TITLE OF THE INVENTION

AMINOPYRIMIDINES AS SYK INHIBITORS

BACKGROUND OF THE INVENTION

Spleen Tyrosine Kinase (Syk) is a protein tyrosine kinase which has been described as a key mediator of immunoreceptor signalling in a host of inflammatory cells including mast cells, B-cells, macrophages and neutrophils. These immunoreceptors, including Fc receptors and the B-cell receptor, are important for both allergic diseases and antibody-mediated autoimmune diseases and thus pharmacologically interfering with Syk could conceivably treat these disorders.

Allergic rhinitis and asthma are diseases associated with hypersensitivity reactions and inflammatory events involving a multitude of cell types including mast cells, eosinophils, T cells and dendritic cells. Following exposure to allergen, high affinity immunoglobulin receptors for IgE and IgG become cross-linked and activate downstream processes in mast cells and other cell types leading to the release of pro-inflammatory mediators and airway spasmogens. In the mast cell, for example, IgE receptor cross-linking by allergen leads to release of mediators including histamine from pre-formed granules, as well as the synthesis and release of newly synthesized lipid mediators including prostaglandins and leukotrienes.

Syk kinase is a non-receptor linked tyrosine kinase which is important in transducing the downstream cellular signals associated with cross-linking Fc.epsilon.R1 and or Fc.epsilon.R1 receptors, and is positioned early in the signalling cascade. In mast cells, for example, the early sequence of Fc.epsilon.R1 signalling following allergen cross-linking of receptor-IgE complexes involves first Lyn (a Src family tyrosine kinase) and then Syk. Inhibitors of Syk activity would therefore be expected to inhibit all downstream signalling cascades thereby alleviating the immediate allergic response and adverse events initiated by the release of pro-inflammatory mediators and spasmogens (Wong et al 2004, Expert Opin. Investig. Drugs (2004) 13 (7) 743-762).

Recently, it has been shown that the Syk kinase inhibitor R112 (Rigel), dosed intranasally in a phase I/II study for the treatment of allergic rhinitis, gave a statistically significant decrease in PGD_2, a key immune mediator that is highly correlated with improvements in allergic rhinorrhea, as well as being safe across a range of indicators, thus providing the first evidence for the clinical safety and efficacy of a topical Syk kinase inhibitor. (Meltzer, Eli O.; Berkowitz, Robert B.; Grossbard, Elliott B, Journal of Allergy and Clinical Immunology (2005), 115(4), 791-796). In a more recent phase II clinical trial for allergic rhinitis (Clinical Trials.gov Identifier NCT0015089), R112 was shown as having a lack of efficacy versus placebo.

Rheumatoid Arthritis (RA) is an auto-immune disease affecting approximately 1% of the population. It is characterised by inflammation of articular joints leading to debilitating destruction of bone and cartilage. Recent clinical studies with Rituximab, which causes a

reversible B cell depletion, (J. C. W. Edwards et al 2004, New Eng. J. Med. 350: 2572-2581) have shown that targeting B cell function is an appropriate therapeutic strategy in auto-immune diseases such as RA. Clinical benefit correlates with a reduction in auto-reactive antibodies (or Rheumatoid Factor) and these studies suggest that B cell function and indeed auto-antibody production are central to the ongoing pathology in the disease.

Studies using cells from mice deficient in the Spleen Tyrosine Kinase (Syk) have demonstrated a non-redundant role of this kinase in B cell function. The deficiency in Syk is characterised by a block in B cell development (M. Turner et al 1995 Nature 379: 298-302 and Cheng et al 1995, Nature 378: 303-306). These studies, along with studies on mature B cells deficient in Syk (Kurasaki et al 2000, Immunol. Rev. 176:19-29), demonstrate that Syk is required for the differentiation and activation of B cells. Hence, inhibition of Syk in RA patients is likely block B cell function and thereby reduce Rheumatoid Factor production. In addition to the role of Syk in B cell function, and of further relevance to the treatment of RA, is the requirement for Syk activity in Fc receptor (FcR) signalling. FcR activation by immune complexes in RA has been suggested to contribute to the release of multiple pro-inflammatory mediators.

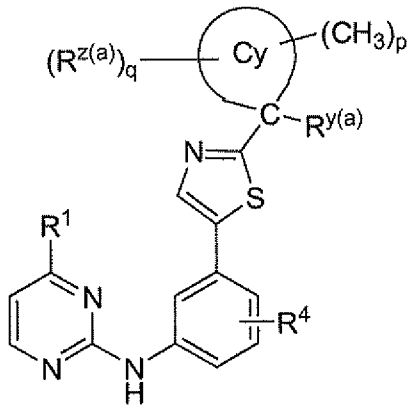
The present invention relates to novel compounds, which are inhibitors of Syk kinase activity. These compounds therefore have potential therapeutic benefit in the treatment of disorders associated with inappropriate Syk activity, in particular in the treatment and prevention of disease states mediated by Syk. Such disease states may include inflammatory, allergic and autoimmune diseases, for example, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, idiopathic thrombocytopenic purpura (ITP), multiple sclerosis, cancer, HIV and lupus.

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are potent inhibitors of SYK as well as pharmaceutical compositions containing them. As SYK inhibitors compounds of the present invention are useful in the treatment and prevention of diseases and disorders mediated by the SYK protein; such diseases and disorders include, but are not limited to, asthma, COPD, rheumatoid arthritis, cancer and idiopathic thrombocytopenic purpura.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

p is 0 to 4;

q is 0, 1 or 2;

Cy is selected from C_{4-7}cycloalkyl, oxetanyl, pyrrolidinyl, piperidinyl, and azepanyl;

R^1 is selected from H, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-6}cycloalkyl, and OC_{1-4}alkyl;

R^4 is selected from H, C_{1-4}alkyl, and C_{3-4}cycloalkyl;

$R^{y(a)}$ is aminomethyl, OH, OCH_3, OCH_2CH_2OH, F, CN, $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$, $NR^{a(a)}R^{a(a)}$, $NHC(O)C_{1-3}$alkyl (optionally substituted with OH), $NHC(O)NH_2$, $NHSO_2NH_2$, $NHSO_2C_{1-3}$alkyl, or $NHSO_2C_{1-3}$haloalkyl;

$R^{z(a)}$ is selected from (A) C_{1-4} alkyl optionally substituted with one to three groups independently selected from OH, NH_2, CN, $CO_2R^{a(a)}$ and $CONH_2$, (B) C_{1-3}fluoroalkyl, (C) halogen, (D) CN, (E) COC_{1-4}alkyl (optionally substituted with one or two groups independently selected from $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (F) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (G) CO-C_{3-6}cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (H) C_{0-3}alkyl-$CO_2R^{a(a)}$, (I) $-C(O)NR^{b(a)}R^{c(a)}$, (J) $-OR^{a(a)}$, (K) $-OC(O)R^{a(a)}$, (L) $-NR^{b(a)}R^{c(a)}$, (M) $-NHC(O)C_{1-4}$alkyl (optionally substituted with one to three OH or a $CONR^{a(a)}R^{a(a)}$), (N) $-NHSO_2C_{1-3}$alkyl, (O) $-NHSO_2NH_2$, (P) oxo, (Q) 1,3,4-oxadiazole-2(3H)-one, (R) 1,2,4-oxadiazole-5(4H)-one, (S) SO_2NH_2, (T) SO_2C_{1-3}alkyl, (U) SO_2C_{1-3}haloalkyl, and (V) SO_2Ph;

$R^{a(a)}$ is H or C_{1-4}alkyl;

$R^{b(a)}$ and $R^{c(a)}$ are independently selected from (A) H, (B) C_{3-6}cycloalkyl optionally substituted with OH, (C) heteroaryl selected from imidazolyl, pyridyl and indolyl, (D) tetrahydrofuranyl, (E) benzyl, (F) phenyl optionally substituted with one or two groups independently selected from $(CH_2)_{0-2}OH$ and F, (G1) C_{1-4}alkyl and (G2) C_{1-4}haloalkyl, wherein (G1) and (G2) are each optionally substituted with one to three groups independently selected from (i) OH, (ii) C_{3-6}cycloalkyl optionally substituted with one or two groups independently selected from C_{1-4}alkyl, $CONH_2$, CO_2H and CH_2OH, (iii) $CONH_2$, (iv) SO_2NH_2, (v) SO_2C_{1-4}alkyl, (vi) 4- to 7-membered monocyclic heterocyclyl optionally substituted with one or two groups independently selected from oxo, $(CH_2)_{0-2}OH$, and C_{1-}

4alkyl, (vii) a 5- or 6-membered heteroaryl optionally substituted with one or two groups independently selected from carboxy, $(CH_2)_{0-2}OH$, and C_{1-4}alkyl, (viii) CN, (x) OC_{1-4}alkyl, (ix) CO_2H, (xii) $NR^{a(a)}C(O)C_{1-4}$alkyl, (x) phenyl optionally substituted with one or two groups independently selected from $(CH_2)_{0-2}OH$, SO_2NH_2, CF_3, F and Cl, (xi) 1-pyrrolidinyl optionally substituted with oxo, (xii) 1-imidazolidinyl optionally substituted with oxo, (xiii) 1-piperidinyl optionally substituted with oxo, and (xiv) 4-morpholinyl; or

$R^{b(a)}$ and $R^{c(a)}$ together with the nitrogen atom to which they are attached form a 6- or 7-membered heterocycle having 0 to 1 additional heteroatom selected from N, O and S, wherein said heterocycle is optionally substituted with one or two groups independently selected from oxo, CN, $(CH_2)_{0-2}OH$, acetyl, benzyl, SO_2C_{1-4}alkyl, $CONH_2$, methoxymethyl, carboxymethyl, $CO_2R^{a(a)}$ and C_{1-4}alkyl.

In one subset of formula (I) are compounds wherein Cy is cyclohexyl. In one aspect the cyclohexyl is substituted with a group selected from $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH, and said cyclohexyl is optionally further substituted with one or two methyl groups.

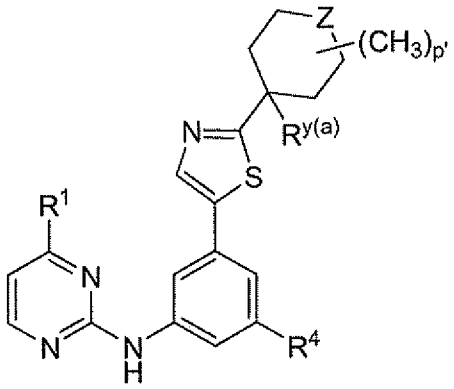
In another subset of formula (I) are compounds wherein Cy is piperidinyl. In one aspect the nitrogen atom of piperidinyl is substituted with a group selected from (i) COC_{1-4}alkyl (optionally substituted with $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (ii) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (iii) CO-C_{3-6}cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (iv) C_{0-3}alkyl-$CO_2R^{a(a)}$, (v) $CONR^{a(a)}R^{a(a)}$, (vi) CONH-phenyl (optionally substituted with one or two groups independently selected from C_{1-4}alkyl, CN, and Cl), (vii) CONH-C_{3-6}cycloalkyl, (viii) SO_2NH_2, (ix) SO_2C_{1-3}alkyl, (x) SO_2C_{1-3}haloalkyl, and (xi) SO_2Ph.

In another subset of formula (I) are compounds wherein Cy is azepanyl. In one aspect azepanyl is substituted with an oxo group at the 2-position of the ring.

In another subset of formula (I) are compounds wherein $R^{Y(a)}$ is OH. In one aspect Cy is cyclohexyl. In one embodiment therof cyclohexyl is substituted with a group selected from selected from $CO_2R^{a(a)}$, $CONHR^{b(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH, and said cyclohexyl is optionally further substituted with one or two methyl groups. In another aspect Cy is 2-oxoazepanyl.

In another subset of formula (I) are compounds wherein $R^{Y(a)}$ is $CONH_2$. In one aspect Cy is cyclohexyl. In one embodiment therof cyclohexyl is substituted with a group selected from selected from $CO_2R^{a(a)}$, $CONHR^{b(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH, and said cyclohexyl is optionally further substituted with one or two methyl groups.

The present invention provides further compounds of formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein

Z is -CR$^{z(b)}$R$^{z(c)}$-, –N(R$^{z(d)}$)-, -CH$_2$-N(R$^{z(d)}$)-, or -NHC(O)-;

p' is 0 to 3, with the proviso that p is 0 when Z is –NHC(O)-;

R$^{z(b)}$ is selected from (A) H, (B) C$_{1-4}$ alkyl optionally substituted with one to three groups independently selected from OH, NH$_2$, CN, CO$_2$R$^{a(a)}$ and CONH$_2$, (C) halogen, (D) CN, (E) -C(O)R$^{a(a)}$, (F) -C(O)$_2$R$^{a(a)}$, (G) -C(O)NR$^{b(a)}$R$^{c(a)}$, (H) -OR$^{a(a)}$, (I) -OC(O)R$^{a(a)}$, (J) -NR$^{b(a)}$R$^{c(a)}$, (K) -NHC(O)C$_{1-4}$alkyl (optionally substituted with OH), (L) -NHSO$_2$C$_{1-3}$alkyl, (M) -NHSO$_2$NH$_2$, (N) 1,3,4-oxadiazole-2(3H)-one, and (O) 1,2,4-oxadiazole-5(4H)-one;

R$^{z(c)}$ is H or methyl;

R$^{z(d)}$ is selected from (A) H, (B) C$_{1-3}$ alkyl optionally substituted with a group selected from CO$_2$R$^{a(a)}$ and CONH$_2$, (C) C$_{1-3}$fluoroalkyl, (D) COC$_{1-4}$alkyl (optionally substituted with one or two groups independently selected from OR$^{a(a)}$, CN, CO$_2$R$^{a(a)}$, CONR$^{a(a)}$R$^{a(a)}$, and NR$^{a(a)}$R$^{a(a)}$), (E) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, CO$_2$R$^{a(a)}$, CN, F and OH), (F) CO-C$_{3-6}$cycloalkyl (optionally substituted with OH or CO$_2$R$^{a(a)}$), (G) C$_{0-3}$alkyl-CO$_2$R$^{a(a)}$, (H) CONR$^{a(a)}$R$^{a(a)}$, (I) CONH-phenyl (optionally substituted with one or two groups independently selected from C$_{1-4}$alkyl, CN, and Cl), (J) CONH-C$_{3-6}$cycloalkyl, (K) SO$_2$NH$_2$, (L) SO$_2$C$_{1-3}$alkyl, (M) SO$_2$C$_{1-3}$haloalkyl, and (N) SO$_2$Ph; and

R^1, R^4, R$^{y(a)}$, R$^{a(a)}$, R$^{b(a)}$ and R$^{c(a)}$ are as defined under formula I.

In one subset of formula (Ia) are compounds wherein Z is –NHC(O)-. In one embodiment thereof R$^{y(a)}$ is OH.

In another subset of formula (Ia) are compounds wherein Z is -CHR$^{z(b)}$ – and p' is 0, 1 or 2. In one aspect thereof R$^{z(b)}$ is CO$_2$H. In another aspect thereof R$^{z(b)}$ is CONHR$^{b(a)}$; in one embodiment R$^{z(b)}$ is CONH$_2$, in another embodiment R$^{z(b)}$ is CONH(CH2)3-(2-oxo-1-pyrrolidinyl). In another aspect thereof R$^{z(b)}$ is NHC(O)C$_{1-4}$alkyl (optionally substituted with OH); in one embodiment R$^{z(b)}$ is NHC(O)CH$_2$OH.

In another subset of formula (Ia) are compounds wherein Z is -CHR$^{z(b)}$–, p' is 0, 1 or 2, and Ry(a) is OH or CONH$_2$. In one aspect thereof R$^{z(b)}$ is CO$_2$H. In another aspect thereof R$^{z(b)}$ is CONHR$^{b(a)}$; in one embodiment R$^{z(b)}$ is CONH$_2$, in another embodiment

$R^{z(b)}$ is CONH(CH2)3-(2-oxo-1-pyrrolidinyl). In another aspect thereof $R^{z(b)}$ is $NHC(O)C_{1-4}$alkyl (optionally substituted with OH); in one embodiment $R^{z(b)}$ is $NHC(O)CH_2OH$.

Representative compounds of the present invention are as follows (each compound is intended to include pharmaceutically acceptable salts thereof):

1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]-cyclohexanecarbonitrile;

1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]-cyclohexanecarboxamide;

(1*S*,4*R*)-4-methoxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]-amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;

4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanone;

cis-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexane-1,4-diol;

trans-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexane-1,4-diol;

-yl *trans*-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2]cyclohexane-1,4-diol;

cis-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol;

5-hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;

cis-4-[(hydroxyacetyl)amino]-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;

(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide;

cis-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;

ethyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate;

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;

cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;

cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile;

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile;

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
3-{cis-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}-1,2,4-oxadiazol-5(4H)-one;
cis-4-methoxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
trans-4-methoxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
1-amino-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*S*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
tert-butyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxylate;
4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-4-ol;
4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide;
4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-sulfonamide;
4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1-(phenylsulfonyl)piperidin-4-ol;
1-{4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-1-yl}ethanone;
4-hydroxy-*N*-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide;
2-{3-Hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoic acid;
4-chloro-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-piperidine-1-sulfonamide;

5-{cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}-1,3,4-oxadiazol-2(3H)-one;
1-[5-(3-methyl-5-{[4-(propan-2-yl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutanol;
N-{3-[2-(3-aminooxetan-3-yl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine;
N-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-oxetan-3-yl}methanesulfonamide;
2-methyl-*N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}propane-2-sulfonamide;
N-{3-[2-(1-aminocyclobutyl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-cyclopropylpyrimidin-2-amine hydrochloride;
N-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}sulfuric diamide;
1-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}urea;
N-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}acetamide;
1-(5-{3-[(4-cyclobutylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)cyclobutanol;
cis-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid;
trans-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid;
(1S,4R)-4-(hydroxymethyl)-3,3-dimethyl-1-(5-(3-methyl-5-(4-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)thiazol-2-yl)cyclohexanol;
(1S, 4R)-4-(5-{3-cyclopropyl-5-[(4-methylpyrimidin-2-yl)amino]phenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
cis-4-hydroxy-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide;
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
ethyl (1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate;
5-(aminomethyl)-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
5-(2-hydroxyethoxy)-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;

trans-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
cis-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
1-{c*is*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}pyrrolidin-2-one;
1,4-*trans*, 1,5-*trans*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
1,4-*cis*, 1,5-*cis*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
cis-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
trans-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-{5-[3-methyl-5-(4-methyl-pyrimidin-2-ylamino)-phenyl]-thiazol-2-yl}-cyclohexanecarboxylic acid;
4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
5-amino-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
(1S,4R)-4-[5-(3-{[4-(difluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1R,4S)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1S,4R)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide; and
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide.

In one subset of the above representative compounds are:

(1R,4S)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1S,4R)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-{5-[3-methyl-5-(4-methyl-pyrimidin-2-ylamino)-phenyl]-thiazol-2-yl}-cyclohexanecarboxylic acid;
(1S,4R)-4-[5-(3-{[4-(difluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
5-hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
cis-4-[(hydroxyacetyl)amino]-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide; and
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*S*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide; and
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
or a pharmaceutically acceptable salt thereof.

The present invention also includes the compounds (1*S*,4*R*) and (1*R*, 4*S*)-4-(5-{3-[(5-fluoro-4-methylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid, 2-[(2-{3-hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoyl)oxy]-2-methyl-propanoic acid, and methyl {[4-hydroxy-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methyl-

phenyl}-1,3-thiazol-2-yl)piperidin-1-yl]sulfonyl}carbamate; or a pharmaceutically acceptable salt thereof.

In the application various terms are as defined below:

"Alkyl" refers to a straight- or branched-chain hydrocarbon radical having the specified number of carbon atoms. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

"Alkenyl" refers to a straight- or branched-chain hydrocarbon radical having at least one carbon-carbon double bond, and having the specified number of carbon atoms. Examples of "alkenyl" include, but are not limited to ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl and n-pentenyl.

"Alkynyl" refers to a straight- or branched-chain hydrocarbon radical having at least one carbon-carbon triple bond, and having the specified number of carbon atoms. Examples of "alkynyl" include, but are not limited to ethynyl, propynyl, 2-butynyl and 3-methylbutynyl.

"Cycloalkyl" refers to a saturated ring containing the specified number of ring carbon atoms, and no heteroatom. In a like manner the term "C_{3-8} cycloalkyl" refers to a saturated ring ring having from 3 to 8 ring carbon atoms. Exemplary "cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

"Halogen" or "halo" refers to fluorine, chlorine, bromine, or iodine.

"Haloalkyl" refers to an alkyl group as defined above in which one and up to all hydrogen atoms are replaced by a halogen; halogen is as defined herein. Examples of such branched or straight chained haloalkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo. Examples of "haloalkyl" include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and perfluoro-n-propyl.

"Hydroxyalkyl" refers to an alkyl group as defined above in which one hydrogen on each carbon atom may be replaced by a hydroxy group. Examples of "hydroxyalkyl" include, but are not limited to, hydroxymethyl, hydroxyethyl, propane-1,2-diol.

"Heterocyclic" or "heterocyclyl" refers to a non-aromatic saturated or partially unsaturated monocyclic ring in which one to three ring atoms are independently selected from N, S and O. Examples of heterocycle include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, imidazolidine, oxazolidine, thiazolidine, dihydroazepine, tetrahydroazepine, azepane, diazepane, dihydro-diazepine, tetrahydro-diazepine, oxetane, tetrahydrofuran, dihydropyran, pyran, tetrahydropyran, tetrahydrothiophen, tetrahydrothiopyran, dihydrothiopyran, 1,3-dioxane, 1,4-dioxane, 1,3-dioxolane.

"Heteroaryl" refers to aromatic monocyclic groups and fused bicyclic aromatic rings containing 1, 2, 3 or 4 heteroatoms selected from N, O and S. Examples of heteroaryl groups include, but are not limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, thiadiazole, pyridine, pyridazine, pyrazine, pyrimidine.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of formula (I), and pharmaceutically acceptable excipients.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "substituted with one or more groups" refers to substitution with the named substituent or substituents, multiple degrees of substitution, up to replacing all hydrogen atoms with the same or different substituents, being allowed unless the number of substituents is explicitly stated. Where the number of substituents is not explicitly stated, one or more is intended.

Each variable is independently defined each time it occurs within the generic structural formula definitions. For example, when there is more than one $R^{z(a)}$ substituents on the Cy ring, each substituent is independently selected at each occurrence, and each substituent can be the same or different from the other(s). As another example, for the group $NR^{a(a)}R^{a(a)}$, each occurrence of the two $R^{a(a)}$ groups may be the same or different.

As used herein, where the notation "C_0" or "$(CH_2)_0$" modifies a substituent, it indicates a bond between the substituent and the rest of the molecule. Thus, the term "C_{0-3}alkyl-CO_2H" means the carboxy group is either directly attached to the rest of the molecule, or there is an intervening C_{1-3}alkyl group therebetween.

The term "Syk inhibitor", is used to mean a compound which inhibits the Syk enzyme.

The term "Syk mediated disease" or a "disorder or disease or condition mediated by inappropriate Syk activity" is used to mean any disease state mediated or modulated by Syk kinase mechanisms. Such disease states may include inflammatory, allergic and autoimmune diseases, for example, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psorasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV and lupus, in particular, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory

distress syndrome (ARDs), allergic rhinitis and rheumatoid arthritis.

As used herein, "a compound of the invention" means a compound of formula (I) or a salt, solvate or physiologically functional derivative thereof.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I), or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, acetone, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent is water.

As used herein, the term "physiologically functional derivative" refers to a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. Prodrugs are such derivatives, and a discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The compounds of formula (I) may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

The compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

It is also noted that the compounds of Formula (I) may form tautomers. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention. Some of the

compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Whilst the embodiments for each variable have generally been listed above separately for each variable, this invention also includes those compounds in which several or each embodiment in formula (I) is selected from each of the embodiments listed above. Therefore, this invention is intended to include all combinations of embodiments for each variable.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge et al, J. Pharm. Sci. 1977, 66, 1-19. Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Suitable pharmaceutically acceptable salts can include acid or base additions salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated, for example, by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be, for example, a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Other, non-pharmaceutically acceptable, salts, e.g. oxalates or trifluoroacetates, may also be used, for example, in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the compounds of formula (I).

In the compounds of formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula (I). For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates

The compounds of formula (I) and salts, solvates and physiologically functional derivatives thereof are believed to be inhibitors of Syk activity, and thus be potentially useful in the treatment of diseases and conditions associated with inappropriate Syk activity.

Compound of formula (I) or its pharmaceutically acceptable salts and pharmaceutical compositions can be used to treat or prevent a variety of conditions or diseases mediated by Spleen tyrosine kinase (SYK). Such conditions and diseases include, but are not limited to: (1) arthritis, including rheumatoid arthritis, juvenile arthritis, psoriatic arthritis and osteoarthritis; (2) asthma and chronic obstruction pulmonary disease including emphysema; (3) autoimmune diseases or disorders, including those designated as single organ or single cell-type autoimmune disorders, those designated as involving systemic autoimmune disorder, for example systemic lupus erythematosis, immune thrombocytopenic purpura, rheumatoid arthritis, multiple sclerosis; (4) cancers or tumors, including solid tumors, and lymphoma and leukemia; (5) eye diseases including keratoconjunctivitis, vernal conjunctivitis, uveitis, keratitis, keratoconjunctivitis sicca (dry eye), allergic conjunctivitis; (6) intestinal inflammations, allergies or conditions including Crohn's disease and/or ulcerative colitis, inflammatory bowel disease; (7) skin diseases including atopic dermatitis, eczema, psoriasis, scleroderma, pruritus and other pruritic conditions; (8) allergic reactions including anaphylaxis, allergic rhinitis, allergic dermatitis, allergic urticaria, angioedema, allergic asthma, or allergic reaction to insect bites, food, drugs, or pollen; (9) transplant rejection.

The invention thus provides compounds of formula (I) and salts, solvates and physiologically functional derivatives thereof for use in therapy, and particularly in the treatment

of diseases and conditions mediated by inappropriate Syk activity. The inappropriate Syk activity referred to herein is any Syk activity that deviates from the normal Syk activity expected in a particular mammalian subject. Inappropriate Syk activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of Syk activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation.

In a further embodiment, the present invention is directed to methods of regulating, modulating, or inhibiting Syk for the prevention and/or treatment of disorders related to unregulated Syk activity.

In a further embodiment, the present invention provides a method of treatment of a mammal suffering from a disorder mediated by Syk activity, which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or a physiologically functional derivative thereof.

In a further embodiment, the present invention provides for the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, in the preparation of a medicament for the treatment of a disorder mediated by Syk activity.

In a further embodiment said disorder mediated by Syk activity is asthma. In a further embodiment said disorder is rheumatoid arthritis. In yet another embodiment, said disorder is cancer. In a further embodiment said disorder is ocular conjunctivitis.

While it is possible that, for use in therapy, a compound of formula (I), as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides a pharmaceutical composition, which comprises a compound of formula (I) and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the formula (I), or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical compositions of the present invention may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 5μg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a

daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), inhaled, nasal, ocular, or parenteral (including intravenous and intramuscular) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the oral route, for treating, for example, rheumatoid arthritis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the nasal route, for treating, for example, allergic rhinitis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the inhaled route, for treating, for example, asthma, COPD or ARDS.

Pharmaceutical compositions of the present invention which are adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride

and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Dosage forms for inhaled administration may conveniently be formulated as aerosols or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt or solvate is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose

inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or salt or solvate thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. It is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 J D Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUS® device(GlaxoSmithKline). Other dry powder inhalers are well

known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including Aerolizer® (Novartis), Airmax™ (IVAX), ClickHaler® (Innovata Biomed), Diskhaler® (GlaxoSmithKline), Accuhaler (GlaxoSmithKline), Easyhaler® (Orion Pharma), Eclipse™ (Aventis), FlowCaps® (Hovione), Handihaler® (Boehringer Ingelheim), Pulvinal® (Chiesi), Rotahaler® (GlaxoSmithKline), SkyeHaler™ or Certihaler™ (SkyePharma), Twisthaler (Schering-Plough), Turbuhaler® (AstraZeneca), Ultrahaler® (Aventis), and the like..

Dosage forms for nasal administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

For pharmaceutical compositions suitable and/or adapted for intranasal administration, the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof may be formulated as a fluid formulation for delivery from a fluid dispenser. Such fluid dispensers may have, for example, a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity.

The following are examples of representative pharmaceutical dosage forms for the compounds of this invention:

Injectable Suspension (I.M.)	mg/ml
Compound of Formula (I)	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1 ml	

Tablet	mg/tablet
Compound of Formula (I)	25
Microcrystalline Cellulose	415
Providone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5

	500

Capsule	mg/capsule
Compound of Formula (I)	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula (I)	24 mg
Lecithin, NF Liquid Concentrate	1.2 mg
Trichlorofluoromethane, NF	4.025 gm
Dichlorodifluoromethane, NF	12.15 gm

It will be appreciated that when the compound of the present invention is administered in combination with other therapeutic agents normally administered by the inhaled, intravenous, oral or intranasal route, that the resultant pharmaceutical composition may be administered by the same routes.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian However, an effective amount of a compound of formula (I) for the treatment of diseases or conditions associated with inappropriate Syk activity, will generally be in the range of 5 μg to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 5 μg to 10 mg/kg body weight per day. This amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se.

Compounds of the present invention, and their salts and solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents for the treatment of diseases and conditions associated with inappropriate Syk activity. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and the use

of at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

For the treatment of the inflammatory diseases, rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis a compound of formula (I) may be combined with one or more other active agents such as: (1) TNF-α inhibitors; (2) non-selective COX-I/COX-2 inhibitors; (3) COX-2 inhibitors; (4) other agents for treatment of rheumatoid arthritis including methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporin, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, Lymphostat-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetics thereof; (5) leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist; (6) LTD4 receptor antagonist; (7) PDE4 inhibitor; (8) antihistaminic H1 receptor antagonists; (9) α1- and α2-adrenoceptor agonist; (10) anticholinergic agents; (11) β-adrenoceptor agonists; (12) insulin-like growth factor type I (IGF-l) mimetic; (13) glucocorticosteroids; (14) kinase inhibitors such as inhibitors of the Janus Kinases (JAK 1 and/or JAK2 and/or JAK 3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologics such as rituximab; (16) selective costimulation modulators such as abatacept; (17) interleukin inhibitors, such as IL-1 inhibitor anakinra and IL-6 inhibitor tocilizumab.

For the treatment of treatment cancer a compound of Formula (I) may be combined with one or more of an anticancer agents. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: (1) estrogen receptor modulator; (2) other hormonal agents including aromatase inhibitors; (3) androgen receptor modulator; (4) retinoid receptor modulator; (5) antiproliferative agent; (6) prenyl-protein transferase inhibitor; (7) HMG-CoA reductase inhibitorn; (8) angiogenesis inhibitor; (9) PPAR-γ agonists, PPAR-δ agonists; (10) inhibitor of inherent multidrug resistance; (11) inhibitor of cell proliferation and survival signaling; (12) a bisphosphonate; (13) γ-secretase inhibitors, (14) agents that interfere with receptor tyrosine kinases (RTKs); (14) agent that interferes with a cell cycle checkpoint including inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors; (15) BTK inhibitors; (16) PARP; (17) mTOR inhibitors; and (18) cytotoxic/cytostatic agents classically used in cancer treatment such as the anthracyclines, platinum compounds, taxanes,

podophyllotoxins, vinca alkaloids, nitrosoureas, bleomycin, mitomycin C, vorinostat, camptothecins and the like.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention. These combinations are of particular interest in respiratory diseases and are conveniently adapted for inhaled or intranasal delivery.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions. Preferably, the individual compounds will be administered simultaneously in a combined pharmaceutical composition. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

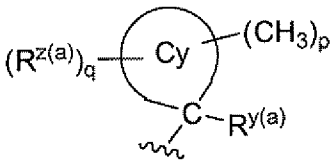
Biological Assay

Homogeneous Time-Resolved Fluorescence (HTRF) assay for the recombinant human SYK enzyme: A recombinant GST-hSYK fusion protein was used to measure potency of compounds to inhibit human SYK activity. The recombinant human GST-SYK (Carna Biosciences #08-176) (5pM final concentration) was incubated with various concentrations of the inhibitor diluted in DMSO (0.1% final concentration) for 10 minutes at room temperature in 15 mM Tris-HCl (pH 7.5), 0.01% tween 20, 2 mM DTT in 384 well plate format. To initiate the reaction the biotinylated substrate peptide (250 nM final concentration) that contains the phosphorylation site for SYK was added with magnesium (5 mM final concentration) and ATP (25 μM final concentration). Final volume of the reaction was 10 μL. Phosphorylation of the peptide was allowed to proceed for 45' at room temperature. To quench the reaction and detect the phosphorylated product, 2 nM of a Europium-anti-phosphotyrosine antibody (Perkin Elmer #AD0161) and 70 nM SA-APC (Perkin-Elmer #CR130-100) were added together in 15 mM Tris pH 7.5, 40 mM EDTA, 0.01% tween 20. Final volume of the quenching solution was 10 μL. The resulting HTRF signal was measured after 30 minutes on a EnVision (Perkin-Elmer) reader using a time-resolved fluorescence protocol. IC_{50} was determined following 10-dose titration (10 μM to 0.508 nM) and four parameter logistic curve fitting using the Merck Assay Data Analyzer. The rhSYK activity (IC50) is expressed as +++ (100nM or less), ++ (between 100 and 1000nM), + (between 1 and 10μM).

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the Examples.

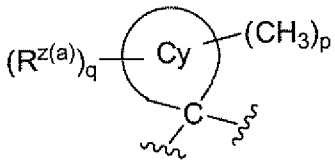
Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of protecting groups as well as the reaction conditions and order of reaction steps shall be consistent with the preparation of compounds of Formula (I). Those skilled in the art will recognize if a stereocenter exists in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and includes not only mixtures of stereoisomers (such as racemic compounds) but the individual stereoisomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

In the following Schemes R^5 represents the moiety



; and

"A" and "B" together with the carbon to which they are attached represent the moiety



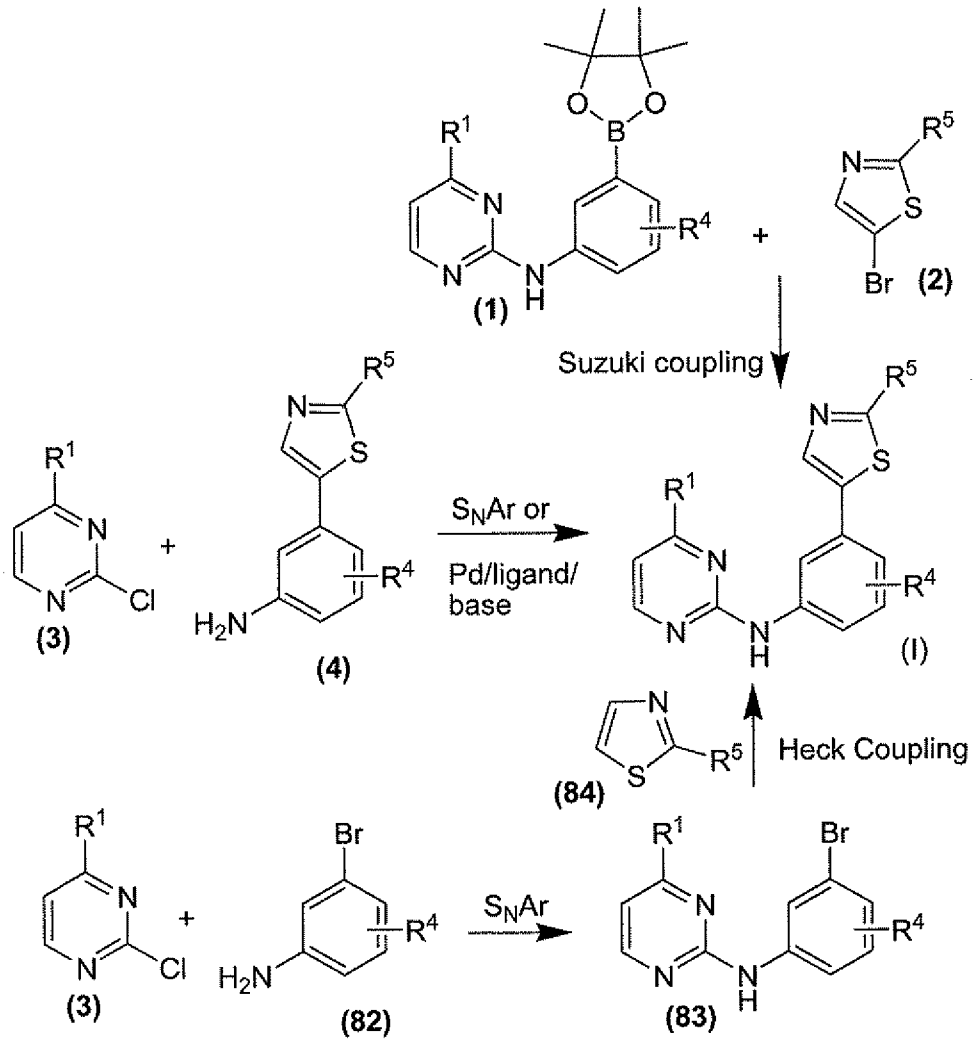
.

The ring noted as "A" represents a suitable ring within the definition of Cy, and is optionally substituted as Cy.

The following abbreviations are used in the schemes and examples: Ac=Acetyl; AcOH=Acetic acid; Bn=benzyl; Boc (t-Boc)=t-butyloxycarbonyl; BOP=(Benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate; DAST=(Diethylamino)sulfur trifluoride; dba=dibenzylideneacetone; DCE=1,2-dichloroethane; DCM=Dichloromethane; Dibal/Dibal-H=Diisobutylaluminum hydride; DIPEA/DIEA=Diisopropylethylamine; DMAP=N,N-dimethyl-aminopyridine; DME=1,2-dimethoxyethane; DMF=Dimethyl formamide; DMSO= Dimethyl-

sulfoxide; Dppf=1,1'-Bis(diphenylphosphino)ferrocene; EDC=N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; EtOAc=Ethyl acetate; HATU=N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; HMDS= Hexamethyldisilazane; HOBT=1-Hydroxybenzotriazole; IPA=Isopropyl alcohol; LDA=Lithium diisopropylamide; mCPBa=Meta-chloroperoxybenzoic acid; Ms=Methanesulfonyl (mesyl); MTBE=Methyl t-butyl ether; NBS=N-bromosuccinimide; Ph=phenyl; TBAF=t-butylammonium fluoride; TBDMS/TBS=t-butyl dimethylsilyl; TFA=Trifluoroacetic/trifluroacetate; THF=Tetrahydrofuran; TLC=Thin-layer chromatography; TMS=Trimethylsilyl; Ts=Toluenesulfonyl (tolyl); TSA=p-toluenesulfonic acid. Abbreviations for alkyl/cycloalkyl groups: Me = methyl, Et = ethyl, nPr = n-propyl, iPr = isopropyl, nBu = n-butyl, t-Bu = tertiary butyl, cPr = cyclopropyl, cBu = cyclobutyl, cPen = cyclopentyl, cHex = cyclohexyl, cHept = cycloheptyl.

SCHEME 1

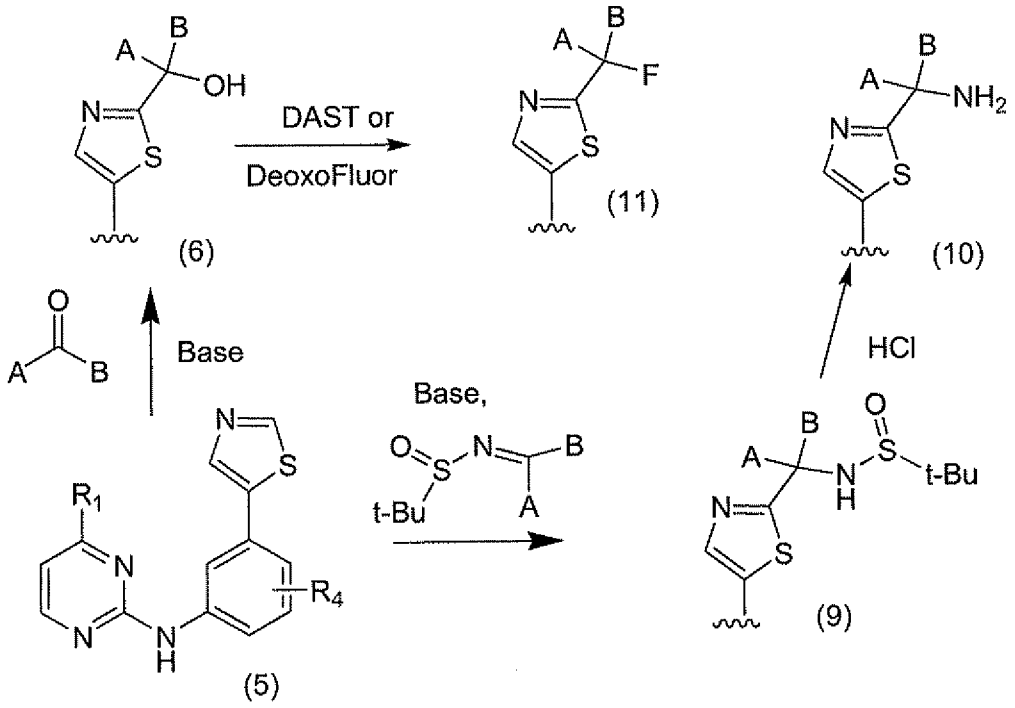


Compounds of formula (I) may be prepared by Suzuki coupling of boronic esters (1) with a thiazole bromides (2). Boronic esters (1) can be obtained by reacting 2-

chloropyrimidines (3) and 3-bromoanilines (82) to form the corresponding *N*-(3-bromophenyl)-pyrimidine-2-amines (83), followed by Miyaura coupling with bis(pinacolato)diboron. Compounds of formula (I) can also be obtained by reacting 2-chloropyrimidines (3) and thiazole-substituted anilines (4) in the presence of a Pd catalyst or alternatively an S_NAr reaction.

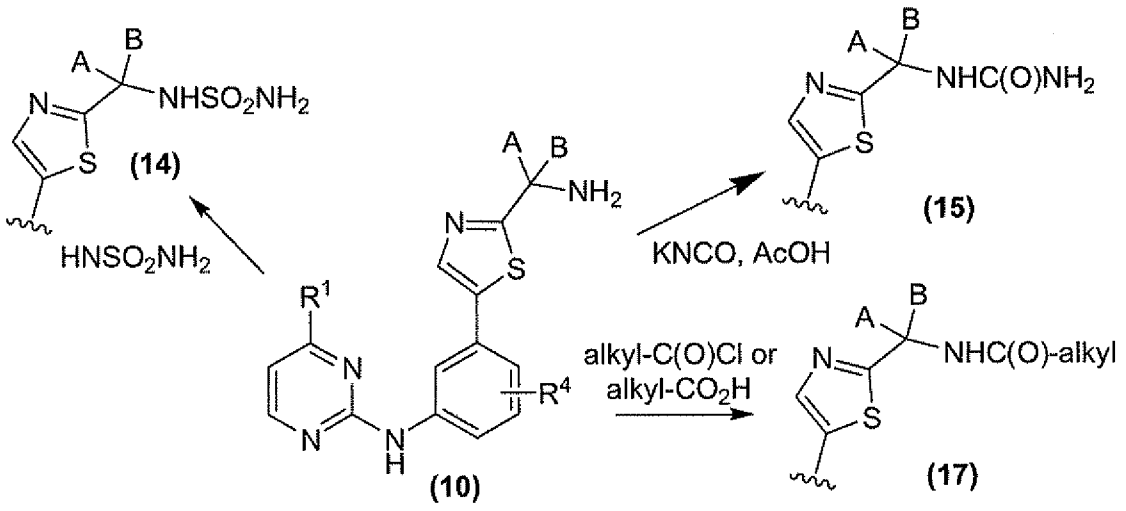
Thiazole-substituted anilines (4), in turn, may be formed under Suzuki coupling conditions using a bromothiazole and nitrophenyl boronic ester, followed by reduction of the nitro group to an amino group using standard conditions known to reduce nitroaromatic compounds to anilines such as Pd-catalyzed hydrogenation. Compounds of formula (I) may also be formed by the Heck reaction between bromo-substituted anilines (83) with substituted thiazoles (84). Bromo-substituted anilines (83) can be prepared by S_NAr reaction between 2-chloropyrimidines (3) and substituted bromo-anilines (82).

