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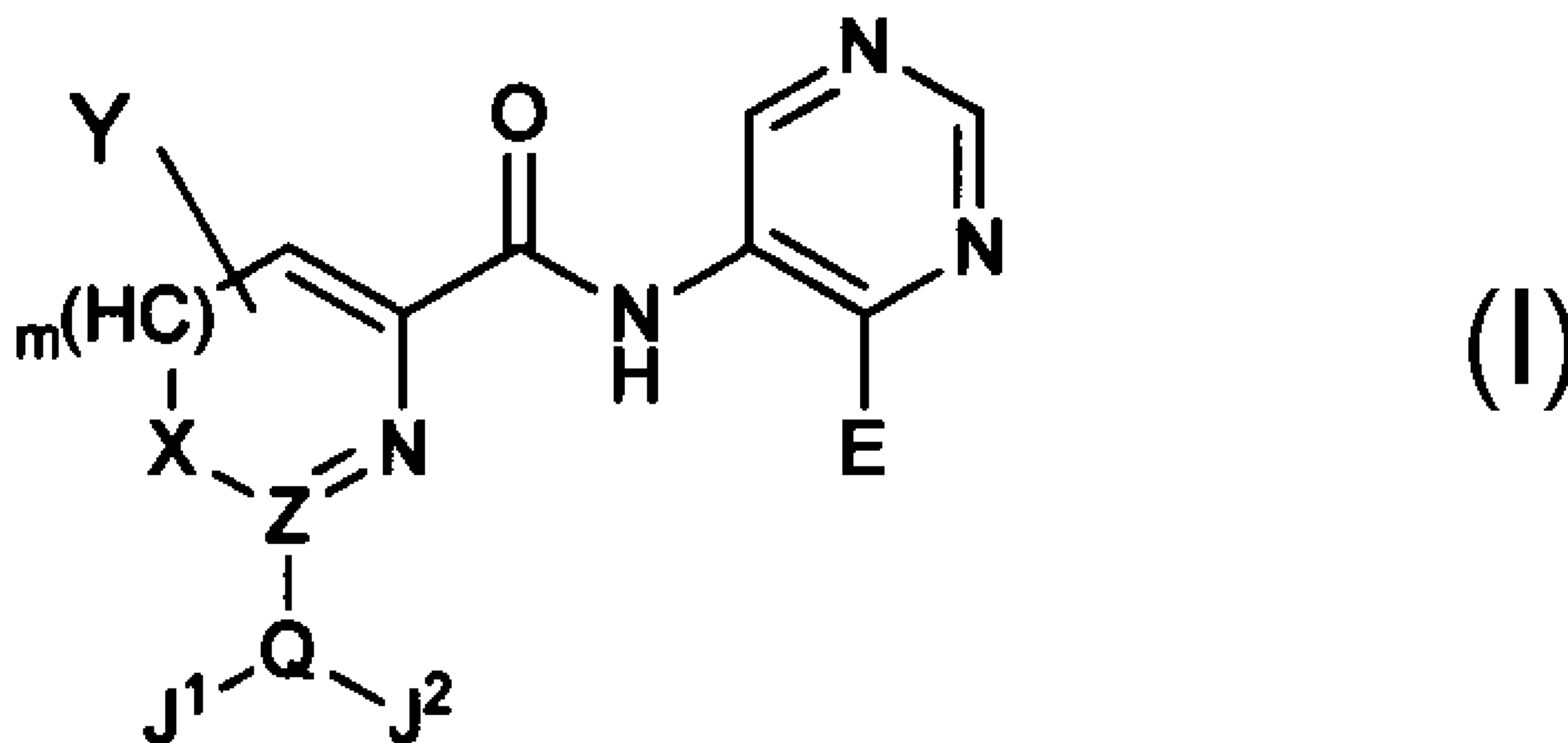
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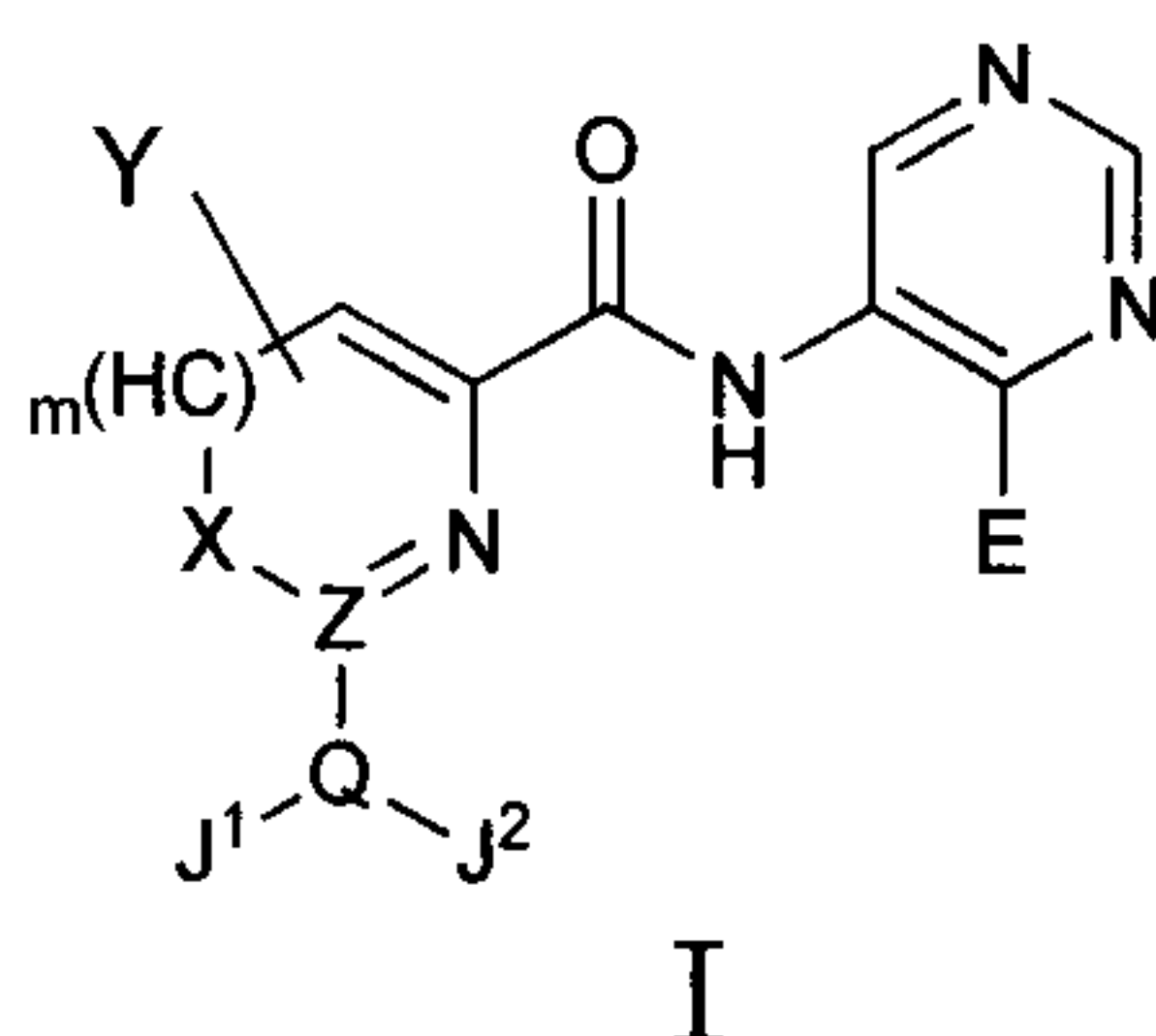
(54) Titre : INHIBITEUR DE PIM KINASE ET PROCEDE DE PREPARATION ET UTILISATION DANS LA FABRICATION
MEDICINALE DE CELUI-CI
(54) Title: PIM KINASE INHIBITORS AND PREPARATION METHODS AND USE IN MEDICINAL MANUFACTURE
THEREOF



(57) Abrégé/Abstract:

Provided is a PIM kinase inhibitor as represented by formula (I), wherein E, J, Q, X, Y, Z, and m are defined in claim 1. The PIM kinase inhibitor of the present invention is used for preparing medicines for treating and preventing cancers, autoimmune diseases, allergic diseases, atherosclerosis and anti-organ transplant rejection reactions.

ABSTRACT



The present invention provided a PIM kinase inhibitor – a compound with a general structural formula represented by Formula I. Also provided are isomers, diastereomers, enantiomers, tautomers, and pharmaceutically acceptable salts represented by Formula 1. E, J¹, J², Q, X, Y, Z and m in Formula I are defined in Claim 1. A PIM biochemical assay shows that the compounds (1-63) of the present invention can significant inhibit PIM-1 kinase activity. At 3 micromolar concentration, the compounds of the present invention can inhibit PIM-2 and PIM-3 activities by as much as 100%. Therefore, the PIM kinase inhibitors of the present invention can be used to prepare drugs to treat PIM kinase mediated diseases such as cancers, autoimmune diseases, allergic reactions, or organ transplant rejection, thus have great clinical value. Also provided are preparation methods for the compounds represented by Formula I.

PIM KINASE INHIBITORS AND PREPARATION METHODS AND USE IN MEDICINAL MANUFACTURE THEREOF

TECHNICAL FIELD

The present invention relates to medicinal chemistry, particularly PIM kinase inhibitors, methods of preparation, and their pharmaceutical application in treating diseases.

BACKGROUND

PIM kinase family consists of three homologous serine/threonine kinases, which belong to calmodulin-dependent protein kinase-related family (CAMK). Researches have shown that PIM kinases are widely expressed in hematopoietic tissues (J. Biol. Chem., 280, 14168-14176, 2005; Blood, 105, 4477-4483, 2005) and play important roles in cell survival and proliferation. Since PIM kinases are overexpressed in a variety of malignancies and inflammations (J. Exp. Med., 201, 259-266, 2005; Biochem. Soc. Trans., 32, 315-319, 2004), they are more and more being targeted for treating cancers and immune dysfunctions. PIM-1 (Provirus Integration of Maloney 1) was originally identified in a series of insertional mutagenesis studies of retroviruses, as a frequent proviral integration site in Moloney murine leukemia virus-induced T-cell lymphomas, and PIM-1 was named based on that finding (Cell, 37, 141-150, 1984). It was found later that the genes encoding PIM-2 (Provirus Integration of Maloney 2) have the same defect (J. Clin. Invest., 115, 2679-2688, 2005). PIM-3 was initially named as KID-1 (Kinase Induced by Depolarization 1), but renamed to Pim-3 because of its high sequence similarity to Pim-1 (Nature, 428, 332-337, 2005; Cell, 56, 673-682, 1989). PIM-1, 2, 3 are overly expressed in many hematopoietic malignancies (PNAS USA, 86, 8857-8861, 1989). PIM-1 was found to be overexpressed in the development of prostate cancer (J. Clin. Pathol., 59, 285-288, 2006). PIM-2 expression is elevated in human chronic lymphocytic leukemia and non-Hodgkin's lymphoma leukemia (Leuk. Lymph., 45, 951-955, 2004), the aberrant expression of PIM-3 is believed to have played an important role in the development and proliferation of live fibroma (Int. J. Cancer, 114, 209-218, 2005) and pancreatic cancer (Cancer Res., 66, 6741-6747, 2006).

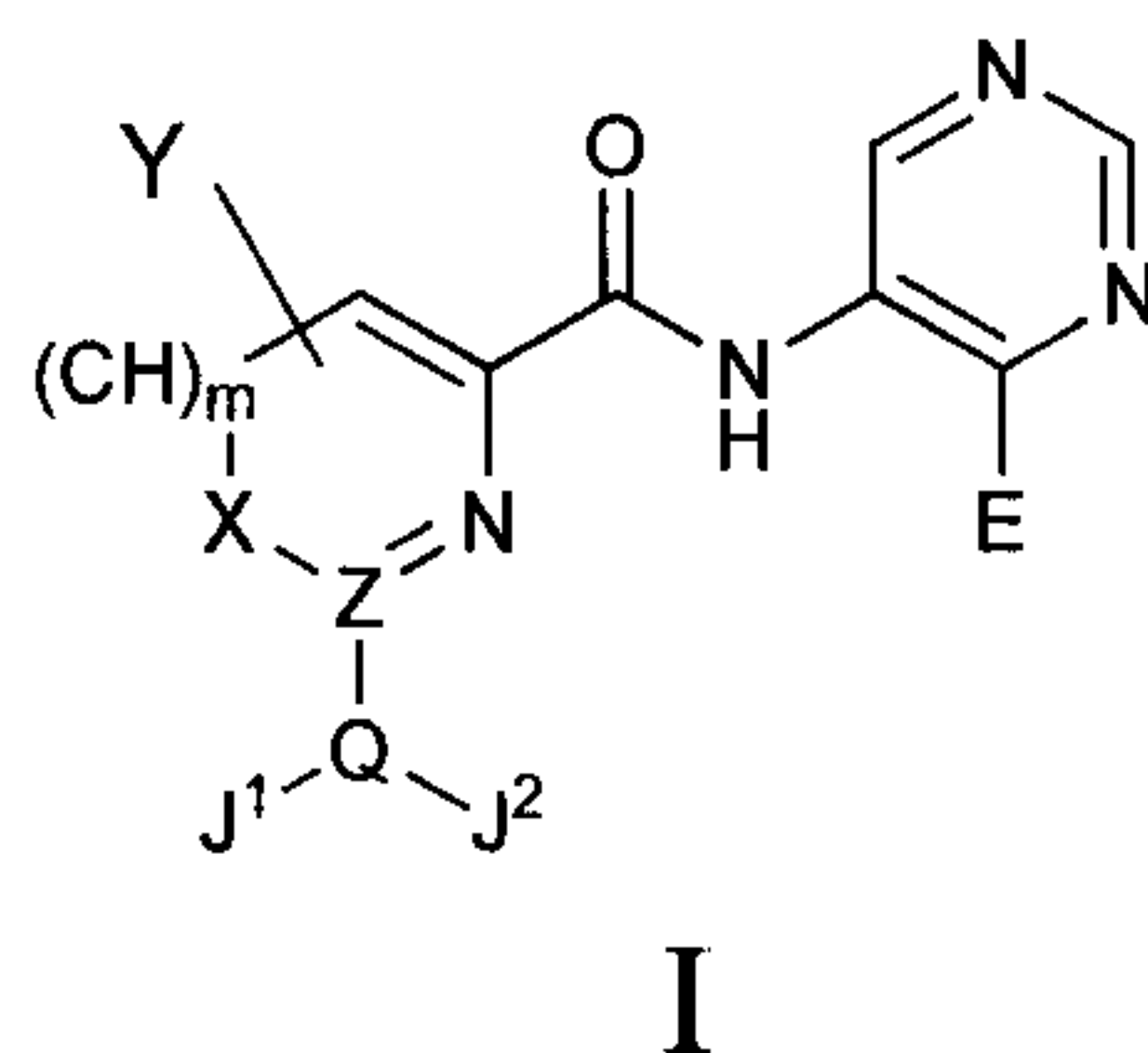
PIM-1, 2, 3 have effects on the survival and proliferation of hematopoietic cells in response to growth factors stimulation. PIM-1, 2, 3 triple knockout mice are viable and fertile while displaying reduced body size and impairment of proliferation of hematopoietic cells in response to growth factors.

Knocking out one of 3 kinases does not have obvious effect on mice, indicating some overlapping functions among PIM kinases (Cell, 56, 673-682, 1989). The substrates of PIM kinases include Bcl-2 family members such as pro-apoptotic BAD protein (FEBS Letters, 571, 43-49, 2004), cell cycle regulating p21 (Biochem. Biophys. Acta, 1593, 45-55, 2002), CDC25A, C-TA (J. Biol. Chem., 279, 48319-48328, 2004), protein synthesis related 4EBP1 (Blood, 105, 4477-4483, 2005). These functions of PIM kinases indicate that PIM kinases can prevent apoptosis and promote cell growth and proliferation. Their overexpression in cancer cells promotes the survival and proliferation of the cancer cells. Therefore, inhibiting the PIM kinase activities in cancer cell is a new effective way of treating cancers. Besides cancer, PIM inhibitors can also be used to treat autoimmune diseases, allergic reactions, and organ transplant rejection (Immunology, 116, 82-88, 2005).

EMBODIMENT OF THE INVENTION

The present invention provides compounds that inhibit the activities of PIM kinases and using these compounds to treat cancers, autoimmune diseases, allergic reactions, and organ transplant rejection.

The PIM kinase inhibitors of the present invention have the following general structural Formula I, and their isomers, diastereomers, enantiomers, tautomers, and pharmaceutically acceptable salts,



Wherein,

E, J, Q, X, Y, Z, m of Formula I are:

When m is 0, X is S, O, N or CH;

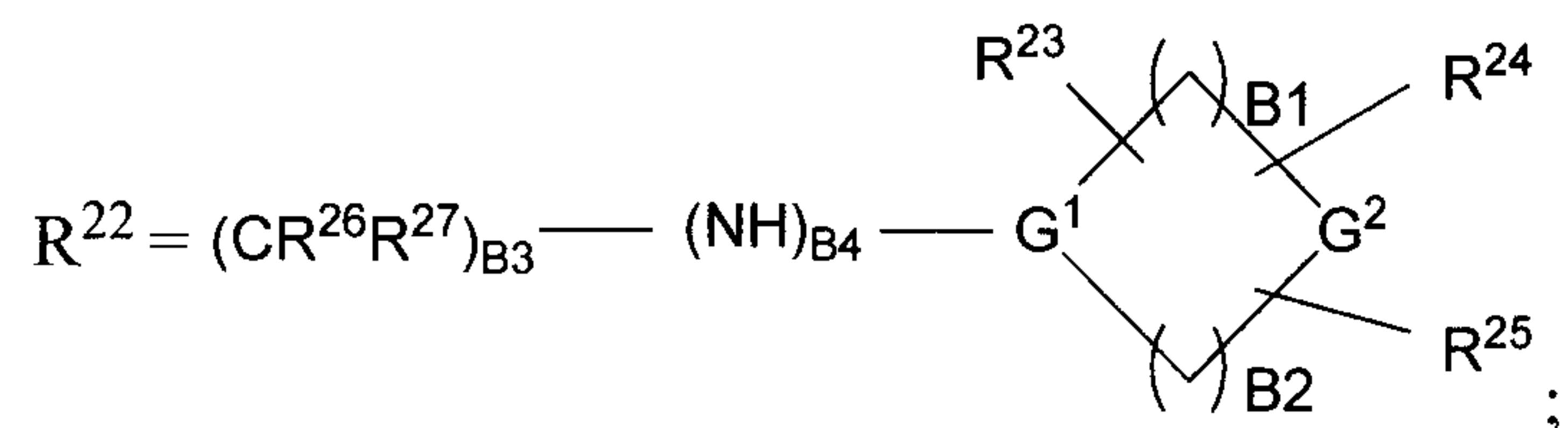
When m is 1, X is CH or N;

Z is CH or N;

Y is H or N(R¹R²), each of R¹, R² is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group; or

Y is H or N(R¹C(=O)R²), each of R¹, R² is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group;

E is OR²², SR²², SO₂R²²; R²² is optionally substituted C₁-C₈ hydrocarbon group or the group described in the following formula:



Wherein,

Each of R²³, R²⁴, R²⁵ is independently selected from H, halo, OR¹⁵, NR¹⁶R¹⁷, C(=O)NR¹⁸R¹⁹ or optionally substituted C₁-C₈ hydrocarbon group; or R²³, R²⁴ and R²⁵, together with the atoms to which they are attached, may be joined together to form a chain so that the ring to which they are attached is a substituted C₆-C₁₄ membered spiral ring, bicyclic ring or fused ring group;

G¹ is CH₂ or N;

G² is NR²⁸, CHR²⁹ or O;

B1 and B2 each independently represents 0, 1, 2 or 3;

B3 is 0, 1 or 2;

B4 is 0, 1;

Each of R²⁶ and R²⁷ is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group;

R²⁸ is H, optionally substituted hydrocarbon group, optionally substituted cyclic hydrocarbon group, optionally substituted heterocyclic hydrocarbon group, C(=O)R³⁰, C(=O)OR³⁰ or C(=O)NHR³⁰;

R²⁹ is OH, NHR³⁰, C(=O)OR³⁰ or C(=O)NHR³⁰;

R^{30} is H or optionally substituted C_1 - C_8 hydrocarbon group;

Q is C, CH or N;

J^1, J^2 is independently selected from H or optionally substituted C_1 - C_8 hydrocarbon group, OR^{31} , NHR^{31} or $C(=O)R^{31}$; or

J^1, J^2 together with CH they are attached, are joined together to form a C_3 - C_8 membered cycloalkyl; or J^1, J^2 together with the atoms to which they are attached and at least one hetero atom to form C_4 - C_7 membered heterocycloalkyl; on such C_3 - C_8 membered cycloalkyl and C_4 - C_7 membered heterocycloalkyl, one or more position can be optionally substituted with halo, OR^{32} , NHR^{33} or optionally substituted C_1 - C_8 hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is a substituted C_6 - C_{14} membered spiral ring, bicyclic ring or fused ring group; or

J^1, J^2 together with C atom they are attached, are joined together to form aromatic rings, such as benzene ring and naphthlene, or J^1, J^2 together with C they are attached and at least one heteroatom, are joined together to form C_5 - C_6 membered aromatic heterocycles, such as pyridine, pyrimidine, pyrazine, imidazole, thiazole, isoxazole, oxazole or pyrrole, on the aromatic rings and hetero aromatic rings, one or more position can be optionally substituted with halo, CN, OR^{32} , NHR^{33} or optionally substituted C_1 - C_8 hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is an optionally substituted C_6 - C_{14} membered aromatic spiral ring, bicyclic ring or fused ring group; or

J^1, J^2 together with N atom they are attached, are joined together to form C_4 - C_7 membered heterocycloalkyl group, or J^1, J^2 together with N atom they are attached, and at least one hetero atom, are joined together to form C_4 - C_7 membered heterocycloalkyl group; on these C_4 - C_7 membered heterocycloalkyl group, one or more position can be optionally substituted with halo, CN, OR^{32} , NHR^{33} or optionally substituted C_1 - C_8 hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is an optionally substituted C_6 - C_{14} membered aromatic spiral ring, bicyclic ring or fused ring group;

R^{31} is H or optionally substituted C_1 - C_8 hydrocarbon group;

Each of R^{32} , R^{33} is independently selected from H or optionally substituted C_1 - C_8 hydrocarbon group, optionally substituted C_3 - C_8 cyclic hydrocarbon group, optionally substituted C_4 - C_7 membered heterocyclic hydrocarbon group, $C(=O)R^{34}$, $C(=O)OR^{34}$ or $C(=O)NHR^{34}$;

R^{34} is H or optionally substituted C_1 - C_8 hydrocarbon group

DEFINITIONS OF THE COMPOUNDS IN THE PRESENT INVENTION

As used herein, the term 'substituent' refers to atom or atomic group that replaces the hydrogen atoms of the molecule. As used herein, 'optionally substituted' substituent refers to substituents that each of the replaceable hydrogen atoms on the substituents may be substituted by other atom or atomic group.

As used herein, the term 'hydrocarbon group' refers to alkyl group (saturated aliphatic group), alkenyl group (having at least one carbon-carbon double bond), alkynyl group (having at least one carbon-carbon triple bond); The 'hydrocarbon group' may be linear, branched or cyclic; the 'hydrocarbon group' may be aliphatic or aromatic.

As used herein, the term 'cyclic hydrocarbon group' refers to cycloalkyl group or cycloalkenyl group (having at least one carbon-carbon double bond), aromatic group; 'cyclic hydrocarbon group' may be monocyclic, bicyclic or multi-cyclic group; 'cyclic hydrocarbon group' may be spiral or fused ring.

As used herein, the term 'hetero cyclic hydrocarbon group' refers to cycloalkyl group or cycloalkenyl group (having at least one carbon-carbon double bond), aromatic group with one or more ring atoms are hetero atoms such as N, O, S, or combination thereof; 'hetero cyclic hydrocarbon group' may be monocyclic, bicyclic or multi-cyclic group; 'hetero cyclic hydrocarbon group' may be spiral or fused ring.

As used herein, the term 'substituent' include but not limited to: halo (F, Cl, Br, I), $-OR^{26}$, $-OC(=O)R^{26}$, $-OC(=O)NR^{26}R^{27}$, $=O$, $-SR^{26}$, $-SOR^{26}$, $-SO_2R^{26}$, $-SO_2NR^{26}R^{27}$, $-C(=O)R^{26}$, $-C(=O)OR^{26}$, $-C(=O)NR^{26}R^{27}$, $-R^{26}CN$, $-NR^{26}R^{27}$, $-NHC(=O)R^{26}$, $-NHC(=O)NR^{26}R^{27}$, $-NHC(=S)NR^{26}R^{27}$, halogenated (F, Cl, Br, I) hydrocarbon;

Wherein;

Each of R^{26} and R^{27} is independently selected from H or optionally substituted C_1 - C_8 hydrocarbon group.

The compounds described in the present invention that are acidic in nature can form pharmaceutically acceptable salts by reacting with physiologically compatible organic or inorganic bases, such as readily soluble alkali and alkaline earth salts, and salts formed from reacting with ammonia, N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, ethanolamine, glucosamine, sarcosine, serine, tris(hydroxymethyl)aminomethane, 1-amino-2,3,4-butanetriol

The compounds described in the present invention that are basic in nature can form pharmaceutically acceptable salts by reacting with physiologically compatible organic or inorganic acids, such as the salts formed by reacting with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, toluene-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, oxalic acid, malonic acid, salicylic acid, malic acid, fumaric acid, maleic acid, acetic acid, ascorbic acid.

The compounds in the present invention may be pure chiral compounds, racemic mixtures, optically active compounds, pure diastereomers, or mixed diastereomers.

The present invention provides PIM kinase inhibitors which include the following compounds:

- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)
- N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)
- 2-(2,6-difluorophenyl)-N-(4-(oxetan-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (6)
- 2-(2,6-difluorophenyl)-N-(4-((3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (7)
- 2-(2,6-difluorophenyl)-N-(4-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (8)
- 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)
- N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)
- 6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (11)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)

- N-(4-(8-azabicyclo[3.2.1]octan-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (14)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)
- N-(4-(3-azabicyclo[3.2.0]heptan-6-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (17)
- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)
- 2-(2,6-difluorophenyl)-N-(4-(quinuclidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (19)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)picolinamide (20)
- N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)
- 5-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiophene-2-carboxamide (23)
- N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)
- 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)
- 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)
- 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)
- 2-(2,6-difluorophenyl)-N-(4-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (31)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)
- 2-isopropyl-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (33)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)thio)pyrimidin-5-yl)thiazole-4-carboxamide (35)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (36)

- 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (38)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-N-(4-((4-carbamoylcyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (43)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-hydroxyethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (44)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (47)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)
- 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2,3-dihydroxypropoxy)pyrimidin-5-yl)thiazole-4-carboxamide (51)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)-5-(methylamino)thiazole-4-carboxamide (54)
- 2-(2,6-difluorophenyl)-5-formamido-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (55)
- 2-(2,6-difluorophenyl)-5-(methylamino)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (56)

2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)oxazole-4-carboxamide (57)
 N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide (58)
 2-(piperidin-4-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (59)
 2-morpholino-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (60)
 2-(piperidin-1-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (61)
 2-acetamido-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (62)
 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)sulfonyl)pyrimidin-5-yl)thiazole-4-carboxamide (63)

Preferred compounds:

2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)
 N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)
 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)
 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)
 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)
 2-(2,6-difluorophenyl)-N-(4-(oxetan-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (6)
 2-(2,6-difluorophenyl)-N-(4-((3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (7)
 2-(2,6-difluorophenyl)-N-(4-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (8)
 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)
 N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)
 6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (11)
 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)
 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)
 N-(4-(8-azabicyclo[3.2.1]octan-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (14)
 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)
 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)
 N-(4-(3-azabicyclo[3.2.0]heptan-6-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (17)

- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)
- 2-(2,6-difluorophenyl)-N-(4-(quinuclidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (19)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)picolinamide (20)
- N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)
- N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)
- 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)
- 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)
- 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)
- 2-(2,6-difluorophenyl)-N-(4-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (31)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)
- 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-N-(4-((4-carbamoylcyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (43)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (47)

2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)

5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)

2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)

5-amino-2-(2,6-difluorophenyl)-N-(4-(2,3-dihydroxypropoxy)pyrimidin-5-yl)thiazole-4-carboxamide (51)

5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)

5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)

N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide (58)

More preferred compounds:

2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)

N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)

2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)

5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)

2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)

2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)

N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)

2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)

2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)

2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)

2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)

2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)

N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)

2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)

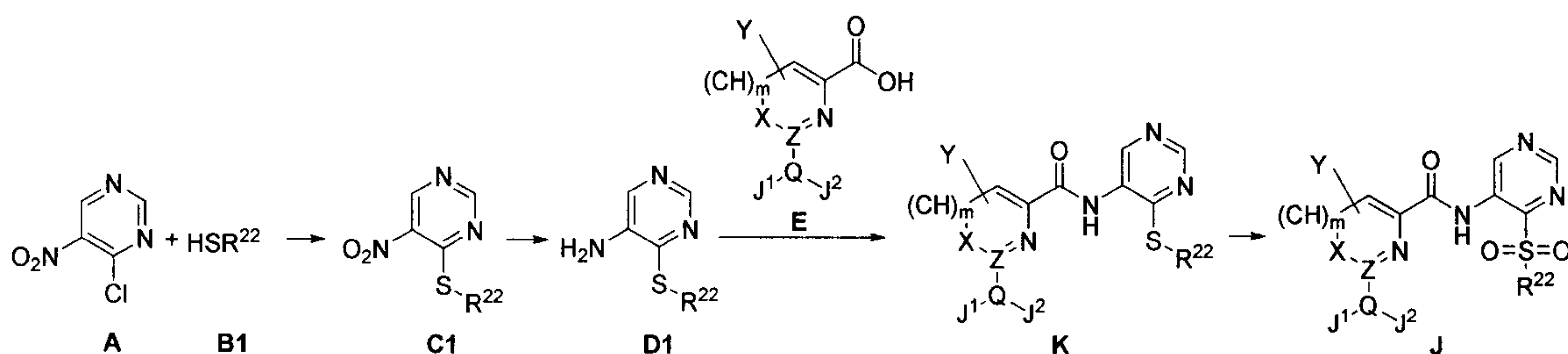
N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)

5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)

- 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)
- 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)
- 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)
- 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (47)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)
- 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)

The present invention also provides the methods of synthesis of the above PIM kinase inhibitors.

The compounds in this invention are made from commercial available starting materials and reagents. This invention is illustrated in the following scheme:



In the above scheme, X, Y, Z, J¹, J², Q, m and R²² are the same as defined earlier

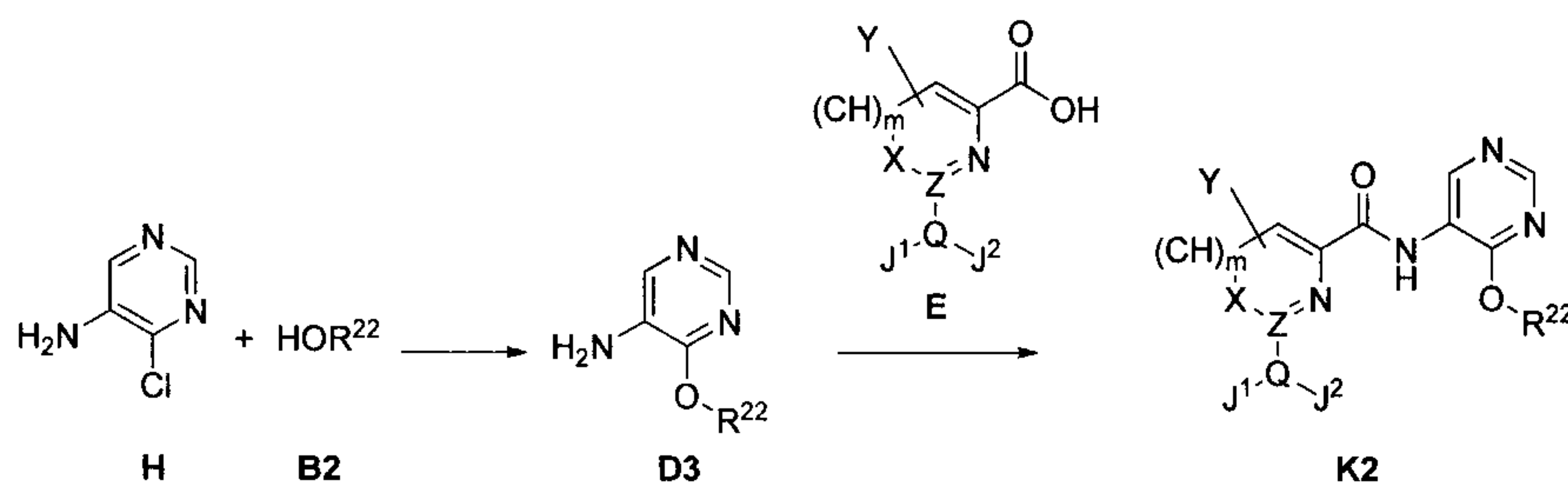
- (1) The general procedure for the synthesis of compounds when E of Formula I is sulfur or sulfone group:

Thiol compound B1 (1 eq.), protected or unprotected, reacts with 4-Chloro-3-nitropyrimidine (A) (1 eq.) in the presence of a base, for example DIEA (N,N-diisopropylethylamine) (3 eq.), in an appropriate solvent, for example dioxane, at 40 °C for 1-16 hours to form thioether C1. C1 (1 eq.) reacts with Na₂S₂O₄ (3 Eq.) in the presence of a base, for example saturated NaHCO₃ water solution (3 eq.), in an appropriate solvent, for example methanol, at 40°C for 1-10 hours, and is reduced to aminopyrimidine D1. Protected or unprotected aromatic carboxylic acid E (1 eq.), in the presence of a coupling reagent, for example HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (1-1.5 eq.), a base, for example DIEA (3 eq.), in a solvent, for example DMF (N,N-dimethyl formaldehyde), at heated conditions, for example 40°C, reacts with amine D1 (1 eq.) for 0.5-8 hours to form thioether K. If there is no protecting group in K, then K is final thioether product of Formula I where E is sulfur group. If K is protected by protecting group, for example BOC (tert-butyloxycarbonyl) or trimethylsilyl group, it's deprotected by treating with mixture of TFA (trifluoroacetic acid) (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final thioether product K of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

Thioether K (1 eq.) is oxidized by m-CPBA (m-chloroperoxybenzoic acid) (2.2 eq.) in a solvent, for example CH₂Cl₂ at room temperature to form sulfone product J. If there is no protecting group in J, then J is final sulfone product of Formula I where E is sulfone group. If J

is protected by protecting group, for example BOC or trimethylsilyl group, it's deprotected by treating with mixture of TFA (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final sulfone product J of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

(2) The general procedure for the synthesis of compounds when E of Formula I is ether group:



Alcohol B2 (1.1 eq.), protected or unprotected, reacted with a base, for example NaH (1.1 eq.), in a solvent, for example THF, at room temperature (25°C) for 1 hour, then reacted with 5-amino-4-chloropyrimidine H (1 eq.) at heated conditions, for example 100 °C for 1-10 hours to form aminopyrimidine ether D3. Protected or unprotected aromatic carboxylic acid E (1 eq.), in the presence of a coupling reagent, for example HATU (1-1.5 eq.), a base, for example DIEA (3 eq.), in a solvent, for example DMF, at heated conditions, for example 40°C, reacts with amine D3 (1 eq.) for 0.5-8 hours to form ether K2. If there is no protecting group in K2, then K2 is final ether product of Formula I where E is ether group. If K2 is protected by protecting group, for example BOC or trimethylsilyl group, it's deprotected by treating with mixture of TFA (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final ether product K2 of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

The present invention also provides the pharmaceutical application of the above PIM kinase inhibitors.

The PIM kinase assays showed that all compounds in all the examples can significantly inhibit the PIM-1 activity. At 3μM concentration, most compounds showed over 50% inhibition of PIM-1 kinase activity, some as high as 100%. The compounds in the examples also show excellent inhibitory activities against PIM-2 and PIM-3 kinase. At 3μM concentration, they can inhibit PIM-2 and PIM-3 by as much as 100%. Therefore, the PIM kinase inhibitors in the present invention can be used for pharmaceuticals.

The present invention provides the use of the above PIM kinase inhibitors as drugs to treat or prevent cancers.

The present invention provides the use of the above PIM kinase inhibitors as drugs to treat or prevent autoimmune diseases.

The present invention provides the use of the above PIM kinase inhibitors as drugs to treat or prevent allergic reactions.

The present invention provides the use of the above PIM kinase inhibitors as drugs to treat or prevent atherosclerosis.

The present invention provides the use of the above PIM kinase inhibitors as drugs to treat or prevent organ transplant rejection.

The drugs in present invention use PIM kinase inhibitors as active ingredients along with pharmaceutical carriers.

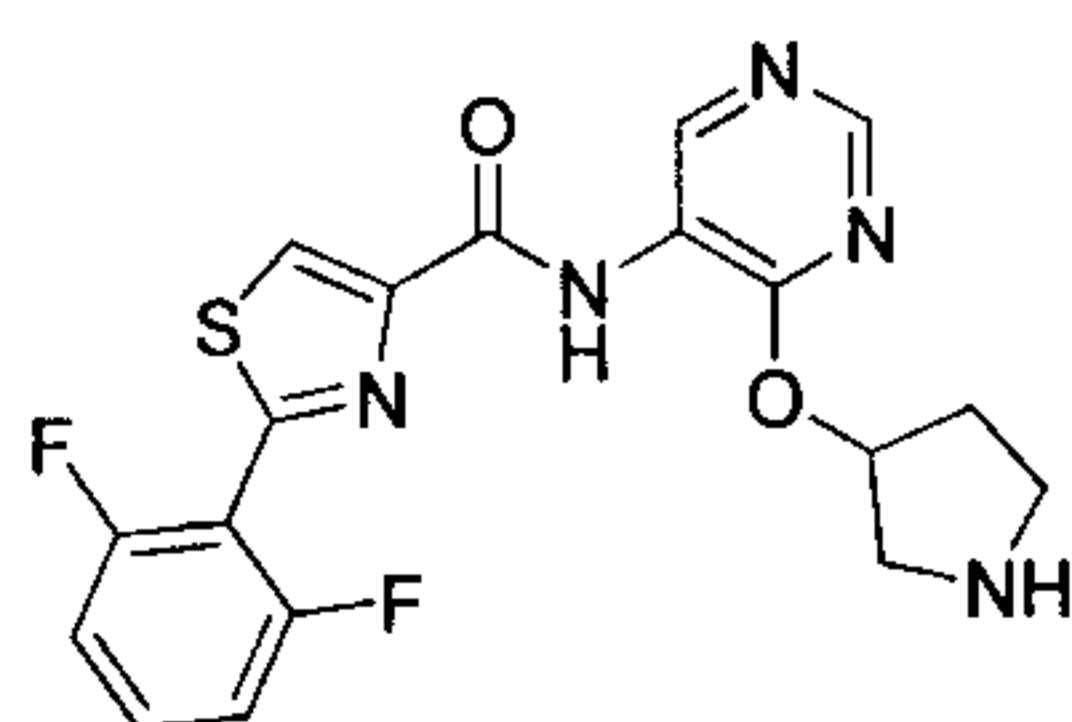
The present invention provides the new application of PIM kinase inhibitors and has significant clinical value.

EXAMPLES

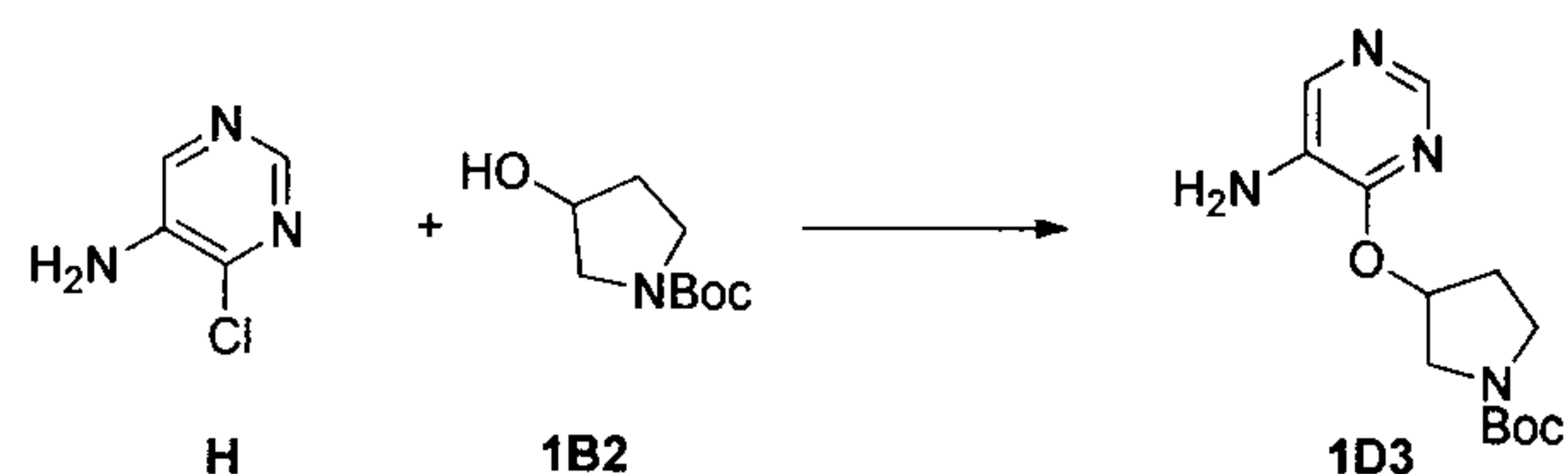
The following examples are set forth for illustration only to help understand the invention described herein and not to be construed as limiting the present invention in any manner.

Example 1

Synthesis of 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)

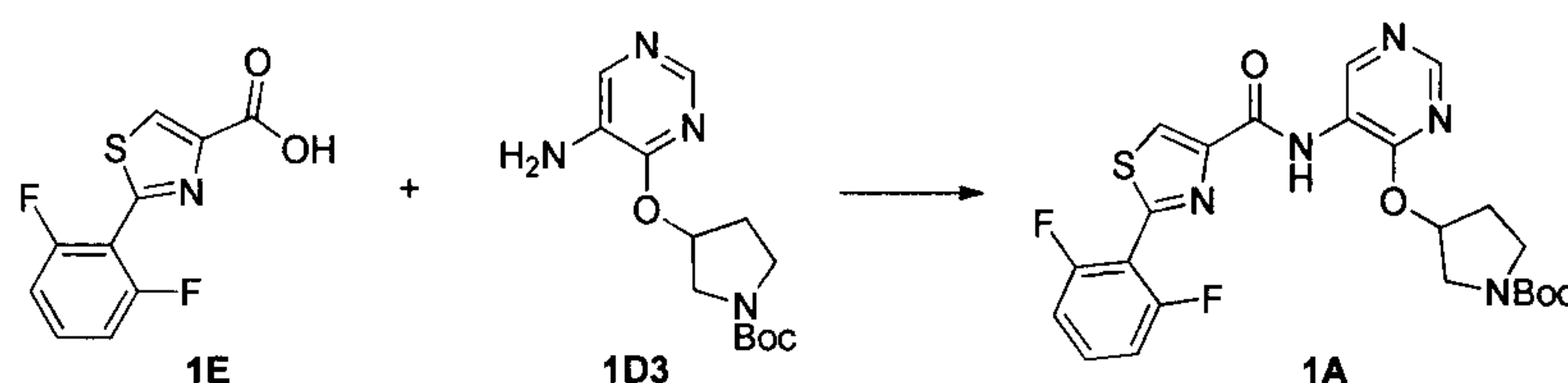


(1) Synthesis of tert-butyl 3-((5-aminopyrimidin-4-yl)oxy)pyrrolidine-1-carboxylate (1D3)



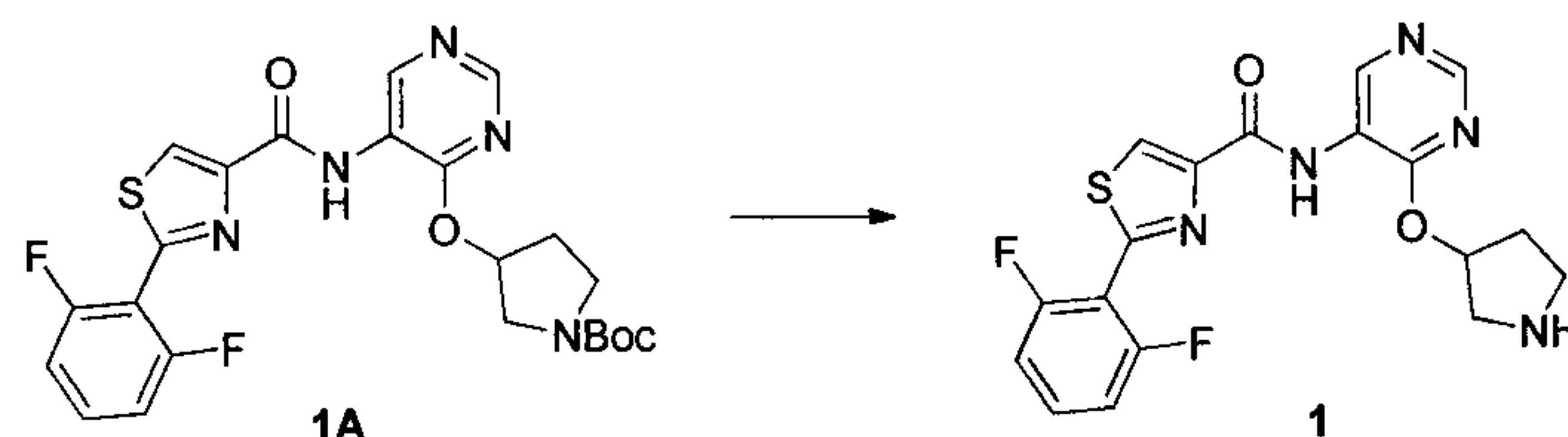
At room temperature, NaH (71mg, 2.94mmol) was added to a solution of tert-butyl-3-hydroxypyrrolidine-1-carboxylate (1B2) (500mg, 2.67mmol) in THF (tetrahydrofuran) (10mL) and stirred for 1 hour. 4-chloropyrimidin-5-amine (H) (348mg, 2.67mmol) was then added. The reaction mixture was then heated to 100°C under nitrogen and stirred for 4 hours, cooled to room temperature (20-30°C) and concentrated in vacuo. The residue was purified with flash column (eluent: 10-30% ethyl acetate/petroleum ether) to obtain the product 1D3 (336mg, 1.2mmol).

(2) Synthesis of tert-butyl 3-((5-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)pyrimidin-4-yl)oxy)pyrrolidine-1-carboxylate (1A)



Compound (1D3) (47mg, 0.169mmol), 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (1E) (40mg, 0.169mmol, HATU (77mg, 0.203mmol) and DIEA (93μL, 0.507mmol) are mixed in DMF (5mL) and stirred at 50°C for 1 hour. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50mL), washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified with flash column (eluent: 10-30% ethyl acetate/petroleum ether) to obtain the product 1A (30mg, 0.0596mmol)

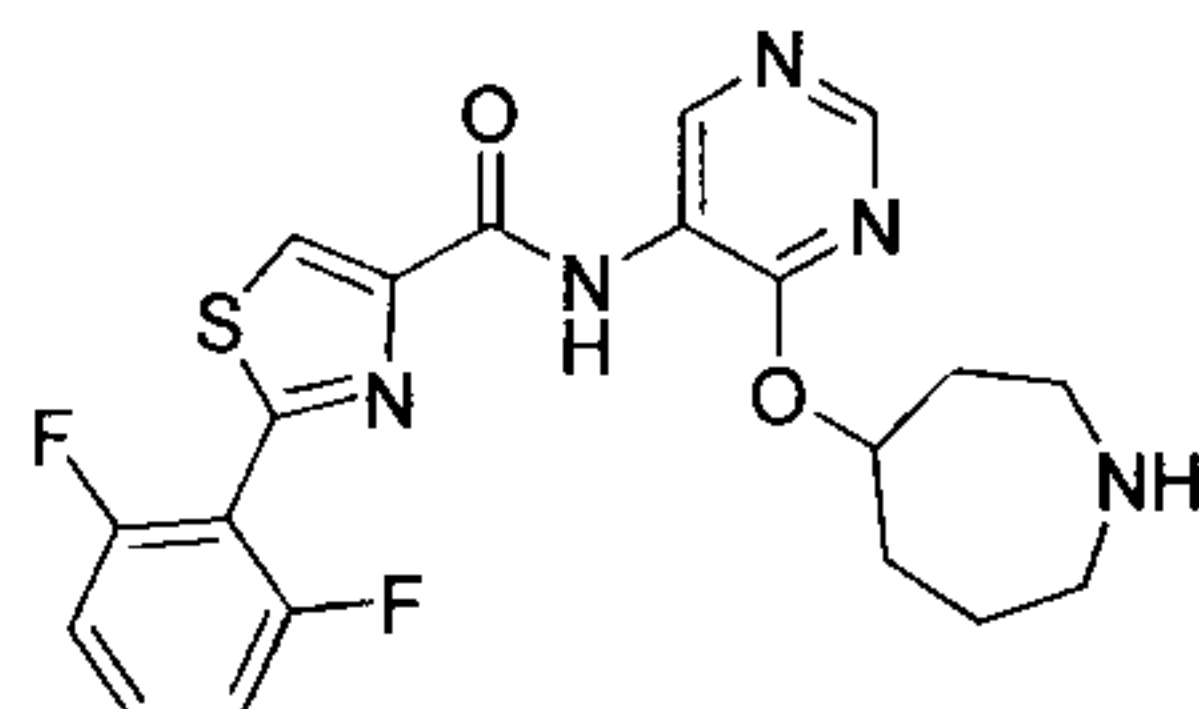
(3) Synthesis of 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)



At room temperature, TFA (trifluoroacetic acid) (0.5mL) was added to a solution of Compound 1A (20mg, 0.0394mmol) in CH₂Cl₂ (1mL) and stirred for 10 min. The mixture was the concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (10mL) and washed with NaOH (5mL) and brine (5mL), dried over Na₂SO₄ and concentrated in vacuo to obtain the title compound **1** (12mg, 0.0298mmol)

Example 2

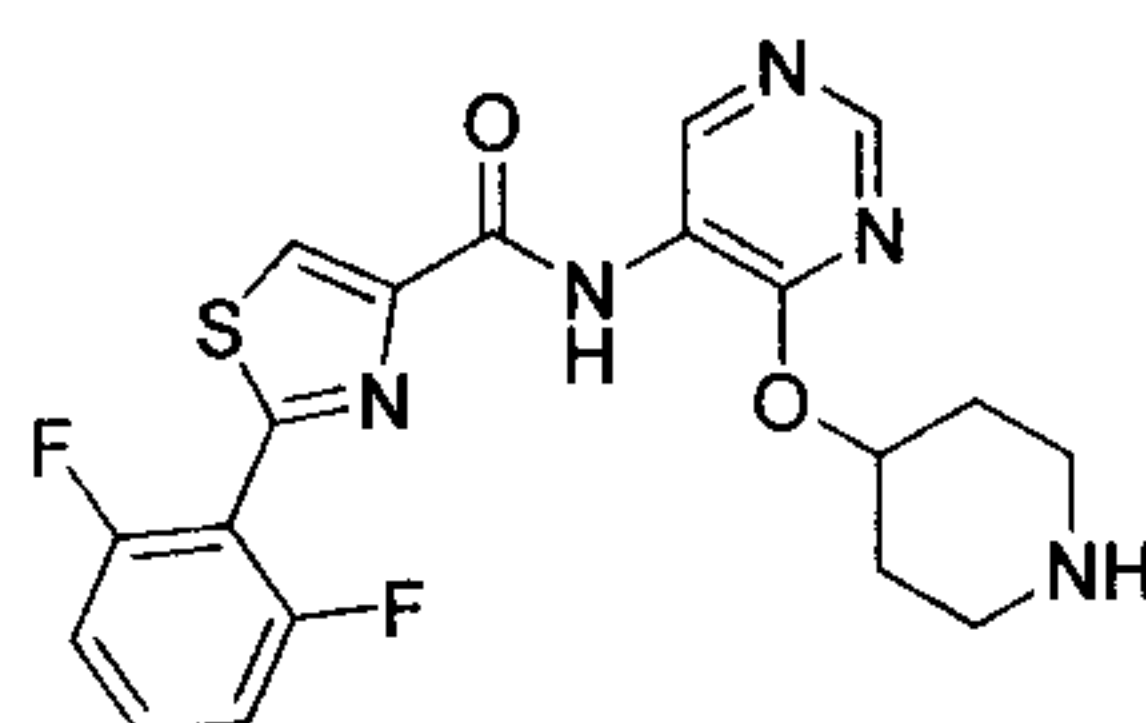
Synthesis of N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)



Following the procedure described in Example 1, and substituting compound 1B2 in Step (1) with tert-butyl 4-hydroxyazepane-1-carboxylate (2B2), the title compound **2** (17mg, 0.039mmol) was obtained.

