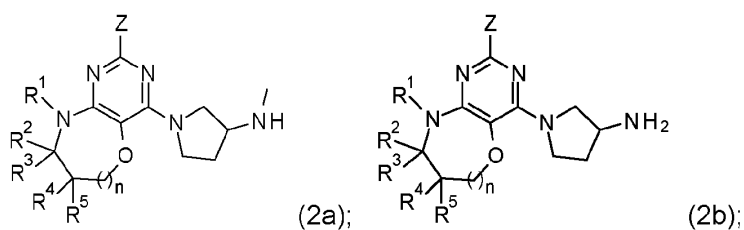
R³ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R¹ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R² to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁴ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R⁴ is H or C₁₋₃ alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R³ to form a ring which is optionally substituted with 1 to 6 fluorine atoms, or is joined to R⁵ to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

R^5 is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms, or is joined to R^4 to form a ring which is optionally substituted with 1 to 6 fluorine atoms;

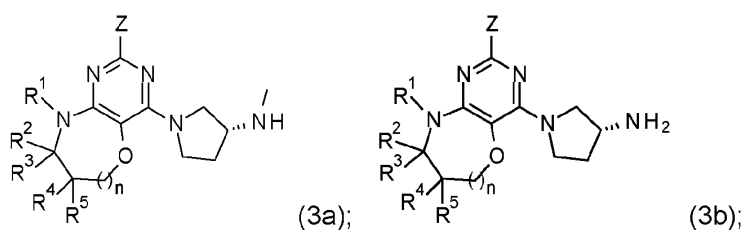
and R^6 is H or methyl.

2. The compound according to claim 1 which is a compound of formula (2a) or (2b):



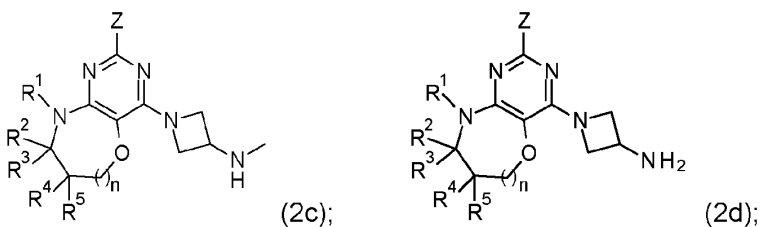
or a salt thereof.

3. The compound according to claim 2 which is a compound of formula (3a) or (3b):



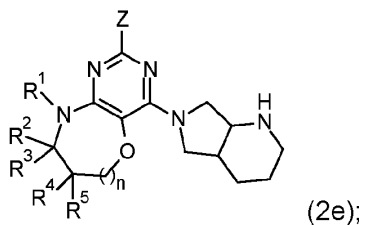
or a salt thereof.

4. The compound according to claim 1 which is a compound of formula (2c) or (2d):



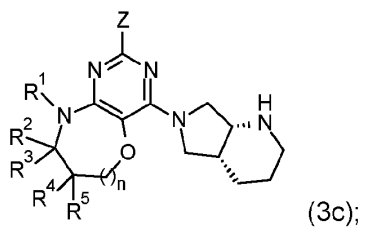
or a salt thereof.

5. The compound according to claim 1 which is a compound of formula (2e):



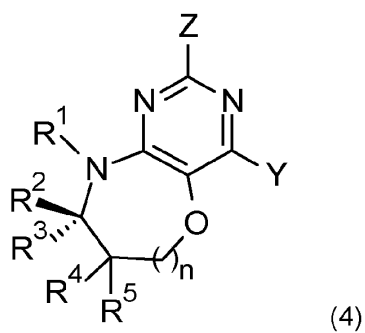
or a salt thereof.

6. The compound according to claim 5 which is a compound of formula (3c):



or a salt thereof.

7. The compound according to claim 1 which is a compound of formula (4):



or a salt thereof.

8. The compound according to any one of claims 1 to 7, wherein Z is H, NH₂ or methyl.

9. The compound according to claim 8, wherein Z is NH₂.

10. The compound according to any one of claims 1 to 9, wherein R¹ is H.
11. The compound according to any one of claims 1 to 10, wherein R² is selected from the group consisting of H, methyl, ethyl, isopropyl, cyclopropyl, isobutyl, trifluoromethyl, CH₂OMe, CH(CH₃)OMe, C(CH₃)₂OMe and oxetanyl.
12. The compound according to claim 11, wherein R² is ethyl or isopropyl.
13. The compound according to any one of claims 1 to 12, wherein R³ is H or methyl.
14. The compound according to any one of claims 1 to 11, wherein R² is ethyl and R³ is methyl.
15. The compound according to any one of claims 1 to 14, wherein R⁴ is H, methyl, ethyl or isopropyl.
16. The compound according to claim 15, wherein R⁴ is H.
17. The compound according to any one of claims 1 to 15, wherein n is 0.
18. The compound according to any one of claims 1 to 15, wherein n is 1.
19. The compound according to claim 1 which is selected from the group consisting of:
(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
7-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(S)-7-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(R)-7-Cyclopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