SCHEME 2



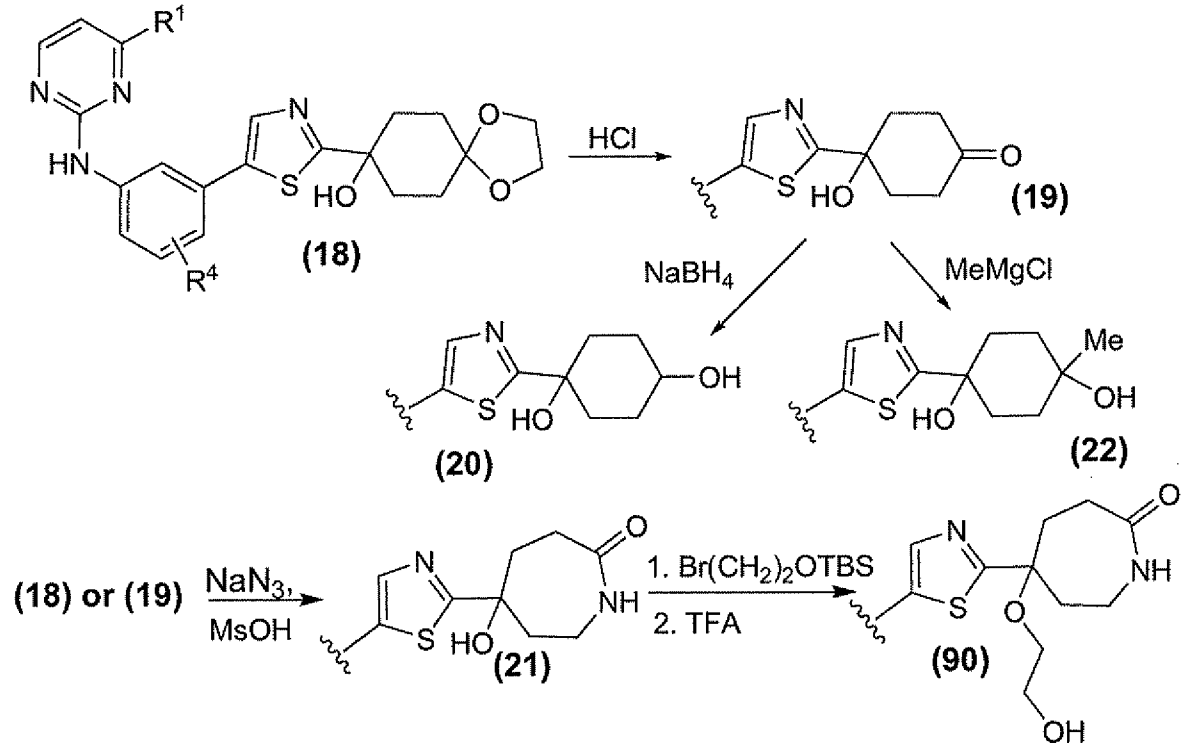
Compounds of formula (I) can also be prepared from compounds (5). Thiazole (5) is treated with a strong base such as LDA, and then with ketones to afford alcohols (6); with sulfimines to provide sulfinamides (9), which can be cleaved under acidic conditions to provide amines (10). Alcohols (6) can be fluorinated using a fluorinating agent such as DAST or deoxofluor to provide compounds (11).

SCHEME 5



Amines (10) can be treated (a) with sulfamide to provide compounds (14); (b) with potassium cyanate in the presence of acetic acid to provide ureas (15); (c) with acylating agents such as acid chlorides and carboxylic acids with a coupling agent to provide amides (17).

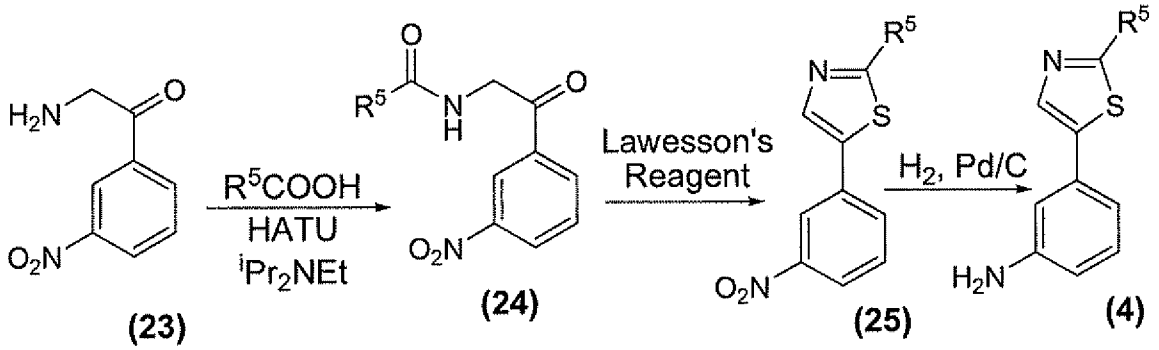
SCHEME 6



Ketals (18), prepared from compounds (5) and 1,4-dioxaspiro[4.5]decan-8-one, can be treated with HCl to afford ketones (19), which can then be reduced with sodium borohydride or treated with methyl Grignard to afford diols (20) or (22), respectively. Alternatively, ketals (18) or ketones (19) are treated with sodium azide and methanesulfonic acid

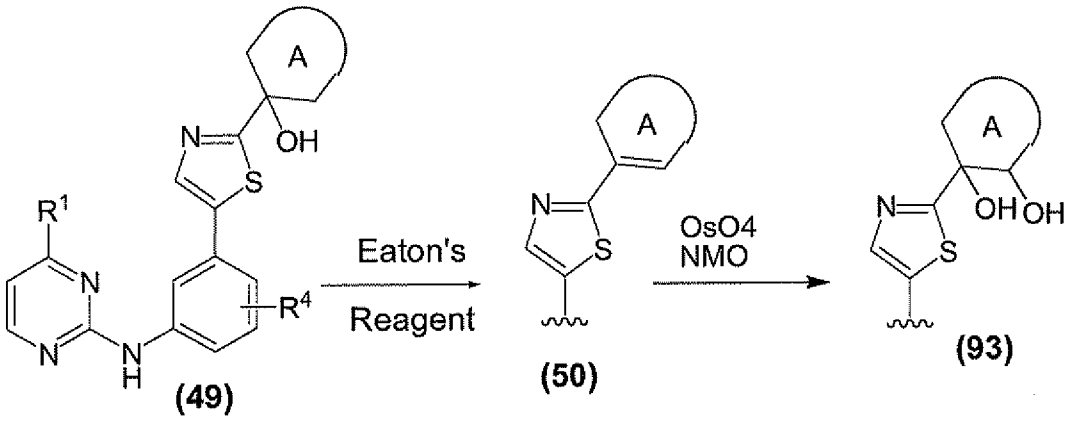
to provided the rearranged lactam (21). Alkylation of compounds (21) followed by deprotection of the intermediate silyl ether yields alcohols (90).

SCHEME 8



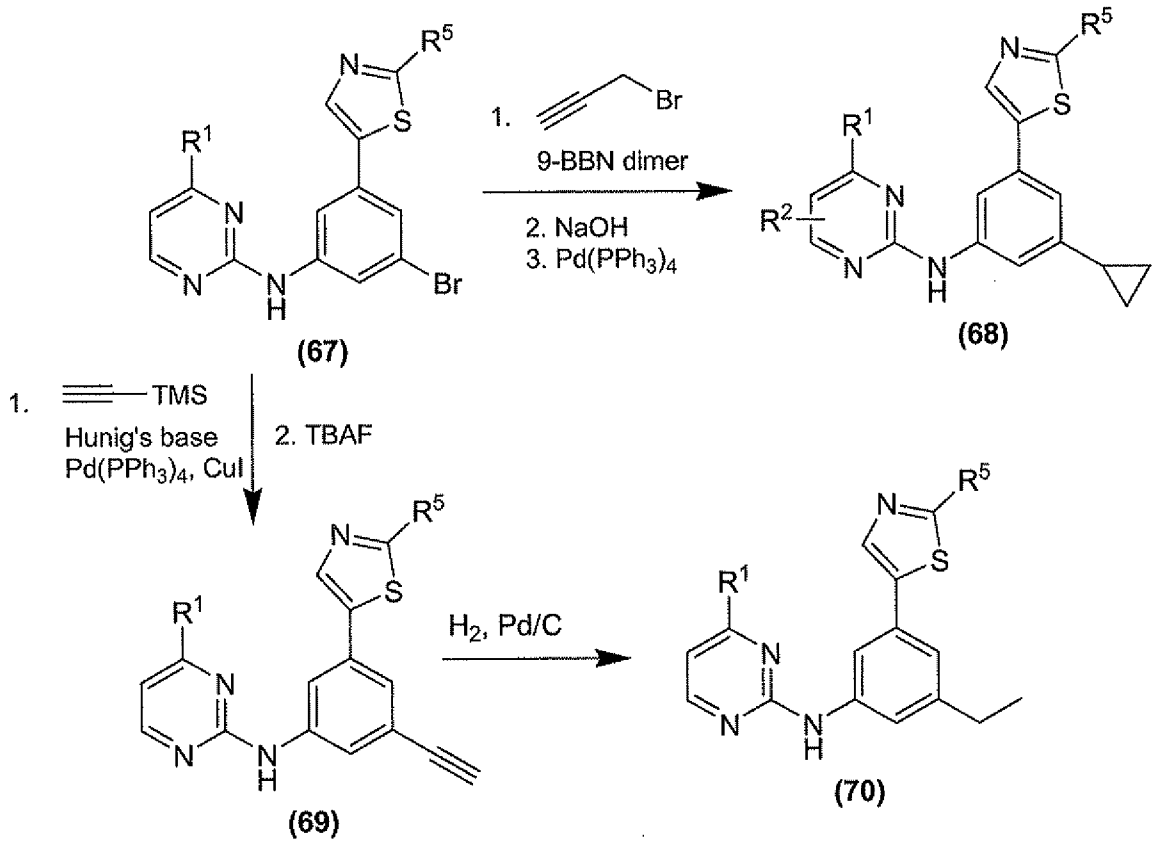
Compounds (4) can be prepared from 2-amino-1-(3-nitrophenyl)ethanone (23). Amide coupling with an acid provides compounds (24), which are treated with Lawesson's reagent resulting in the formation of nitrophenyls (25). Palladium-mediated reduction of nitroarenes (25) by hydrogen yields anilines (4).

SCHEME 10



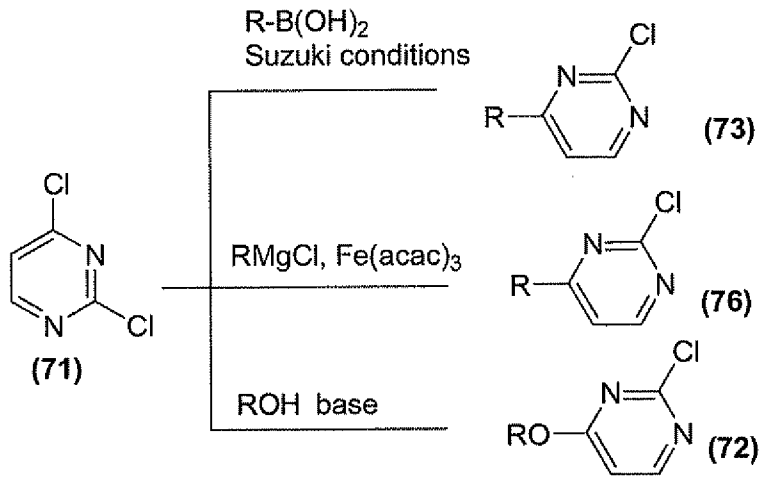
Dehydration of compounds (49) with Eaton's reagent provides the cycloalkenes (50), which yield the the diols (93) following dihydroxylation.

SCHEME 12



The bromides (67) are subjected to Sonogashira coupling with TMS-acetylene and subsequent silyl deprotection yields the acetylene compounds (69), which are reduced to yield compounds (70). Palladium-mediated coupling of (67) with cyclopropylboronate (prepared according to literature; see: J. A.; Huertas, R.; Leon-Colon, G. *Tetrahedron Lett.* **2000**, *41*, 4251-4255) provides the cyclopropyl compound (68).

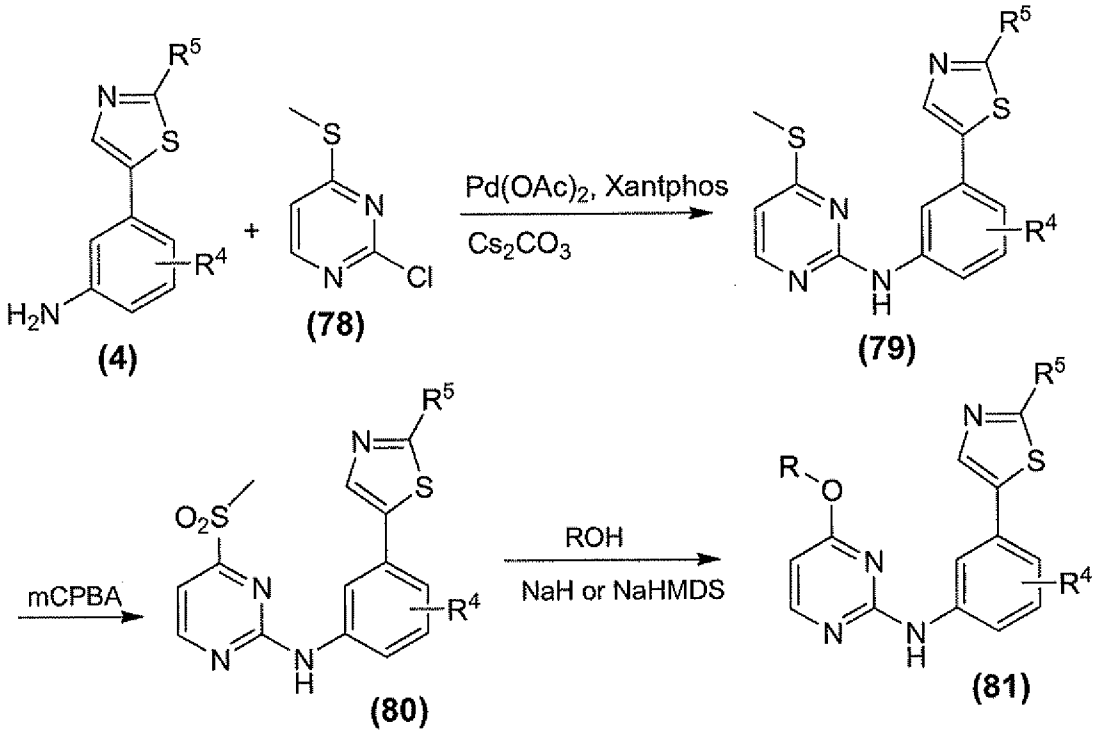
SCHEME 14



Preparation of 2-chloropyrimidine building blocks starting with 2,4-dichloropyrimidines (71) is illustrated in Scheme 14. Pyrimidine functionalization via Suzuki

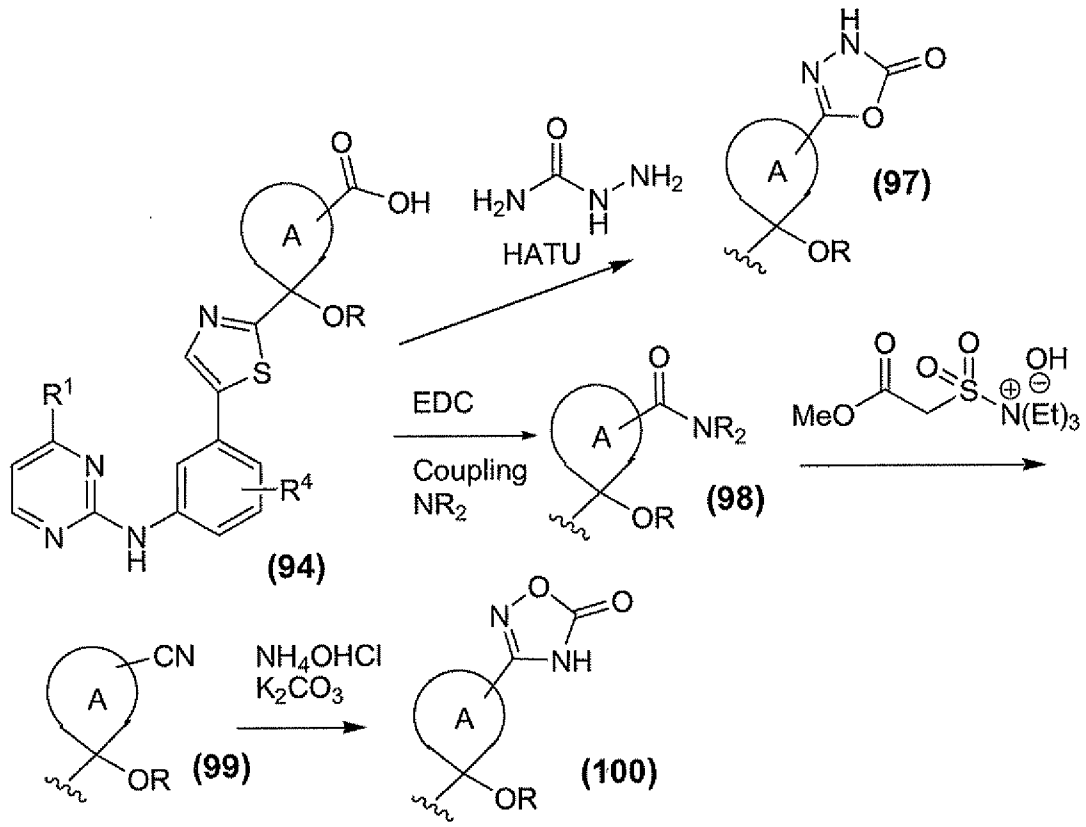
coupling yields substituted 2-chloropyrimidines (73), while a base mediated S_NAr reaction with substituted alcohol nucleophile provides ethers (72). Compounds (76) are prepared by an iron promoted coupling of Grignard reagents with compounds (71). In the Scheme R is alkyl or cycloalkyl.

SCHEME 15



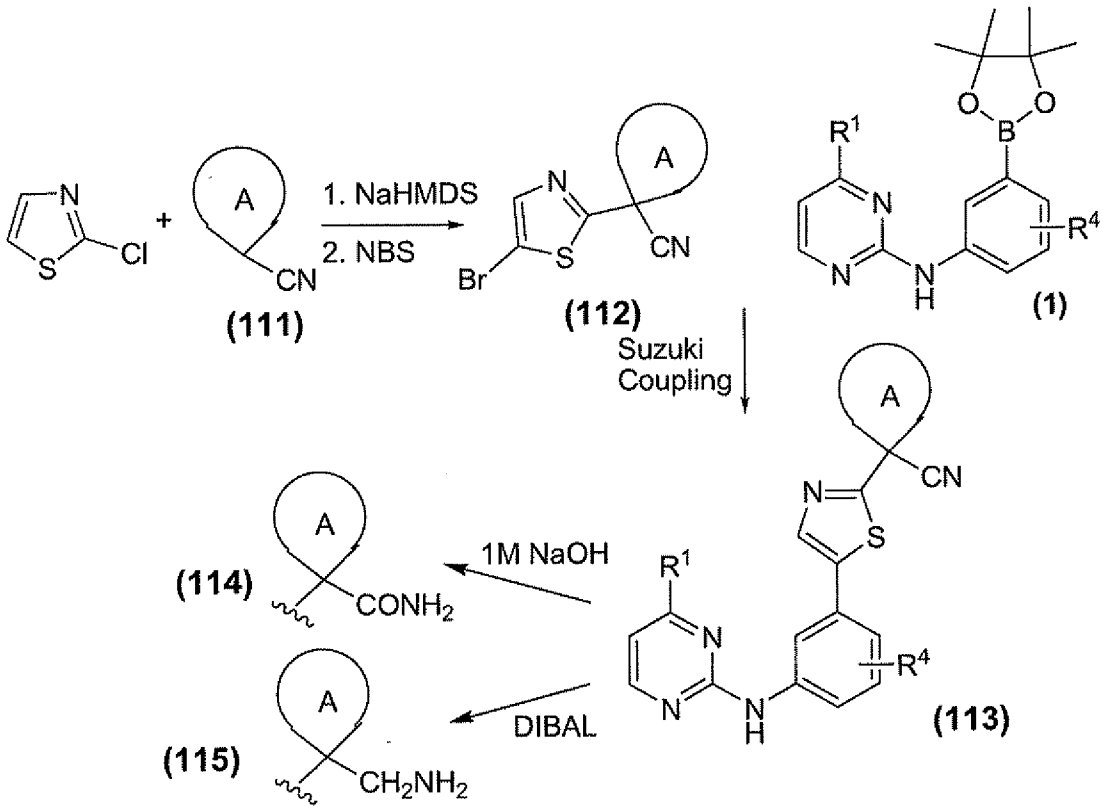
Coupling of compounds (4) with 2-chloro-4-(methylsulfanyl)pyrimidine (78) provided anilines (79), which are oxidized to the sulfones (8) by mCPBA. Displacement of the sulfone moiety with alcohols or thiols under basic conditions provided compounds (81).

SCHEME 16



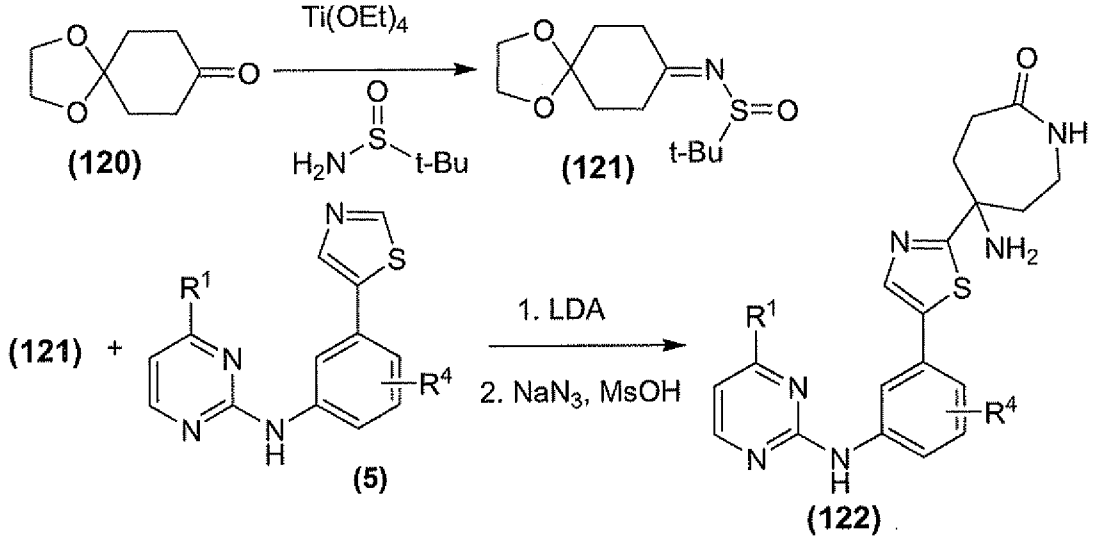
Reaction of acids (94) with hydrazine carboxamide yields the 1,3,4-oxadiazoles (97). Alternatively, amide coupling with acids (94) yields amides (98). Dehydration of the amides (98) with a sulfamoyl salt affords the nitriles (99). Cyclization of the nitriles (99) with ammonium hydroxide yields the 1,2,4-oxadiazoles (100).

SCHEME 20



2-Chlorothiazole is reacted with (111) in the presence of NaHMDS followed by bromination provides (112). Suzuki coupling of (1) with (112) yields (113). Hydrolysis of (113) gives amide (114), and reduction of (113) with DIBAL gives the amine (115).

SCHEME 22



Ketone (120) is reacted with *t*-butyl sulfonamide in the presence of titanium ethoxide to afford (121). Deprotonation of compound (5) with LDA followed by the addition of (121) and then ring expansion by he action of acid and azide gives (122).

Compounds of formula (I), as well as intermediates for their synthesis, can be prepared according to the procedures described in the Schemes, Preparation of Intermediates, and Examples herein, using appropriate materials and are further exemplified by the following specific intermediates and examples. The compounds exemplified are representative of the invention, and are not to be construed as limiting the scope of the invention in any manner. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of protecting groups, of reagents, as well as of the conditions and processes of the following preparative procedures, can be used to prepare intermediates and compounds of the instant invention. It is also understood that whenever a chemical reagent is not commercially available, such a chemical reagent can be readily prepared by those skilled in the art by either following or adapting known methods described in the literature. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured either by electrospray ion-mass spectroscopy (ESI) or by atmospheric pressure chemical ionization mass spectroscopy (APCI).

PREPARATION OF INTERMEDIATES AND MODEL COMPOUNDS

INTERMEDIATE 1: 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol

Step 1: Isopropylmagnesium chloride/lithium chloride complex (1.3 M in THF, 582 mL, 756 mmol) was cooled to 0 °C. Thiazole (53.2 mL, 749 mmol) was added over 15 minutes, resulting in an orange/red solution. Stirred for 20 min at 0 °C, then removed cooling bath and allowed to warm to rt. Stirred an additional 2 h, then recooled to 0 °C. Cyclobutanone (53.3 mL, 713 mmol) was added over 50 min. Removed the cooling bath and allowed to warm to rt and stirred 20 min at that temperature. The reaction mixture was cooled to 0 °C and saturated aqueous ammonium chloride was slowly added. The mixture was diluted with EtOAc, the layers separated and the organic portion washed with water. The aqueous layer was washed with ethyl acetate. The combined organic portions were dried over $MgSO_4$ and concentrated *in vacuo* to provide 127.5 g of material containing 1-(1,3-thiazol-2-yl)cyclobutanol, which was used without further purification.

Step 2: The product of Step 1 (171.9 g, 1.107 mol) was dissolved in DMF (860 mL) and cooled to 0 °C. Added NBS (236 g, 1.327 mol) and stirred 1 h at 0 °C. Removed the cooling bath and allowed to warm to rt. Followed by LC until the starting material was consumed. The solution was poured into cooled water (2 L) containing Na_2SO_3 (30 g), washing with MTBE (1 L). The mixture was stirred 10 min, then diluted with MTBE (1.5 L) and water (500 mL). Separated the layers and washed the organic portion with water (2 L). The aqueous portions were extracted with MTBE (2 L). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to provide an orange oil. Diluted in hexanes at 50 °C (1 L). Stirred while slowly allowing to cool. Added seed crystals, and crystallization began around 35 °C. Stirred overnight at rt. Cooled to -20 °C and stirred 20 min. Filtered, washing with hexane at -20 °C. Dried under a nitrogen bag to provide 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol (172.9 g, 739 mmol, 67%).

The filtrate and all remaining material in the flask was diluted in CH_2Cl_2 and concentrated *in vacuo*. Hexane added, concentrated to ~300 mL cooled to rt and seed crystals were added. Began to crystallize. Cooled to -10 °C and filtered, washing with hexane at -10 °C. Second crop of crystals allowed to air dry providing 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol (38.8 g, 166 mmol, 15%). The mother liquor from the second filtration was concentrated and purified by column chromatography on silica gel (Biotage EtOAc/Hex) then dried under vacuum to provide 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol (10.6 g, 45 mmol, 4%). Overall, obtained 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol (222 g, 948 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1 H); 3.56 (br s, 1 H); 2.69-2.60 (m, 2 H); 2.47-2.36 (m, 2 H); 2.09-1.87 (m, 2 H).

INTERMEDIATE 2: *N*-(3-bromo-5-methylphenyl)-4-(trifluoromethyl)pyrimidin-2-amine
A solution of 3-bromo-5-methylaniline (162.5 g, 873.66 mmol) in 1,4-dioxane (2 L) was prepared, and 2-chloro-4-(trifluoromethyl)pyrimidine (182 g, 994.54 mmol) and methanesulfonic acid (97.5 g, 1.02 mol) were added sequentially. The resulting solution was heated to reflux overnight. The resulting mixture was cooled and concentrated *in vacuo*. The residue was diluted with 2 L of water, then adjusted to pH 7-8 with aqueous sodium bicarbonate solution, followed by extraction with EtOAc (2x2 L) The organic layers were combined, washed with water (2x 2 L), dried over anhydrous sodium sulfate and concentrated *in vacuo*. This resulted in *N*-(3-bromo-5-methylphenyl)-4-(trifluoromethyl)pyrimidin-2-amine (200 g, 602 mmol, 69%) as a light yellow solid. MS(ESI): $[M + H]^+$ 334.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.9 Hz, 1 H); 7.79 (s, 1 H); 7.30 (s, 2 H); 7.10-7.06 (m, 2 H); 2.36 (s, 3 H).

INTERMEDIATE 3: *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine
To a solution of **Intermediate 2** (250 g, 753.01 mmol,) in 1,4-dioxane (3 L) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (225 g, 885.83 mmol), KOAc (225 g, 2.30 mol) and $Pd(dppf)Cl_2$ (19 g, 25.23 mmol). The resulting solution was heated to reflux overnight. The solid was filtered. The filtrate was decolorized by passing through a silica gel column. The fractions were collected and concentrated *in vacuo*. This resulted in 110 g pure and 150 g crude product. The crude product was decolorized again with active carbon to provide an additional 125 g of pure product. This resulted in *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (235 g, 620 mmol, 82%) as a white solid. MS APCI: $[M + H]^+$ *m/z* 380. ^{1}H NMR (400MHz, $CDCl_3$, ppm): 1.350 (12H, s), 2.386 (3H, s), 6.993-7.006 (1H, d, J = 5.2 Hz), 7.385-7.427 (2H, s,), 7.636 (1H, s), 7.753 (1H, s), 8.608-8.621 (1H, d, J = 5.2Hz).

INTERMEDIATE 4: *N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine

To a solution of **Intermediate 3** (80 g, 211.08 mmol) in 1,4-dioxane (800 mL) was added 5-bromo-1,3-thiazole (28 g, 171.78 mmol), $Pd(dppf)Cl_2$ (8 g, 10.62 mmol) and a solution of sodium carbonate (44.7 g, 421.70 mmol) in water (447 mL). The resulting solution was heated to reflux for 1 hour. Then it was allowed to cool and concentrated *in vacuo*. The residue was diluted with EtOAc (500 mL) and filtered. The filtrate was washed with brine (2x300 mL) and water (2x300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized from EtOAc:DCM in the ratio of 1:5 to get 34 g of product. The mother liquor was applied onto a silica gel column and eluted with dichloromethane/ethyl acetate (2:1). This resulted in *N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (42 g, 125 mmol, 73%) as a pale yellow solid. MS APCI: $[M + H]^+$ *m/z* 337. ^1H NMR (400MHz, CD_3COCD_3, ppm): 2.413 (3H, s), 7.250-7.263 (2H, m), 7.636 (1H, s), 8.204-8.213 (2H, m), 8.834-8.846 (1H, d, $J = 4.8$Hz), 8.970 (1H, s), 9.210 (1H, br). rhSYK activity = +++.

INTERMEDIATE 5: *N*-(3-bromophenyl)-4-(trifluoromethyl)pyrimidin-2-amine

A solution of 3-bromoaniline (250 g, 1.46 mol) in 1,4-dioxane (2.5 L) was prepared, and 2-chloro-4-(trifluoromethyl)pyrimidine (267 g, 1.47 mol) and methanesulfonic acid (155 g, 1.61 mol) were added sequentially. The resulting solution was heated to 100 °C overnight. The resulting mixture was cooled and concentrated *in vacuo*. The residue was adjusted to pH 7-8 with aqueous sodium bicarbonate solution. The solid was filtered, and the filtrate was extracted with EtOAc (4x500 mL) The organic layers were combined, washed with water (2x 2 L), dried over anhydrous sodium sulfate and concentrated *in vacuo*. This resulted in *N*-(3-bromophenyl)-4-(trifluoromethyl)pyrimidin-2-amine (200 g, 629 mmol, 43%) as a light yellow solid. MS APCI: $[M + 3]^+$ *m/z* 319. ^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, $J = 4.9$ Hz, 1 H); 7.95 (s, 1 H); 7.53-7.50 (m, 1 H); 7.44 (br s, 1 H); 7.22 (m, 2 H); 7.08 (d, $J = 4.9$ Hz, 1 H).

INTERMEDIATE 6: *N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine

To a solution of **Intermediate 5** (200 g, 631 mmol,) in 1,4-dioxane (2 L) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (177 g, 697 mmol), KOAc (187 g, 1.91 mol) and $Pd(dppf)Cl_2$ (24 g, 32 mmol). The resulting solution was heated to 100 °C for 2 h. The reaction was allowed to cool, and the solid was filtered. The filtrate was concentrated *in vacuo*. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10). This resulted in *N*-[3- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (140 g, 384 mmol, 61%) as a white solid. MS APCI: $[M + H]^+$ *m/z* 366. ^1H NMR (400MHz, DMSO-d6, ppm): 1.300 (12H, s), 7.237-7.249 (1H, m), 7.331-7.342 (2H, m), 7.882-7.910 (1H, m), 8.000 (1H, s), 8.796-8.806 (1H, m), 10.130 (1H, s).

INTERMEDIATE 7: *N*-[3-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine
$Pd(dppf)Cl_2$ (1.01 g, 1.23 mmol) and **Intermediate 6** (9.0 g, 25 mmol) were combined in a flask and were evacuated and back-filled with nitrogen (x3). Added 2-Me THF (90 mL), 5-bromothiazole (4.45 g, 27.1 mmol), and aqueous sodium carbonate (24.7 mL, 49.3 mmol) sequentially. Sealed the flask and heated to 80 °C for 15 h. The brown solution was allowed to cool to rt, then diluted with water and EtOAc. The layers were separated, and the aqueous portion was extracted with EtOAc (2x). The combined organic portions were washed with saturated aqueous $NaHCO_3$, then Brine, then dried over Na_2SO_4 and concentrated *in vacuo*. Trituration with CH_2Cl_2 and collection of the beige solid via filtration provided 5.94 g of the desired product. The mother liquor was concentrated in vacuo and subsequent purification via silica gel column chromatography (CH_2Cl_2-40% EtOAc:CH_2Cl_2) provided an additional 1.41 g of the desired product. In total, *N*-[3-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (7.35 g, 22.8 mmol, 93%) was isolated as a beige solid. MS APCI: $[M + H]^+$ *m/z* 323. ^1H NMR (600 MHz, DMSO-D_6, ppm) δ 10.32 (s, 1H), 9.06 (s, 1H), 8.82 (d, $J = 4.8$, 1H), 8.20 (d, $J = 8.2$, 1H), 8.20 (s, 1H), 7.64 (d, $J = 7.5$, 1H), 7.40 – 7.31 (m, 2H), 7.27 (d, $J = 4.9$, 1H). rhSYK activity = ++.

INTERMEDIATE 9: *N*-[3-(2-bromo-1,3-thiazol-5-yl)-5-methylphenyl]-4-(trifluoromethyl)-pyrimidin-2-amine
Lithium diisopropylamide (1.8 M in THF/heptane/ethylbenzene, 11.4 mL, 20.5 mmol) was cooled to -70 °C. **Intermediate 4** (2.3 g, 6.8 mmol) in THF (23 mL) was added slowly over 15 minutes, keeping the temperature at -65 °C. The reaction was allowed to stir for 30 minutes following the addition and then bromine (0.53 mL, 10.3 mmol) was added. The reaction was stirred for 30 minutes and then quenched with 20 mL of water and warmed to rt. The reaction was diluted with EtOAc (50 mL). The layers were separated and the organic portion was washed with Na_2SO_3 (10% aqueous), brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification via column chromatography (ISCO, dry load with silica gel, Hexane-50% EtOAc:Hexane) to provide N-[3-(2-bromo-1,3-thiazol-5-yl)-5-methylphenyl]-4-(trifluoromethyl)pyrimidin-2-amine (1.88 g, 4.53 mmol, 66%). MS APCI: $[M + H]^+$ *m/z* 414.8, 416.8. ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (d, $J = 4.9$, 1H), 7.88 (s, 1H), 7.74 (s, 1H), 7.33 (s, 1H), 7.05 (t, $J = 6.4$, 1H), 7.01 (s, 1H), 2.38 (s, 3H).

INTERMEDIATE 10: *N*-[3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine
Step 1: To a solution of 3,5-dibromoanaline (4.47 g, 17.8 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (2.36 mL, 19.6 mmol) was added *p*-toluenesulfonic acid (4.06 g, 21.4 mmol), resulting in the formation of a thick suspension. This mixture was heated to 100 °C overnight, during which it became a deep red solution. The mixture was diluted with 200 mL EtOAc and washed with 200 mL sat. $NaHCO_3$ (aq) and 200 mL brine. The organic layer was

dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography on silica gel (220 g; load w/toluene; 100:0 to 85:15 hexanes:EtOAc over 45 minutes) provided *N*-(3,5-dibromophenyl)-4-(trifluoromethyl)pyrimidin-2-amine (5.85 g, 14.7 mmol, 83%) as a light yellow solid. MS APCI: $[M + H]^+$ *m/z* 397.8. ^1H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.9 Hz, 1 H); 7.84 (s, 2 H); 7.39 (s, 1 H); 7.34 (s, 1 H); 7.14 (d, *J* = 4.9 Hz, 1 H).

Step 2: To a solution of the product of Step 1 (2.0g, 5.0 mmol) in DMSO (10.1 mL) were added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.4 g, 5.5 mmol), KOAc (1.48 g, 15.1 mmol) and $Pd(dppf)Cl_2$ (123 mg, 0.151 mmol), and the mixture was heated to 125 °C for 30 minutes in the microwave. The mixture was diluted with 100 mL EtOAc and washed with 2 x 100 mL 1:1 H_2O:brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by Chromatography on silica gel (80 g; load w/CH_2Cl_2; 100:0 to 70:30 hexanes:EtOAc over 40 minutes) provided *N*-[3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (755 mg, 1.70 mmol, 34%) as an off-white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (d, *J* = 4.9, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.32 (d, *J* = 4.9, 1H), 1.34 (s, 12H).

INTERMEDIATE 11: *N*-[3-bromo-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine

A solution of $Pd(OAc)_2$ (19 mg, .085 mmol) and butyl di-1-adamantyl phosphine (61 mg, 0.18 mmol) in THF (12.8 mL) was stirred for 15 min. **Intermediate 10** (755 mg, 1.70 mmol), 5-bromo-1,3-thiazole (760 µL, 8.50 mmol), potassium fluoride (296 mg, 5.10 mmol), and water (4.25 mL) were then added, and the mixture was heated to 75 °C overnight. After cooling to rt, the mixture was diluted with 100 mL EtOAc and washed with 100 mL brine. A bright yellow solid remained undissolved on the walls of the separatory funnel, which was thus rinsed with 100 mL THF. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by Chromatography on silica gel (40 g; dry load; 100:0 to 50:50 hexanes:EtOAc over 25 minutes) provided *N*-[3-bromo-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (449 mg, 1.12 mmol, 66%) as an off-white solid. MS APCI: $[M + H]^+$ *m/z* 403.0. ^1H NMR (400 MHz,$(CD_3)_2CO$): δ 9.46 (s, 1 H); 9.03 (s, 1 H); 8.89 (d, *J* = 4.9 Hz, 1 H); 8.32-8.26 (m, 2 H); 8.16 (s, 1 H); 7.59 (s, 1 H); 7.33 (d, *J* = 4.9 Hz, 1 H). rhSYK activity = ++.

INTERMEDIATE 15: 1-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]cyclobutanol

Step 1: Dioxane (720 mL) in a 1 L three-necked round bottom flask was degassed for 30 min. 3-Bromo-5-methylaniline (60g, 193 mmol), (bispinacolato)diboron (96 g, 377 mmol), potassium acetate (42.7 g, 435 mmol), X-Phos (8.3 g, 17.41 mmol) and Pd_2dba_3 (3.99 g, 4.35 mmol) were added to the degassed solvent under $N_2(g)$. After stirring for 10 min at room temperature, the reaction mixture was heated to an internal temperature of 80 °C. After ca. 4 hours, the heating mantle was removed and replaced with an ice water bath. The reaction mixture was cooled to 30 °C, and was then filtered through a pad of celite (washing with 500 mL of MTBE). This was

transferred to a 4 L separatory funnel containing 500 mL pH 8 phosphate buffer, 500 mL brine, and an additional 500 mL of MTBE. The layers were cut and the organic washed with 1 L of a 1:1 mixture of brine and water. The aqueous layers were combined and sequentially back extracted with a second 500 mL portion of MTBE. The combined organics were treated with 100 g of $MgSO_4$ and the resulting mixture stirred for 20 min. This was then filtered and concentrated *in vacuo*. The resultant residue was purified by chromatography on silica gel (Biotage, 0-25% ethyl acetate in hexanes) to yield 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (66 g, 255 mmol, 88%) as a light orange solid. MS APCI: $[M + H]^+$ *m/z* 234.2.

Step 2: To 500 mL three-necked round bottom flask were added 2-methyl THF (720 mL) and an aqueous solution of sodium carbonate (2 M, 367 mL, 734 mmol). The solution was degassed for 30 min. The product of Step 1 (90 g, 367 mmol), **Intermediate 1** (86 g, 367 mmol) and $PdCl_2$(dppf) (8.05 g, 11 mmol) were added to the degassed solution under N_2(g). The resulting mixture was stirred for 5 min at room temperature and was then heated to 80° C. After ca. 9 hours, the heating mantle was removed and the reaction was cooled to 30 °C. The reaction mixture was filtered through a pad of SolkaFloc employing water (500 mL) and ethyl acetate (500 mL) to complete the transfer. The filtrate was then transferred to a separatory funnel, using an additional 500 mL ethyl acetate and 250 mL brine to complete the transfer. The layers were cut, the organic washed with a mixture of water and brine (500 mL and 250 mL, respectively), and then the aqueous was back extracted with ethyl acetate (400 mL). The organics were combined, dried over $MgSO_4$ (100 g), filtered, and concentrated *in vacuo* to yield a brown crystalline solid. This material was recrystallized from hot ethyl acetate (250 mL at 60 °C), using hexanes as a counter-solvent (750 mL) to yield 1-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]cyclobutanol (88 g, 338 mmol, 92%). MS APCI: $[M + H]^+$ *m/z* 261.2. ^1H NMR (500 MHz, DMSO-D_6) δ 7.87 (s, 1H), 6.59 (s, 1H), 6.58 (s, 1H), 6.45 (s, 1H), 6.34 (s, 1H), 5.14 (s, 2H), 2.52 – 2.48 (m, 2H), 2.31 (q, J = 9.3, 2H), 2.17 (s, 3H), 1.93 – 1.80 (m, 2H).

INTERMEDIATE 16: 3-Methyl-5-(1,3-thiazol-5-yl)aniline

3-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (20.98 g, 90 mmol), 5-bromothiazole (8.85 mL, 99 mmol), and sodium carbonate (90 mL, 180 mmol) were combined in a flask. 2-Methyl-THF (326 mL) was added and the flask was degassed with N_2 for 1.5 h before 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (3.67 g, 4.50 mmol) was added. The reaction was heated to 100 °C overnight and was then cooled to room temperature. The reaction mixture was filtered though a pad of Celite, washing with ethyl acetate. The layers were separated and the aqueous layer was back-extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (0-40% ethyl acetate in hexanes). 3-Methyl-5-(1,3-thiazol-5-yl)aniline was isolated as a yellowish brown solid (15.33 g, 81 mmol, 90%). MS ESI: $[M + H]^+$ *m/z* 191.1. ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.02 (s, 1H), 6.80 (s, 1H), 6.71 (s, 1H), 6.50 (s, 1H), 3.71 (s, 2H), 1.79 (s, 3H).

INTERMEDIATE 18: 4-methyl-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine

Step 1: Acetic acid (0.234 mL, 4.08 mmol) was added to 2-chloro-4-methylpyrimidine (0.5 g, 3.89 mmol) and 3-bromo-5-methylaniline (1.096 g, 3.89 mmol) suspended in dioxane (7.78 mL). The reaction was heated to 120 °C overnight. Then, the reaction was cooled to room temperature and was directly purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to give *N*-(3-bromo-5-methylphenyl)-4-methylpyrimidin-2-amine (1.08 g, 3.89 mmol, quant.) as a white solid. MS ESI: $[M + H]^+$ *m/z* 278.0 and 280.0.

Step 2: A 40 mL vial was charged with the product of Step 1 (500 mg, 1.798 mmol), bis(pinacolato)diboron (502 mg, 1.977 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (44.0 mg, 0.054 mmol) and potassium acetate (529 mg, 5.39 mmol). The solid mixture was dissolved with DMSO (7.19mL) and was heated to 120 °C. After stirring for 2 h, the mixture was cooled to room temperature. The reaction was diluted with ethyl acetate, washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes to give 4-methyl-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine (331 mg, 1.018 mmol, 56.6 % yield) as an orange oil. MS ESI: $[M + H]^+$ *m/z* 326.2. ^1H NMR (500 MHz, DMSO-D_6) δ 9.40 (s, 1H), 8.31 (d, *J* = 5.0 Hz, 1H), 7.77 (s, 2H), 7.07 (s, 1H), 6.70 (d, *J* = 5.0 Hz, 1H), 2.33 (s, 3H), 2.26 (s, 3H), 1.27 (s, 12H).