Example 3

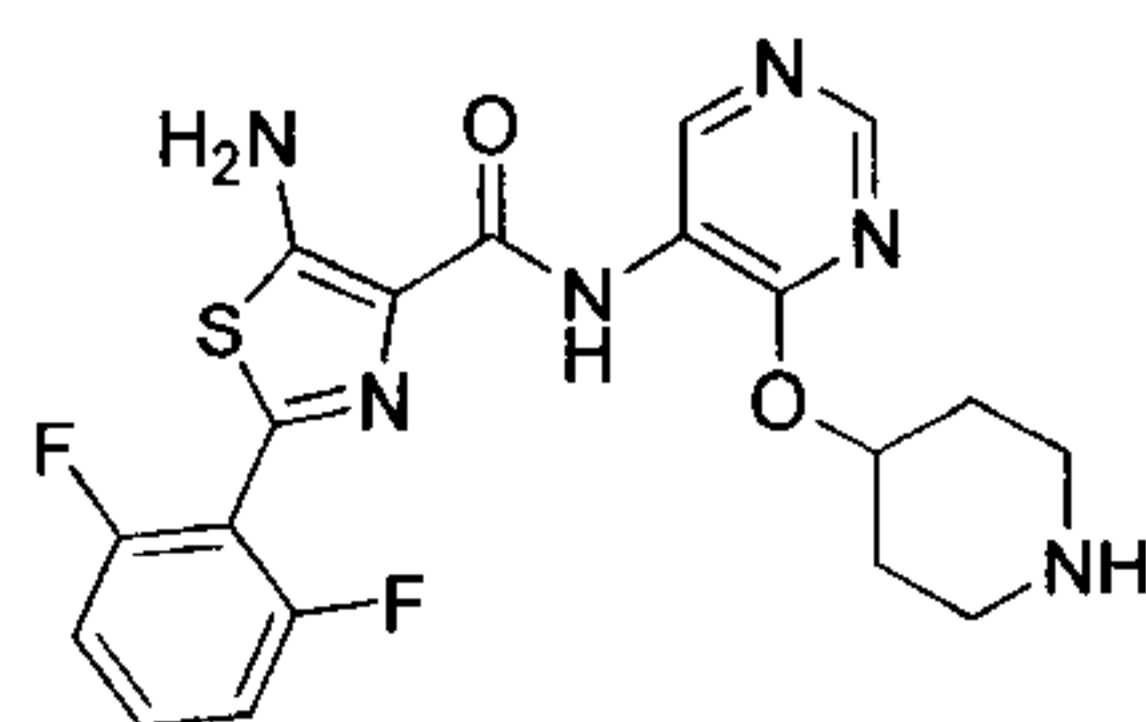
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)



Following the procedure described in Example 1, and substituting compound 1B2 in Step (1) with tert-butyl 4-hydroxypiperidine-1-carboxylate (3B2) (250mg, 1.276mmol), the title compound **3** (22mg, 0.0526mmol) was obtained.

Example 4

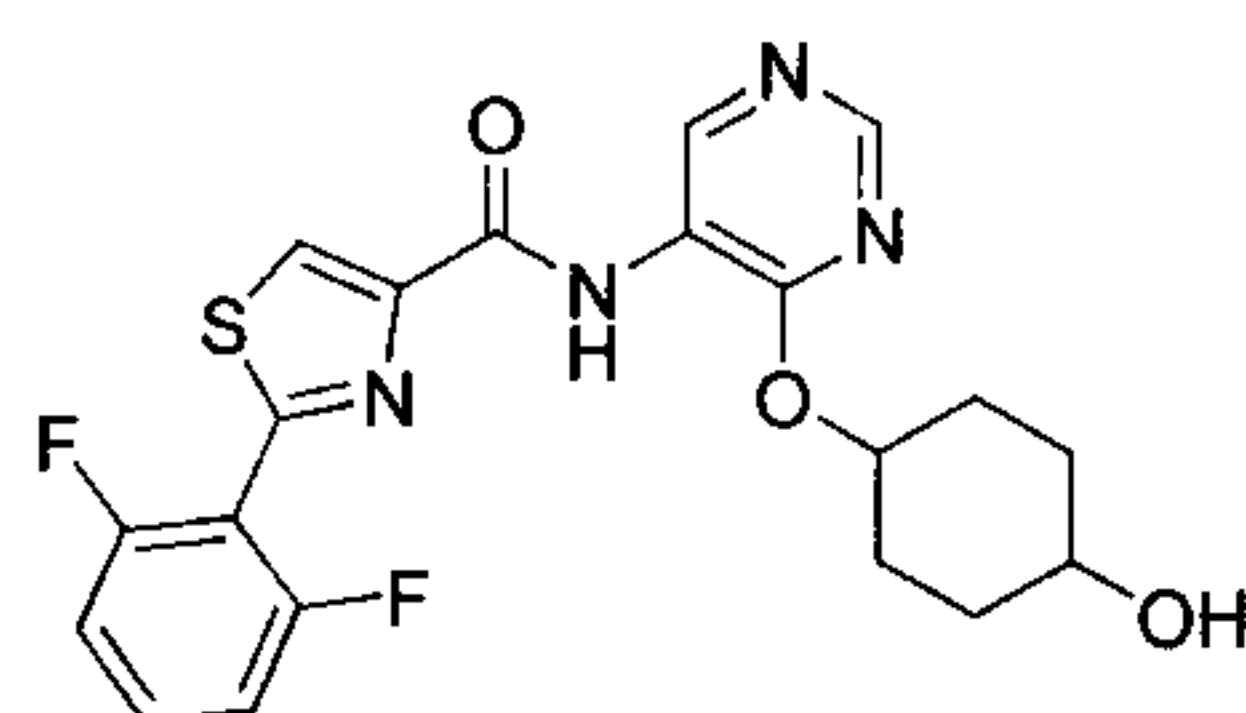
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2E) (40mg, 0.156mmol), the title compound **4** (18mg, 0.0431mmol) was obtained.

Example 5

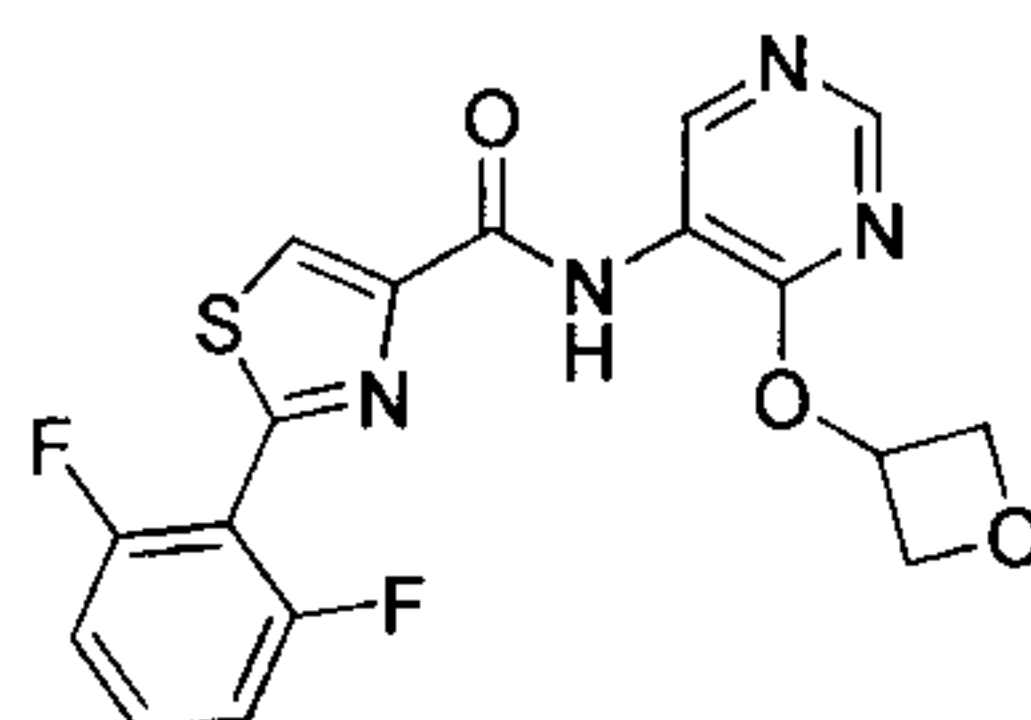
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)



Following the procedure described in Step (1) and Step (2) of Example 1, and substituting the Compound 1B2 in Step (1) with cyclohexane-1,4-diol (5B2) (250mg, 1.47mmol), the title compound **5** (16mg, 0.0370mmol) was obtained

Example 6

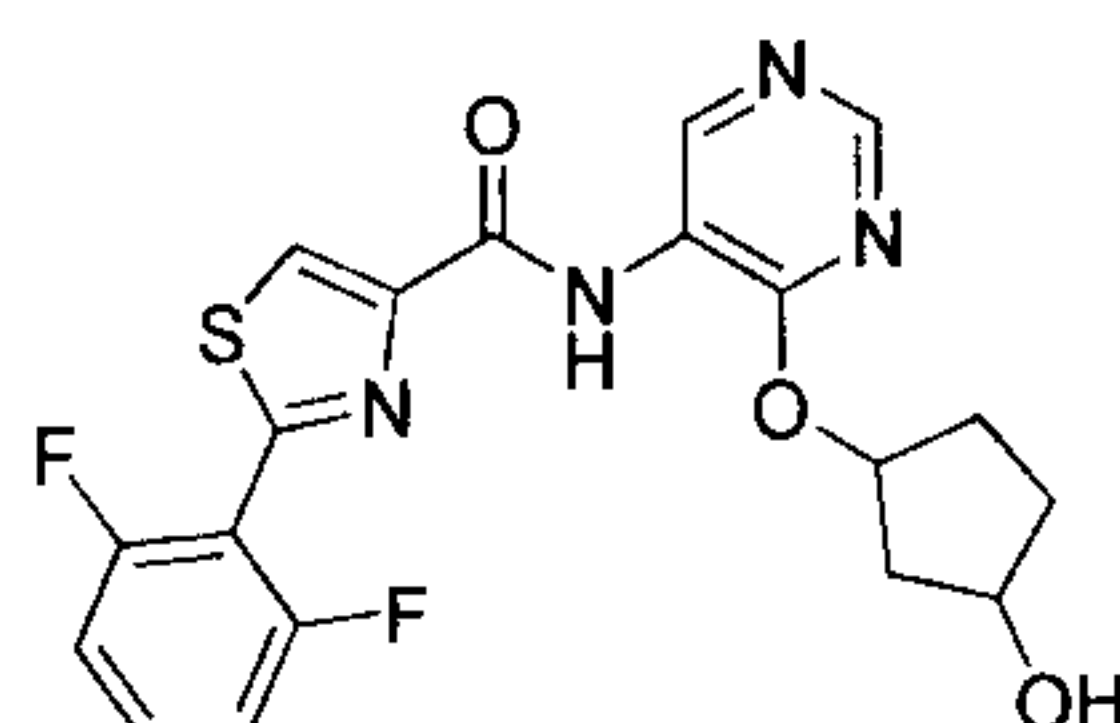
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(oxetan-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (**6**)



Following the procedure described in Example 5, and substituting Compound 1B2 in Step (1) with oxetan-3-ol (6B2) (125mg, 1.69mmol), the title compound **6** (23mg, 0.0588mmol) was obtained

Example 7

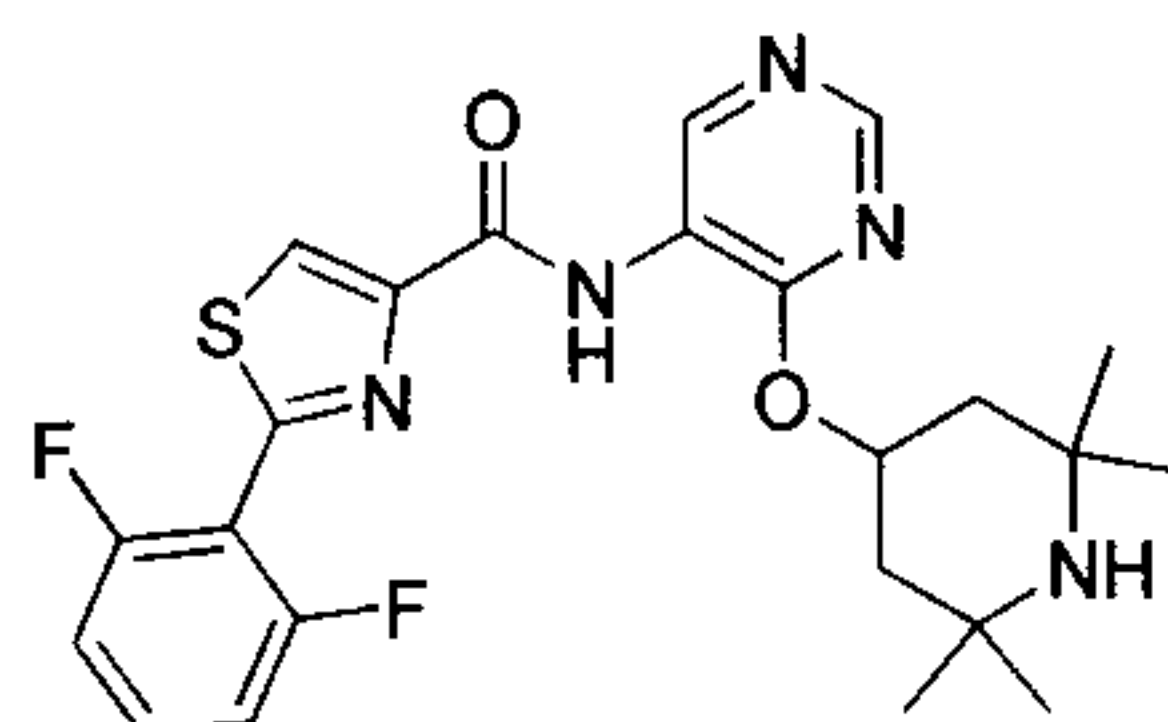
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (**7**)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with cyclopentane-1,3-diol (7B2) (125mg, 1.23mmol), the title compound **7** (17mg, 0.0406mmol) was obtained.

Example 8

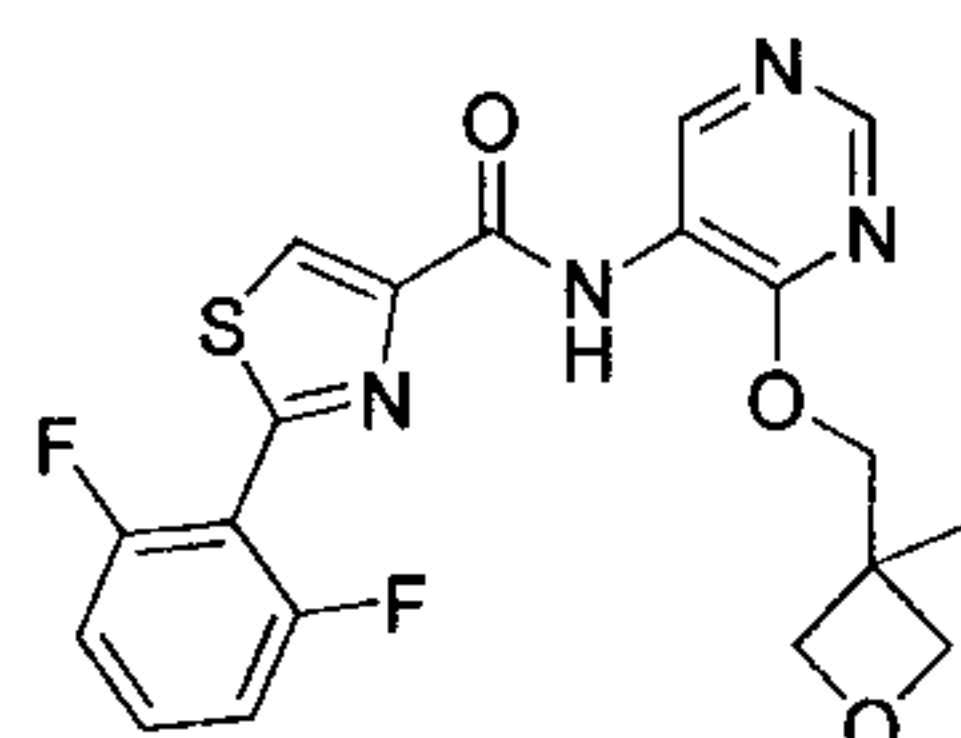
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (**8**)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-carboxylate (8B2) (250mg, 1.09mmol), the title compound **8** (24mg, 0.0507mmol) was obtained.

Example 9

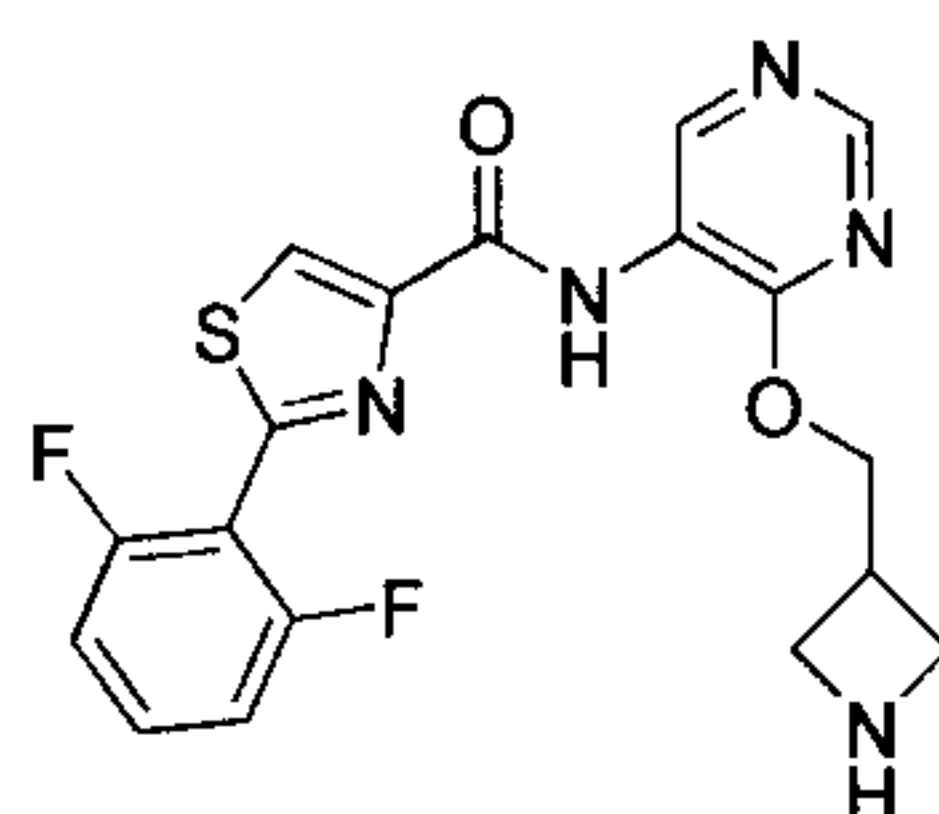
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with (3-methyloxetan-3-yl)methanol (9B2) (125mg, 1.23mmol), the title compound **9** (25mg, 0.0571mmol) was obtained.

Example 10

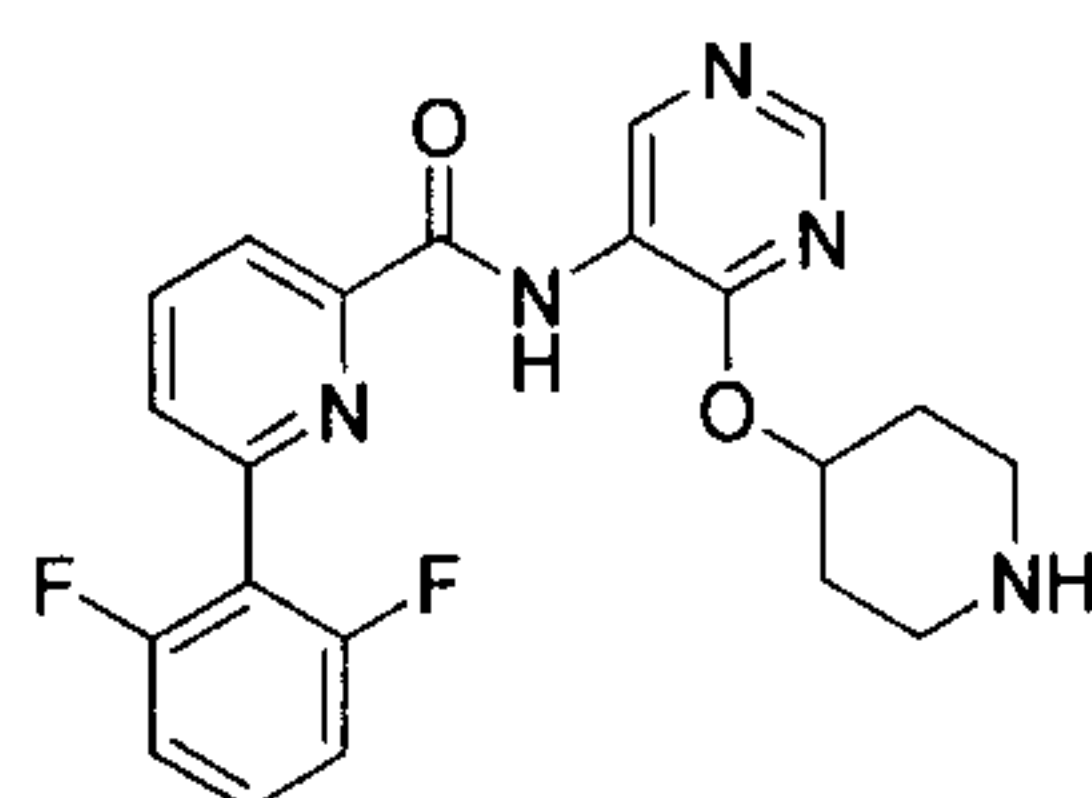
Synthesis of N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (10B2) (250mg, 1.30mmol), the title compound **10** (14mg, 0.0347mmol) was obtained.

Example 11

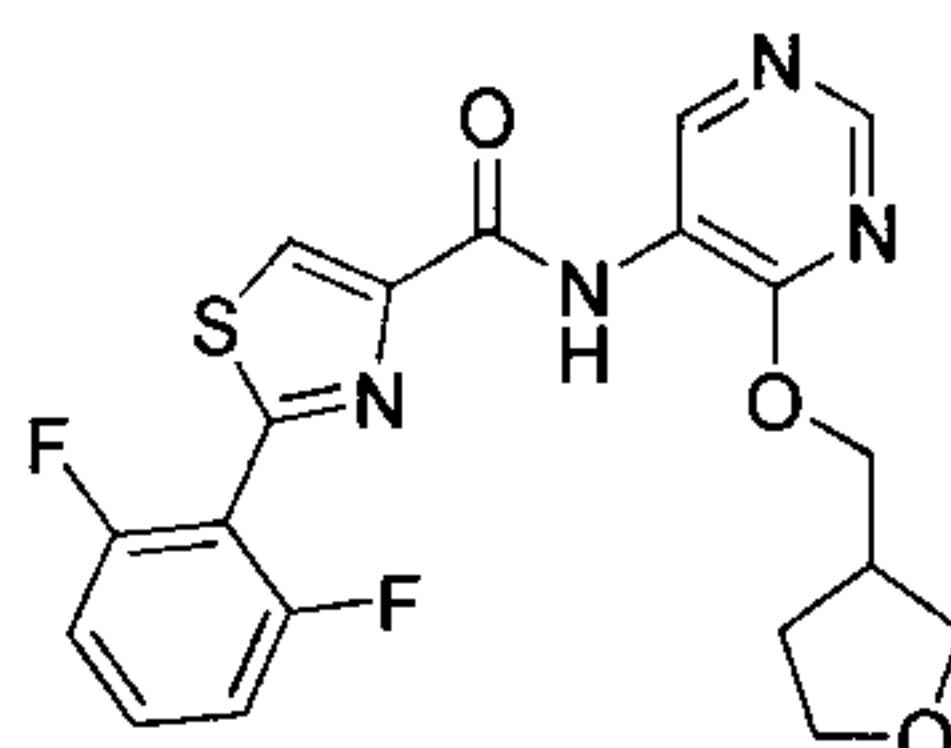
Synthesis of 6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (11)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 6-(2,6-difluorophenyl)picolinic acid (11E) (40mg, 0.170mmol), the title compound **11** (19mg, 0.0462mmol) was obtained

Example 12

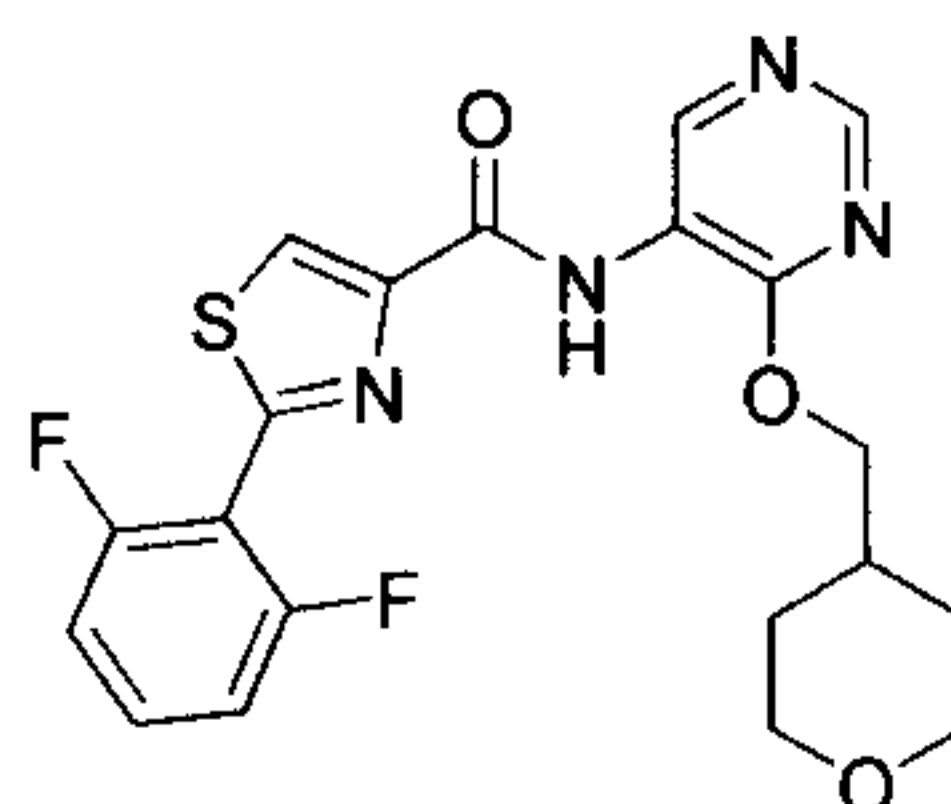
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with (tetrahydrofuran-3-yl)methanol (12B2) (30mg, 0.294mmol), the title compound **12** (12mg, 0.0286mmol) was obtained.

Example 13

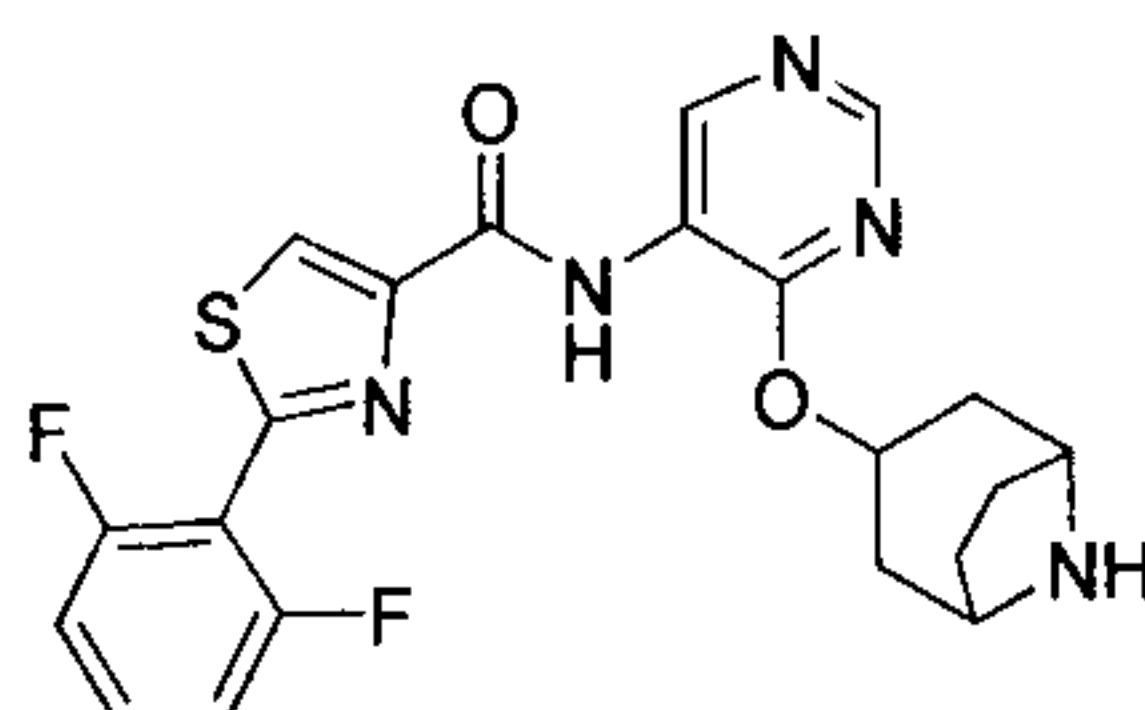
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with (tetrahydro-2H-pyran-4-yl)methanol (13B2) (30mg, 0.259mmol), the title compound **13** (12mg, 0.0286mmol) was obtained

Example 14

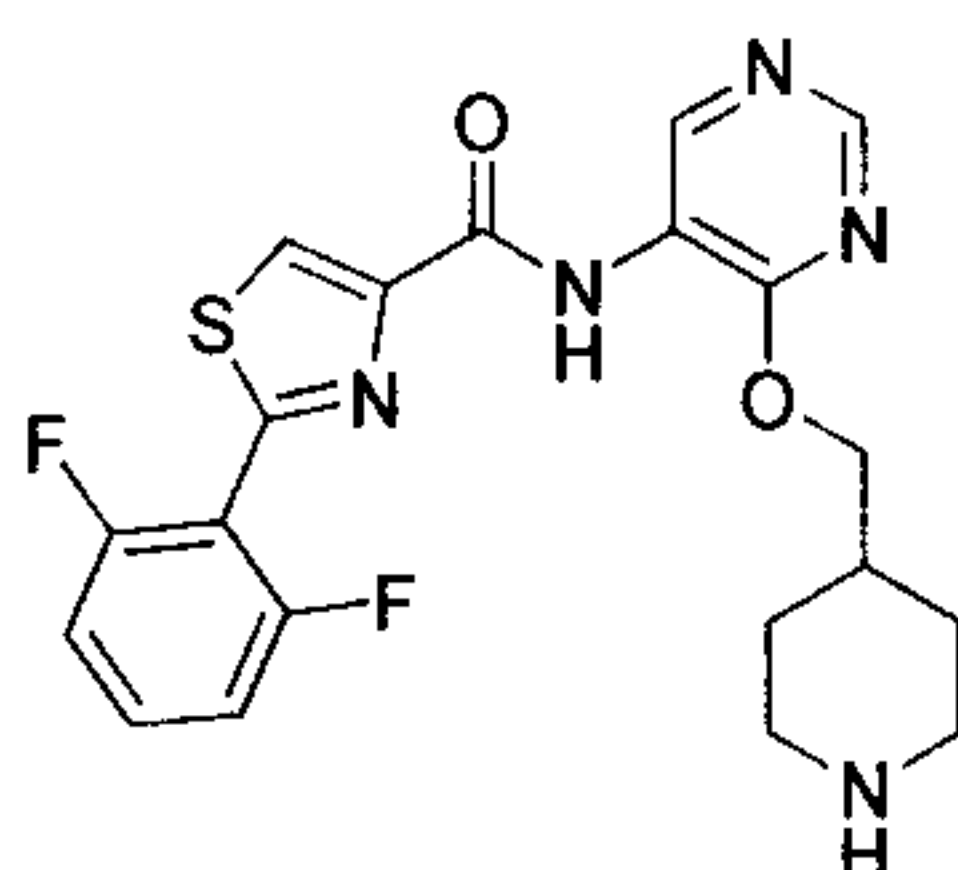
Synthesis of N-(4-(8-azabicyclo[3.2.1]octan-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (14)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (14B2) (250mg, 1.10mmol), the title compound **14** (14mg, 0.0347mmol) was obtained

Example 15

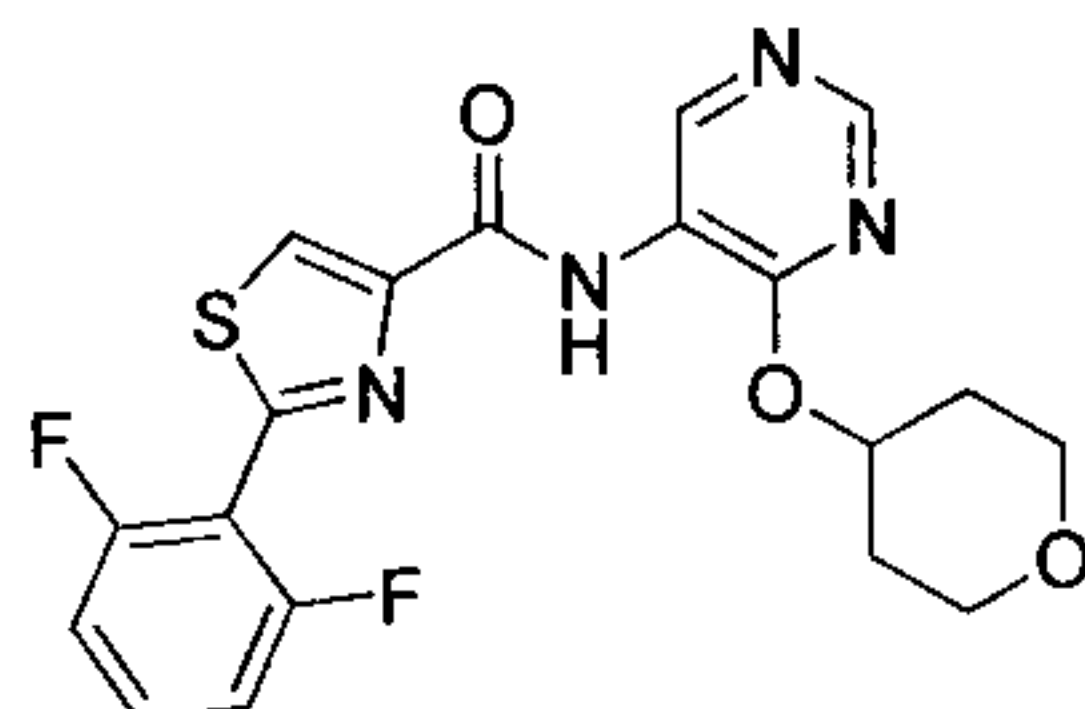
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (15B2) (250mg, 1.16mmol), the title compound **15** (12mg, 0.0278mmol) was obtained.

Example 16

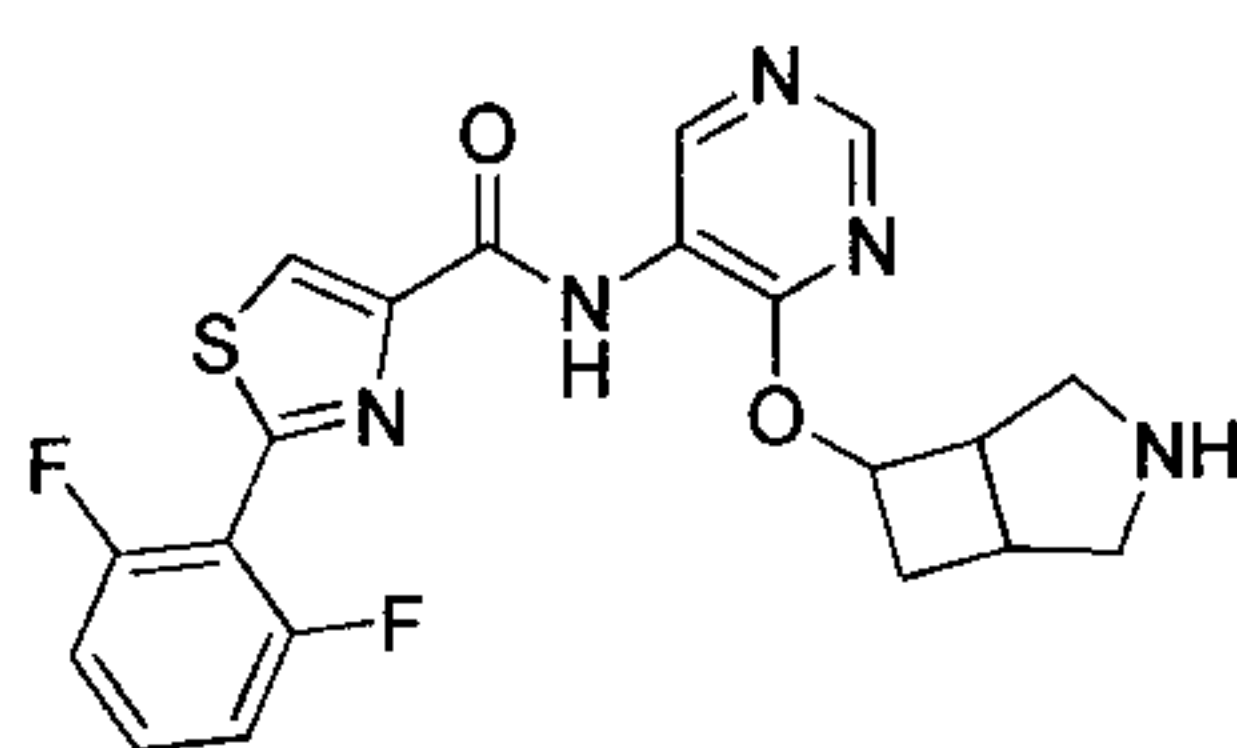
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with tetrahydro-2H-pyran-4-ol (16B2) (30mg, 0.290mmol), the title compound **16** (17mg, 0.0406mmol) was obtained.

Example 17

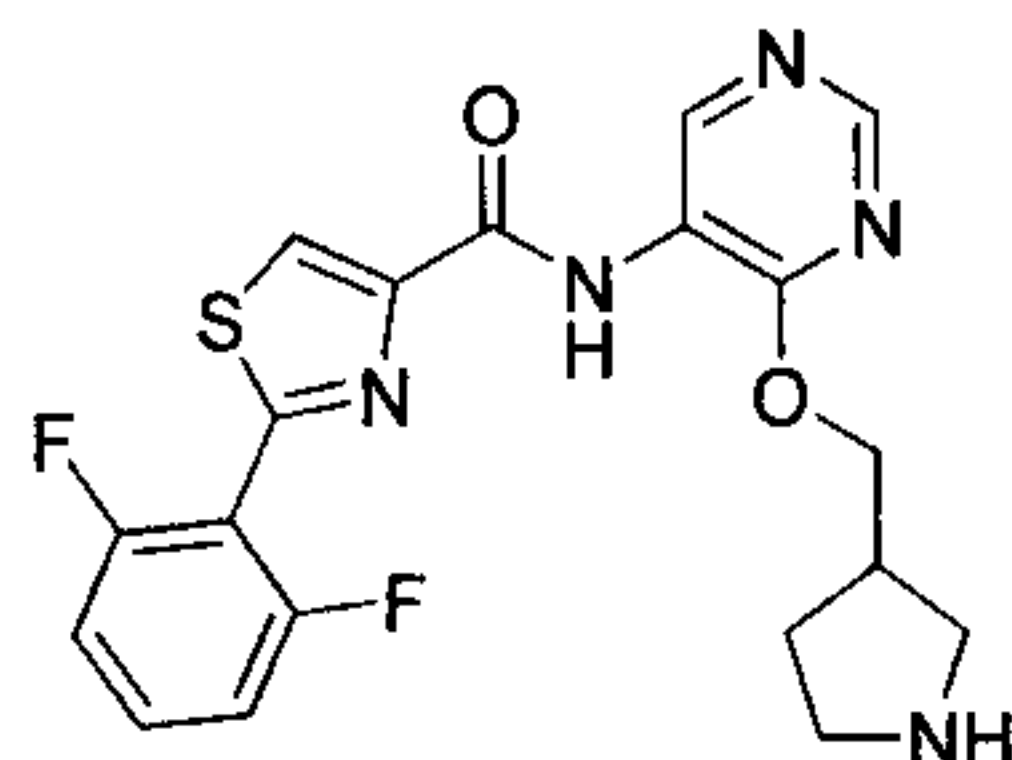
Synthesis of N-(4-(3-azabicyclo[3.2.0]heptan-6-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (17)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 6-hydroxy-3-azabicyclo[3.2.0]heptane-3-carboxylate (17B2) (250mg, 1.17mmol), the title compound **17** (16mg, 0.0372mmol) was obtained

Example 18

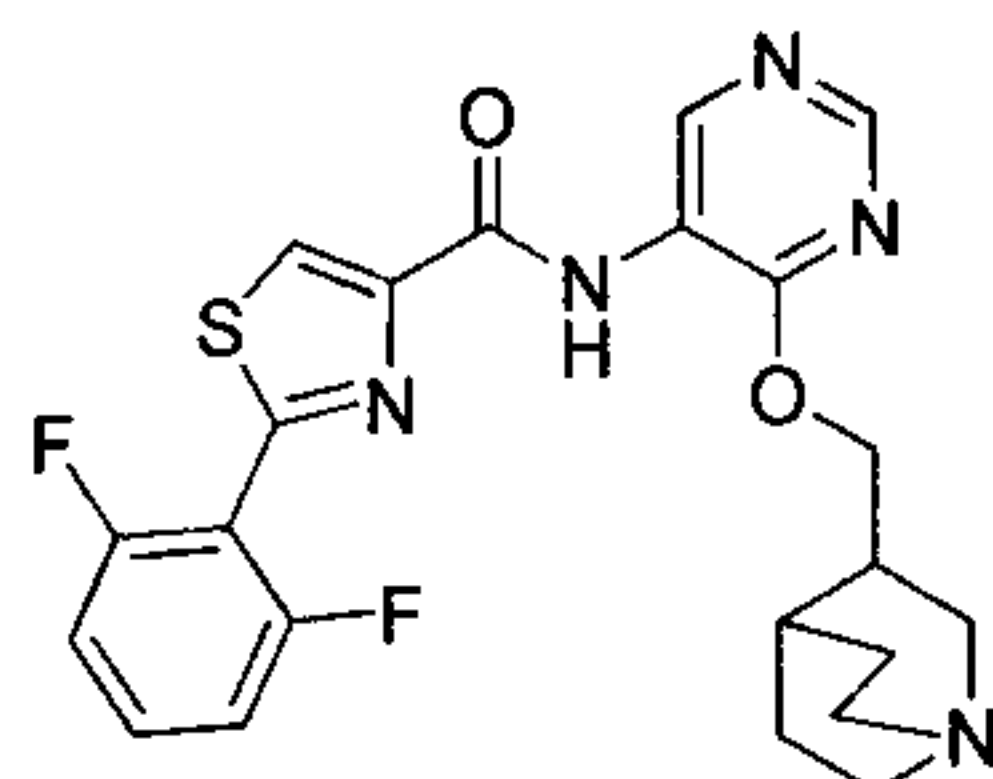
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (18B2) (250mg, 1.24mmol), the title compound **18** (22mg, 0.0526mmol) was obtained.

Example 19

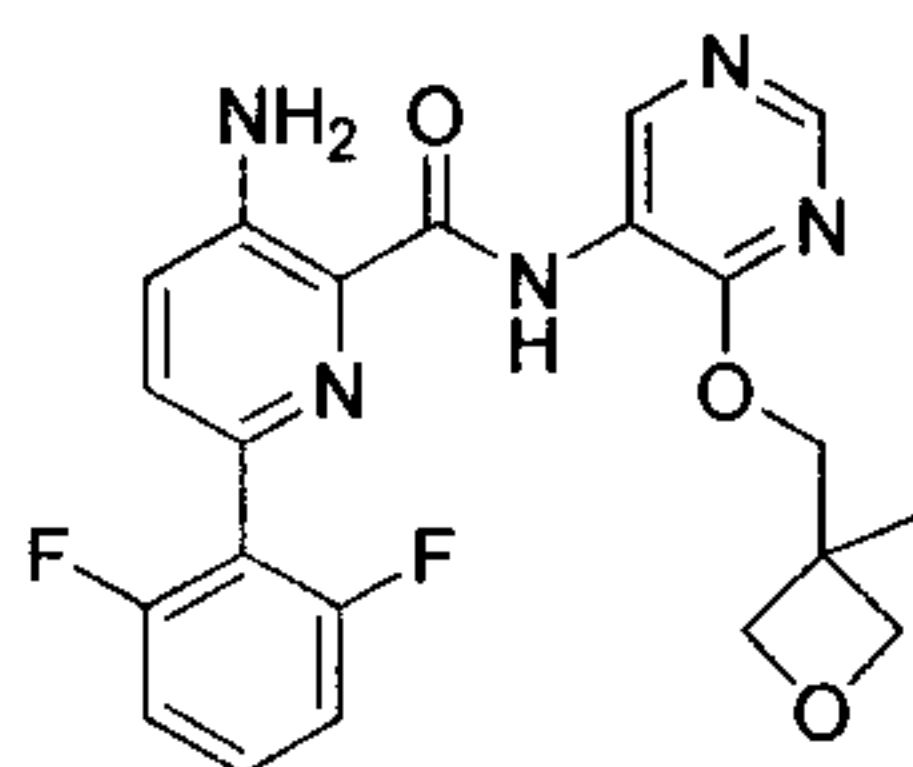
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(quinuclidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (19)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with quinuclidin-3-ylmethanol (19B2) (30mg, 0.214mmol), the title compound **19** (15mg, 0.0328mmol) was obtained

Example 20

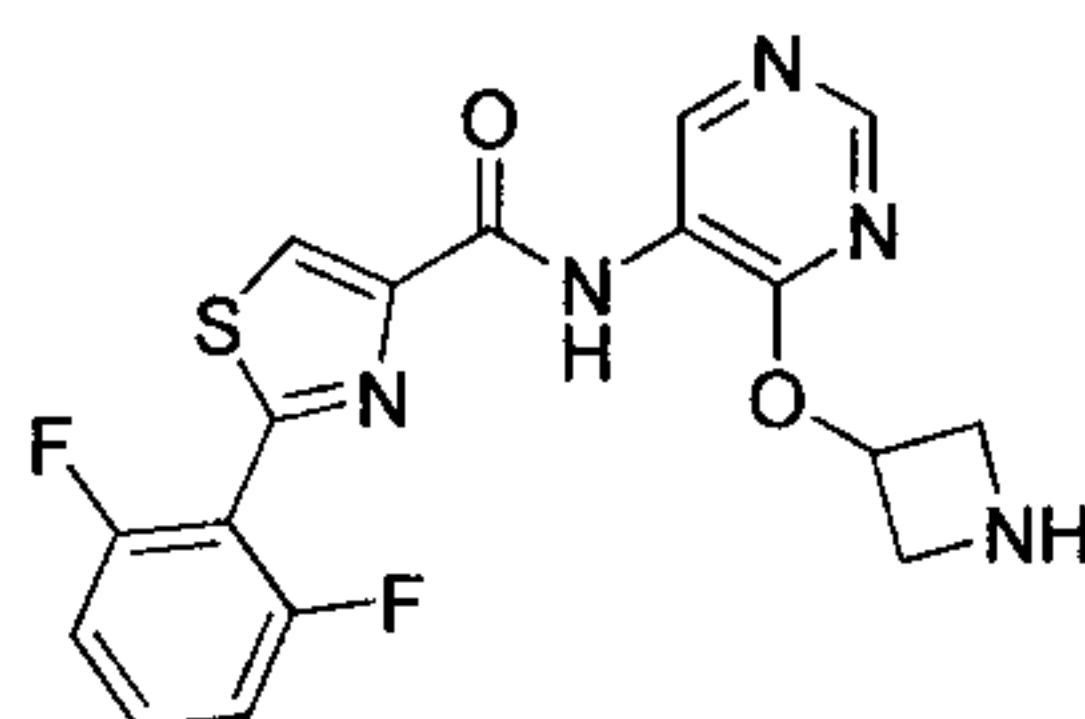
Synthesis of 3-amino-6-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)picolinamide (20)



Following the procedure described in Example 9, and substituting Compound 1E in Step (2) with 3-amino-6-(2,6-difluorophenyl)picolinic acid (20E) (40mg, 0.160mmol), the title compound **20** (20mg, 0.0467mmol) was obtained.

Example 21

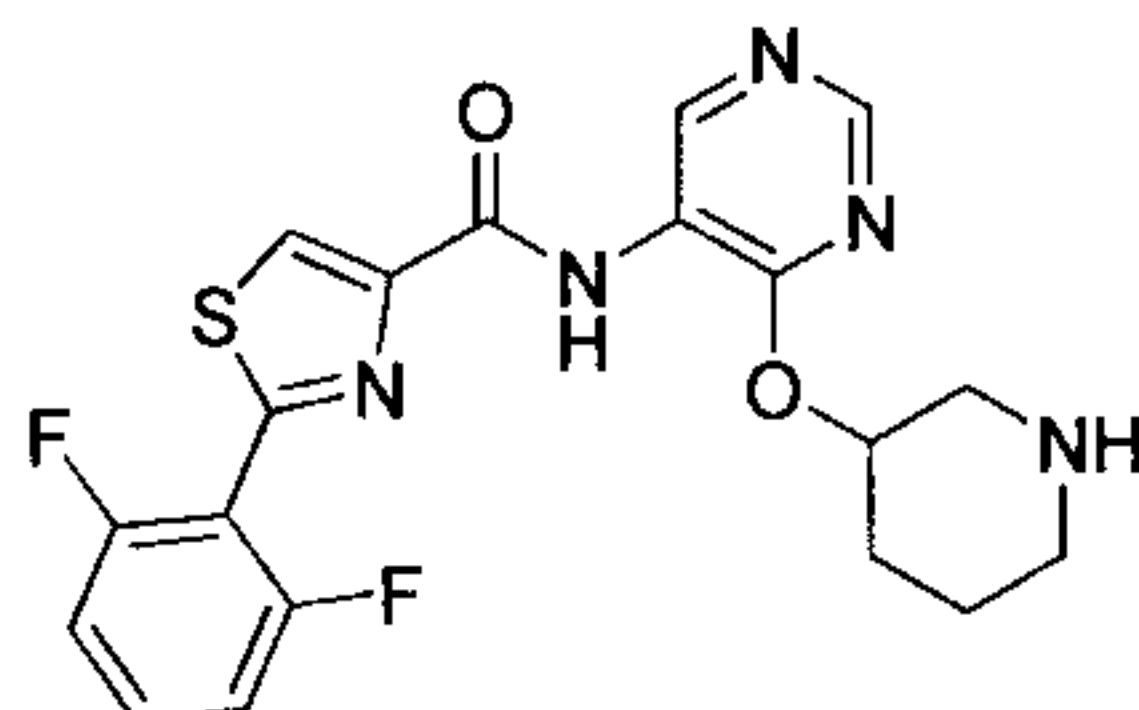
Synthesis of N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 3-hydroxyazetidine-1-carboxylate (21B2) (250mg, 1.45mmol), the title compound **21** (10mg, 0.0256mmol) was obtained.

Example 22

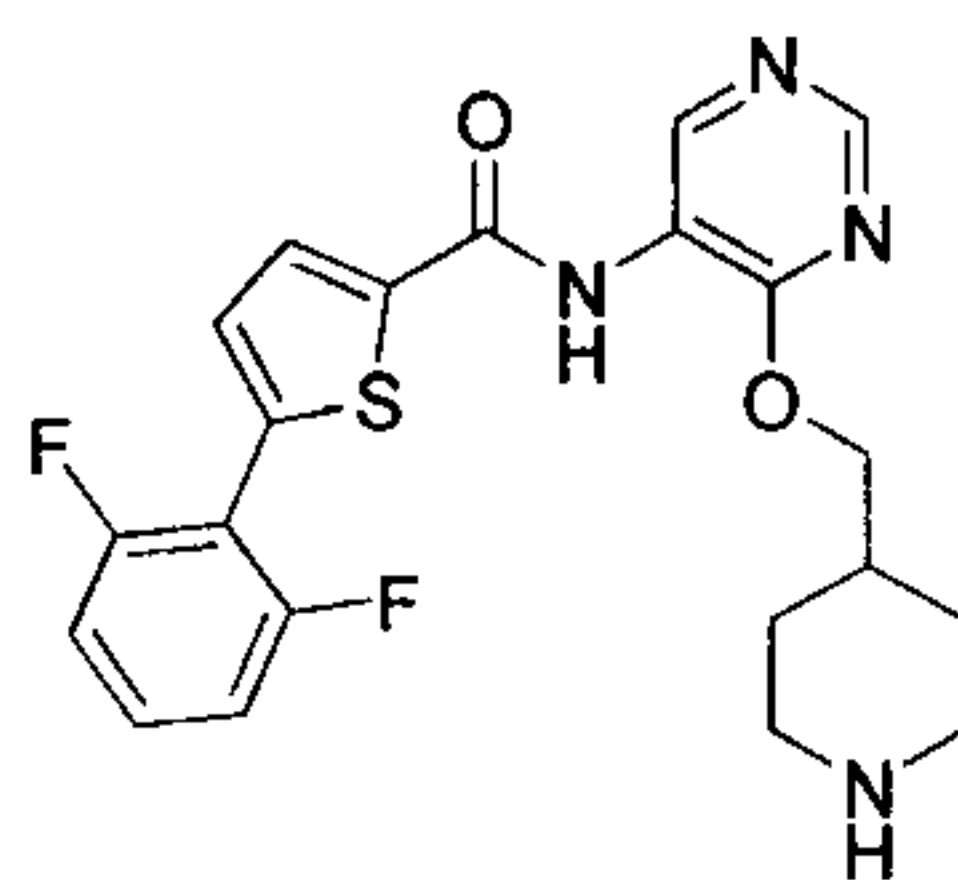
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl 3-hydroxypiperidine-1-carboxylate (22B2) (250mg, 1.24mmol), the title compound **22** (13mg, 0.0311mmol) was obtained.