7-isobutyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((R)-3-(Methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(R)-7-(Methoxymethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(S)-7-((R)-1-Methoxyethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(S)-7-((S)-1-Methoxyethyl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(S)-7-(2-Methoxypropan-2-yl)-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((R)-3-(Methylamino)pyrrolidin-1-yl)-7-(oxetan-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(R)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

6-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6S,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6R,7R)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6S,7S)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(6R,7S)-6,7-Dimethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

7-Isopropyl-8-methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine;
(*R*)-6a-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine;
(*S*)-6a-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6a,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine;
(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
4-((*R*)-3-Aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-((*R*)-1-methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-((*S*)-1-methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-(2-methoxypropan-2-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-7-Ethyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-7-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-7-Cyclopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-7-((*R*)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-7-((*S*)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*S*)-7-(2-Methoxypropan-2-yl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
(*R*)-4-(3-Aminoazetidin-1-yl)-7-ethyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-4-(3-Aminoazetidin-1-yl)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine

(*R*)-7-Isopropyl-4-(4-methylpiperazin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Isopropyl-4-(piperazin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-1-((*R*)-7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-1-((*R*)-7-Cyclopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(3*R*)-1-(7-(Methoxymethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(3*R*)-*N*-Methyl-1-(6-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-((*R*)-7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-((*S*)-7-((*R*)-1-Methoxyethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-1-(7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylazetidin-3-amine;

(3*R*)-1-(7-Isopropyl-2-methyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)-*N*-methylpyrrolidin-3-amine;

(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*R*)-8-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(S)-8-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(R)-8-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
7-Methyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
7-Ethyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
7-Isopropyl-4-((R)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(S)-4-((R)-3-(Methylamino)pyrrolidin-1-yl)-6,7,7*a*,8,9,10-hexahydropyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazepin-2-amine;
(S)-4-((R)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(R)-4-((R)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(S)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(R)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
(R)-1-((S)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;
(R)-1-((R)-8-Isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;
4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;
4-[(3*R*)-3-aminopyrrolidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;
4-[3-(methylamino)azetidin-1-yl]-6*a*,7,8,9,9*a*,10-hexahydro-6*H*-cyclopenta[*e*]pyrimido[5,4-*b*][1,4]oxazepin-2-amine;
4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;

7,7-dimethyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
 8-ethyl-4-[3-(methylamino)azetidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
 4-[(3*R*)-3-aminopyrrolidin-1-yl]-8-ethyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
 8-ethyl-4-[(4*aR*,7*aR*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
 (3*R*)-1-(8-ethyl-8-methyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-4-yl)-*N*-methylpyrrolidin-3-amine;
 8-ethyl-8-methyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;
 4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclopentane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;
 (3*R*)-*N*-methyl-1-(6'*H*,8'*H*-spiro[cyclopentane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-4'-yl)pyrrolidin-3-amine;
 (3*R*)-1-(3,3-difluoro-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-4'-yl)-*N*-methylpyrrolidin-3-amine;
 7-ethyl-7-methyl-4-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
 3,3-difluoro-4'-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]-6'*H*,8'*H*-spiro[cyclobutane-1,7'-pyrimido[5,4-*b*][1,4]oxazin]-2'-amine;
 or a salt thereof.

20. The compound according to claim 19 which is selected from the group consisting of:

(*R*)-4-(3-(Methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
 (*R*)-7-Ethyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
 (*R*)-7-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;
 4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-(Methoxymethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-((*R*)-1-Methoxyethyl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-(2-Methoxypropan-2-yl)-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7,7-Dimethyl-4-(3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

6-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

4-((*R*)-3-(Methylamino)pyrrolidin-1-yl)-6*a*,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]pyrrolo[1,2-*d*][1,4]oxazin-2-amine;

(*R*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-7-isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

4-((*R*)-3-Aminopyrrolidin-1-yl)-7-(trifluoromethyl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*S*)-7-((*R*)-1-Methoxyethyl)-4-(3-(methylamino)azetidin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-7-Isopropyl-4-(piperazin-1-yl)-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-2-amine;

(*R*)-1-((*R*)-7-Isopropyl-7,8-dihydro-6*H*-pyrimido[5,4-*b*][1,4]oxazin-4-yl)pyrrolidin-3-amine;

(*R*)-8-Methyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Isopropyl-4-((*R*)-3-(methylamino)pyrrolidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-4-((*R*)-3-Aminopyrrolidin-1-yl)-8-isopropyl-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

(*S*)-8-Isopropyl-4-(3-(methylamino)azetidin-1-yl)-6,7,8,9-tetrahydropyrimido[5,4-*b*][1,4]oxazepin-2-amine;

or a salt thereof.

21. The compound according to any one of claims 1 to 20 having H4 receptor activity.
22. The compound according to claim 21 which exhibits low hERG activity.
23. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 22 and a pharmaceutically acceptable excipient.
24. The compound or composition according to any one of claims 1 to 23 for use in medicine.
25. The compound or composition according to any one of claims 1 to 23 for use in the treatment of inflammatory disorders including asthma, chronic pruritus, dermatitis, rheumatoid arthritis, gastric ulcerogenesis and colitis.