INTERMEDIATE 19: 4-methyl-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine

A microwave vial was charged with **Intermediate 18** (218 mg, 0.670 mmol), 5-bromo-1,3-thiazole (59.9 μL, 0.670 mmol), $Pd_2(dba)_3$ (30.7 mg, 0.034 mmol), X-Phos (32.0 mg, 0.067 mmol) and cesium carbonate (437 mg, 1.341 mmol). The system was purged and flushed with Ar(g) four times before adding dioxane (918 μL) and water (92 μL). Again, the system was purged and flushed five times before sealing the vial and heating at 100 °C. LCMS showed ~60% desired product, ~35% de-borolated product and remaining unreacted starting material. The reaction mixture was diluted with ethyl acetate, filtered through a celite plug and concentrated. The resultant residue was purified by column chromatography on silica gel (Biotage, 0-20% ethyl acetate in hexanes) to afford 4-methyl-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine (105 mg, 0.372 mmol, 55.5%). MS ESI: $[M + H]^+$ *m/z* 283.0. ^1H NMR (500 MHz, DMSO-D_6) δ 9.60 (s, 1H), 9.04 (s, 1H), 8.35 (d, *J* = 6.6, 1H), 8.18 (s, 1H), 8.04 (s, 1H), 7.54 (s, 1H), 7.10 (s, 1H), 6.75 (d, *J* = 6.3, 1H), 2.37 (s, 3H), 2.30 (s, 3H).

INTERMEDIATE 20: 4-methoxy-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine

Step 1: A 10-20 mL microwave vial was charged with 2-chloro-4-methoxypyrimidine (0.835 g, 5.78 mmol), 3-bromo-5-methylaniline (1.075 g, 5.78 mmol), acetic acid (0.347 mL, 6.06 mmol) and dioxane (11.55 mL). The system was purged and flushed with Ar(g) three times before sealing and heating to 120 °C for 3 hours. The mixture was cooled and stirred overnight. The light brown solids were collected by filtration and were dried in a vacuum oven overnight to yield *N*-(3-bromo-5-methylphenyl)-4-methoxypyrimidin-2-amine (1.7 g, 5.78 mmol, 100 % yield) as a tan solid. MS ESI: $[M + H]^+$ *m/z* 296.0.

Step 2: A10-20 mL microwave vial was charged with the product of Step 1 (1.6 g, 5.44 mmol), bispinacolatodiboron (1.519 g, 5.98 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)-dichloride dichloromethane complex (0.133 g, 0.163 mmol), potassium acetate (1.602 g, 16.32 mmol) and DMSO (10.88 mL). The system was flushed and purged five times with Ar(g) before sealing the vial and heating to 120 °C for 1 hour. The reaction was the cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug and was concentrated to dryness. The resultant residue was purified by column chromatography on silica gel (Biotage, 5-60% ethyl acetate in hexanes) to afford 4-methoxy-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine (900 mg, 2.64 mmol, 48.5 % yield) as a tan solid. MS ESI: $[M + H]^+$ *m/z* 342.1. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.46 (s, 1H), 8.17 (d, *J* = 5.8, 1H), 8.04 (s, 1H), 7.62 (s, 1H), 7.06 (s, 1H), 6.25 (d, *J* = 5.8, 1H), 3.92 (s, 3H), 2.26 (s, 3H), 1.26 (s, 12H).

INTERMEDIATE 21: 4-methoxy-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine

To a round-bottom flask were added 2-chloro-4-methoxypyrimidine (1.58 g, 10.93 mmol), **Intermediate 20** (2g, 10.51 mmol), cesium carbonate (6.85 g, 21.02 mmol) and degassed dioxane (105 mL). The system was flushed and purged with Ar(g) and palladium(II) acetate (0.236 g, 1.051 mmol) and Xantphos (0.912 g, 1.577 mmol) were added. The system was flushed and purged again three times with Ar(g) and then was heated to 90 °C for 2 hours. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure and the residue was directly purified by column chromatography on silica gel (0 to 100%, 10:1 ethyl acetate: methanol in hexanes) to afford 4-methoxy-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]-pyrimidin-2-amine (3.1 g, 10.39 mmol, 99%). MS ESI: $[M + H]^+$ *m/z* 299.1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.13 (d, *J* = 5.7, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 7.05 (s, 1H), 6.21 (d, *J* = 5.7, 1H), 3.98 (s, 3H), 2.37 (s, 3H).

INTERMEDIATE 24: Methyl 2,2-dimethyl-4-oxocyclohexanecarboxylate

Step 1: Methyl 3-oxobutanoate (232 g, 2.00 mol) and paraformaldehyde (30 g, 999.00 mmol) were combined, and to the mixture was added piperidine (10 g, 117.44 mmol). The resulting solution was stirred for 2 h at 0 °C. The solution was heated to 60 °C for 2 h. Extracted with Et_2O (3x), and the organic layers were combined and dried over Na_2SO_4. Filtered and

concentrated *in vacuo*. This resulted in 370 g (crude) of dimethyl 2-methyl-6-oxocyclohex-1-ene-1,3-dicarboxylate as a brown oil. MS: [M + H]+ *m/z* 227.

Step 2: To a solution of sodium methanolate (90 g, 1.67 mol) in methanol (300 mL) was added the product of Step 1 (150 g, 663.04 mmol) in methanol (150 mL) dropwise with stirring over 30 min. The resulting solution was heated to 80 °C for 30 min. and the mixture was concentrated *in vacuo*. The reaction mixture was then quenched by the addition of H_2O/ice (120 mL), then diluted with acetic acid (130 mL). The resulting solution was extracted with Et_2O (3x), and the organic layers were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The final product was purified by distillation under reduced pressure (5 mm Hg) and the fraction was collected at 110~120 °C. This resulted in 100 g (88%) of methyl 2-methyl-4-oxocyclohex-2-enecarboxylate as a yellow oil. MS: [M + H]+ *m/z* 169.

Step 3: Copper iodide (121.8 g, 639.54 mmol) was added to Et_2O (800 mL). Methyllithium (1.6 M in diethyl ether, 800 mL, 1.28 mol) was added dropwise at -40 °C over 3 h. Added a solution of the product of Step 2 (53.8 g, 319.88 mmol) in Et_2O (400 mL) at -40 °C over 2 min. The resulting solution was stirred 5 h at -20 °C. Quenched via the addition of saturated aqueous ammonium chloride (2.5 L). Extracted with EtOAc (3 x 2 L). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by eluting through a silica gel column with a 1:20 EtOAc/PE solvent system. This resulted in 45 g (73%) of methyl 2,2-dimethyl-4-oxocyclohexanecarboxylate as a yellow oil. MS: [M + H]+ *m/z* 185. ^1H NMR (600 MHz, $CDCl_3$) δ 3.49 (s, 3H), 2.43 - 2.40 (m, 1H), 2.35 - 2.29 (m, 1H), 2.21 - 2.17 (m, 1H), 2.11 - 2.04 (m, 1H), 2.00 - 1.96 (m, 1H), 1.91 - 1.85 (m, 1H), 0.85 (s, 3H), 0.77 (s, 3H).

INTERMEDIATE 25: Racemic *cis*-methyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate

Step 1: *n*-Butyllithium (2.2 mL, 5.5 mmol, 2.5 M solution in hexanes) was added dropwise over 12 minutes to a solution of thiazole (0.515 g, 6.05 mmol) in tetrahydrofuran (15 mL) at -78 °C. After 30 minutes, the opaque yellow suspension was transferred over 5 minutes via a dry ice-cooled cannula to a solution of **INTERMEDIATE 24** (1.013 g, 5.5 mmol) in tetrahydrofuran (15 mL) at -78 °C. The resulting yellow solution was kept at -78 °C for 1 hour, moved to a 0 °C bath for 15 minutes, and then cooled back to -78 °C. Aqueous saturated ammonium chloride solution (10 mL) was added and the mixture was allowed to warm to room temperature. The biphasic mixture was partitioned between ethyl acetate (50 mL) and water (5 mL); the layers were separated and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel chromatography (Biotage 100g SNAP column, 90:10 to 65:35 hexane:ethyl acetate) to afford racemic *cis*-methyl 4-hydroxy-2,2-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate as a white solid (1.08 g, 73% yield). MS APCI: $[M + H]^+$ *m/z* 270.1.

Step 2: To a solution of the product of Step 1 (0.35 g, 1.3 mmol) in *N*,*N*-dimethylformamide (1.9 mL) was added *N*-bromosuccinimide (0.254 g, 1.429 mmol). After three hours an additional portion of *N*-bromosuccinimide (0.046 g, 0.258 mmol) was added. After an additional hour, the reaction mixture was partitioned between ethyl acetate (25 mL), aqueous saturated sodium thiosulfate (10 mL), and water (5 mL). The layers were separated, and the organic layer was washed with water (3 x 5 mL) and brine (10 mL), dried over sodium sulfate, filtered, and concentrated. The crude reaction was purified via silica gel chromatography (Biotage 100g SNAP column, 95:5 to 75:25 hexane:ethyl acetate) to afford racemic *cis*-methyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate as a white solid (286.8 mg, 63% yield). MS APCI: $[M + H]^+$ *m/z* 348.0, 350.0. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (s, 1 H); 3.69 (s, 3 H); 2.45 (s, 1 H); 2.36 (m, 1 H); 2.21 (m, 1 H); 1.94 (m, 3 H); 1.75 (m, 2 H); 1.19 (s, 3 H); 1.06 (s, 3 H).

INTERMEDIATE 26: 5-Bromo-2-(1-methoxycyclobutyl)-1,3-thiazole

Sodium hydride (60% dispersion in mineral oil) (47.0 mg, 1.175 mmol) was added to a 0 °C solution of **Intermediate 1** (250 mg, 1.068 mmol) in DMF (3 mL) and THF (3 mL) and the mixture was allowed to react for 1 hour. Methyl iodide (0.080 ml, 1.281 mmol) was added and the mixture further reacted for 2 hours. The reaction mixture was poured in dilute aqueous NH_4Cl and extracted twice with diethyl ether. The organic fraction was concentrated and the residue was passed through a plug of silica eluting with 1:10 ethyl acetate:hexane to yield 2-bromo-5-(1-methoxycyclobutyl)-1,3-thiazole (225 mg, 85 %). ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 7.73 (s, 1 H); 3.19 (s, 3 H); 2.54-2.40 (m, 4 H); 1.92-1.82 (m, 2 H).

INTERMEDIATE 27: 2-chloro-4-ethylpyrimidine

Ethylmagnesium bromide (1.0 M in THF, 71.4 mL, 71.4 mmol) was added dropwise to a -78 °C solution of 2,4-dichloropyrimidine (10 g, 67.1 mmol) in THF (125 mL). After stirring for 1h, saturated aqueous NH_4Cl was added at -78°C and the reaction was allowed to come to room temperature with stirring. Then, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate and hexanes to provide 2-chloro-4-ethylpyrimidine (5.031g, 18.70 mmol, 27.9%) as a 53:47 regioisomeric mixture.

INTERMEDIATE 29: 2-chloro-4-cyclopropylpyrimidine

2,4-Dichloropyrimidine (15 g, 101 mmol), cyclopropylboronic acid (8.65 g, 101 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (8.22 g, 10.07 mmol), and potassium phosphate (53.4 g, 252 mmol) were combined in a 1L round-bottom flask. THF (503 mL) was added and the suspension was heated to reflux with stirring overnight. The reaction was then cooled to room temperature, concentrated to ~100 mL under reduced pressure, extracted with ethyl acetate, washed with

saturated aqueous $NaHCO_3$, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes to give 2-chloro-4-cyclopropylpyrimidine (10.124g, 58.3 mmol, 57.9%) as an 89:11 mixture of regioisomers.

INTERMEDIATE 32: 4-methyl-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine

To a flask containing 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.50 g, 6.85 mmol) and 2-chloro-4-methylpyrimidine (1.01 g, 7.87 mmol) were added dioxane (69 mL) and methanesulfonic acid (0.51 mL, 7.87 mmol). The reaction was heated at 100°C overnight. The reaction was then cooled to room temperature, diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield 4-methyl-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine (1.23 g, 3.95 mmol, 58% yield).

MS ESI: $[M + H]^+$ *m/z* 312. ^1H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.30 (d, *J* = 5.0, 1H), 7.98 (d, *J* = 8.0, 1H), 7.95 (s, 1H), 7.29-7.20 (m, 2H), 6.71 (d, *J* = 5.0, 1H), 2.33 (s, 3H), 1.28 (s, 12H).

INTERMEDIATE 35: 4-Ethyl-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine

Step 1: To a 1 L 3 neck flask containing 3-bromo-5-methylaniline (60 g, 290 mmol), bis(pinacolato)diboron (96 g, 377 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (8.3 g, 17.4 mmol), palladium dibenzylideneacetone (3.99 g, 4.35 mmol), and potassium acetate (42.7 g, 435 mmol) was added 1,4-dioxane (720 mL) that had been degassed via sparging with nitrogen for 30 minutes. After flushing the flask with nitrogen for 2 minutes, the reaction was heated to an internal temperature of 80 °C for 4 hours. Upon cooling, the reaction mixture was filtered through a pad of Celite, and then the Celite was washed with methyl *tert*-butyl ether (500 mL). The resulting solution was diluted with methyl *tert*-butyl ether (500 mL), pH 8 phosphate buffer (500 mL), and brine (500 mL). The layers were separated and the organic layer was washed with a half-saturated brine solution (1 L). The aqueous layers, which were kept separately, were sequentially back extracted with methy *tert*-butylether (500 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by silica gel flash chromatography (0-90% ethyl acetate/hexanes) and the resulting light orange solid was dried overnight under nitrogen to give 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (67.7 g, 255 mmol, 88% yield, 90% purity). MS ESI: $[M + H]^+$ *m/z* 234.1.

Step 2: A solution of 2-chloro-4-ethyl pyrimidine (0.98 g, 7.00 mmol), the product of Step 1 (1.794 g, 7.70 mmol), and methanesulfonic acid (0.50 mL, 7.70 mmol) in 1,4-dioxane (30 mL) was sealed in a 100 mL screw-top pressure flask and heated at 110 °C for 15 hours. The flask

was cooled, an additional portion of 2-chloro-4-ethyl pyrimidine (0.145 g, 1.05 mmol) was added, and the flask was resealed and heated for another 6.5 hours. The reaction mixture was cooled, diluted with ethyl acetate (70 mL), washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over sodium sulfate, filtered, and concentrated. The resulting reddish brown solid 4-ethyl-*N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidin-2-amine (3.44 g as a 80:20 w/w mixture with 1,4-dioxane) was used without further purification. MS ESI: $[M + H]^+$ *m/z* 340.1

INTERMEDIATE 36: *N*-[3-Cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] -4-methylpyrimidin-2-amine

Step 1: A solution of 3,5-dibromoaniline (2.93 g, 11.67 mmol), 2-chloro-4-methyl pyrimidine (1.5 g, 11.67 mmol), and acetic acid (0.701 mL, 12.25 mmol) in 1,4-dioxane (23.5 mL) was sealed in a pressure vessel under an argon atmosphere and heated at 120 °C for 17 hours. After being cooled to room temperature, the reaction mixture was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate solution (40 mL). The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. Silica gel flash chromatography (10% to 30% ethyl acetate/hexanes) afforded *N*-(3,5-dibromophenyl)-4-methylpyrimidin-2-amine (3.6 g, 9.97 mmol, 85% yield, 95% purity) as a light yellow solid. MS ESI: $[M + H]^+$ *m/z* 343.8.

Step 2: A mixture of 1,4-dioxane (40 mL) and aqueous sodium carbonate (2 M, 10.50 mL, 20.99 mmol) was sparged with argon for 15 minutes and then poured into a flask containing the product of Step 1 (3.6 g, 9.97 mmol, 85% yield, 95% purity) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.686 g, 0.840 mmol). Cyclopropyl boronic acid (1.037 g, 12.07 mmol) was added followed by a condenser and the whole system was placed under argon via five vacuum/argon flush cycles. The reaction mixture was heated to reflux for 18 hours and then cooled to room temperature and diluted with ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified via reverse phase HPLC (45-80% acetonitrile / water with a 0.10% TFA buffer). The fractions containing the desired product were diluted with ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to give *N*-(3-bromo-5-cyclopropylphenyl)-4-methylpyrimidin-2-amine (443.6 mg, 1.31 mmol, 13% yield) as a brown oil. MS ESI: $[M + H]^+$ *m/z* 306.0.

Step 3: A solution of the product of Step 2 (443.6 mg, 1.458 mmol), Bis(pinacoloato)diboron (407 mg, 1.604 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (119 mg, 0.146 mmol), and potassium acetate (429 mg, 4.37 mmol) in dimethylsulfoxide was heated under argon in a microwave for 10 minutes at 150 °C. The reaction mixture was diluted with diethyl ether (40 mL), ethyl acetate (40 mL), and saturated aqueous sodium bicarbonate solution (30 mL) and then filtered to remove any solids that did not dissolve. The layers were separated and the organic layer was washed

with water (3 x 25 mL) and brine (25 mL), dried over sodium sulfate, filtered, and concentrated. The resulting crude product was purified via silica gel chromatography (5-30% ethyl acetate/hexanes) to provide *N*-[3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] -4-methylpyrimidin-2-amine (186.1 mg, 0.53 mmol, 36% yield, about 75% pure) as a white solid. The material was used in subsequent steps in this crude form. MS ESI: $[M + H]^+$ *m/z* 352.2.

INTERMEDIATE 39: (4-Difluoromethyl-pyrimidin-2-yl)-[3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amine

Step 1: To a solution of difluoroacetic anhydride (50 g, 287 mmol) in CH_2Cl_2 (300 mL) cooled to -20 °C was added DMAP (0.351 g, 2.87 mmol) followed by the additon of ethyl vinyl ether (13.8 mL, 144 mmol) at such a rate that the internal temperature did not exceed -10 °C. When complete the flask was stirred at 0 °C for 12 h before slowly warming to room temperature over the next 6 h. Water along with CH_2Cl_2 were added, the layers separated and the organic washed sequentually with aqueous saturated $NaHCO_3$ and then brine. The organic layer was dried with $MgSO_4$, filtered, concentrated *in vacuo*. The residue was subsequentually taken up in EtOH (162 mL), immersed in an ice water bath and then urea (17.25 g, 287 mmol) followed by conc. HCl (43 mL) were added at such a rate that the internal temperature did not exceed 20 °C. When the addition was complete, the cooling bath was removed and the resulting mixture stirred for 18 h before concentration *in vacuo*. EtOH was added and the mixture concentrated a second time, then repeated 2x with EtOAc. The residue was diluted with EtOAc (100 mL), the heterogenous mixture stirred for 10 min and then the solvent decanted This was repeated twice more then the light brown solid was dried under vaccum for 48 h before dilution with phosphous oxychloride (215 mL, 2310 mmol). The resulting suspension was heated to 105 °C for 90 min during which time it was observed to become homogenous. The reaction mixture was cooled to room temperature, poured carefully into a 4 L cooled flask containing 2 L of ice and a temperature probe. The mixture was stirred for 1 h until the exotherm had ceased at which time the contents were transferred to a separatory funnel with additional CH_2Cl_2. The layers were cut, the aqueous layer extracted with CH_2Cl_2 (2x), then the combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* (200 Torr, 40 °C) to an orange oil. The product was placed under vacuum for 1 min to yield 2-chloro-4-difluoromethyl-pyrimidine (31 g, 62.5 wt% solution in CH_2Cl_2 by 1H NMR, 118 mmol). ^1H NMR (600 MHz, $CDCl_3$) δ 8.82 (d, J = 5.0, 1H), 7.57 (d, J = 5.0, 1H), 6.51 (t, J = 54.4, 1H).

Step 2: The product of Step 1 (4.75 g, 23 mmol) and 3-bromo-5-methylaniline (5.59 g, 30 mmol) were diluted with dioxane (33 mL) to which AcOH (1.32 mL, 23 mmol) was added. The resulting mixture was heated to reflux and kept stirring for 30 h after which it was recooled to room temperature, diluted with CH_2Cl_2 and absorbed on silica prior to purification by flash chromatography to afford *N*-(3-bromo-5-methylphenyl)-4-(difluoromethyl)pyrimidin-2-amine

(5.2 g, 16.6 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 4.9, 1H), 7.75 (s, 1H), 7.32 (s, 1H), 7.21 (s, 1H), 7.06 – 6.92 (m, 2H), 6.50 – 6.27 (m, 1H), 2.30 (s, 3H).

Step 3: The product of Step 2 (0.5 g, 1.6 mmol), bis(pinacolato)diboron (0.465 g, 1.83 mmol), potassium acetate (0.469 g, 4.78 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.065 g, 0.08 mmol) were diluted with degassed dioxane (3.5 mL) and heated to reflux for 2 h then recooled to room temperature. The mixture was diluted with CH_2Cl_2 and water was added. The layers were cut, the organic dried with $MgSO_4$, filtered and concentrated *in vacuo*, and the crude residue purified by flash chromatography to afford (4-difluoromethyl-pyrimidin-2-yl)-[3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amine (550 mg, 1.52 mmol) MS ESI: $[M + H]^+$ *m/z* 362.1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J = 4.1, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.45 (s, 1H), 7.35 (s, 1H), 6.94 (d, J = 4.2, 1H), 6.38 (t, J = 55.0, 1H), 2.36 (s, 3H), 1.33 (s, 12H).

INTERMEDIATE 41: *N*-[3-cyclopropyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine

To a flask were added *N*-[3-(bromomethyl)-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)-pyrimidin-2-amine (523 mg, 1.30 mmol), cyclopropyl boronic acid (336 mg, 3.91 mmol), potassium phosphate (968 mg, 4.56 mmol), $Pd(OAc)_2$ (15 mg, 0.07 mmol) and tricyclohexylphosphine (37 mg, 0.13 mmol). Degassed toluene (10 mL) and water (0.5 mL) were added and the solution was evacuated and then purged with argon 5 times. The mixture was then heated in the microwave at 130°C for 30 minutes. The reaction was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield *N*-[3-cyclopropyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (384 mg, 1.06 mmol, 81% yield). MS ESI: $[M + H]^+$ *m/z* 363. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H), 9.06 (s, 1H), 8.83 (d, J = 4.8, 1H), 8.23 (s, 1H), 7.92 (s, 1H), 7.41 (s, 1H), 7.28 (d, J = 4.9, 1H), 7.12 (s, 1H), 2.03 – 1.80 (m, 1H), 1.05 – 0.92 (m, 2H), 0.78 – 0.61 (m, 2H).

INTERMEDIATE 43: 4-cyclopropyl-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine

To a solution of 4-cyclopropyl-*N*-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidin-2-amine (750 mg, 2.14 mmol) in 2-methyl tetrahydrofuran (10.7 mL) were added 5-bromothiazole (406 mg, 2.35 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (87 mg, 0.11 mmol), and aqueous sodium carbonate (2 M, 2.14 mL). The reaction was sealed and purged with N_2 for 5 minutes. The reaction was stirred at 80 °C for 16h and cooled to room temperature. Water was added and extracted with EtOAc (3x). The combined organic layers were dried (magnesium sulfate), concentrated, and purified by flash chromatography to afford 4-cyclopropyl-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine (600 mg, 1.95 mmol, 91% yield) as an off-white solid. MS ESI: $[M + H]^+$ *m/z* 309.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (s, 1H), 9.06

(s, 1H), 8.26 (d, J = 5.0, 1H), 8.19 (s, 1H), 8.04 (s, 1H), 7.43 (s, 1H), 7.10 (s, 1H), 6.82 (d, J = 5.0, 1H), 2.29 (s, 3H), 2.00 (m, 1H), 1.17 – 0.93 (m, 4H).

INTERMEDIATE 44: 4-isopropyl-*N*-(3-methyl-5-(thiazol-5-yl)phenyl)pyrimidin-2-amine

To a solution of 4-isopropyl-*N*-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidin-2-amine (500 mg, 1.42 mmol) in 2-methyl tetrahydrofuran (7.1 mL) were added 5-bromothiazole (318 mg, 1.84 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (58 mg, 0.07 mmol), and aqueous sodium carbonate (2 M, 1.42 mL). The reaction was sealed and purged with N_2 for 5 minutes. The reaction was stirred at 80 °C for 16h and cooled to room temperature. Water was added and extracted with EtOAc (3x). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash chromatography to give 4-isopropyl-*N*-(3-methyl-5-(thiazol-5-yl)phenyl)pyrimidin-2-amine (366 mg, 1.18 mmol, 83% yield) as an off-white solid. MS ESI: $[M + H]^+$ *m/z* 311.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.05 (s, 1H), 8.38 (d, J = 4.7, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 6.77 (d, J = 5.1, 1H), 2.87 (m, 1H), 2.30 (s, 3H), 1.25 (d, J = 6.8, 6H).

INTERMEDIATE 46: 3-methyl-*N*-[3-(pentafluoroethyl)phenyl]-5-(1,3-thiazol-5-yl)aniline

To a solution of 2-chloro-4-(pentafluoroethyl)pyrimidine (61 mg, 0.26 mmol) and 3-methyl-5-(1,3-thiazol-5-yl)aniline (50 mg, 0.26 mmol) in degassed 1,4-dioxane (1.1 mL) were added Xantphos (23 mg, 0.039 mmol), $Pd(OAc)_2$ (5.9 mg, 0.026 mmol) and Cs_2CO_3 (172 mg, 0.53 mmol) and the reaction was heated to 100 °C for 30 minutes. After cooling, the reaction was partitioned between EtOAc (10 mL) and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted EtOAc (10 mL). The combined organic phases were washed with saturated aqueous sodium chloride (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification on silica (20-60% ethyl acetate in hexanes) afforded 3-methyl-*N*-[3-(pentafluoroethyl)phenyl]-5-(1,3-thiazol-5-yl)aniline (13 mg, 13%) as a colorless foam. MS ESI: $[M + H]^+$ *m/z* 387.0.

INTERMEDIATE 54: 2-chloro-4-(propan-2-yloxy)pyrimidine

To a solution of 2,4-dichloropyrimidine (5.0 g, 34 mmol) in 2-propanol (84 mL) was added Cs_2CO_3 (12 g, 37 mmol) and the mixture was stirred at rt for 16 h. The reaction was then heated to 65 °C for 3 h, after which time the reaction was filtered and concentrated. Purification on silica using a gradient solvent system of 0-10% EtOAc/Hexanes furnished 2-chloro-4-(propan-2-yloxy)pyrimidine (2.4 g, 41%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 5.7, 1H), 6.56 (d, J = 5.7, 1H), 5.38 (hept, J = 6.2, 1H), 1.34 (d, J = 6.2, 6H).

INTERMEDIATE 55: 4-*tert*-butyl-2-chloropyrimidine

To a dry flask containing 2-chloropyrimidine (1.0 g, 8.7 mmol) was added anhydrous Et_2O (8.7 mL) and the solution was cooled to -30 °C. *t*BuLi (1.7 M solution in *n*-pentane, 5.7 mL, 9.6

mmol) was added dropwise and the reaction was held at -30 °C for 30 min. The reaction was warmed to 0 °C and stirred at that temperature for 30 min, at which time the reaction was quenched by dropwise addition of a solution of acetic acid (0.60 mL, 10.5 mmol) in THF (3 mL) and water (1 mL). The reaction was maintained at 0 °C and a solution of DDQ (2.38 g, 10.5 mmol) in THF (8.7 mL) was added. After 15 minutes, NaOH (1 M, 1 mL) and water (10 mL) were added, and the dark reaction mixture was transferred to a separatory funnel containing EtOAc (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted once with EtOAc (50 mL). The combined organic phases were washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Adsorption of the oily black residue on silica, followed by chromatography on silica using a gradient solvent system of 5→30% EtOAc/hexanes furnished 4-*tert*-butyl-2-chloropyrimidine (1.00 g, 67%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 5.2, 1H), 7.24 (d, J = 5.2, 1H), 1.33 (s, 9H).

INTERMEDIATE 62: 2-chloro-4-(1-fluoroethyl)pyrimidine

To a solution of 1-(2-chloropyrimidin-4-yl)ethanol (150 mg, 0.950 mmol) in dichloromethane (3 mL) at 0 °C was added diethylaminosulfur trifluoride (183 mg, 1.14 mmol) dropwise and stirred for 3 hr. The solution was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated to dryness. Purification on silica gel by flash chromatography (0-50% EtOAc/hexanes) afforded 2-chloro-4-(1-fluoroethyl)pyrimidine (75 mg, 0.467 mmol, 49% yield) as a yellow oil. MS ESI: $[M+H]^+$ *m/z* 161.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.2, 1H), 7.46 (d, J = 4.2, 1H), 5.58 (dq, J = 6.7, 48, 1H), 1.74-1.57 (m, 3H).

INTERMEDIATE 70: 2-chloro-4-(difluoromethyl)pyrimidine

Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-chloropyrimidine-4-carbaldehyde (15.0 g, 104 mmol, 1.00 equiv, 98%) in dichloromethane (200 mL). This was followed by the addition of Bis[(2-methoxyethyl)amino]sulfur trifluoride (46.0 g, 208 mmol, 2.00 equiv, 100%) dropwise with stirring at 0°C over 30 min. The resulting solution was stirred for 2 h at 0°C, then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x100 mL of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with DCM/Pentane (2:1) to afford 2-chloro-4-(difluoromethyl)pyrimidine (2.38 g, 14% yield) as a yellow oil. GC-MS ESI: $[M]^+$ *m/z* 164. ^{1}H-NMR (300MHz, $CDCl_3$): 8.87 (t, 1H), 7.61 (d, 1H), 6.55 (m, 1H). ^{19}F-NMR (300MHz, $CDCl_3$): -119.37

INTERMEDIATE 71: *tert*-butyl 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate

Step 1: To a flask containing THF (82 mL) was added isopropylmagnesium chloride/lithium chloride (1.2 M in THF, 37.7 mL, 45 mmol). A solution of thiazole (3.5 g, 41 mmol) in THF (20 mL) was added slowly. The reaction was stirred for one hour. A solution of *tert*-butyl 4-oxocyclohexanecarboxylate (12.23 g, 62 mmol) in THF (20 mL) was added and the reaction was stirred for 3 hours. The reaction was then quenched slowly with saturated ammonium chloride and diluted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield *tert*-butyl 4-hydroxy-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (9.25 g, 33 mmol, 79% yield). MS ESI: $[M + H]^+$ *m/z* 284.1.

Step 2: To a flask containing the product of Step 1 (9.25 g, 33 mmol) was added DMF (36 mL) and then *n*-bromosuccinimide (6.97 g, 32 mmol). The reaction was allowed to stir until complete by LCMS. The reaction was diluted with water and ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield *tert*-butyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexane-carboxylate (9.24 g, 25.5 mmol, 78% yield). MS ESI: $[M + H]^+$ *m/z* 364.0.

Step 3: To a flask containing 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.6 g, 6.96 mmol), the product of Step 2 (2.52 g, 6.96 mmol), dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (0.33 g, 0.70 mmol), $Pd_2(dba)_3$ (0.32 g, 0.35 mmol), cesium carbonate (6.80 g, 20.9 mmol) was added a degassed mixture of dioxane (23 mL) and water (2.3 mL). The solution was evacuated and then purged with argon 5 times and then heated at 100°C overnight. The reaction was then cooled to room temperature, diluted with ethyl aceate, washed with aqueous saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield *tert*-butyl 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 389.

INTERMEDIATE 72: ethyl 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2-methylcyclohexanecarboxylate

To a round bottom flask containing 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (402 mg, 1.7 mmol), ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2-methylcyclohexanecarboxylate (400 mg, 1.1 mmol), $Pd_2(dba)_3$ (105 mg, 0.11 mmol), X-phos (55 mg, 0.11 mmol) and Cs_2CO_3 (1.12 g, 3.45 mmol) was added 4.3 mL of degassed 10:1 1,4 dioxane/H_2O. The reaction was heated to 100 °C for 16 h, then cooled and partitioned between EtOAc (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The layers were separated and the aqueous phase was extracted once with EtOAc (50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the resulting residue on silica furnished ethyl 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2-methylcyclohexanecarboxylate (344 mg, 80%) as a colorless foam. MS ESI: $[M + H]^+$ *m/z* 375.2.

INTERMEDIATE 74: *cis*-methyl-4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylate

cis-Methyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (1.372 g, 3.94 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.918 g, 3.94 mmol), cesium carbonate (3.85 g, 11.82 mmol), X-Phos (0.188 g, 0.394 mmol) and $Pd_2(dba)_3$ (0.180 g, 0.197 mmol) were placed in a flask and evacuated / purged with N_2 three times. Dioxane (13 mL) and water (1.3 mL) were degassed by undersurface N_2 bubbling and added to the reaction vessel. The resulting reaction mixture was stirred at 100 °C for 16 hrs and then diluted with EtOAc (25 mL), washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2% to 12% EtOAc in hexanes) to give *cis*-methyl-4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (1.33 g, 3.54 mmol, 90 % yield) as an orange foam. MS ESI: $[M + H]^+$ *m/z* 375.1. ^1H NMR (500 MHz, CD_3OD) δ 7.80 (s, 1H), 6.78-6.74 (m, 2H), 6.53 (br s, 1H), 3.68 (s, 3H), 2.45-2.36 (m, 2H), 2.25-2.12 (m, 4H), 2.01-1.94 (m, 2H), 1.76-1.62 (m, 2H), 1.19 (s, 3H), 1.04 (s, 3H).

INTERMEDIATE 75: 8-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

Step 1: Thiazole (25.0 mL, 352 mmol) was diluted with THF (300 mL) and cooled to -78 °C. *n*-BuLi (220 mL, 352 mmol) was added at such a rate that the internal temperature did not exceed -65 C. A yellow slurry formed and the addition took 40 min. The reaction was aged for 20 min then 1,4-dioxaspiro[4.5]decan-8-one (50 g, 320 mmol) was added as a solution in THF (420 mL) dropwise via addition funnel. After 2 h, the reaction was quenched with water, the cooling bath removed and the mixture stirred until the internal temperature reached 0 °C. The mixture was diluted with EtOAc and the layers were separated followed by extraction of the aqueous portion with EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to a viscous orange oil. EtOAc was added and concentrated to 100 mL. Hexanes was added dropwise via an addition funnel. The mixture was stirred for 1 h then cooled to -10 °C and filtered. The white cake was washed with hexanes (2x) then dried under a nitrogen bag to afford 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (66 g, 85%) as a white solid.

Step 2: The product of Step 1 (60.5 g, 251 mmol) was diluted with DMF (365 mL). *N*-bromosuccinimide (49.1 g, 276 mmol) was added, and the solution was heated to 50 °C and stirred for 2h. The reaction was removed from heat and cooled to 45 °C and H_2O (600 mL) containing 15.8 g Na_2SO_3 was added dropwise affording a solid. The mixture was stirred at room temperature for 1 h, then filtered and washed 2x with H_2O (300 mL). The cake was dried overnight under a nitrogen bag to afford 8-(5-bromo-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (68.2 g, 85%) as a white solid.

Step 3: 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.00 g, 8.58 mmol), the product of Step 2 (2.75 g, 8.58 mmol), X-Phos (0.409 g, 0.858 mmol), cesium carbonate (8.39 g, 25.7 mmol), and $Pd_2(dba)_3$ (0.393 g, 0.429 mmol) were placed in a flask flushed with Argon. Degassed Dioxane (30 ml) and Water (3 mL) were added and the reaction was heated to 100 °C for 40 h. The reaction was then cooled to room temperature, quenched with saturated aqueous sodium bicarbonate and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash chromatography (40%-100% EtOAc:hexanes) afforded 8-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (1.93 g, 65%) as a brown foam. MS ESI: $[M + H]^+$ *m/z* 347.

INTERMEDIATE 77: 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2,3-trimethylcyclohexanecarboxylic acid

Lithium diisopropylamide (5110 µl, 9.20 mmol) was added to a -78 °C solution of 3-methyl-5-(1,3-thiazol-5-yl)aniline (500 mg, 2.63 mmol) in THF (7 mL). The reaction was allowed to warm to -60 °C while aging for 30 min. The solution was cooled to -78 °C and 2,2,3-trimethyl-4-oxocyclohexanecarboxylic acid (600 mg, 3.26 mmol) in THF (6 mL) was added portionwise, maintaining an internal temperature below -65 °C. After 5 min at -78 °C the reaction was warmed to room temperature, diluted with EtOAc and washed with aqueous saturated ammonium chloride (3x). The combined aqueous portion was extracted with 10% IPA:$CHCl_3$ (3x). The combined organic layers were dried under reduced pressure to yield 4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2,3-trimethylcyclohexanecarboxylic acid (121 mg, 12%) as a yellow oil. MS ESI: $[M + H]^+$ *m/z* 375.

INTERMEDIATE 78: Cis-1-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol

Step 1: Thiazole (25.02 mL, 352 mmol) was diluted with THF (300 mL) and cooled to -78°C. *n*-BuLi (1.6 M, 220 mL, 532 mmol) was added at such a rate that the internal temperature did not exceed -65°C. The mixture was aged for 20 min, then 1,4-dioxaspiro[4.5]decan-8-one (50g, 320 mmol) was added as a solution in THF (420 mL) drop wise via addition funnel. The mixture was stirred for 2 h and then quenched with water. The flask was removed from the cooling bath and stirred until it reached 0°C. The mixture was transferred to a separatory funnel with EtOAc and brine and then extracted with EtOAc. The combined organics were dried with $MgSO_4$, filtered and concentrated to an orange viscous oil. The oil was diluted with EtOAc and concentrated to ~100 mL. A stir bar was added to the flask and hexanes was added drop wise via addition funnel. The mixture was stirred for 1 h then cooled to -10°C and filtered. The filtrate was washed with hexanes (2x) and dried to afforded 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (66 g, 274 mmol, 85% yield).

Step 2: The product of Step 1 (60.5 g, 251 mmol) was diluted with DMF (5 mL). To this solution, NBS (49.1 g, 276 mmol) was added. The reaction was heated to 50°C for 2 h. The reaction was cooled to 45°C and H_2O (600 mL) containing Na_2SO_3 (15.8 g, 125 mmol) was added drop wise. The reaction was stirred at room temperature for 1 h then filtered and washed with H_2O (2x, 300 mL). The filtrate was dried under nitrogen to afford 8-(5-bromo-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (68.15 g, 213 mmol, 85% yield).

Step 3: The product of Step 2 (15 g, 46.8 mmol) was diluted with THF (10 mL). HCl (6 N, 78 mL) was added and stirred at 60°C for 3 h. The reaction was cooled to RT and NaOH (6 N, 78 mL) was added. The reaction was diluted with EtOAc. The layers were separated and the aqueous layer back extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was diluted with EtOAc to transfer and concentrated to ~20 mL where hexanes (60 mL) was added drop wise. The slurry was cooled to room temperature, stirred for 1 h then filtered, washed with hexanes (2 x 15 mL) and dried to afford 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexanone (11.25 g, 40.8 mmol, 87% yield).

Step 4: The product of Step 3 (6.5 g, 23.54 mmol) was diluted with THF (10 mL) then cooled to -76°C. $LiBH_4$ (2M in THF, 14.1 mL, 28.2 mmol) was added drop wise, keeping internal temp < -75°C. The reaction was stirred for 1 h and quenched with aqueous saturated NH_4Cl. The reaction was diluted with EtOAc. The layers were separated and the aqueous layer was back extracted with EtOAc (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography and drying under high vacuum afforded *cis*-1-(5-bromo-1,3-thiazol-2-yl)cyclohexane-1,4-diol (5.2 g, 18.69 mmol, 79% yield) as a white solid.

Step 5: A vial was charged with 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.84 g, 3.60 mmol), the product of Step 4 (1.002 g, 3.60 mmol), cesium carbonate (3.52 g, 10.81 mmol), $Pd_2(dba)_3$ (0.165 g, 0.180 mmol), x-phos(0.172 g, 0.360 mmol), dioxane (14.62 ml) and water (1.462 ml). The mixture was reacted under Argon at 110°C for 5 hours. The reaction was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with aqueous saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica (0-20% MeOH/DCM) to afford cis-1-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol (871.5 mg, 2.86 mmol, 79 % yield). MS ESI: $[M + H]^+$ *m/z* 305.1.

INTERMEDIATE 80: 4-(5-Bromo-thiazol-2-yl)-4-hydroxy-*trans*-2-methyl-cyclohexanecarboxylic acid methyl ester

Step 1: To a cooled (-78 °C) solution of *trans*-2-methyl-4-oxo-cyclohexanecarboxylic acid methyl ester (13 g, 76 mmol) and thiazole (10.9 mL, 153 mmol) in THF (130 mL) was added *n*BuLi (2.5 M in Hex, 30.6 mL, 76 mmol) dropwise at such a rate that the internal temperature was maintained < -70 °C. The reaction mixture was stirred for 30 min, MeOH (3.1 mL, 76 mmol) was introduced, and the reaction warmed to room temperature where it was diluted with water and EtOAc. The layers were separated; the organic layer dried with $MgSO_4$, filtered and

adsorbed to silica gel by concentrating *in vacuo*. The crude residue was purified by flash chromatography to afford *trans*-4-hydroxy-*trans*-2-methyl-4-thiazol-2-yl-cyclohexanecarboxylic acid methyl ester (4.1 g, 16 mmol) along with the other diastereomer (7.0g, 27 mmol).

Step 2: To a solution of the product of Step 1 (4.1 g, 16 mmol) in DMF (30 mL) was added NBS (3.43 g, 19.3 mmol). After the initial exotherm had subsided the reaction mixture was heated to 50 °C and stirred for 1 h. It was then cooled to room temperature and water (280 mL containing 7 g of sodium sulfite) was added followed by EtOAc. The layers were cut and the aqueous layer was extracted EtOAc (2x). The combined organics were washed with H_2O, dried with $MgSO_4$, filtered and adsorbed to silica gel by concentration *in vacuo*. The crude residue was purified by flash chromatography to afford 4-(5-bromo-thiazol-2-yl)-*trans*-4-hydroxy-*trans*-2-methyl-cyclohexanecarboxylic acid methyl ester (4.75 g, 16.1 mmol), MS ESI: $[M + H]^+$ *m/z* 333.9.

INTERMEDIATE 81: propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6 dimethylcyclohexanecarboxylate

Step 1: Propan-2-yl 2,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate (20 g, 95.1 mmol) was prepared according to a literature procedure (*J. Org. Chem.* **2007**, *72(4)*, 1458-1453) using isopropyl acetoacetate in place of ethyl acetoacetate and diluted with EtOH (300 mL). To the resulting solution under a nitrogen blanket was added 5% Pd/C (0.8 g) after which the vessel was shaken under an initial hydrogen pressure of 50 psi for 2 h. The reaction contents were then filtered through celite using additional EtOH, concentrated *in vacuo* and purified by flash chromatography to afford propan-2-yl 2,6-dimethyl-4-oxocyclohexanecarboxylate (5.2 g, 24.5 mmol).

Step 2: The product of Step 1 (5.2 g, 24.5 mmol) was diluted with THF (50 mL) to which thiazole (2.63 mL, 36.7 mmol) was added. The resulting solution was cooled to -78 °C and *n*BuLi (2.5 M in Hex, 10.3 mL, 25.7 mmol) was added dropwise at such a rate to keep the internal temperature < -65 °C. When the addition was completed, the reaction mixture was stirred for a further 1 h then quenched by the addition of water and brought to room temperature. EtOAc was added, the layers separated and the organic layer was dried with $MgSO_4$, filtered, concentrated *in vacuo* and the crude residue purified by flash chromatography to afford propan-2-yl- 4-hydroxy-2,6-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (2.0 g, 6.7 mmol).

Step 3: To a solution of the product of Step 2 (2.0 g, 6.7 mmol) in DMF (16 mL) was added NBS (1.38 g, 7.73 mmol) and the resulting solution heated to 55 °C. After 60 min the reaction was cooled and a solution of sodium sulfite (500 mg) in water (30 mL) was added followed by EtOAc. The layers were separated, the aqueous layer was back extracted with EtOAc (2x). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6 dimethylcyclohexanecarboxylate (2.2 g, 5.85 mmol) MS ESI: $[M + H]^+$ *m/z* 375.9.

INTERMEDIATE 82: propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6 dimethylcyclohexanecarboxylate

Step 1: Propan-2-yl 2,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate (20 g, 95.1 mmol) was prepared according to a literature procedure (*J. Org. Chem.* **2007**, *72(4)*, 1458-1453) using isopropyl acetoacetate in place of ethyl acetoacetate and diluted with EtOH (300 mL). To the resulting solution under a nitrogen blanket was added 5% Pd/C (0.8 g) after which the vessel was shaken under an initial hydrogen pressure of 50 psi for 2 h. The reaction contents were then filtered through celite using additional EtOH, concentrated *in vacuo* and purified by flash chromatography to afford propan-2-yl 2,6-dimethyl-4-oxocyclohexanecarboxylate (6.4 g, 30.1 mmol).