Example 23

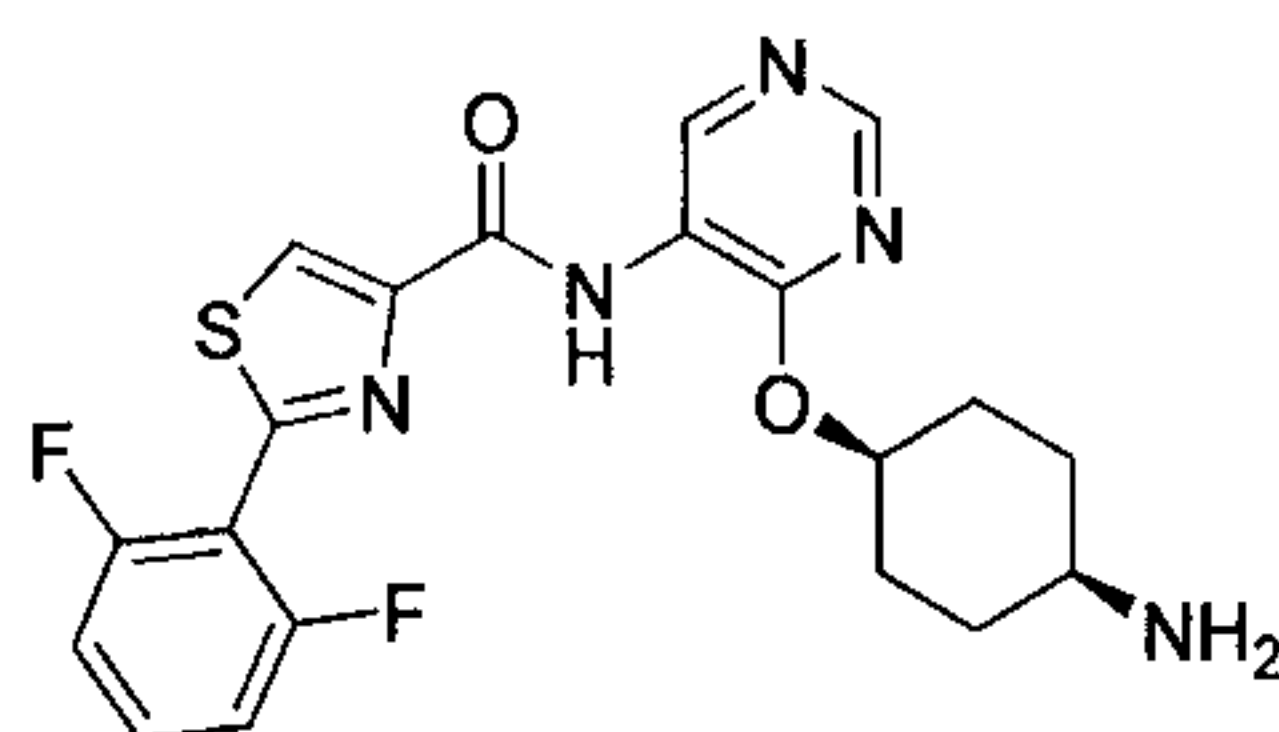
Synthesis of 5-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiophene-2-carboxamide (23)



Following the procedure described in Example 15, and substituting Compound 1E in Step (2) with 5-(2,6-difluorophenyl)thiophene-2-carboxylic acid (23E) (40mg, 0.170mmol), the title compound **23** (40mg, 0.170mmol) was obtained.

Example 24

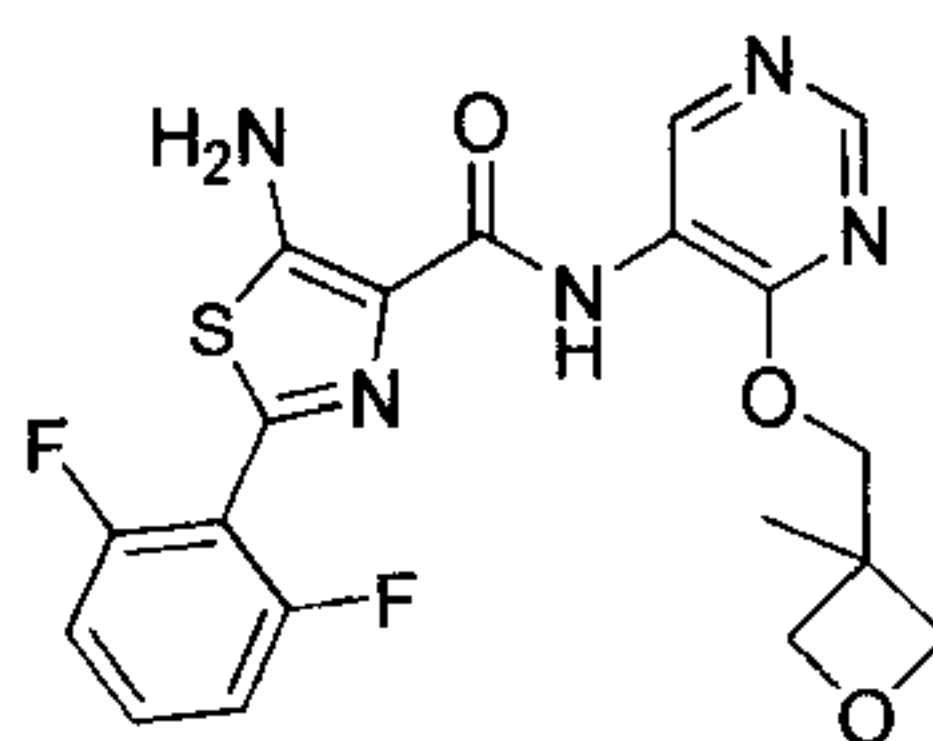
Synthesis of N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with tert-butyl (cis-4-hydroxycyclohexyl)carbamate (24B2) (250mg, 1.16mmol), the title compound **24** (13mg, 0.0311mmol) was obtained.

Example 25

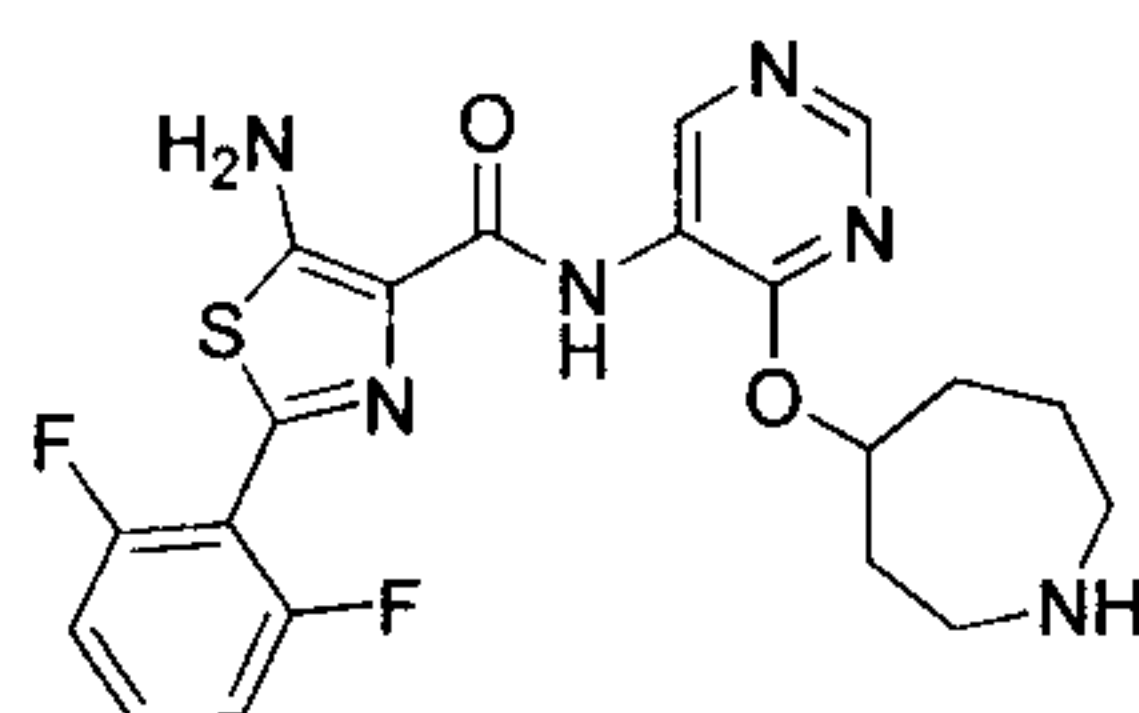
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)



Following the procedure described in Example 9, and substituting Compound 1E in Step (2) with 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2E) (40mg, 0.156mmol), the title compound **25** (27mg, 0.0644mmol) was obtained.

Example 26

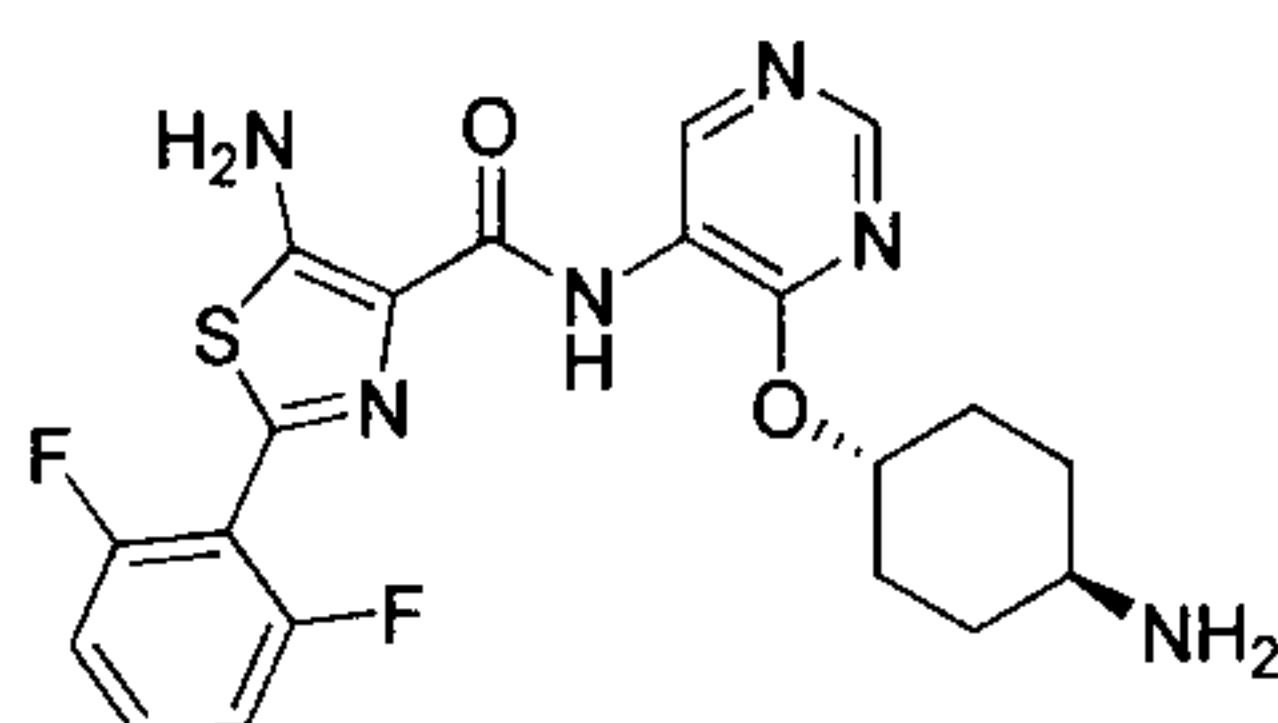
Synthesis of 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)



Following the procedure described in Example 2, and substituting Compound 1E in Step (2) with 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2E) (40mg, 0.156mmol), the title compound **26** (17mg, 0.0380mmol) was obtained.

Example 27

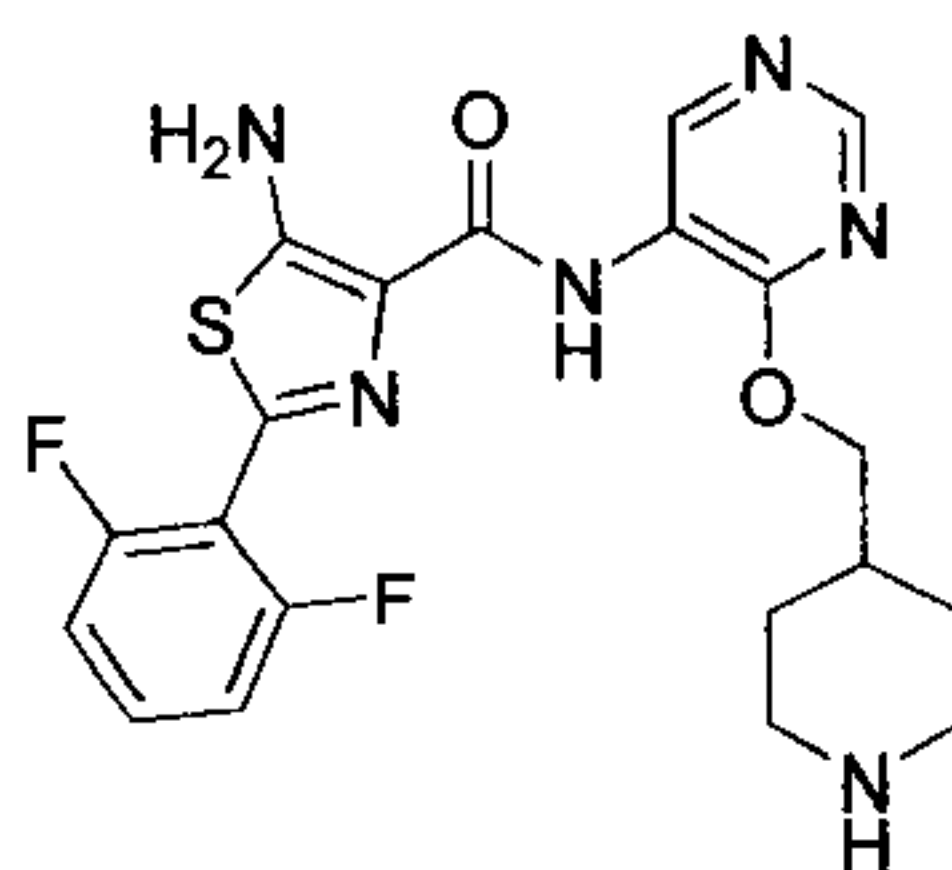
Synthesis of 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)



Following the procedure described in Example 4, and substituting Compound 3B2 in Step (1) with tert-butyl (trans-4-hydroxycyclohexyl)carbamate (27B2) (250mg, 1.16mmol), the title compound **27** (16mg, 0.0358mmol) was obtained.

Example 28

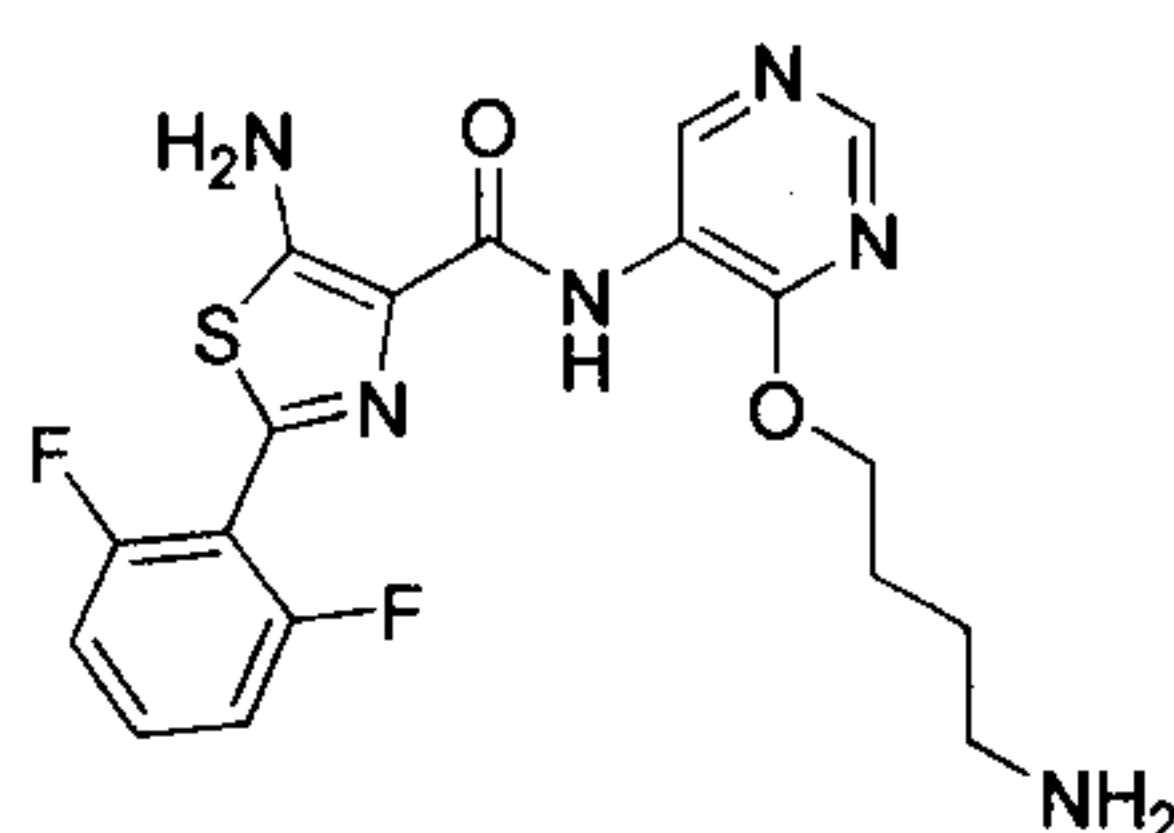
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)



Following the procedure described in Example 15, and substituting Compound 1E in Step (2) with 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2E) (40mg, 0.156mmol), the title compound **28** (21mg, 0.0470mmol) was obtained.

Example 29

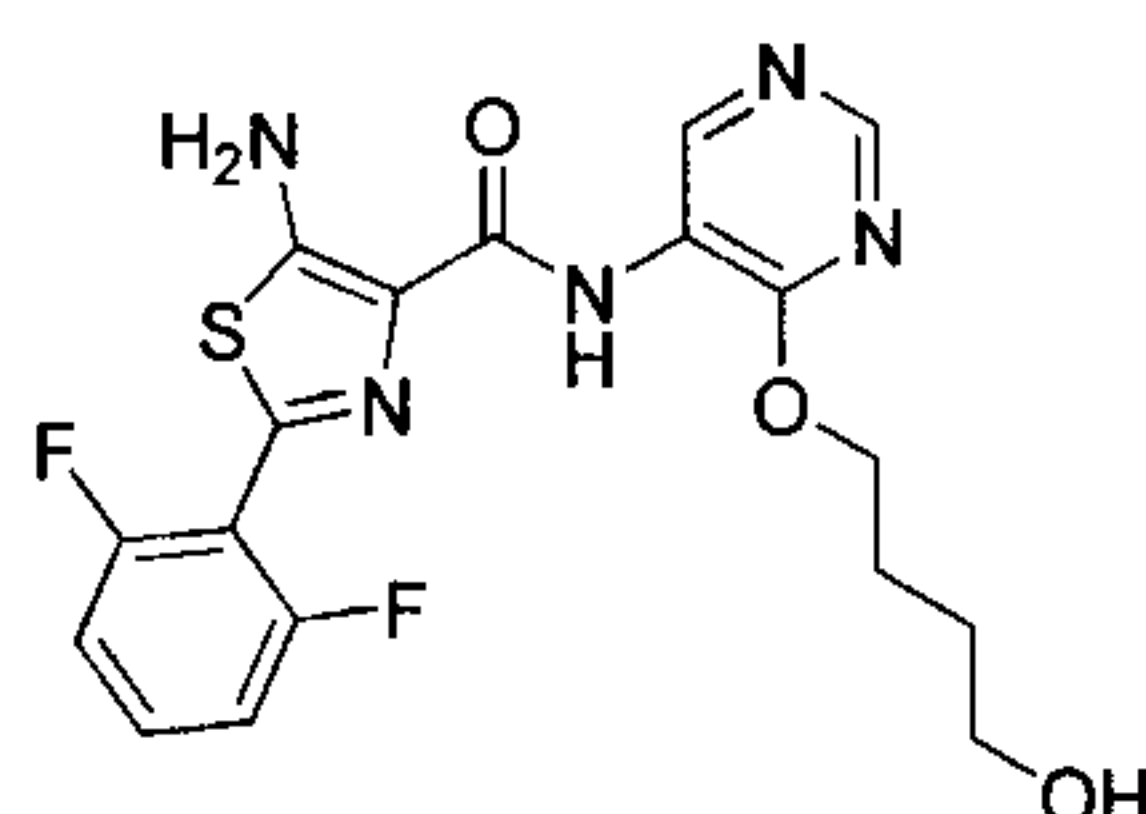
Synthesis of 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)



Following the procedure described in Example 4, and substituting Compound 3B2 in Step (1) with tert-butyl (4-hydroxybutyl)carbamate (29B2) (100mg, 0.529mmol), the title compound **29** (30mg, 0.0713mmol) was obtained.

Example 30

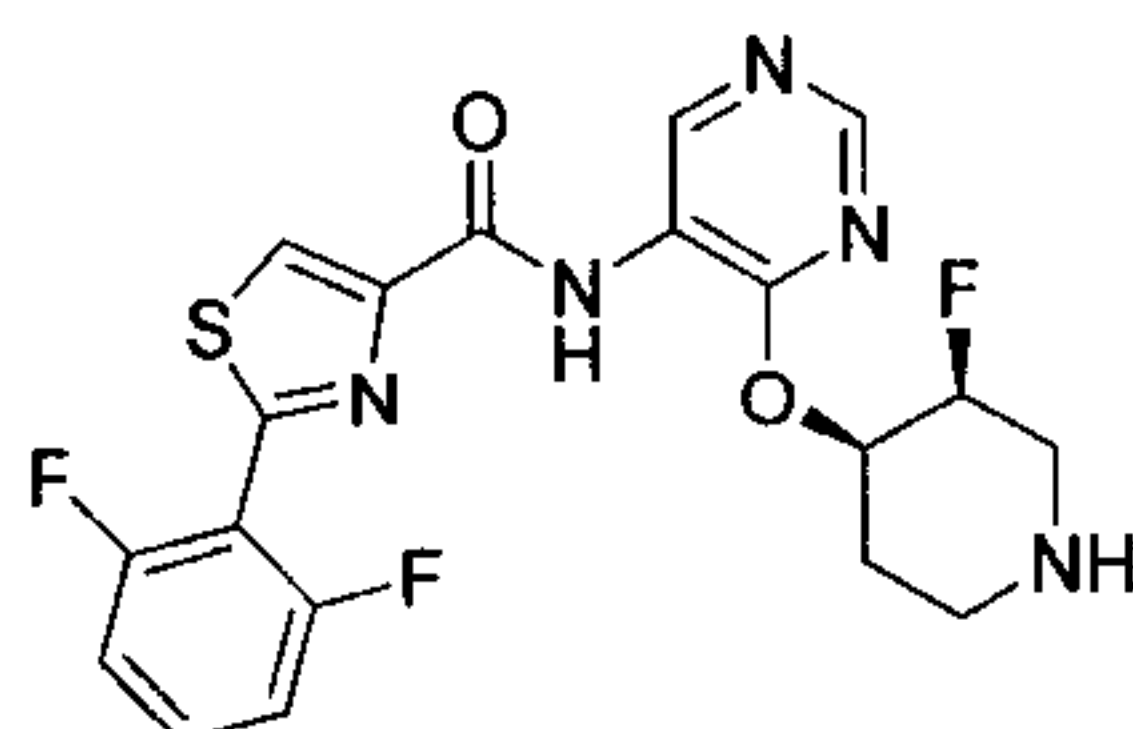
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)



Following the procedure described in Example 1, and substituting Compound 4 in Step (1) with 4-((trimethylsilyl)oxy)butan-1-ol (30B2) (100mg, 0.617mmol), the title compound **30** (32mg, 0.0760mmol) was obtained.

Example 31

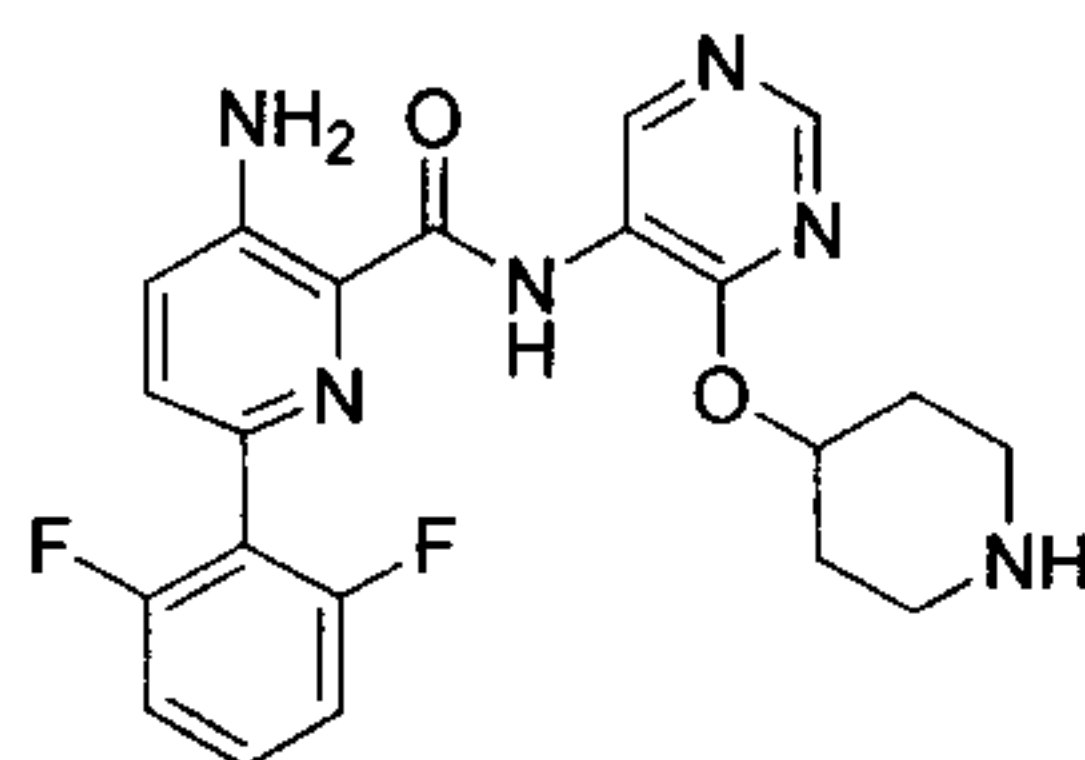
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (31)



Following the procedure described in Example 1, and substituting Compound 1B2 in Step (1) with (3S,4R)-tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (31B2) (250mg, 1.14mmol), the title compound **31** (16mg, 0.0367mmol) was obtained.

Example 32

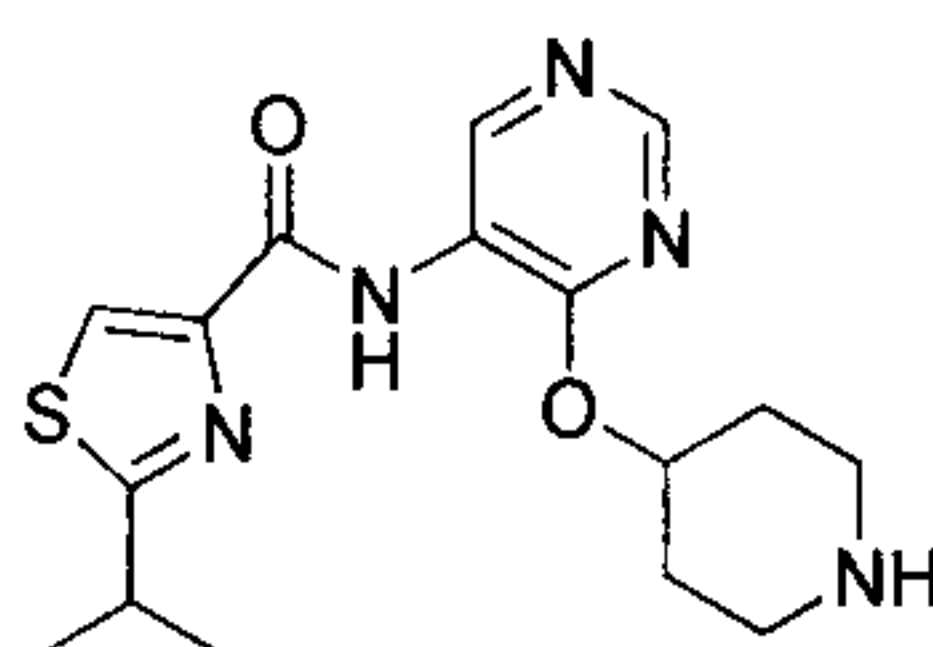
Synthesis of 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 3-amino-6-(2,6-difluorophenyl)picolinic acid (20E) (40mg, 0.156mmol), the title compound **32** (23mg, 0.0539mmol) was obtained.

Example 33

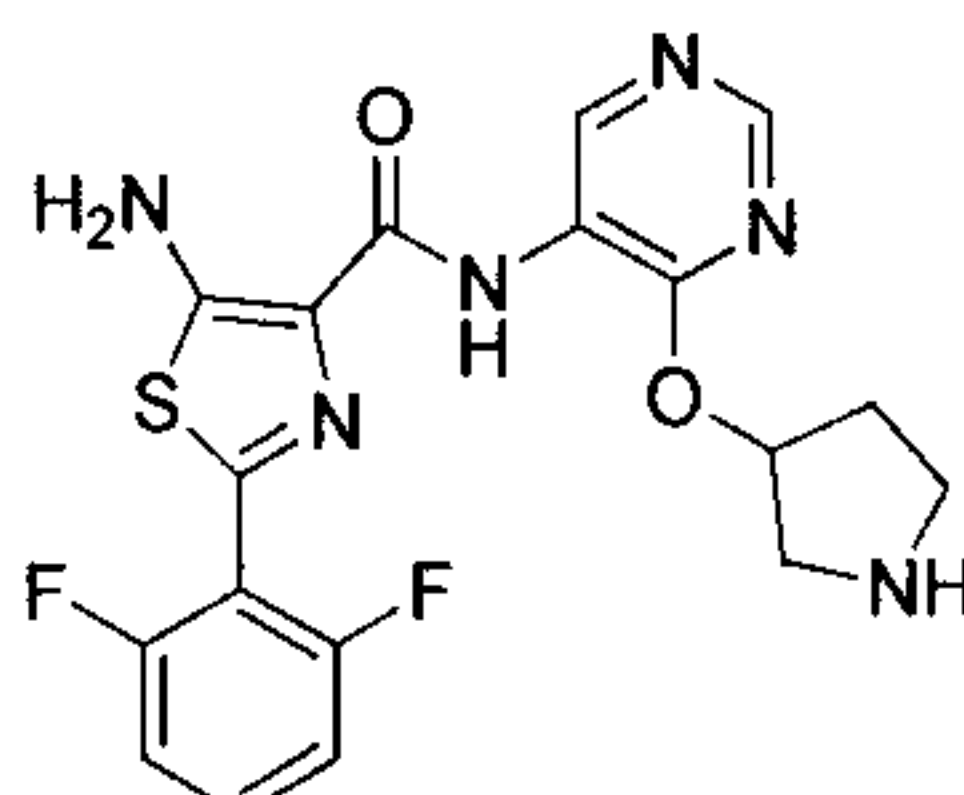
Synthesis of 2-isopropyl-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (33)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-isopropylthiazole-4-carboxylic acid (33E) (40mg, 0.234mmol), the title compound **33** (27mg, 0.0776mmol) was obtained.

Example 34

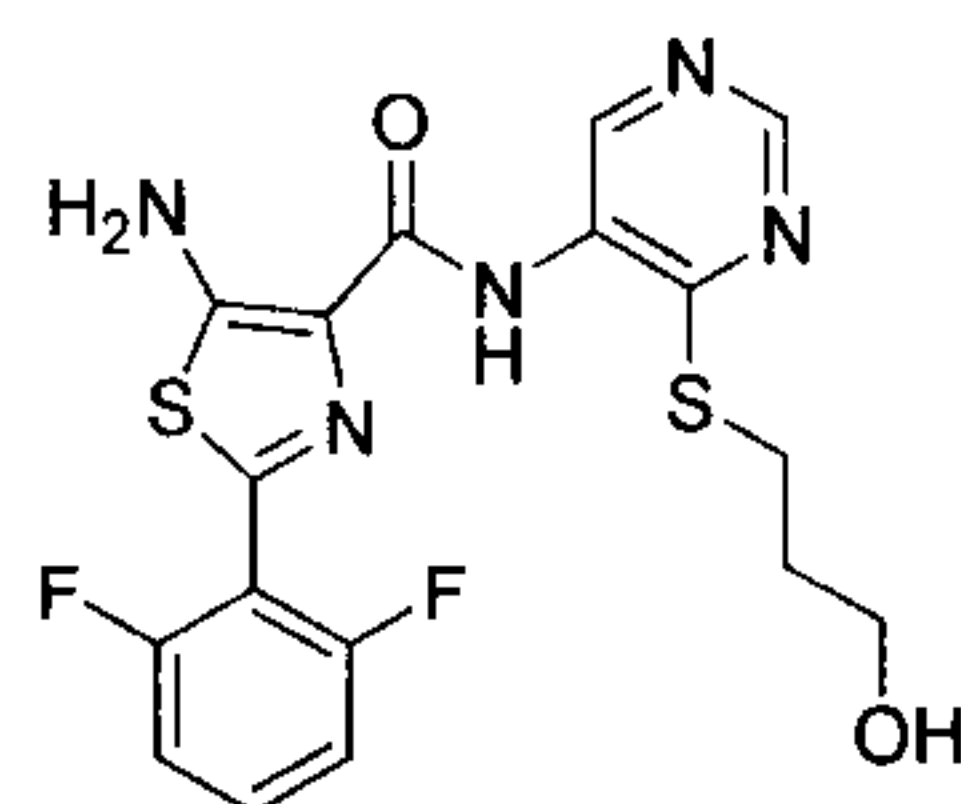
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)



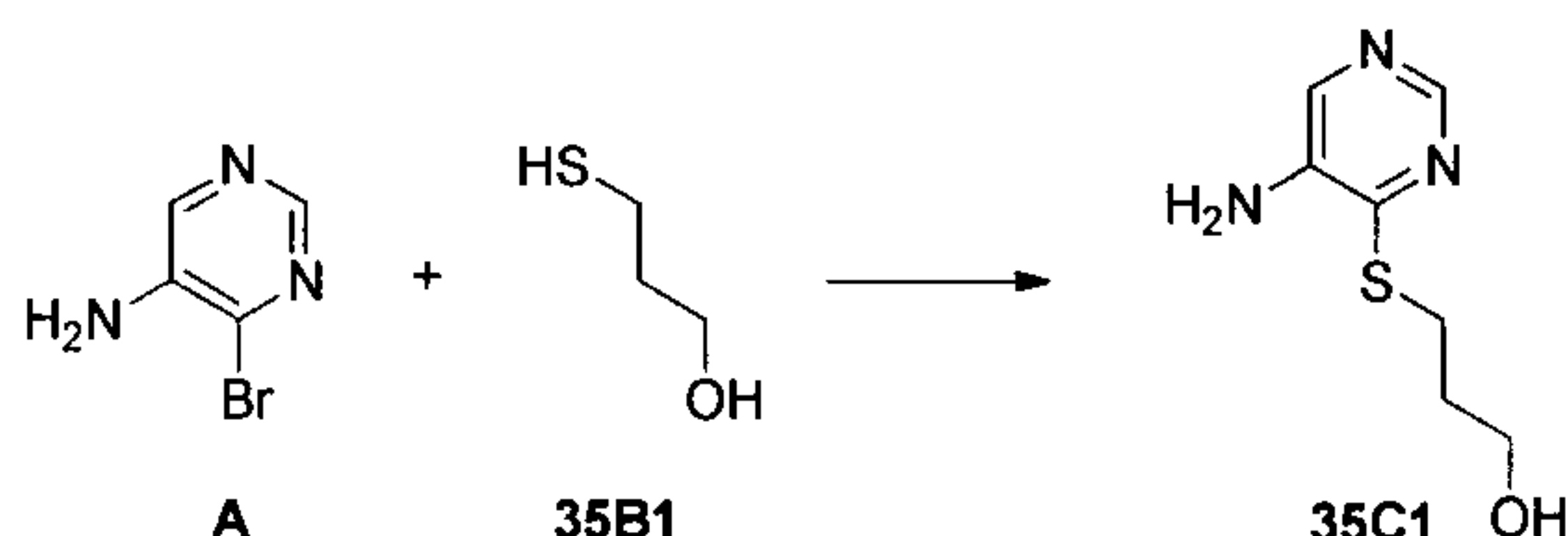
Following the procedure described in Example 1, and substituting Compound 1E in Step (2) with 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (2E) (40mg, 0.156mmol), the title compound **34** (18mg, 0.0430mmol) was obtained.

Example 35

Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)thio)pyrimidin-5-yl)thiazole-4-carboxamide (35)



(1) Synthesis of 3-((5-aminopyrimidin-4-yl)thio)propan-1-ol (35C1)



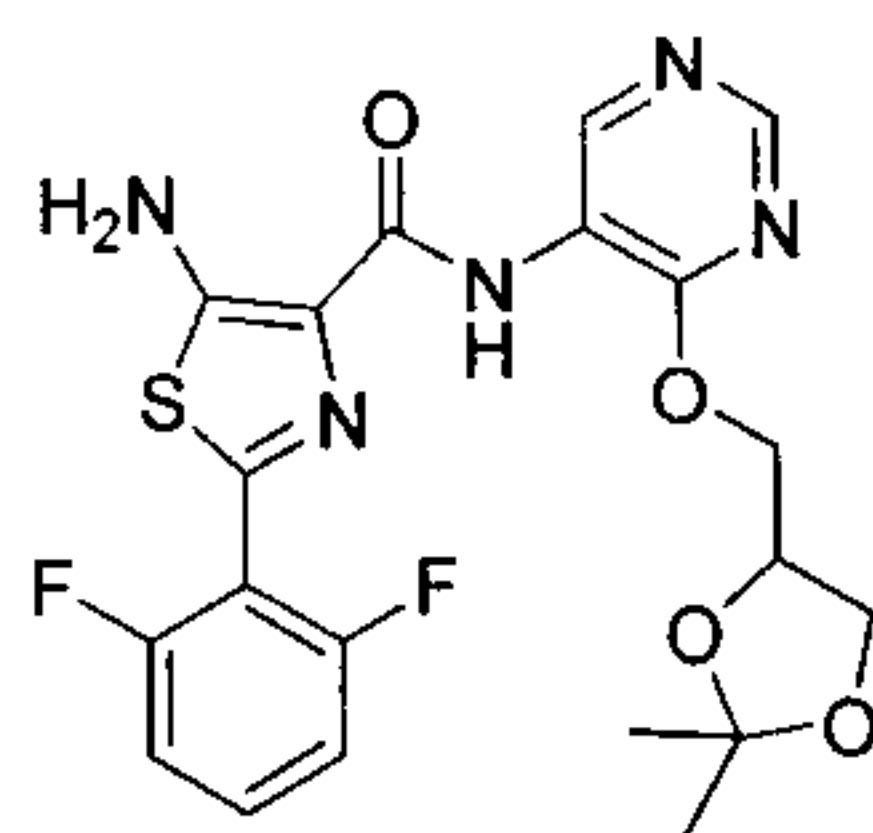
DIEA (1.11g, 8.61mmol) was added to a solution of 4-bromopyrimidin-5-amine (A) (1.0g, 5.74mmol) and 3-mercaptopropan-1-ol (35B1) (0.53g, 5.74mmol) in dioxane (5mL). The reaction mixture was heated to 50°C under nitrogen and stirred for 30 min. The LC/MS spectrum showed that the reaction had completed. Water (50mL) was added and a solid precipitated. The off white solid product (35C1) (913mg, 4.93mmol) was obtained after filtration and air drying at 25°C.

(2) Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)thio)pyrimidin-5-yl)thiazole-4-carboxamide (35)

Following the procedure described in Example 1, and substituting Compound 1D3 in Step (2) with 3-((5-aminopyrimidin-4-yl)thio)propan-1-ol (35C1) (29mg, 0.156mmol), the title compound **35** (23mg, 0.0545mmol) was obtained.

Example 36

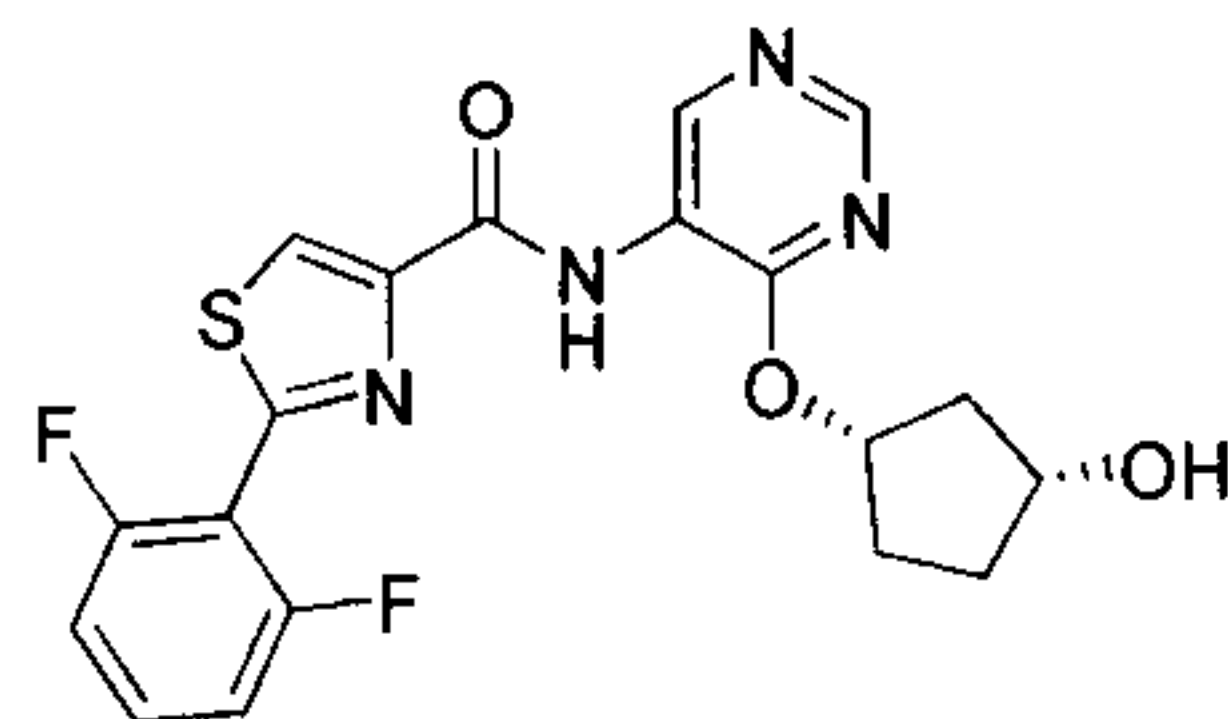
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (36)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (36B2) (100mg, 0.758mmol), the title compound **36** (27mg, 0.0646mmol) was obtained.

Example 37

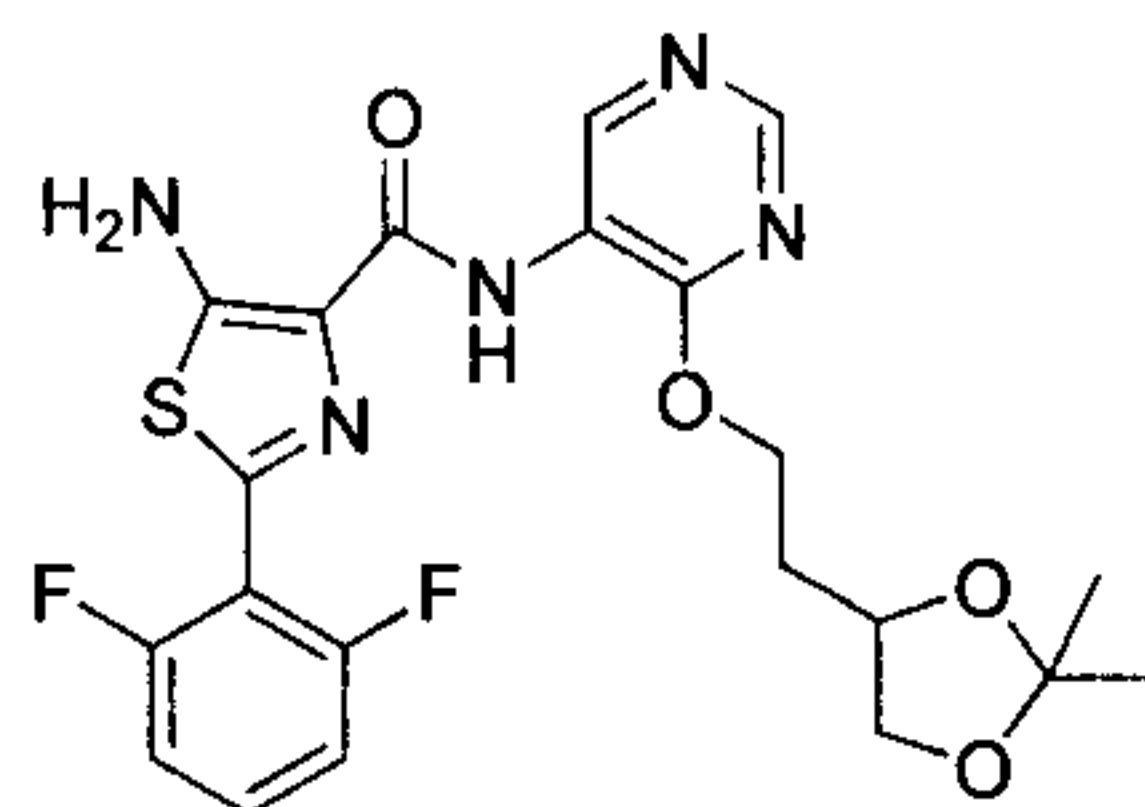
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with (1R,3S)-cyclopentane-1,3-diol (37B2) (100mg, 0.980mmol), the title compound **37** (14mg, 0.0335mmol) was obtained.

Example 38

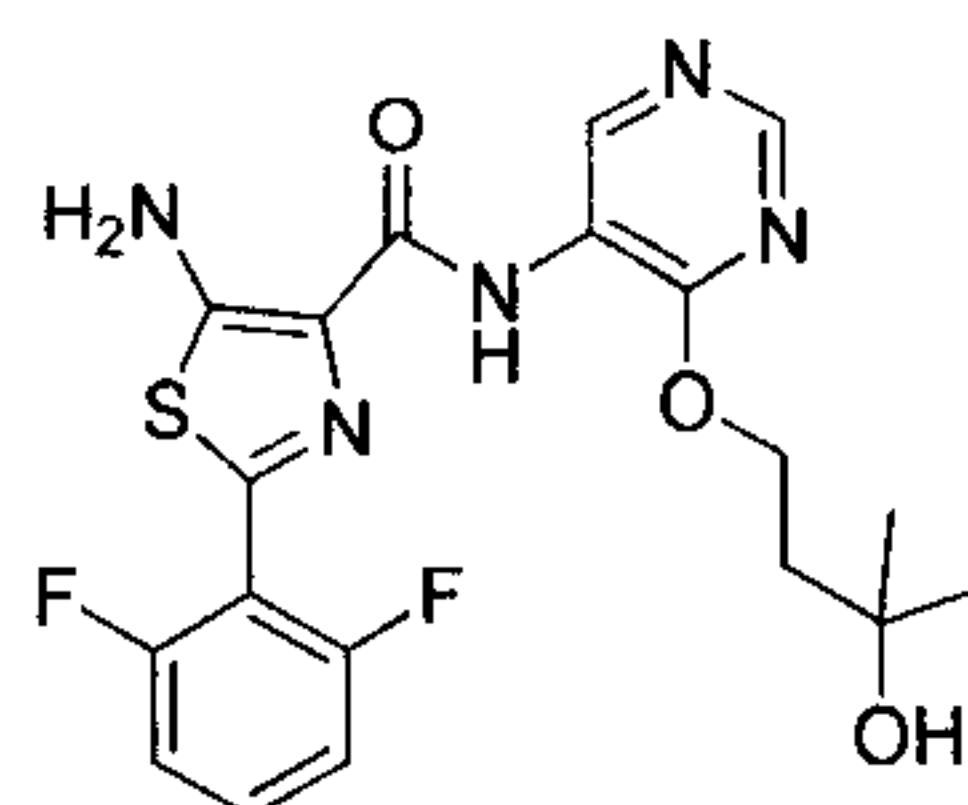
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (38)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (38B2) (100mg, 0.684mmol), the title compound **38** (21mg, 0.0440mmol) was obtained.

Example 39

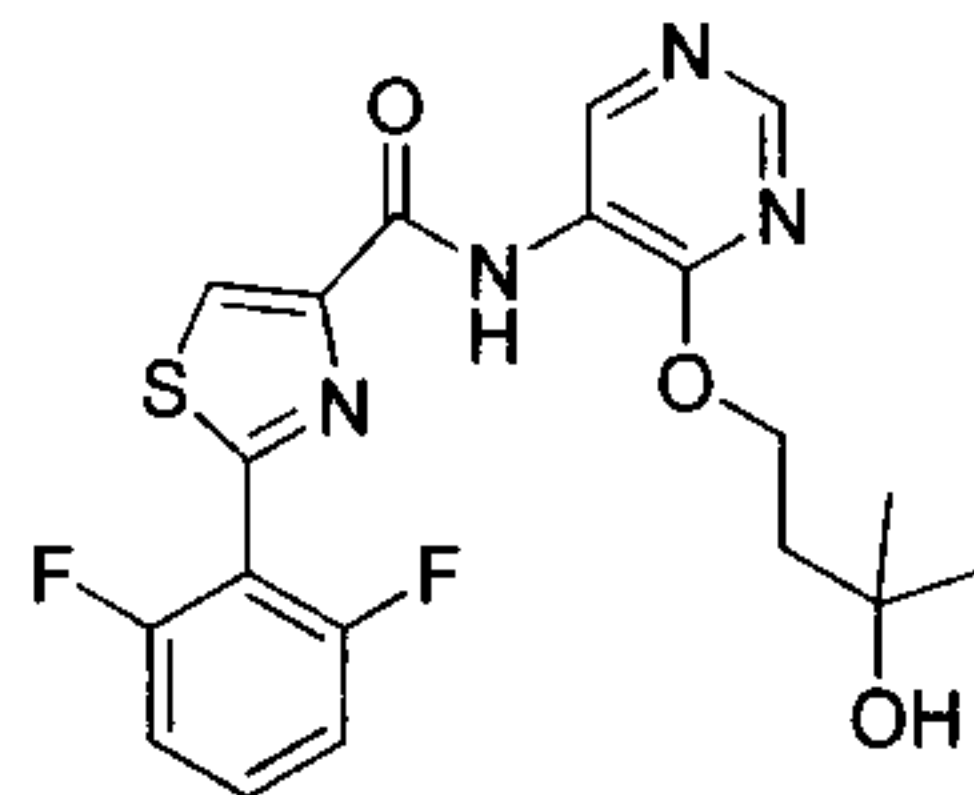
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with 3-methylbutane-1,3-diol (39B2) (100mg, 0.960mmol), the title compound **39** (18mg, 0.0414mmol) was obtained.

Example 40

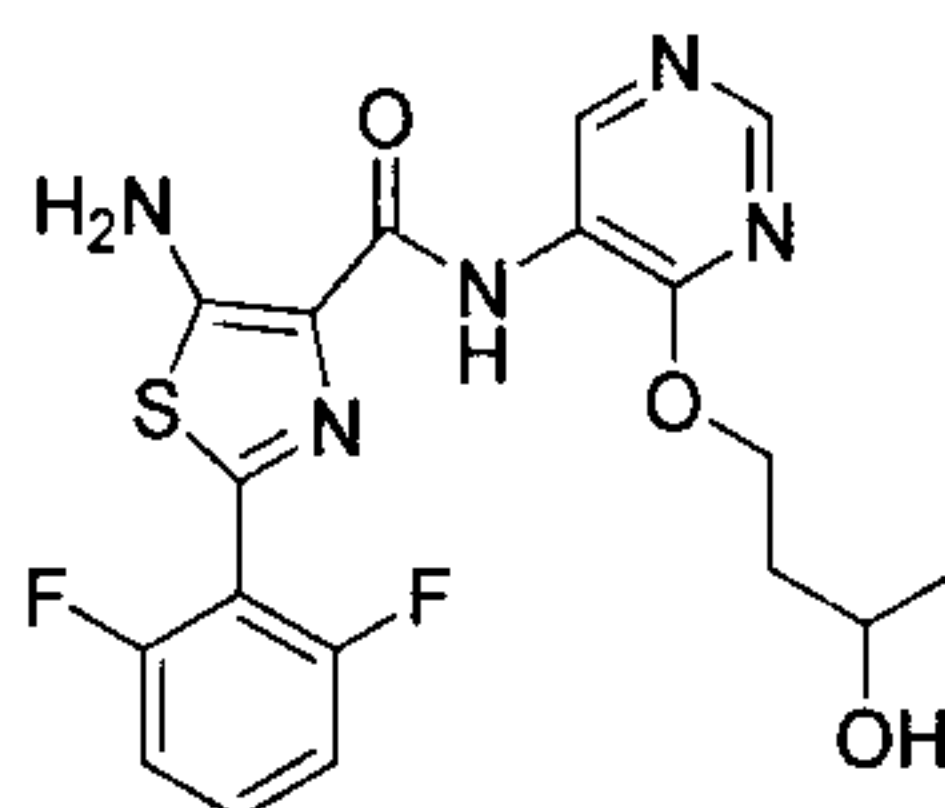
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with 3-methylbutane-1,3-diol (39B2) (100mg, 0.960mmol), the title compound **40** (24mg, 0.0571mmol) was obtained.