Step 2: The product of Step 1 (6.4 g, 30.1 mmol) was diluted with THF (65 mL) to which thiazole (3.24 mL, 45.2 mmol) was added. The resulting solution was cooled to -78 °C and *n*BuLi (2.5 M in Hex, 12.7 mL, 31.7 mmol) was added dropwise at such a rate to keep the internal temperature < -65 °C. When the addition was completed, the reaction mixture was stirred for a further 1 h then quenched by the addition of water and brought to room temperature. EtOAc was added, the layers separated and the organic layer was dried with $MgSO_4$, filtered, concentrated *in vacuo* and the crude residue purified by flash chromatography to afford all-*cis*-propan-2-yl- 4-hydroxy-2,6-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (4.45 g, 15.0 mmol).

Step 3: To a solution of all-*cis*-propan-2-yl- 4-hydroxy-2,6-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (4.4 g, 14.8 mmol) in DMF (34 mL) was added NBS (3.03 g, 17.0 mmol) and the resulting solution heated to 55 °C. After 60 min the reaction was cooled and a solution of sodium sulfite (500 mg) in water (30 mL) was added followed by EtOAc. The layers were separated and the aqueous layer was back extracted with EtOAc (2x). The combined organics were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to give impure product. The product was swirled up in some hexanes, filtered and washed with more hexanes to afford all-*cis*-propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6 dimethylcyclohexanecarboxylate (2.4 g, 6.38 mmol) MS ESI: $[M + H]^+$ *m/z* 375.9.

INTERMEDIATE 84(a): ethyl 4-hydroxy-3-methyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate

INTERMEDIATE 84(b): ethyl 4-hydroxy-3,5-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate

INTERMEDIATE 84(c): ethyl 4-hydroxy-3,3-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate

Step 1: Lithium bis(trimethylsilyl)amide (41.1 ml, 41.1 mmol) was added to a -78 °C solution of ethyl 4-oxocyclohexanecarboxylate (7 g, 41.1 mmol) in THF (153 ml) making sure that the temperature never exceeded -70 °C. After the addition, the reaction was aged for 30 min before

slowly adding iodomethane (15 ml, 240 mmol). The reaction was aged below -70 °C for 10 min before slowly warming to room temperature over the course of 1 h. The reaction was then heated to 50 °C for 5 h. The heating source was removed, and the reaction was aged at rt for 14 h. The solution was mixed with water and extracted three times with EtOAc. The combined organic layer was dried under reduced pressure to obtain a dark red oil (9 g). The crude product was used directly in the next step without further purification.

Step 2: The crude dark red oil (9 g) from the previous step was mixed with thiazole (4.41 mL, 61.7 mmol) in THF (150 mL) and cooled to -78 °C. *n*-Butyllithium (2.5 M, 16.46 ml, 41.1 mmol) was added, and the solution was maintained at -78 °C for 1 h, then allowed to warm to rt. The reaction was quenched with water and extracted three times with CH_2Cl_2. The combined organic layer was dried under reduced pressure and purified by silica gel column chromatography (5-100% EtOAc:Hexanes) to give ethyl 4-hydroxy-3-methyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (2.69 g, 24%) as a brown oil and a mixture of ethyl 4-hydroxy-3,5-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate and ethyl 4-hydroxy-3,3-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (1.09 g, 9%) as a brown oil. MS ESI: $[M + H]^+$ *m/z* 270 (for **84a**) + 284 (for **84 b/c**)

INTERMEDIATE 85: ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3-methylcyclohexanecarboxylate

N-bromosuccinimide (2222 g, 12.48 mmol) was added to solution of **Intermediate 84(a)** (2.69 g, 9.99 mmol) in DMF (10.51 ml). The reaction was aged at room temperature for 2 h. The reaction was then quenched with aqueous saturated sodium bicarbonate and mixed with water. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were concentrated under reduced pressure and purified by silica gel flash chromatography (0-30% EtOAc:Hexanes) to give ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3-methylcyclohexanecarboxylate (2.27 g, 65%) as a yellow oil. MS ESI: $[M + H]^+$ *m/z* 348, 350.

INTERMEDIATE 86(a): ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,5-dimethylcyclohexanecarboxylate

INTERMEDIATE 86(b): ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,3-dimethylcyclohexanecarboxylate

N-bromosuccinimide (1.01 g, 5.64 mmol) was added to solution of **Intermediate 84(b)** and **Intermediate 84(c)** (1.09 g, 3.85 mmol) in DMF (5.94 ml). The reaction was aged at rt for 2 h and then quenched with aqueous saturated sodium bicarbonate and mixed with water. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography (0-40% Et_2O:Heptane) to give ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,5-dimethylcyclohexanecarboxylate and ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,3-dimethylcyclohexanecarboxylate (1.04 g, 75%) as a yellow oil. MS ESI: $[M + H]^+$ *m/z* 362, 364. 240 mg of this material was further purified using

chiral HPLC (5% EtOH:Heptane) to give ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,5-dimethylcyclohexanecarboxylate (71 mg, 30%) (MS ESI: $[M + H]^+$ *m/z* 362, 364) as a yellow oil and ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-3,3-dimethylcyclohexanecarboxylate (110 mg, 46%) (MS ESI: $[M + H]^+$ *m/z* 362, 364) as a yellow oil.

INTERMEDIATE 90: 4-(5-Bromo-thiazol-2-yl)-4-hydroxy-2-methyl-cyclohexanecarboxylic acid ethyl ester

Step 1: To a cooled (-78 °C) solution of *cis*-2-methyl-4-oxo-cyclohexanecarboxylic acid ethyl ester (22 g, 119 mmol) and thiazole (16.9 mL, 239 mmol) in THF (154 mL) was added *n*BuLi (1.6 M in Hex, 74.6 mL, 119 mmol) dropwise at such a rate that the internal temperature was maintained < -65 °C. The reaction mixture was stirred for 30 min, MeOH (4.83 mL, 119 mmol) was introduced, and the reaction warmed to room temperature where it was diluted with water and EtOAc. The layers were separated, the organic layer dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford 4-hydroxy-2-methyl-4-thiazol-2-yl-cyclohexanecarboxylic acid ethyl ester (21 g, 78 mmol).

Step 2: To a solution of the product of Step 1 (20 g, 74.3 mmol) in DMF (140 mL) was added NBS (15.9 g, 89 mmol). After the initial exotherm had subsided the reaction mixture was heated to 50 °C and stirred for 1 h. It was then cooled to room temperature and water (280 mL containing 7 g of sodium sulfite) was added followed by EtOAc. The layers were cut and the aqueous layer was back extracted with EtOAc (2x), and then the combined organics washed with H_2O. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford 4-(5-bromo-thiazol-2-yl)-4-hydroxy-2-methyl-cyclohexanecarboxylic acid ethyl ester (20 g, 57.4 mmol), MS ESI: $[M + H]^+$ *m/z* 347.9.

INTERMEDIATE 91: 4-(5-Bromo-thiazol-2-yl)-4-hydroxy-2,5-dimethyl-cyclohexanecarboxylic acid ethyl ester

Step 1: *cis*-2-Methyl-4-oxo-cclohexanecarboxylic acid ethyl ester (25 g, 136 mmol) was dissolved in tetrahydrofuran (250 mL) and cooled to -78 °C in a dry ice/acetone bath. Lithium hexamethyldisilazide (136 mL, 136 mmol) was added dropwise over one hour, keeping the internal temperature of the reaction under -70 °C. The reaction was aged for 30 minutes at -78 °C, and then methyl iodide (9.33 mL, 149 mmol) was added. The reaction was aged for 2 hours and then warmed to room temperature and stirred over night, at which point TLC analysis ($KMnO_4$staining) indicated complete consumption of the starting ester. The reaction was diluted with water (200 mL) and ethyl acetate (200 mL), and extracted with ethyl acetate (3 x 100 mL). The organic extracts were washed with brine (100mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo* to an orange residue. The crude mixture was taken up in tetrahydrofuran (250 mL) and cooled to -78°C with a dry ice/acetone bath. Thiazole (14.6 mL, 204 mmol) was added, followed by n-butyllithium (54.3 mL, 136 mmol) dropwise, keeping the internal temperature below -70 °C. The reaction was aged for 1.25 hours, then quenched with water (100

mL) and warmed to room temperature. The solution was extracted with ethyl acetate (3 x 100 mL) and the organic extracts were washed with brine (100mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography yielded a 4:6 mixture of two isomers of 4-hydroxy-2,5-dimethyl-4-thiazol-2-yl-cyclohexanecarboxylic acid ethyl ester (4.6 g, 16.1 mmol) and impure fractions that were purified a second time by flash chromatography which provided 4-hydroxy-2,5-dimethyl-4-thiazol-2-yl-cyclohexanecarboxylic acid ethyl ester (3.84 g (13.6 mmol) as a colorless oil. MS ESI: $[M + H]^+$ *m/z* 284.2.

Step 2: To a solution of the product of Step 1 (3.84 g, 8.54 mmol) in dimethylformamide (33.5 mL) was added *N*-bromosuccinimide (1.75 g, 9.82 mmol) and the solution stirred at 55°C for 3 hours. A solution of sodium sulfite (0.538 g, 4.27 mmol) in water (60 mL) was added dropwise to the reaction. The mixture was diluted with ethyl acetate (100 mL) and washed the organic extract with water (2 x 100 mL). The combined aqueous layers were back extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography provided a solid, which was triturated with hexanes, to give 4-(5-bromo-thiazol-2-yl)-4-hydroxy-2,5-dimethyl-cyclohexanecarboxylic acid ethyl ester (1.07 g, 2.95 mmol). MS ESI: $[M]^+$ *m/z* 362.1.

INTERMEDIATE 92: 4-(5-Bromo-thiazol-2-yl)-4-hydroxy-2,3-dimethyl-cyclohexanecarboxylic acid ethyl ester

To a DMF (15.6 mL) solution of a 4:6 mixture of two isomers of 4-hydroxy-2,5-dimethyl-4-thiazol-2-yl-cyclohexanecarboxylic acid ethyl ester (1.2 g, 4.03 mmol) was added NBS (0.83 g, 4.64 mmol). The resulting solution was heated to 55 °C for 1 h, then cooled to room temperature and a solution of sodium sulfite (0.54 g, 4.27 mmol) in water (30 mL) was added. The mixture was diluted with EtOAc and the layers separated. The aqueous layer was back extracted with EtOAc (2x). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford a 4:6 mixture of geometrical isomers of 4-(5-bromo-thiazol-2-yl)-4-hydroxy-2,3-dimethyl-cyclohexanecarboxylic acid ethyl ester (700 mg, 1.93 mmol). This was further separated by SFC to afford 4-(5-bromo-thiazol-2-yl)-4-hydroxy-2,3-dimethyl-cyclohexanecarboxylic acid ethyl ester as shown above. ^1H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 4.08 (m, 2H), 2.68 (q, J = 4.5 Hz, 1H), 2.34 (m, 1H), 2.26 (m, 1H), 2.20 (dd, J = 9.5, 6.7 Hz, 1H), 2.09 (td, J = 13.1, 2.5 Hz, 1H), 1.94 (dt, J = 13.1, 3.4, 1H), 1.85 (dq, J = 15.0, 3.6 Hz, 1H), 1.22 (t, J = 7.5 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H).

INTERMEDIATE 93: propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6-dimethylcyclohexanecarboxylate

Step 1: Propan-2-yl 2,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate (20 g, 95.1 mmol) was prepared according to a literature procedure (*J. Org. Chem.* **2007**, *72(4)*, 1458-1453) using isopropyl acetoacetate in place of ethyl acetoacetate and diluted with EtOH (300 mL). To the

resulting solution under a nitrogen blanket was added 5% Pd/C (0.8 g) after which the vessel was shaken under an initial hydrogen pressure of 50 psi for 2 h. The reaction contents were then filtered through celite using additional EtOH, concentrated *in vacuo* and purified by flash chromatography to afford propan-2-yl 2,6-dimethyl-4-oxocyclohexanecarboxylate (5.2 g, 24.5 mmol).

Step 2: The product of Step 1 (5.2 g, 24.5 mmol) was diluted with THF (50 mL) to which thiazole (2.63 mL, 36.7 mmol) was added. The resulting solution was cooled to -78 °C and *n*BuLi (2.5 M in Hex, 10.3 mL, 25.7 mmol) was added dropwise at such a rate to keep the internal temperature < -65 °C. When the addition was complete, the reaction mixture was stirred for a further 1 h then quenched by the addition of water and brought to room temperature. EtOAc was added, the layers separated and the organic dried with $MgSO_4$, filtered, concentrated *in vacuo* and the crude residue purified by flash chromatography to afford propan-2-yl- 4-hydroxy-2,6-dimethyl-4-(1,3-thiazol-2-yl)cyclohexanecarboxylate (1.4 g, 4.7 mmol).

Step 3: To a solution of the product of Step 2 (1.4 g, 4.7 mmol) in DMF (15 mL) was added NBS (0.963 g, 5.41 mmol) and the resulting solution heated to 55 °C. After 60 min the reaction was cooled and a solution of sodium sulfite (500 mg) in water (30 mL) was added followed by EtOAc. The layers were separated, the aqueous layer was back extracted twice with EtOAc and the combined organics were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford propan-2-yl-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,6 dimethylcyclohexanecarboxylate (1.04 g, 2.76 mmol) MS ESI: $[M + H]^+$ *m/z* 375.9.

INTERMEDIATE 94: *tert*-butyl (4R)-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxyazepane-1-carboxylate

Step 1: Azepan-4-one (40.0 g, 267 mmol) in DCM (320 mL) was treated with triethylamine (27.0 g, 225 mmol) and then Boc_2O (88.0 g, 401 mmol) was added slowly using an ice water bath to maintain the temperature at 10-20 °C. Additional triethylamine (27.0 g, 225 mmol) was then added and the solution was stirred for 12 hours. The reaction was then treated with saturated aqueous NH_4Cl (180 mL) and EtOAc (250 mL). The aqueous layer was extracted with EtOAc (150 mL) and the organic layer was concentrated and purified by flash chromatagraphy on silica gel to afford *tert*-butyl 4-oxoazepane-1-carboxylate as a viscous oil (45.9 g, 233 mmol).

Step 2: Thiazole (21.3 g, 250 mmol) in THF (160 mL) was cooled to -70 °C and then *n*-BuLi (100 mL, 250 mmol) was added slowly over 5 minutes, keeping the temperature at -60 °C or lower. The resulting slurry was stirred for 45 minutes at this temperature and then the product of Step 1 (48.55 g, 228 mmol) in THF (50 mL) was added dropwise, maintaining the temperture at -60 °C. The solution was stirred for one hour and then the cooling bath removed. At -20 °C, 2M HCl (114 mL) was added and upon warming to RT the homogeneous solution was diluted with EtOAc(150 mL). The phases were separated and the aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (150 mL),

brine (150 mL) and then concentrated to a thick syrup. This was dissolved in EtOAc (140 mL) and then treated with hexane (210 mL) and the slurry filtered to afford *tert*-butyl 4-hydroxy-4-(1,3-thiazol-2-yl)azepane-1-carboxylate as a white solid (68.0 g, 220 mmol) and the material was then subjected to chiral chromatography to afford tert-butyl (4R)-4-hydroxy-4-(1,3-thiazol-2-yl)azepane-1-carboxylate (14.5 g, 48,6 mmol).

Step 3: The product of Step 2 (14.5 g, 48,6 mmol) was dissolved in DMF (58 mL) and then treated with NBS (11.24 g, 63.2 mmol) and warmed to 40 °C for 3 hours. The reaction was quenched with Na_2SO_3 (3.0 g, 24.30 mmol) in H_2O (50 mL) and the solution was then extracted with EtOAc (100 mL), washed with brine (50 mL) and then chromatographed on silica gel to afford *tert*-butyl (4R)-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxyazepane-1-carboxylate (18.3 g, 46 mmol). MS ESI: $[M+H-t\text{Bu}]^+$ *m/z* 320.

INTERMEDIATE 95: ethyl *cis*-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylate

Step 1: Isopropylmagnesium chloride/lithium chloride complex (1.3 M, 119 mL, 154 mmol) was added to a flask and cooled to 0 °C and then diluted with 50mL THF. Thiazole (13.0 g, 154 mmol) was added over 30 minutes making sure the temperature did not exceed 5 °C. The orange slurry was stirred for 45 minutes and then cooled to -20 °C and ethyl 4-oxocyclohexane-carboxylate (25.0 g, 147 mmol) in THF (25 mL) was added and then stirred for 50 minutes. The solution was cooled to 5 °C and then quenched with HCl (2 M, 100 mL) and extracted with EtOAc (250 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ solution (100 mL), brine (100 mL), evaporated and purified by flash chromatography on silica gel to afford ethyl 4-hydroxy-4-(1,3-thiazol-2-yl)cyclohexanecarboylate as an oil (23.6g, 92 mmol).

Step 2: The product of Step 1 (23.5g, 92 mmol) was dissolved in DMF (94 mL) and then treated with NBS (19.66 g, 110 mmol) and stirred at RT for 10 hours. The reaction was then treated with Na_2SO_3 (5.8 g, 465 mmol) in H_2O (150 mL) and then extracted with EtOAc (100 mL) and the oil was purified by flash chromatography on silica gel to afford ethyl 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylate as an oil (31g, 77 mmol), which was subjected to chiral chromatography to afford ethyl *cis*-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexane-carboxylate as an oil (15g, 33 mmol). MS ESI: $[M+H]^+$ m/z 333.

INTERMEDIATE 96: 5-(5-bromo-1,3-thiazol-2-yl)-5-hydroxyazepan-2-one

Step 1: To a solution of 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (15.0 g, 62.2 mmol) in DMF (75 mL) was added NBS (6.9 g, 55 mmol) and the solution warmed to 45 °C for 8 hours. The solution was treated with Na_2SO_3(3.9 g, 31 mmol) in H_2O (150 mL) and the resulting slurry was filtered and washed with water (70 mL) to afford 8-(5-bromo-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol as a white solid (16.8 g, 52.5 mmol).

Step 2: The product of Step 1 (3.0 g, 9.4 mmol) was dissolved in 30mL of 1:1 THF:HCl (3N) and heated at 50 °C for 8 hours and the solution neutralized with solid $KHCO_3$ and then EtOAc (100 mL) and water (20 mL) were added. The aqueous layer was then extracted with EtOAc (50

mL) and the combined organic layers were washed with brine (50 mL), evaporated to a slurry which was treated with hexanes (20 mL). Filtration and drying afforded 4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexanone as a white solid (2.1g, 7.7 mmol).

Step 3: To the product of Step 2 (10 g, 36.2 mmol) in THF (60.0 mL) was added hydroxylaminehydrochloride (5.0 g, 72.4 mmol) in water (7.0 mL) and Na_2CO_3 (2 M, 36.2 mL) added. The solution was stirred for 30 minutes and the resulting slurry was heated to 50 °C for 8 hours and then allowed to cool to RT over 12 hours. To the slurry was added H_2O (240.0 mL). Slow filtration afforded 1-(5-bromo-1, 3-thiazol-2-yl) 4-hydroxyimino) cyclohexnanol as a white solid (10.15 g, 35 mmol).

Step 4: The product of Step 3 (10.0g, 34.3 mmol) was suspended in acetonitrile (75.0 mL) and then TsCl (7.2 g, 37.8 mmol) and DABCO (4.2 g, 37.8 mmol) were added, maintaining the temperature at 20 °C with an ice/water bath. The slurry was stirred for 5 hours and then H_2O (10.0 mL) added. The slurry was filtered slowly and washed with water. The liquors were concentrated and the residue dissolved with heating in MeOH (25 mL). Filtration afforded 5-(5-bromo-1,3-thiazol-2-yl)-5-hydroxyazepan-2-one as a white solid (4.0 g combined, 23 mmol) as a white solid. MS ESI: $[M+H]^+$ *m/z* 291.

INTERMEDIATE 100: methyl (*cis*)-4-oxo-2-(propan-2-yl)cyclohexanecarboxylate

Step 1: Methyl isobutyryl acetate (7.20 g, 49.9 mmol) and sodium methoxide (0.896 g, 4.14 mmol) were cooled to 0 °C. Methyl vinyl ketone (4.12 ml, 49.9 mmol) was added dropwise, and the solution was allowed to warm to rt and stirred 1 h at that temperature.

Acetic acid (0.249 ml, 4.34 mmol) was added, followed by a mixture of MeOH (6.75 ml):Water (750 µL), and finally a solution of pyrrolidine (0.349 ml, 4.21 mmol) in acetic acid (0.309 ml, 5.39 mmol). The resultant solution was heated to reflux (115 °C) for 2 h. The reaction was allowed to cool to room temperature and then diluted with Et_2O and water. The layers were separated and the aqueous portion extracted again with Et_2O (1x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 4-oxo-2-(propan-2-yl)cyclohex-2-ene-1-carboxylate (5.11 g, 52%) as a yellow oil, which was used in the subsequent step without further purification.

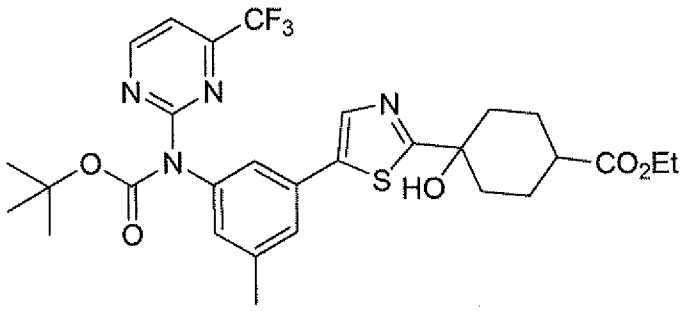
Step 2: The product of Step 1 (5.11 g, 26.0 mmol) was dissolved in MeOH (80 ml). Palladium on carbon (0.416 g, 0.391 mmol) was added, and the flask was fitted with a hydrogen balloon. The flask was evacuated and backfilled with hydrogen (3x) and stirred 15 h at room temperature. The reaction was then filtered through Celite and the celite was washed with EtOAc. The filtrate was concentrated *in vacuo*. Purification via silica gel flash chromatography (0-15% EtOAc:Hexanes) gave methyl (*cis*)-4-oxo-2-(propan-2-yl)cyclohexanecarboxylate (2.63 g, 51%) as a colorless oil.

INTERMEDIATE 101: methyl 2,2-dimethyl-4-oxocycloheptanecarboxylate

TMS-Diazomethane (5.97 ml, 11.94 mmol) was added to a stirred, cooled -30 °C mixture of methyl 2,2-dimethyl-4-oxocyclohexanecarboxylate (2 g, 10.86 mmol) and BF_3-OEt_2 (1.513 ml,

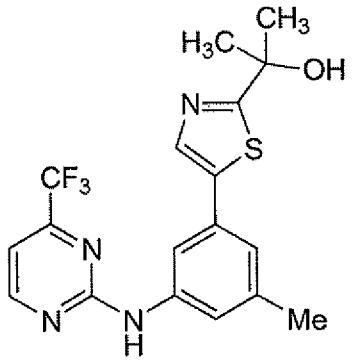
11.94 mmol) in CH_2Cl_2 (65.0 ml). The reaction was aged at -30 °C for 2 h. The reaction was then quenched with water and allowed to warm to room temperature. The mixture was extracted three times with CH_2Cl_2 and the combined organic layers were concentrated under reduced pressure. The remaining residue was purified by flash chromatography (0-100% EtOAc:Hexanes) to afford a mixture of regioisomers, including methyl 2,2-dimethyl-4-oxocycloheptanecarboxylate (992 mg, 18%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 – 3.57 (m, 3H), 2.76 (d, J = 12.9, 0.4H), 2.61 (ddd, J = 3.1, 8.0, 15.5, 0.6H), 2.55 – 2.27 (m, 4H), 1.96 – 1.50 (m, 4H), 0.95 (m, 6H).

INTERMEDIATE 119: Ethyl 4-[5-(3-{(*tert*-butoxycarbonyl)[4-(trifluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate



To ethyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (**Example 32,** 0.15 g, 0.29 mmol) in THF (1.4 mL) was added di-tert-butyl-dicarbonate (0.069 mg, 0.32 mmol), 4-dimethylaminopyridine (0.04 g, 0.03 mmol), and triethylamine (0.043 g, 0.43 mmol). The reaction was heated at 50 °C overnight. The reaction was cooled, diluted with dichloromethane and washed with water. The organic layer was extracted two more times with dichloromethane and the organic layers were combined, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography was used to give ethyl 4-[5-(3-{(*tert*-butoxycarbonyl)[4-(trifluoromethyl)-pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate (0.15 mg, 85% yield). MS ESI: $[M+H]^+$ *m/z* 607.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 5.5, 1H), 7.78 (s, 1H), 7.39 – 7.29 (m, 1H), 7.27 (d, J = 5.6, 1H), 7.19 (s, 1H), 7.02 (s, 1H), 4.31 – 3.95 (m, 2H), 2.64 – 2.49 (m, 1H), 2.37 (s, 3H), 2.30 – 2.18 (m, 1H), 2.13 – 1.87 (m, 6H), 1.87 – 1.74 (m, 1H), 1.49 (s, 9H), 1.26-1.23 (m, 4H). rhSYK activity = +

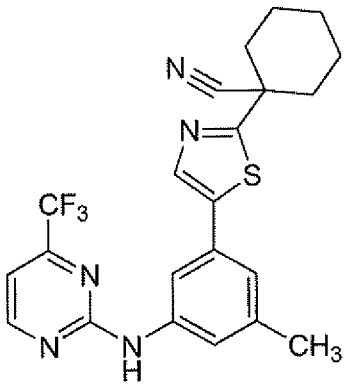
MODEL COMPOUND 1. 2-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]propan-2-ol



INTERMEDIATE 4 (100 mg, 0.297 mmol) in THF (1.5 mL) was added slowly to LDA (496 µL, 0.892 mmol) pre-cooled to -78 °C over 5 min with stirring. The reaction mixture was left to stir for 30 min and treated with acetone (32.7 µL, 0.446 mmol). After 1 h, the reaction mixture was treated with 5 mL sat NH_4Cl and allowed to warm to room temperature. The mixture was extracted with EtOAc, and the organic layer washed with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography to give 2-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]propan-2-ol (95 mg, 0.241 mmol, 81 % yield) as a colorless oil. APCI: $[M + H]^+$ *m/z* 395.0. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.95 (s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 6.03 (s, 1H), 2.31 (s, 3H), 1.51 (s, 6H). rhSYK activity = +++

EXAMPLE 1

1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]cyclohexanecarbonitrile



Step 1: To a solution of cyclohexanecarbonitrile (0.913 g, 8.36 mmol) in toluene (25 ml) at 0 °C was added sodium bis(trimethylsilyl)amide (1M solution in THF, 10.0 ml, 10.0 mmol) and the resulting mixture was stirred for 1 hr at 0 °C. 2-Chlorothiazole (1 g, 8.36 mmol) was then added dropwise as a solution in toluene (0.5 mL) over a period of 5 minutes and the resulting mixture was allowed to warm up from 0 °C to room temperature over 16 hrs. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (2x50 mL). The

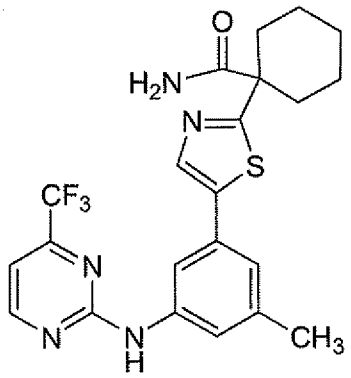
combined organic layers were washed with brine (60 mL, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (gradient elution 2% to 12% EtOAc in Hexanes) to afford 1-(1,3-thiazol-2-yl)cyclohexanecarbonitrile (686 mg, 3.57 mmol, 42.7 % yield) as a pale yellow oil which solidified upon standing. MS ESI: $[M + H]^+$ *m/z* 193.

Step 2: *N*-Bromosuccinimide (0.33 g, 1.87 mmol) was added to a solution of the product from Step 1 (300 mg, 1.56 mmol) in DMF (5 ml) and the resulting reaction mixture was stirred at room temperature for 2 hrs. 2 aliquots of *N*-bromosuccinimide (0.33 g, 1.87 mmol) were added over a period of 23 hrs before addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was then extracted with EtOAc (2x 20 mL) and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (gradient elution 7% to 60% EtOAc in Hexanes) to afford 1-(5-bromo-1,3-thiazol-2-yl)cyclohexanecarbonitrile (96 mg, 0.35 mmol, 22.7 % yield) as a pale yellow oil. MS ESI: $[M + H]^+$ *m/z* 272.

Step 3: *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (**INTERMEDIATE 3**, 134 mg, 0.35 mmol), the compound from Step 2 (96 mg, 0.35 mmol), cesium carbonate (346 mg, 1.06 mmol), X-Phos (16.9 mg, 0.035 mmol) and $Pd_2(dba)_3$ (16.2 mg, 0.018 mmol) were placed in a flask and evacuated / purged with N_2 for three times. Dioxane (1.5 mL) and water (0.15 mL) were degassed by undersurface N_2 bubbling and added to the reaction vessel. The resulting reaction mixture was stirred at 100 °C for 5 hrs and then diluted with EtOAc (5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (gradient elution 7% to 60% EtOAc in Hexanes) to give the title compound (128 mg, 0.289 mmol, 82 % yield) as an off white foam. MS ESI: $[M + H]^+$ *m/z* 444.1. ^1H NMR (500 MHz, CD_3-OD) δ 8.72 (d, *J* = 5.0, 1H), 8.06 (bs, 1H), 8.00 (s, 1H), 7.48 (bs, 1H), 7.16 (bs, 1H), 7.14 (d, *J* = 4.9, 1H), 2.41-2.37 (m, 5H), 2.06-2.00 (m, 2H), 1.94-1.89 (m, 2H), 1.85-1.73 (m, 3H), 1.40 (m, 1H). rhSYK activity = ++.

EXAMPLE 2

1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]cyclohexanecarboxamide

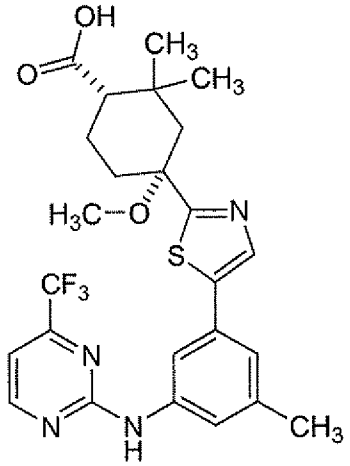


A mixture of 1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]cyclohexanecarbonitrile (45 mg, 0.10 mmol) and NaOH (1M in MeOH, 0.5 ml, 0.50 mmol) was heated at 100 °C in the microwave for 16 hrs. The mixture was brought to pH = 3 by addition of HCl (1.0 N in H_2O) and then partitioned between EtOAc (5 mL) and brine (5 mL). The organic layer was separated, dried (Na_2SO_4), filtered and the volatiles were removed under reduced pressure. The residue was purified by HPLC (gradient elution 40% to 100% CH_3CN in H_2O / 0.1% TFA, 20 mins, 20 ml/min) to give the title compound (4.0 mg, 8.67 μmol, 8.5 % yield) as a white solid.

MS ESI: $[M + H]^+$ *m/z* 462.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, *J* = 5.3, 1H), 7.97 (s, 2H), 7.46 (bs, 1H), 7.28 (d, *J* = 5.2, 1H), 7.20 (bs, 1H), 7.15 (bs, 2H), 2.31-2.24 (m, 5H), 2.00-1.94 (m, 2H), 1.51-1.41 (m, 5H), 1.33 (m, 1H). rhSYK activity = +++.

EXAMPLE 3

(1*S*,4*R*)-4-methoxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid



Step 1: A mixture of methyl *cis*-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylate (416 mg, 1.195 mmol) and iodomethane (112 μl, 1.792 mmol) in DMF (5500 μl) was cooled to 0 °C and aged while stirring for 10 min. Sodium hydride (47.8 mg, 1.195 mmol) was then added and the reaction aged at 0 °C for 5 min before warming to rt. The reaction was aged at rt for 2 h. The reaction was cooled to 0 °C and quenched with methanol. The mixture was warmed back to

room temperature, mixed with water, and extracted with CH_2Cl_2 (3X). The combined organic layers were dried under reduced pressure and purified by silica gel column chromatography (0-100% EtOAc:Hexanes) afforded methyl *cis*-4-(5-bromo-1,3-thiazol-2-yl)-4-methoxycyclohexanecarboxylate (306 mg, 71%) as a colorless oil. ESI: [M + H – MeOH]+ *m/z* 330, 332.

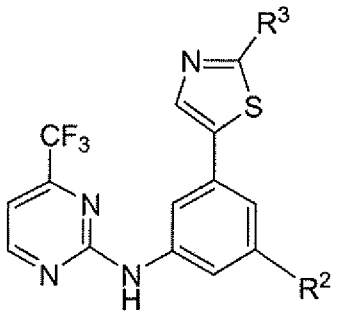
Step 2: *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (**INTERMEDIATE 3,** 320 mg, 0.845 mmol), the product of Step 1 (306 mg, 0.845 mmol), and sodium carbonate (845 µL, 1.689 mmol) in 2-Methyl THF (5631 µl) were degassed by sparging with Ar for 5 minutes. $PdCl_2(dppf)$-CH_2Cl_2Adduct (34.5 mg, 0.042 mmol) was added and the temperature increased to 85 °C. The reaction was aged for 5 hours. The cooled reaction was mixed with water and extracted with CH_2Cl_2 (3X). The organic layers were dried under reduced pressure. The crude product was purified by silica gel column chromatography (0-100% EtOAc:Hexanes) afforded methyl (1*S*,4*R*)-4-methoxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (156 mg, 29%) as a colorless oil. MS ESI: [M + H]+ *m/z* 535.

Step 3: Potassium hydroxide in methanol (3.0 mL, 3.0 mmol) was added to the product of Step 2 (150 mg, 0.23 mmol) and the reaction mixture heated to 65 °C for 110 h. The reaction mixture was cooled and then quenched with HCl (2N in H_2O). The mixture was filtered and washed with ~20 mL of water to obtain an off-white solid. The solid was dried under reduced pressure at 40 °C in a vacuum oven for 1.5 h to provide the title compound (95 mg, 79%) as a yellow solid. ESI: $[M + H]^+$ *m/z* 521. ^1H NMR (500 MHz, DMSO-d_6) δ 12.15 – 11.94 (m, 1H), 10.26 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.45 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.16 (s, 1H), 3.07 (s, 3H), 2.31 (s, 3H), 2.22 – 2.09 (m, 2H), 1.99 – 1.80 (m, 3H), 1.72 (d, *J* = 14.5, 1H), 1.62 (s, 1H), 1.07 (s, 3H), 1.01 (s, 3H). rhSYK activity = +++

The following compounds were prepared in an analogous manner to that described for Model Compound 1. Entries in this and all subsequent Tables without explicit reported stereochemistry (absolute or relative) are either single isomers of unknown configuration or a mixture of isomers. Indicators of relative stereochemistry (*cis* or *trans*) refer to the relative relationship of the corresponding substituents with the highest CIP priority respectively.

EXAMPLES 4B/4C/4D

TABLE 4B



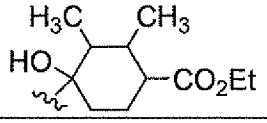
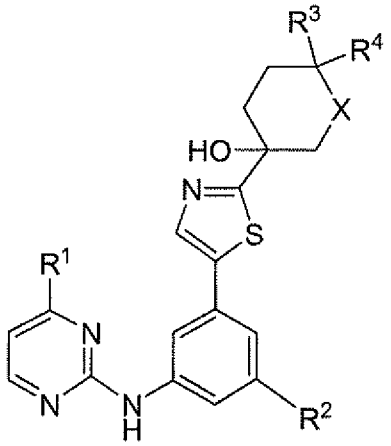
Ex.	R^2	R^3	rhSYK Activity	[M+H] + Obs'd	Form(s)
4B-1	CH_3	1-OH-c-Bu	+++	407.1	Free Base
4B-2	H	1-OH-2-CH_3-c-Pen	+++	421.3	Free Base
4B-3	H	1-OH-2-(CH_2CH_2CN)-c-Hex	++	474.2	Free Base
4B-4	CH_3		+++	535	Free Base

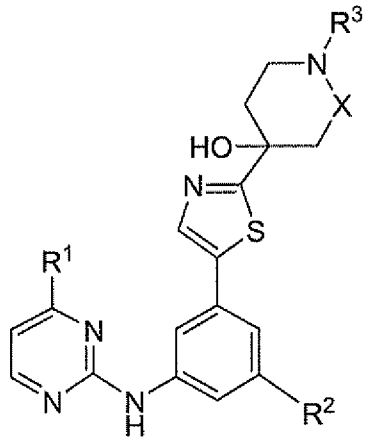
TABLE 4C



Ex.	R^1	X	R^3/R^4	rhSYK Activity	[M+H] + Obs'd	Form(s)
R^2 = H						
4C-1	CF_3	CH_2CH_2	H/H	+++	435.1	Free base
R^2 = CH_3						
4C-2	CH_3	CH_2	H/CH_2NH_2 (cis)	+++	410.2	TFA Salt
4C-3	CH_3	CH_2	H/CH_2NH_2 (trans)	+++	410.2	TFA Salt
4C-4	CF_3	CH_2	H/CH_2NH_2	+++, +++	464.2	Free Base TFA Salt
4C-5	CF_3	CH_2	H/$CH_2CH_2NH_2$	+++	478.2	TFA Salt
4C-6	CF_3	CH_2	H/CH_2OH (trans)	+++	465.2	Free Base
4C-7	CF_3	CH_2	H/CH_2OH	+++	465.2	Free Base
4C-8	CF_3	CH_2	H/CH_2OH (cis)	+++	465.2	Free Base
4C-9	CH_3	CH_2	H/CH_2OH	+++	411.2	Free Base
4C-10	CH_3	CH_2	NH_2/CO_2H	+++	440.0	TFA Salt
4C-11	CH_3	CH_2	CH_3/CH_2CO_2H (isomer 1)	+++	453.1	TFA Salt
4C-12	CH_3	CH_2	CH_3/CH_2CO_2H (isomer 2)	+++	453.1	TFA Salt
4C-14	CF_3	CH_2	H/CH_2CO_2H (cis)	+++	493.1	Free Base

4C-15	CF_3	CH_2	H/CH_2CO_2H (trans)	+++	493.1	Free Base
4C-17	CH_3	CH(i-Pr)	H/CO_2CH_3	+++	481.1	Free Base
4C-21	CF_3	$CH(CO_2Et)$	H/H	++	507.1, 507.2	Free Base
4C-22	CF_3	$C(CH_3)(CH_2CO_2H)$	H/H (1R, 3S)	+++	507.1	TFA Salt
4C-23	CF_3	$C(CH_3)(CH_2CO_2H)$	H/H (1R, 3R)	+++	507.1	TFA Salt
4C-25	CF_3	CH(i-Pr)	H/CO_2CH_3	++	535.0	Free Base
4C-26	CF_3	CH_2	H/$CH_2C(CH_3)_2CO_2H$	+++	535.2	TFA Salt
4C-33	CF_3	CH_2	H/$N(CH_3)_2$	+++	478	Formate Salt

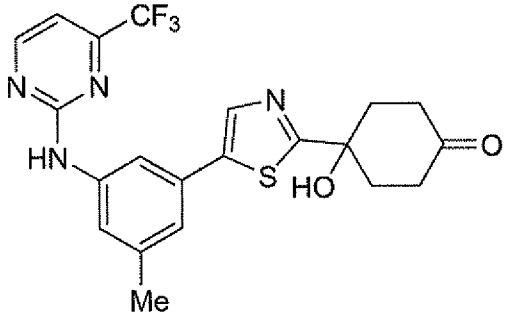
TABLE 4D



Ex.	R^1	R^2	X	R^3	rhSYK Activity	[M+H] + Obs'd	Form(s)
4D-1	CF_3	H	CH_2	$C(O)CH_3$	+++	464.3	Free Base
4D-2	CF_3	H	CH_2	CO_2Et	+++	494.1	Free Base
4D-3	CF_3	H	CH_2	i-Pr	++	464.1	Free Base
4D-4	CF_3	H	CH_2	C(O)Ph	+++	526.1	Free Base
4D-5	CH_3	CH_3	$CH_2C(O)$ (lactam formed)	H	+++	410.2	Free Base
4D-6	CF_3	CH_3	CH_2	$C(O)(CH_2)_3CO_2H$	+++	550.1	Formate Salt
4D-7	CF_3	CH_3	$CH(CO_2CH_3)$	$CO_2C(CH_3)_3$	++	594.1	Free Base
4D-8	CF_3	CH_3	$CH(CF_3)$	$CO_2C(CH_3)_3$	++	604.1	Free Base

EXAMPLE 7

4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanone

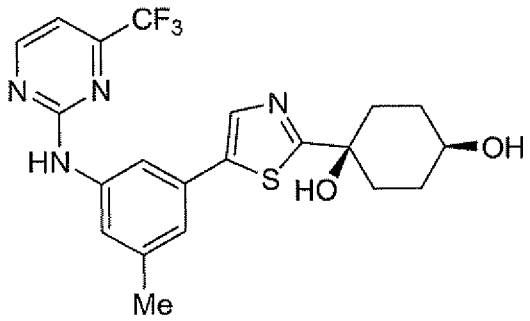


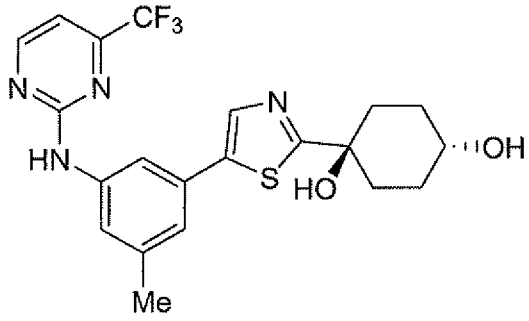
To a stirred solution of 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (prepared in a manner analogous of that described for Model Compound 1, 785 mg, 1.59 mmol) in THF (6 mL) was added HCl (6 M, 5.3 mL, 32 mmol) and the reaction was left to stir for 6 h. The mixture was brought to pH 8 with saturated aqueous sodium bicarbonate, extracted with ethyl acetate (x 3), and the combined organic portion was washed with saturated aqueous sodium bicarbonate. The solution was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to afford 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanone (625 mg, 1.39 mmol) as a white foam. APCI: $[M + H]^+$ *m/z* 449.1. ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.9, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 7.46 (s, 1H), 7.26 (s, 1H), 7.06 (s, 1H), 7.04 (d, *J* = 4.9, 1H), 2.92 – 2.82 (m, 2H), 2.49 – 2.29 (m, 6H), 2.38 (s, 3H). rhSYK activity = +++

EXAMPLES 8(1) AND 8(2)

cis-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexane-1,4-diol

trans-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexane-1,4-diol





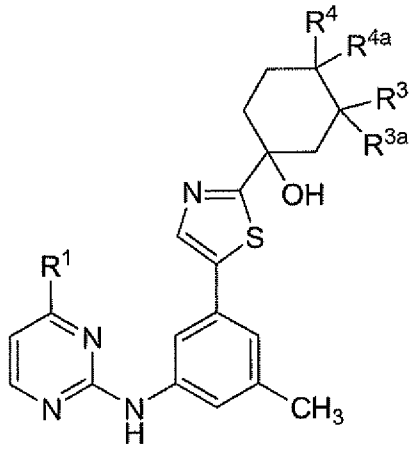
To a stirred solution of 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanone (500 mg, 1.115 mmol) in MeOH (11 mL) was added sodium borohydride (63.3 mg, 1.672 mmol) at -20 °C and the reaction was aged for 20 min. The mixture was treated with water and extracted with ethyl acetate. The combined organics were dried, filtered, concentrated, and purified by flash chromatography to afford *cis*-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol (250

mg, 0.56 mmol). APCI: $[M + H]^+$ *m/z* 451.1. ^1H NMR (600 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.9, 1H), 7.89 – 7.79 (m, 2H), 7.45 (s, 1H), 7.26 (s, 1H), 7.06 (s, 1H), 7.02 (d, *J* = 4.9, 1H), 3.81 – 3.72 (m, 1H), 2.98 (s, 1H), 2.37 (s, 3H), 2.11 – 1.72 (m, 8H). rhSYK activity = +++

trans-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexane-1,4-diol (40 mg, 0.09 mmol) APCI: $[M + H]^+$ *m/z* 451.1. ^1H NMR (600 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.9, 1H), 7.88 – 7.79 (m, 2H), 7.46 (s, 1H), 7.27 (s, 1H), 7.06 (s, 1H), 7.02 (d, *J* = 4.9, 1H), 3.67 (t, *J* = 6.3, 1H), 3.56 (m, 1H), 2.43 – 1.62 (m, 8H), 2.37 (s, 3H). rhSYK activity = +++

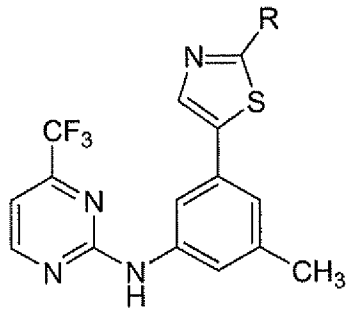
Compounds in the following Table(s) were prepared in an analogous manner of that described in Example 8(1)/8(2):

TABLE 8A

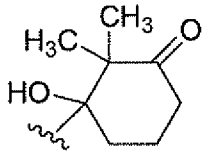
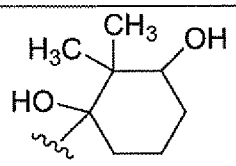


Example	R^1	R^3/R^{3a}	R^4/R^{4a}	rhSYK Activity	[M+H]+ Observed	Form(s)
8A-6	CF_3	CH_3/CH_3	H/OH (1S,4R)	+++	479.1	Free Base
8A-7	CF_3	CH_3/CH_3	H/OH (1R,4S)	+++	479.1	Free Base

TABLE 8B



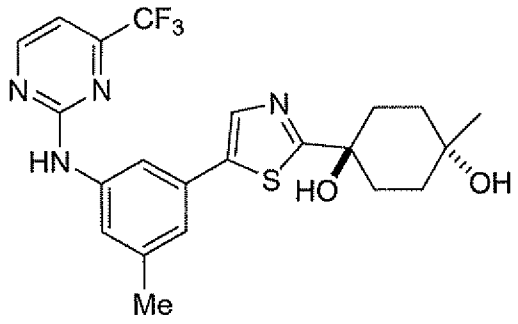
Example	R	rhSYK Activity	[M+H]+ Obs'd	Form(s)

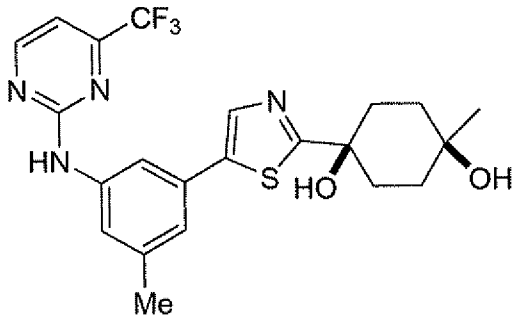
8B-1		+++	477.1	Free Base
8B-2 & 8B-3	 (cis and trans isomers isolated)	+++, +++	479.1	Free Base

EXAMPLE 9(1) AND 9(2)

trans-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol

cis-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol





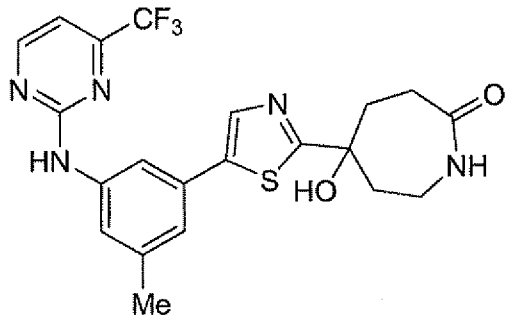
To a stirred solution of 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanone (104 mg, 0.232 mmol) in THF (4 mL) was added MeMgCl (3.0 M, 0.464 mL, 1.39 mmol) at 0 °C. The resultant orange suspension was stirred for1 h at 0 °C, treated with saturated aqueous ammonium chloride, and extracted with ethyl acetate (x 3). The combined organics were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography gave:

trans-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol (6 mg, 0.013 mmol) as a white solid. APCI: $[M + H]^+$ *m/z* 465.1. ^1H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.81 (d, *J* = 4.9, 1H), 7.92 (s, 1H), 7.90 (s, 1H), 7.43 (s, 1H), 7.25 (d, *J* = 4.9, 1H), 7.12 (s, 1H), 5.74 (s, 1H), 4.03 (s, 1H), 2.29 (s, 3H), 2.21 (td, *J* = 3.9, 13.3, 2H), 1.71 – 1.36 (m, 6H), 1.10 (s, 3H). rhSYK activity = +++)

cis-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-1,4-diol (23 mg, 0.050 mmol) as a colorless oil. APCI: $[M + H]^+$ *m/z* 465.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.8, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.13 (s, 1H), 2.31 (s, 3H), 1.96 – 1.40 (m, 8H), 1.13 (s, 3H). rhSYK activity = +++.