Example 41

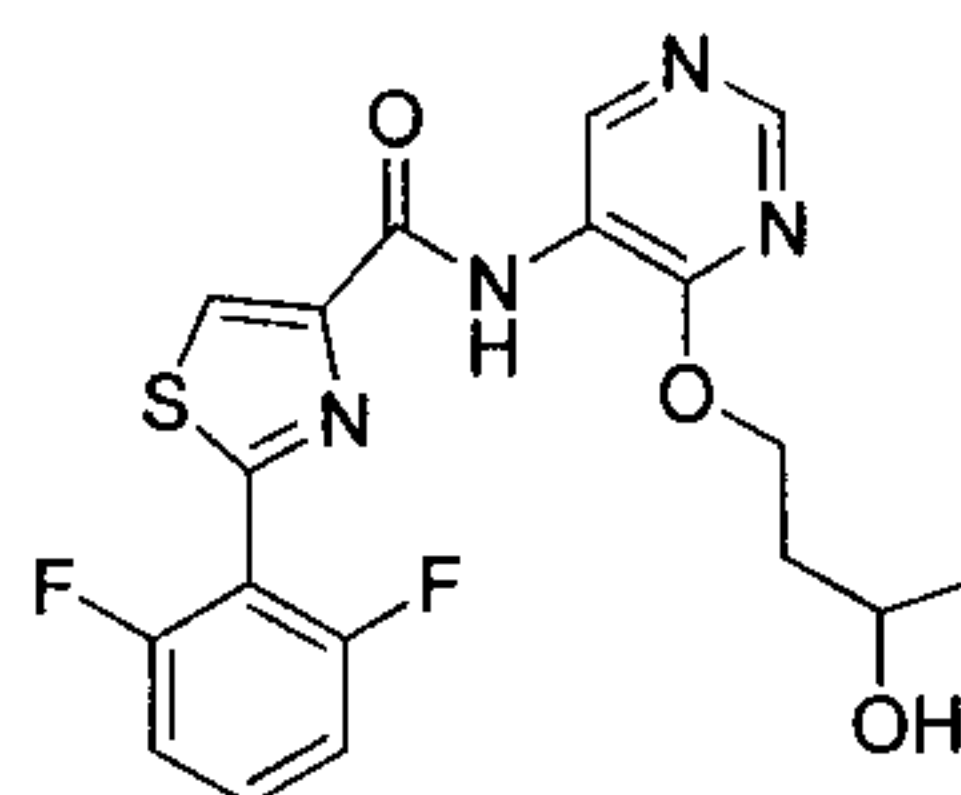
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with butane-1,3-diol (41B2) (100mg, 1.11mmol), the title compound **41** (11mg, 0.0261mmol) was obtained.

Example 42

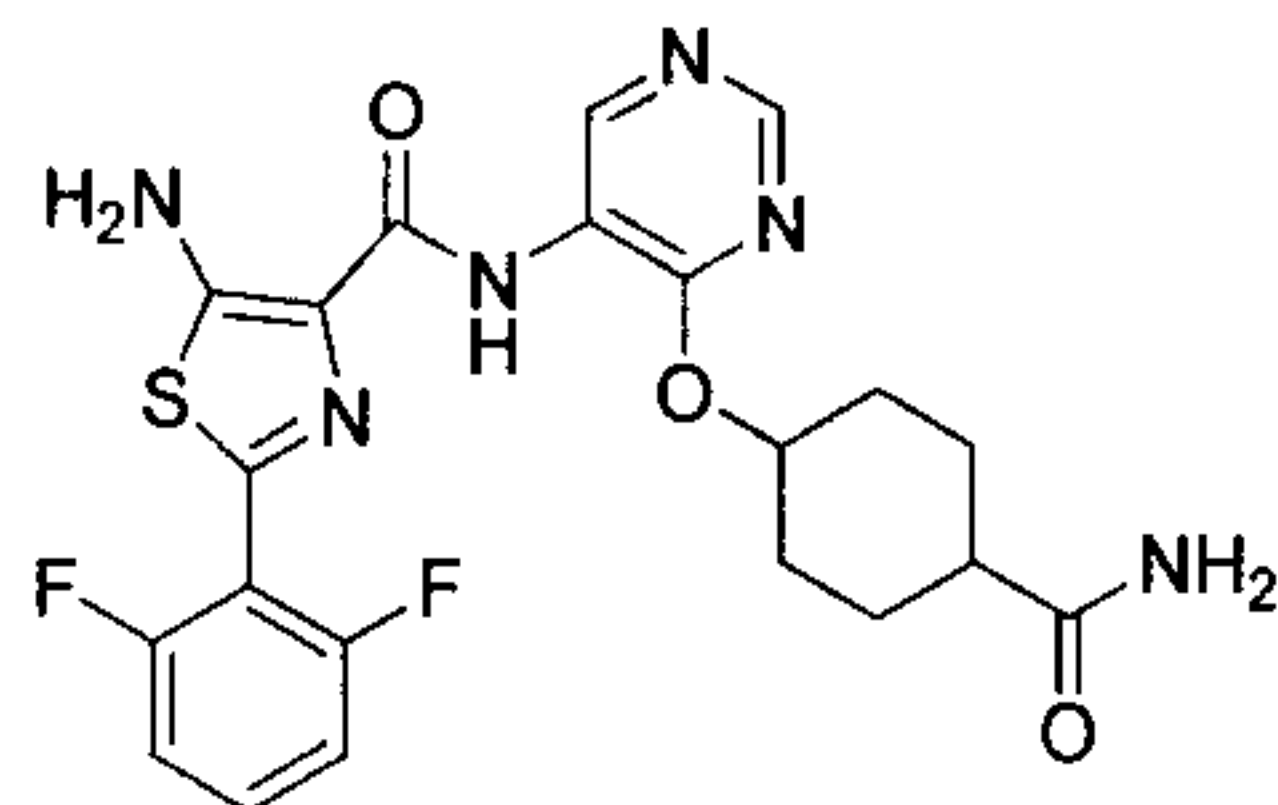
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with butane-1,3-diol (41B2) (100mg, 1.11mmol), the title compound **42** (24mg, 0.0571mmol) was obtained.

Example 43

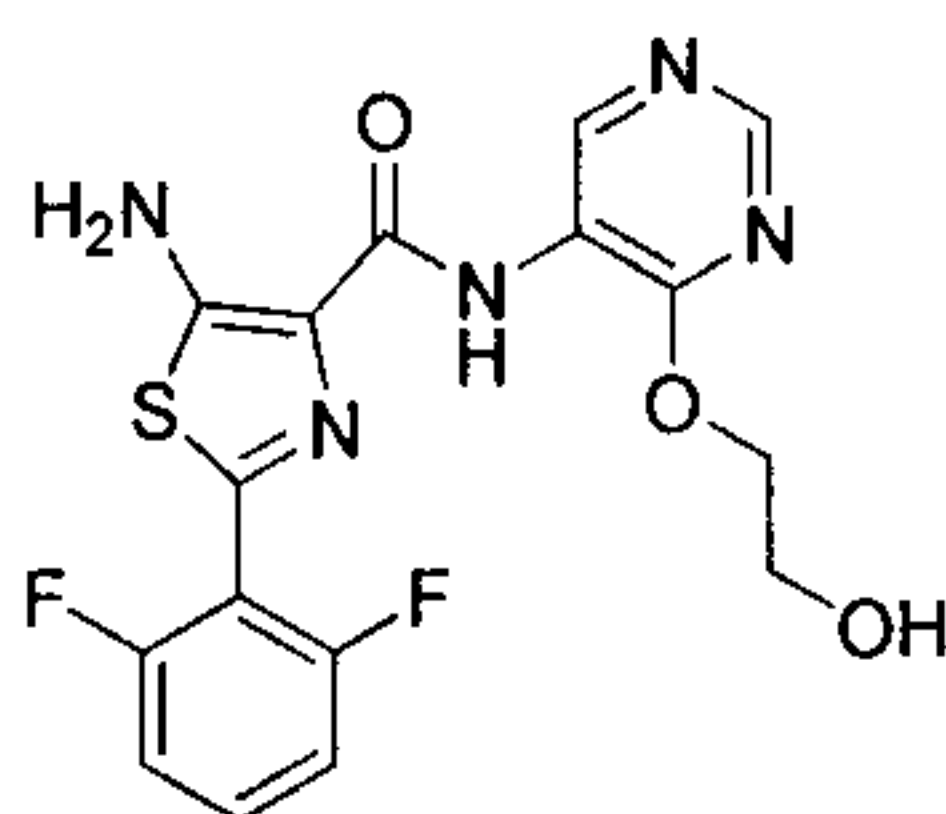
Synthesis of 5-amino-N-(4-((4-carbamoylcyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (43)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with 4-hydroxycyclohexanecarboxamide (43B2) (100mg, 0.699mmol), the title compound **43** (12mg, 0.0253mmol) was obtained.

Example 44

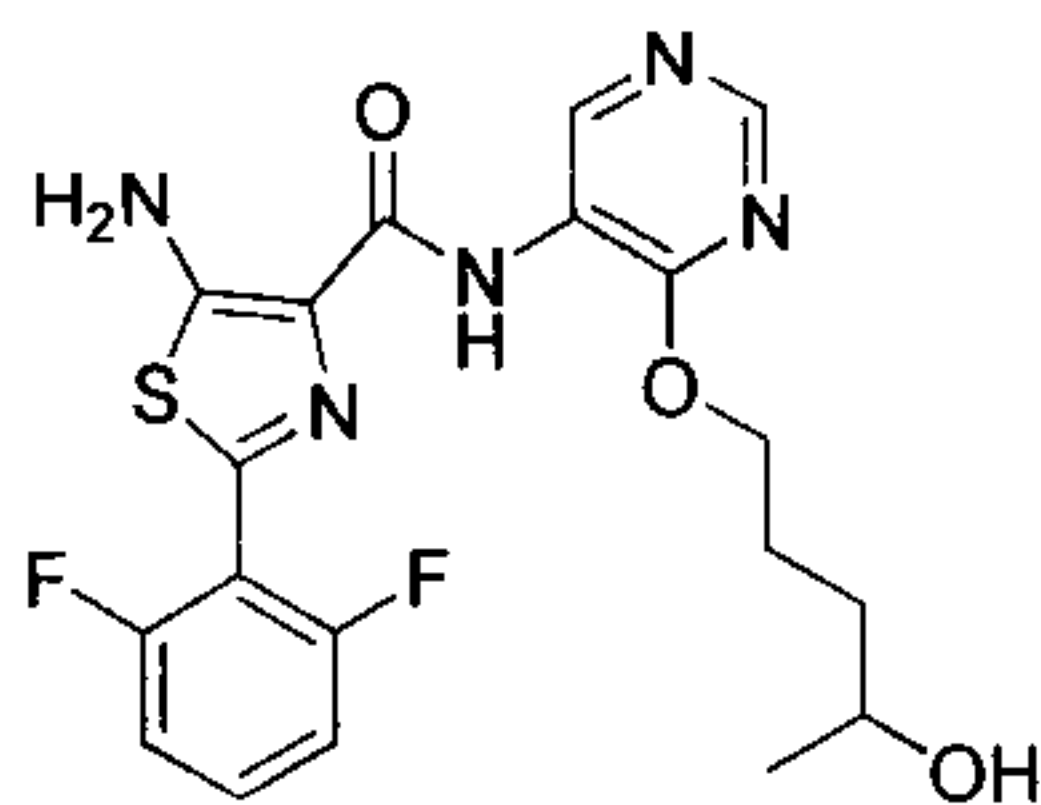
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-hydroxyethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (44)



Following the procedure described in Example 4, and substituting Compound 3B2 in Step (1) with 2-((trimethylsilyl)oxy)ethanol (44B2) (100mg, 0.746mmol), the title compound **44** (29mg, 0.0738mmol) was obtained.

Example 45

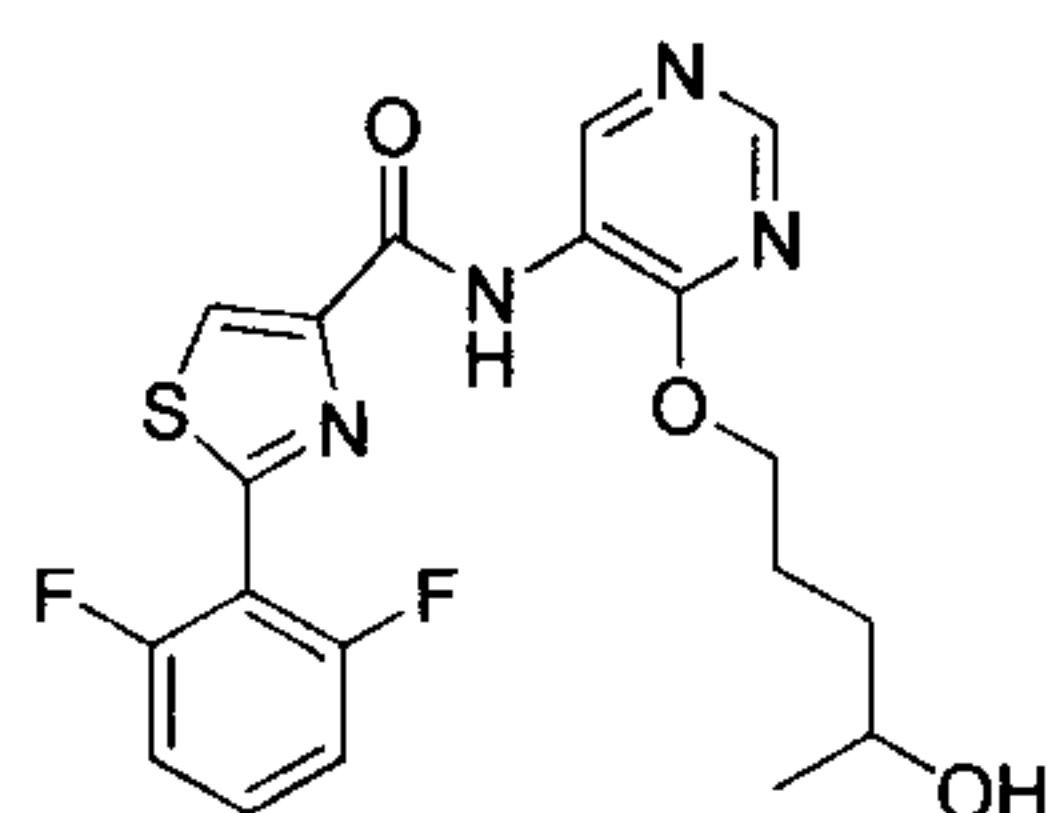
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with pentane-1,4-diol (45B2) (100mg, 0.960mmol), the title compound **45** (22mg, 0.0506mmol) was obtained.

Example 46

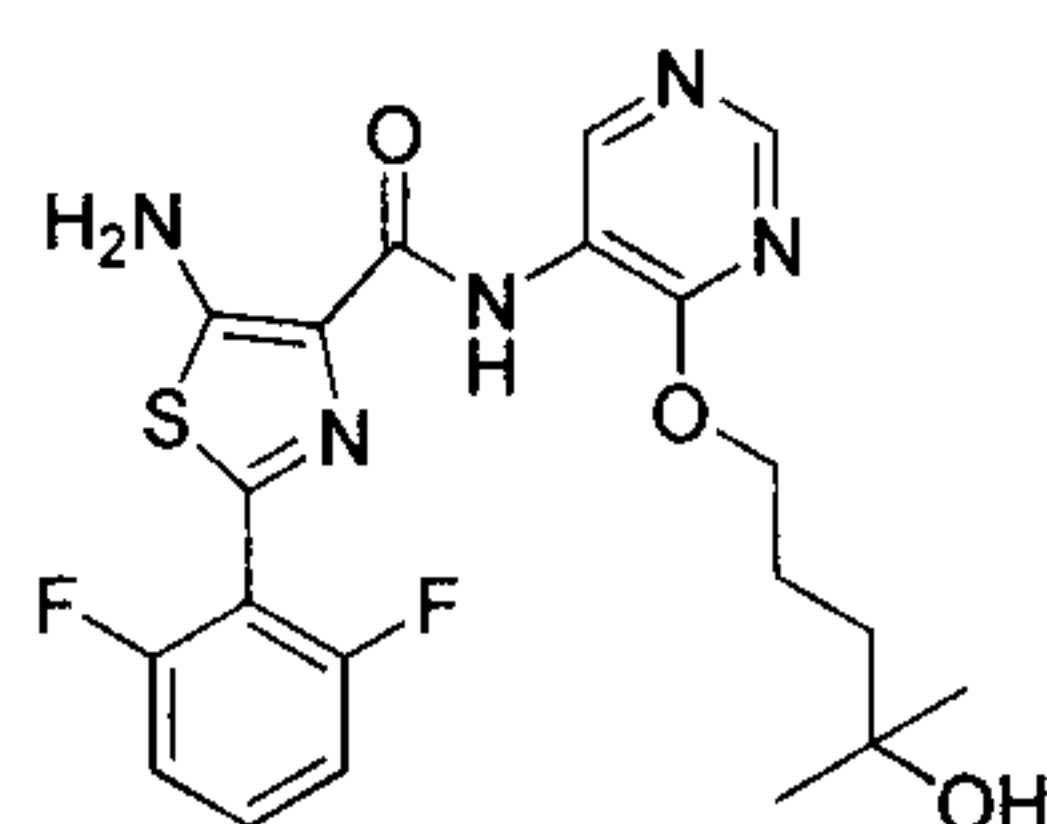
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with pentane-1,4-diol (45B2) (100mg, 0.960mmol), the title compound **46** (26mg, 0.0619mmol) was obtained.

Example 47

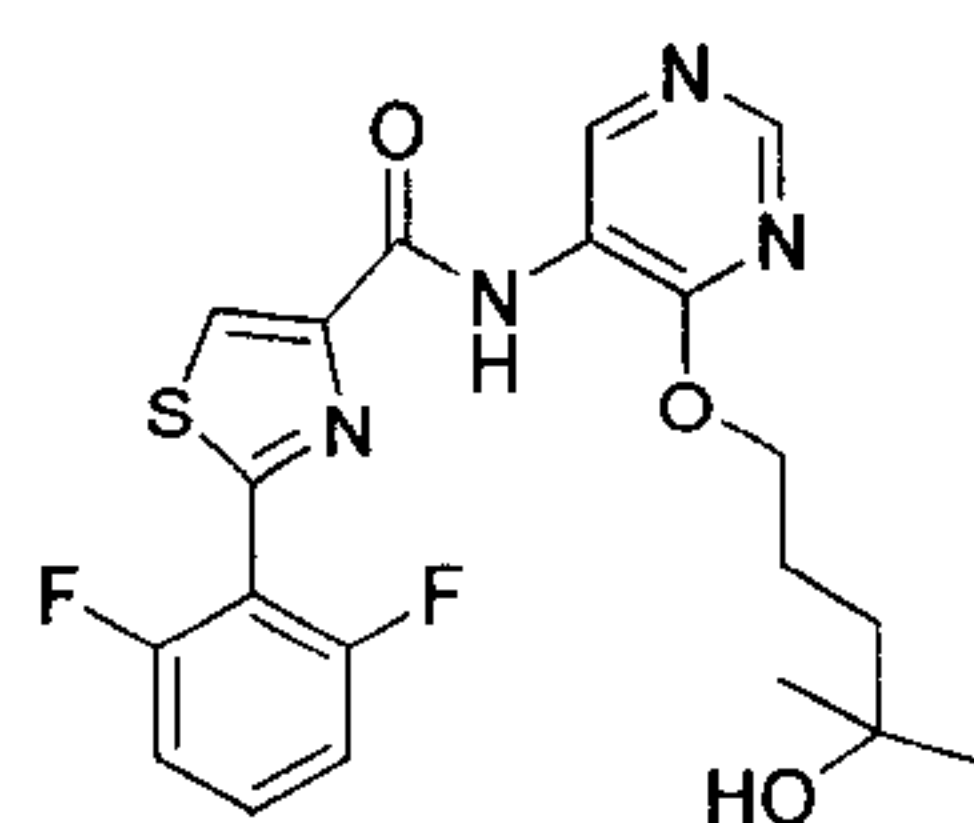
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide(47)



Following the procedure described in Example 25, and substituting Compound 9B2 in Step (1) with 4-methylpentane-1,4-diol (47B2) (100mg, 0.848mmol), the title compound **47** (23mg, 0.0512mmol) was obtained.

Example 48

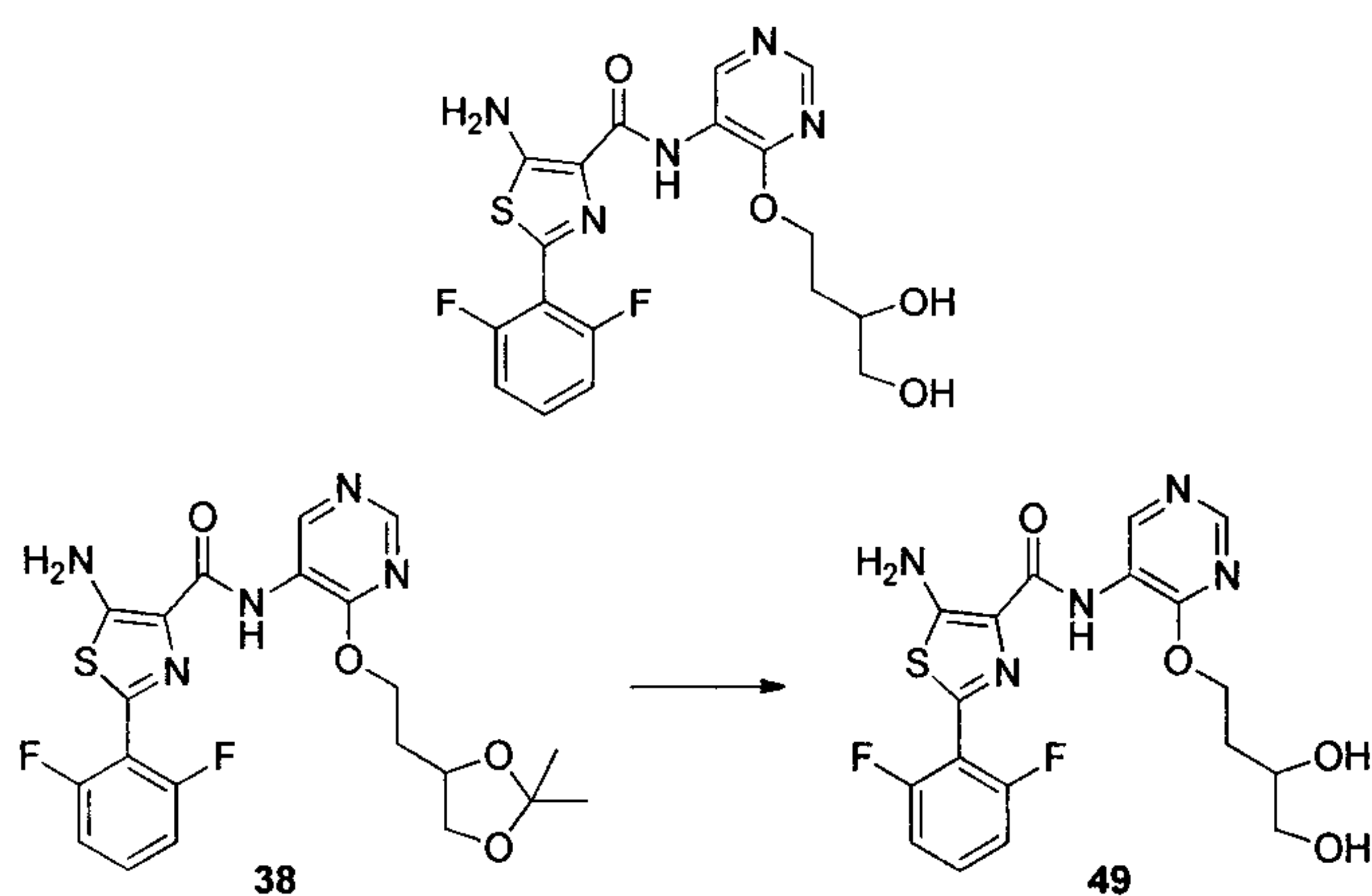
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)



Following the procedure described in Example 5, and substituting Compound 5B2 in Step (1) with 4-methylpentane-1,4-diol (48B2) (100mg, 0.848mmol), the title compound **48** (25mg, 0.0576mmol) was obtained.

Example 49

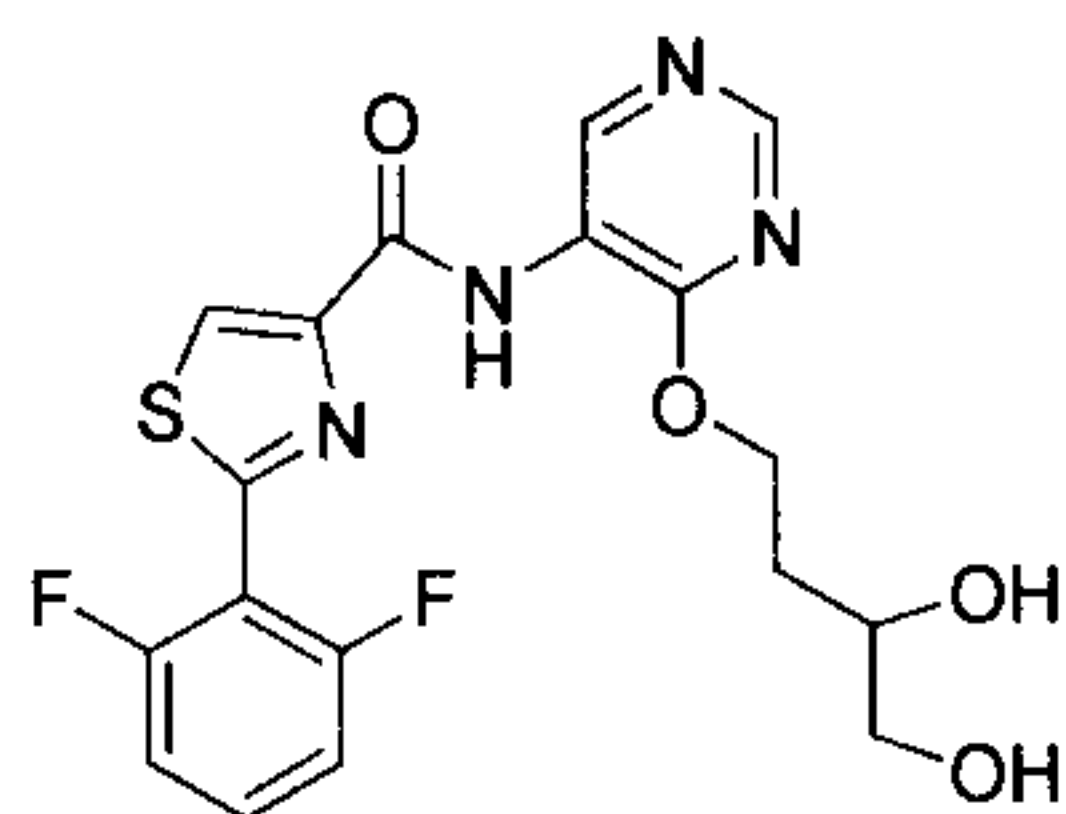
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)



At room temperature (25°C), to a solution of 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (**38**) (20mg, 0.0419mmol) in methanol (2mL) was added concentrated HCl (0.5mL) and the solution was stirred for 4 hours. 10% Na₂CO₃ solution was added to neutralize the solution to pH=7, the water (20mL) was added and a precipitate was formed. An off white solid product **49** (11mg, 0.0252mmol) was obtained after filtration and air drying at 25°C.

Example 50

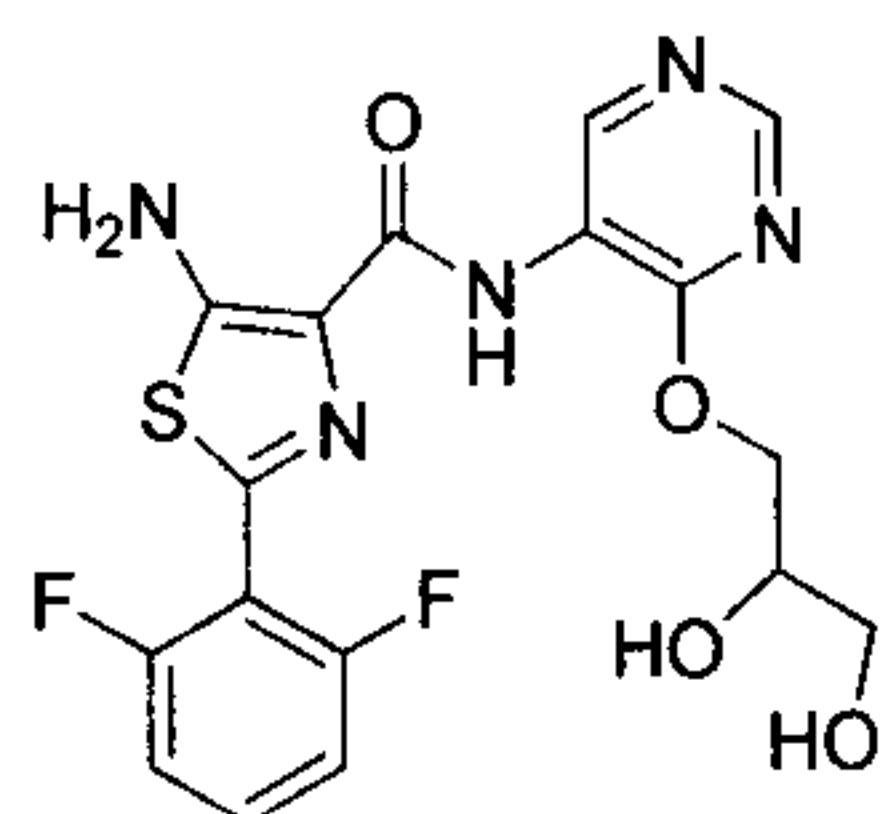
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (**50**)



Following the procedure described in Example 38 and 49, and substituting Compound 2E in Step (1) of Example 38 with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (**1E**) (40mg, 0.166mmol), the title compound **50** (15mg, 0.0355mmol) was obtained.

Example 51

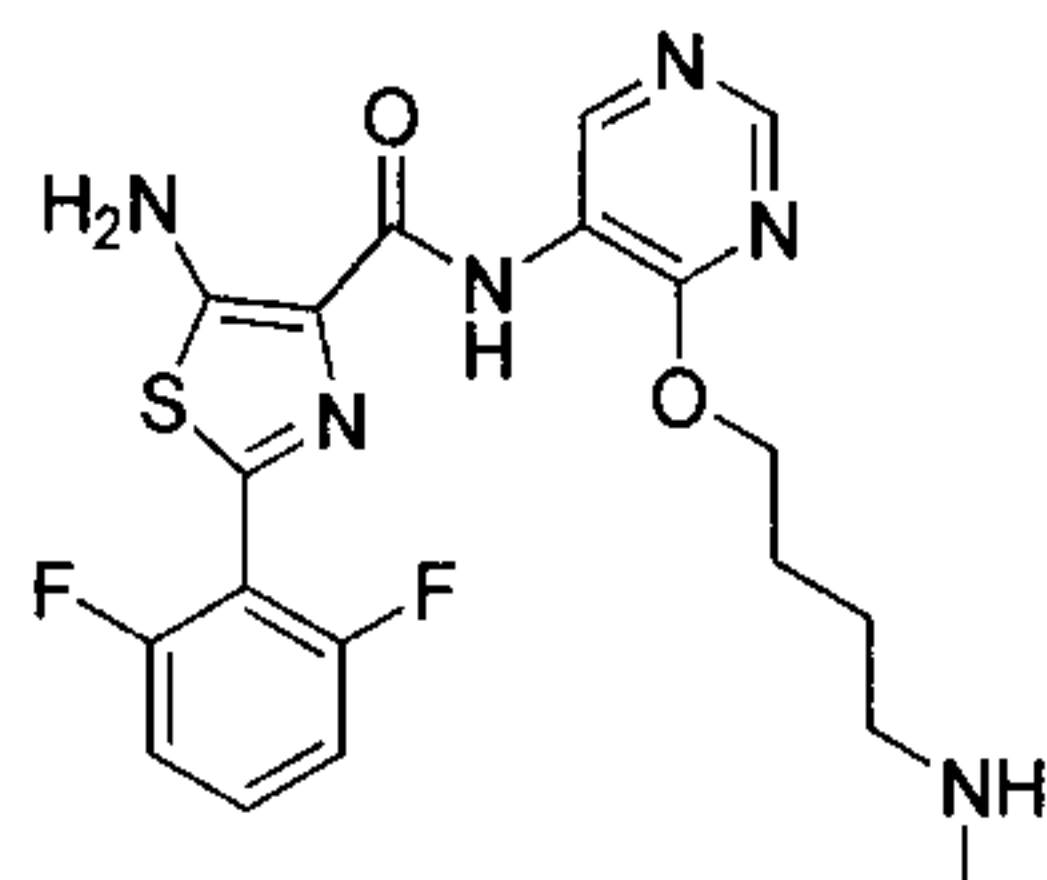
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(2,3-dihydroxypropoxy)pyrimidin-5-yl)thiazole-4-carboxamide (**51**)



Following the procedure described in Example 48, and substituting Compound 38 in Step (1) with 5-amino-2-(2,6-difluorophenyl)-N-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (36) (20mg, 0.0432mmol), the title compound **51** (9mg, 0.0213mmol) was obtained.

Example 52

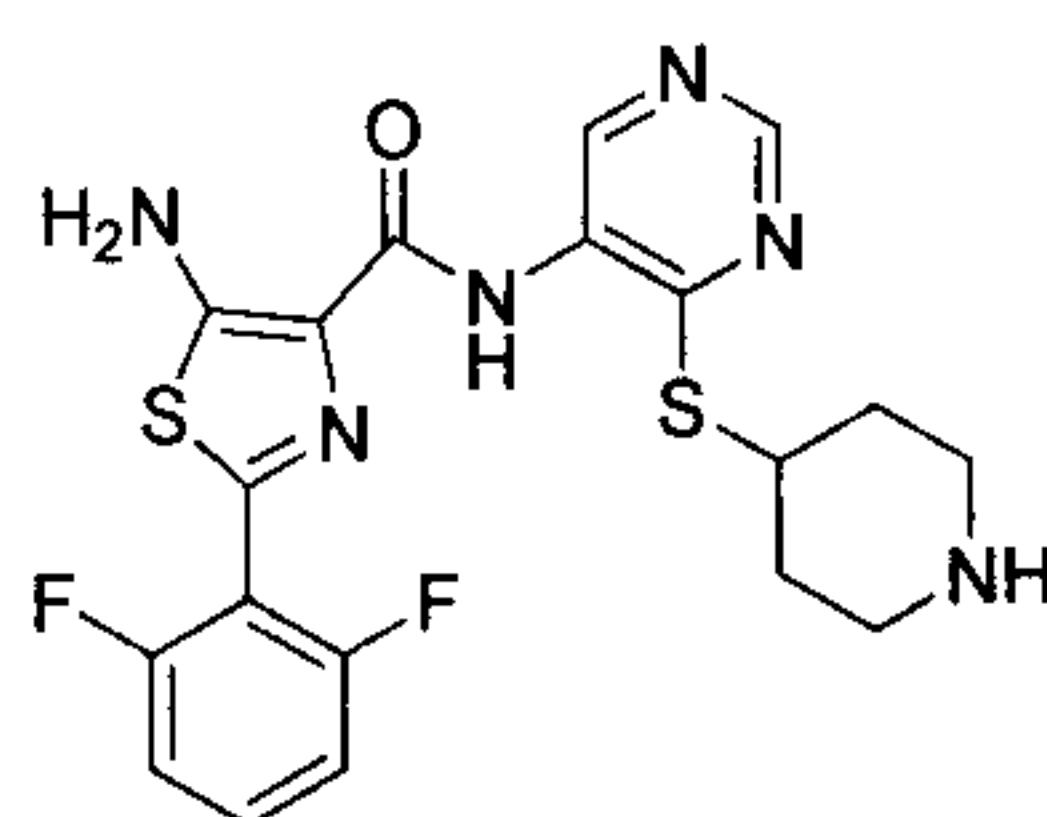
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)



Following the procedure described in Example 29, and substituting Compound 29B2 in Step (1) with tert-butyl (4-hydroxybutyl)(methyl)carbamate (52B2) (50mg, 0.246mmol), the title compound **52** (13mg, 0.0299mmol) was obtained.

Example 53

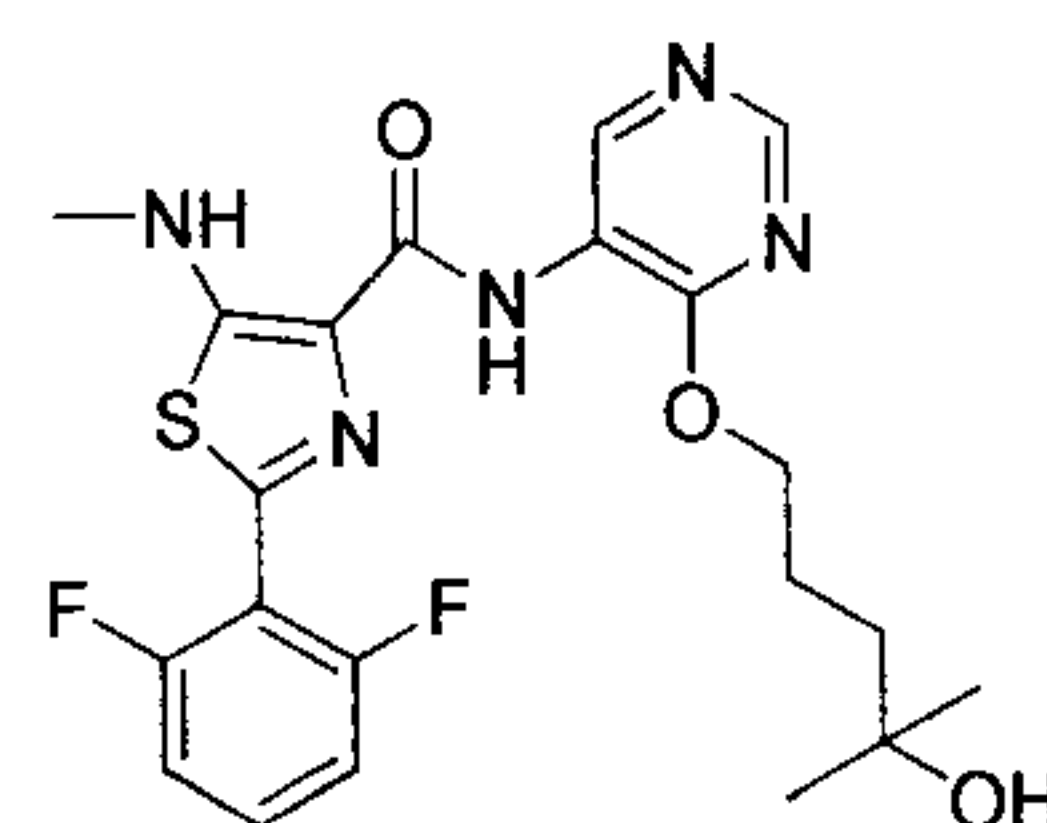
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)



Following the procedure described in Example 35 and Step (3) of Example 1, and substituting Compound 35B1 in Step (1) of Example 35 with tert-butyl 4-mercaptopiperidine-1-carboxylate (53B1) (250mg, 1.15mmol), the title compound **53** (16mg, 0.0356mmol) was obtained.

Example 54

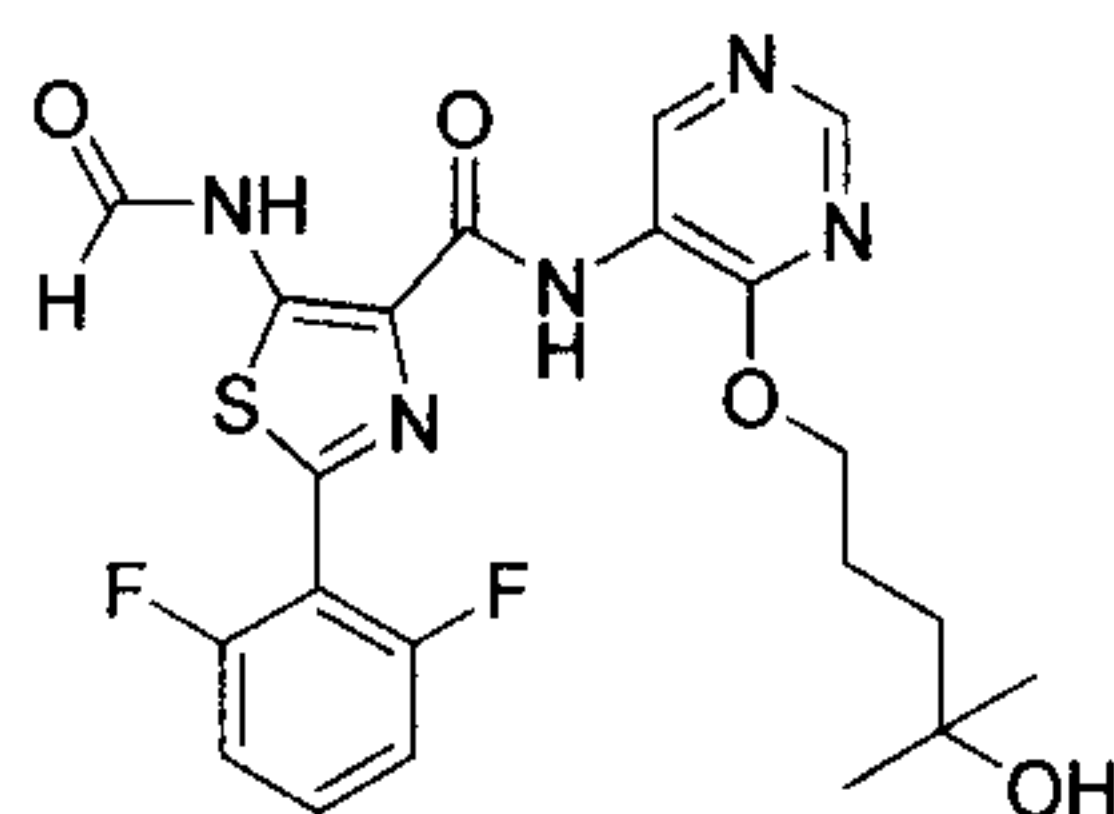
Synthesis of 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)-5-(methylamino)thiazole-4-carboxamide (54)



Following the procedure described in Example 47, and substituting Compound 2E in Step (2) with 2-(2,6-difluorophenyl)-5-(methylamino)thiazole-4-carboxylic acid (54E) (40mg, 0.148mmol), the title compound **54** (24mg, 0.0518mmol) was obtained.

Example 55

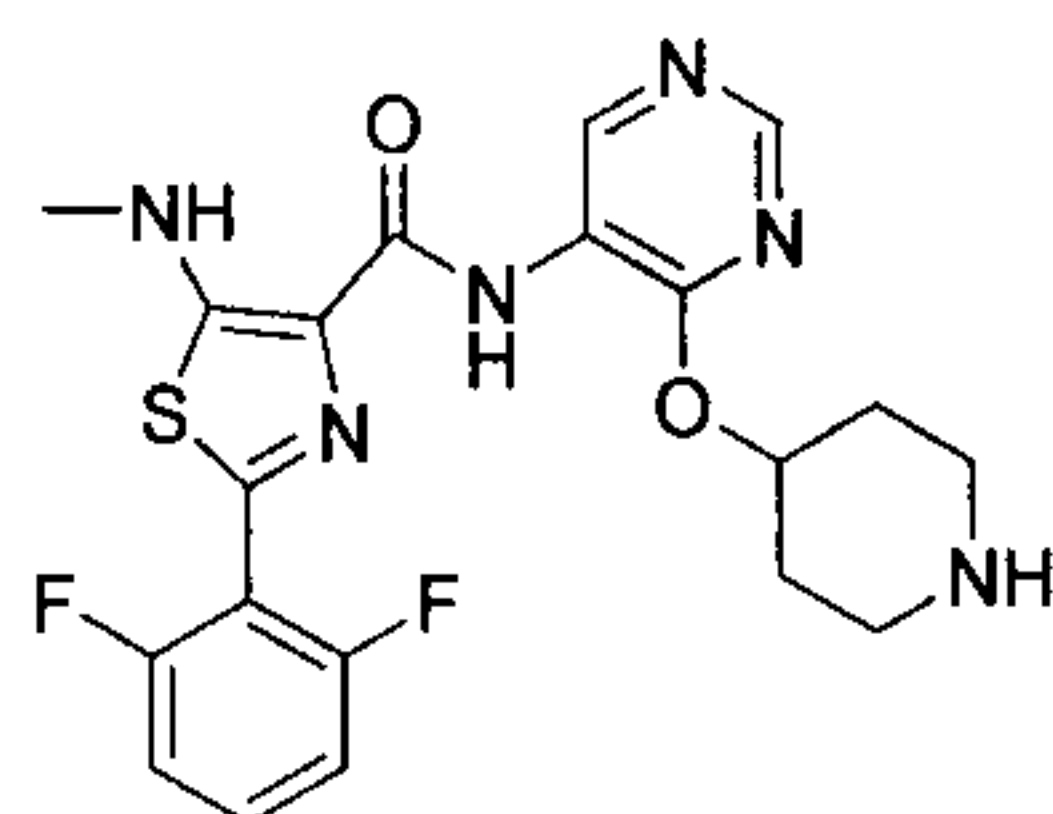
Synthesis of 2-(2,6-difluorophenyl)-5-formamido-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (55)



Following the procedure described in Example 47, and substituting Compound 2E in Step (2) with 2-(2,6-difluorophenyl)-5-formamidothiazole-4-carboxylic acid (55E) (40mg, 0.141mmol), the title compound **55** (24mg, 0.0518mmol) was obtained.

Example 56

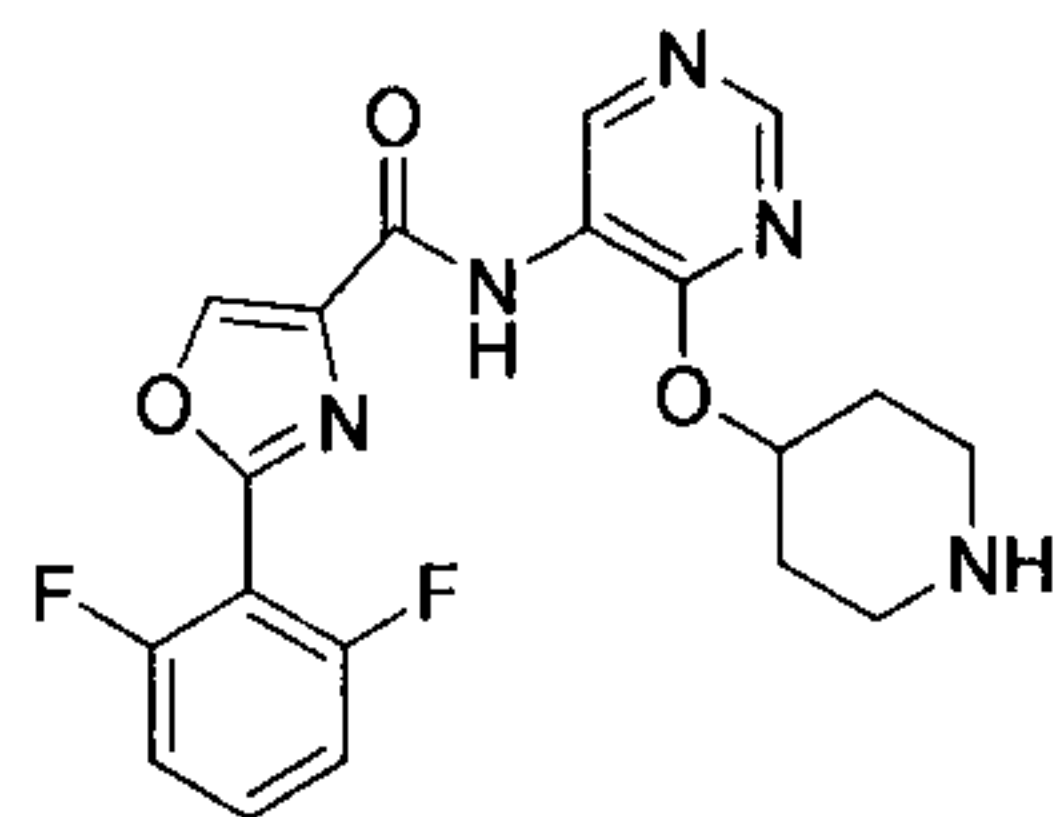
Synthesis of 2-(2,6-difluorophenyl)-5-(methylamino)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (56)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-(2,6-difluorophenyl)-5-(methylamino)thiazole-4-carboxylic acid (54E) (40mg, 0.148mmol), the title compound **56** (19mg, 0.0425mmol) was obtained.

Example 57

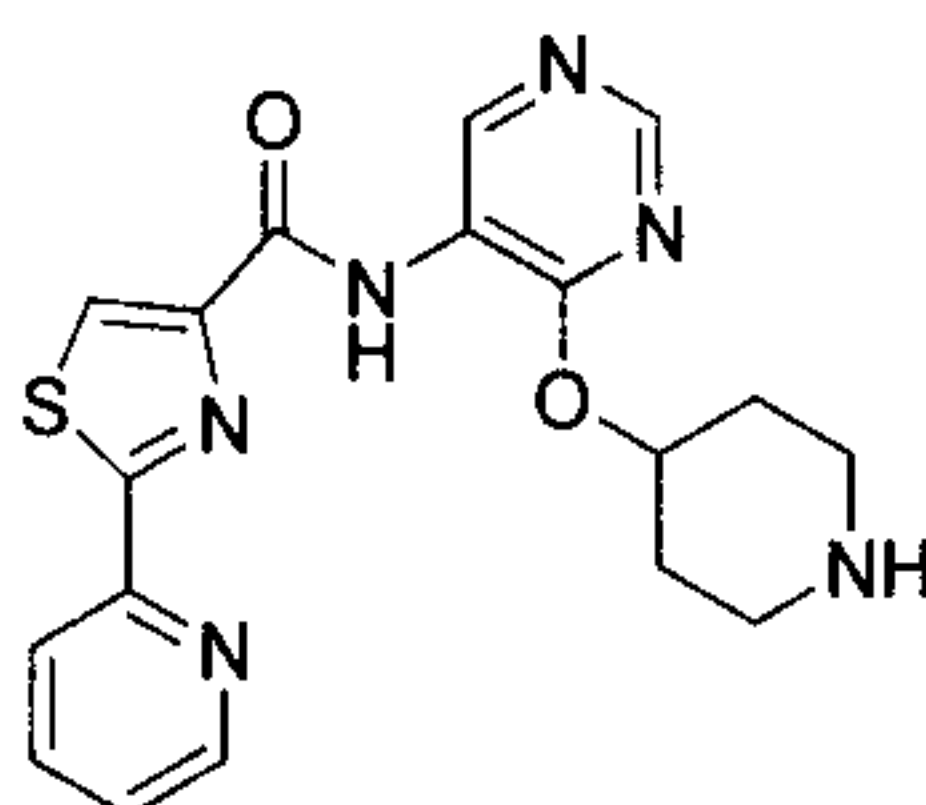
Synthesis of 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)oxazole-4-carboxamide (57)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-(2,6-difluorophenyl)oxazole-4-carboxylic acid (57E) (40mg, 0.180mmol), the title compound **57** (19mg, 0.0473mmol) was obtained.

Example 58

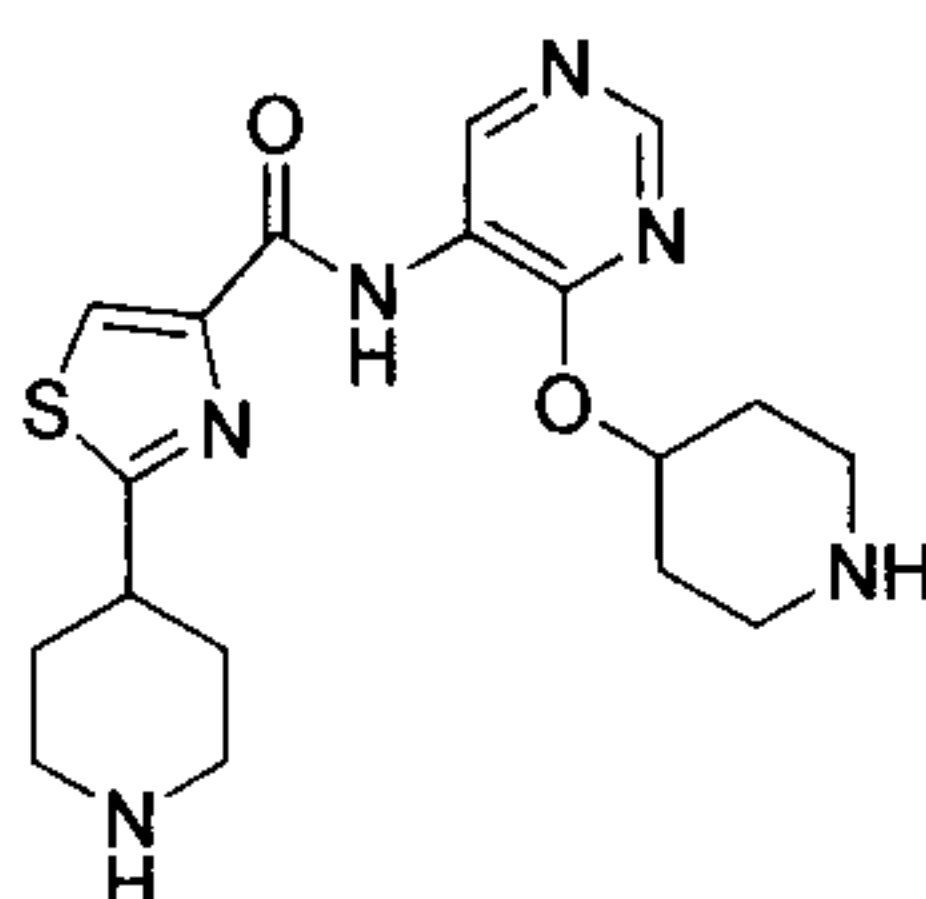
Synthesis of N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide (58)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-(pyridin-2-yl)thiazole-4-carboxylic acid (58E) (40mg, 0.194mmol), the title compound was **58** (15mg, 0.0392mmol) obtained.

Example 59

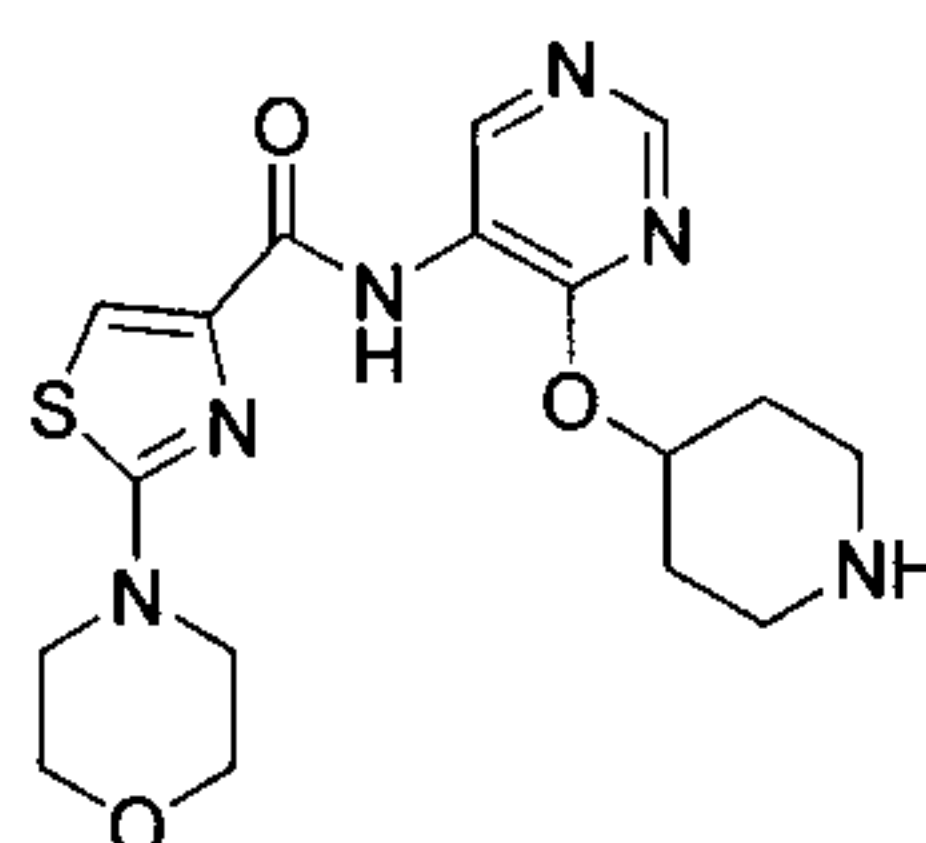
Synthesis of 2-(piperidin-4-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (59)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)thiazole-4-carboxylic acid (59E) (40mg, 0.157mmol), the title compound **59** (8mg, 0.0206mmol) was obtained.

Example 60

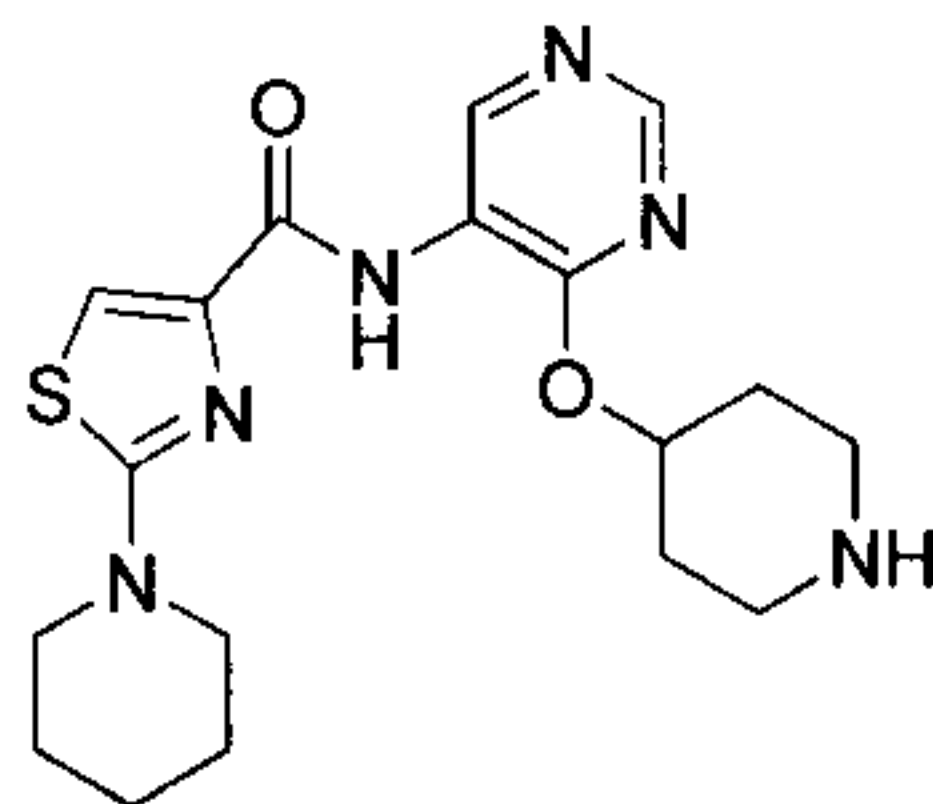
Synthesis of 2-morpholino-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (60)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-morpholinothiazole-4-carboxylic acid (60E) (40mg, 0.187mmol), the title compound was **60** (14mg, 0.0358mmol) obtained.

Example 61

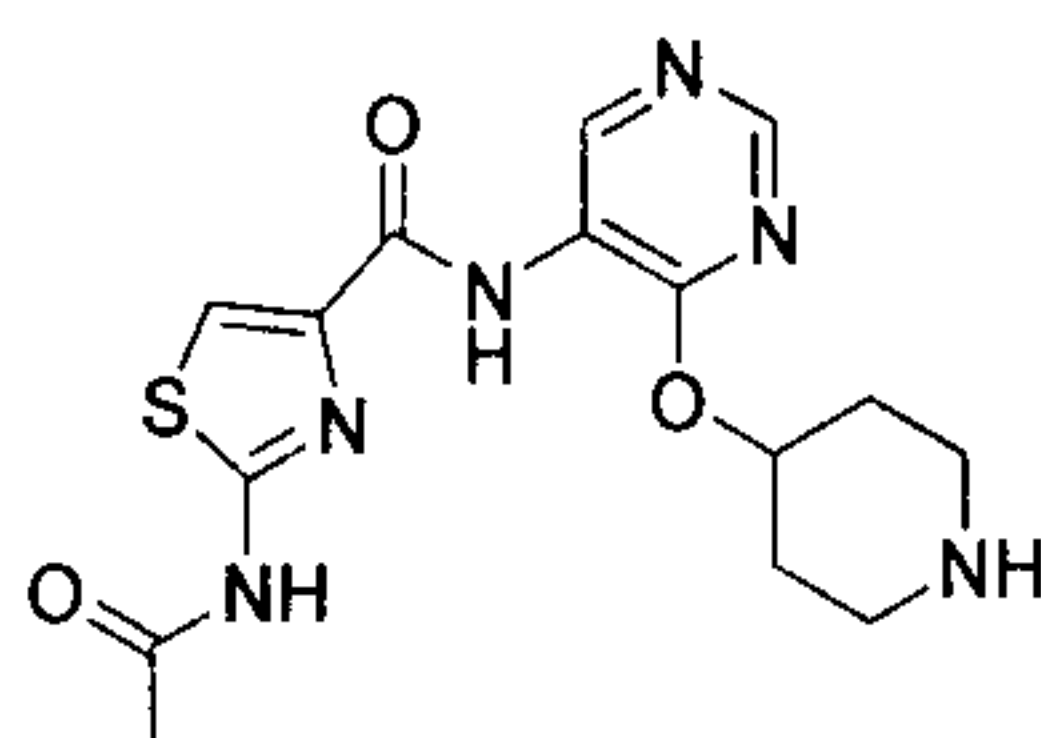
Synthesis of 2-(piperidin-1-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (61)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-(piperidin-1-yl)thiazole-4-carboxylic acid (61E)(40mg, 0.189mmol), the title compound **61** (18mg, 0.0463mmol) was obtained.

Example 62

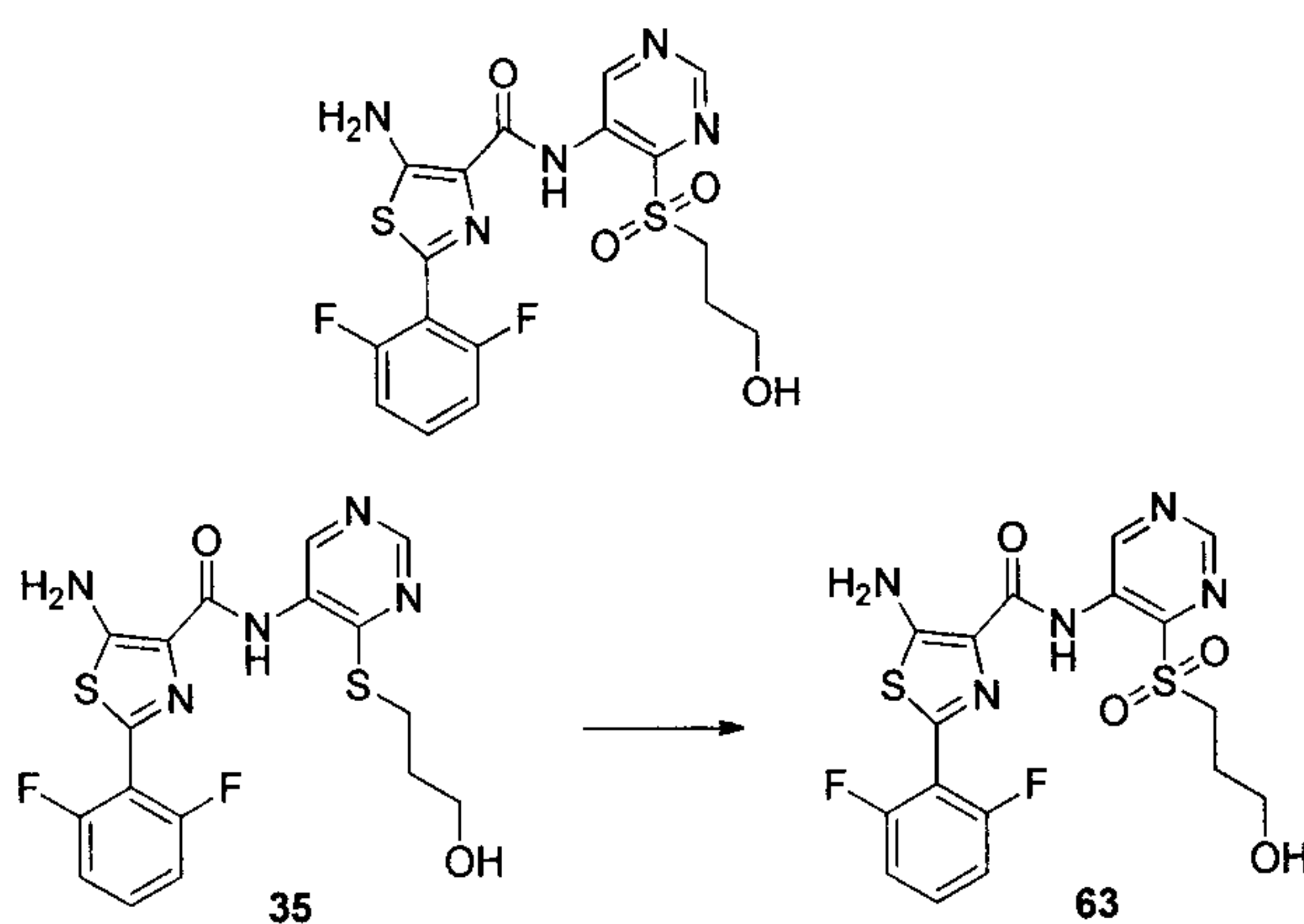
Synthesis of 2-acetamido-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (62)



Following the procedure described in Example 3, and substituting Compound 1E in Step (2) with 2-acetamidothiazole-4-carboxylic acid (62E) (40mg, 0.215mmol), the title compound **62** (13mg, 0.0358mmol) was obtained.

Example 63

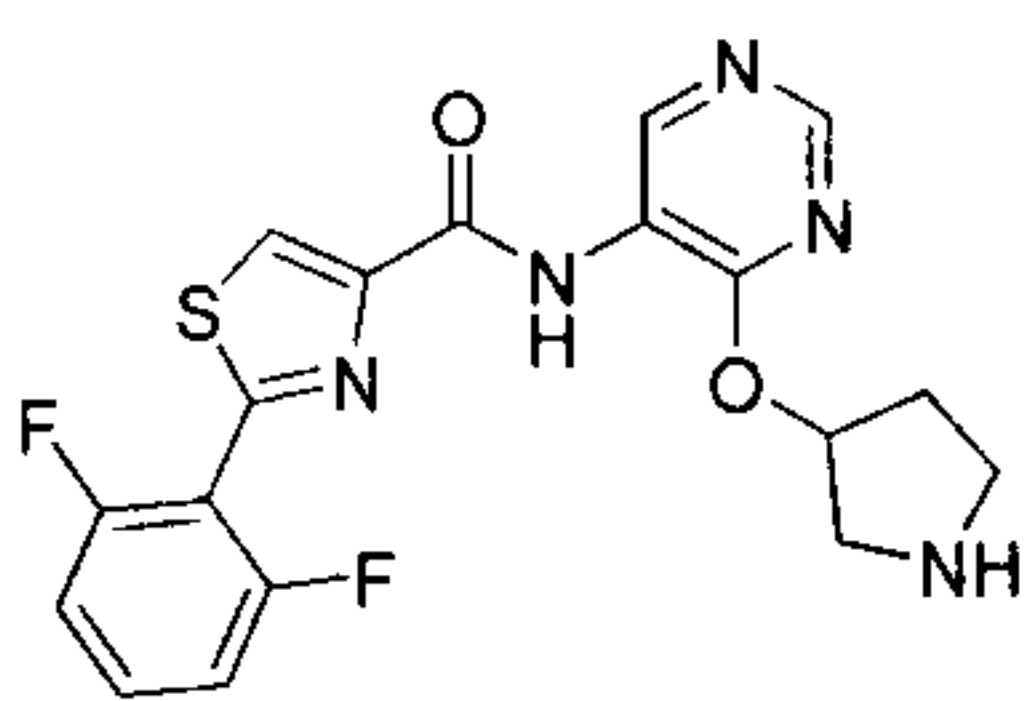
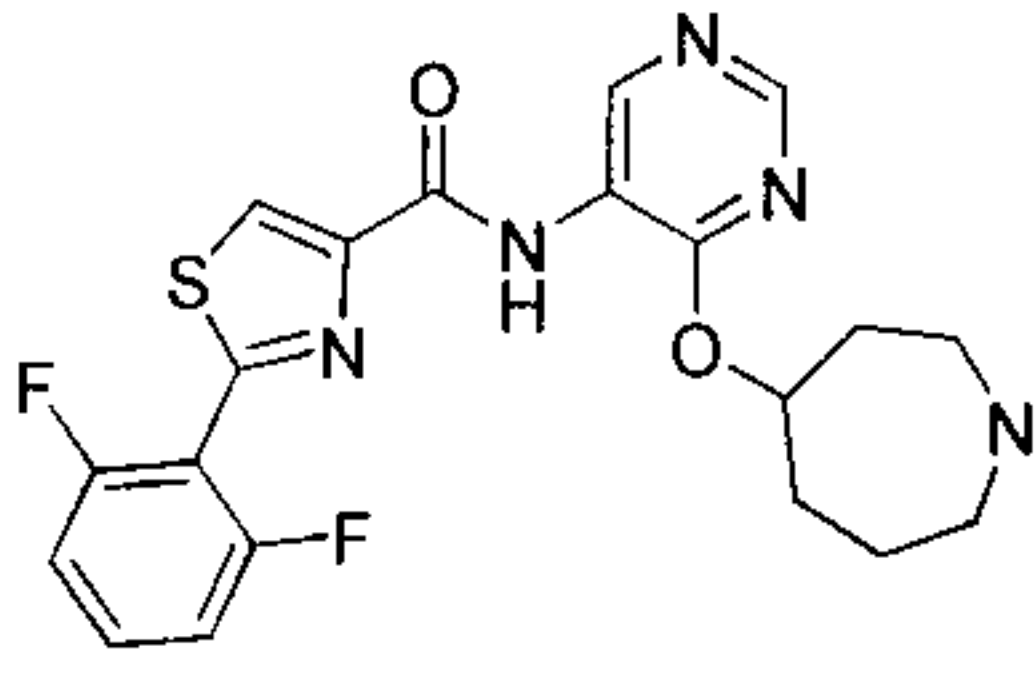
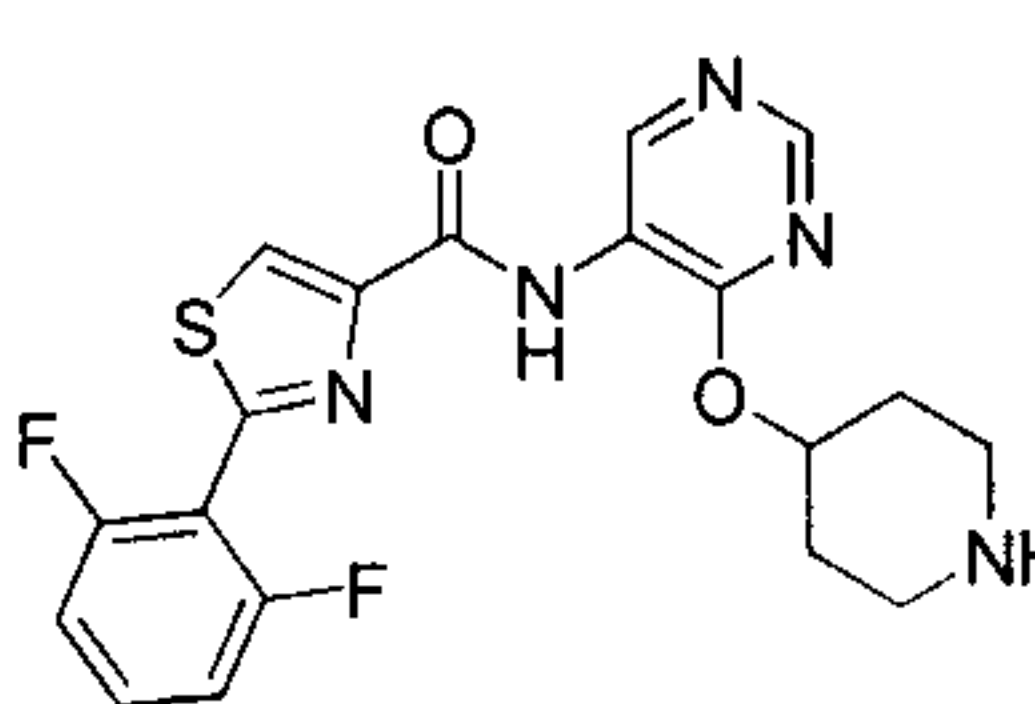
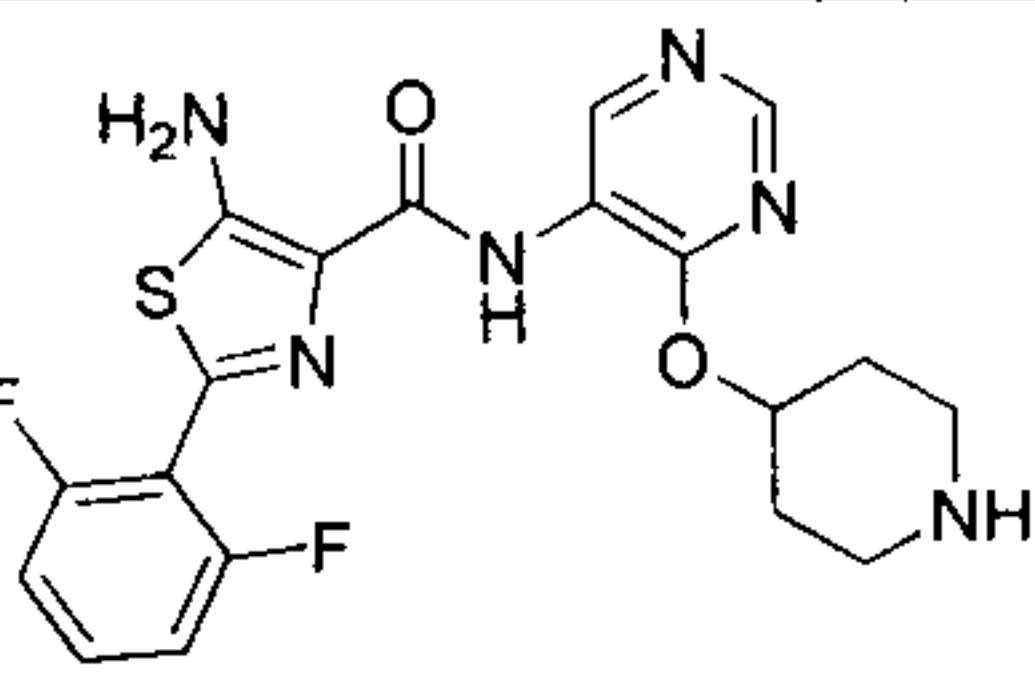
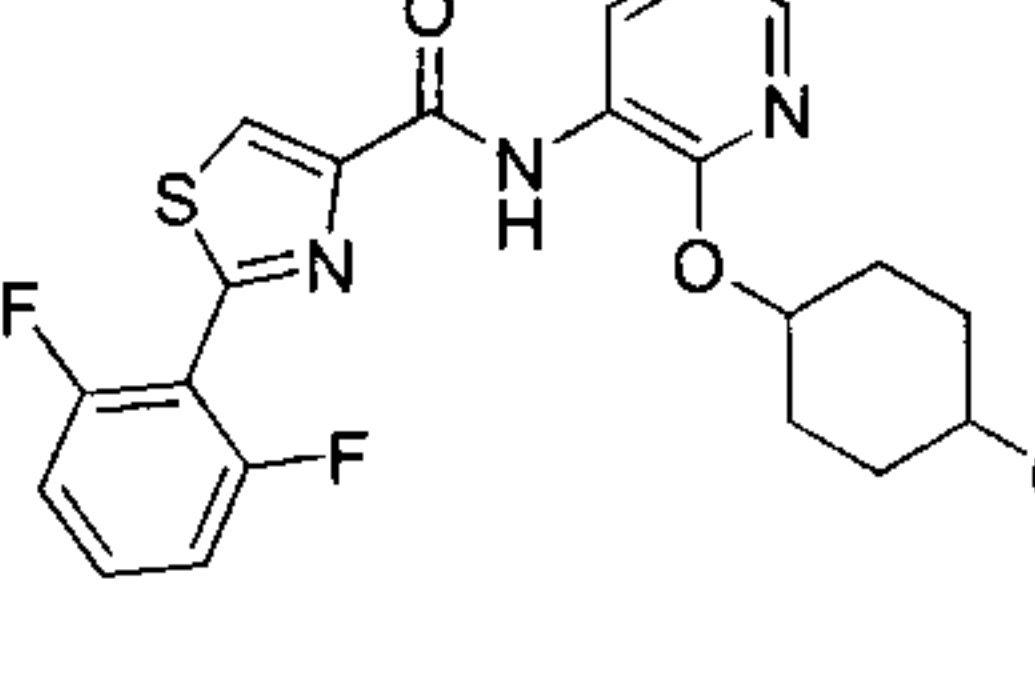
Synthesis of 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)sulfonyl)pyrimidin-5-yl)thiazole-4-carboxamide (63)

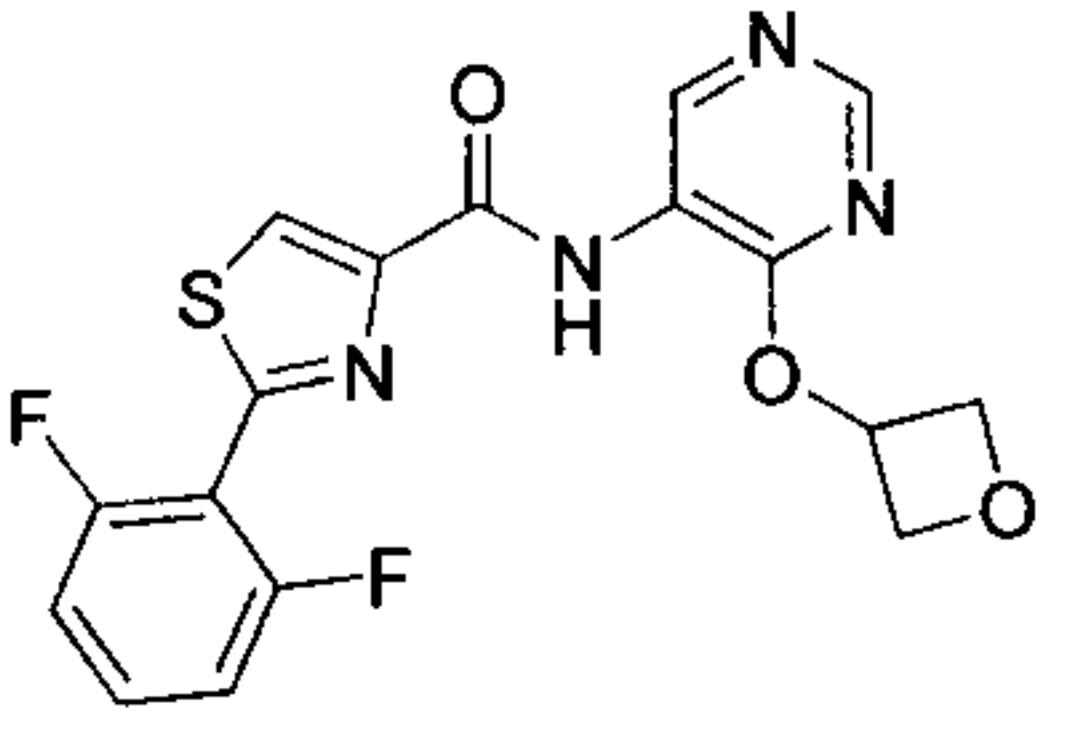
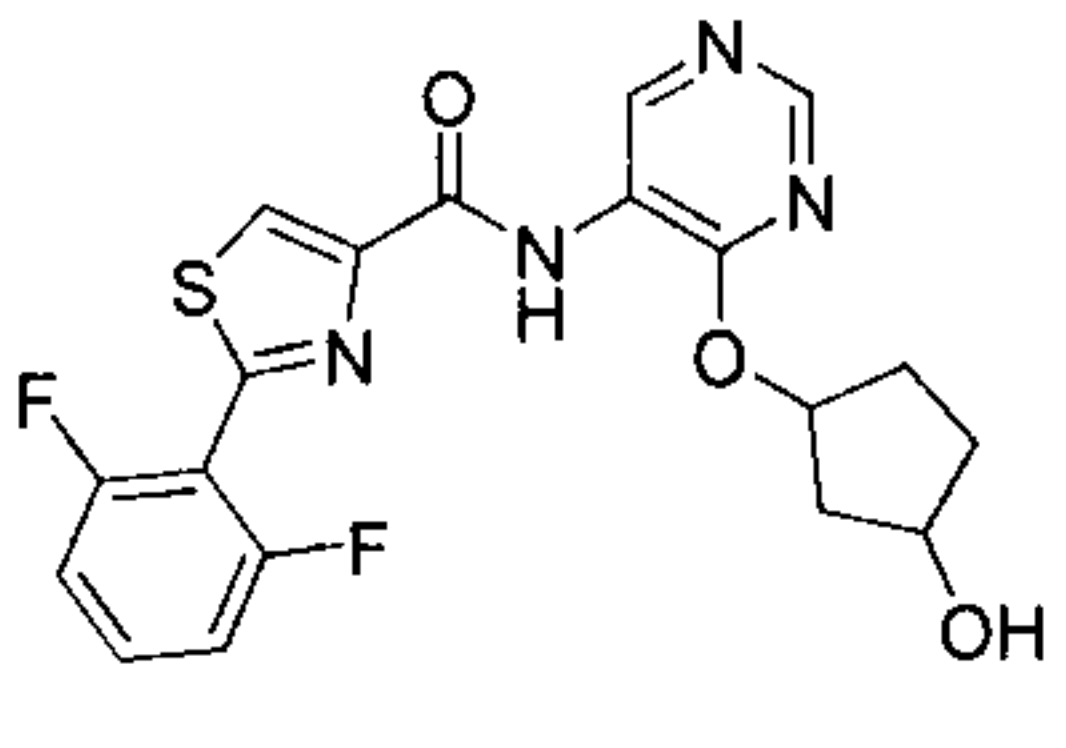
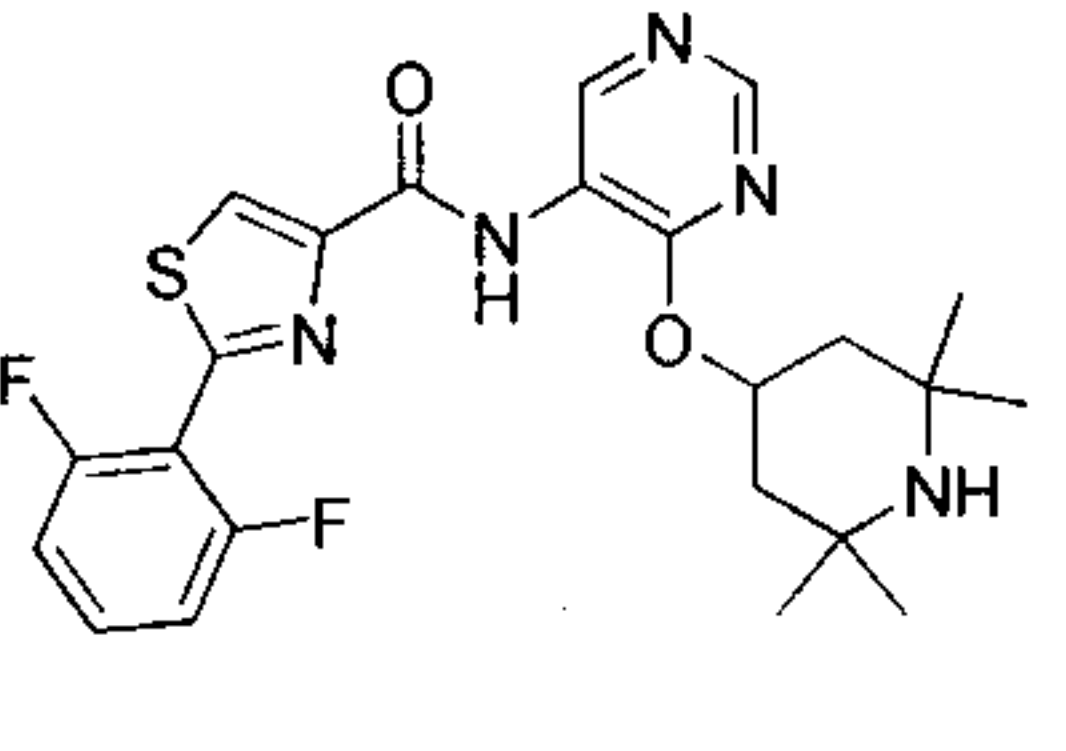
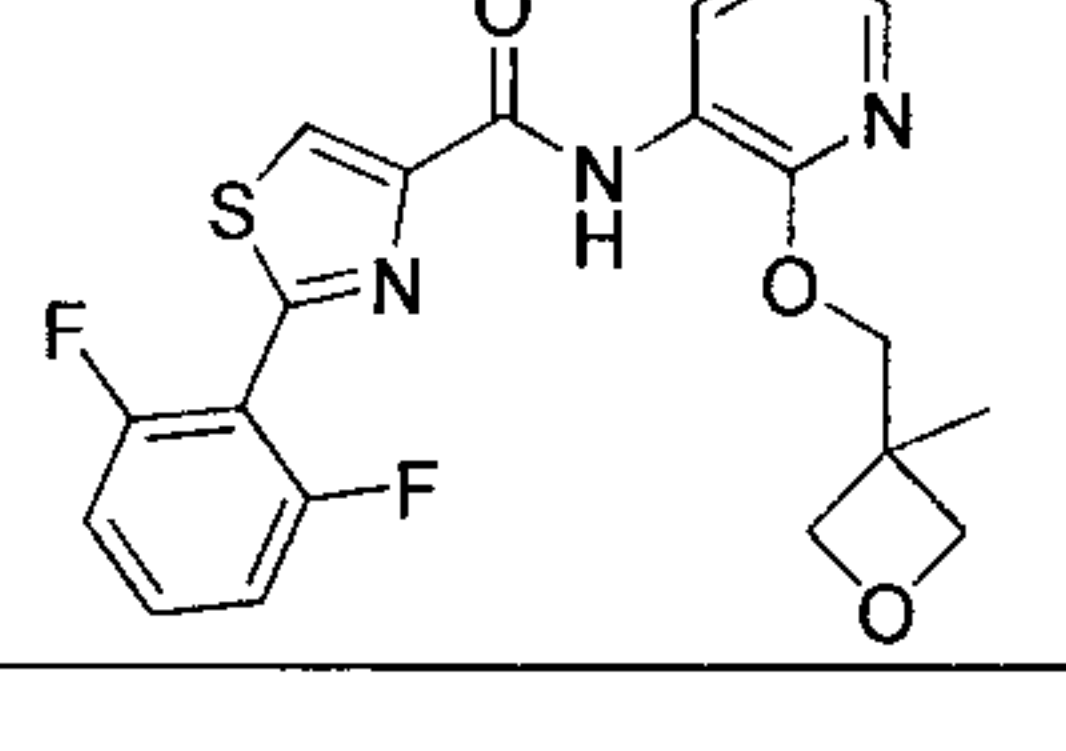
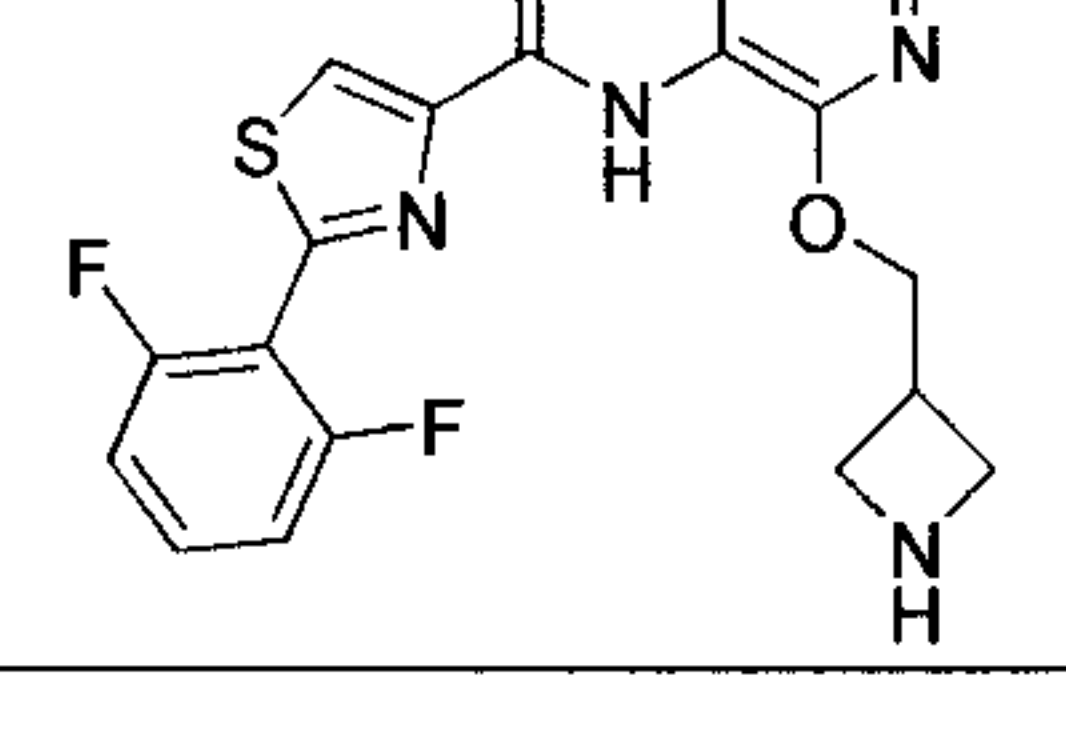
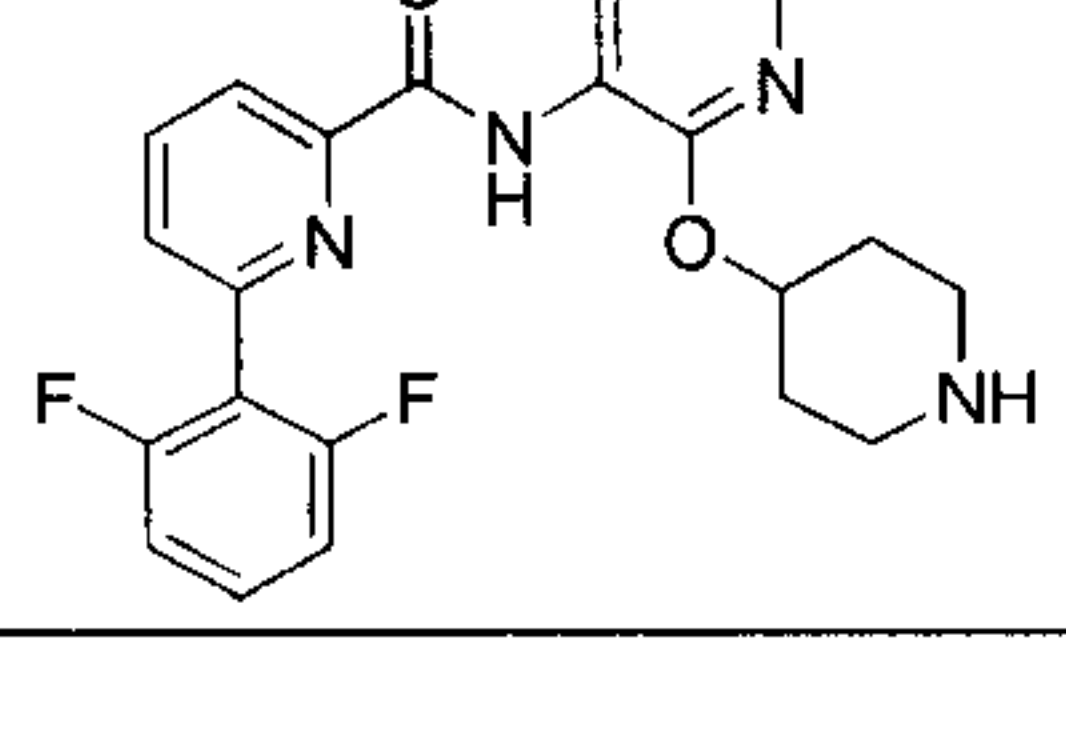
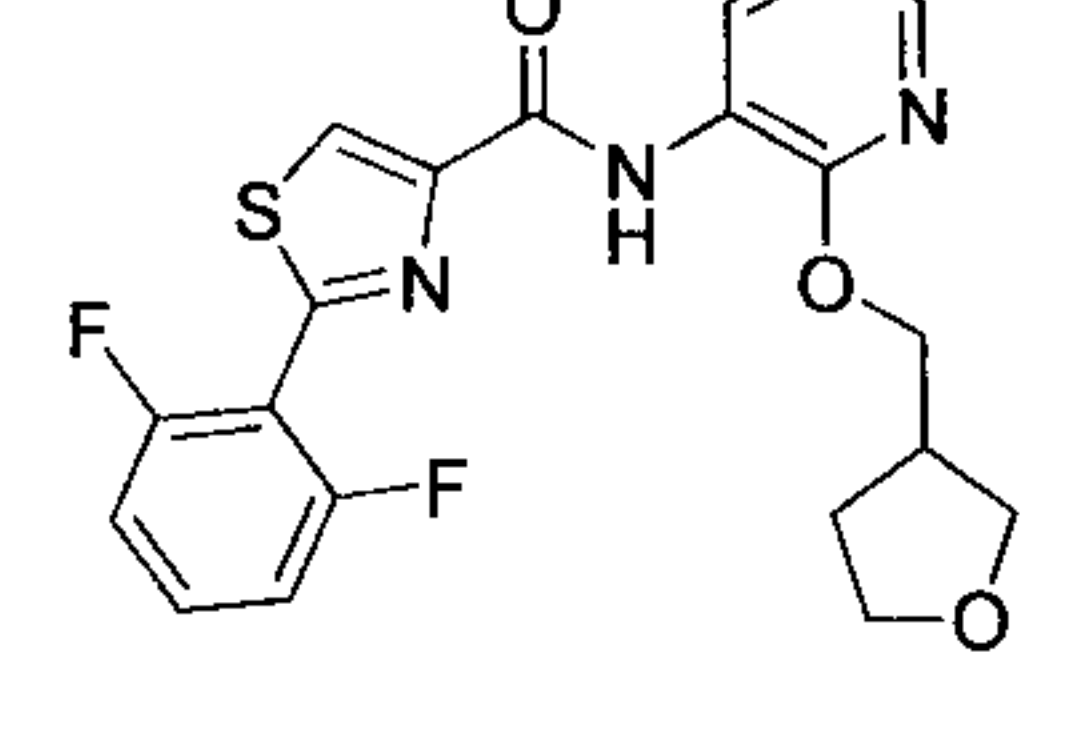
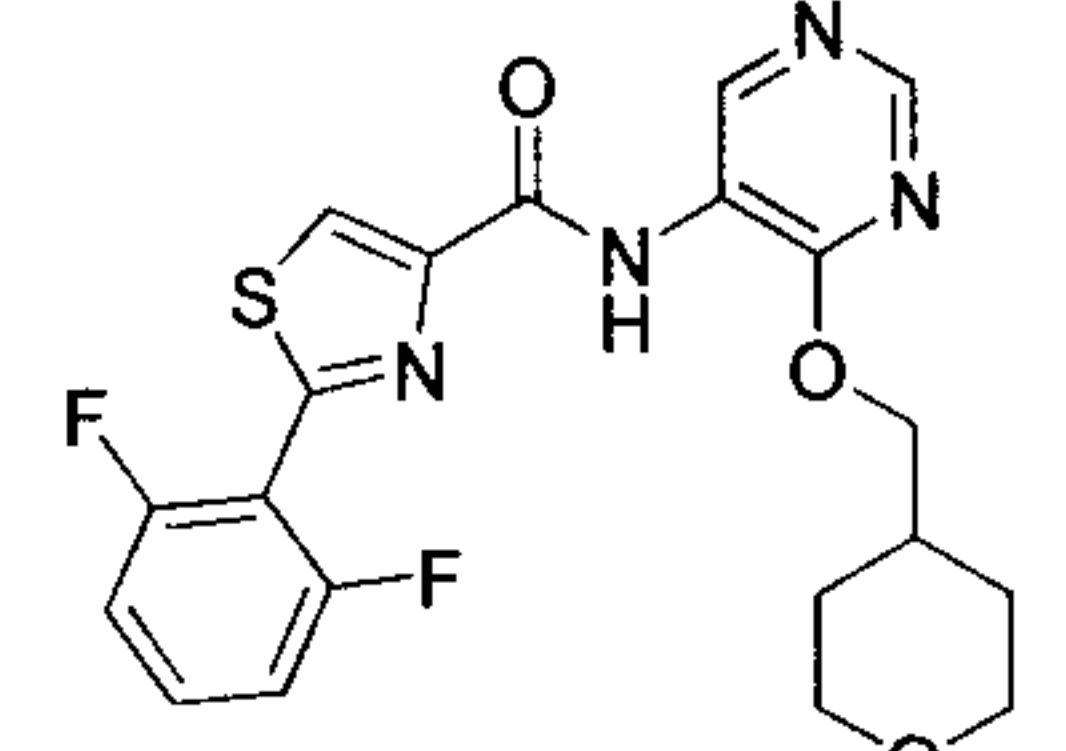


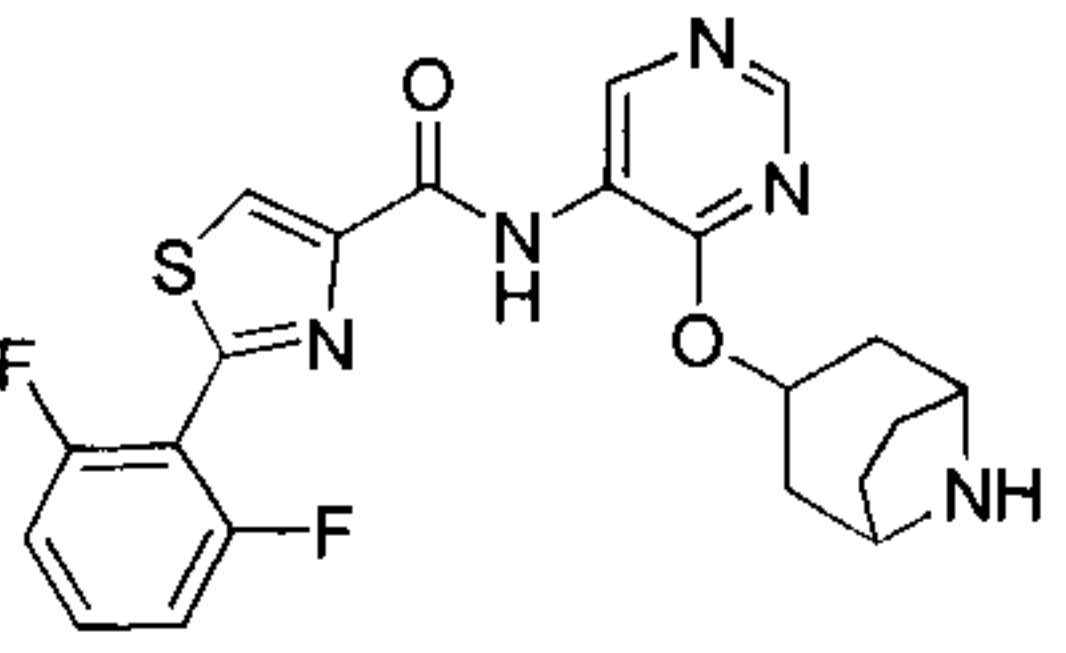
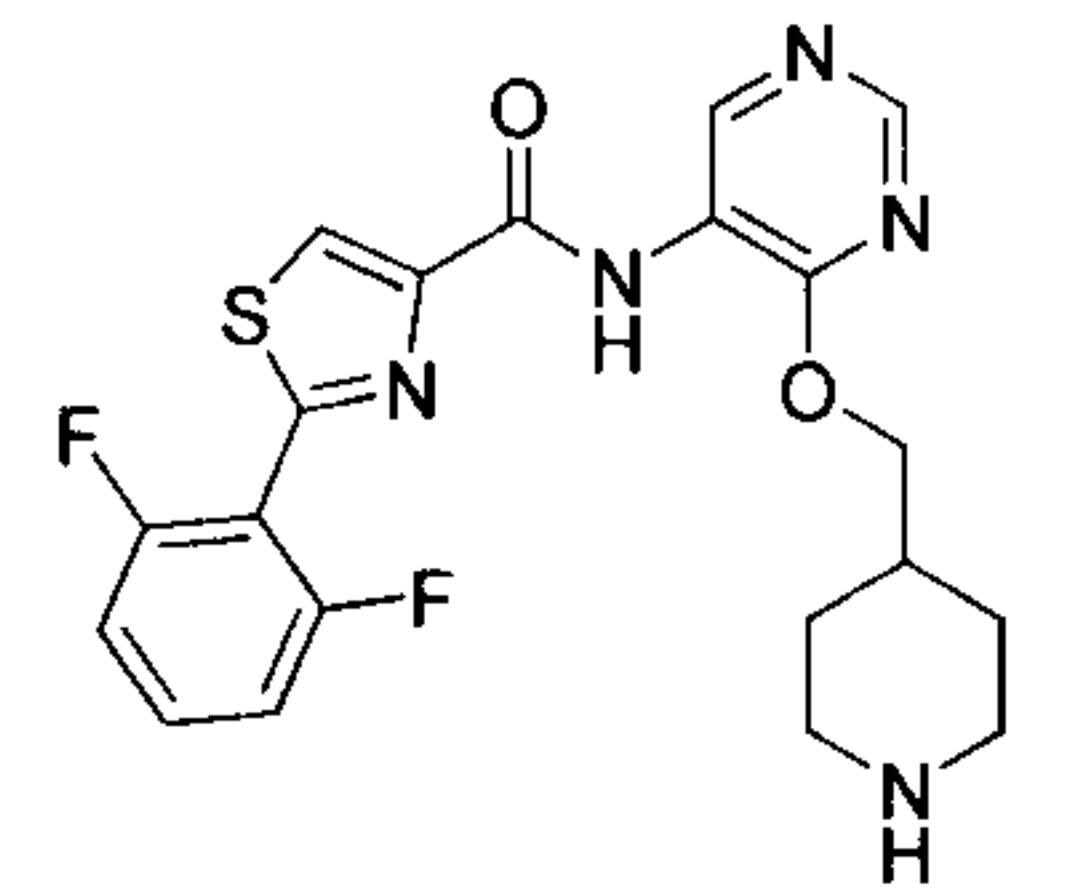
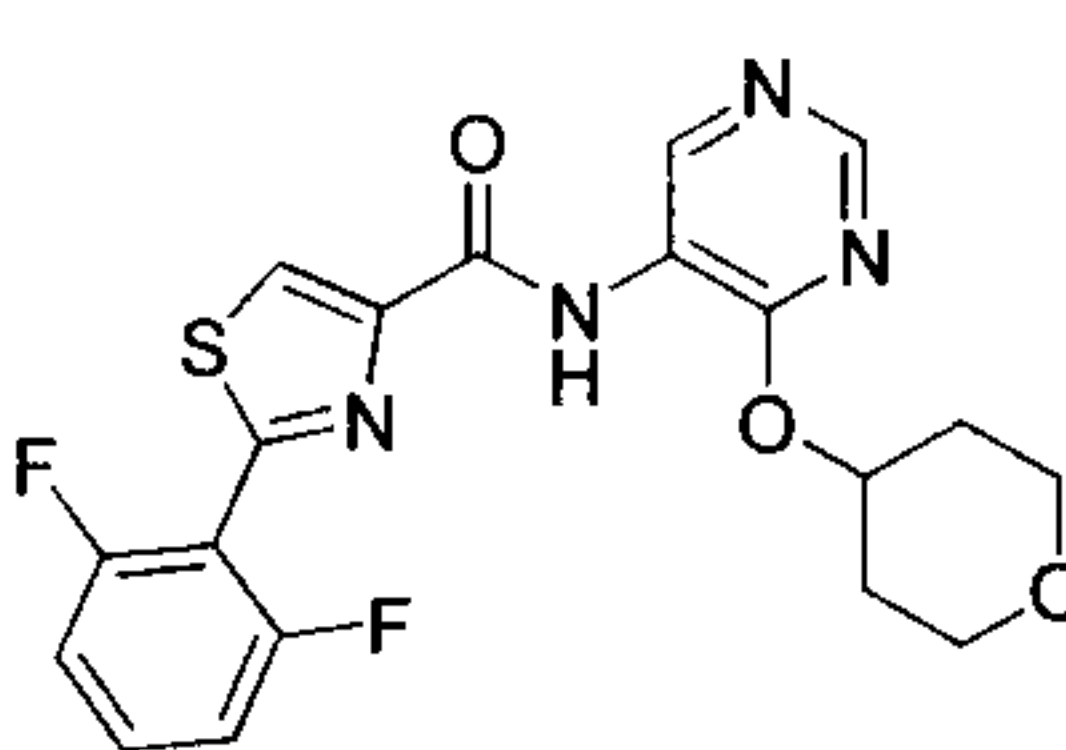
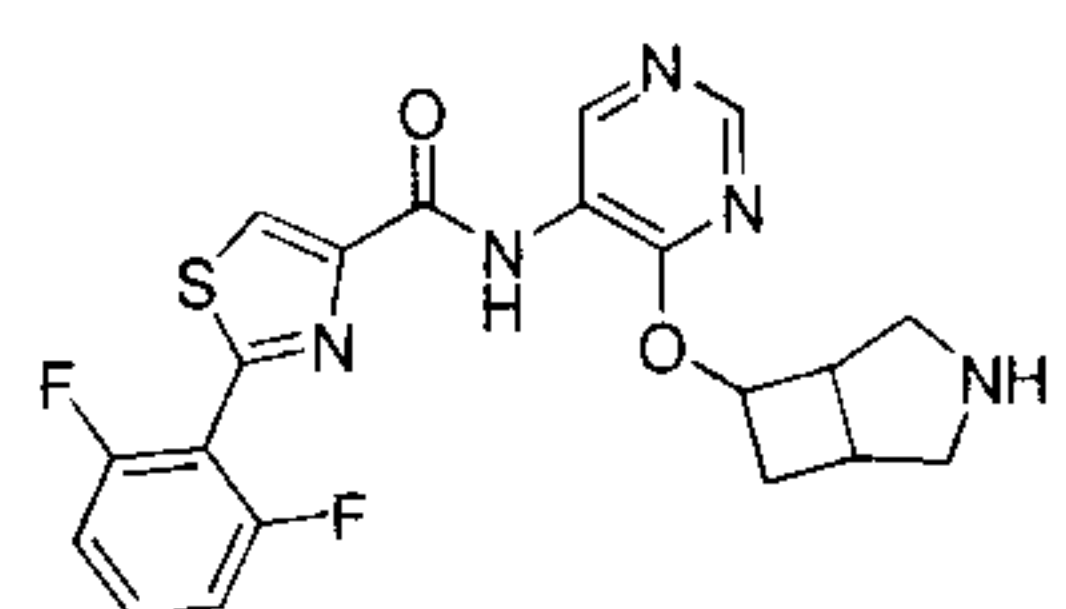
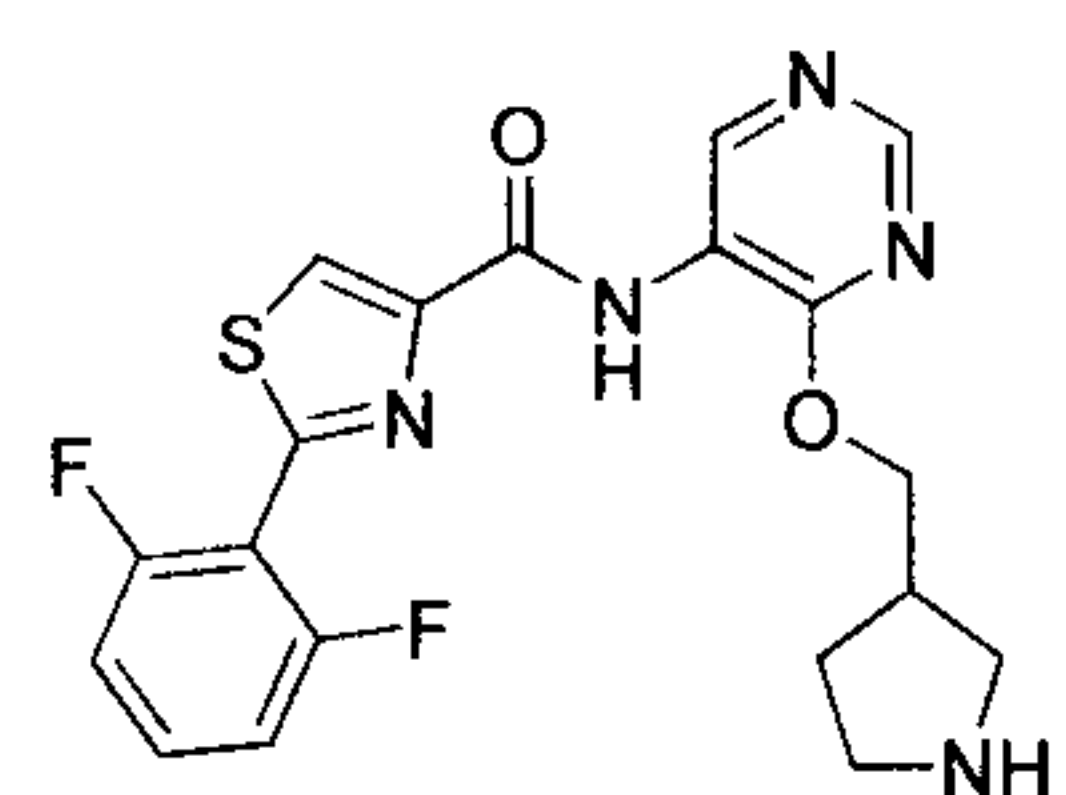
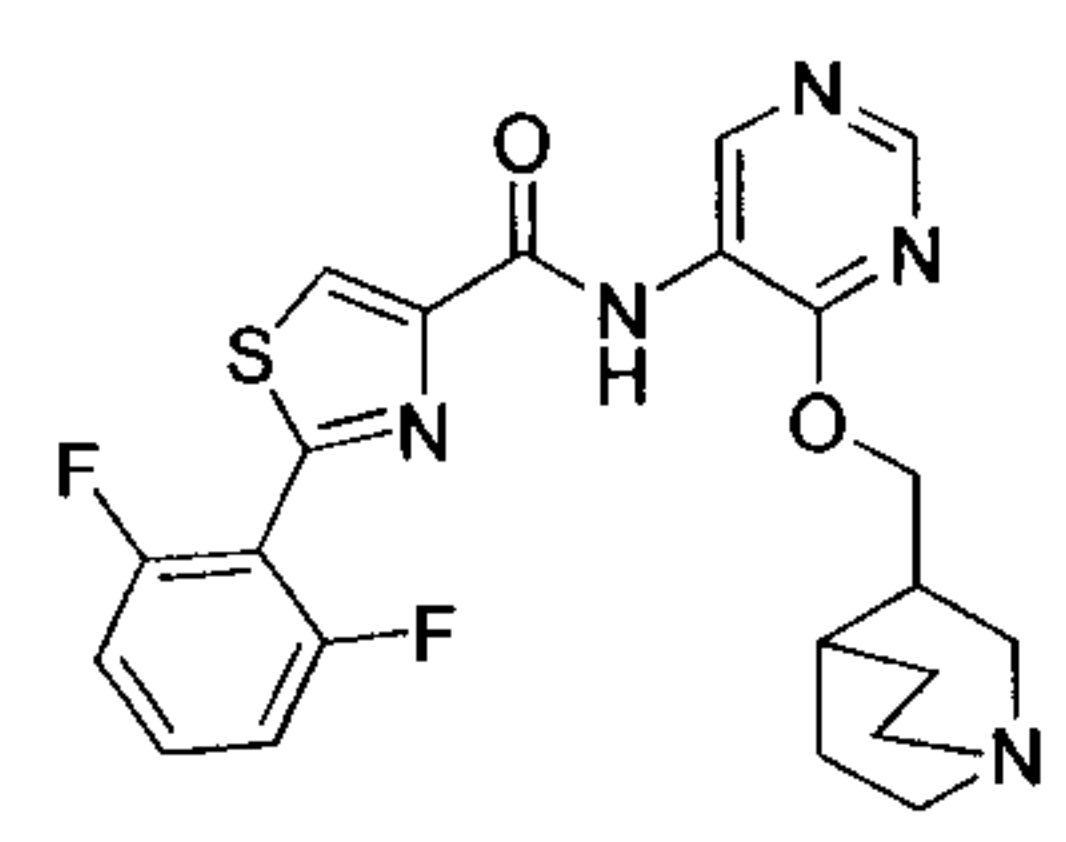
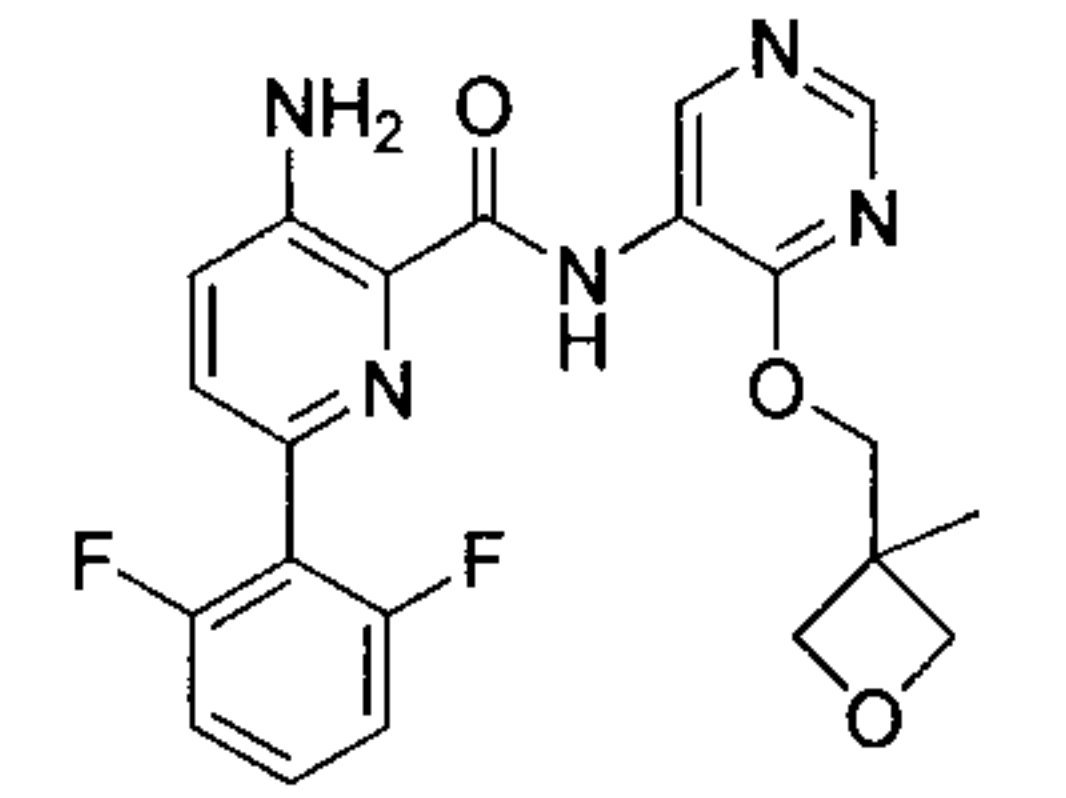
To a solution of 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)thio)pyrimidin-5-yl)thiazole-4-carboxamide (35)(60mg, 0.142mmol) in THF (2mL) at room temperature (25°C) was added imidazole (20mg, 0.284mmol) and trimethylsilyl chloride (17mg, 0.156mmol) and stirred for