EXAMPLE 10

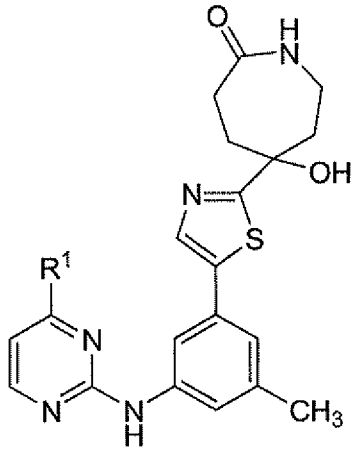
5-hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one



A mixture of 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (60 mg, 0.122 mmol), sodium azide (23.76 mg, 0.365 mmol) and methanesulfonic acid (95 μL, 1.462 mmol) in $CHCl_3$ (1.2 mL) was heated at 65 °C for 1 h and cooled to room temperature. The mixture was treated with water, and extracted with ethyl acetate. The combined organics were dried, filtered, concentrated and purified by flash chromatography to afford 5-hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (36 mg, 0.078 mmol). APCI: $[M + H]^+$ *m/z* 464.2. ^1H NMR (600 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.9, 1H), 7.89 (s, 1H), 7.83 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 7.05 (s, 1H), 7.03 (d, *J* = 4.9, 1H), 6.21 (s, 1H), 3.81 (s, 1H), 3.46 (s, 1H), 3.21 – 3.03 (m, 2H), 2.41 (dd, *J* = 7.5, 14.4, 1H), 2.37 (s, 3H), 2.24 (t, *J* = 13.3, 1H), 2.18 – 2.04 (m, 3H). rhSYK activity = +++

The following compounds were prepared as the free base in an analogous manner of that described in Example 10:

TABLE 10

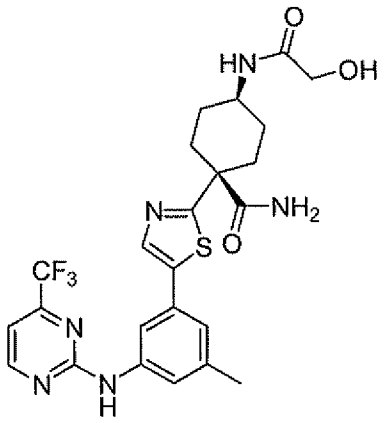


Example	R^1	rhSYK Activity	[M+H]+ Obs'd
10A-1	OCH_3	+++	426.2

10A-2 & 10A-3	$CH(CH_3)_2$ (Enantiomers 1 &2 isolated)	+++	438.2

EXAMPLE 14

cis-4-[(hydroxyacetyl)amino]-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide



Step 1: To a solution of ethyl 4-oxocyclohexanecarboxylate (5.0 g, 40 .6 mmol) in benzene (20 ml) were added ethylene glycol (2.83 ml, 50.8 mmol) and catalytic sulfuric acid (772 mg, 4.1 mmol) and the mixture was refluxed under a Dean-Stark trap for 18 h. The mixture was cooled to 23°C, diluted with saturated aqueous $NaHCO_3$ (85 ml) and extracted with EtOAc (2x75 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated and the crude product was purified via flash column chromatography to afford 1,4-dioxaspiro[4.5]decane-8-carbonitrile (6.15 g, 34.9 mmol, 86% yield) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 3.85-3.3.80 (m, 4H), 2.61-2.53 (m, 1H), 1.90-1.77 (m, 4H), 1.75-1.69 (m, 2H), 1.56-1.48 (m, 2H).

Step 2: To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (3 g, 17.9 mmol) in anhydrous toluene (95 ml) at 0°C, was added sodium bis(trimethylsilyl)amide (1M in toluene, 21.5 ml, 21.5 mmol). The resulting orange solution was maintained at 0°C for 1 h, before introducing a solution of 2-Chlorotriazole (2.14 g, 17.9 mmol) in anhydrous toluene (10 ml) via cannulation. The residual dark brown solution was allowed to slowly warm to 23°C over 16 h. The reaction was diluted with saturated aqueous NH_4Cl (100 ml) and extracted with EtOAc (2x80 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified via flash column chromatography (SiO_2: 100% Hex to 80:20 Hex:EtOAc) to provide 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (1.78 g, 6.74 mmol, 37.5% yield) as a fluffy, off-white solid. MS ESI: $[M+H]^+$ *m/z* 251.1. ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, 1H, J = 3.2 Hz), 7.35 (d, 1H, J = 3.5 Hz), 4.01-3.95 (m, 4H), 2.44-2.31 (m, 4H), 2.09-2.03 (m, 2H), 1.89-1.86 (m, 2H).

Step 3: To a solution of 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (1.78 g, 7.11 mmol) in anhydrous DMF (25 ml) was added *N*-bromosuccinimide (1.52 g, 8.53 mmol). The solution was heated at 50°C for 2 h. The reaction was cooled to 23°C then diluted with

saturated aqueous NaS_2O_3 (175 ml) and extracted with EtOAc (2x130 ml). The combined organic layers were washed with brine (150 ml), dried over Na_2SO_4, filtered and concentrated. The crude yellow oil was purified via flash column chromatography (SiO_2: 100% Hex to 60:40 Hex:EtOAc), to afford 8-(5-bromo-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (1.43 g, 4.13 mmol, 58% yield) as an off-white solid. MS ESI: $[M+H]^+$ *m/z* 331.1. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 4.01-3.93 (m, 4H), 2.39-2.26 (m, 4H), 2.07-2.01 (m, 2H), 1.88-1.86 (m, 2H).

Step 4: *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (1.60 g, 4.22 mmol), 8-(5-bromo-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (1.40 g, 4.22 mmol), cesium carbonate (4.12 g, 12.6 mmol), $Pd_2(dba)_3$ (193 mg, 0.21 mmol) and X-Phos (201 mg, 0.42 mmol) were added to a flame-dried flask, deoxygenated, and diluted with anhydrous 1,4-dioxane (15 ml) and water (1.5 ml). The resulting dark mixture was heated to 100°C for 5 h. The reaction mixture was diluted with 1:1 saturated aquoeus $NaHCO_3$: brine (100 ml) and extracted with EtOAc (2x85 ml). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude dark maroon oil was purified via flash column chromatography (SiO_2: 100% Hex to 60:40 Hex:EtOAc) which afforded 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decane-8-carbonitrile (1.77 g, 3.35 mmol, 79% yield) as an off-white solid. MS ESI: $[M+H]^+$ *m/z* 502.1. ^1H NMR (500 MHz, CD_3OD): δ 11.1 (s, 1H), 9.65 (d, 1H, J = 4.9 Hz), 8.93 (s, 1H), 8.83 (s, 1H), 8.30 (s, 1H), 8.10 (d, 1H, J = 4.9 Hz), 8.02 (s, 1H), 4.73-4.72 (m, 4H), 3.21-3.18 (m, 2H), 3.13 (s, 3H), 3.01-2.97 (m, 2H), 2.69-2.61 (m, 4H). rhSYK activity = +++

Step 5: To a solution of 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decane-8-carbonitrile (250 mg, 0.50 mmol) in anhydrous DMSO (4 ml) were added potassium carbonate (172 mg, 1.25 mmol) and hydrogen peroxide (218 μL, 2.49 mmol). The resulting solution was stirred at 70°C for 1.5 h, cooled to room temperature and diluted with water (70 ml) and washed with EtOAc (2x60 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude oil was triturated with diethyl ether and hexanes, and the resulting tan solid was collected via filtration and air dried to provide 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decane-8-carboxamide (171 mg, 0.31 mmol, 63% yield) as a tan solid. MS ESI: $[M+H]^+$ *m/z* 520.1. ^1H NMR (500 MHz, CD_3OD): δ 11.0 (s, 1H), 9.64 (d, 1H, J = 4.9 Hz), 8.79 (s, 1H), 8.76 (bs, 1H), 8.28 (bs, 1H), 8.12-8.05 (m, 3H), 7.97 (s, 1H), 4.68-4.64 (m, 4H), 3.23-3.15 (m, 2H), 3.12 (s, 3H), 2.95-2.85 (m, 2H), 2.44-2.38 (m, 4H).

Step 6: To a suspension of 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decane-8-carboxamide (700 mg, 1.35 mmol) in anhydrous THF (2 ml) and was added concentrated HCl (5.53 ml, 67.4 mmol). The resulting dark yellow solution was stirred at 23°C for 6 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (80 ml) and extracted with EtOAc (2x70 ml). The combined organic layers were dried over

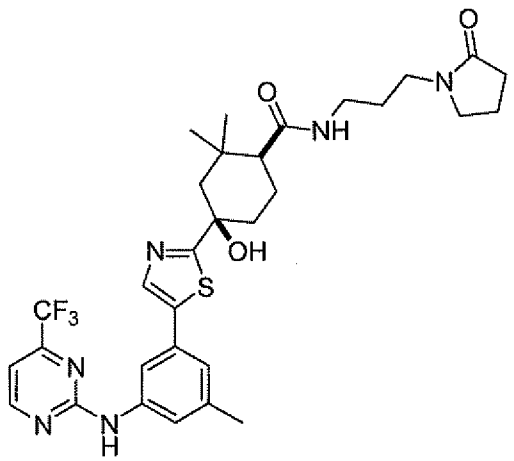
Na_2SO_4, filtered and concentrated. The crude oil was triturated with hexanes and diethyl ether which afforded 1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-oxocyclohexanecarboxamide (683 mg, 1.01 mmol, 74.6%) as an tan solid. MS APCI: $[M+H]^+$ *m/z* 476.1.

Step 7: To a solution of 1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-oxocyclohexanecarboxamide (683 mg, 1.44 mmol) in anhydrous MeOH (6 ml) were added ammonium acetate (221 mg, 2.87 mmol) and sodium cyanoborohydride (95 mg, 1.508 mmol). The resulting mixture was stirred at 23°C for 6 d. The reaction was quenched with 0.5M NaOH (100 ml) and extracted with EtOAc (2x75 ml). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to an orange oil, which was purified via reverse-phase HPLC (C_{18} column, Acetonitrile/ Water gradient with 0.1% TFA present). Purification yielded a mixture of diastereomers, which were separated via separation on a chiral stationary phase (SFC, 35% /65% Methanol/CO2 (no other modifiers) to provide both *cis*-4-amino-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide (92 mg, 0.18 mmol, 29% yield) and *trans*-4-amino-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide (103 mg, 0.21 mmol, 32% yield) as off-white solids. MS ESI: $[M+H]^+$ *m/z* 477.1. For molecule A, rhSYK activity = +++; for molecule B, rhSYK activity = +++

Step 8: To a solution of *cis*-4-amino-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide (30 mg, 0.06 mmol) in anhydrous DMF (1.5 ml) were added sequentially glycolic acid (7.18 mg, 0.09 mmol), EDC (18.1 mg, 0.09 mmol), HOBT (14.5 mg, 0.09 mmol), and Et_3N (0.03 ml, 0.19 mmol). The mixture was stirred at 23°C for 16 h, then diluted with water (55 ml) and washed with EtOAc (2x40 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via reverse-phase HPLC (Acetonitrile/ Water gradient with 0.1% TFA present) and the fractions containing product were diluted with saturated aqueous $NaHCO_3$ (50 ml) and washed with EtOAc (45 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford *cis*-4-[(hydroxyacetyl)amino]-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide (16.5 mg, 0.03 mmol, 47% yield) as an off-white solid. MS ESI: $[M+H]^+$ *m/z* 535.1. ^1H NMR (500 MHz, DMSO) δ 10.26 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.96 (s, 1H), 7.94 (s, 1H), 7.55 (d, *J* = 8.2, 1H), 7.45 (m, 2H), 7.32 – 7.22 (m, 2H), 7.14 (s, 1H), 5.29 (t, *J* = 5.9, 1H), 3.75 (d, *J* = 6.0, 2H), 3.70 – 3.60 (m, 1H), 2.67 – 2.58 (m, 2H), 2.31 (s, 3H), 1.82 – 1.68 (m, 4H), 1.54 – 1.41 (m, 2H). rhSYK activity = +++

EXAMPLES 25

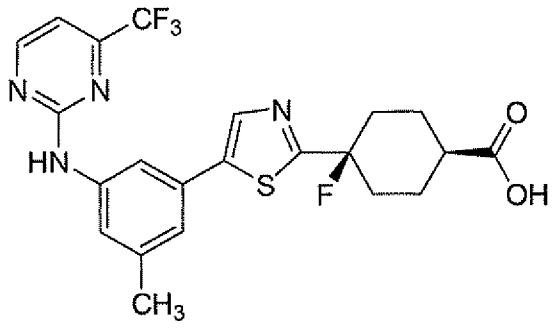
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide



To (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (102 mg, 0.20 mmol), *N*-(3-aminopropyl)-2-pyrrolidinone (85 µL, 0.60 mmol), EDC (58 mg, 0.30 mmol), and HOBt (46 mg, 0.30 mmol) was added *N,N*-dimethylformamide (2 mL) and triethylamine (140 µL, 1.01 mmol). The mixture was stirred at room temperature for 16 h, quenched with 1:1 water:brine, and extracted with EtOAc. The organic layer was washed with 1:1 water:brine (3x). The organic layer was dried over magnesium sulfate, filtered and purified by reverse phase HPLC (C-18, eluting with a 45:55 to 80:20 gradient of acetonitrile:water + 0.1% TFA). The combined fractions were diluted with ethyl acetate and dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to afford the title compound (97 mg, 0.15 mmol, 76% yield) as a white solid. MS ESI: $[M + H]^+$ *m/z* 631.2. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.93 (s, 1H), 7.92 (s, 1H), 7.68 (t, *J* = 5.6, 1H), 7.46 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 5.86 (s, 1H), 3.29 (s, 1H), 3.24 – 3.12 (m, 2H), 3.12 – 3.03 (m, 1H), 2.99 – 2.88 (m, 1H), 2.31 (s, 3H), 2.19 (m, 2H), 2.02 (m, 2H), 1.86 (m, 5H), 1.66 – 1.50 (m, 3H), 1.40 (m, 1H), 1.11 (s, 3H), 0.92 (s, 3H).

EXAMPLE 26

cis-4-Fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

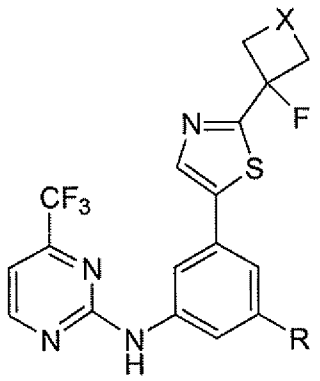


Step 1: To solution of *tert*-butyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (400 mg, 0.748 mmol) in dichloromethane (3.74 mL) and ethanol (2.2 μL, 0.037 mmol) was added Deoxofluor (690 μL, 3.74 mmol). The reaction was complete after stirring for one hour at room temperature. The reaction was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Column chromatography was used for purification to provide the two isomers of *tert*-butyl 4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. Cis-isomer (141 mg, 0.210 mmol, 28.1%). MS ESI: $[M+H]^+$ *m/z* 537.2. ^1H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.83 (d, *J* = 5.2, 1H), 8.07 (d, *J* = 2.9, 1H), 8.03 (s, *J* = 8.3, 1H), 7.47 (s, 1H), 7.29 (d, *J* = 5.1, 1H), 7.20 (s, 1H), 2.32 (s, 5H), 2.20 – 1.93 (m, 3H), 1.93 – 1.78 (m, 2H), 1.76 – 1.57 (m, 2H), 1.40 (s, 9H). Trans-isomer (175 mg, 0.326 mmol, 43.6%). MS ESI: $[M+H]^+$ *m/z* 537.2. ^1H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.83 (d, *J* = 5.3, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.47 (s, 1H), 7.29 (d, *J* = 5.2, 1H), 7.20 (s, 1H), 2.53 (s, 3H), 2.32 (s, 4H), 2.08 – 1.93 (m, 2H), 1.93 – 1.82 (m, 2H), 1.84 – 1.61 (m, 1H), 1.39 (s, 9H).

Step 2: To a solution of *cis- tert*-butyl 4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (67 mg, 0.125 mmol) in dichloromethane (2.50 mL) was added 2,6-lutidine (145 μL, 1.249 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (860 μL, 3.75 mmol). The reaction was complete after 1 hour at room temperature. The reaction was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Column chromatography was used for purification to yield a mixture of the fluoro carboxylic acid and the des-fluoro carboxylic acid. SFC was then used for further purification (Berger Multigram II SFC, column: Chiral Technology OJ 2.1 X 25cm, 5 uM, mobile phase: 40% to 60% methanol in CO_2(l), flow rate: 70 mL/min, 7.5 min run time) to yield *cis*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (17 mg, 0.035 mmol, 28.3%). MS ESI: $[M+H]^+$ *m/z* 481.1. ^1H NMR (600 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.82 (d, *J* = 4.9, 1H), 8.06 (d, *J* = 2.8, 1H), 8.00 (s, 1H), 7.45 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.18 (s, 1H), 2.40 (t, *J* = 12.1, 1H), 2.30 (s, 3H), 2.16 (t, *J* = 11.8, 2H), 2.05 (dtd, *J* = 4.4, 14.0, 40.0, 2H), 1.91 (d, *J* = 13.3, 2H), 1.68 (tt, *J* = 6.5, 12.9, 2H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Example 26.

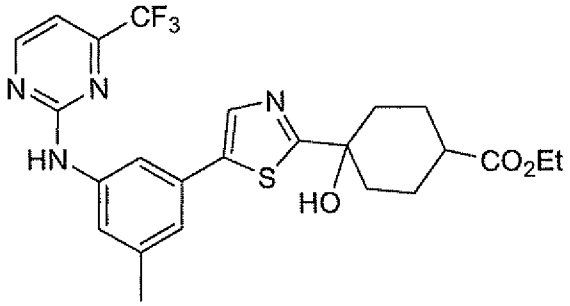
TABLE 26



Example	R	X	rhSYK Activity	[M+H]+ Observed	Form(s)
26-1	CH_3	(trans) -CH_2-CH(CO_2H)-CH_2-	+++	481.1	Free Base
26-3	H	-CH_2-	++	395.0	Free Base
25-6	H	(trans) -CH_2CH(CO_2H)-CH_2-	+++	467.0	Free Base

EXAMPLE 32

ethyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate



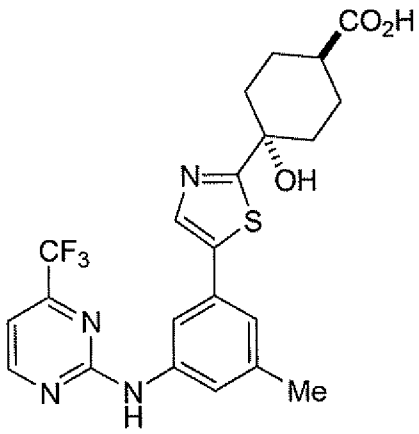
Tetrahydrofuran was placed in a flask and cooled to -78°C. Lithium diisopropylamide (9.91 mL, 17.84 mmol) was added and the mixture was allowed to cool to -78°C. **INTERMEDIATE 4** (2.0 g, 5.95 mmol) was dissolved in tetrahydrofuran (60 mL) and added to the reaction mixture in one portion and stirred for 30 minutes. Ethyl 4-oxocyclohexanecarboxylate (1.52 g, 8.92 mmol) was dissolved in tetrahydrofuran (60 mL) and added in one portion. After 1 hour, the reaction was quenched with saturated ammonium chloride and allowed to warm to room temperature. The solution was diluted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography was used for purification to yield a 1:1 mixture of diastereomers of ethyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (1.96 g, 65.1%). MS ESI: $[M+H]^+$ *m/z* 507.2. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.83 (d, *J* = 5.2, 1H), 8.02 – 7.85 (m, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 5.0, 1H), 7.14 (s, 1H), 5.97 (m, 1H),

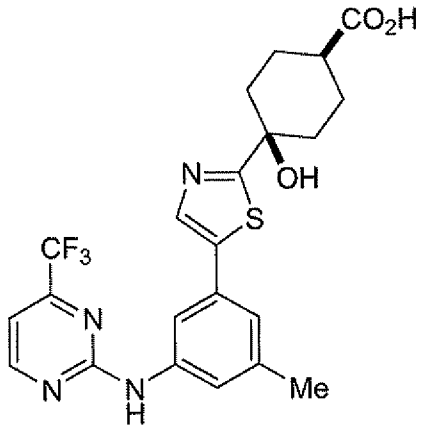
4.12 – 4.01 (m, 2H), 2.62 – 2.54 (m, 1H), 2.31 (s, 3H), 2.12 – 1.99 (m, 1H), 1.93 – 1.58 (m, 7H), 1.24 – 1.05 (m, 3H). rhSYK activity = +++

EXAMPLES 33(1) AND 33(2)

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid





Part A: Ethyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (3.72 g, 7.3 mmol) was suspended in methanol (42 mL) and sodium hydroxide (1M in water, 15 mL) was added. The solution was split between 3 20-mL microwave tubes. The reaction was irradiated at 100°C in the microwave for 15 minutes. Upon completion, the solution was acidified with HCl (1M in water, 18 mL). The solution was extracted with ethyl acetate and a small amount of 9:1 $CHCl_3$:isopropanol. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated.

Part B: Supercritical fluid separation was used for purification with an OJ-H 2.1 X 25 cm, 5 μM column. The mobile phase used was a 3:7 methanol/CO_2 with a flow rate of 70 mL/min with a 7 minute run time, to yield:

Isomer 1: *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (1.11 g, 32% yield). MS ESI: $[M+H]^+$ *m/z* 479.1. ^1H NMR (600 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.81 (d, *J* = 4.9, 1H), 8.00 – 7.75 (m, 2H), 7.44 (s, 1H), 7.25 (d, *J* = 4.9, 1H), 7.12 (s, 1H), 5.92 (s, 1H), 2.62 (s, 1H), 2.29 (s, 3H), 2.11 – 1.95 (m, 2H), 1.92 – 1.75 (m, 4H), 1.71 – 1.54 (m, 2H). rhSYK activity = +++

Isomer 2: *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (1.13 g, 32%). MS ESI: $[M+H]^+$ *m/z* 479.1. ^1H NMR (500 MHz, DMSO-d_6) δ 12.1 (s, 1H), 10.25 (s, 1H), 8.83 (d, *J* = 5.2, 1H), 8.04 – 7.83 (m, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 5.0, 1H), 7.15 (s, 1H), 5.95 (s, 1H), 2.31 (s, 3H), 2.13 – 1.99 (m, 1H), 1.91 – 1.73 (m, 2H), 1.71 – 1.53 (m, 6H). rhSYK activity = +++

EXAMPLES 33(1) - NA

Sodium *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

cis-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (15 mg, 0.031 mmol) was dissolved in acetonitrile (272 μL) and water (54 μL). Sodium hydroxide (31 μL, 0.031 mmol) was added, and the mixture was heated to 40 °C for 1 h. The reaction was allowed to cool to room temperature, before freezing and lyophilization to dryness to afford sodium *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 479.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (s, 1H), 8.06 – 7.73 (m, 2H), 7.46 (s, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 5.89 – 5.60 (m, 1H), 2.31 (s, 3H), 1.91 – 1.54 (m, 9H). rhSYK activity = +++

EXAMPLES 33(1) - K

Potassium *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

cis-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (15 mg, 0.031 mmol) was dissolved in acetonitrile (272 μL) and water (54 μL). Potassium hydroxide (31 μL, 0.031 mmol) was added, and the mixture was heated to 40 °C for 1 h. The reaction was allowed to cool to room temperature, before freezing and lyophilization to dryness to afford potassium *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 479.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, $J = 4.9$, 1H), 7.99 – 7.83 (m, 2H), 7.46 (s, 1H), 7.27 (d, $J = 4.9$, 1H), 7.13 (s, 1H), 5.88 – 5.63 (m, 1H), 2.31 (s, 3H), 1.88 – 1.59 (m, 9H). rhSYK activity = +++

EXAMPLES 33(2) - NA

Sodium *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

trans-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (15 mg, 0.031 mmol) was dissolved in acetonitrile (272 μL) and water (54 μL). Sodium hydroxide (31 μL, 0.031 mmol) was added, and the mixture was heated to 40 °C for 1 h. The reaction was allowed to cool to room temperature, before freezing and lyophilization to dryness to afford sodium *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 479.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, $J = 4.9$, 1H), 8.04 – 7.76 (m, 2H), 7.46 (s, 1H), 7.27 (d, $J = 4.9$, 1H), 7.14 (s, 1H), 5.68 (s, 1H), 2.31 (s, 3H), 2.21 – 1.96 (m, 3H), 1.90 – 1.63 (m, 4H), 1.62 – 1.42 (m, 2H). rhSYK activity = +++

EXAMPLES 33(2) - K

Potassium *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

trans-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (15 mg, 0.031 mmol) was dissolved in acetonitrile (272 μL) and water (54 μL). Potassium hydroxide (31 μL, 0.031 mmol) was added, and the mixture was heated to 40 °C for 1 h. The reaction was allowed to cool to room temperature, before freezing and lyophilization to dryness to afford potassium *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 479.1. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 8.02 – 7.78 (m, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 5.69 (s, 1H), 2.31 (s, 3H), 2.19-2.07 (m, 2H), 1.99 – 1.85 (m, 1H), 1.81 – 1.60 (m, 4H), 1.57 – 1.42 (m, 2H). rhSYK activity = +++

Compounds in the following Tables 33A to 33D were prepared in an analogous manner as that described in Examples 32-33.

TABLE 33-A

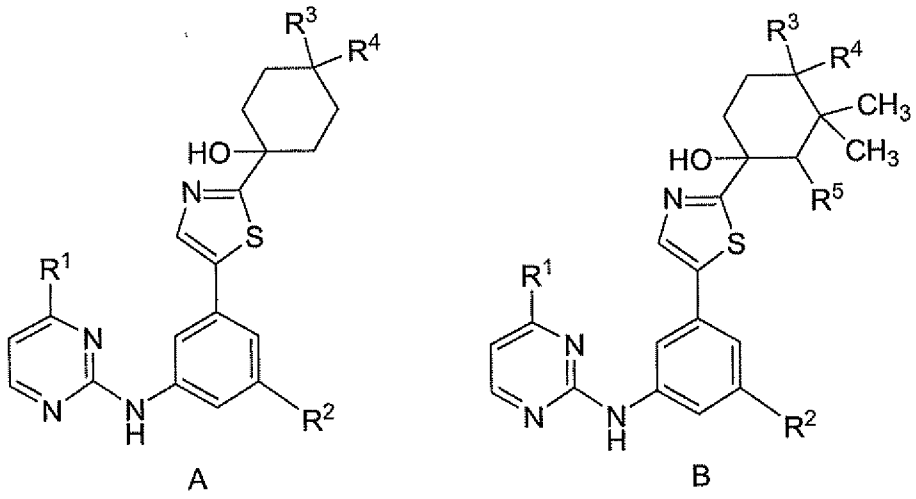


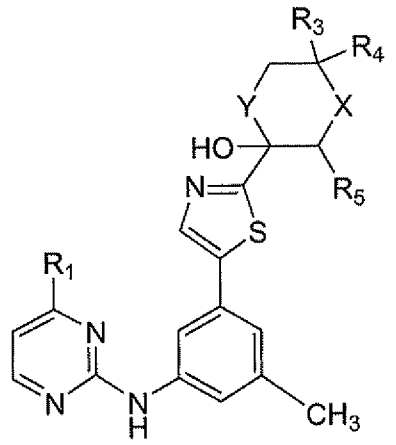
TABLE 33A

Ex.	R^1	R^2	R^3/R^4	rhSYK Activity	[M+H] + Obs'd	Form(s)
Formula A						
33A-5	CF_3	CH_3	H/CO_2Et	+++	507.2	Free Base
33A-6	CF_3	CH_3	H/CO_2H (cis)	+++	479.1	Free Base
33A-7	CF_3	CH_3	H/CO_2Et (trans)	+++	507.2	Free Base
33A-8	CF_3	CH_3	H/CO_2H (trans)	+++	479.1	Free Base

33A-10	CF_3	CH_3	CH_3/CO_2Et (cis)	+++	521.1	Free Base
33A-11	CF_3	CH_3	CH_3/CO_2Et (trans)	++	521.1	Free Base
33A-12	CF_3	CH_3	CH_3/CO_2H (trans)	+++	493.1	Free Base
33A-13	CF_3	CH_3	CH_3/CO_2H (cis)	+++	493.1	Free Base
33A-16	CF_3	CH_3	H/CH_2CO_2H (trans)	+++	493	Formate Salt
33A-18	CF_3	CH_3	$H/CH_2CH_2CO_2H$	+++	507.2	Free Base
33A-19	CF_3	CH_3	$H/CH_2CH_2CO_2H$ (cis)	+++	507.2	Free Base
33A-20	CF_3	CH_3	$H/CH_2CH_2CO_2H$ (trans)	+++	507.2	Free Base
33A-21	CF_3	CH_3	$H/CH_2CH_2CO_2CH_2CH_3$	+++	535.2	Free Base
33A-23	CF_3	H	H/CO_2H (trans)	+++	465.0	Free Base
33A-24	CF_3	H	H/CO_2H (cis)	+++	465.0	Free Base
33A-25	CF_3	H	H/CO_2Et (cis)	+++	493.1	Free Base
33A-26	CF_3	H	H/CO_2Et (trans)	++	493.1	Free Base
33A-27	CF_3	H	CH_3/CO_2H (trans)	+++	479.1	Free Base
33A-28	CF_3	H	CH_3/CO_2H (cis)	+++	479.1	Free Base
33A-29	iPr	CH_3	$H/CO_2C(CH_3)_3$ (cis)	++	509.2	Free Base
33A-30	CH_3	CH_3	H/CO_2H (cis)	+++	425.1	Free Base
33A-31	CH_3	CH_3	H/CO_2H (trans)	+++	425.1	Free Base
33A-32	CH_3	CH_3	$H/CH2CO_2H$ (cis)	+++	439.1	Free Base
33A-33	CH_3	CH_3	$H/CH2CO_2H$ (trans)	+++	439.0	Free Base
33A-34	O-iPr	CH_3	$H/CO_2C(CH_3)_3$ (cis)	++	525.2	Free Base
33A-35	OCH_3	CH_3	H/CO_2H (cis)	+++	441.1	Free Base
33A-36	OCH_3	CH_3	H/CO_2H (trans)	+++	441.1	Free Base
33A-37	OCH_3	CH_3	CH_3/CO_2H (cis)	+++	455.1	Free Base
33A-38	OCH_3	CH_3	CH_3/CO_2H (trans)	+++	455.1	Free Base
Formula B; R^5 = H						
33A-54	CF_3	CH_3	H/CO_2H (trans)	+++	507	Free Base
33A-59	CF_3	c-Pr	H/CO_2H (enantiomer 1)	+++	533.2	Free Base
33A-60	CF_3	c-Pr	H/CO_2H (enantiomer 2)	+++, +++	533.2	Free Base, TFA Salt
33A-61	CF_3	c-Pr	H/CO_2CH_3	+++	547.2	Free Base
33A-62	CF_3	c-Pr	H/CO_2H	+++	533.2	TFA Salt
33A-65	CF_3	H	H/CO_2CH_3	++	507.1	Free Base
33A-66	CF_3	H	H/CO_2H (cis, enantiomer 1)	+++	493	Free Base
33A-67	CF_3	H	H/CO_2H (cis, enantiomer 2)	+++	493	Free Base
33A-68	CH_3	CH_3	H/CO_2H (cis)	+++	452.1	Free Base
33A-69	CH_3	CH_3	H/CO_2CH_3 (cis)	+++	467.2	Free Base
33A-70	c-Pr	CH_3	H/CO_2CH_3	+++	493.2	Free Base

33A-71	c-Pr	CH_3	H/CO_2H	+++	479.2	Free Base
33A-72	OCH_3	CH_3	H/CO_2H (isomer 1)	+++	469.1	Free Base
33A-73	OCH_3	CH_3	H/CO_2H (isomer 2)	+++	469.1	Free Base
Formula B; $R^5 = CH_3$						
33A-75 to 33A-77	CF_3	CH_3	H/CO_2H (3 isolated isomers)	+++	521	Free Base

TABLE 33B



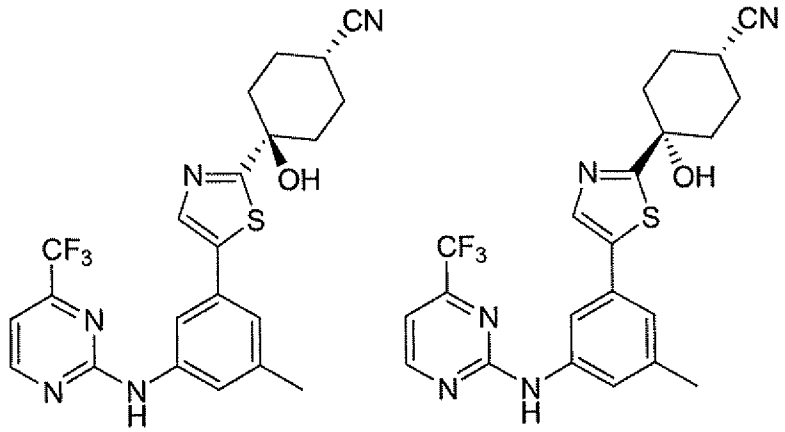
Ex.	X	Y	R^3/R^4	rhSYK Activity	[M+H] + Obs'd	Form(s)
$R^1 = CF_3$, $R^5 = H$						
33B-1	Bond	Bond	H/CO_2H	+++	451.0	Ammonium salt
33B-2 to 33B-5	$C(CH_3)2$	Bond	H/CO_2H (4 isolated isomers)	+++	493	Free Base
33B-6 to 33B-9	$C(CH_3)2$	CH_2CH_2	H/CO_2H (4 isolated isomers)	+++	521	Free Base
33B-13	$CH(OCH_3)$	CH_2	H/CO_2H	+++	509	Free Base
33B-14	$CH(OCH_3)$	CH_2	H/CO_2H (cis,cis)	+++	509	Free Base
33B-18	$CH(CH_3)$	CH_2	H/CO_2H (isomer 1)	+++	493.1	Free Base
33B-19	$CH(CH_3)$	CH_2	H/CO_2H (isomer 2)	+++	493.2	TFA Salt
33B-20	$CH(CH_3)$	CH_2	H/CO_2H (isomer 3)	+++, +++	493.1	Free Base, TFA Salt
33B-21	$CH(CO_2H)$	CH_2	H/H	+++	479.1	Free Base
33B-24	CH(iPr)	CH_2	H/CO_2H	+++	521	Free Base
33B-22	CH(iPr)	CH_2	H/CO_2H (enantiomer 1)	+++	521	Free Base
33B-23	CH(iPr)	CH_2	H/CO_2H (enantiomer 2)	+++	521	Free Base

33B-24	CH_2	bond	H/CO_2H	+++	465.0	Ammonium salt
33B-25	CH_2	bond	H/CH_2CO_2H (trans, enantiomer 1)	+++	479	Free Base
33B-26	CH_2	bond	H/CH_2CO_2H (cis, enantiomer 1)	+++	479	Free Base
33B-27	CH_2	bond	H/CH_2CO_2H (trans, enantiomer 2)	+++	479	Free Base
33B-28	CH_2	bond	H/CH_2CO_2H (cis, enantiomer 2)	+++	479	Free Base
$R^1 = CH_3$, $R^5 = H$						
33B-32	$CH(CH_3)$	CH_2	H/CO_2H (isomer 1)	+++	439.2	Free Base
33B-33	$CH(CH_3)$	CH_2	H/CO_2H (isomer 2)	+++	439.2	Free Base
33B-34	CH(iPr)	CH_2	H/CO_2H	+++	467	Free Base
33B-35	CH(iPr)	CH_2	H/CO_2H (isomer 1)	+++	467	Free Base
33B-36	CH(iPr)	CH_2	H/CO_2H (isomer 2)	+++	467	Free Base
$R^1 = CF_3$, $R^5 = CH_3$						
33B-38	$CH(CH_3)$	CH_2	H/CO_2H (isomer 1)	+++	507	TFA Salt
33B-39	$CH(CH_3)$	CH_2	H/CO_2H (isomer 2)	+++	507	Free Base
$R^1 = CF_3$, $R^5 = CH_2CH_3$						
33B-40	$CH(CH_3)$	CH_2	H/CO_2H	+++	521	TFA Salt
33B-41	$CH(CH_3)$	CH_2	H/CO_2H (isomer 1)	+++	521	TFA Salt
33B-42	$CH(CH_3)$	CH_2	H/CO_2H (isomer 2)	+++	521	TFA Salt

EXAMPLES 37(1) AND 37(2)

cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile



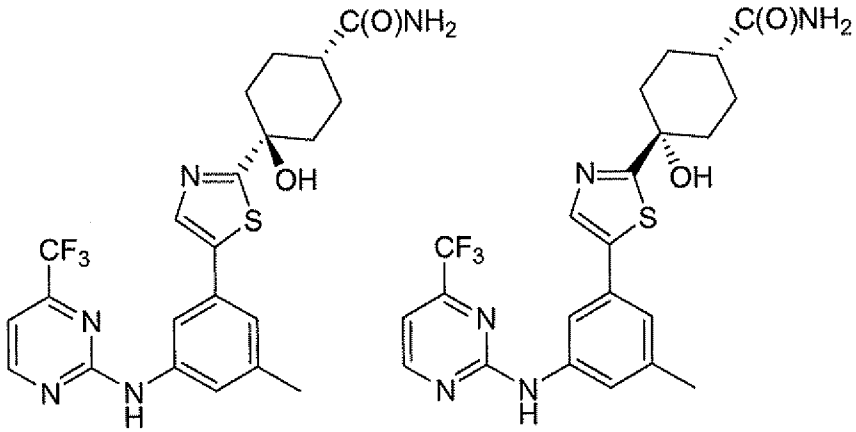
To a flask was added tetrahydrofuran (3.0 mL) and the flask was cooled to -78 °C. Lithium diisopropylamide (1.0 mL, 1.78 mmol) was added and the mixture was cooled to -78 °C. **INTERMEDIATE 4** (0.20 g, 0.60 mmol) was dissolved in tetrahydrofuran (3.0 mL) and added to the reaction mixture in one portion and stirred for 30 minutes. 4-oxocyclohexanecarbonitrile (0.073 g, 0.60 mmol) was dissolved in THF (3.0 mL) and then added over a period of five minutes and the solution was then allowed to warm to room temperature. The reaction was diluted with ethyl acetate, washed with saturated ammonium chloride, dried over magnesium sulfate, filtered and concentrated. Column chromatography was used to yield: *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile (0.72 g, 26%) Analysis for *cis* isomer: MS ESI: $[M+H]^+$ *m/z* 460.1. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.81 (d, *J* = 4.9, 1H), 7.93 (m, 2H), 7.44 (s, 1H), 7.26 (d, *J* = 4.9, 1H), 7.13 (s, 1H), 6.11 (s, 1H), 2.82 (s, 1H), 2.29 (s, 3H), 1.99 – 1.72 (m, 8H). rhSYK activity = +++

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile (0.78 g, 29%). MS ESI: $[M+H]^+$ *m/z* 460.1. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.81 (d, *J* = 4.9, 1H), 8.00 – 7.89 (m, 2H), 7.45 (s, 1H), 7.25 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 6.11 (s, 1H), 3.13 (s, 1H), 2.30 (s, 3H), 2.07 (m, 2H), 2.00 – 1.89 (m, 2H), 1.77 (m, 4H). rhSYK activity = +++

EXAMPLES 38(1) AND 38(2)

trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide

cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide

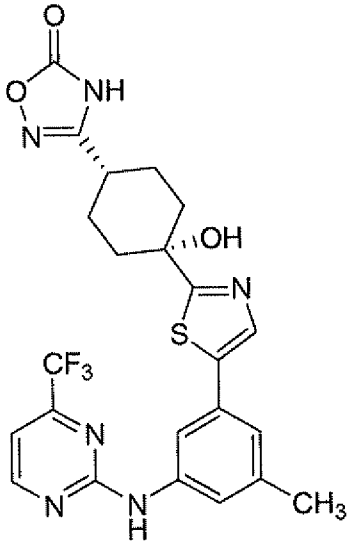


To *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarbonitrile (0.78 g, 0.17 mmol) was added DMSO (1.4 mL). Potassium carbonate (0.13 mg, 0.92 mmol) and 30% hydrogen peroxide (0.17 mL, 1.70 mmol) were added and the reaction was heated at 70°C. Upon completion, the solution was cooled and filtered. The filtrate was purified by reverse phase HPLC (10-100% acetonitrile gradient with water over 12 minutes with a 0.05% trifluoroacetic acid buffer) to yield *trans*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-carboxamide (0.040 g, 49%). MS ESI: $[M+H]^+$ *m/z* 478.1. ^1H NMR (500 MHz, CD_3OD) δ 8.72 (d, *J* = 5.3, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.45 (s, 1H), 7.22 – 6.90 (m, 2H), 2.57 – 2.40 (m, 3H), 2.38 (s, 3H), 2.00 – 1.69 (m, 6H). rhSYK activity = +++

In an analogous manner of that describedabove, cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide was prepared as the free base. [M+H]+ Observed: 478.1. rhSYK Activity: +++

EXAMPLE 39

3-{cis-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}-1,2,4-oxadiazol-5(4H)-one



Step 1: *cis*-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (500 mg, 1.05 mmol), ammonium chloride (112 mg, 2.09 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (795 mg, 2.09 mmol), and diisopropylethylamine (730 µl, 4.18 mmol) were taken-up in dimethylformamide (4.2 mL) under argon. The vessel was sealed and stirred at 65 °C for 4 hours. Upon cooling, the reaction mixture was diluted with water, and the resulting precipitate was collected via filtration. The solids were washed with water and diethyl ether and dried *in vacuo* overnight to afford *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide (437.6 mg, 0.916 mmol, 88% yield) as a white solid. MS ESI: $[M + H]^+$ *m/z* 478.1.

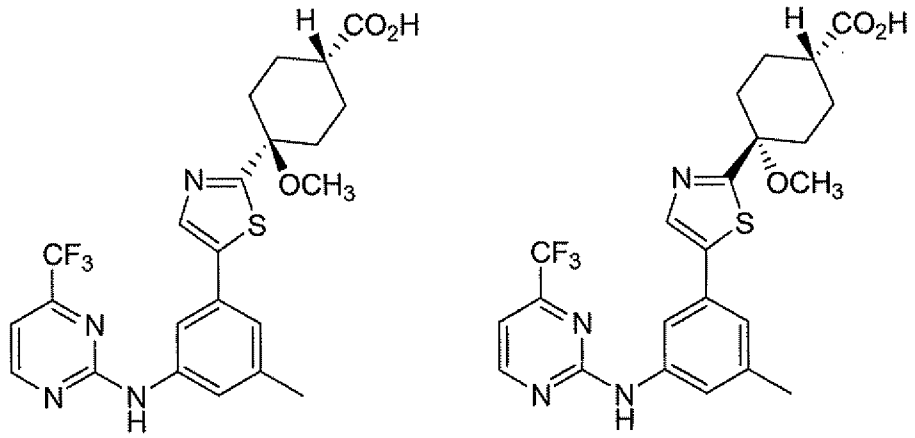
Step 2: In a dry vessel, the product from Step 1 (350 mg, 0.733 mmol) was taken-up in dichloromethane (4.9 mL) and tetrahydrofuran (2.4 mL) under argon. (Methoxycarbonyl-sulfamoyl)triethylammonium hydroxide, inner salt (218 mg, 0.916 mmol) was added, and the resulting mixture was sealed and stirred at room temperature for 18 hours. Another portion of (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (218 mg, 0.916 mmol) was then added, and the resulting mixture was sealed and stirred at room temperature for 18 hours. The reaction mixture was quenched with water and directly concentrated. Reverse-phase HPLC purification (water-acetonitrile, trifluoroacetic acid modifier) afforded *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexane-carbonitrile (28.6 mg, 0.062 mmol, 8.5% yield) as a white solid. MS ESI: $[M + H]^+$ *m/z* 460.1.

Step 3: The product from Step 2 (25 mg, 0.054 mmol), hydroxylamine hydrochloride (18.90 mg, 0.272 mmol), and potassium carbonate (41.4 mg, 0.299 mmol) were taken-up in ethanol (0.5 mL) under argon. The vessel was sealed and stirred at 80 °C for 18 hours. The reaction mixture was directly concentrated, and the solids were taken-up in tetrahydrofuran (0.5 mL). Triethylamine (22.8 µl, 0.163 mmol) was added, and the mixture was cooled to 0 °C. Carbonyldiimidazole (13.2 mg, 0.082 mmol) was added, and the resulting mixture was allowed to warm to room temperature over 18 hours. The reaction was quenched with trifluoroacetic acid and diluted with 1 ml DMSO. The resulting mixture was filtered and directly subjected to reverse-phase HPLC (water-acetonitrile, trifluoroacetic acid modifier). This purification afforded the title compound (14.7 mg, 0.028 mmol, 52% yield) as a white solid. MS ESI: $[M + H]^+$ *m/z* 519.1. ^1H NMR (500 MHz, dmso) δ 12.23 (s, 1H), 10.26 (s, 1H), 8.83 (d, $J = 4.8$, 1H), 7.94 (d, $J = 10.8$, 2H), 7.46 (s, 1H), 7.28 (d, $J = 4.9$, 1H), 7.15 (s, 1H), 6.06 (s, 1H), 2.68 (m, 1H), 2.31 (s, 3H), 2.03 – 1.79 (m, 8H). rhSYK activity = +++

EXAMPLE 40(1) AND 40(2)

2-({3-[2-(*cis*-4-Carboxy-1-methoxycyclohexyl)-1,3-thiazol-5-yl]-5-methylphenyl}amino)-4-(trifluoromethyl)pyrimidin-1-ium trifluoroacetate

2-({3-[2-(*trans*-4-Carboxy-1-methoxycyclohexyl)-1,3-thiazol-5-yl]-5-methylphenyl}amino)-4-(trifluoromethyl)pyrimidin-1-ium trifluoroacetate



Step 1: To a solution of ethyl 4-[5-(3-{(*tert*-butoxycarbonyl)[4-(trifluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate (**Intermediate 119,** 0.148 g, 0.24 mmol) and DMF (1.2 mL) was added iodomethane (0.042 g, 0.29 mmol). The solution was cooled to 0°C and then 60% sodium hydride in mineral oil (0.011 g, 0.27 mmol) was added and the reaction was allowed to warm up overnight. The next morning, iodomethane (1.14 g, 8.03 mmol) was added and the mixture was cooled to 0 °C. Sodium hydride in mineral oil (60%, 0.011 g, 0.27 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was complete after warming. The solution was cooled to 0°C and carefully quenched with methanol and then water. The mixture was extracted with dichloromethane. The organic layer was washed three times with water, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography was used to yield ethyl 4-[5-(3-{(*tert*-butoxycarbonyl)[4-(trifluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-methoxycyclohexanecarboxylate. MS ESI: $[M+H]^+$ *m/z* 621.2.

Step 2: To the product of Step 1 (0.15 g, 0.243 mmol) in dichlormethane (2 mL) was added trifluoroacetic acid (1.48 g, 12.98 mmol) and the reaction was stirred until complete. The reaction was diluted with water and the mixture extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give ethyl 4-methoxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M+H]^+$ *m/z* 521.2.

Step 3: To the product of Step 2 (0.13, 0.24 mmol) in methanol (1 mL) was added potassium hydroxide (1M in water, 0.24 mL, 0.24 mmol) and the reaction was stirred at room temperature overnight. The reaction was quenched with hydrochloric acid (2N in water) and the solution was extracted 3 times with dichloromethane. The combined organic layer was concentrated and the residue was subject to purification by supercritical fluid chromatography with an OJ-H 2.1 X 25 cm, 5 μM column. The mobile phase was a 2:8 methanol/CO_2 with a flow rate of 70 mL/min with a 12 minute run time to yield:

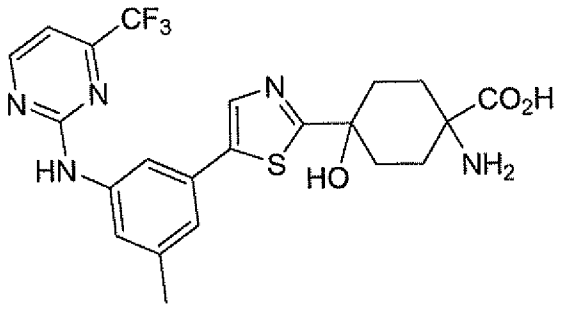
2-({3-[2-(*cis*-4-Carboxy-1-methoxycyclohexyl)-1,3-thiazol-5-yl]-5-methylphenyl}amino)-4-(trifluoromethyl)pyrimidin-1-ium trifluoroacetate (0.03 g, 19% yield). MS ESI: $[M+H]^+$ *m/z* 493.1. ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.93 (m, 2H), 7.28 (s, 1H), 7.12 (s, 1H),

7.07 (d, J = 4.9, 1H), 3.27, (s, 3H), 2.41 (s, 3H), 2.29 (m, 1H), 1.96 (m, 8H). rhSYK activity = +++.

2-({3-[2-(*trans*-4-Carboxy-1-methoxycyclohexyl)-1,3-thiazol-5-yl]-5-methylphenyl}amino)-4-(trifluoromethyl)pyrimidin-1-ium trifluoroacetate (0.02 g, 15% yield). MS ESI: $[M+H]^+$ *m/z* 493.1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.41 (s, 1H), 7.08 (s, 1H), 7.04 (d, J = 5.0, 1H), 3.16 (s, 3H), 2.64 (s, 1H), 2.37 (s, 3H), 2.05 – 1.89 (m, 8H). rhSYK activity = +++.

EXAMPLE 41

1-amino-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid



Step 1: 1-{[(9*H*-Fluoren-9-yloxy)carbonyl]amino}-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (0.079 g, 0.11 mmol) was dissolved in DMF (1.0 mL). Piperidine (0.086 g, 1.01 mmol) was added. After 15 minutes, the reaction mixture was directly purified by reverse phase HPLC to yield 1-amino-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (0.005 g, 0.01 mmol) as its TFA salt. MS ESI: $[M+H]^+$ *m/z* 494.1. ^{1}H NMR (600 MHz, CD_3OD) δ 8.70 (d, J = 4.9, 1H), 8.04 (s, 1H), 7.94 – 7.80 (m, 2H), 7.69 (d, J = 7.6, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.34 (m, 1H), 7.18 – 7.00 (m, 2H), 2.60 – 2.42 (m, 2H), 2.36 (s, 3H), 2.28 – 2.07 (m, 4H), 2.05 – 1.89 (m, 2H). rhSYK activity = +++. The starting material was prepared generally following the procedures described in Examples 32 and 33 using commercially available 1-{[{9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-4-oxocyclohexanecarboxylic acid.

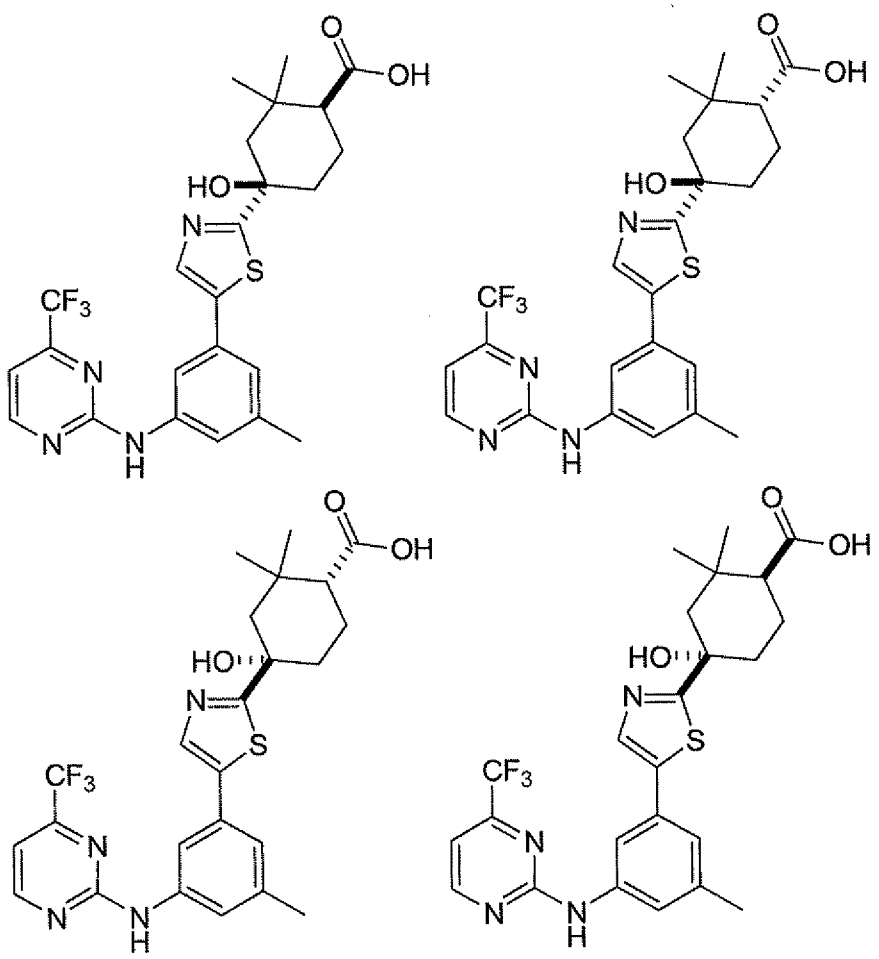
EXAMPLES 42(1) AND 42(2) AND 42(3) AND 42(4)

(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

(1*R*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

(1*S*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

(1*R*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid



Method 1

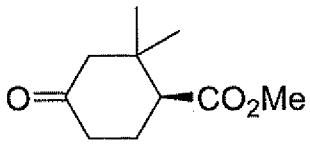
Lithium diispropylamide (1.31 M, 10.0 mL, 13.1 mmol) was cooled to -78 °C and *N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (**INTERMEDIATE 4,** 2.0 g, 5.95 mmol) in THF (20 mL) was added portionwise. While stirring at -78 °C additional lithium diisopropylamide (1.31 M, 4.55 mL, 5.95 mmol) was added. In a separate flask, lithium diisopropylamide (1.31 M, 10.0 mL, 13.1 mmol) was cooled to 0 °C and 2,2-dimethyl-4-oxo-cyclohexanecarboxylic acid (2.02 g, 11.9 mmol) in THF (20 mL) was added. The resulting solution of the carboxylate anion was transferred *via cannula* to the previously prepared thiazole anion solution, maintaining an internal reaction temperature below -68 °C. The resultant mixture was stirred at -78 °C for 1 h, then methanol (5 mL) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was poured into water (200 mL) and extracted with MTBE (2x). The layers were separated and the aqueous portion was acidified to pH=3 with 2 *N* aqueous HCl then extracted with ethyl acetate (2x). The combined organic portions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide a yellow foam. The foam was then purified and the enantiomers separated via supercritical fluid

chromatography (30% MeOH:CO_2) to give (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (**Example 42(1)**, 12.9 g, 25.5 mmol, 21%) as a yellow solid. MS ESI: $[M + H]^+$ *m/z* 507.1. ^1H NMR (500 MHz, DMSO-d_6) δ 12.13 – 11.86 (br s, 1H), 10.24 (s, 1H), 8.82 (m, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.46 (s, 1H), 7.27 (m, 1H), 7.14 (s, 1H), 5.89 (s, 1H), 2.31 (s, 3H), 2.16 (d, *J* = 12.7, 1H), 2.02 (m, 1H), 1.86 (m, 3H), 1.64 (d, *J* = 13.8, 1H), 1.57 (d, *J* = 13.1, 1H), 1.11 (s, 3H), 0.99 (s, 3H). rhSYK activity = +++.

(1*R*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid, (1*S*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid and (1*R*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (**Examples 42(2), 42(3), 42(4)**) were prepared in an analogous manner of that described above for the (1*S*,4*R*) isomer. MS ESI: $[M + H]^+$ *m/z* 507. rhSYK Activity: +++

Method 2 for the Preparation of Example 42(1)

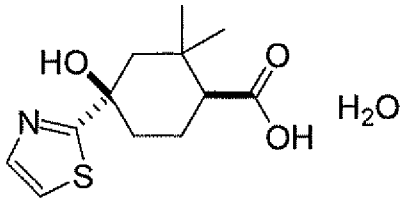
Step 1: Methyl (1*S*)-2,2-dimethyl-4-oxocyclohexanecarboxylate



NADPH-dependent ketoreductase KRED-119 (668 mg, 3% w/w, available from Codexis, Inc., Redwood City, CA), NADP (668 mg, 3% w/w), glucose dehydrogenase CDX-901 (668 mg, 3% w/w, available from Codexis, Inc., Redwood City, CA) and D-(+)-glucose (11.16 g, 61.9 mmol) were dissolved in KH_2PO_4/K_2HPO_4 buffer solution (0.1 M aqueous, pH=6.8, 445 mL) at ambient temperature. In a separate flask, racemic methyl 2,2-dimethyl-4-oxocyclohexanecarboxylate (**INTERMEDIATE 24,** 22.26 g, 113 mmol) was dissolved in DMSO (6 mL) and the resulting solution was added to the KH_2PO_4/K_2HPO_4 buffered solution described above. The pH of the combined mixture was adjusted to 6.9 with 17.6 M aqueous NaOH solution and the reaction mixture stirred for 19 h at pH 6.9. The pH was adjusted to 4 using 11.7 M HCl (aq.) solution and the reaction mixture was stirred for 30 minutes, and then MTBE (100 mL), 2-propanol (100 mL) and sodium chloride (40.0 g) were added. The phases were separated and the organic layer was filtered through a pad of Solka Floc 200. The aqueous layer and the residual aqueous layer from the filtrate were combined and then extracted with MTBE (100 mL). The combined organic layers were concentrated *in vacuo* to 100 mL, and treated twice with sodium bisulfite (7.03 g, 67.6 mmol) and water (100 mL), each time the biphasic mixture was stirred vigorously for 30 min. The combined aqueous phase was treated with potassium carbonate (22.0 g, 159.2 mmol) then diluted with MTBE (100 mL) and the layers were separated.

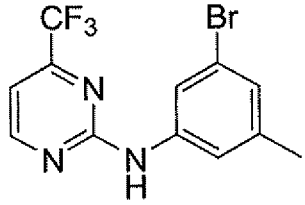
The combined organic layers were concentrated *in vacuo* to afford (1*S*)-2,2-dimethyl-4-oxo-cyclohexanecarboxylate (9.66 g, 96.2% ee) as an oil. MS ESI: M^{+}· *m/z* 184. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.62 (t, *J* = 6.6, 1H), 2.57 (m, 1H), 2.44 (dd, *J* = 13.7,1.8, 1H), 2.29 (m, 1H), 2.19 (d, *J* = 13.7, 1H), 2.11 (m, 2H), 1.07 (s, 3H), 1.00 (s, 3H).

Step 2: (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-(1,3-thiazol-2-yl) cyclohexanecarboxylic acid hydrate



To a solution of methyl (1*S*)-2,2-dimethyl-4-oxocyclohexanecarboxylate (10g, 54.28 mmol)) in THF (16.3g) was added additional THF (184 mL) followed by thiazole (6.93g, 81.42 mmol). The resulting solution was then cooled to -78 °C. Boron trifluoride diethyletherate (9.24g, 65.14 mmol) was added over 24 minutes and the resulting mixture aged at -78 °C for 5 minutes. *n*-Butyllithium (2.5M in hexanes, 20.05g, 71.98 mmol) was added to the mixture subsurface over 4 hours and the mixture was aged for 15 mins. Sodium hydroxide (1M aqeous solution, 54.3 mL, 54.3 mmol) was added followed by MTBE (54 mL) and the mixture was warmed to 20 °C. The aqueous layer was separated and the organic layer was washed with a half saturated aqeous solution of sodium chloride (54 mL) resulting in a light yellow solution of methyl (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-(1,3-thiazol-2-yl) cyclohexanecarboxylate, which was then concentrated under partial vacuum to a low volume. Methanol (124 mL) was added and the solution concentrated to an oil under partial vacuum. The solution was then diluted with methanol (124 mL) and heated to 40 °C. A solution of 1M sodium hydroxide (92 mL, 92.0 mmol) was added over 5 minutes and the resulting mixture heated to 50 °C then aged for 16 hours before being cooled to 20 °C. The solution was washed three times with dichloromethane (124 mL, 62 mL, 62 mL) and the aqueous methanol solution of the product was crystallised by addition of 6M aqueous HCl (15.3 mL, 92 mmol) over 30 mins. The slurry was aged for 2 hours then the mixture was concentrated under partial vacuum to a total volume of 124 mL. The solid was collected by filtration and washed with water-methanol (1:1 v:v, 62 mL) then water (62 mL) to give the title compound (11.44g, 41.86 mmol, 99.9% ee) as a pale yellow solid. MS ESI : $[M+H]^{+}$ 256.1 ^{1}H NMR (400 MHz, DMSO-d_6): 11.89-12.09 (br s, 1H), 7.67 (d, *J* = 3.5 Hz, 1H), 7.53 (d, *J* = 3.5 Hz, 1H), 5.79 (s, 1H), 3.36 (br s, 2H), 2.13-2.20 (m, 2H), 1.95-2.09 (m, 1H), 1.76-1.91 (m, 3H), 1.53-1.65 (m, 2H), 1.11 (s, 3H), 0.99 (s, 3H).

Step 3: *N*-(3-bromo-5-methylphenyl)-4-(trifluoromethyl)pyrimidin-2-amine



To a solution of 3-bromo-5-methylaniline (45.77 g, 246 mmol) in toluene (500 ml) were sequentially added 2-chloro-4-(trifluoromethyl)pyrimidine (53.9 g, 295 mmol) and methanesulfonic acid (28.4 g, 295 mmol) . The resulting solution was heated to 105 °C overnight. The resulting mixture was cooled, diluted with water (500 mL) and adjusted to pH 14 via addition of a concentrated aqueous sodium hydroxide solution (26.6g of a solution containing 320 mmol of sodium hydroxide). The resulting solution was extracted with MTBE (500 mL), the layers separated, and the organic layer subsequently washed with water (300 ml) then 50% saturated brine solution (200 mL). The organic layer was concentrated *in vacuo* to 200ml resulting in product crystallization. To the slurry was added heptane (660 mL) over 40 minutes followed by a 2 hr aging at 20 °C. The solid was isolated via filtration, washed with heptane (200 mL) and dried in a vacuum oven at 40 °C overnight to provide the title compound (69.5 g, 209 mmol) as a light yellow solid. MS ESI: $[M + H]^+$ *m/z* 334.0. ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 4.9 Hz, 1 H); 7.79 (s, 1 H); 7.30 (s, 2 H); 7.10-7.06 (m, 2 H); 2.36 (s, 3 H).

Step 4: (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]-amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

A mixture of the product of Step 2 (8.5g, 31.2 mmol), the product of Step 3 (11 g, 33.4 mmol), palladium(II) acetate (0.15 g, 0.68 mmol), pivalic acid (3.5g, 35.3 mmol), potassium carbonate (15.1 g, 109 mmol) and diadamantyl *n*-butyl phosphine (0.74 g, 2.1 mmol) was purged with nitrogen. Dimethyl acetamide (60 ml) was added and the suspension was purged with nitrogen. The mixture was stirred at 120 °C for 20 hours, cooled and poured into water (90 ml) and MTBE (40 ml). The aqueous phase was separated and washed with MTBE (2x). The aqueous phase was acidified with 6N HCl to pH <1 and extracted with MTBE (1x). The organic phase was washed with water (2x) then MBTE was distilled off to concentrate the solution. Acetonitrile was added to the residue resulting in crystallization of the title compound, which was isolated by filtration and dried *in vacuo* . The crude product was recrystallised from MeCN : THF (3:1) to give (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (11.9 g, 23.4 mmol) as a yellow solid.

MS ESI: $[M + H]^+$ *m/z* 507.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.03 – 11.95 (br s, 1H), 10.24 (s, 1H), 8.84 (d, *J* = 4.7, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.46 (s, 1H), 7.27 (d, *J* = 4.8, 1H), 7.13 (s, 1H), 5.89 (s, 1H), 2.32 (s, 3H), 2.16 (d, *J* = 12.7, 1H), 2.10 – 1.95 (m, 1H), 1.86 (m, 3H), 1.65 (d, *J* = 13.8, 1H), 1.59 (d, *J* = 13.1, 1H), 1.13 (s, 3H), 1.01 (s, 3H). rhSYK Activity: +++

EXAMPLE 42(1)-Na

Sodium (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]-amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

Method 1

(1*S*,4*R*)-4-Hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (9.8 mg, 0.019 mmol) was dissolved in acetonitrile (20 μL) and water (20 μL). Sodium hydroxide (19 μL, 0.019 mmol) was added, and the mixture was heated to 35 °C for 10 min. The mixture was allowed to cool to rt, diluted with water, froze to a solid, and lyophilized to dryness to afford sodium (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-cyclohexanecarboxylate.

Method 2

(1*S*,4*R*)-4-Hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (7.15 g, 14.12 mmol) was dissolved in tetrahydrofuran (35 ml). Sodium hydroxide (10 M, 1.383 ml, 13.83 mmol) was added, and the mixture was aged for 15 minutes. Ethyl acetate (50 ml) was slowly added over 45 minutes and the mixture was aged for 1 hr at 20 °C. A further aliquot of ethyl acetate (25 ml) was added and 55 ml of solvent was removed *in vacuo*. The slurry was filtered and washed with ethyl acetate (35 ml). The solid was dried *in vacuo* at 70 °C to afford the title compound (7.02 g, 13.28 mmol).

MS ESI: $[M + H]^+$ *m/z* 507.1. ^1H NMR (400 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.48 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.12 (s, 1H), 5.82 (br s, 1H), 2.31 (s, 3H), 1.96 – 1.85 (m, 1H), 1.84 – 1.68 (m, 4H), 1.60 – 1.45 (m, 2H), 1.12 (s, 3H), 1.01 (s, 3H). rhSYK activity = +++

EXAMPLE 42(1)-K

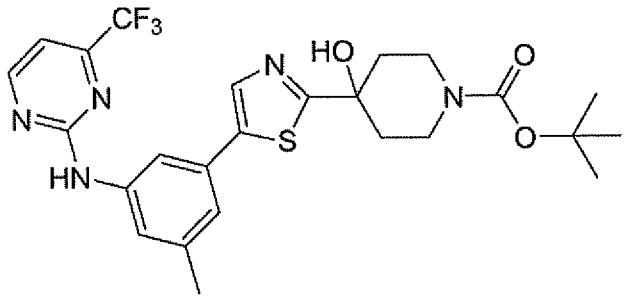
Potassium (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate

(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (9.8 mg, 0.019 mmol) was dissolved in acetonitrile (20 μL) and water (20 μL). Potassium hydroxide (19 μL, 0.019 mmol) was added, and the mixture was heated to 35 °C for 10 min. The mixture was allowed to cool to room temperature, diluted with water, froze to a solid, and lyophilized to dryness to afford potassium (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate. MS ESI: $[M + H]^+$ *m/z* 507.1. ^1H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.91 (s, 1H), 7.88 (s, 1H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.12 (s, 1H), 5.97 (s, 2H), 2.31 (s, 3H), 1.92 – 1.82 (m, 2H),

1.81 – 1.65 (m, J = 13.8, 5H), 1.54 – 1.48 (m, 1H), 1.47 – 1.39 (m, 1H), 1.05 (s, 3H), 0.95 (s, 3H). rhSYK activity = +++

EXAMPLE 45

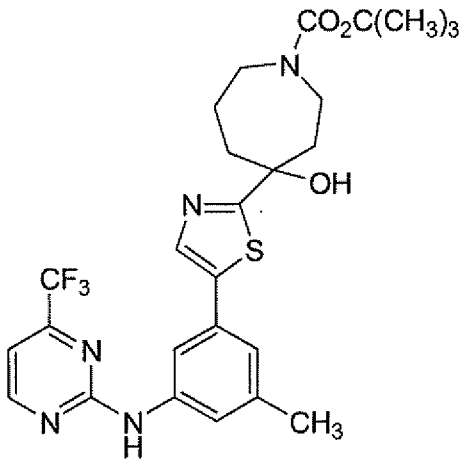
tert-butyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxylate



At -78 °C, **INTERMEDIATE 4** (200 mg, 0.595 mmol) in THF (3.0 mL)was added to LDA (892 µL, 1.784 mmol) and the reaction aged for 10 min followed by addition of *tert*-butyl 4-oxo-piperidine-1-carboxylate (474 mg, 2.379 mmol). The reaction was allowed to slowly warm to -20 °C over 4 hrs. To the mixture was added saturated aqueousammonium chloride solution and the product was extracted with ethyl acetate. The organic layer was washed with water and brine. The combined organic layer was dried, filtered and solvent reduced by rotovap. The residue was purified by column chromatography on silica gel (0-50% ethyl acetate in DCM) to give 260 mg (0.485 mmol, 82%) *tert*-butyl4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxylate as off-white solid. MS ESI: $[M + H]^+$ *m/z* 536.2. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (d, J = 4.8 Hz, 1H); 7.81 (appr s, 2H); 7.74 (br s, 1H); 7.28 (s, 1H); 7.02 (s, 1H); 7.00 (d, J = 4.8 Hz, 1H); 4.0 (br s, 2H); 3.28 (br s, 2H); 2.34 (s, 3H); 2.09 (m, 2H); 1.88 (m, 2H); 1.41 (s, 9H). rhSYK = ++

Compounds in the following Table(s) were prepared as the free base in an analogous manner of that described in Example 45:

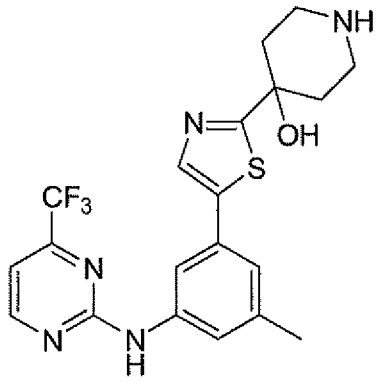
TABLE 45



Ex.	Structure	rhSYK Activity	[M+H]+ Obs'd
45-1	Enantiomer 1	++	550.2
45-2	Enantiomer 2	++	550.2

EXAMPLE 46

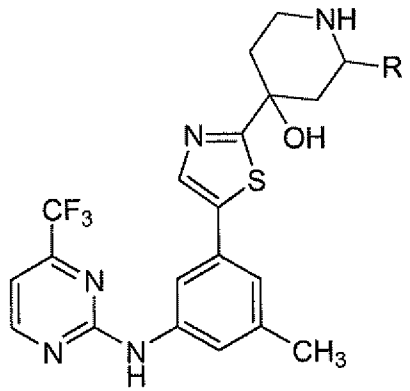
4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-4-ol



To *tert*-butyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxylate (50 mg, 0.093 mmol) in DCM (1 mL) was added 144 uL TFA (20 eq) and the reaction stirred at rt for 4h. To the mixture was added saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water and brine. The combined organic layer was dried, filtered. The solvent was reduced *in vacuo* to give 40 mg (0.092 mmol, 98%) of 4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-4-ol. MS ESI: $[M + H]^+$ *m/z* 436.2. ^1H NMR (600 MHz, DMSO-d_6): δ 8.81 (d, *J* = 4.7 Hz, 1H); 7.93 (m, 2H), 7.44 (s, 1H); 7.25 (d, *J* = 4.9 Hz, 1H); 7.13 (s, 1H); 5.97 (br s, 1H), 2.78-2.98 (m, 4H); 2.29 (s, 3H); 1.93-1.98 (m, 2H), 1.63-1.65 (m, 2H). rhSYK activity = +++

Compounds in the following Table(s) were prepared in a manner analogous of that described in Examples 45/46:

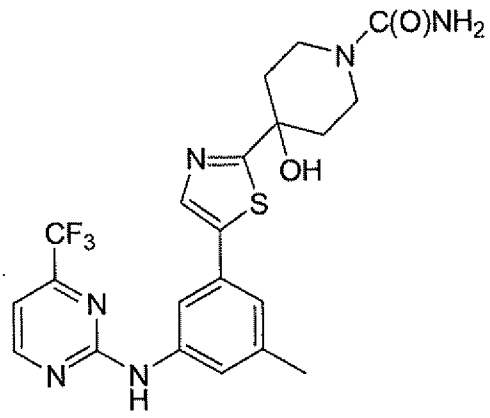
TABLE 46



Ex.	R	rhSYK Activity	[M+H]+ Obs'd	Form(s)
46-1	CF_3	+++	504.1	Free Base
46-2	CO_2CH_3	+++	494.1	Free Base

EXAMPLE 47

4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide

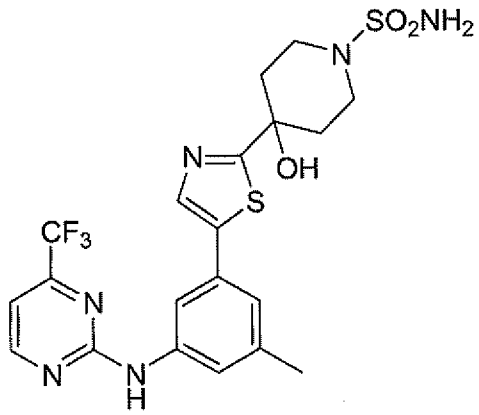


To 15 mg (0.034 mmol) of 4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3- thiazol-2-yl]piperidin-4-ol in THF/Water (3:1, 1 mL) was added 4.2 mg (0.052 mmol, 1.5 eq) of potassium cyanate and 2N hydrochloric acid (22 µL, 1.3eq). The mixture was heated at 50 °C for 6h and then another 1.5 eq of potassium cyanate and 1.5 eq HCl added and the mixture stirred at 50°C overnight. The reaction was diluted with saturated aqueous $NaHCO_3$ and was partitioned with ethyl acetate. The organic layer was washed with water and dried, filtered and solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (0-100% ethyl acetate in hexanes) to give 12 mg (0.025mmol, 73%)

of 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide as off-white solid. MS ESI: $[M + H]^+$ *m/z* 479.2. ^1H NMR (600 MHz, CD_3OD): δ 8.68 (d, *J* = 4.8 Hz, 1H); 7.99 (s, 1H); 7.87 (s, 1H); 7.40 (s, 1H); 7.10 (m, 2H); 3.91 (m,\2H); 3.28 (m, 2H); 2.34 (s, 3H); 2.16 (m, 2H); 1.83 (m, 2H). rhSYK activity = +++

EXAMPLE 49

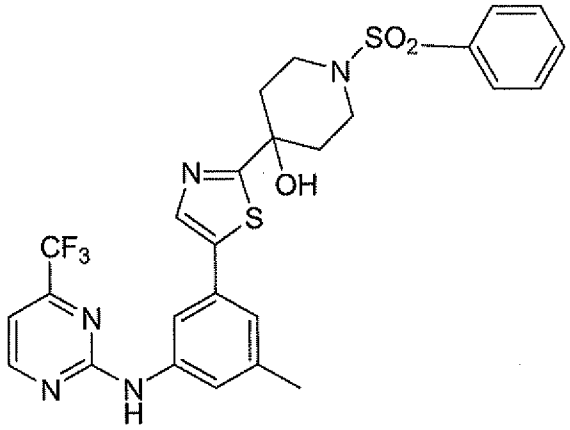
4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-sulfonamide



To a solution of *tert*-butyl({4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-1-yl}sulfonyl)carbamate (45 mg, 0.073 mmol) in DCM (0.7 mL) was added TFA (0.120 mL, 1.5 mmol) and the reaction was stirred at room temperature for 80 min, then more TFA (0.120 mL, 1.5 mmol) was added. After 90 min most volatiles were removed by N_2 flow and vacuum. The residue was diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The combined organic layers were dried and evaporated to give 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-sulfonamide (31 mg, 0.06 mmol, 82% yield). MS ESI: $[M + H]^+$ *m/z* 515.2. ^1H NMR (600 MHz, $CDCl_3$): δ 8.59 (d, *J* = 4.8 Hz, 1H); 7.87 (s, 1H); 7.81 (s, 1H); 7.25 (s, 1H); 7.02 (s, 1H); 7.00 (d, *J* = 4.8 Hz, 1H); 3.59 (d, *J* = 12 Hz, 2H); 3.14 (m, 2H); 2.34 (s, 3H); 2.26 (m, 2H); 1.94 (d, *J* = 12 Hz, 2H). rhSYK activity = +++

EXAMPLE 50

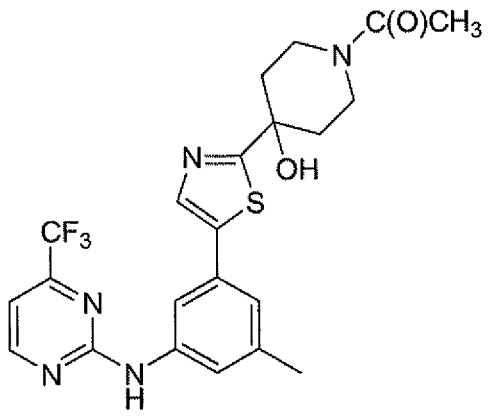
4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1-(phenylsulfonyl)piperidin-4-ol



4-[5-(3-Methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]piperidin-4-ol (**Example 46,** 50 mg, 0.115 mmol) was dissolved in CH_2Cl_2 (1 mL). *N,N*-diisopropylethylamine (50 μL, 0.287 mmol) and benzenesulfonyl chloride (29 μL, 0.230 mmol) were added sequentially. The solution was stirred overnight at room temperature, then concentrated *in vacuo* on a Genevac. The resultant residue was dissolved in DMSO and purified via HPLC (48-82% CH_3CN:H_2O) to provide 4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1-(phenylsulfonyl)piperidin-4-ol. MS ESI: $[M + H]^+$ *m/z* 576.1. ^1H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.80 (d, *J* = 5.2 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 2H), 7.75 (dd, *J* = 8.7, 10.3 Hz, 2H), 7.73 (s, 1H), 7.65 (t, *J* = 8.1 Hz, 1H), 7.43 (s, 1H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.12 (s, 1H), 6.10 (s, 1H), 3.54 (d, *J* = 12.3 Hz, 1H), 2.58 (t, *J* = 12.3 Hz, 2H), 2.54 – 2.37 (m, 1H), 2.28 (s, 3H), 2.08 (t, *J* = 16.1 Hz, 2H), 1.80 (d, *J* = 14.6 Hz, 2H). rhSYK activity = ++

EXAMPLE 51

1-{4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-1-yl}ethanone

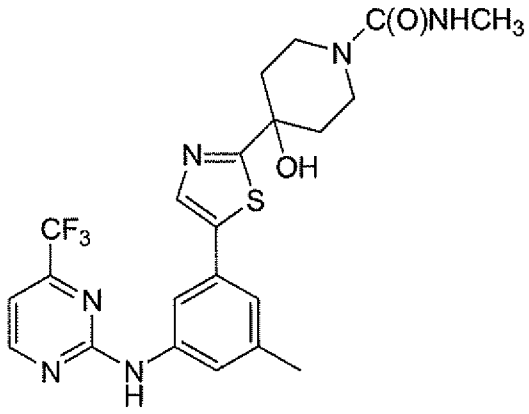


To a mixture of acetic acid (9 μL, 0.15 mmol) and Si-carbonyl diimidazole (266 mg, 0.287 mmol) was added a solution of 4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]piperidin-4-ol (**Example 46,** 50 mg, 0.115 mmol) and hydroxybenzotriazole (26 mg, 0.17 mmol) dissolved in *N,N*-dimethylformamide, and the

resultant suspension was shaken in a Bohdan block overnight at room temperature. The reaction mixture was filtered and concentrated *in vacuo*, and the resultant residue was dissolved in DMSO and purified via HPLC (30-64% CH_3CN:H_2O) to provide 1-{4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidin-1-yl}ethanone. MS ESI: $[M + H]^+$ *m/z* 478.1. ^1H NMR (600 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 7.95 (s, 2H), 7.44 (s, 1H), 7.26 (d, *J* = 5.1Hz, 1H), 7.14 (s, 1H), 6.30 (s, 1H), 4.25 – 3.99 (m, 1H), 3.73 (m, 1H), 3.41 – 3.34 (m, 1H), 3.07 – 2.97 (m, 1H), 2.47 (s, 3H), 2.32 (s, 3H), 2.25 – 2.14 (m, 1H), 1.93 (m, 2H), 1.75 (m, 1H). rhSYK activity = +++

EXAMPLE 52

4-hydroxy-*N*-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide

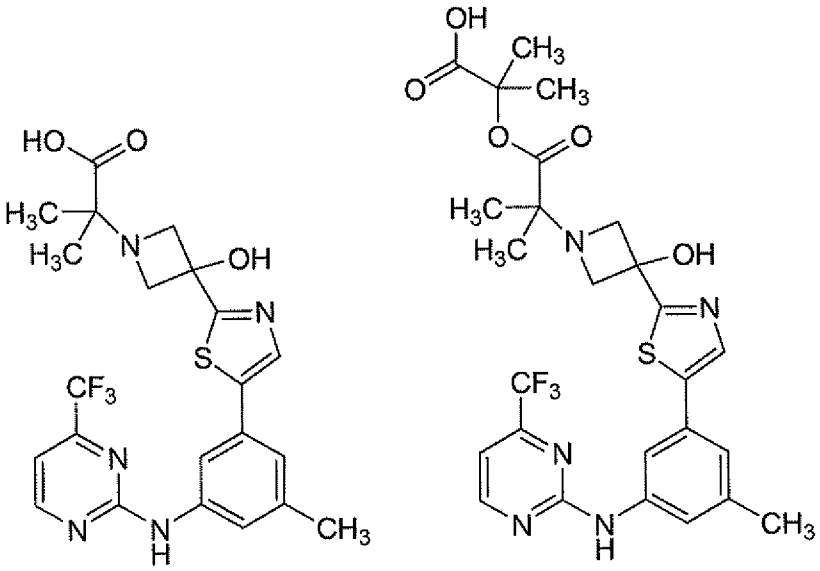


4-[5-(3-Methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3- thiazol-2-yl]piperidin-4-ol (**Example 46,** 50 mg, 0.115 mmol) was dissolved in CH_2Cl_2 (1 mL). *N,N*-diisopropylethylamine (30 μL, 0.172 mmol) and methyl isocyanate (7 μL, 0.130 mmol) were added sequentially. The solution was stirred overnight at rt, then concentrated *in vacuo* on a Genevac. The resultant residue was dissolved in DMSO and purified via HPLC (30-64% CH_3CN:H_2O) to provide 4-hydroxy-*N*-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]piperidine-1-carboxamide (36 mg, 0.073 mmol). MS ESI: $[M + H]^+$ *m/z* 493.1. ^1H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 7.93 (s, 2H), 7.44 (s, 1H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.13 (s, 1H), 6.43 (d, *J* = 4.8 Hz, 1H), 6.15 (s, 1H), 3.83-3.74 (m, 2 H) (d, *J* = 14.0 Hz, 2H), 3.07 (t, *J* = 14.5 Hz, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.98 – 1.82 (m, 2H), 1.65 (d, *J* = 13.9 Hz, 2H). rhSYK activity = +++

EXAMPLES 53(1) AND 53(2)

2-{3-Hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoic acid

2-[(2-{3-Hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoyl)oxy]-2-methylpropanoic acid



A solution of 3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-3-ol (50 mg, 0.123 mmol), 2-bromo-2-methyl propionic acid (20.5 mg, 0.123 mmol), and triethylamine (0.043 mL, 0.307 mmol) in tetrahydrofuran (1 mL) was heated in a microwave for 100 min for 5 min. An additional amount of 2-bromo-2-methyl propionic acid (8 mg, 0.048 mmol), triethylamine (0.060 mL, 0.428 mmol), and tetrahydrofuran (1 mL) were added and the reaction was heated in a microwave oven for an additional 10 min. The reaction was concentrated and then purified by reverse phase HPLC (15% to 50% acetonitrile in water). The fractions containing the desired products were lyophilized to afford:

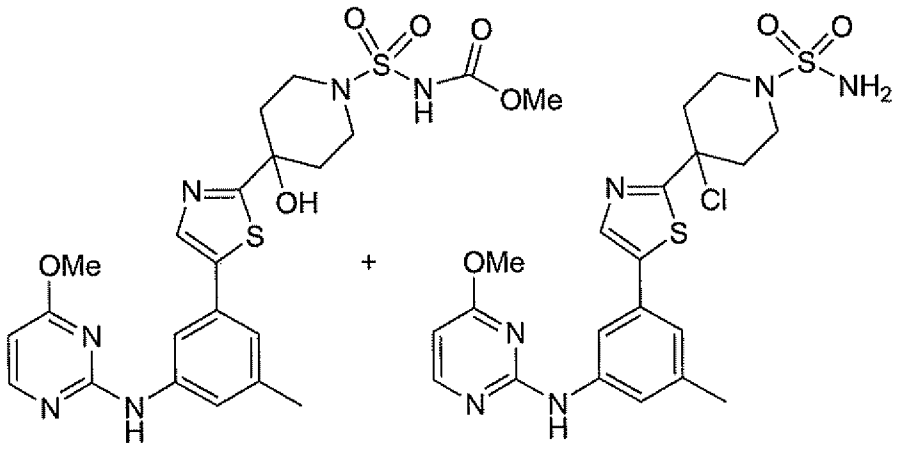
2-{3-Hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoic acid (**Example 53(1)**, 32.5 mg). MS ESI: $[M + H]^+$ *m/z* 494.1. ^{1}H NMR (500 MHz, d$_6$-DMSO): δ 10.30 (s, 1 H); 8.85 (d, *J* = 4.9 Hz, 1 H); 8.19 (s, 1 H); 8.04 (s, 1 H); 7.73 (s, 1 H); 7.47 (s, 1 H); 7.29 (d, *J* = 4.9 Hz, 1 H); 7.22 (s, 1 H); 4.82-4.50 (m, 2 H); 4.33-4.11 (m, 2 H); 2.33 (s, 3 H); 1.53 (s, 6 H). rhSYK activity = +++

2-[(2-{3-Hydroxy-3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azetidin-1-yl}-2-methylpropanoyl)oxy]-2-methylpropanoic acid (**Example 53(2)**, 8 mg). MS ESI: $[M + H]^+$ *m/z* 580.2. ^{1}H NMR (500 MHz, d$_6$-DMSO): δ 10.29 (s, 1 H); 8.83 (d, *J* = 4.6 Hz, 1 H); 8.18 (s, 1 H); 8.03 (s, 1 H); 7.81 (s, 1 H); 7.46 (s, 1 H); 7.29 (d, *J* = 5.1 Hz, 1 H); 7.21 (s, 1 H); 4.83 (br s, 1 H); 4.72-4.41 (m, 2 H); 4.34-4.12 (m, 1H); 2.32 (s, 3 H); 1.52 (br s, 12 H). rhSYK activity = +++

EXAMPLES 54(1) AND 54(2)

Methyl {[4-hydroxy-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)piperidin-1-yl]sulfonyl}carbamate

4-Chloro-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-piperidine-1-sulfonamide



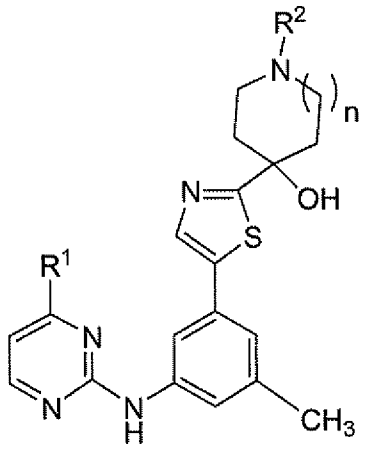
At 0 °C, chlorosulfonyl isocyanate (16.38 μL, 0.189 mmol) in dichloromethane was added methanol (7.63 μL, 0.189 mmol). After stirring for 30min, to the mixture was added 4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)piperidin-4-ol (50 mg, 0.126 mmol) and triethylamine (52.6 μL, 0.377 mmol). The reaction was aged for 20 min and ice bath removed, and stirred for 3 h. LCMS indicates product formation. The material was directly subject to column chromatography on silica gel (0-100% 10:1 ethyl acetate: methanol in hexanes) to afford:

Methyl {[4-hydroxy-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)piperidin-1-yl]sulfonyl}carbamate (7 mg, 0.013 mmol, 10 %). MS ESI: $[M + H]^+$ *m/z* 535.1. ^{1}H NMR (600 MHz, CD_3OD): δ 8.09 (d, *J* = 6.0 Hz, 1H); 7.91 (s, 1H); 7.88 (s, 1H); 7.38 (s, 1H); 7.08 (s, 1H); 6.23 (d, *J* = 6.0 Hz, 1H); 3.98 (s, 3H); 3.73 (m, 3H); 3.34 (m, 2H); 3.19 (m, 2H); 2.35 (s, 3H); 2.25 (m, 2H); 1.90 (m, 2H). rhSYk activity = +++

4-Chloro-4-(5-{3-[(4-methoxypyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-piperidine-1-sulfonamide (18 mg, 0.036 mmol, 28%). MS ESI: $[M + H]^+$ *m/z* 495.2. ^{1}H NMR (500 MHz, CD_3OD): δ 8.09 (d, *J* = 6.0 Hz, 1H); 7.89 (s, 2H); 7.38 (s, 1H); 7.09 (s, 1H); 6.24 (d, *J* = 6.0 Hz, 1H); 4.37 (m, 1H); 3.99 (s, 3H); 3.97 (m, 1H); 3.68 (m, 1H); 3.36 (m, 1H); 2.35 (s, 3H); 2.19 (m, 2H); 1.94 (m, 2H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Examples 47-54 for *N,N*-disubstituted urea (Example 47), disubstituted sulfamoyl *t*-butyl carbamate (Example 48), *N,N,N'*-trisubstituted sulfuric diamide (Example 49), *N,N*-disubstituted sulfonamide or sulfamic acid (Example 50), amide (Example 51), *N,N,N'*-trisubstituted urea (Example 52), *N*-alkylated azetidine, pyrrolidine, piperidine or azepane (Example 53), and *N,N,N'*-trisubstituted sulfamoyl carbamate (Example 54).