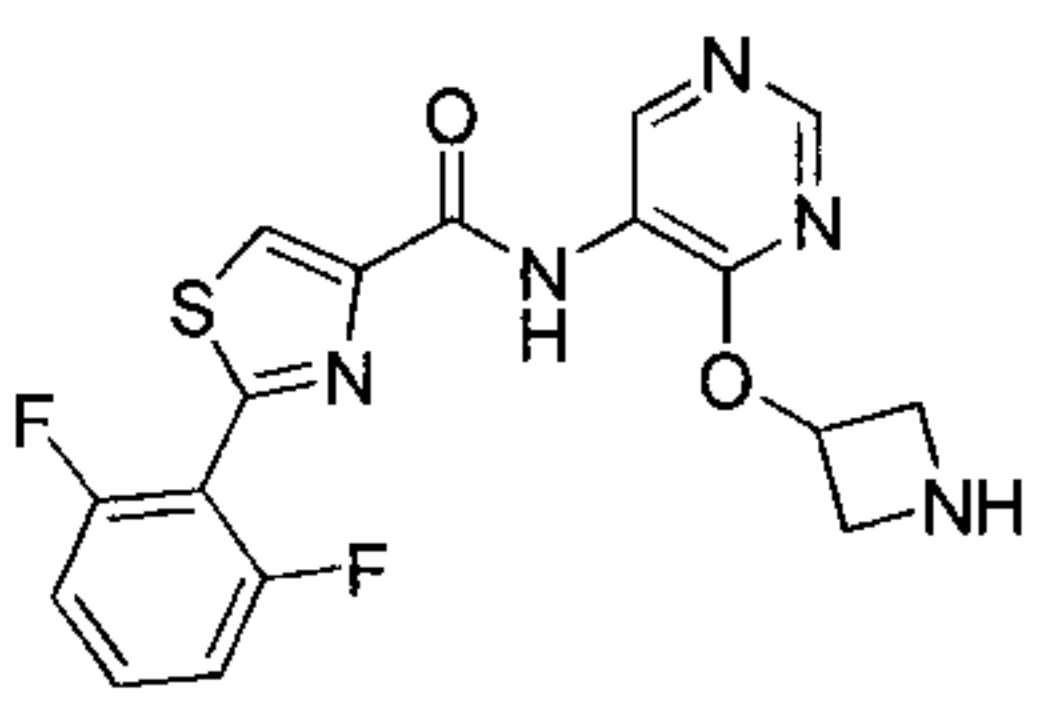
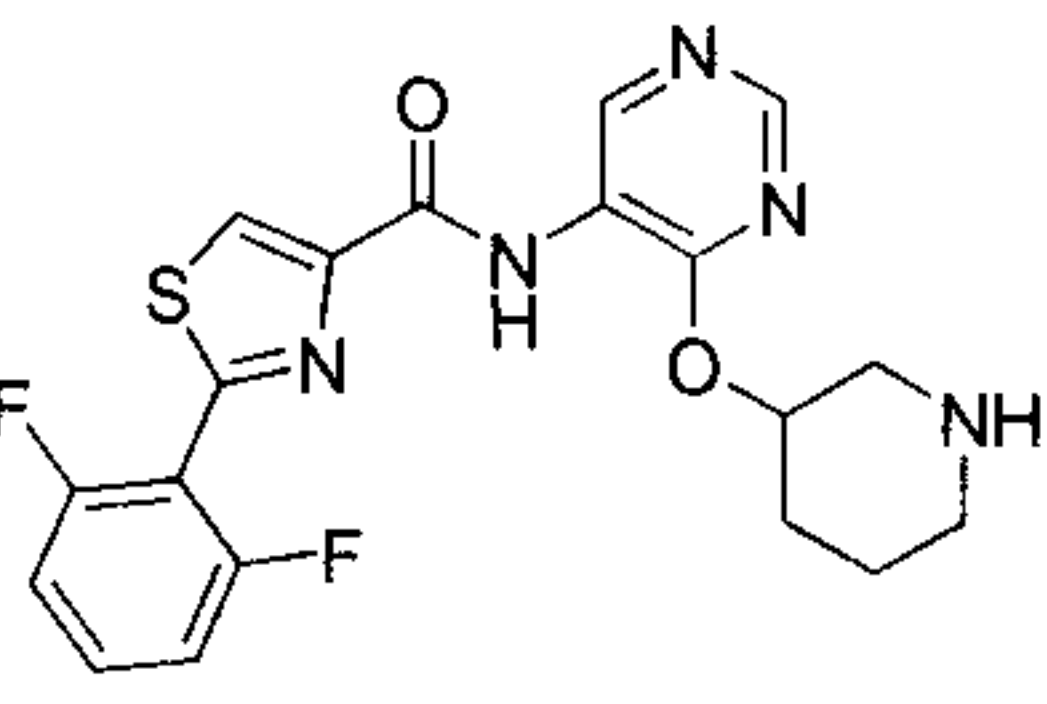
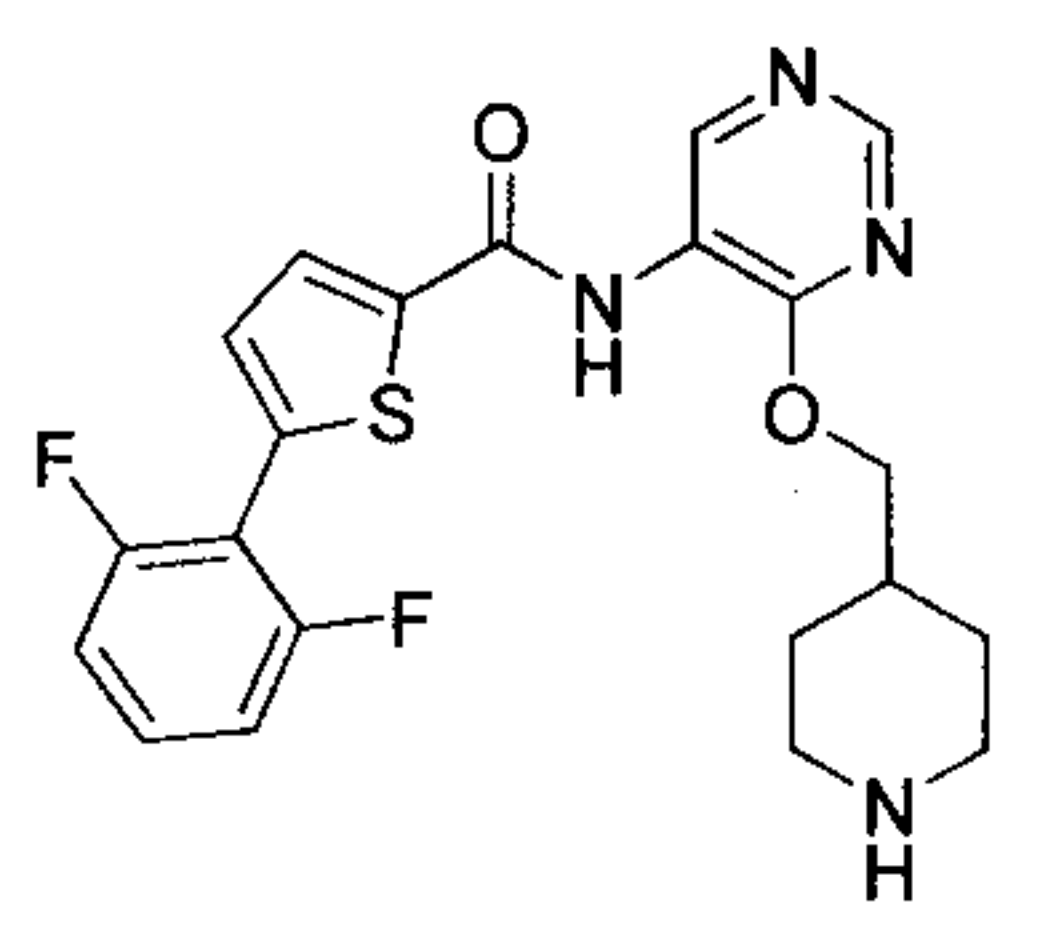
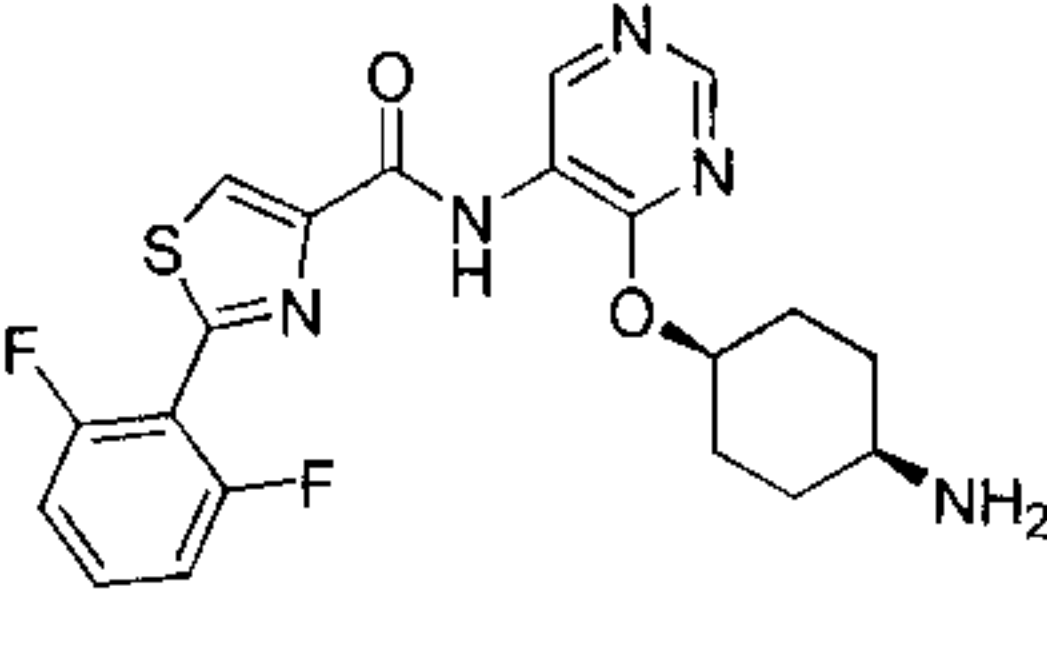
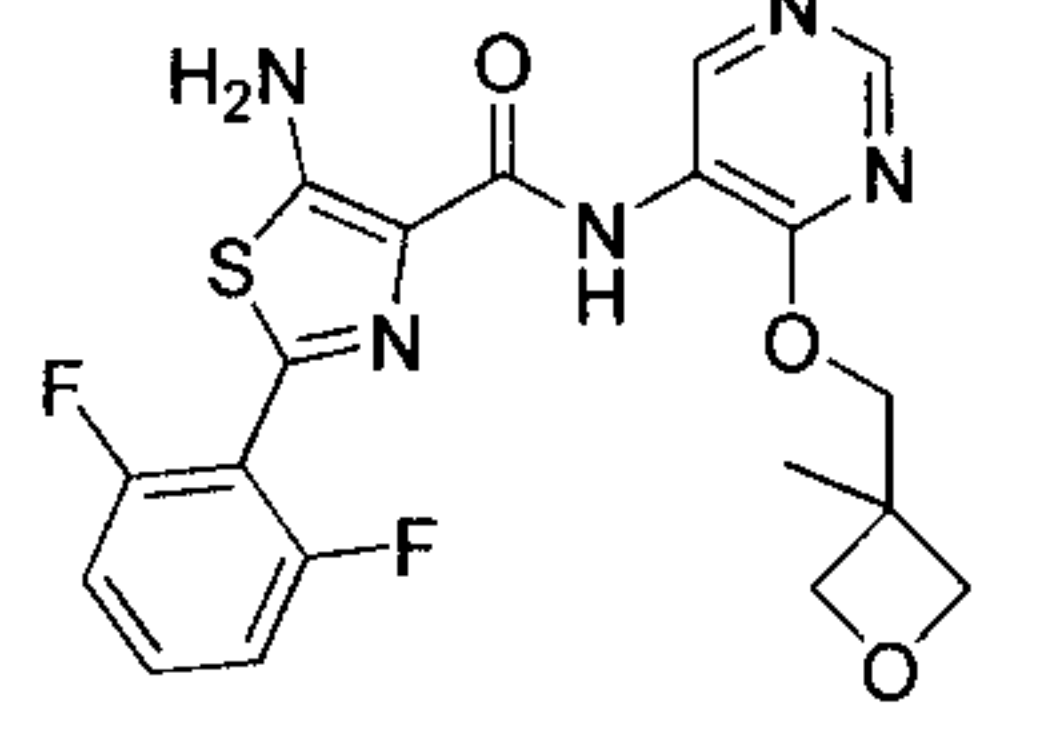
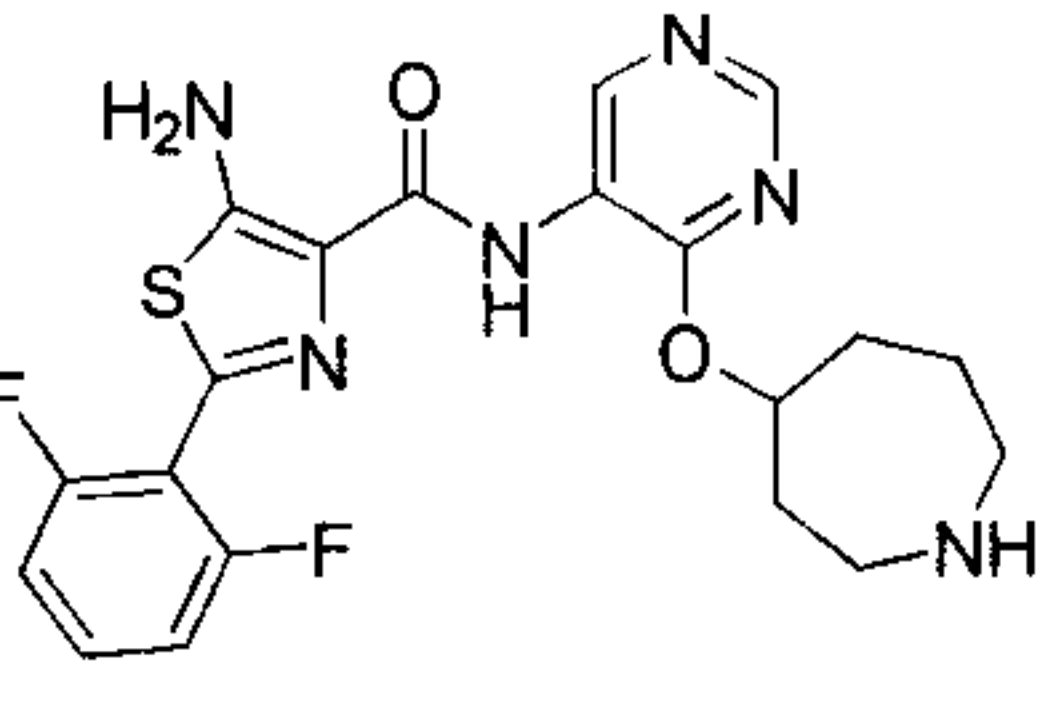
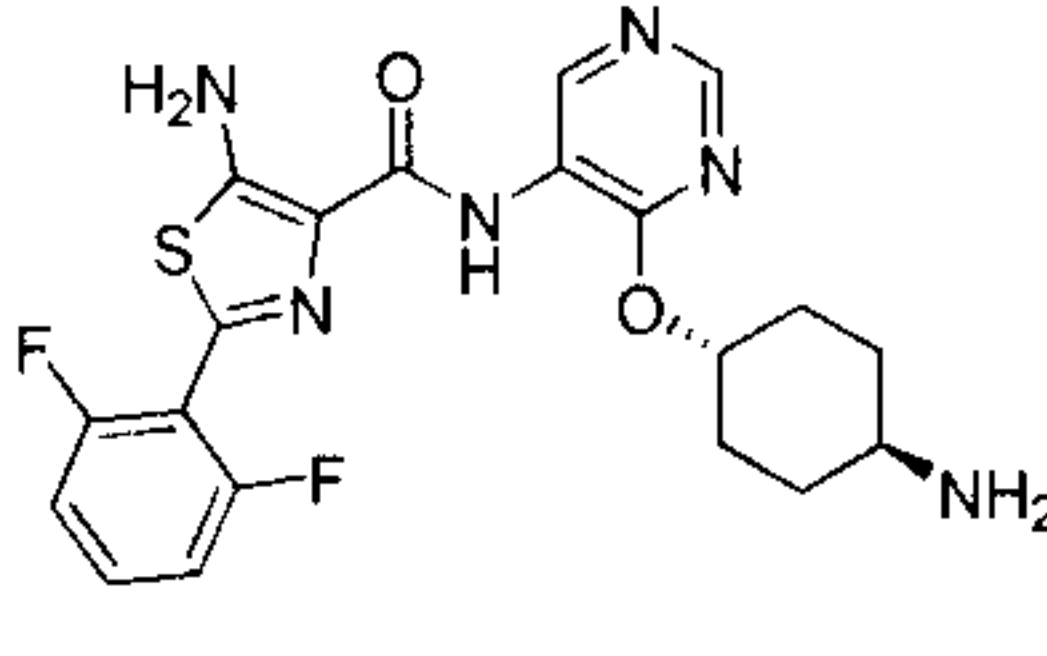
30 min, then water (20mL) was added. A solid was obtained after filtration and then directly dissolved in CH₂CH₂ (1mL). Then m-CPBA (54mg, 0.312mmol) was added. The solution was stirred over night. TLC showed the reaction had completed. The solution was washed with 1mL each of 10% Na₂SO₃ solution, 1N HCl, saturated solution, and dried over anhydrous Na₂SO₄. The solution was the concentration in vacuo at room temperature (25°C). The residue was then purified with flash column (eluent: 10-40% ethyl acetate/petroleum ether) to obtained the title compound **63** (22mg, 0.0482mmol).

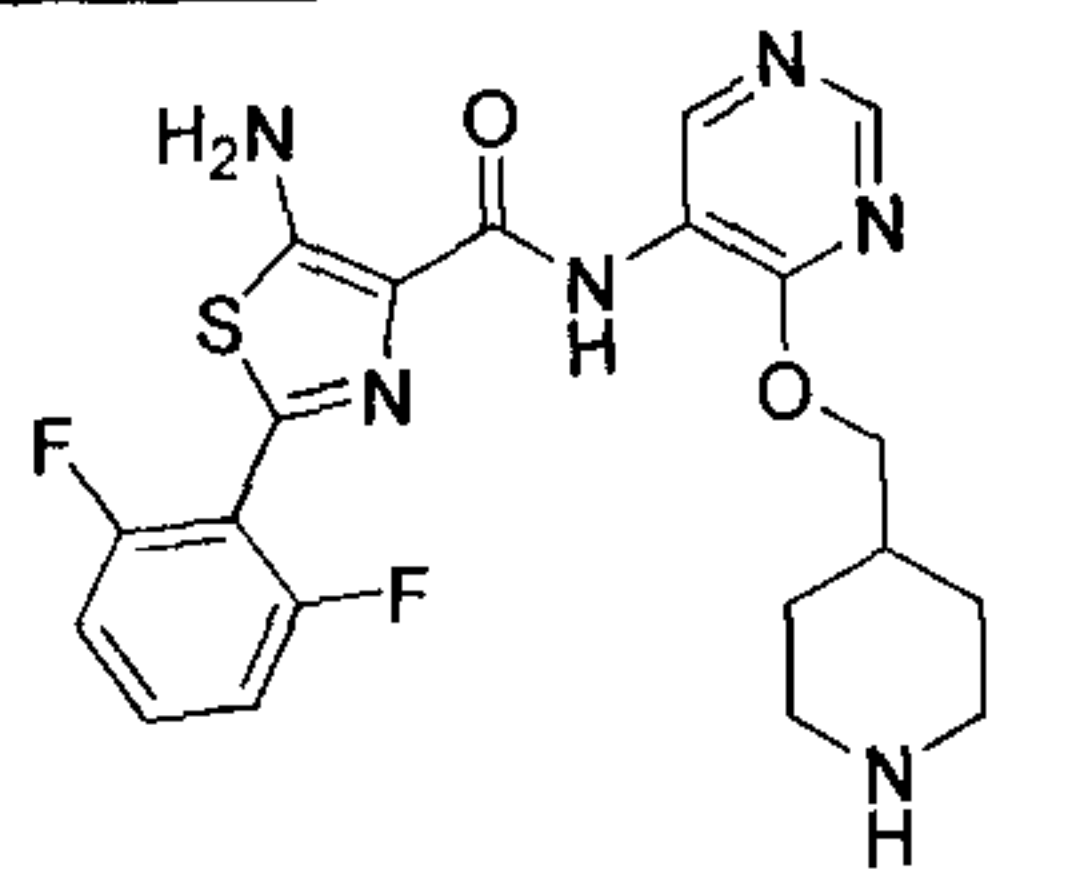
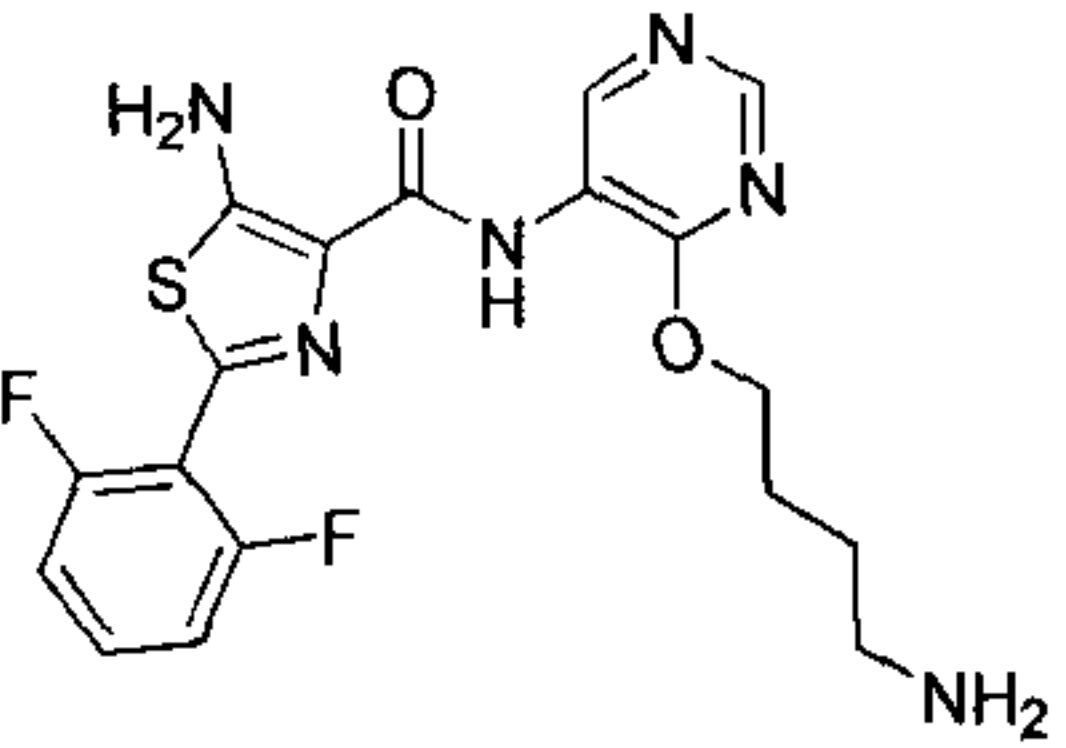
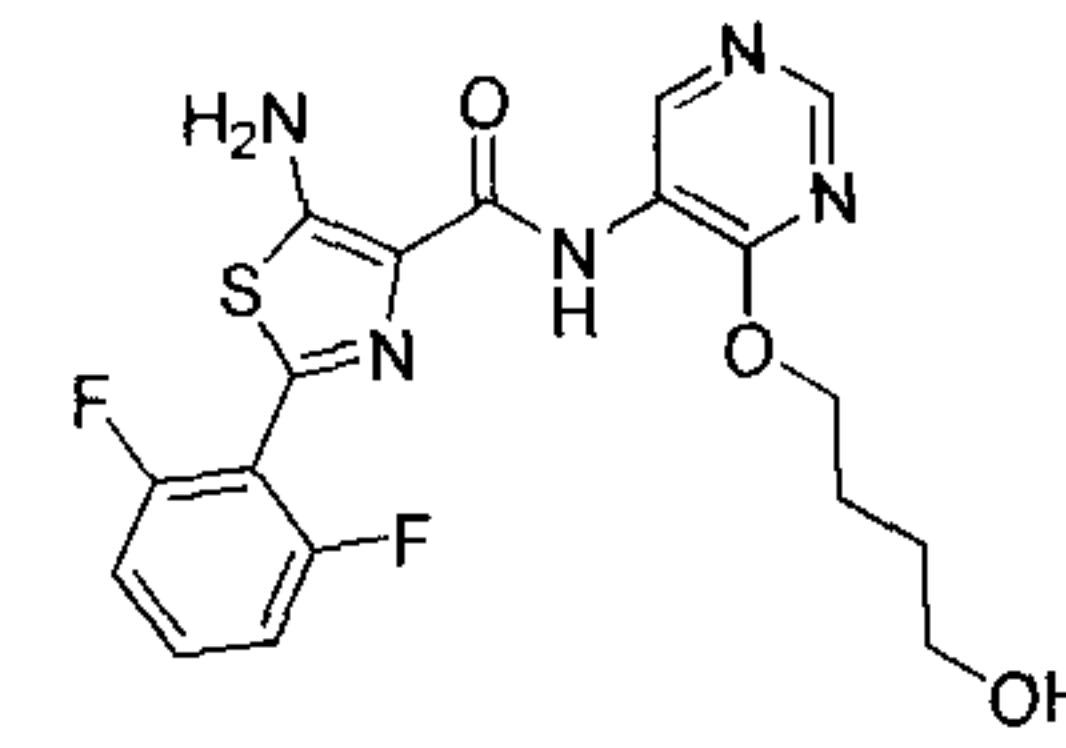
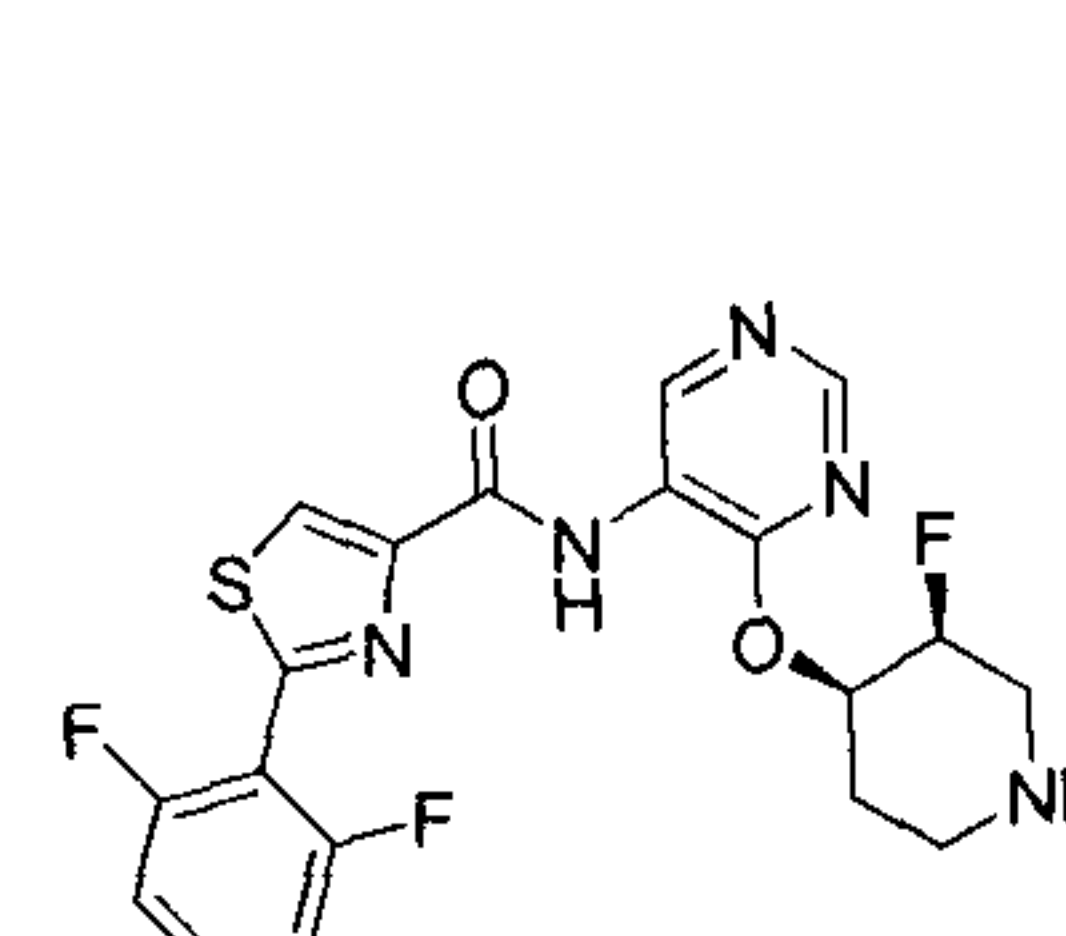
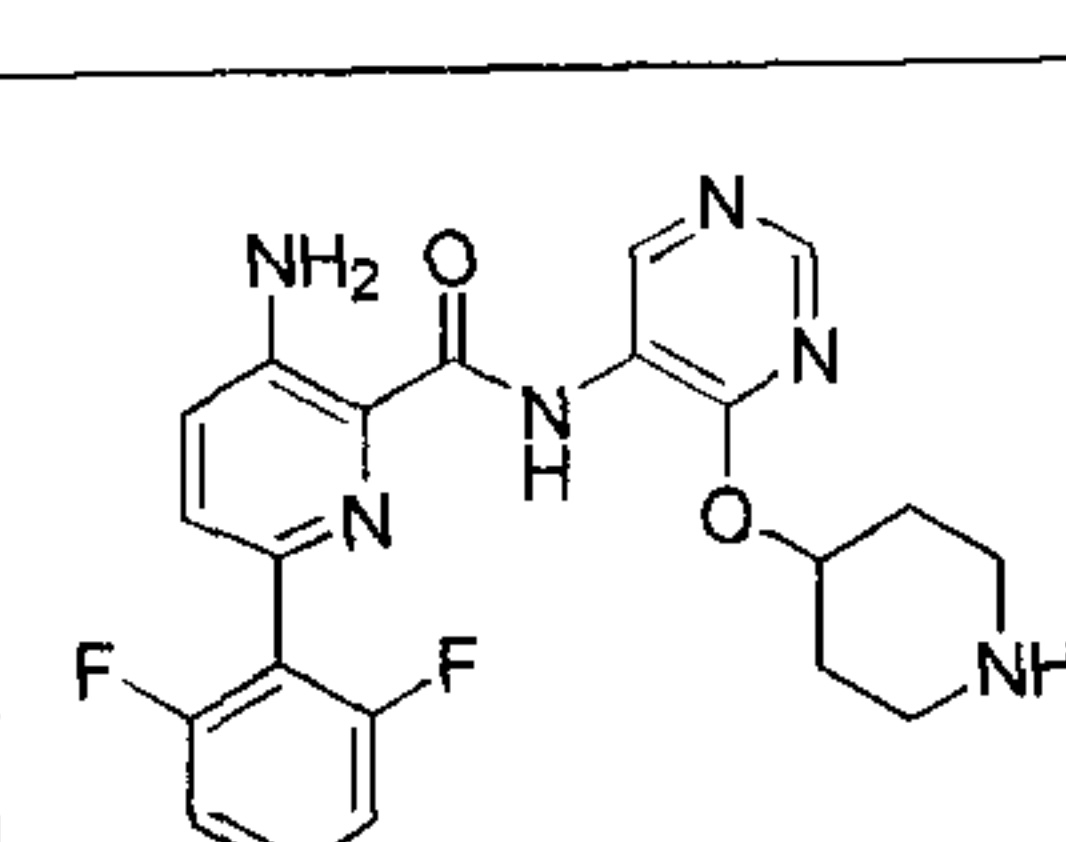
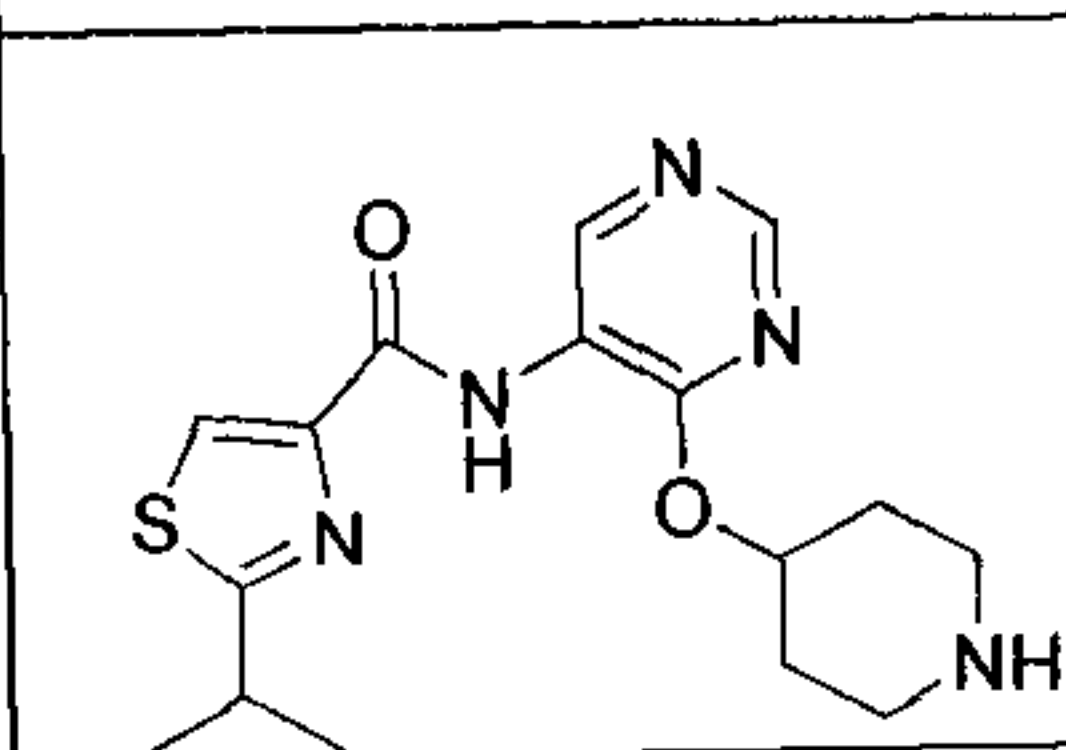
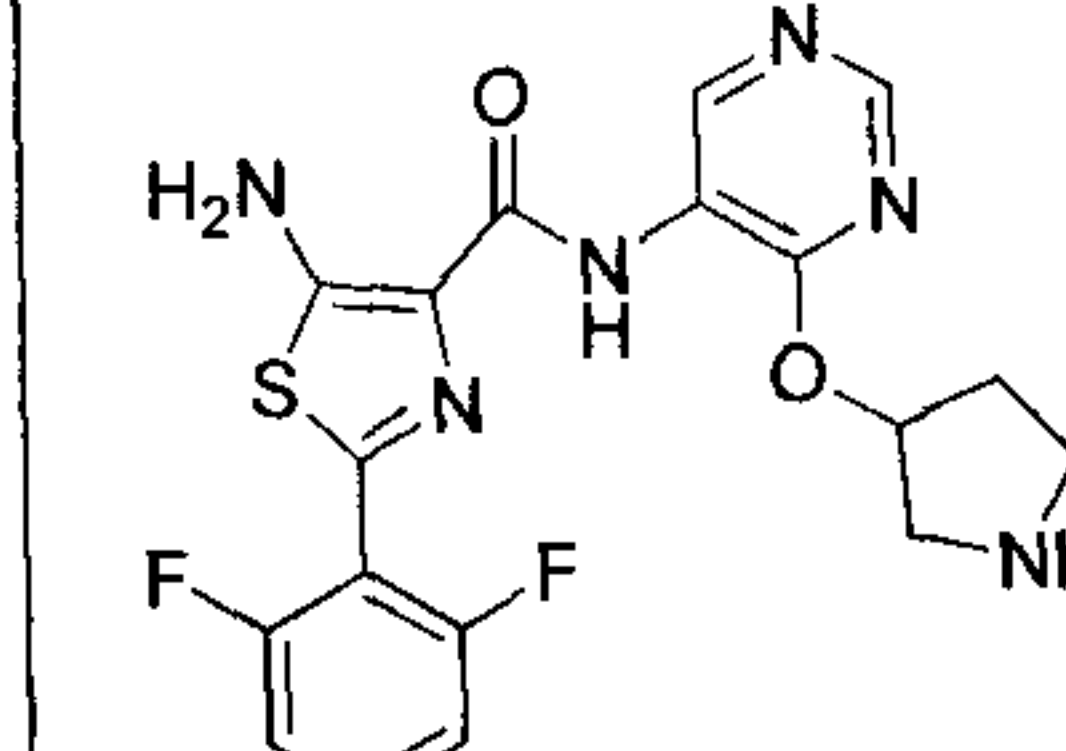
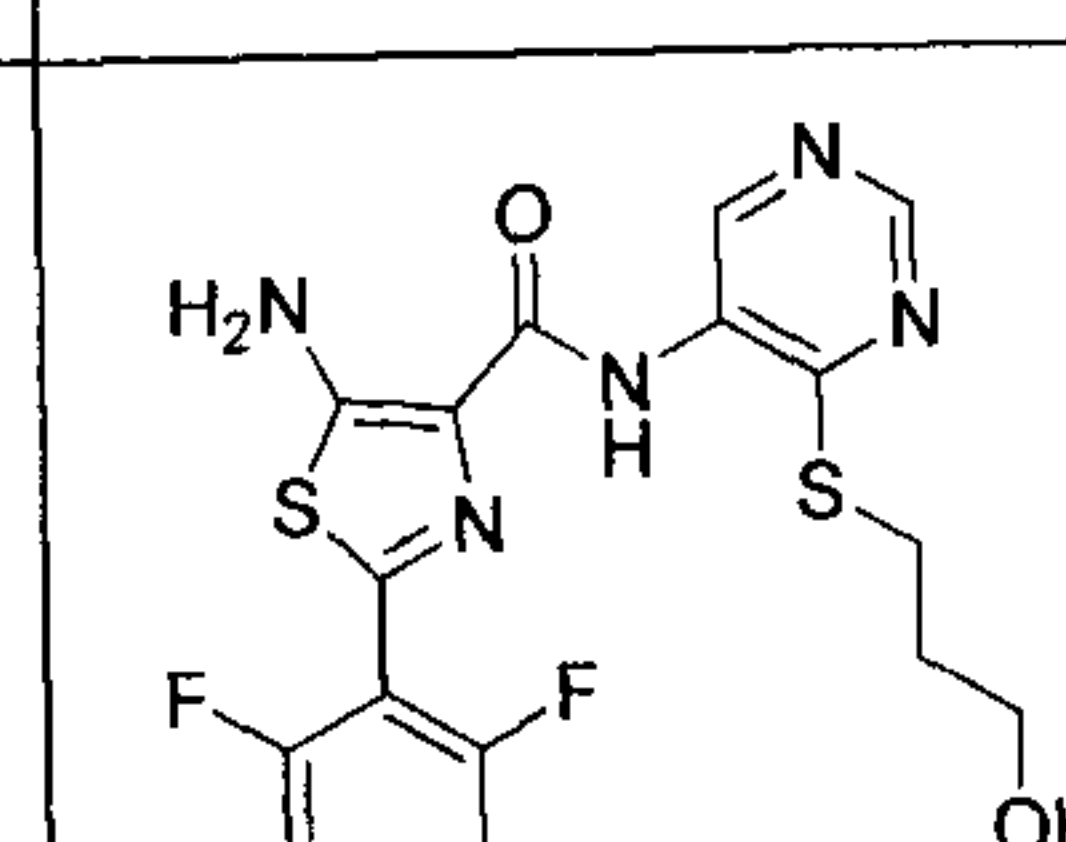
Analytical data of the compound described in the examples of the present invention:

	Structure	¹ H NMR	MS
1		¹ H NMR (400 MHz, CDCl ₃) δ 2.10-2.22 (m, 1H), 2.28 – 2.31 (m, 1H), 3.00 – 3.02 (m, 1H), 3.28-3.31 (m, 1H), 3.30 – 3.34 (m, 2H), 5.71 (m, 1H), 7.11 – 7.15 (m, 2H), 7.45-7.49 (m, 1H), 8.40 (s, 1H), 8.56 (s, 1H), 9.63 (s, 1H), 9.75 (s, 1H),	M+1 :404
2		¹ H NMR (400 MHz, CDCl ₃) δ 1.68 (m, 1H), 2.06-2.08 (m, 2H), 2.07 – 2.15 (m, 3H), 2.90 – 3.00 (m, 4H), 5.53 (m, 1H), 7.07 – 7.09 (m, 2H), 7.42 (m, 1H), 8.37 (s, 1H), 8.51 (s, 1H), 9.61 (s, 1H), 9.75 (s, 1H),	M+1 :432
3		¹ H NMR (400 MHz, CDCl ₃) δ 1.86 (d, J = 8.84, 2H), 2.14 (t, J = 10.23, 2H), 2.85 (t, J = 10.23, 2H), 3.22 (t, J = 10.23, 2H), 5.22 - 5.52 (m, 1H), 7.14 (bs, 2H), 7.37 - 7.60 (m, 1H), 8.43 (s, 1H), 8.51 - 8.61 (m, 1H), 9.52 - 9.70 (m, 1H), 9.72- 9.95 (m, 1H)	M+1: 418
4		¹ H NMR (400 MHz, CD ₃ OD) δ 2.27-2.35 (m, 4H), 3.35-3.37 (m, 2H), 3.44-3.51 (m, 2H), 5.57-5.60 (m, 1H), 7.16 - 7.21 (m, 2H), 7.46 - 7.50 (m, 1H), 8.52 (s, 1H), 9.53 (s, 1H)	M+1: 433
5		¹ H NMR (400 MHz, CDCl ₃) δ 1.44-1.54 (m, 2H), 1.69-1.86 (m, 2H), 1.99-2.11 (m, 2H), 2.15-2.30 (m, 2H), 3.86 - 3.94 (m, 1H), 4.50 - 4.67 (m, 1H), 5.29 (s, 1H), 7.06 - 7.14 (m, 2H), 7.37 - 7.50 (m, 1H), 8.38 (s, 1H), 8.46 (s, 1H), 9.66 (s, 1H), 9.81 (bs, 1H)	M+1: 433