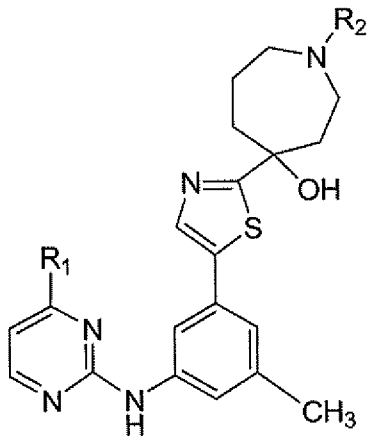
TABLE 54A



Ex.	R^1	R^2	rhSYK Activity	[M+H]+ Observed	Form(S)
n = 1					
54A-1	CF_3	$-SO_2$-iPr	+++	542.1	Formate Salt
54A-2	CF_3	$-SO_2-CF_3$	+++	568.1	Formate Salt
54A-4	CF_3	-C(O)Et	+++	492.1	Formate Salt
54A-5	CF_3	$-C(O)CH_2OH$	+++	494.1	Formate Salt
54A-6	CF_3	$-C(O)CH_2CN$	+++	503.1	Formate Salt
54A-7	CF_3	$-C(O)CH_2N(CH_3)_2$	+++	521.2	Formate Salt
54A-11	CF_3	-C(O)-c-Pr	+++	504.1	Formate Salt
54A-12	CF_3	-C(O)NHc-Hex	+++	561.2	Formate Salt
54A-13	CF_3	-C(O)NH-iPr	+++	521.2	Formate Salt
54A-14	CF_3	-C(O)NH-nPr	+++	521.2	Formate Salt
54A-15	CF_3	$-C(O)N(CH_3)_2$	+++	507.1	Free Base
54A-16	CF_3	$-SO_2NH_2$	+++	515.2	Free Base
54A-19	OCH_3	$-C(O)NH_2$	+++	441:2	Free Base
54A-20	OCH_3	H	+++	398.2	Free Base
54A-21	CF_3	$-C(O)CH(OH)CH_3$ (R)	+++	508.2	Formate Salt
54A-22	CF_3	$-C(O)CH_2CH_2OH$	+++	508.2	Free Base
54A-23	CF_3	$-C(O)CH_2CH_2CN$	+++	517.2	Formate Salt
54A-24	CF_3	$-CH_2CF_3$	+++	518.1	Free Base
54A-25	CF_3	$-C(O)CH_2C(O)NH_2$	+++	521.2	Formate Salt
54A-26	CF_3	$-C(O)CH_2C(O)_2H$	+++	522.1	Free Base
54A-27	CF_3	$-C(O)CH_2CH(OH)CH_3$	+++	522.2	Free Base
54A-33	CF_3	-C(O)-(3-OH-cBu)	+++	534.2	Formate Salt
54A-34	CF_3	-C(O)-Ph	+++	540.2	Formate Salt

54A-43	CF_3	-C(O)CH_2-CO_2Et	+++	550.2	Free Base
54A-44	CF_3	-C(O)C(CH_2OH)$_2CH_3$	+++	552.2	Formate Salt
54A-54	CF_3	-C(O)-(1-CO_2CH_3)-cPr	+++	562.2	Free Base
54A-55	CF_3	-C(O)-(4-C≡CH)Ph	+++	564.2	Formate Salt
54A-56	CF_3	-C(O)-(4-CN)Ph	+++	565.2	Formate Salt
54A-57	CF_3	-C(O)-(3-F, 4-OH)Ph	+++	574.2	Formate Salt
54A-59	CF_3	-C(O)-(4-CO_2CH_3)Ph	+++	604.2	Formate Salt
54A-61	CF_3	$(CH_2)_3CH_3$	+++	535.2	Free Base
54A-70	CF_3	$CH_2CO_2CH_3$	+++	508.2	Free Base
54A-71	CF_3	$CH_2CH_2CO_2CH_3$	+++	522.2	Free Base
54A-72	CF_3	$CH(CH_3)CO_2CH_3$	+++	522.2	Free Base
54A-73	CF_3	$(CH_2)_3CO_2CH_3$	+++	536.2	Free Base
n = 2					
54A-74	CF_3	CH_3	+++	507.2	Free Base
54A-75	CF_3	CH_3 (Enantiomer 1)	+++	507.2	Free Base
54A-76	CF_3	CH_3 (Enantiomer 2)	+++	507.2	Free Base
54A-78	CF_3	$CH_2CH_2CH_3$	+++	535.2	Free Base
54A-79	CF_3	$CH(CH_3)_2$	+++	535.2	Free Base
54A-80	CF_3	CH_2CO_2Et	+++	579.2	Free Base
54A-81	CF_3	$(CH_2)_3CO_2Et$	+++	607.2	Tfa Salt
54A-82	CF_3	CH_2CH_2F	+++	496.2	Tfa Salt
54A-83	CF_3	CH_2CO_2H	++	508.2	Tfa Salt
54A-84	CF_3	$CH_2CH_2CO_2H$	+++	522.2	Free Base
54A-85	CF_3	CH_2CF_3 (Enantiomer 1)	+++	532.2	Free Base
54A-86	CF_3	CH_2CF_3 (Enantiomer 2)	+++	532.2	Free Base
54A-87	CF_3	CH_2CF_3	+++	532.2	Tfa Salt
54A-88	CF_3	$CH_2CH_2CO_2CH_3$	+++	536.2	Formate Salt
54A-89	CF_3	$CH_2CO_2C(CH_3)_3$	+++	564.2	Free Base

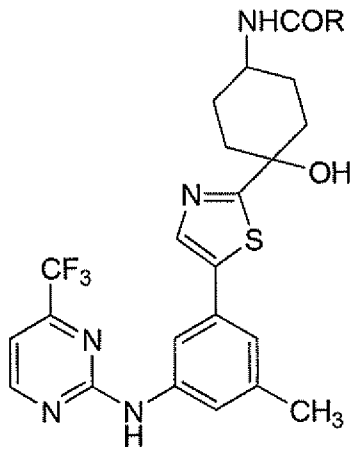
TABLE 54D



Ex.	R1	R2	rhSYK Activity	[M+H]+ Obs'd	Form(s)
54D-1	iPr	H	+++	424.2	Free Base
54D-2	CF_3	-C(O)CH_3	+++	492.2	Free Base
54D-3	iPr	-(*S*)-C(O)CH(OH)CH_3	+++	496.2	Free Base
54D-4	iPr	-C(O)CH(OH)CH_3	+++	496.2	Free Base
54D-5	CF_3	-C(O)Et	+++	506.2	Free Base
54D-6	iPr	-C(O)CH_2C(O)NH_2	+++	509.2	Free Base
54D-7	iPr	-C(O)CH_2CO_2H	+++	510.2	Free Base
54D-8	iPr	-C(O)CH(OH)CH_2OH	+++	512.2	Free Base
54D-9	CF_3	-C(O)CH_2CN	+++	517.2	Free Base
54D-10	CF_3	-C(O)-cPr	+++	518.2	Free Base
54D-12	CF_3	-C(O)CH_2OCH_3	+++	522.2	Free Base
54D-13	CF_3	-C(O)CH_2CH_2OH	+++	522.2	Formate Salt
54D-14	CF_3	-C(O)CH(OH)CH_3	+++	522.2	Formate Salt
54D-15	iPr	-C(O)CH_2CH_2C(O)NH_2	+++	523.2	Free Base
54D-16	CF_3	-C(O)CH_2CH_2CN	+++	531.2	Free Base
54D-21 & 54D-22	CF_3	-C(O)CH_2C(O)NH_2 (2 isolated enantiomers)	+++	535.2	Free Base
54D-23	CF_3	-C(O)CH_2CH(OH)CH_3	+++	536.2	Formate Salt
54D-24 & 54D-25	CF_3	-C(O)CH_2CO_2H (2 isolated enantiomers)	+++	536.2	Free Base
54D-27 & 54D-28	CF_3	-C(O)CH(OH)CH_2OH (2 isolated isomers)	+++	538.2	Formate Salt
54D-30	iPr	-C(O)CH_2CO_2Et	+++	538.2	Free Base
54D-31	iPr	-C(O)C(CH_2OH)$_2CH_3$	+++	540.3	TFA Salt

54D-41 & 54D-42	CF_3	-C(O)$(CH_2)_2$C(O)NH_2 (2 isolated enantiomers)	+++	549.2	TFA Salt
54D-43	CF_3	-C(O)$CH_2CH_2CO_2H$	+++	550.2	TFA Salt
54D-44	CF_3	-C(O)$CH_2C(CH_3)_2OH$	+++	550.2	Formate Salt
54D-45	CF_3	-C(O)-Ph	+++	554.2	Free Base
54D-70	CF_3	-C(O)-(1-CO_2H-cPr)	+++	562.2	Formate Salt
54D-71	CF_3	-C(O)-(2-CO_2H-cPr)	+++	562.2	Formate Salt
54D-72	CF_3	-C(O)$CH_2CH_2CO_2CH_3$	+++	564.2	Free Base
54D-73 & 54D-74	CF_3	-C(O)$CH_2CO_2CH_2CH_3$ (2 isolated enantiomers)	+++	564.2	Free Base
54D-77	CF_3	-C(O)CH(OH)$C(CH_3)_2OH$	+++	566.2	Formate Salt
54D-78 & 54D 79	CF_3	-C(O)$C(CH_2OH)_2CH_3$ (2 isolated enantiomers)	+++	566.2	TFA Salt
54D-84	CF_3	-C(O)-(4-OH)Ph	+++	570.2	Free Base
54D-95	CF_3	-C(O)-(1-CO_2CH_3)-cPr	+++	576.2	Formate Salt
54D-98	CF_3	-C(O)$CH_2CH_2C(O)N(CH_3)_2$	+++	577.2	Free Base
54D-99	CF_3	-C(O)-(4-C≡CH)Ph	+++	578.2	Free Base
54D-102	CF_3	-C(O)$C(CH_2OH)_2CH_2CH_3$	+++	580.2	Free Base
54D-103	CF_3	-C(O)-(3-F, 4-OH)Ph	+++	588.2	Free Base
54D-104	CF_3	-C(O)-(2-F, 5-OH)Ph	+++	588.2	Free Base
54D-111	CF_3	-C(O)-(4-CO_2CH_3)-cHex	+++	618.2	Free Base
54D-112	CF_3	C(O)$CH_2C(OH)(CF_3)CO_2CH_3$	+++	648.2	Formate Salt
54D-115 54D-116	CF_3	SO_2NH_2 (2 isolated enantiomers)	+++	529.1	Free Base
54D-119 & 54D-120	CF_3	C(O)NH_2 (2 isolated enantiomers)	+++	493.1	Free Base
54D-121 & 54D-122	CF_3	C(O)CH_2OH (2 isolated enantiomers)	+++	508.2	Free Base

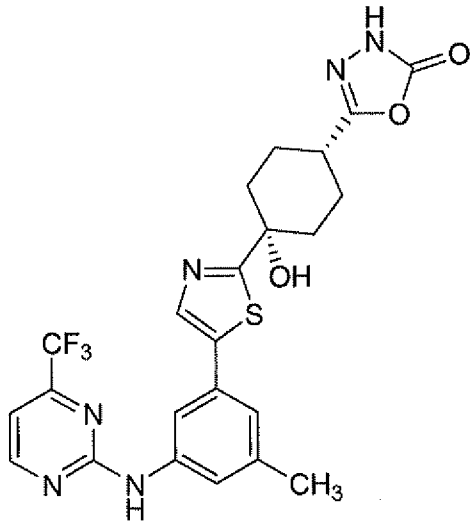
TABLE 54E



Ex.	R	rhSYK Activity	[M+H]+ Observed	Form(s)
54E-1	$CH(OH)CH_3$ (2R; cis)	+++	522.2	Formate Salt
54E-2	$CH(OH)CH_3$ (2S; cis)	+++	522.2	Formate Salt
54E-3	$CH_2C(O)NH_2$ (cis)	+++	535.2	Formate Salt
54E-8	$CH_2CH_2C(O)NH_2$ (cis)	+++	549.2	Formate Salt
54E-20	$C(CH_2OH)_2CH_3$ (cis)	+++	566.2	Formate Salt
54E-31	$CH_2CH_2CON(CH_3)_2$ (cis)	+++	577.2	Formate Salt
54E-34	$C(CH_2OH)_3$	+++	580.2	Formate Salt

EXAMPLE 55

5-{cis-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}-1,3,4-oxadiazol-2(3H)-one

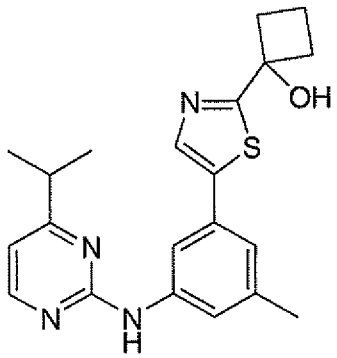


Step 1: *cis*-4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (150 mg, 0.313 mmol), hydrazinecarboxamide hydrochloride (52.4 mg, 0.470 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (149 mg, 0.392 mmol), and diisopropylethylamine (164 µl, 0.940 mmol) were taken-up in dimethylformamide (1.3 mL) under argon. The vessel was sealed and stirred at 125 °C for 18 hours. The reaction mixture was cooled to room temperature, filtered, and directly subjected to reverse-phase HPLC (water-acetonitrile, trifluoroacetic acid modifier). This purification afforded 5-{*cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}-1,3,4-oxadiazol-2(3H)-one as a white solid (39.1 mg, 0.075 mmol, 24% yield). MS ESI: $[M + H]^+$ *m/z* 519.1. ^1H NMR (500 MHz, dmso) δ 12.10 (s, 1H), 10.25 (s, 1H), 8.82 (d, *J* = 4.8, 1H), 8.02 – 7.88 (m, 2H), 7.45 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.15 (s, 1H), 6.06 (s, *J* = 27.1, 1H), 2.67 (s, 1H), 2.31 (s, 3H), 2.09 – 1.75 (m, 8H). rhSYK activity = +++

EXAMPLE 56

1-[5-(3-methyl-5-{[4-(propan-2-yl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutanol HCl salt



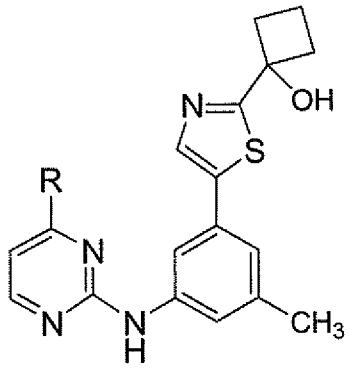
Step 1: Acetic acid (0.192 mL, 3.35 mmol) was added to commercially available 2-chloro-4-(propan-2-yl)pyrimidine (0.5 g, 3.19 mmol) and 3-bromo-5-methylaniline (0.900 g, 3.19 mmol) suspended in dioxane (6.39 mL). Reaction was heated to 120 °C (bath temp) overnight. Then, the reaction was cooled to room temperature and purified by column chromatography on silica gel eluting with ethyl acetate and hexanes to give *N*-(3-bromo-5-methylphenyl)-4-(propan-2-yl)-pyrimidin-2-amine (959.8 mg, 3.13 mmol, 98%) as a white solid.

Step 2: A 40 mL vial was charged with the product of Step 1 (500 mg, 1.633 mmol), bis(pinacolato)diboron (456 mg, 1.796 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (40.0 mg, 0.049 mmol) and potassium acetate (481 mg, 4.90 mmol). The solid mixture was dissolved with DMSO (6.5mL) and heated to 120 °C. After stirring for 2 h, the mixture was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes to give *N*-[3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-(propan-2-yl)pyrimidin-2-amine (249 mg, 0.705 mmol, 43.2 % yield) as a white solid.

Step 3: A 2 dram vial was charged with the product of Step 2 (100 mg, 0.283 mmol) 1-(5-bromo-1,3-thiazol-2-yl)cyclobutanol (**INTERMEDIATE 1**, 72.9 mg, 0.311 mmol), butyldi-1-adamantylphosphine (14.21 mg, 0.040 mmol), palladium(II) acetate (4.45 mg, 0.020 mmol), potassium fluoride (49.3 mg, 0.849 mmol), THF (1166 μL) then water (348 μL). The vial was sealed and then heated to 80 °C overnight. Then, the reaction was cooled to room temperature. The reaction mixture was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes. The fractions were combined, conentrated and redissolved in acetonitrile/ water + HCl (1M, 200 uL) and lyophylized to give 1-[5-(3-methyl-5-{[4-(propan-2-yl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutanol HCl salt (16.8 mg, 0.040 mmol, 14.23 % yield) as a white solid. MS ESI: $[M + H]^+$ *m/z* 381.1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (s, 1 H); 8.38 (d, *J* = 5.5 Hz, 1 H); 8.02 (s, 1 H); 7.97 (s, 1 H); 7.50 (s, 1 H); 7.07 (m, 1 H); 6.79 (m, 1 H); 2.90 (m, 1H); 2.53 (m, 2H); 2.33 (m, 2H); 2.30 (s, 3H); 1.88 (m, 2H); 1.25 (d, *J* = 7 Hz, 6H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Example 56.

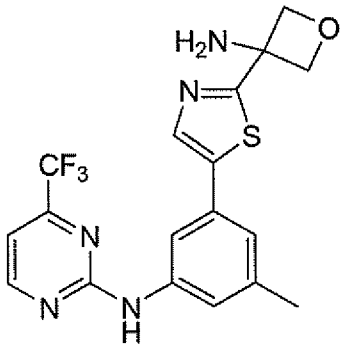
TABLE 56



Example	R	rhSYK Activity	[M+H]+ Observed	Form(s)
56-1	CH_3	+++	353.1	HCl salt
56-2	Et	+++	367.1	HCl salt
56-3	cPr	+++	379.1	HCl salt
56-5	t-Bu	+++	395.2	Free Base

EXAMPLE 59

N-{3-[2-(3-aminooxetan-3-yl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine



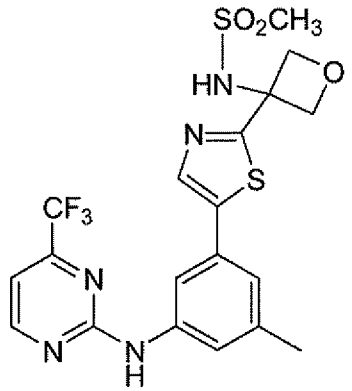
Step 1: To a solution of oxetan-3-one (600 mg, 8.33 mmol) and 2-methylpropane-2-sulfinamide (1.01 g, 8.33 mmol) in tetrahydrofuran (14 mL), titanium ethoxide (3.45 mL, 16.65 mmol) was added. The mixture was stirred at 50 °C overnight. The reaction mixture was poured over brine. The suspension was filtered through celite and washed with ethyl acetate. The solution was partitioned between ethyl acetate and brine. The organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (0-70% ethyl acetate in hexanes) to afford 2-methyl-*N*-(oxetan-3-ylidene)propane-2-sulfinamide (692 g, 3.20 mmol, 38 % yield) as a clear oil. MS ESI: [M + H]+ *m/z* 176.1.

Step 2: A solution of lithium diisopropylamine (1.8 M, 4.96 mL, 8.92 mmol) in THF (8 mL) was placed under an Argon atmosphere and was cooled to -78 °C. A solution of *N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]-4-(trifluoromethyl)pyrimidin-2-amine (**Intermediate 4**, 1200 mg, 3.57 mmol) in THF (8 mL) was cooled to -78 °C and added drop wise to the LDA solution. The reaction mixture was stirred 30 minutes at -78 °C. The product of Step 1 (625 mg, 3.57 mmol) in THF (8 mL) was added drop wise and the reaction was allowed to warm to room temperature overnight. The mixture was quenched with brine, diluted with ethyl acetate. The organics were washed with saturated $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (20-100% ethyl acetate in hexanes) to afford 2-methyl-*N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}propane-2-sulfinamide (1.10 g, 2.140 mmol, 60.0 % yield). MS ESI: [M + H]+ *m/z* 512.1.

Step 3: To a solution the product of Step 2 (1.01 g, 1.964 mmol) in methanol (9.8 mL), 4M HCl in Dioxane (1.97 mL, 7.86 mmol) was added. The mixture was stirred at room temperature for 15 minutes. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (40-100% ethyl acetate in hexanes) to afford *N*-{3-[2-(3-aminooxetan-3-yl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine (386.6 mg, 0.954 mmol, 53.5 % yield) as a pale yellow solid. MS ESI: [M + H]+ *m/z* 408.0. ^1H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.83 (d, J = 4.8, 1H), 8.07 (s, 1H), 7.97 (s, 1H), 7.47 (s, 1H), 7.28 (d, J = 4.9, 1H), 7.17 (s, 1H), 4.87 (d, J = 5.6, 2H), 4.58 (d, J = 5.7, 2H), 2.32 (s, 3H).

EXAMPLE 60

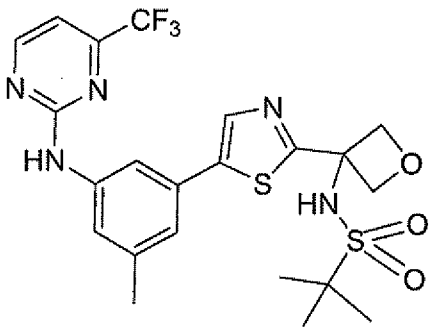
N-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-oxetan-3-yl}methanesulfonamide



Step 4: To a solution of *N*-{3-[2-(3-aminooxetan-3-yl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine (200 mg, 0.491 mmol) and Et_3N (82 μL, 0.589 mmol) in dichloromethane (3.9 mL), methanesulfonyl chloride (57 μL, 0.736 mmol) was added. The reaction mixture was stirred at room temperature for 95 minutes. The mixture was then diluted with ethyl acetate, washed with saturated $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (10-100% ethyl acetate in hexanes) and lyophilized to afford *N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}methanesulfonamide (113 mg, 0.233 mmol, 47.4 % yield) as a white powder. MS ESI: [M + H]+ *m/z* 486.0. ^1H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.83 (m, 2H), 8.11 (s, 1H), 7.99 (s, 1H), 7.50 (s, 1H), 7.29 (m, 1H), 7.21 (s, 1H), 4.91 (dd, *J* = 6.6, 16.1, 4H), 2.98 (s, 3H), 2.33 (s, 3H). rhSYK activity = +++

EXAMPLE 61

2-methyl-*N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}propane-2-sulfonamide

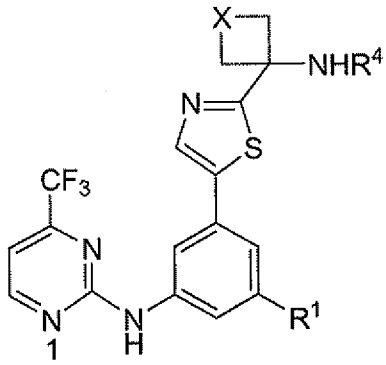


Step 5: A solution of 2-methyl-*N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}propane-2-sulfinamide (**Example 59, Step 2,** 75

mg, 0.147 mmol) in dichloromethane (1.5 mL) was cooled to 0°C. *m*-CPBA (37.8 mg, 0.219 mmol) was added and the resulting mixture was warmed to room temperature. The reaction mixture was diluted with dichloromethane, washed with 2M NaOH (2x), saturated $NaHCO_3$ (1x), brine (1x), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (10-100% ethyl acetate in hexanes) and lyophilized to afford 2-methyl-*N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}propane-2-sulfonamide (45.6 mg, 0.086 mmol, 59.0 % yield) as a light yellow solid. MS ESI: [M + H]+ *m/z* 510.1. ^{1}H NMR (500 MHz, dmso) δ 10.29 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.53 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.18 (s, 1H), 4.90 (dd, *J* = 6.6, 33.0, 4H), 2.33 (s, 3H), 1.35 (s, 9H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Examples 59-61.

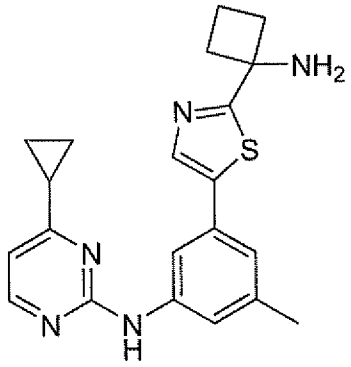
TABLE 61B



Example	R^1	X	R^4	rhSYK Activity	[M+H]+ Observed	Form(s)
61B-1	CH_3	CH_2	H	+++	406.1	Free Base
61B-2	CH_3	CH_2	$SO_2CH_2CF_3$	+++	552.0	Free Base
61B-3	CH_3	CH_2	SO_2CH_2F	+++	502.0	Free Base
61B-4	CH_3	CH_2	SO_2CH_3	+++	484.0	Free Base
61B-5	CH_3	CH_2	SO_2CF_3	+++	538.0	Free Base
61B-6	CH_3	O	SO_2CF_3	+++	540.0	Free Base
61B-7	CH_3	O	$SO_2CH_2CF_3$	+++	554.0	Free Base
61B-8	CH_3	O	$SOCHF_2$	+++	506.0	Free Base
61B-9	H	O	SO_2CH_3	+++	472.0	Free Base

EXAMPLE 62

N-{3-[2-(1-aminocyclobutyl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-cyclopropylpyrimidin-2-amine hydrochloride



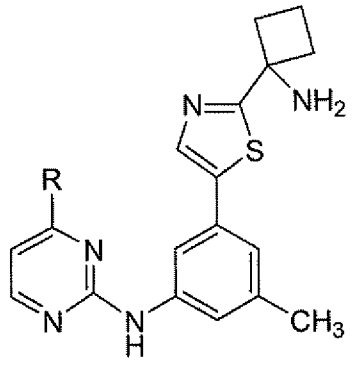
Step 1: A 20 mL microwave vial was charged with 3-methyl-5-(1,3-thiazol-5-yl)aniline (500 mg, 2.63 mmol), cesium carbonate (2.99 g, 9.20 mmol), 2-chloro-4-cyclopropylpyrimidine (**INTERMEDIATE 29,** 406 mg, 2.63 mmol), and dioxane (10.4 mL). The system was purged and flushed with argon (3x) before adding XantPhos (228 mg, 0.394 mmol) and palladium(II) acetate (59 mg, 0.263 mmol). The system was then purged and flushed with argon (3x) before sealing and heating to 100 °C for 2 h. Upon completion the mixture was cooled to room temperature, diluted with ethyl acetate, filtered through celite washing with ethyl acetate, and concentrated under reduced pressure. Purification by column chromatography on silica gel (0-60% ethyl acetate in hexanes) provided 603 mg (1.96 mmol, 74%) of 4-cyclopropyl-*N*-[3-methyl-5-(1,3-thiazol-5-yl)phenyl]pyrimidin-2-amine as a yellow solid. MS ESI: $[M + H]^+$ *m/z* 309.2.

Step 2: To a solution of the product of Step 1 (250 mg, 0.81 mmol) in tetrahydrofuran (5.0 mL) at -78 °C was added LDA (1.62 mL, 2.0 M, 3.24 mmol). The mixture was stirred for 15 min at -78 °C. *N*-cyclobutylidene-2-methylpropane-2-sulfinamide (169 mg, 0.97 mmol) in tetrahydrofuran (3 mL) was added dropwise at -78 °C and the reaction was allowed to warm to room temperature and stirred over 2 h. The mixture was quenched with aqueous ammonium chloride and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic fractions were washed with brine, dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (0-100% ethyl acetate in hexanes) provided 182 mg (0.38 mmol, 47%) of *N*-[1-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)cyclobutyl]-2-methylpropane-2-sulfinamide. MS ESI: $[M + H]^+$ *m/z* 482.2.

Step 3: To a solution of the product of Step 2 (182 mg, 0.38 mmol) in dioxane (3.8 mL) was added hydrochloric acid 4.0 M in dioxane (0.95 mL, 3.78 mmol) and the mixture was stirred for at room temperature for 2 h. The mixture was concentrated under reduced pressure to provide 170 mg (0.41 mmol, 109%) of *N*-{3-[2-(1-aminocyclobutyl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-cyclopropylpyrimidin-2-amine hydrochloride. MS ESI: $[M + H]^+$ *m/z* 378.2. ^{1}H NMR (600 MHz, *d6*-DMSO) δ 9.54 (s, 1H), 8.95 (s, 2H), 8.25 (d, *J* = 4.8, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.40 (s, 1H), 7.11 (s, 1H), 6.83 (d, *J* = 4.8, 1H), 2.66 (m, 2H), 2.57 (m, 2H), 2.28 (s, 3H), 2.14 (m, 1H), 2.03 (m, 2H), 1.10-1.04 (m, 4H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Example 62.

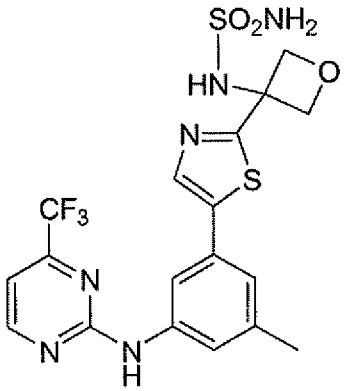
TABLE 62



Example	R	rhSYK Activity	[M+H]+ Observed	Form(s)
62-1	H	+++	338.2	Chloride Salt
62-2	-OCH_3	+++	368.1	Chloride Salt

EXAMPLE 63

N-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}sulfuric diamide

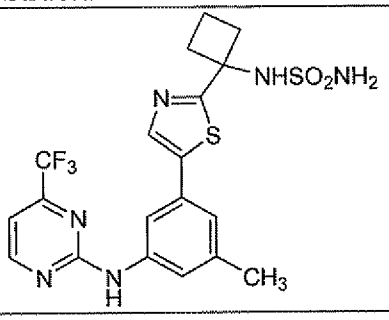


To a solution of *N*-{3-[2-(3-aminooxetan-3-yl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine (**Example 59,** 25 mg, 0.061 mmol) in dioxane (600 uL), sulfamide (70 mg, 0.725 mmol) was added. The reaction mixture was stirred at 100 °C. The resulting mixture was stirred at 100 °C for 4 days. The mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica (10-100% ethyl acetate in hexanes) and lyophilized to afford *N*-{3-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]oxetan-3-yl}sulfuric diamide (16.3 mg, 0.034 mmol, 54.6 % yield) as a pale yellow solid. MS ESI: [M + H]+ *m/z* 487.0. ^1H

NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 2H), 8.85 (m, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.51 (s, 1H), 7.28 (m, 1H), 7.17 (s, 1H), 6.98 (s, 2H), 5.02 (m, 2H), 4.84 (m, 2H), 2.32 (s, 3H). rhSYK activity = +++

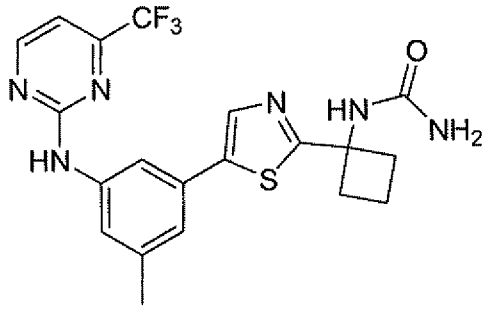
Compounds in the following Table(s) were prepared in an analogous manner of that described in Example 63:

TABLE 63

Example	Structure	rhSYK Activity	[M+H]+ Obs'd	Form(s)
63-1		+++	485.0.	Free Base

EXAMPLE 64

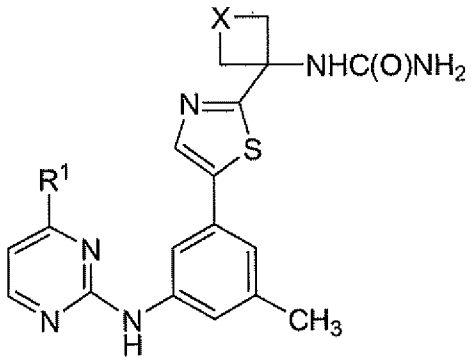
1-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}urea



To a solution of *N*-{3-[2-(1-aminocyclobutyl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine (**Example 61B-1,** 50 mg, 0.123 mmol) and acetic acid (7 μL, 0.123 mmol) in THF/water (1.6:1, 2.1 mL), potassium cyanate (10 mg, 0.123 mmol) was added. The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was purified by column chromatography on silica (50-100% ethyl acetate in hexanes, 0-20% methanol in dichloromethane) and lyophilized to afford 1-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}urea (31.3 mg, 0.068 mmol, 54.9%) as a white powder. MS ESI: [M + H]+ m/z 449.1. ^{1}H NMR (500 MHz, DMSO-d_6 δ 10.23 (s, 1H), 8.82 (d, J = 4.9, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 7.47 (s, 1H), 7.27 (d, J = 4.9, 1H), 7.15 – 7.00 (m, 2H), 5.58 (s, 2H), 2.63 – 2.51 (m, 2H), 2.32 (m, 5H), 1.96 (m, 2H). rhSYK activity = +++

The following examples were prepared in an analogous manner of that described in Example 64.

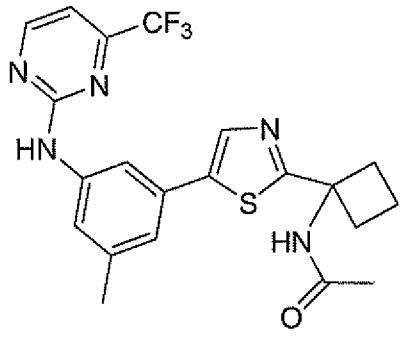
TABLE 64



Example	R^1	X	rhSYK Activity	[M+H]+ Obs'd	Form(s)
64-1	CF_3	O	+++	451.0	Free Base
64-2	cPr	CH_2	+++	421.2	Free Base
64-3	H	CH_2	+++	381.2	Free Base
64-4	OCH_3	CH_2	+++	411.2	Free Base
64-5	CF_3	$-CH_2C(O)NHCH_2-$	+++	506	Free Base

EXAMPLE 66

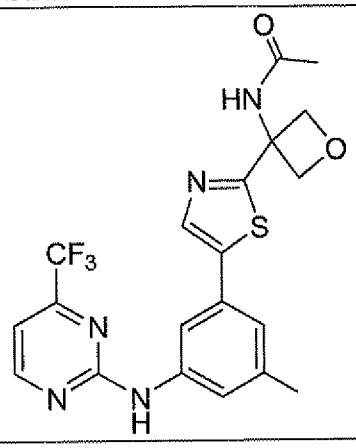
N-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}acetamide



To a solution of *N*-{3-[2-(1-aminocyclobutyl)-1,3-thiazol-5-yl]-5-methylphenyl}-4-(trifluoromethyl)pyrimidin-2-amine (**Example 61B-1**, 75 mg, 0.185 mmol) and Et_3N (25.8 µL, 0.185 mmol) in THF (1000 µL), acetyl chloride (13.15 µL, 0.185 mmol) was added. The mixture was stirred at room temperature for 70 minutes. Additional acetyl chloride (6 µL) was added to drive the reaction to completion. The mixture was stirred for 10 additional minutes, then diluted with ethyl acetate, washed with saturated $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered and concentrated to afford *N*-{1-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclobutyl}acetamide (80.8 mg, 0.171 mmol,

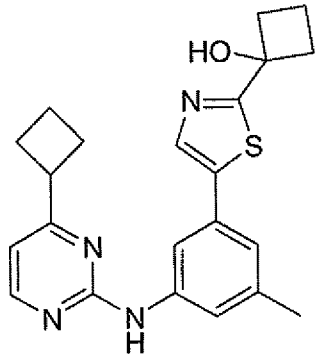
92%). MS ESI: [M + H]+ *m/z* 480.0. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.25 (s, 1H), 8.93 (s, 1H), 8.83 (d, *J* = 4.9 Hz, 1H), 8.00 (s, 1H), 7.94 (s, 1H), 7.42 (s, 1H), 7.28 (d, *J* = 4.9 Hz, 1H), 7.14 (s, 1H), 3.32-2.60 (m, 2H), 2.43-2.41 (m, 2H), 2.31 (s, 3H), 1.99-1.95 (m, 2H), 1.88 (s, 3H). rhSYK activity = +++

Compounds in the following Table(s) were prepared in an analogous manner of that described in Example 66:

Example	Structure	hSYK Activity	[M+H]+ Obs'd	Form(s)
66-1		+++	450.0	

EXAMPLE 107

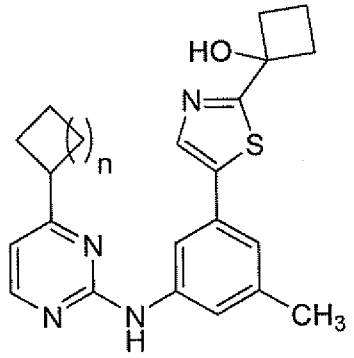
1-(5-{3-[(4-cyclobutylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)cyclobutanol



Step1: 2,4-Dichloropyrimidine (250 mg, 1.68 mmol) and ferric acetylacetonate (30 mg, 0.08 mmol) were taken up in tetrahydrofuran (3.4 mL) and the reaction was cooled to -78 °C. Cyclobutylmagnesium chloride (0.5 M, 3.4 mL, 1.68 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 min. The mixture was quenched with aqueous saturated ammonium chloride and extracted with ethyl acetate. The combined organic fractions were washed with aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (0-5% ethyl acetate in hexanes) to provide 121 mg (0.72 mmol, 43%) of 2-chloro-4-cyclobutylpyrimidine as a colorless oil. MS ESI: [M + H]$^+$ *m/z* 169.1.

Step 2: 2-Chloro-4-cyclobutylpyrimidine (65 mg, 0.39 mmol), **INTERMEDIATE 15** (100 mg, 0.39 mmol), and acetic acid (22 μL, 0.39 mmol) were combined in dioxane (1.9 mL) and the mixture was stirred at 120 °C for 3 h. The mixture was cooled to room temperature and directly purified by Combiflash chromatography on silica gel, eluting with ethyl acetate/isohexane to provide 66 mg (0.17mmol, 44%) of 1-(5-{3-[(4-cyclobutylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)cyclobutanol. MS ESI: $[M + H]^+$ *m/z* 393.2. ^1H NMR (600 MHz, DMSO-d6) δ 9.56 (s, 1H), 8.33 (d, *J* = 4.8, 1H), 8.12 (s, 1H), 7.95 (s, 1H), 7.48 (s, 1H), 7.05 (s, 1H), 6.68 (d, *J* = 5.4, 1H), 6.46 (s, 1H), 3.53 – 3.50 (m, 1H), 2.52-2.46 (m, 2H), 2.33-2.22 (m, 9 H), 1.99 (m, 1H), 1.87-1.83 (m, 3H). rhSYK activity = +++

Compounds in the following Table(s) were prepared in a manner analogous of that described in Example 107:

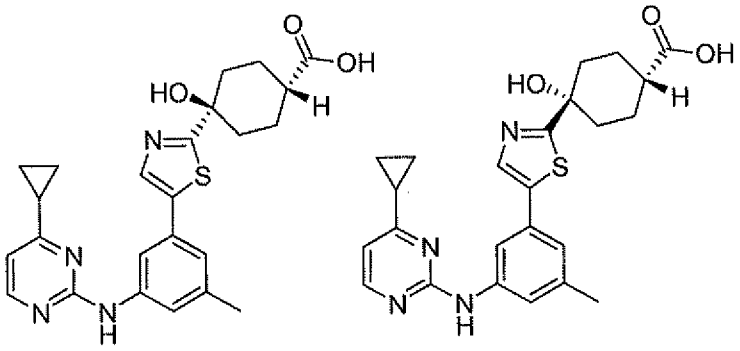


Example	n	hSYK Activity	[M+H]+ Obs'd	Form(s)
107-1	2	+++	407.2	Free Base
107-2	3	+++	421.2	Free Base

EXAMPLES 110(1) AND 110(2)

Cis-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid

trans-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid



Step 1: To a flask containing *tert*-butyl *trans*-4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxycyclohexanecarboxylate (125 mgs, 0.32 mmol) was added a solution of 2-chloro-4-cyclopropylpyrimidine (**INTERMEDIATE 29**, 57 mgs, 0.37 mmol) in dioxane (1.0 mL). Acetic acid (19 μL, 0.33 mL) was added and the reaction was heated at 100°C overnight. The reaction was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with water (10 mL), dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography to give *tert*-butyl *trans*-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylate (36 mgs, 0.071 mmol, 22% yield). ESI: $[M + H]^+$ *m/z* 507.2.