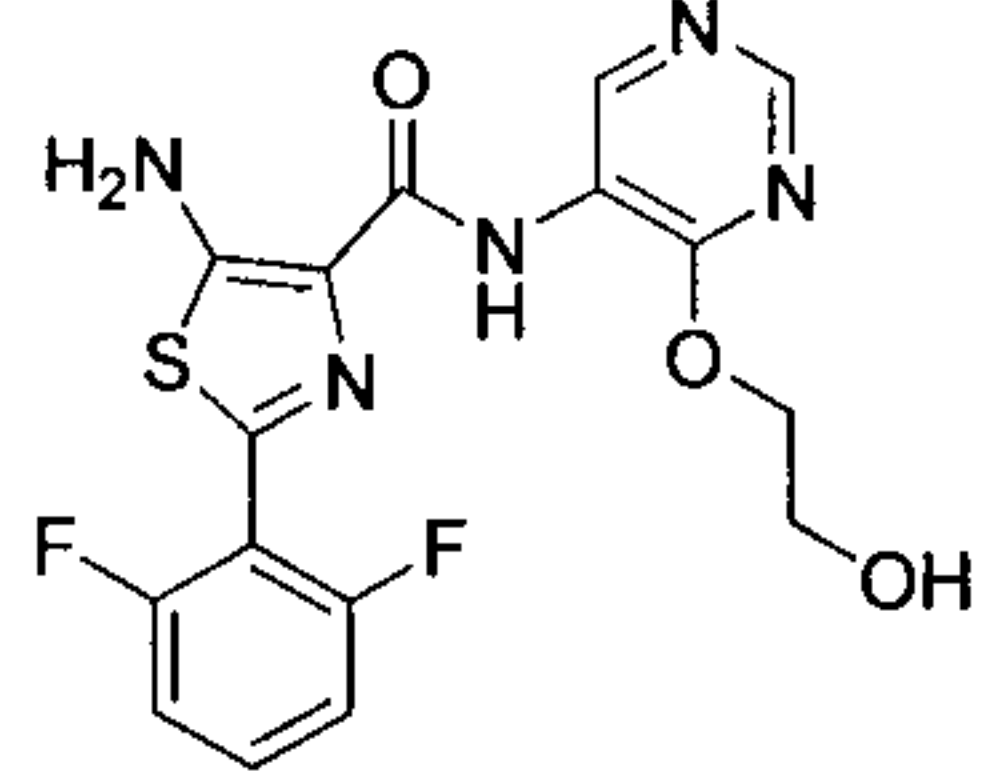
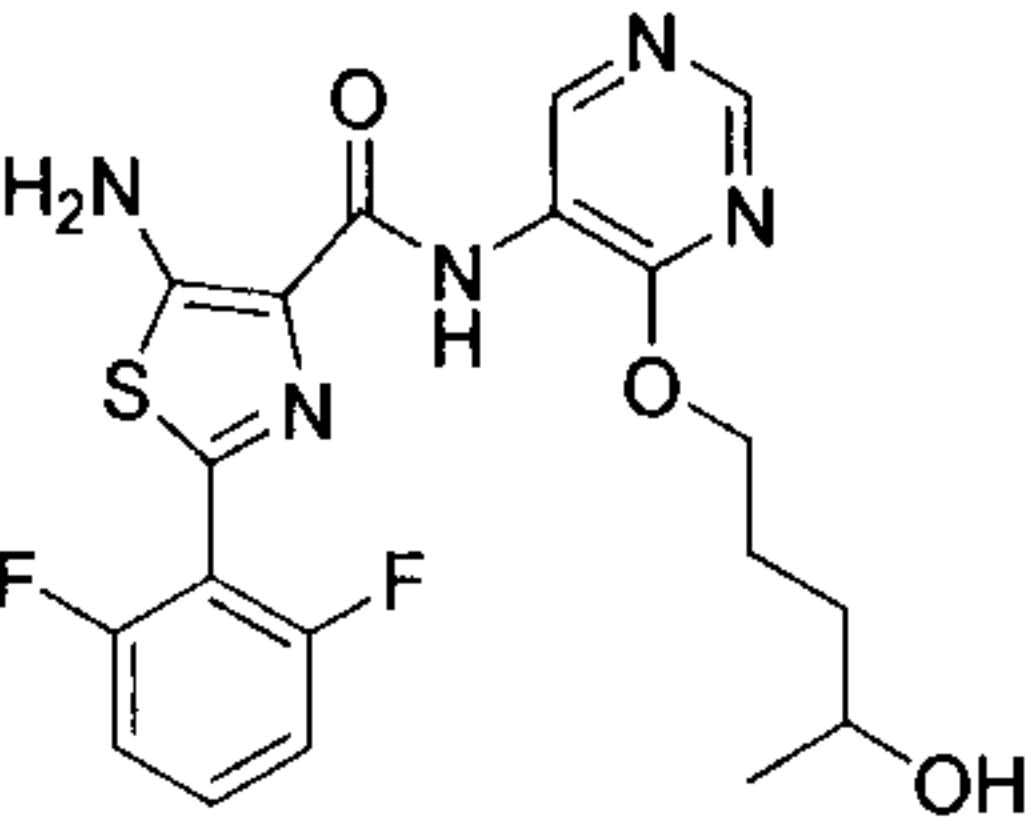
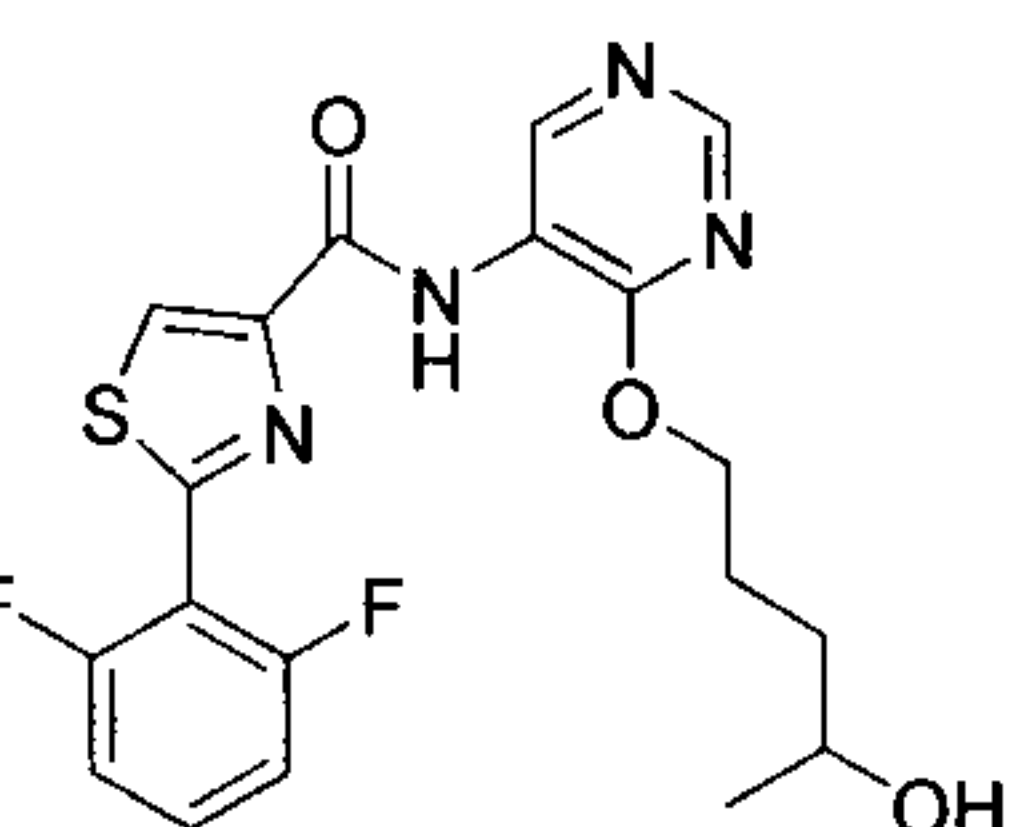
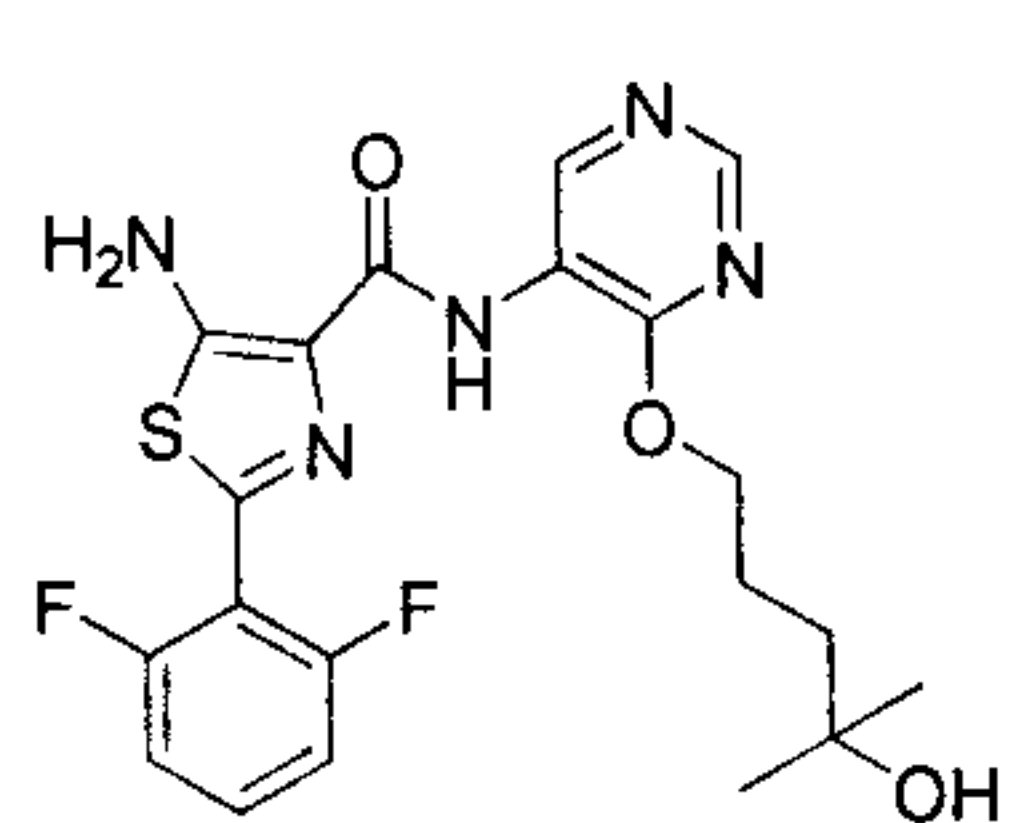
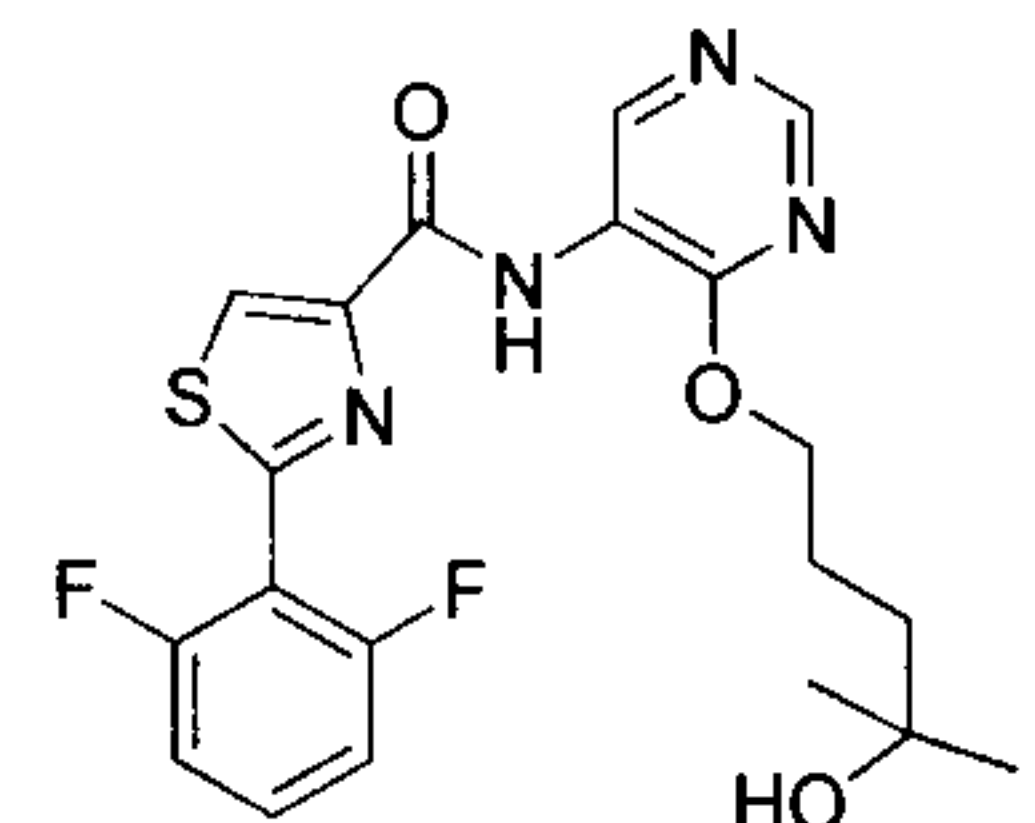
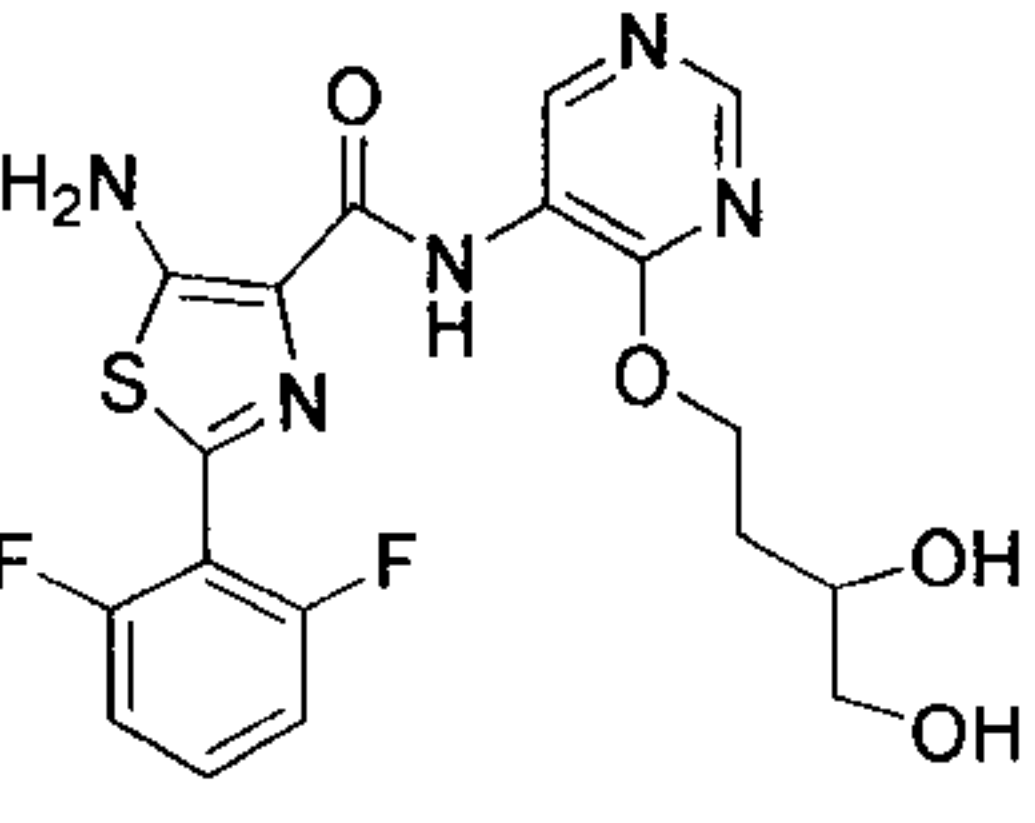
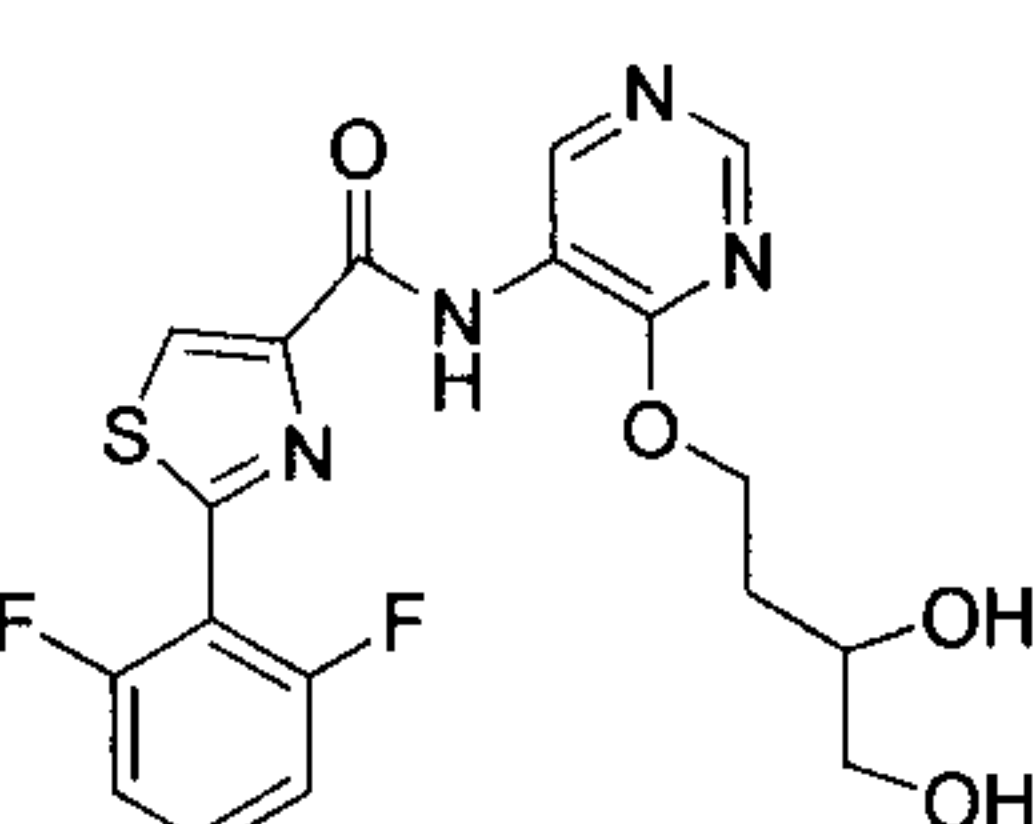
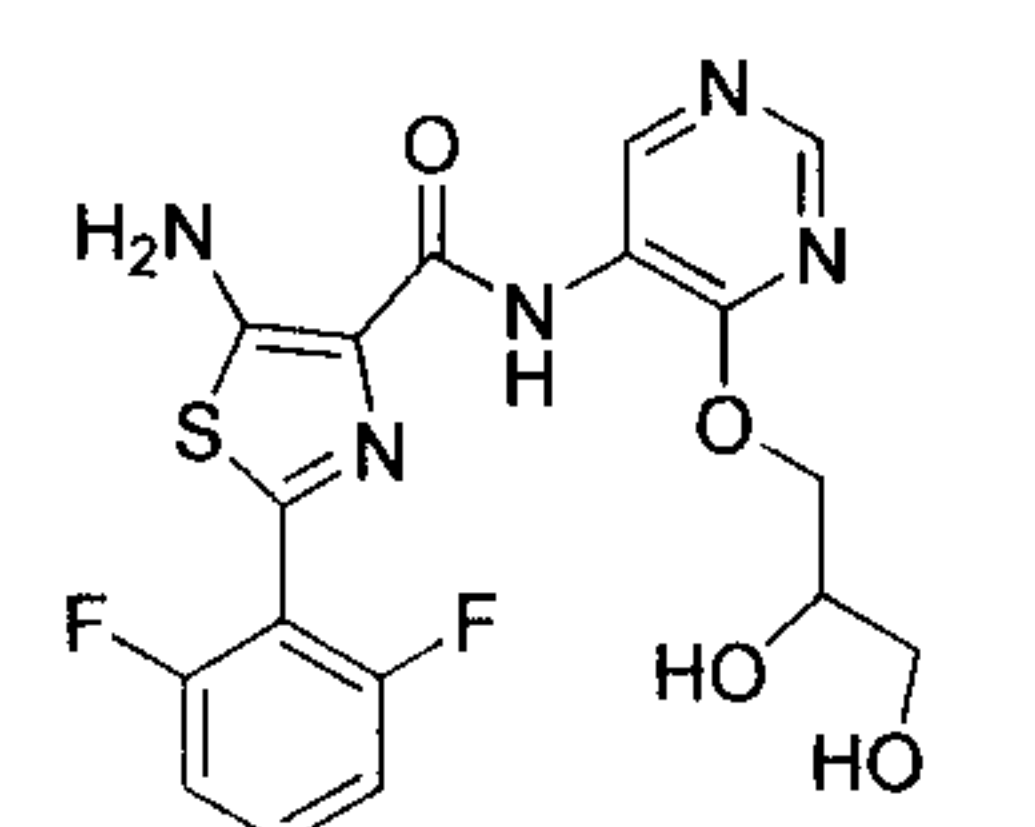
6		^1H NMR (400 MHz, CDCl_3) δ 4.76 - 4.90 (m, 2H), 5.02 - 5.12 (m, 2H), 5.76 (quin, $J = 5.56$ Hz, 1H), 7.02 - 7.13 (m, 2H), 7.35 - 7.51 (m, 1H), 8.39 (s, 1H), 8.45 (s, 1H), 9.60 (s, 1H), 9.80 (bs, 1H)	M+1: 391
7		^1H NMR (400 MHz, DMSO-d_6) δ 1.22-1.23 (m, 1H), 1.55-1.62 (m, 1H), 1.77 - 1.83 (m, 2H), 1.92-2.08 (m, 2H), 2.19 - 2.29 (m, 1H), 4.34 (bs, 1H), 5.62 (bs, 1H), 7.39 (t, $J = 8.72$ Hz, 2H), 7.65- 7.72 (m, 1H), 8.57 (s, 1H), 8.79 (s, 1H), 9.31 (s, 1H), 9.71(s, 1H),	M+1: 419
8		^1H NMR (400 MHz, DMSO-d_6) δ 1.45 (s, 6H), 1.49(s, 6H), 1.80 (s, 2H), 2.32 - 2.36 (m, 2H), 5.58 - 5.64 (m, 1H), 7.38 (t, $J = 8.72$ Hz, 2H), 7.67 - 7.74 (m, 1H), 8.63 (s, 1H), 8.81 (s, 1H), 9.28 (s, 1H), 9.81 (s, 1H)	M+1: 474
9		^1H NMR (400 MHz, CD_3OD) δ 1.37 (s, 3H), 4.39 -3.40 (m, 2H), 4.53 - 4.54 (m, 2H), 4.56 (s, 2H), 7.05 - 7.15 (m, 2H), 7.38-7.49 (m, 1H), 8.52 (s, 1H), 9.63 (bs, 1H), 9.69 (bs, 1H)	M+1: 418
10		^1H NMR (400 MHz, DMSO-d_6) δ 2.99 - 3.13 (m, 1H), 3.35 (d, $J = 7.78$ Hz, 2H), 3.59 (t, $J = 7.53$ Hz, 2H), 4.39 (d, $J = 6.27$ Hz, 2H), 7.05 - 7.15 (m, 2H), 7.38 - 7.49 (m, 1H), 8.38 (s, 1H), 8.52 (s, 1H), 9.63 (bs, 1H), 9.69 (bs, 1H)	M+1: 404
11		^1H NMR (400 MHz, DMSO-d_6) δ 2.14 (t, $J = 10.23$, 2H), 2.85 (t, $J = 10.23$, 2H), 3.22 (t, $J = 10.23$, 4H), 5.22 - 5.52 (m, 1H), 7.37-7.40 (m, 2H), 7.70 (s, 1H), 8.00 -8.01 (m, 1H), 8.26-8.29 (m, 2H), 8.45 (m, 1H), 8.60 (s, 1H), 9.39 (s, 1H), 10.34 (s, 1H)	M+1: 412
12		^1H NMR (400 MHz, CDCl_3) δ 1.79 (d, $J=6.32$ Hz, 1H), 2.15 (dd, $J = 12.63$, 5.05 Hz, 1H), 2.83 (t, $J = 6.69$ Hz, 1H) 3.64 - 3.82 (m, 2H), 3.85-4.04 (m, 2H), 4.39 (d, $J=8.08$ Hz, 1H), 4.48 (d, $J = 3.79$ Hz, 1H), 7.05 - 7.15 (m, 2H), 7.38 - 7.49 (m, 1H), 8.38 (s, 1H), 8.52 (s, 1H), 9.63 (bs, 1H), 9.69 (bs, 1H)	M+1: 419
13		^1H NMR (400 MHz, CDCl_3) δ 1.43 - 1.54 (m, 4H), 1.79 - 1.92 (m, 1H), 3.36 - 3.57 (m, 2H), 3.93 - 4.09 (m, 2H), 4.33 (d, $J = 6.82$ Hz, 2H), 7.01 - 7.17 (m, 2H), 7.41 - 7.58 (m, 1H), 8.41 (s, 1H), 8.54 (s, 1H), 9.67 (s, 1H), 9.79 (bs, 1H)	M+1: 433

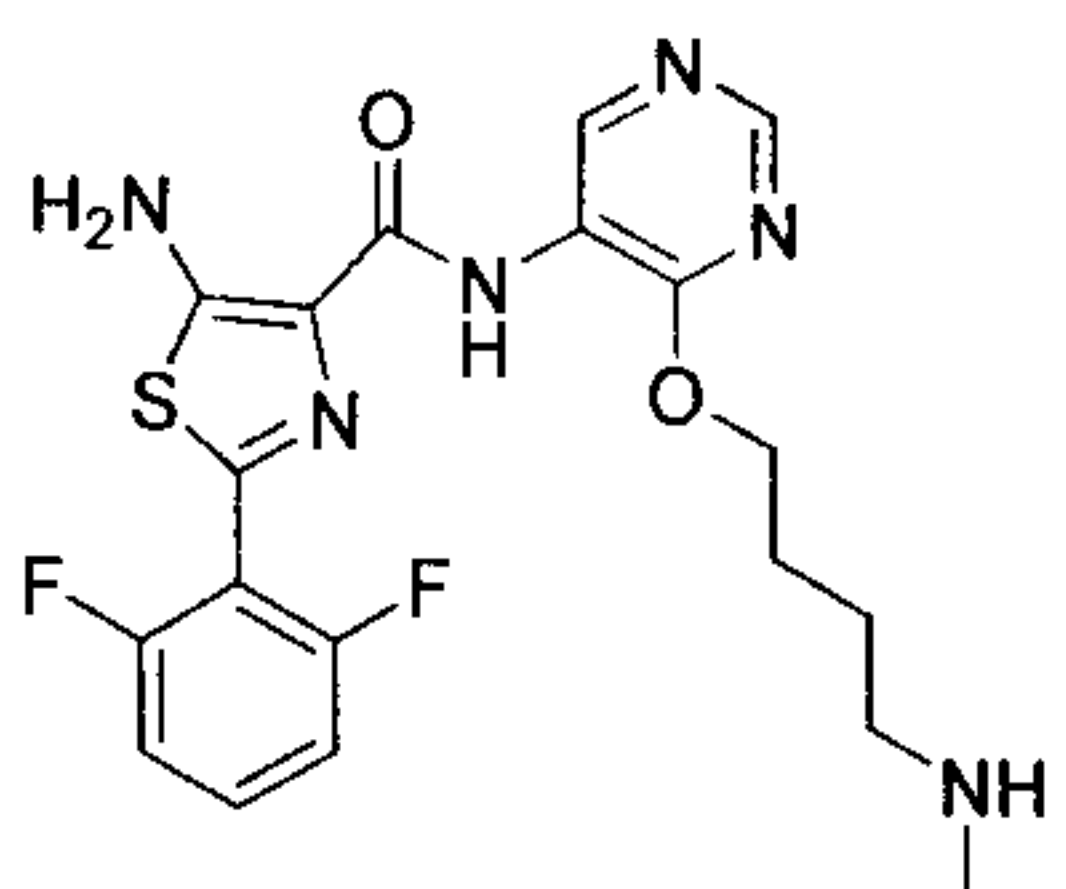
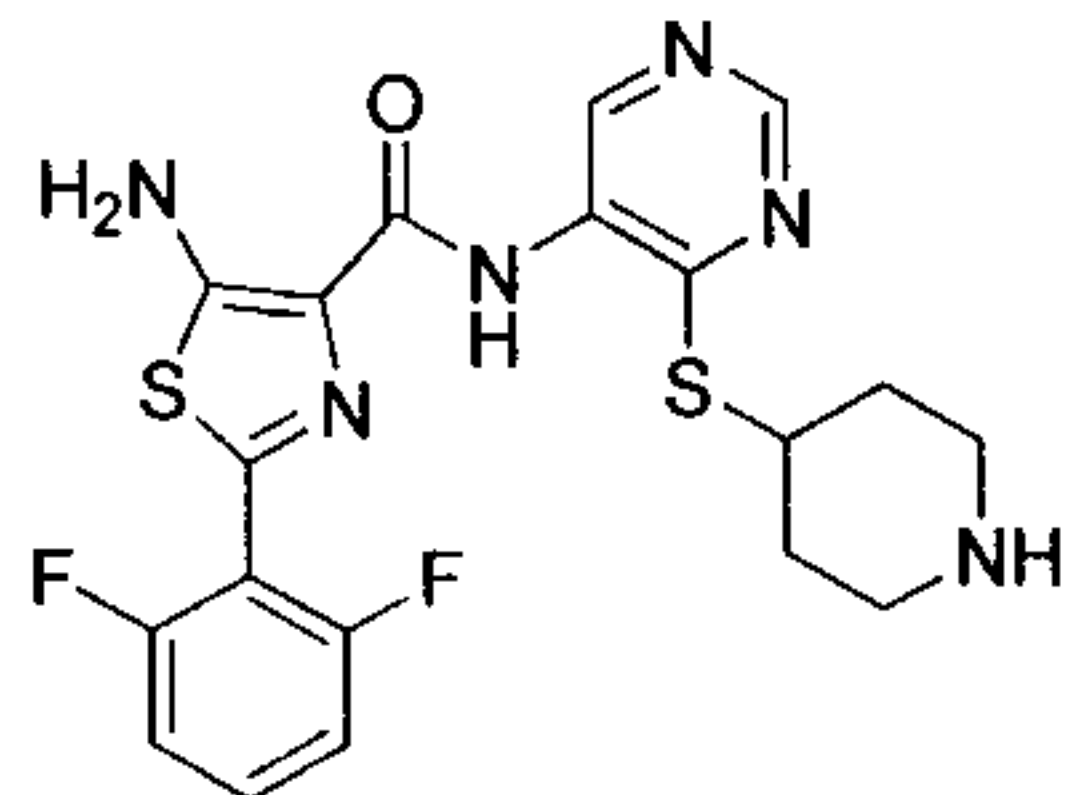
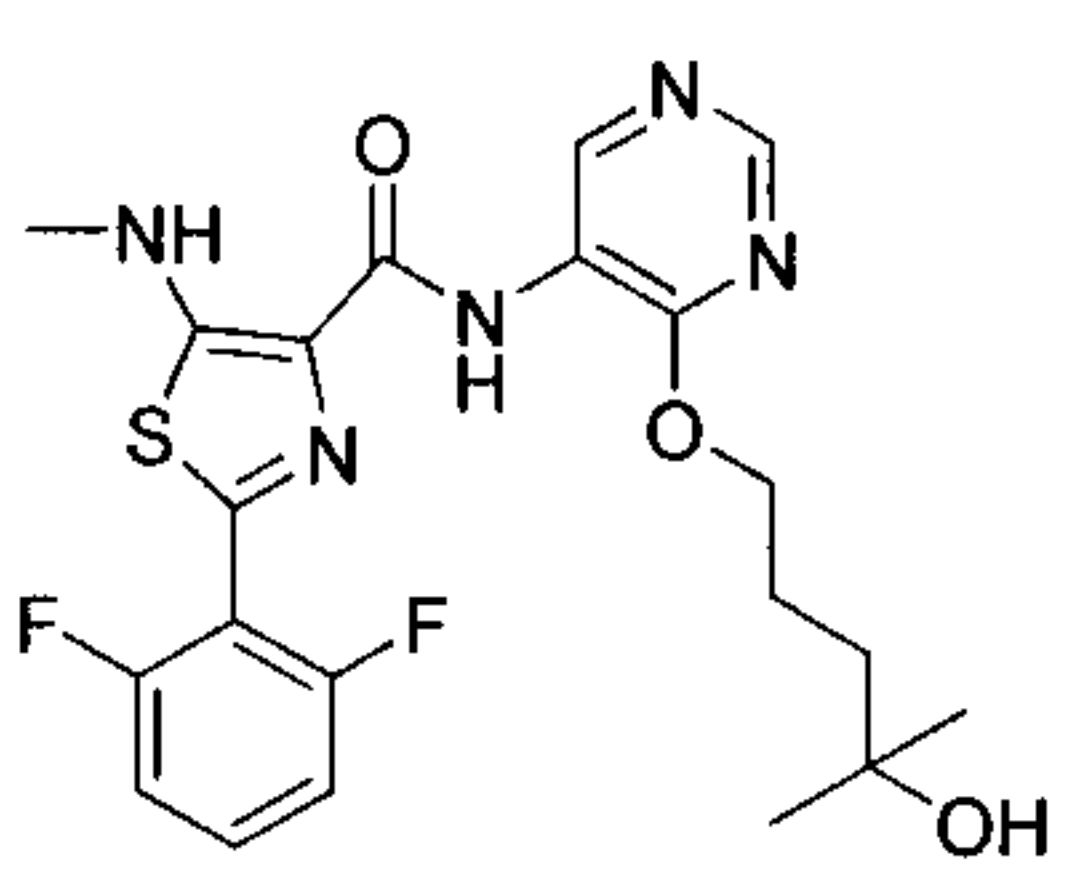
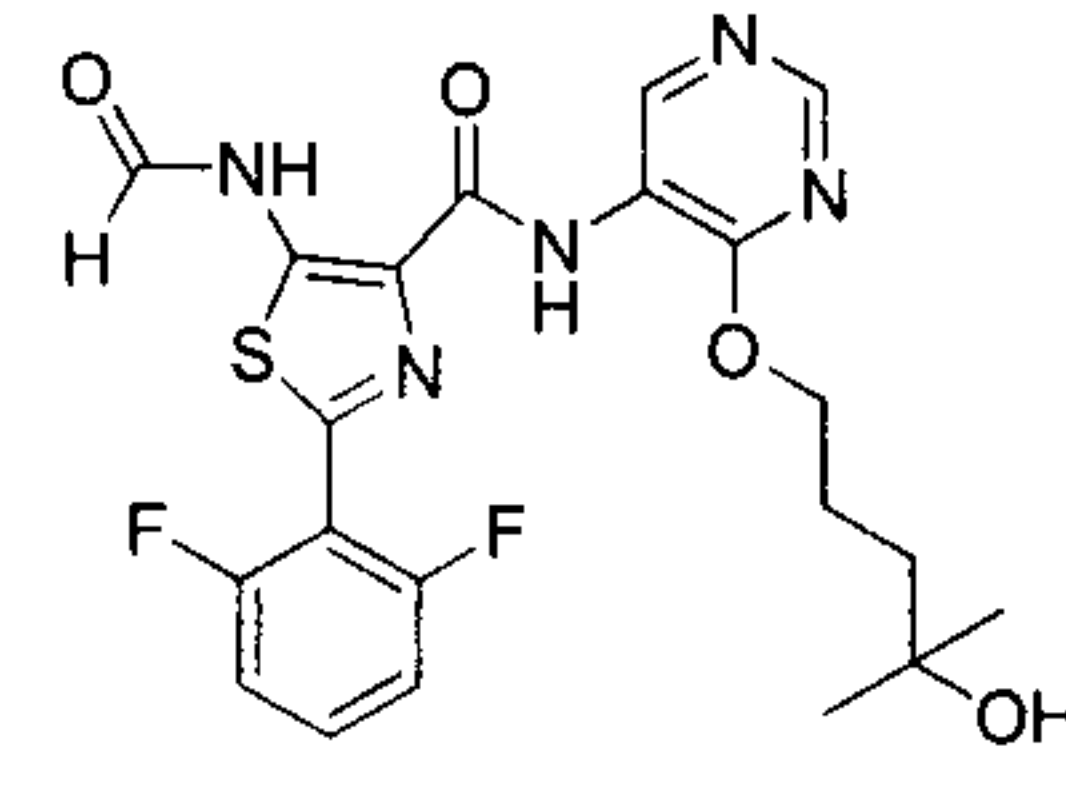
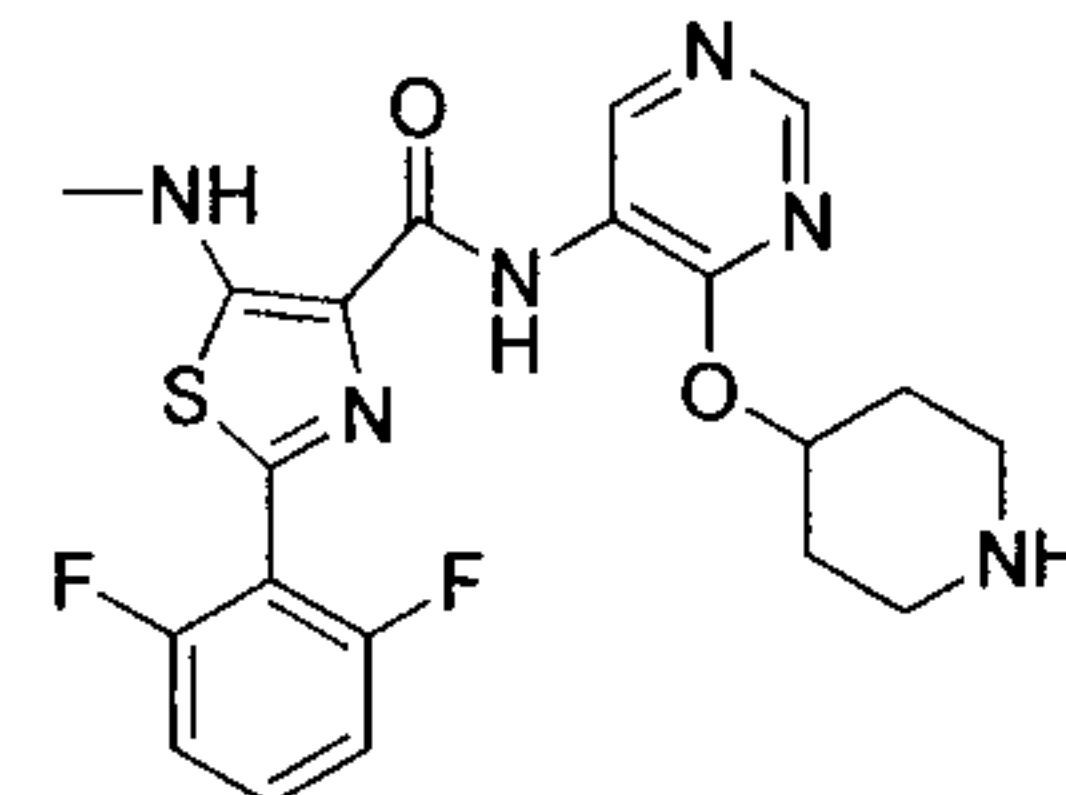
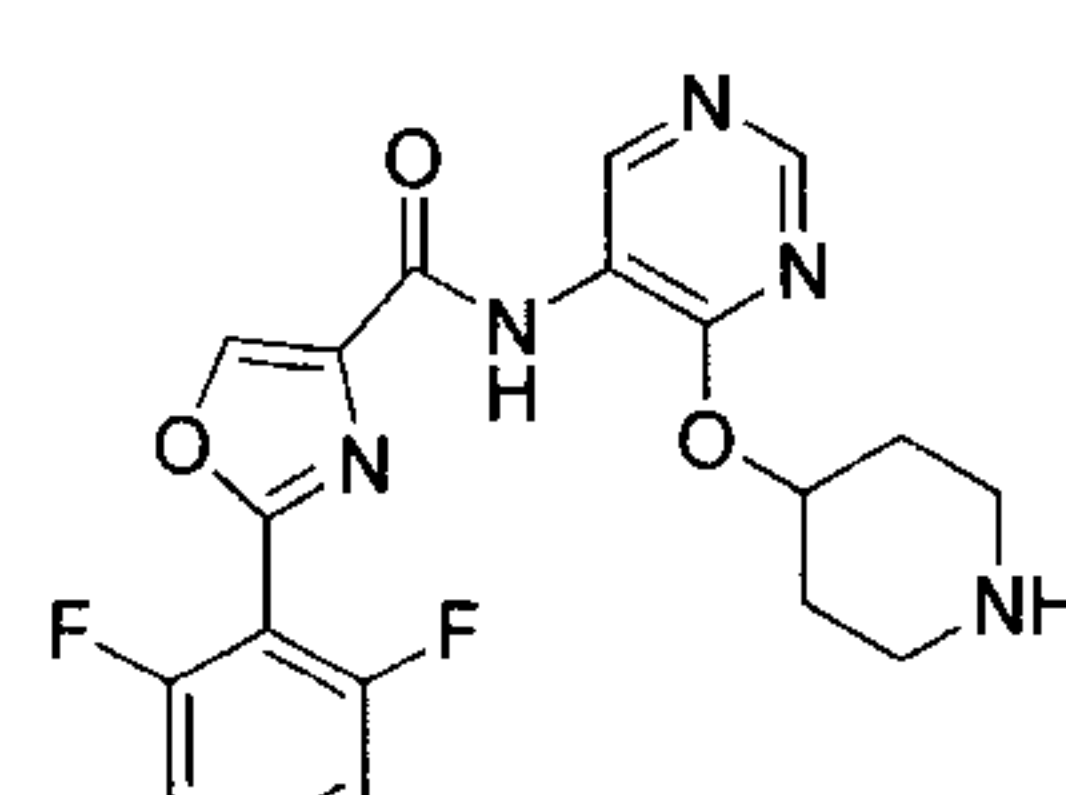
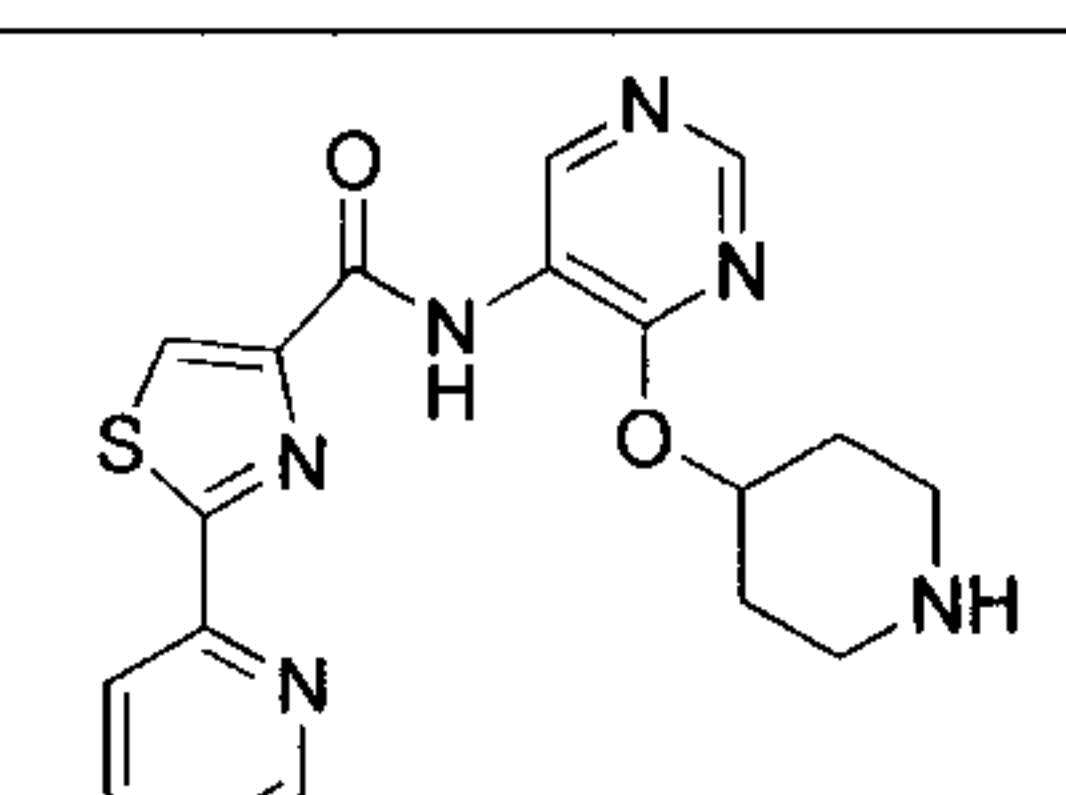
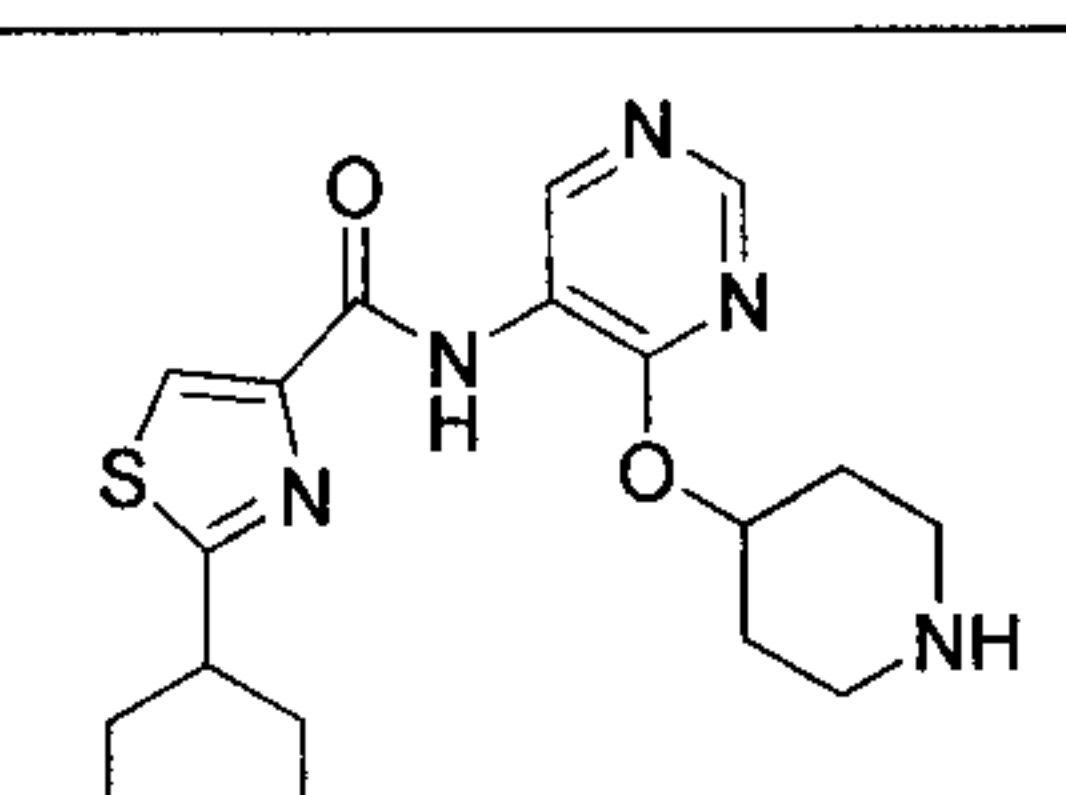
14		^1H NMR (400 MHz, CDCl_3) δ 1.20 - 1.32 (m, 1H), 1.78 - 1.98 (m, 6H), 2.17 - 2.35 (m, 2H), 3.67 (bs, 2H), 5.51 (s, 1H), 7.05- 7.17 (m, 2H), 7.36-7.52 (m, 1H), 8.35 (s, 1H), 8.48 (s, 1H), 9.59 (s, 1H) 9.65 (s, 1H)	M+1: 444
15		^1H NMR (400 MHz, CD_3OD) δ 1.25 - 1.35 (m, 2H), 1.99 -2.01 (m, 2H), 2.02 - 2.08 (m, 1H), 2.60 - 2.67 (m, 2H), 3.07 - 3.09 (m, 2H), 4.30 - 4.31 (m, 2H), 7.18 - 7.23 (m, 2H), 7.54 - 7.61 (m, 1H), 8.45 (s, 1H), 8.55 (s, 1H), 9.44 (s, 1H)	M+1: 432
16		^1H NMR (400 MHz, DMSO-d_6) δ 1.60-1.80 (m, 2H), 1.95-2.15 (m, 2H), 3.49-3.62 (m, 2H), 3.78-3.98 (m, 2H), 4.85-5.03 (m, 1H), 7.24-7.28 (m, 2H), 7.58-7.65 (m, 1H), 8.51 (s, 1H), 8.61 (s, 1H), 9.48 (s, 1H), 9.88 (s, 1H)	M+1: 419
17		^1H NMR (400 MHz, DMSO-d_6) δ 1.73 - 1.79 (m, 1H), 2.45 - 2.48 (m, 2H), 2.55 - 2.66 (m, 3H), 2.71- 2.73 (m, 1H), 3.12 - 3.14 (m, 1H), 3.17 - 3.19 (m, 1H), 5.21 - 5.27 (m, 1H), 7.37 - 7.42 (m, 2H), 7.64 - 8.73 (m, 1H), 8.54 (s, 1H), 8.82 (s, 1H), 9.25 (s, 1H), 9.80 (s, 1H)	M+1: 430
18		^1H NMR (400 MHz, CD_3OD) δ 1.67-1.74 (m, 1H), 2.08-2.17 (m, 1H), 2.71-2.78 (m, 1H), 2.83-2.97 (m, 2H), 3.02-3.08 (m, 1H), 3.16-3.21 (m, 1H), 4.42-4.47 (m, 1H), 4.54-4.58 (m, 1H), 7.24-7.28 (m, 2H), 7.58-7.65 (s, 1H), 8.51 (s, 1H), 8.61 (s, 1H), 9.48 (s, 1H)	M+1: 418
19		^1H NMR (400 MHz, CD_3OD) δ 1.51 (m, 1H), 1.69 (m, 1H), 1.82 (m, 1H), 2.09 (m, 1H), 2.39-2.43, (m, 1H), 2.56-2.60 (m, 1H), 2.85-2.89 (m, 4H), 3.14-3.21 (m, 2H), 4.24- 4.26 (m, 2H), 7.39 (t, J=8.8 Hz, 2H), 7.72-7.65 (m, 1H), 8.81(s, 1H), 9.31(s, 1H), 9.77 (s, 1H),	M+1: 458
20		^1H NMR (400 MHz, CD_3OD) δ 1.37 (s, 3H), 4.39 (d, J = 7.8 Hz, 2H), 4.53 (d, J = 7.6 Hz, 2H), 4.56 (s, 2H), 7.10 - 7.24 (m, 5H), 7.33 - 7.38 (m, 1H), 7.49 - 7.56 (m, 2H), 8.17- 8.19 (d, J = 5.6 Hz, 1H), 9.51 (s., 1H), 10.57 (s, 1H)	M+1: 428

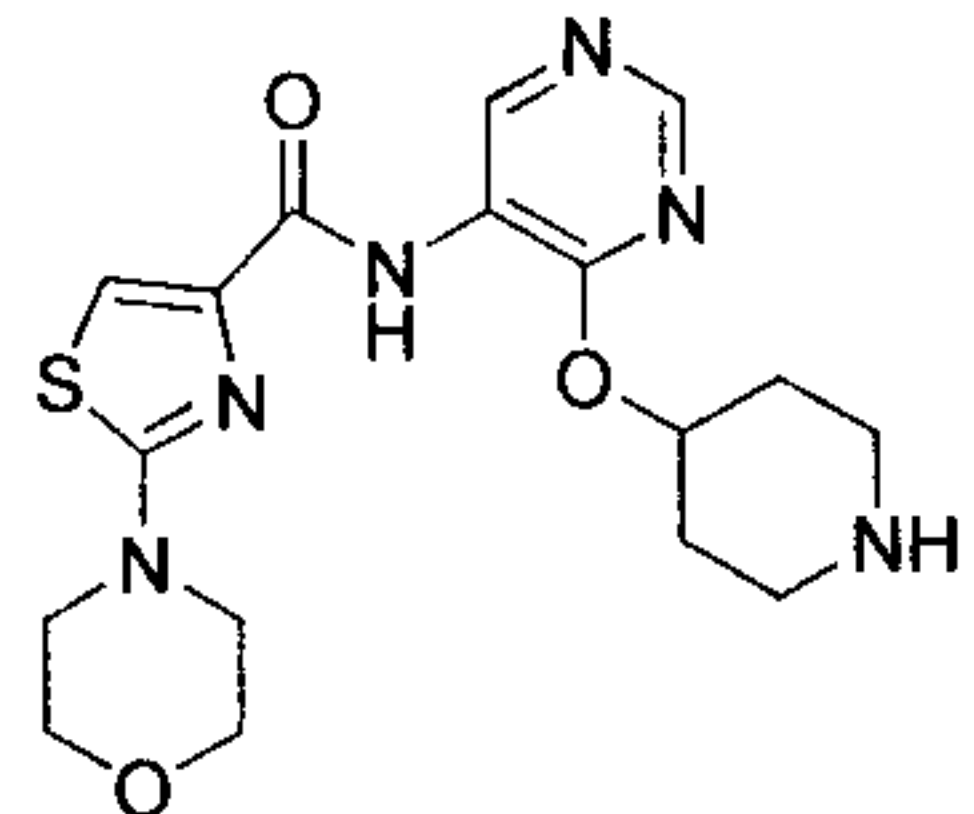
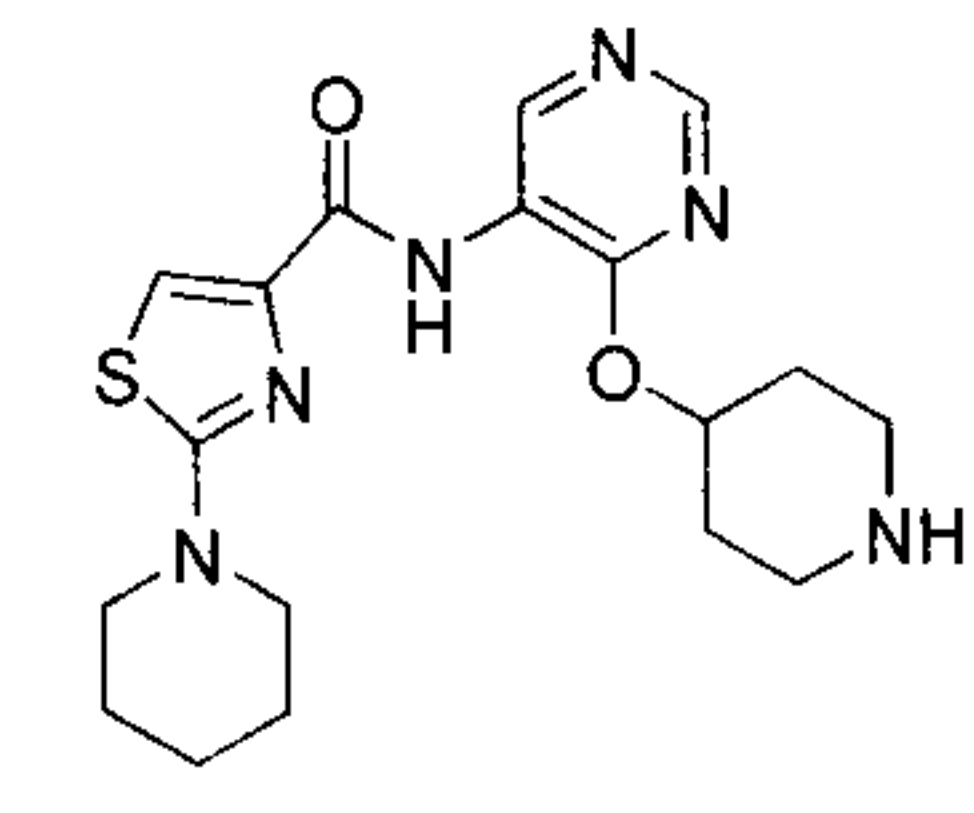
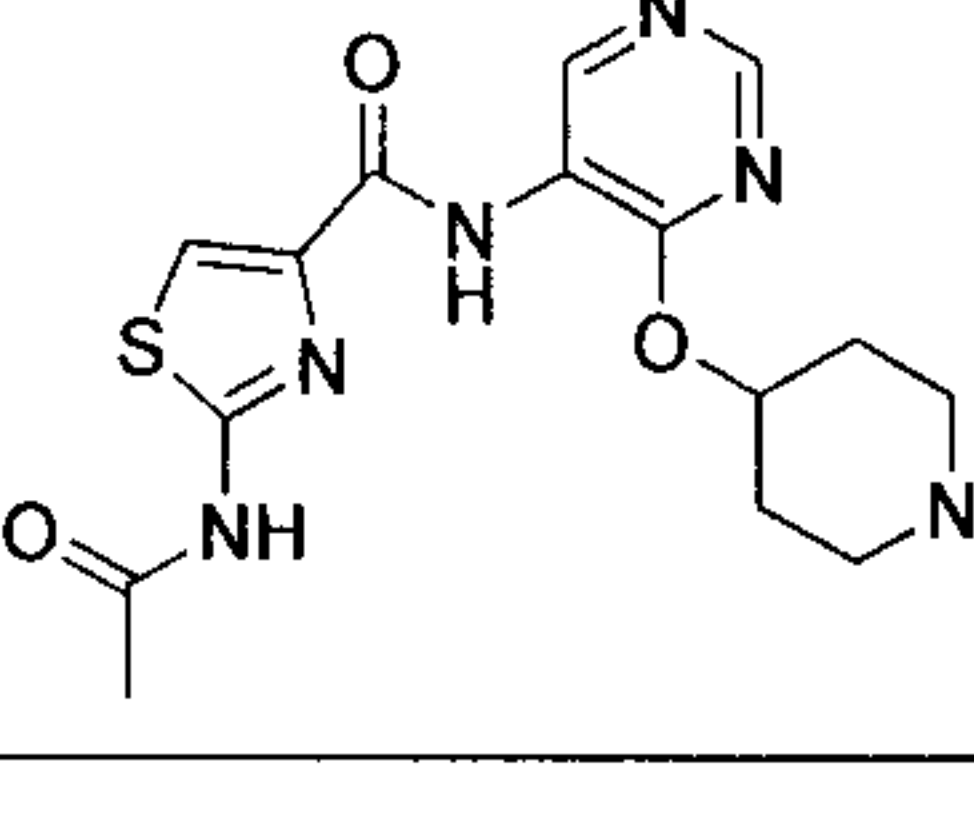
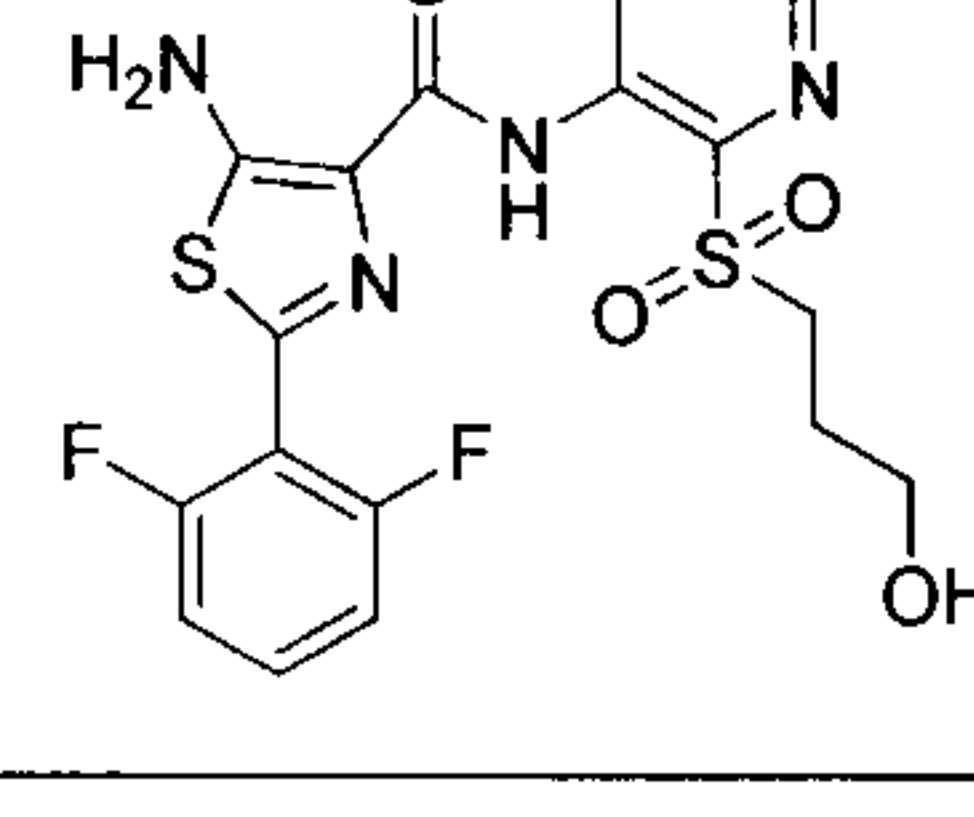
21		^1H NMR (400 MHz, DMSO- d_6) δ 4.12 - 4.19 (m, 2H), 4.43 - 4.51 (m, 2H), 5.53 - 5.59 (m, 1H), 7.41 (t, J = 8.8 Hz, 2H), 7.68 - 7.75- (m, 1H), 8.62 (s, 1H), 8.84 (s, 1H), 9.29 (s, 1H), 9.84 (s, 1H)	M+1: 390
22		^1H NMR (400 MHz, DMSO- d_6) δ 1.39 - 1.50 (m, 1H), 1.66 - 1.81 (m, 2H), 2.03 - 2.08 (m, 1H), 2.21 - 2.28 (m, 1H), 2.54 - 2.60 (m, 1H), 2.70 - 2.76 (m, 2H), 3.06 - 3.10 (m, 1H), 5.07 - 5.13 (m, 1H), 7.39 (t, J = 8.8 Hz, 2H), 7.65 - 7.72 (m, 1H), 8.56 (s, 1H), 8.81 (s, 1H), 9.31 (s, 1H), 9.77 (s, 1H),	M+1: 418
23		^1H NMR (400 MHz, CD_3OD) δ 1.53 - 1.63 (m, 2H), 2.09 - 2.12 (m, 2H), 2.20 - 2.26 (m, 1H), 3.00 - 3.06 (m, 2H), 3.42 - 3.45 (m, 2H), 4.47 - 4.49 (d, 2H), 7.13 - 7.16 (m, 2H), 7.43-7.47 (m, 1H), 7.61-7.64 (m, 1H), 7.91-7.92 (m, 1H), 8.63 (s, 1H), 8.87 (s, 1H),	M+1: 431
24		^1H NMR (400 MHz, CDCl_3) δ 1.58 - 1.65 (m, 4H), 1.65 - 1.87 (m, 4H), 2.06 - 2.30 (m, 2H), 2.71 - 2.85 (m, 1H), 5.40 - 5.53 (m, 1H), 7.00 - 7.18 (m, 2H), 7.37 - 7.52 (m, 1H), 8.44 (s, 1H), 8.53 (s, 1H), 9.66 (s, 1H), 9.73 (bs, 1 H)	M+1: 432
25		^1H NMR (400 MHz, CD_3OD) δ 1.37 (s, 3H), 4.39 (d, J = 5.6 Hz, 2H), 4.53 (d, J = 5.6 Hz, 2H), 4.56 (s, 2H), 7.01 - 7.05 (m, 2H), 7.32-7.39 (m, 1H), 8.35 (s, 1H), 9.41 (s, 1H),	M+1: 419
26		^1H NMR (400 MHz, CD_3OD) δ 1.55 - 1.65 (m, 1H), 1.83 - 1.96 (m, 1H), 2.03 - 2.13 (m, 4H), 2.76 - 2.79 (m, 1H), 2.81 - 2.85 (m, 2H), 2.90 - 2.96 (m, 1H), 5.44 - 5.50 (m, 1H), 7.02 - 7.06 (m, 2H), 7.31 - 7.38 (m, 1H), 8.31 (s, 1H), 9.36 (s, 1H),	M+1: 447
27		^1H NMR (400 MHz, CD_3OD) δ 1.20 - 1.51 (m, 2H), 1.64 - 1.69 (m, 2H), 1.98 - 2.02 (m, 2H), 2.20 - 2.23 (m, 2H), 2.84 - 2.90 (m, 1H), 4.35-4.41 (m, 1H), 7.02-7.06 (m, 2H), 7.31 7.38 (m, 1H), 8.31 (s, 1H), 9.36 (s, 1H)	M+1: 447

28		^1H NMR (400 MHz, CD_3OD) δ 1.26 – 1.29 (m, 2H), 1.91 – 1.94 (m, 2H), 2.04 – 2.12 (m, 1H), 2.66–2.69 (m, 2H), 3.10–3.13 (m, 2H), 3.90–3.98 (m, 2H), 6.99–7.02 (m, 2H), 7.31 – 7.41 (m, 1H), 8.33 (s, 1H), 9.40 (s, 1H)	M+1: 447
29		^1H NMR (400 MHz, CD_3OD) δ 1.48 - 1.61 (m, 2H), 1.75 - 1.82 (m, 2H), 2.79 - 2.82 (m, 2H), 4.26 (t, J = 5.96 Hz, 2H), 7.00 - 7.04 (m, 2H), 7.29 - 7.41 (m, 1H), 8.36 (s, 1H), 9.42 (s, 1H)	M+1: 421
30		^1H NMR (400 MHz, CD_3OD) δ 1.44 - 1.50 (m, 2H), 1.70 - 1.78 (m, 2H), 3.32 - 3.45 (m, 2H), 4.22 (t, J = 5.96 Hz, 2H), 7.01 - 7.04 (m, 2H), 7.31 - 7.42 (m, 1H), 8.35 (s, 1H), 9.39 (s, 1H)	M: 421
31		^1H NMR (400 MHz, CD_3OD) δ 1.42 - 1.58 (m, 1H), 2.01 - 2.15 (m, 1H), 2.35 (bs, 1H), 2.54 - 2.70 (m, 2H), 2.82 (d, J = 9.80 Hz, 1H), 3.22 (ddd, J = 5.00, 8.04, 12.40 Hz, 1H), 4.45 - 4.70 (m, 1H), 7.00 - 7.18 (m, 2H), 7.37 - 7.52 (m, 1H), 8.53 (s, 1H), 9.66 (s, 1H), 9.73 (bs, 1H)	M+1: 436
32		^1H NMR (400 MHz, CD_3OD) δ 2.20 - 2.33 (m, 4H), 3.34 - 3.37 (m, 2H), 3.42 - 3.49 (m, 2H), 5.57 - 5.61 (m, 1H), 7.09 - 7.24 (m, 3H), 7.33 - 7.38 (m, 1H), 8.17 - 8.19 (d, J = 5.6 Hz, 1H), 9.51 (s, 1H), 10.57 (s, 1H)	M+1: 427
33		^1H NMR (400 MHz, CD_3OD) δ 1.45-1.46(d, J=6.80 Hz, 6H), 2.22-2.31 (m, 5H), 3.34-3.35 (m, 2H), 3.46-3.49 (m, 2H), 5.60 - 5.61 (m, 1H), 8.49 (s, 1H), 9.47 (s, 1H), 9.65 (s, 1H)	M+1: 348
34		^1H NMR (400 MHz, CD_3OD) δ 2.09-2.20 (m, 1H), 2.30–2.32 (m, 1H), 2.99–3.02(m, 1H), 3.30-3.32 (m, 1H), 3.32–3.34 (m, 2H), 5.69 - 5.71 (m, 1H), 7.13 - 7.19 (m, 2H), 7.39 - 7.50 (m, 1H), 8.52 (s, 1H), 9.53 (s, 1H)	M+1: 419
35		^1H NMR (400 MHz, CD_3OD) δ 1.65 - 1.81 (m, 2H), 3.01 (t, J = 6.92 Hz, 2H), 3.51 (t, J = 6.00, 2H), 6.95 - 7.00 (m, 2H), 7.29 - 7.38 (m, 1H), 8.29 (s, 1H), 9.37 (s, 1H)	M: 423

36		^1H NMR (400 MHz, CD_3OD) δ 1.40 (s, 6H), 4.00 (t, J = 4.68 Hz, 1H), 4.05 (t, J = 4.20 Hz, 1H), 4.19 - 4.24 (m, 2H), 4.50 - 4.65 (m, 1H), 7.18 - 7.21 (m, 2H), 7.41 - 7.48 (m, 1H), 8.50 (s, 1H), 9.55 (s, 1H)	M: 463
37		^1H NMR (400 MHz, CD_3OD) δ 1.68 - 1.79 (m, 1H), 1.98 - 2.09 (m, 1H), 2.12 - 2.24 (m, 2H), 2.25 - 2.43 (m, 2H), 4.55 - 4.64 (m, 1H), 4.98 - 5.07 (m, 1H), 7.00 - 7.20 (m, 2H), 7.41 - 7.50 (m, 1H), 8.55 (s, 1H), 9.66 (s, 1H), 9.73 (s, 1H)	M: 418
38		^1H NMR (400 MHz, CD_3OD) δ 1.27 (s, 6H), 2.05 - 2.19 (m, 2H), 4.00 - 4.13 (m, 2H), 4.19 - 4.31 (m, 1H), 4.32 - 4.42 (m, 2H), 7.14 - 7.19 (m, 2H), 7.48 - 7.50 (m, 1H), 8.50 (s, 1H), 9.49 (s, 1H)	M: 477
39		^1H NMR (400 MHz, CD_3OD) δ 1.09 (s, 6H), 1.88 - 1.96 (m, 2H), 4.30 (t, J = 6.80 Hz, 2H), 7.18 - 7.21 (m, 2H), 7.51 - 7.53 (m, 1H), 8.53 (s, 1H), 9.57 (s, 1H)	M: 435
40		^1H NMR (400 MHz, CD_3OD) δ 1.10 (s, 6H), 1.89 - 2.01 (m, 2H), 4.29 (t, J = 6.80 Hz, 2H), 7.15 - 7.18 (m, 2H), 7.44 - 7.52 (m, 1H), 8.50 (s, 1H), 9.62 (s, 1H), 9.79 (s, 1H)	M: 420
41		^1H NMR (400 MHz, CD_3OD) δ 1.07 (s, 3H), 1.70 - 1.87 (m, 2H), 3.41 - 3.53 (m, 1H), 4.20 - 4.26 (m, 2H), 7.12 - 7.21 (m, 2H), 7.38 - 7.44 (m, 1H), 8.45 (s, 1H), 9.48 (s, 1H)	M: 421
42		^1H NMR (400 MHz, CD_3OD) δ 1.02 (s, 3H), 1.77-1.87 (m, 2H), 3.52 - 3.56 (m, 1H), 4.12 - 4.20 (m, 2H), 7.04 - 7.20 (m, 2H), 7.37 - 7.52 (m, 1H), 8.57 (s, 1H), 9.71 (s, 1H), 9.80 (s, 1H)	M: 406
43		^1H NMR (400 MHz, CD_3OD) δ 1.28 - 1.60 (m, 4H), 1.82 - 1.92 (m, 2H), 2.08 - 2.27 (m, 3H), 3.46 (m, 1H), 7.16 - 7.19 (m, 2H), 7.41 - 7.48 (m, 1H), 8.39 (s, 1H), 9.47 (s, 1H)	M: 474

44		^1H NMR (400 MHz, CD_3OD) δ 3.81 - 3.87 (m, 2H), 4.24 (t, J = 4.64 Hz, 2H), 7.15 - 7.21 (m, 2H), 7.42 - 7.50 (m, 1H), 8.50 (s, 1H), 9.50 (s, 1H)	M: 393
45		^1H NMR (400 MHz, CD_3OD) δ 1.11 (s, 3H), 1.37 - 1.42 (m, 2H), 1.80 - 1.84 (m, 2H), 3.40 - 3.46 (m, 1H), 4.30 (t, J = 6.84 Hz, 2H), 7.07 - 7.17 (m, 2H), 7.39 - 7.46 (m, 1H), 8.39 (s, 1H), 9.46 (s, 1H)	M: 435
46		^1H NMR (400 MHz, CD_3OD) δ 1.07 (s, 3H), 1.40 - 1.45 (m, 2H), 1.77 - 1.81 (m, 2H), 3.36 - 3.42 (m, 1H), 4.29 (t, J = 6.80 Hz, 2H), 7.05 - 7.14 (m, 2H), 7.44 - 7.52 (m, 1H), 8.55 (s, 1H), 9.60 (s, 1H), 9.69 (s, 1H)	M: 420
47		^1H NMR (400 MHz, CD_3OD) δ 1.11 (s, 6H), 1.42 - 1.48 (m, 2H), 1.72 - 1.80 (m, 2H), 4.21 (t, J = 6.84 Hz, 2H), 7.16 - 7.21 (m, 2H), 7.46 - 7.50 (m, 1H), 8.52 (s, 1H), 9.53 (s, 1H)	M: 449
48		^1H NMR (400 MHz, CD_3OD) δ 1.09 (s, 6H), 1.36-1.44 (m, 2H), 1.68-1.80 (m, 2H), 4.18 (t, J = 6.80 Hz, 2H), 7.01 - 7.22 (m, 2H), 7.40 - 7.50 (m, 1H), 8.52 (s, 1H), 9.66 (s, 1H), 9.72 (bs, 1H)	M: 434
49		^1H NMR (400 MHz, CD_3OD) δ 1.79-1.96 (m, 2H), 3.20 (bs, 2H), 3.68-3.70 (m, 1H), 4.16-4.33 (m, 2H), 7.19 - 7.23 (m, 2H), 7.51 - 7.53 (m, 1H), 8.50 (s, 1H), 9.50 (s, 1H)	M: 437
50		^1H NMR (400 MHz, CD_3OD) δ 1.90 - 2.80 (m, 2H), 3.22 (bs, 2H), 3.70 - 3.77 (m, 1H), 4.10 - 4.30 (m, 2H), 6.99 - 7.19 (m, 2H), 7.40 - 7.52 (m, 1H), 8.46 (s, 1H), 9.60 (s, 1H), 9.71 (s, 1H)	M: 422
51		^1H NMR (400 MHz, CD_3OD) δ 3.50 (bs, 2H), 3.98 - 4.15 (m, 1H), 4.15 - 4.22 (m, 2H), 7.15 - 7.21 (m, 2H), 7.44 - 7.52 (m, 1H), 8.53 (s, 1H), 9.50 (s, 1H)	M: 423

52		^1H NMR (400 MHz, CD_3OD) δ 1.51 - 1.59 (m, 2H), 1.80 - 1.84 (m, 2H), 2.81 - 2.85 (m, 2H), 2.92 (s, 3H), 4.27 (t, J = 6.00 Hz, 2H), 7.16 - 7.19 (m, 2H), 7.42 - 7.48 (m, 1H), 8.47 (s, 1H), 9.49 (s, 1H)	M+1: 435
53		^1H NMR (400 MHz, CD_3OD) δ 0.84-0.86 (m, 2H), 1.21-1.24 (m, 2H), 1.83-1.87 (m, 2H), 2.82-2.90(m,2H),2.90-2.93(m,1H),7.20-7.23 (m,2H), 7.45-7.50(m,1H),8.50 (s,1H), 9.50 (s,1H)	M+1: 449
54		^1H NMR (400 MHz, CD_3OD) δ 1.14 (s, 6H), 1.40 - 1.50 (m, 2H), 1.70 - 1.80 (m, 2H), 3.20 (s, 3H), 4.21 (t, J = 6.84 Hz, 2H), 7.11 - 7.21 (m, 2H), 7.44 - 7.51 (m, 1H), 8.51 (s, 1H), 9.54 (s, 1H)	M: 463
55		^1H NMR (400 MHz, CD_3OD) δ 1.11 (s, 6H), 1.39 - 1.49 (m, 2H), 1.72 - 1.79 (m, 2H), 4.20 (t, J = 6.80 Hz, 2H), 7.15 - 7.21 (m, 2H), 7.42 - 7.53 (m, 1H), 8.50 (s, 1H), 9.55 (s, 1H), 12.01 (s, 1H)	M: 477
56		^1H NMR (400 MHz, CD_3OD) δ 2.20 - 2.30 (m, 4H), 3.22 (s, 3H), 3.33 - 3.35 (m, 2H), 3.48 - 3.51 (m, 2H), 5.57 - 5.60 (m, 1H), 7.14 - 7.20 (m, 2H), 7.41 - 7.47 (m, 1H), 8.50 (s, 1H), 9.52 (s, 1H)	M+1: 447
57		^1H NMR (400 MHz, CD_3OD) δ 2.17 - 2.29 (m, 4H), 3.29 - 3.34 (m, 2H), 3.50 - 3.52 (m, 2H), 5.54 - 5.59 (m, 1H), 7.22 - 7.26 (m, 2H), 7.64 - 7.69 (m, 1H), 8.83 (s,1H), 9.60 (s,1H), 9.71 (s, 1H)	M+1: 402
58		^1H NMR (400 MHz, CD_3OD) δ 2.23-2.31 (m, 4H), 3.34-3.35 (m, 2H), 3.46-3.49 (m, 2H), 5.60-5.61 (m, 1H), 7.00-7.09 (m, 1H), 7.36-7.46 (m, 1H), 7.79-7.95 (m, 1H), 8.13-8.20 (m, 1H), 8.60-8.76(m,1H),9.61(s,1H),9.70 (s,1H)	M+1: 383
59		^1H NMR (400 MHz, CD_3OD) δ 1.91-1.93 (m, 2H), 2.20-2.26 (m, 3H), 2.26 - 2.31 (m, 4H), 3.13-3.15 (m, 4H), 3.34 - 3.35 (m, 2H), 3.46 - 3.49 (m, 2H), 5.60 - 5.61 (m, 1H), 8.17 (s, 1H), 9.59 (s, 1H), 9.68 (s, 1H)	M+1: 389

60		^1H NMR (400 MHz, CD_3OD) δ 2.10-2.28 (m, 4H), 3.10-3.15 (m, 4H), 3.51 - 3.61 (m, 4H), 3.85-3.87 (m, 4H), 5.54 - 5.57 (m, 1H), 8.19 (s, 1H), 9.50 (s, 1H), 9.70 (s, 1H)	M+1: 391
61		^1H NMR (400 MHz, CD_3OD) δ 1.61 - 1.79 (m, 6H), 3.26 - 3.38 (m, 4H), 3.49 - 3.60 (m, 4H), 3.85-3.87 (m, 4H), 5.54 - 5.57 (m, 1H), 8.39 (s, 1H), 9.40 (s, 1H), 9.60 (s, 1H)	M+1: 389
62		^1H NMR (400 MHz, CD_3OD) δ 2.18 - 2.29 (m, 4H), 2.34 (s, 3H), 3.34 - 3.35 (m, 2H), 3.46 - 3.49 (m, 2H), 5.60 - 5.61 (m, 1H), 8.49 (s, 1H), 9.47 (s, 1H), 9.65 (s, 1H)	M+1: 363
63		^1H NMR (400 MHz, CD_3OD) δ 1.70 (m, 2H), 3.39 (m, 2H), 3.48 (m, 2H), 7.03 - 7.21 (m, 2H), 7.40 - 7.52 (m, 1H), 8.59 (s, 1H), 9.71 (s, 1H), 9.86 (s, 1H)	M+1: 456

Example 64

The biochemical assays used to test the activities of the compounds of the present invention and their results.

In the present invention, the PIM activities of the compounds were tested by BioDuro (Building E, No. 29 Life Science Park Road, Changping District, Beijing, 102206, P.R. China). The method used for testing is PIM Kinase Activity Assay-IMAP Fluorescence Polarization Assay

PIM Kinase Activity Assay-IMAP Fluorescence Polarization Assay

1. Principle

PIM Is a serine / threonine protein kinase, they can phosphorylate 5-FAM labeled small peptide substrates. Fluorescence polarization is less for non-phosphorylated substrates since that can not bind to the binder (metal binding nanoparticles). On the other hand, fluorescence polarization is more for phosphorylated substrates since that can bind to the binder. The level of 5-FAM labeled

small peptide substrates phosphorylation reflects the activities of PIM kinase. By measuring their ability of inhibiting PIM kinase of the compounds of the present invention, their activities of inhibiting PIM kinases can be determined.

2. Instrument

EnVision (PerkinElmer, Waltham, Massachusetts)

3. Reagents and 384 well plates

PIM1 (Millipore Cat. # 14-573) (Millipore Corporation, Billerica, MA)

PIM2 (Millipore Cat.# 14-607) (Millipore Corporation, Billerica, MA)

5-FAM labeled peptide (5-FAM-RSRHSSYPAGT, AnaSpec Cat.# 63801) (AnaSpec Inc., Fremont, CA)

IMAP FP Screening Express kit (IMAP FP Screening kit) (Molecular Devices Cat.# R8127) (Molecular Devices, Sunnyvale, California)

IMAP Progressive binding reagent

IMAP Progressive binding buffer A (5X)

IMAP Progressive binding buffer B (5X)

384-well black plate (Corning Cat.# 3573) (Corning, Midland MI)

4. Assay Buffer

Tris-HCl (pH 7.2): 10 mM

MgCl₂:10 mM

Triton X-100: 0.01%

DTT: 2 mM

5. Procedure

- a) 10mM compound stock solution is diluted to appropriate concentration with 100% DMSO, then diluted 10 fold to targeted concentration with test butter to keep DMSO concentration at 10%
- b) Assay volume 10ul:
 1ul of compound solution and 4ul of enzyme (PIM-1 final concentration 0.025nM, PIM-2 concentration 3nM) is incubated at 23°C for 15min, 2.5ul ATP (for PIM-1 and PIM-2, the final ATP concentrations are 30uM and 5uM respectively) 2.5ul 5-FAM labeled peptide (final concentration 100 nM) was added to start the reaction. The reaction is run at 23°C for 60min. DMSO is used in place of compound stock solution as maximum reference and assay buffer is used in place of enzyme as minimum reference.

- c) add 30ul IMAP binding reagent (containing 75% IMAP Buffer A, 25% IMAP Buffer B, 1/600 dilution of beads) to stop the reaction, incubated at room temperature for 60 min
- d) Measure fluorescence polarization, excitation wavelength: 485nm, emission wavelength 530nm.

6. Data process

IC₅₀ values were calculated using Graphpad Prism[®].

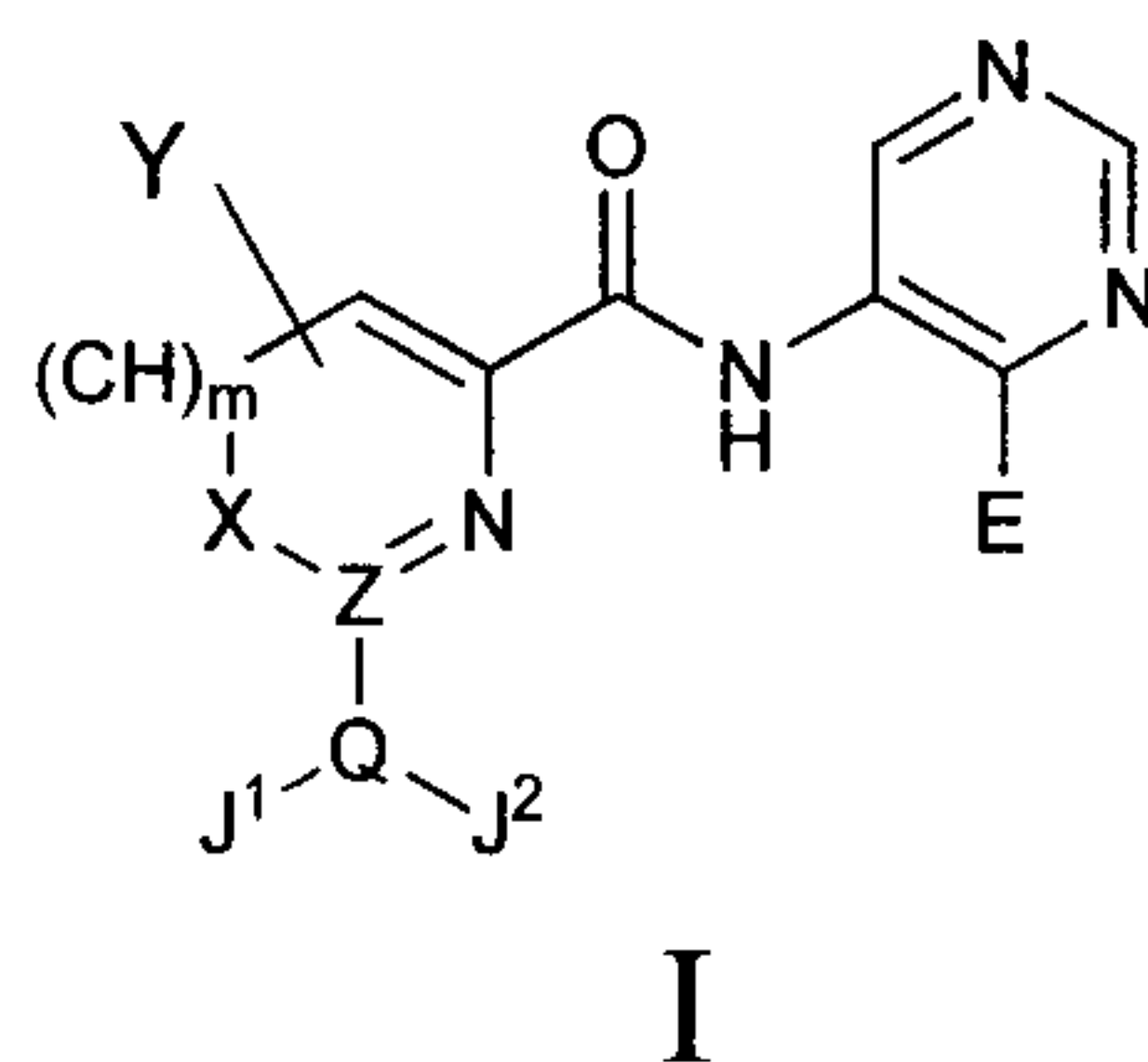
PIM kinase assays showed that all 63 compounds in Example 1 through 63 can significantly inhibit PIM kinase activities. At 3μM concentration, almost all compounds except the compounds listed below showed greater than 50% inhibition against PIM-1 kinase activity, some showed 100% inhibition. These compounds can also inhibit the PIM-2 and PIM-3 activities and some can inhibit 100% of the activities at 3μM concentration.

The following compounds showed 20-50% inhibition of PIM-1 activity 3μM concentration:

2-isopropyl-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (33)
 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)oxazole-4-carboxamide (57)
 2-(piperidin-4-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (59)
 2-morpholino-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (60)
 2-(piperidin-1-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (61)
 2-acetamido-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (62)
 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)sulfonyl)pyrimidin-5-yl)thiazole-4-carboxamide (63)

CLAIM

1. A compound with the following general structural Formula I:



Wherein,

E, J, Q, X, Y, Z, m of Formula I are described as follow:

When m is 0, X is S, O, N or CH;

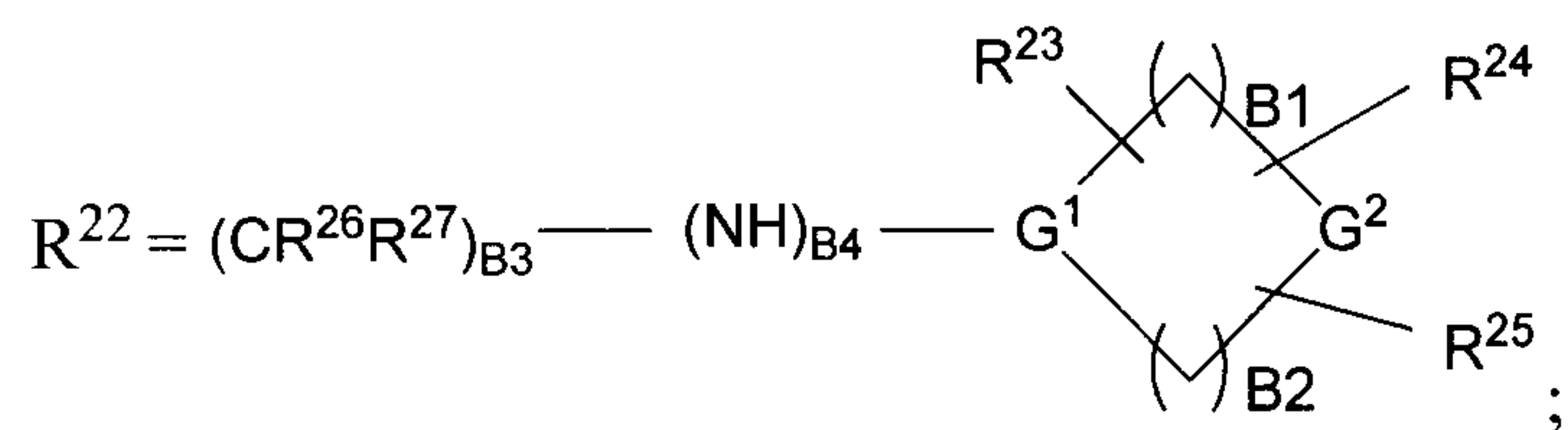
When m is 1, X is CH or N;

Z is CH or N;

Y is H or N(R¹R²), each of R¹, R² is independently selected from H or optionally substituted C₁-C₈ aliphatic group; or

Y is H or N(R¹C(=O)R²), each of R¹, R² is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group;

E is OR²², SR²², SO₂R²², R²² is optionally substituted C₁-C₈ hydrocarbon group or the group discribed in the following formula:



Wherein,

Each of R²³, R²⁴, R²⁵ is independently selected from H, halo, OR¹⁵, NR¹⁶R¹⁷, C(=O)N R¹⁸R¹⁹ or optionally substituted C₁-C₈ hydrocarbon group; or R²³, R²⁴ and R²⁵, together with the atoms to

which they are attached, may be joined together to form a chain so that the ring to which they are attached is a substituted C₆-C₁₄ membered spiral ring, bicyclic ring or fused ring group;

G¹ is CH₂ or N;

G² is NR²⁸, CHR²⁹ or O;

B1 and B2 each independently represents 0, 1, 2 or 3;

B3 is 0, 1 or 2;

B4 is 0, 1;

Each of R²⁶ and R²⁷ is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group;

R²⁸ is H, optionally substituted hydrocarbon group, optionally substituted cyclic hydrocarbon group, optionally substituted heterocyclic hydrocarbon group, C(=O)R³⁰, C(=O)OR³⁰ or C(=O)NHR³⁰;

R²⁹ is OH, NHR³⁰, C(=O)OR³⁰ or C(=O)NHR³⁰;

R³⁰ is H or optionally substituted C₁-C₈ hydrocarbon group;

Q is C, CH or N;

J¹, J² is independently selected from H or optionally substituted C₁-C₈ hydrocarbon group, OR³¹, NHR³¹ or C(=O)R³¹; or

J¹, J² together with CH they are attached, are joined together to form a C₃-C₈ membered cycloalkyl, or J¹, J² together with the atoms to which they are attached and at least one hetero atom to form C₄-C₇ membered heterocycloalkyl; on such C₃-C₈ membered cycloalkyl and C₄-C₇ membered heterocycloalkyl, one or more position can be optionally substituted with halo, OR³², NHR³³ or optionally substituted C₁-C₈ hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is a substituted C₆-C₁₄ membered spiral ring, bicyclic ring or fused ring group; or

J^1 , J^2 together with C atom they are attached, are joined together to form aromatic rings, such as benzene ring and naphthlene, or J^1 , J^2 together with C they are attached and at least one heteroatom, are joined together to form C_5 - C_6 membered aromatic heterocycles, such as pyridine, pyrimidine, pyrazine, imidazole, thiazole, isoxazole, oxazole or pyrrole, on the aromatic rings and hetero aromatic rings, one or more position can be optionally substituted with halo, CN, OR^{32} , NHR^{33} or optionally substituted C_1 - C_8 hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is an optionally substituted C_6 - C_{14} membered aromatic spiral ring, bicyclic ring or fused ring group; or

J^1 , J^2 together with N atom they are attached, are joined together to form C_4 - C_7 membered heterocycloalkyl group, or J^1 , J^2 together with N atom they are attached, and at least one hetero atom, are joined together to form C_4 - C_7 membered heterocycloalkyl group; on these C_4 - C_7 membered heterocycloalkyl group, one or more position can be optionally substituted with halo, CN, OR^{32} , NHR^{33} or optionally substituted C_1 - C_8 hydrocarbon group, or such substituents are joined together to form a chain so that the ring to which they are attached is an optionally substituted C_6 - C_{14} membered aromatic spiral ring, bicyclic ring or fused ring group;

R^{31} is H or optionally substituted C_1 - C_8 hydrocarbon group;

Each of R^{32} , R^{33} is independently selected from H or optionally substituted C_1 - C_8 hydrocarbon group, optionally substituted C_3 - C_8 cyclic hydrocarbon group, optionally substituted C_4 - C_7 membered heterocyclic hydrocarbon group, $C(=O)R^{34}$, $C(=O)OR^{34}$ or $C(=O)NHR^{34}$;

R^{34} is H or optionally substituted C_1 - C_8 hydrocarbon group.

2. The compounds according to Claim 1 wherein the compounds are isomers, diastereomers, enantiomers, tautomers, and pharmaceutically acceptable salts represented by Formula 1;
3. The PIM kinase inhibitors according to Claim 1 wherein the compounds are the following:

2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)

N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)

2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)

- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)
- 2-(2,6-difluorophenyl)-N-(4-(oxetan-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (6)
- 2-(2,6-difluorophenyl)-N-(4-((3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (7)
- 2-(2,6-difluorophenyl)-N-(4-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (8)
- 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)
- N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)
- 6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (11)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)
- N-(4-(8-azabicyclo[3.2.1]octan-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (14)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)
- N-(4-(3-azabicyclo[3.2.0]heptan-6-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (17)
- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)
- 2-(2,6-difluorophenyl)-N-(4-(quinuclidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (19)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)picolinamide (20)
- N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)

5-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiophene-2-carboxamide (23)

N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)

5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)

5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)

5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)

5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)

5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)

5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)

2-(2,6-difluorophenyl)-N-(4-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (31)

3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)

2-isopropyl-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (33)

5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)

5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)thio)pyrimidin-5-yl)thiazole-4-carboxamide (35)

5-amino-2-(2,6-difluorophenyl)-N-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (36)

2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)

5-amino-2-(2,6-difluorophenyl)-N-(4-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (38)

5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)

- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-N-(4-((4-carbamoylcyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (43)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2-hydroxyethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (44)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (47)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)
- 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2,3-dihydroxypropoxy)pyrimidin-5-yl)thiazole-4-carboxamide (51)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)-5-(methylamino)thiazole-4-carboxamide (54)
- 2-(2,6-difluorophenyl)-5-formamido-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (55)
- 2-(2,6-difluorophenyl)-5-(methylamino)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (56)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)oxazole-4-carboxamide (57)
- N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide (58)

2-(piperidin-4-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (59)
 2-morpholino-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (60)
 2-(piperidin-1-yl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (61)
 2-acetamido-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (62)
 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-hydroxypropyl)sulfonyl)pyrimidin-5-yl)thiazole-4-carboxamide (63)

4. The PIM kinase inhibitors according to Claim 3 wherein the compounds are the following:

2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)
 N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)
 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)
 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)
 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)
 2-(2,6-difluorophenyl)-N-(4-(oxetan-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (6)
 2-(2,6-difluorophenyl)-N-(4-((3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (7)
 2-(2,6-difluorophenyl)-N-(4-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (8)
 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)
 N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)
 6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (11)
 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)
 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)
 N-(4-(8-azabicyclo[3.2.1]octan-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (14)
 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)

- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)
- N-(4-(3-azabicyclo[3.2.0]heptan-6-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (17)
- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)
- 2-(2,6-difluorophenyl)-N-(4-(quinuclidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (19)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)picolinamide (20)
- N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)
- N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)
- 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)
- 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)
- 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)
- 2-(2,6-difluorophenyl)-N-(4-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (31)
- 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)
- 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)

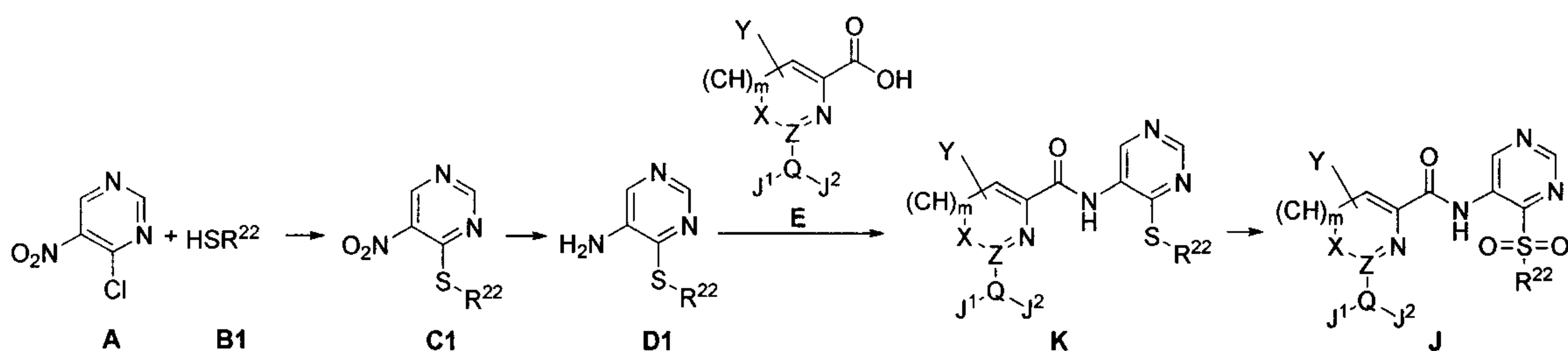
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-N-(4-((4-carbamoylcyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (43)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (47)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)
- 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(2,3-dihydroxypropoxy)pyrimidin-5-yl)thiazole-4-carboxamide (51)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)
- N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide (58)

5. According to Claim 4 wherein PIM kinase inhibitors are the following:

- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (1)
- N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (2)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (3)

- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (4)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxycyclohexyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (5)
- 2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (9)
- N-(4-(azetidin-3-ylmethoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (10)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydrofuran-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (12)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (13)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (15)
- 2-(2,6-difluorophenyl)-N-(4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (16)
- 2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (18)
- N-(4-(azetidin-3-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (21)
- 2-(2,6-difluorophenyl)-N-(4-(piperidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (22)
- N-(4-((cis-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (24)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)thiazole-4-carboxamide (25)
- 5-amino-N-(4-(azepan-4-yloxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (26)
- 5-amino-N-(4-((trans-4-aminocyclohexyl)oxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (27)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylmethoxy)pyrimidin-5-yl)thiazole-4-carboxamide (28)
- 5-amino-N-(4-(4-aminobutoxy)pyrimidin-5-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (29)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (30)

- 3-amino-6-(2,6-difluorophenyl)-N-(4-(piperidin-4-yloxy)pyrimidin-5-yl)picolinamide (32)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(pyrrolidin-3-yloxy)pyrimidin-5-yl)thiazole-4-carboxamide (34)
- 2-(2,6-difluorophenyl)-N-(4-(((1S,3R)-3-hydroxycyclopentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (37)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (39)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxy-3-methylbutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (40)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (41)
- 2-(2,6-difluorophenyl)-N-(4-(3-hydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (42)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (45)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxypentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (46)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide(47)
- 2-(2,6-difluorophenyl)-N-(4-((4-hydroxy-4-methylpentyl)oxy)pyrimidin-5-yl)thiazole-4-carboxamide (48)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (49)
- 2-(2,6-difluorophenyl)-N-(4-(3,4-dihydroxybutoxy)pyrimidin-5-yl)thiazole-4-carboxamide (50)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(4-(methylamino)butoxy)pyrimidin-5-yl)thiazole-4-carboxamide (52)
- 5-amino-2-(2,6-difluorophenyl)-N-(4-(piperidin-4-ylthio)pyrimidin-5-yl)thiazole-4-carboxamide (53)
6. According to Claim 1 through 5, the preparation of PIM kinase inhibitors wherein the procedures are as follow:



Wherein,

X, Y, Z, J¹, J², Q, m and R²² are the same as defined in Claim 1;

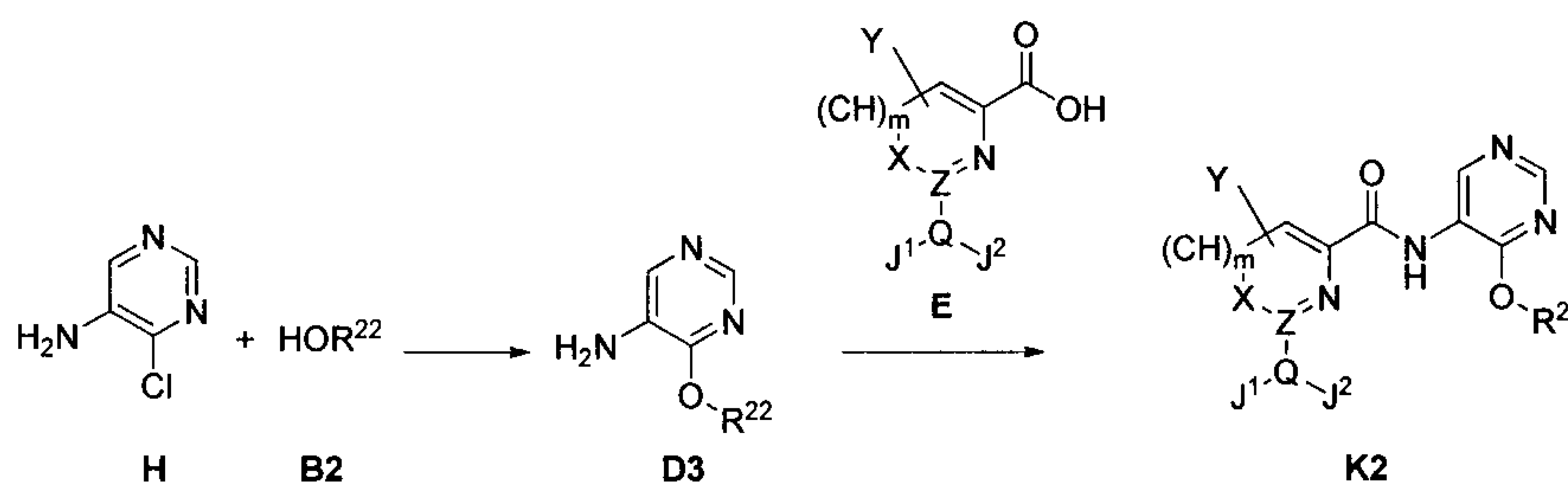
- (1) The general procedure for the synthesis of compounds when E of Formula I is sulfur or sulfone group

Thiol compound B1 (1 eq.), protected or unprotected, reacts with 4-Chloro-3-nitropyrimidine (A) (1 eq.) in the presence of a base, for example DIEA (N,N-diisopropylethylamine) (3 eq.), in an appropriate solvent, for example dioxane, at 40 °C for 1-16 hours to form thioether C1. C1 (1 eq.) reacts with Na₂S₂O₄ (3 Eq.) in the presence of a base, for example saturated NaHCO₃ solution (3 eq.), in an appropriate solvent, for example methanol, at 40°C for 1-10 hours, and is reduced to aminopyrimidine D1. Protected or unprotected aromatic carboxylic acid E (1 eq.), in the presence of a coupling reagent, for example HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (1-1.5 eq.), a base, for example DIEA (3 eq.), in a solvent, for example DMF (N,N-dimethylformaldehyde), at heated conditions, for example 40°C, reacts with amine D1 (1 eq.) for 0.5-8 hours to form thioether K. If there is no protecting group in K, then K is final thioether product of Formula I where E is sulfur group. If K is protected by protecting group, for example BOC (tert-butyloxycarbonyl) or trimethylsilyl group, it's deprotected by treating with mixture of TFA (trifluoroacetic acid) (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final thioether product K of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

Thioether K (1 eq.) is oxidized by m-CPBA (m-chloroperoxybenzoic acid) (2.2 eq.) in a solvent, for example CH₂Cl₂ (dichloromethane) at room temperature to form sulfone product J. If there is no protecting group in J, then J is final sulfone product of

Formula I where E is sulfone group. If J is protected by protecting group, for example BOC or trimethylsilyl group, it's deprotected by treating with mixture of TFA (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final sulfone product J of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

- (2) The general procedure for the synthesis of compounds when E of Formula I is ether group:



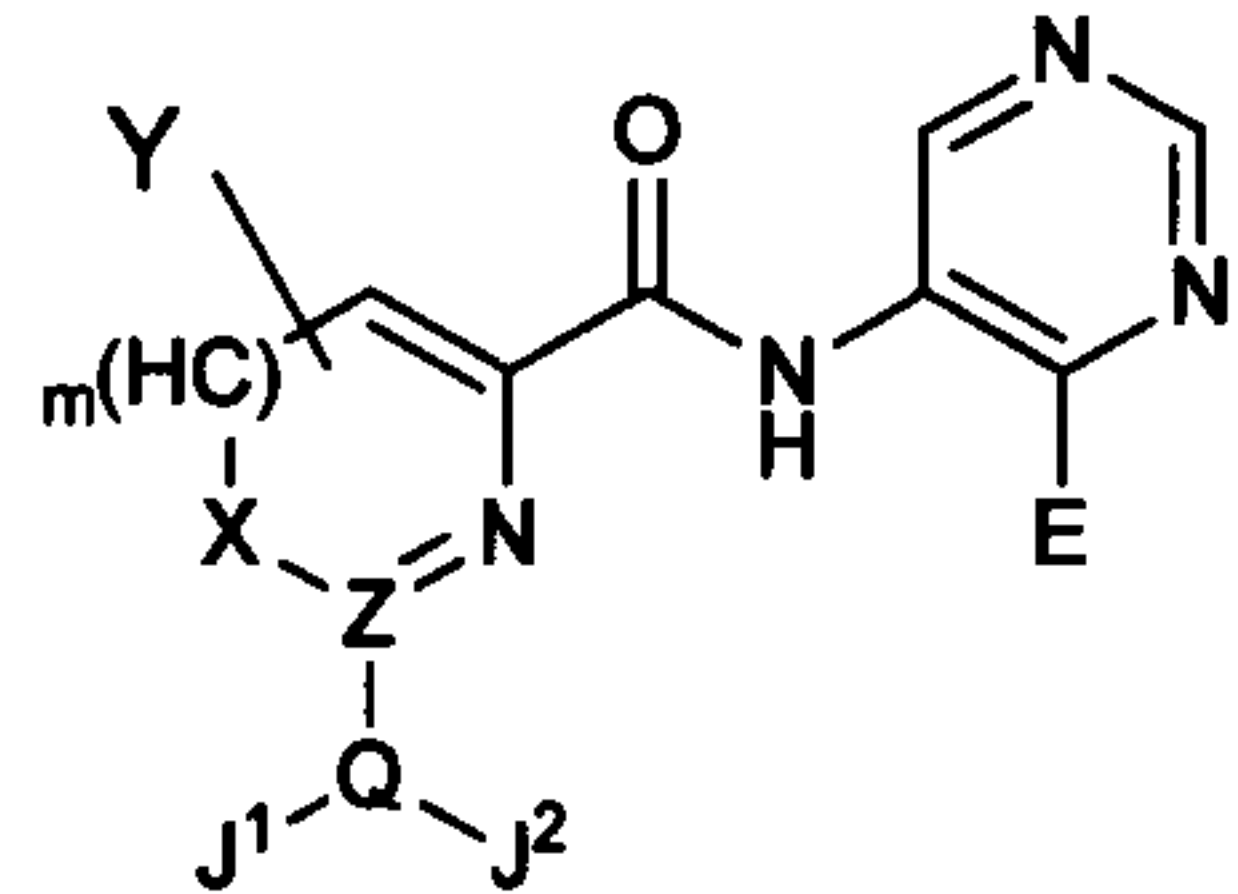
Wherein,

X, Y, Z, J¹, J², Q, m and R²² are the same as defined in Claim 1

Alcohol B2 (1.1 eq.), protected or unprotected, reacted with a base, for example NaH (1.1 eq.), in a solvent, for example THF, at room temperature (25°C) for 1 hour, then reacted with 5-amino-4-chloropyrimidine H (1 eq.) at heated conditions, for example 100 °C for 1-10 hours to form aminopyrimidine ether D3. Protected or unprotected aromatic carboxylic acid E (1 eq.), in the presence of a coupling reagent, for example HATU (1-1.5 eq.), a base, for example DIEA (3 eq.), in a solvent, for example DMF (N,N-dimethylformaldehyde), at heated conditions, for example 40°C, reacts with amine D3 (1 eq.) for 0.5-8 hours to form ether K2. If there is no protecting group in K2, then K2 is final ether product of Formula I where E is ether group. If K2 is protected by protecting group, for example BOC or trimethyl silyl group, it's deprotected by treating with mixture of TFA (trifluoroacetic acid) (10-100 eq.) with equal volume of dichloromethane at room temperature (25°C) for 1-16 hours. The final ether product K2 of Formula I is obtained after removing the solvent in vacuo at room temperature (25°C).

7. Pharmaceutical applications of PIM kinase inhibitors according Claim 1.

8. Pharmaceutical applications of PIM kinase inhibitors according Claim 2.
9. Pharmaceutical applications of PIM kinase inhibitors according Claim 3.
10. Pharmaceutical applications of PIM kinase inhibitors according Claim 4.
11. Pharmaceutical applications of PIM kinase inhibitors according Claim 5.
12. According to any one of Claim 7-11, wherein the PIM kinase inhibitors are used to treat or prevent cancers.
13. According to any one of Claim 7-11, wherein the PIM kinase inhibitors are used to treat or prevent autoimmune diseases.
14. According to any one of Claim 7-11, wherein the PIM kinase inhibitors are used to treat or prevent allergic reactions.
15. According to any one of Claim 7-11, wherein the PIM kinase inhibitors are used to treat or prevent atherosclerosis.
16. According to any one of Claim 7-11, wherein the PIM kinase inhibitors are used to treat or prevent organ transplant rejection
17. According to any one of Claim 7-11, wherein the pharmaceutical composition comprises of PIM kinase inhibitors as active pharmaceutical ingredient and pharmaceutically acceptable carriers and adjuvants.



(I)