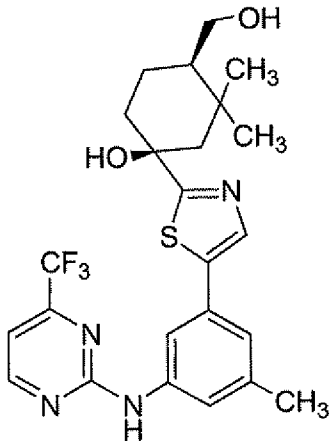
Step 2: To a flask containing the product of Step 1 (36 mgs, 0.071 mmol) was added methanol (0.80 mL) and aqueous sodium hydroxide (1M, 0.14 mL, 0.14 mmol). The reaction was heated at 100°C overnight. The reaction was cooled, acidified with HCl (1M, 0.2 mL, 0.20 mmol) and diluted with water (5 mL) and ethyl acetate (5 mL). The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. During the reaction, the starting material isomerized. The mixture of *syn* and *anti* isomers was diluted in DMSO and purified by HPLC to yield:

cis-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid (**example 110(1)**). MS ESI: $[M + H]^+$ *m/z* 451.1. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.46 (s, 1H), 8.48 (s, 1H), 8.26 (d, *J* = 5.0 Hz, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 7.02 (s, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 5.90 (s, 1H), 2.28 (s, 3H), 2.20 (m 1H), 2.01 (m, 1H), 1.88-1.85 (m 2H), 1.82-1.74 (m, 6H), 1.08-1.05 (m, 4H). rhSYK activity = +++

trans-4-(5-{3-[(4-cyclopropylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxycyclohexanecarboxylic acid (**example 110(2)**. ESI: $[M + H]^+$ *m/z* 451.1. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.46 (s, 1H), 8.47 (s, 1H), 8.26 (d, *J* = 5.0 Hz, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.44 (s, 1H), 7.03 (s, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 5.90 (s, 1H), 2.42 (m, 1H), 2.28 (s, 3H), 2.09-2.06 (m, 2H), 2.02-2.00 (m, 1H), 1.84-1.82 (m, 4H), 1.66-1.63 (m, 2H), 1.08-1.05 (m, 4H). rhSYK activity = +++

EXAMPLE 112

(1S,4R)-4-(hydroxymethyl)-3,3-dimethyl-1-(5-(3-methyl-5-(4-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)thiazol-2-yl)cyclohexanol



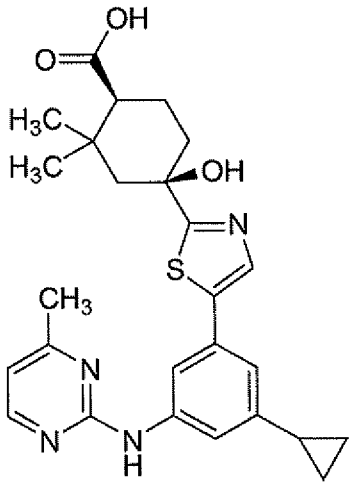
Step 1: (1*S*,4*R*)-Methyl 4-(5-bromothiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (110 mg, 0.316 mmol) was placed in a 25-mL flask under nitrogen and THF (3 ml) was added. $LiAlH_4$ (1M in THF, 0.6 mL, 0.600 mmol) was added in 1 portion and the reaction mixture turned into a white gel-like suspension. After 2 hours methanol was added and the solvents were evaporated. The residue was purified by reverse phase HPLC (10-50% acetonitrile gradient with water + 0.1% TFA)to afford (1*S*,4*R*)-4-(hydroxymethyl)-3,3-dimethyl-1-(thiazol-2-yl)cyclohexanol TFA salt (40 mg, 0.113 mmol, 35.6 % yield) as a colorless oil.

Step 2: A 4-mL screw-cap pressure vial was charged with with N-(3-bromo-5-methylphenyl)-4-(trifluoromethyl)pyrimidin-2-amine (**INTERMEDIATE 2,** 74.8 mg, 0.225 mmol), stir bar, pivalic acid (2.61 µl, 0.023 mmol), potassium carbonate (46.7 mg, 0.338 mmol), (1*S*,4*R*)-4-(hydroxymethyl)-3,3-dimethyl-1-(thiazol-2-yl)cyclohexanol TFA salt (40 mg, 0.113 mmol), and $Pd(PPh_3)_4$ (13.01 mg, 0.011 mmol). The vial was closed, evacuated and back-filed with nitrogen 3 times. DMA (0.5 ml) (dry, over molecular sieves, Fluka) was added and the reaction mixture heated to 120 °C for 16 hours. LCMS showed product formation and some remaining starting materials. Filtered and concentrated in vacuo. The residue was purified by reverse phase HPLC(10-60% acetonitrile gradient with water + 0.1% TFA)to afford (1*S*,4*R*)-4-(hydroxymethyl)-3,3-dimethyl-1-(5-(3-methyl-5-(4-(trifluoromethyl)pyrimidin-2-ylamino)-phenyl)thiazol-2-yl)cyclohexanol (14 mg, 0.023 mmol, 20.51 % yield over 2 steps) as a yellow solid.

MS ESI: $[M + H]^+$ *m/z* 492.2. ^1H NMR (500 MHz, DMSO-d_6): δ 10.24 (s, 1H), 8.83 (d, J = 4.9 Hz, 1H), 7.94 (s, 1H), 7.92 (d, J = 6.8 Hz, 1H), 7.46 (s, 1H), 7.28 (d, J = 4.9 Hz, 1H), 7.14 (s, 1H), 3.66 (dd, J = 10.2, 3.5 Hz, 1H), 3.08 (app t, J = 10.2 Hz, 1H), 2.31 (s, 3H), 1.98-1.44 (m, 7H), 0.96 (s, 3H), 0.93 (s, 3H). rhSYK activity = +++

EXAMPLE 113

(1S, 4R)-4-(5-{3-cyclopropyl-5-[(4-methylpyrimidin-2-yl)amino]phenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid

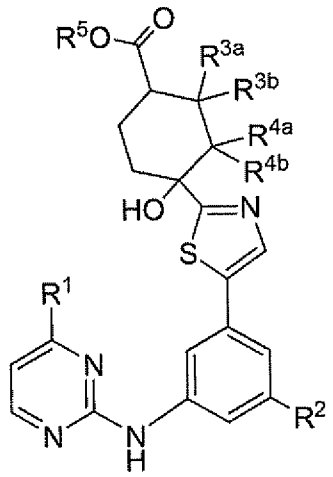


Step 1: A reaction mixture containing *N*-[3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-methylpyrimidin-2-amine (60 mg, 0.171 mmol), methyl (1*S*, 4*R*)-4-(5-bromo-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (62.5 mg, 0.179 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (27.9 mg, 0.034 mmol), 1,4-dioxane (1.2 mL), water (0.1 mL), and aqueous sodium bicarbonate solution (2 M, 0.171 mL, 0.342 mmol) was irradiated in the microwave for 15 minutes at 160 °C. The reaction mixture was partitioned between ethyl acetate (30 mL) and saturated aqueous sodium bicarbonate solution (15 mL). The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel flash column chromatography (25-50% ethyl acetate/hexanes) to afford methyl (1*S*, 4*R*)-4-(5-{3-cyclopropyl-5-[(4-methylpyrimidin-2-yl)amino]phenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (41.3 mg, 0.084 mmol, 49% yield) as an off-white solid.

Step 2: To a solution of the product from Step 1 (41.3 mg, 0.084 mmol) in tetrahydrofuran (0.4 mL) and methanol (0.8 mL) was added sodium hydroxide (1 M in water, 0.153 mL, 0.153 mmol). The reaction mixture was heated to 120 °C for 10 minutes in a microwave oven. An additional charge of sodium hydroxide was added (1 M in water, 0.300 mL, 0.300 mmol) and the vessel was heated again for 10 minutes at 120 °C. Upon cooling aqueous hydrogen chloride (2M in water, 0.235 mL, 0.470 mmol) was added and the resulting mixture was diluted with 10% v/v isopropanol/chloroform (20 mL), brine (10 mL), and water (1 mL). The layers were separated and the aqueous layer was re-extracted with 10% v/v isopropanol/chloroform (10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. Lyophilization of the residue from methanol/water provided (1*S*, 4*R*)-4-(5-{3-cyclopropyl-5-[(4-methylpyrimidin-2-yl)amino]phenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid (34.3 mg, 0.072 mmol, 84% yield) as an off-white solid. MS ESI: $[M + H]^+$ *m/z* 461.1.

Compounds in the following Table(s) were prepared in a manner analogous of that described in Example 113:

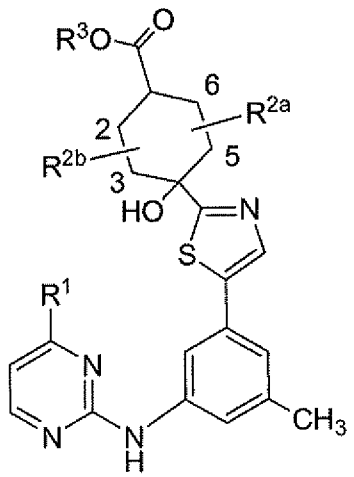
TABLE 113A



Example	R^1	R^2	R^{3a}/R^{3b}	R^5	rhSYK Activity	[M+H]+ Obs'd	Form(s)
R^{4a}/R^{4b} = H/H							
113A-1 to 113A-4	CH_3	CH_3	H/CH_3 (4 isolated isomers)	H	+++	439	Free Base
113A-5 to 113-A-8	CH_3	CH_3	H/CH_3 (6 isolated isomers)	CH_3	+++ (4); ++ (2)	453	Free Base
113A-9 to 113A-10	Et	CH_3	H/CH_3 (2 isolated isomers)	H	+++	453.1	Free Base
113A-11	OCH_3	CH_3	H/CH_3 (1S,2R,4R)	H	+++	455	Formate Salt
113A-12	OCH_3	CH_3	H/CH_3 (1R,2S,4S)	H	+++	455	Formate Salt
113A-13	cPr	CH_3	H/CH_3 (1R,2S,4S)	H	+++	465	Formate Salt
113A-14	cPr	CH_3	H/CH_3 (1S,2R,4R)	H	+++	465.1	Formate Salt
113A-15 to 113A-16	CH_3	cPr	H/CH_3 (2 isolated isomers)	H	+++	465.1	Free Base
113A-17	iPr	CH_3	H/CH_3 (1S,2R,4R)	H	+++	467.2	Free Base
113A-18	iPr	CH_3	H/CH_3 (1R,2S,4S)	H	+++	467.2	Free Base
113A-19 to 113A-20	Et	CH_3	H/CH_3 (2 isolated isomers)	Et	+++	481.1	Free Base
113A-21	O-iPr	CH_3	H/CH_3 (1R,2S,4S)	H	+++	483	Formate Salt
113A-22	Et	CH_3	CH_3/CH_3 (1S, 4R)	H	+++	467.1	Free Base
113A-23	cPr	CH_3	CH_3/CH_3 (cis)	H	+++	479	Free Base
113A-24	iPr	CH_3	CH_3/CH_3 (cis)	H	+++	481	Free Base
113A-25	Et	CH_3	CH_3/CH_3 (1S, 4R)	CH_3	+++	481.1	Free Base
113A-26	OCH_3	CH_3	CH_3/CH_3 (1S, 4R)	CH_3	+++	483.1	Free Base
113A-27	OCH_3	CH_3	CH_3/CH_3 (1R, 4S)	CH_3	+++	483.2	Free Base
113A-28	cPr	CH_3	CH_3/CH_3 (cis)	CH_3	+++	493	Free Base
R^{4a}/R^{4b} = H/CH_3							
113A-29 to 113A-32	CH_3	CH_3	H/CH_3 (4 isolated isomers)	H	+++	453	Free Base

113A-33 to 113A-36	CH_3	CH_3	H/CH_3 (4 isolated isomers)	Et	+++	481	Free Base
113A-37 to 113A-39	CH_3	CH_3	H/CH_3 (3 isolated isomers)	H	+++	507	Free Base
113A-40 to 113A-42	CF_3	CH_3	H/CH_3 (3 isolated isomers)	Et	+++	535	Free Base
113A-43	CH_3	CH_3	H/H	H	+++	439	Free Base
113A-44 to 113A-49	CH_3	CH_3	H/H (6 isolated isomers)	H	+++	439	Free Base
113A-50	CH_3	CH_3	H/H	Et	+++	467	Free Base
113A-51	CF_3	CH_3	H/H	H	+++	493	Free Base
113A-52	CF_3	CH_3	H/H	Et	+++	521	Free Base
R^{4a}/R^{4b} = H/OH							
113A-53 to 113A-54	CH_3	CH_3	H/H (2 isolated isomers)	H	+++	441	Free Base
R^{4a}/R^{4b} = CH_3/CH_3							
113A-92	CH_3	CH_3	H/H	H	+++	453	Free Base

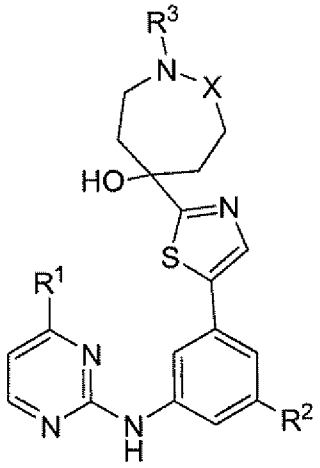
TABLE 113B



Example	R^1	R^{2a}/R^{2b}	R^3	rhSYK Activity	[M+H]+ Obs'd	Form(s)
113B-1 to 113B-5	CH_3	2,5-di(CH_3) (5 isolated isomers)	H	+++	453	Free Base
113B-6 to 113B-9	CH_3	2,5-di(CH_3) (4 isolated isomers)	Et	+++ (3); ++ (1)	481	Free Base
113B-10 to 113B-13	CF_3	2,5-di(CH_3) (4 isolated isomers)	H	+++	507	Free Base
113B-14 to 113B-16	CF_3	2,5-di(CH_3) (3 isolated isomers)	Et	+++ (2); ++ (1)	535	Free Base
113B-17	CH_3	2,6-di(CH_3) (trans,trans,trans)	H	+++	453	Free Base

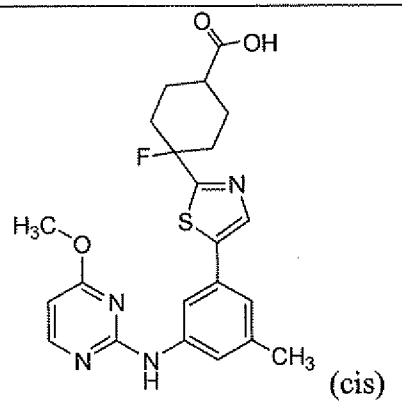
113B-18	CH_3	2,6-di(CH_3)	iPr	++	495	Free Base
113B-19	CF_3	2,6-di(CH_3) (trans,trans,trans)	H	+++	507	Free Base
113B-20 to 113B-21	CF_3	2,6-di(CH_3) (2 isolated isomers)	iPr	+, ++	549	Free Base
113B-28	CH_3	3,5-di(CH_3)	H	+++	453	Free Base
113B-29	CH_3	3,5-di(CH_3)	Et	+++	481	Free Base
113B-30	CF_3	3,5-di(CH_3)	H	+++	507	Free Base
113B-31	CF_3	3,5-di(CH_3)	Et	+++	535	Free Base

TABLE 113C



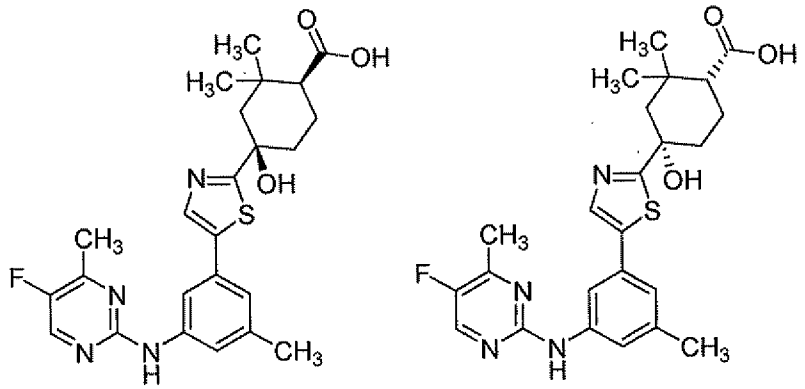
Ex.	R^1	R^2	R^3	X	rhSYK Activity	[M+H]+ Obs'd	Form(s)
113C-2	cPr	CH_3	H	C(O)	+++	436.2	TFA Salt
113C-3	CH(F)-CH_3	CH_3	H (enantiomer 1)	C(O)	+++	442.1	Free Base
113C-4	CH(F)-CH_3	CH_3	H (enantiomer 2)	C(O)	+++	442.2	Free Base
113C-7	CHF_2	CH_3	H	C(O)	+++	446.1	Free Base
113C-8	CF_3	H	H	C(O)	+++	450.1	TFA Salt
113C-9	tBu	CH_3	H	C(O)	+++	452.2	Free Base
113C-10	O-iPr	CH_3	H	C(O)	+++	454.2	Free Base
113C-13	cPr	CH_3	H	CH_2	+++	422.2	Free Base
113C-14	iPr	CH_3	H	CH_2	+++	424.2	Free Base
113C-17	cPr	CH_3	BOC (enantiomer 1)	CH_2	+++	522.3	Free Base
113C-18	cPr	CH_3	BOC (enantiomer 2)	CH_2	++	522.3	Free Base
113C-19	iPr	CH_3	BOC	CH_2	+++	524.3	Free Base
113C-20	iPr	CH_3	BOC (enantiomer 1)	CH_2	++	524.3	Free Base
113C-21	iPr	CH_3	BOC (enantiomer 2)	CH_2	+	524.3	Free Base

Ex.	Structure	rhSYK Activity	[M+H]+ Obs'd	Form(s)

113D-13	 (cis)	+++	443.1	Free Base

EXAMPLE 116

(1*S*,4*R*) and (1*R*, 4*S*)-4-(5-{3-[(5-fluoro-4-methylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid



Step 1: Racemic 2-chloro-5-fluoro-4-methylpyrimidine (50.0 mg, 0.341 mmol), methyl-4-[5-(3-amino-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (128 mg, 0.341 mmol), $Pd(OAc)_2$ (15.3 mg, 0.0680 mmol), Xantphos (59.2 mg, 0.102 mmol), and Cs_2CO_3 (222 mg, 0.682 mmol) were combined in a flask and degassed with argon. To this solid mixture was added dioxane (2.0 mL), and the resulting mixture was degassed with argon for 5 min. The reaction mixture was heated to 110 °C for 1.5 h. The reaction was cooled to ambient temperature, then diluted with saturated aqueous NaCl and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography on silica (10-30% EtOAc/hexanes gradient) to afford racemic methyl -4-(5-{3-[(5-fluoro-4-methylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (143 mg, 0.295 mmol, 86% yield). MS ESI: $[M + H]^+$ *m/z* 485.

Step 2: To a solution of racemic methyl (1*S*,4*R*)-4-(5-{3-[(5-fluoro-4-methylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylate (70 mg, 0.14 mmol) in Methanol (1 mL) was added sodium hydroxide (1M, 0.87 ml, 0.87 mmol).

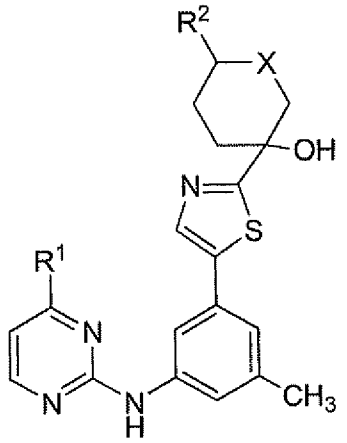
The resulting suspension was heated to 110 °C for 10 min under microwave irradiation. The reaction was cooled to ambient temperature, and the pH was adjusted to a range of 3-4 (pH paper) using HCl (1 N in water). The resulting mixture was extracted with 10% IPA:$CHCl_3$ (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to provide racemic 4-(5-{3-[(5-fluoro-4-methylpyrimidin-2-yl)amino]-5-methylphenyl}-1,3-thiazol-2-yl)-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid (58 mg, 0.12 mmol, 58% yield). The racemate was subjected to purification by chiral supercritical fluid chromatography (35% / 65% Methanol/CO_2, with a flow rate of 70 mL/min and a 4 minute run time).

Enantiomer 1 (26 mg, 0.055 mmol, 38% yield). MS ESI: $[M+H]^+$ *m/z* 471. ^1H NMR (500 MHz, DMSO) δ 12.00 (br s, 1H), 9.68 (s, 1H), 8.42 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.47 (s, 1H), 7.05 (m, 1H), 5.89 (br s, 1H), 2.41 (s, 3H), 2.29 (s, 3H), 2.16 (br d, *J* = 12.5, 1H), 2.02 (m, 1H), 1.84 (br m, 3H), 1.64 (br d, *J* = 14.0, 1H), 1.58 (br d, *J* = 13.5, 1H), 1.11 (s, 3H), 1.01 (s, 3H).

Enantiomer 2 (27 mg, 0.057 mmol, 40% yield). MS ESI: $[M+H]^+$ *m/z* 471. ^1H NMR (500 MHz, DMSO) δ 12.00 (br s, 1H), 9.68 (s, 1H), 8.42 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.47 (s, 1H), 7.05 (m, 1H), 5.89 (br s, 1H), 2.41 (s, 3H), 2.29 (s, 3H), 2.16 (br d, *J* = 12.5, 1H), 2.02 (m, 1H), 1.84 (br m, 3H), 1.64 (br d, *J* = 14.0, 1H), 1.58 (br d, *J* = 13.5, 1H), 1.11 (s, 3H), 1.01 (s, 3H).

Compounds in the following Table(s) were prepared in a manner analogous of that described in Example 116:

TABLE 116A

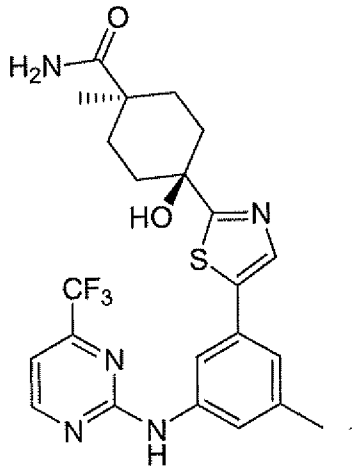


Ex.	R^1	R^2	X	rhSYK Activity	[M+H]+ Obs'd	Form(s)
116A-3	iPr	CO_2H (cis)	CH_2	+++, +++	453.2	Free Base, TFA Salt
116A-6	tBu	CO_2H (cis)	CH_2	+++	467.2	TFA Salt
116A-7	O-iPr	CO_2H (cis)	CH_2	+++	469.2	TFA Salt

116A-10	$CH(F)CH_3$	$CO_2C(CH_3)_3$	CH_2	+++	513.2	Free Base
116A-12	tBu	$CO_2C(CH_3)_3$ (cis)	CH_2	++	523.2	Free Base
116A-13	CF_2CF_3	CO_2H (cis)	CH_2	+++	529.1	TFA Salt
116A-16	CF_2CF_3	$CO_2C(CH_3)_3$ (cis)	CH_2	+	585.2	TFA Salt
116A-18	CHF_2	CO_2H (isomer 1)	$CH(CH_3)$	+++	475.2	Free Base
116A-19	CHF_2	CO_2H (isomer 2)	$CH(CH_3)$	+++	475.2	Free Base
116A-20	tBu	CO_2H	$CH(CH_3)$	+++	481.2	Free Base
116A-21	O-iPr	CO_2H	$CH(CH_3)$	+++, +++	483.2	Free Base, Formate Salt
116A-30	CHF_2	CO_2H (1S, 4R)	$C(CH_3)_2$	+++	489.2	Free Base
116A-31	cBu	CO_2H (1S, 4R)	$C(CH_3)_2$	+++	493.2	TFA Salt
116A-32	tBu	CO_2H (cis)	$C(CH_3)_2$	+++	495.2	Free Base
116A-33	O-iPr	CO_2H (1S,4R)	$C(CH_3)_2$	+++	497.2	Free Base
116A-37	CF_3	CO_2H (1S,4R)	$C(CH_3)_2$	+++	507.1	TFA Salt

EXAMPLE 117

cis-4-hydroxy-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide

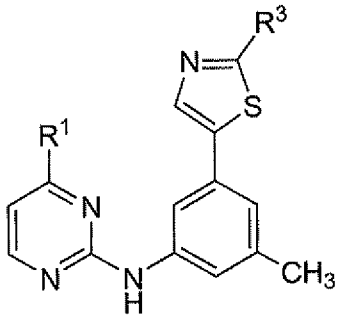


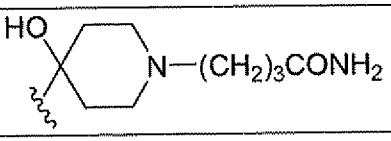
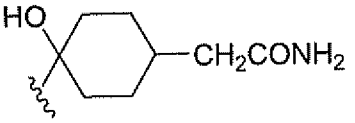
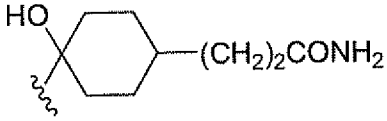
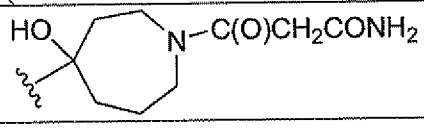
To a stirred solution of *cis*-4-hydroxy-1-methyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (442 mg, 0.90 mmol) in DMF (9.0 mL) was added ammonium chloride (144 mg, 2.69 mmol), EDC (344 mg, 1.80 mmol), HOBt (243 mg, 1.80 mmol) and diisopropylethyl amine (0.94 mL, 5.38 mmol). The solution was allowed to stir at room temperature for 16h. The reaction was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with aqueous saturated sodium bicarbonate, brine, then dried (magnesium sulfate), filtered and concentrated. The residue was purified by column chromatography to give the title compound as a white solid. ESI: $[M + H]^+$ *m/z* 492.2. ^1H NMR (500 MHz, CD_3OD) δ 8.71 (d, $J = 4.9$, 1H),

8.03 (s, 1H), 7.91 (s, 1H), 7.44 (s, 1H), 7.13 (s, 2H), 2.37 (s, 3H), 2.22 (d, J = 13.0, 2H), 2.15 (d, J = 12.2, 2H), 1.84 (d, J = 14.1, 2H), 1.63 (d, J = 13.4, 2H), 1.30 (s, 3H).

Compounds in the following Table(s) were prepared in a manner analogous of that described in Example 117:

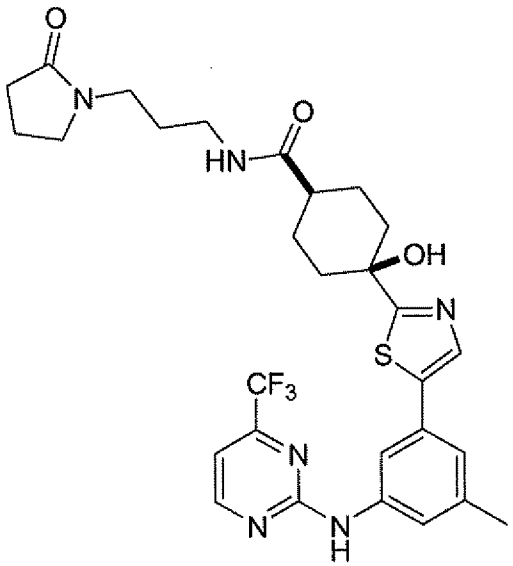
TABLE 117



Ex.	R1	R3	rhSYK Activity	[M+H] + Obs'd	Form(s)
117-7	CF_3		+++	521.1	Free Base
117-8	CF_3	 (cis and trans isomers isolated)	+++, +++	492.2	Free Base
117-11	CF_3	 (cis and trans isomers isolated)	+++, +++	506.2	Free Base
117-13	iPr		+++	509.2	Free Base

EXAMPLE 118

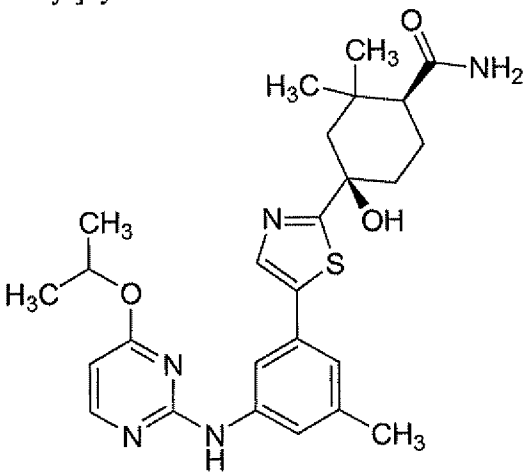
cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide



To *N*-(3-aminopropyl)-2-pyrrolidinone (14.1 μL, 0.12 mmol) was added a solution of *cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (48 mg, 0.1 mmol) in *N,N*-dimethylformamide (1 mL). *N,N*-diisopropylethylamine (35 μL, 0.2 mmol) was added and the solution was then cooled to 0 °C. 1-propanephosphonic acid cyclic anhydride (70 μL, 0.12 mmol) was added andthe mixture was warmed to room temperature and stirred for 16 h, filtered, then purified by mass triggered reverse phase (C-18) HPLC to give the title product (21.5 mg, 0.036 mmol, 36% yield) as a pale yellow solid. MS ESI: $[M + H]^+$ *m/z* 603.2. ^{1}H NMR (600 MHz, DMSO) δ 10.22 (s, 1H), 8.80 (d, J = 4.9, 1H), 7.91 (s, 2H), 7.73 (s, 1H), 7.43 (s, 1H), 7.25 (d, J = 4.9, 1H), 7.12 (s, 1H), 3.29 (t, J = 7.0, 1H), 3.13 (t, J = 7.2, 2H), 2.98 (d, J = 6.0, 2H), 2.29 (s, 3H), 2.17 (t, J = 8.1, 3H), 1.91 – 1.75 (m, 9H), 1.60 – 1.50 (m, 5H).

EXAMPLE 119

(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide

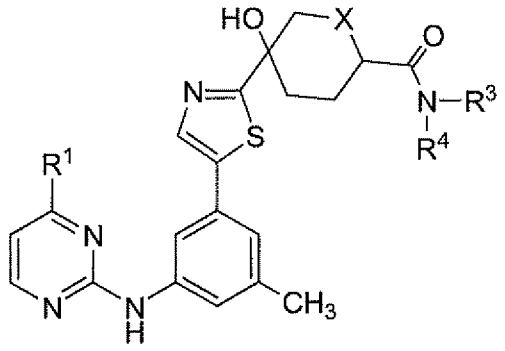


To a solution of (1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (30 mg, 0.060

mmol) in DMF (3.0 mL) was added ammonium chloride (19 mg, 0.36 mmol), HATU (35 mg, 0.09 mmol) and Hunig's base (0.13 mL, 0.72 mmol) and the reaction was stirred at rt for 16 hrs. The reaction was then partitioned between 10 mL each of EtOAc and water and the layers were separated. The aqueous phase was extracted once with 10 mL of EtOAc, and the combined organic phases were washed with 10 mL of saturated aqueous sodium chloride, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by reverse phase HPLC (10-100% MeCN gradient in H_2O, 0.1% TFA) afforded (1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide trifluoroacetate (12 mg, 33%) as a colorless foam. MS ESI: $[M + H]^+$ *m/z* 496.2. ^1H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.45 (s, 1H), 7.14 (s, 1H), 7.11 (s, 1H), 6.71 (s, 1H), 6.24 (d, J = 5.9 Hz, 1H), 5.40 (septet, J = 6.1 Hz, 1H), 2.30 (s, 3H), 2.04-1.60 (m, 6H), 1.34 (d, J = 6.1 Hz, 6H), 1.34 (s, 3H), 1.11 (s, 3H) rhSTK activity = +++

Compounds in the following Table(s) were prepared in a manner analogous of those described in Examples 117 (Method A), 118 (Method B) and 119 (Method C). The particular method used is indicated in the Table(s):

TABLE 119



Ex.	R1	R3/R4 or R3+R4	X	rhSYK Activity	[M+H]+ Obs'd	Form(s)	*
119-5	CH_3	H/H	$CH(CH_3)$ (isomer 1)	+++	438.2	Free Base	A
119-6	CH_3	H/H	$CH(CH_3)$ (isomer 2)	+++	438.2	Free Base	A
119-7	CH_3	H/H	$C(CH_3)_2$ (cis)	+++	452.2	Free Base	A
119-8	iPr	H/H	CH_2 (cis)	+++	452.2	Free Base	C
119-9	tBu	H/H	CH_2 (cis)	+++	466.2	Free Base	C
119-10	iPr	H/H	$CH(CH_3)$ (isomer 1)	+++	466.2	Free Base	A
119-11	iPr	H/H	$CH(CH_3)$ (isomer 2)	+++	466.2	Free Base	A
119-12	O-iPr	H/H	$CH(CH_3)$	+++	468.2	Free Base	C

			(cis)				
119-13	OCH_3	H/H	$C(CH_3)_2$ (1S,4R)	+++	468.2	Free Base	A
119-15	CF_3	H/CH_3	CH_2 (cis)	+++	492.1	Free Base	A
119-17	CF_3	CH_3/CH_3	CH_2 (cis)	+++	506.2	Free Base	A
119-18	CF_3	H/CH_2CN	CH_2 (cis)	+++	517	Formate Salt	B
119-20	CF_3	H/iPr	CH_2 (cis)	+++	520	Formate Salt	B
119-21	CF_3	CH_3/Et	CH_2 (cis)	+++	520	Formate Salt	B
119-22	CF_3	H/CH_2CH_2OH	CH_2 (cis)	+++	522	Formate Salt	B
119-23	CF_3	H/CH_2-cPr	CH_2 (cis)	+++	532	Formate Salt	B
119-25	CF_3	H/$CH_2CH_2OCH_3$	CH_2 (cis)	+++	536	Formate Salt	B
119-26	CF_3	H/CH_2CO_2H	CH_2 (cis)	+++	536	Formate Salt	B
119-27	CF_3	H/2-imidazolyl	CH_2 (cis)	+++	544	Formate Salt	A
119-28	CF_3	CH_3/CH_2CH_2CN	CH_2 (cis)	+++	545	Formate Salt	B
119-29	CF_3	-$CH_2CH_2OCH_2$-CH_2-	CH_2 (cis)	+++	548.2	Free Base	A
119-30	CF_3	H/$CH_2CH_2CONH_2$	CH_2 (cis)	+++	549	Formate Salt	B
119-31	CF_3	H/$(CH_2)_3OCH_3$	CH_2 (cis)	+++	550	Formate Salt	B
119-32	CF_3	H/$CH_2CH(OH)$-CH_2OH	CH_2 (cis)	+++	552	Formate Salt	B
119-33	CF_3	H/$CH(CH_2OH)_2$	CH_2 (cis)	+++	552	Formate Salt	B
119-34	CF_3	H/4-pyridyl	CH_2 (cis)	+++	555	Formate Salt	B
119-35	CF_3	H/2-pyridyl	CH_2 (cis)	+++	555	Formate Salt	B
119-36	CF_3	H/3-pyridyl	CH_2 (cis)	+++	555	Formate Salt	B
119-37	CF_3	-$CH_2CH_2CH(CN)$-CH_2-	CH_2 (cis)	+++	557	Formate Salt	B
119-38	CF_3	H/CH_2-2-imidazolyl	CH_2 (cis)	+++	558	Formate Salt	A
119-39	CF_3	H/CH_2-3-pyrazolyl	CH_2 (cis)	+++	558.2	Free Base	A
119-40	CF_3	Et/CH_2CH_2CN	CH_2 (cis)	+++	559	Formate Salt	B
119-41	CF_3	H/CH_2-4-isoxazolyl	CH_2 (cis)	+++	559	Formate Salt	A

119-42	CF_3	H/CH_2-4-oxazolyl	CH_2 (cis)	+++	559	Formate Salt	A
119-43	CF_3	H/CH_2-5-isoxazolyl	CH_2 (cis)	+++	559	Formate Salt	A
119-44	CF_3	H/cHex	CH_2 (cis)	+++	560	Formate Salt	B
119-45	CF_3	H/CH_2-1,2,4-oxadiazol-3-yl	CH_2 (cis)	+++	560	Formate Salt	A
119-46	CF_3	-$CH_2CH_2N(CH_3)$-CH_2CH_2-	CH_2 (cis)	+++	561	Formate Salt	B
119-47	CF_3	-$CH_2CH_2CH(OH)$-CH_2CH_2-	CH_2 (cis)	+++	562	Formate Salt	B
119-48	CF_3	CH_3/3-tetrahydrofuranyl	CH_2 (cis)	+++	562	Formate Salt	B
119-49	CF_3	H/$CH_2CH_2NHCOCH_3$	CH_2 (cis)	+++	563	Formate Salt	B
119-50	CF_3	CH_2CH_2OH/CH_2-CH_2OH	CH_2 (cis)	+++	566	Formate Salt	B
119-51	CF_3	H/benzyl	CH_2 (cis)	+++	568	Formate Salt	B
119-52	CF_3	H/CH_2-3-pyridyl	CH_2 (cis)	+++	569	Formate Salt	B
119-53	CF_3	H/CH_2-4-pyridyl	CH_2 (cis)	+++	569	Formate Salt	B
119-54	CF_3	H/CH_2-2-pyridyl	CH_2 (cis)	+++	569	Formate Salt	B
119-55	CF_3	H/4-OH-Ph	CH_2 (cis)	+++	570	Formate Salt	B
119-56	CF_3	H/2-OH-Ph	CH_2 (cis)	+++	570	Formate Salt	B
119-57	CF_3	H/CH_2-5-pyrimidinyl	CH_2 (cis)	+++	570	Formate Salt	A
119-58	CF_3	H/CH_2-3-pyridazinyl	CH_2 (cis)	+++	570	Formate Salt	A
119-59	CF_3	-$CH_2CH_2CH(CN)$-CH_2CH_2-	CH_2 (cis)	+++	571	Formate Salt	B
119-60	CF_3	-$CH_2CH(CN)CH_2$-CH_2CH_2-	CH_2 (cis)	+++	571	Formate Salt	B
119-62	CF_3	H/4-F-Ph	CH_2 (cis)	+++	572	Formate Salt	B
119-63	CF_3	H/CH_2-2-thienyl	CH_2 (cis)	+++	574	Formate Salt	B
119-64	CF_3	H/CH_2CH_2-1-pyrrolidinyl	CH_2 (cis)	+++	575	Formate Salt	B
119-65	CF_3	H/CH_2-(3-OH-5-isoxazolyl)	CH_2 (cis)	+++	575	Formate Salt	A
119-66	CF_3	H/CH_2-(5-	CH_2 (cis)	+++	575	Formate	A

		isothiazolyl)				Salt	
119-67	CF_3	H/CH_2-(1,3,4-thiadiazol-2-yl)	CH_2 (cis)	+++	576	Formate Salt	A
119-68	CF_3	H/$CH_2CH_2N(CH_3)COCH_3$	CH_2 (cis)	+++	577	Formate Salt	B
119-69	CF_3	CH_3/benzyl	CH_2 (cis)	+++	582	Formate Salt	B
119-70	CF_3	H/CH_2CH_2Ph	CH_2 (cis)	+++	582	Formate Salt	B
119-71	CF_3	H/CH_2-(3-OH)-Ph	CH_2 (cis)	+++	584	Formate Salt	B
119-72	CF_3	H/(4-CH_2OH)-Ph	CH_2 (cis)	+++	584	Formate Salt	B
119-73	CF_3	H/(3-CH_2OH)-Ph	CH_2 (cis)	+++	584	Formate Salt	B
119-74	CF_3	H/CH_2-(2-OH)-Ph	CH_2 (cis)	+++	584	Formate Salt	B
119-75	CF_3	H/CH_2-(4-OH)-Ph	CH_2 (cis)	+++	584	Formate Salt	B
119-76	CF_3	H/(2,4-diOH)-Ph	CH_2 (cis)	+++	586	Formate Salt	B
119-77	CF_3	H/CH_2-(4-F)-Ph	CH_2 (cis)	+++	586	Formate Salt	B
119-78	CF_3	H/CH_2CH_2-(2-oxo-1-pyrrolidinyl)	CH_2 (cis)	+++	589	Formate Salt	B
119-79	CF_3	H/CH_2CH_2-(2-oxo-1-imidazolidinyl)	CH_2 (cis)	+++	590	Formate Salt	B
119-80	CF_3	H/CH_2CH_2-(4-morpholinyl)	CH_2 (cis)	+++	591	Formate Salt	B
119-81	CF_3	H/$(CH_2)_4NHCO$-CH_3	CH_2 (cis)	+++	591	Formate Salt	B
119-82	CF_3	H/5-indolyl	CH_2 (cis)	+++	593.1	Free Base	A
119-83	CF_3	H/$(CH_2)_3Ph$	CH_2 (cis)	+++	596	Formate Salt	B
119-85	CF_3	H/CH_2-(4-CH_2OH)-Ph	CH_2 (cis)	+++	598	Formate Salt	B
119-86	CF_3	H/CH_2-(3,4-diOH)-Ph	CH_2 (cis)	+++	600	Formate Salt	B
119-87	CF_3	H/CH_2-(4-Cl)-Ph	CH_2 (cis)	+++	602	Formate Salt	B
119-88	CF_3	H/$(CH_2)_3$-(2-oxo-1-pyrrolidinyl)	CH_2 (cis)	+++	603	Formate Salt	B
119-89	CF_3	H/CH_2CH_2-(2-oxo-1-piperidinyl)	CH_2 (cis)	+++	603	Formate Salt	B
119-90	CF_3	H/4-$CONH_2$-cHex	CH_2	+++	603.2	Free Base	A
119-91	CF_3	H/4-CO_2H-cHex	CH_2	+++	604	Formate Salt	B
119-92	CF_3	-CH_2CH_2N-	CH_2	+++	605	Formate	B

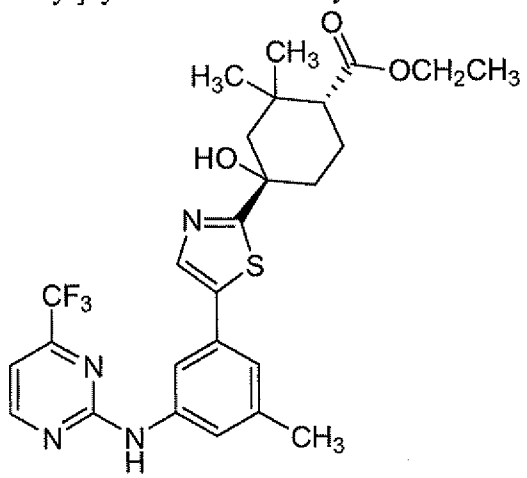
		$(CO_2CH_3)CH_2CH_2$-				Salt	
119-100	CF_3	H/CH_2-(4-CF_3)Ph	CH_2 (cis)	+++	636	Formate Salt	B
119-101	CF_3	H/CH2-(3-(2-pyridyl)-isoxazol-5-yl)	CH_2 (cis)	+++	636	Formate Salt	A
119-102	CF_3	-CH_2CH_2CH(Bn)-CH_2CH_2-	CH_2 (cis)	++	636	Formate Salt	B
119-104	CF_3	H/CH_2-(4-SO_2NH_2)Ph	CH_2 (cis)	+++	647	Formate Salt	A
119-108	CH_3	H/CH_2CN	$CH(CH_3)$ (cis)	+++	477.2	Free Base	A
119-109	tBu	H/H	$CH(CH_3)$	+++	480.2	TFA Salt	C
119-110	O-iPr	H/H	$CH(CH_3)$	+++	482.2	TFA Salt	C
119-111	CF_3	H/H	$CH(CH_3)$ (isomer 1)	+++, +++	492.1	Free Base	A
119-112	CF_3	H/H	$CH(CH_3)$ (isomer 2)	+++	492.1	Free Base	A
119-113	iPr	H/CH_2CN	$CH(CH_3)$	+++	505.2	Free Base	A
119-114	CH_3	H/CH_2-3-pyridyl	$CH(CH_3)$	+++	529.2	Free Base	A
119-115	iPr	H/CH_2-3-pyridyl	$CH(CH_3)$	+++	557.3	Free Base	A
119-116	CH_3	H/$(CH_2)_3$-(2-oxo-1-pyrrolidinyl)	$CH(CH_3)$	+++	563.3	Free Base	A
119-117	OCH_3	H/H	$C(CH_3)_2$ (1S,4R)	+++	468.2	Free Base	A
119-118	cPr	H/H	$C(CH_3)_2$ (1S,4R)	+++	478.2	Free Base	A
119-119	iPr	H/H	$C(CH_3)_2$ (1S,4S)	+++	480.2	TFA Salt	C
119-122	(S)-CH(F)-CH_3	H/H	C(CH3)2 (1S,4R)	+++	484.2	TFA Salt	A
119-123	(R)-CH(F)-CH_3	H/H	$C(CH_3)_2$ (1S,4R)	+++	484.2	TFA Salt	A
119-124	CH_3	H/CH_2CN	$C(CH_3)_2$ (cis)	+++	491.2	Formate Salt	A
119-125	tBu	H/H	$C(CH_3)_2$ (1S,4R)	+++	494.2	TFA Salt	C
119-126	O-iPr	H/H	$C(CH_3)_2$ (1S,4R)	+++	496.2	TFA Salt	C
119-131	CF_3	H/H	$C(CH_3)_2$ (1R,4S)	+++	506.2	Free Base	A
119-132	CF_3	H/H	$C(CH_3)_2$ (1S,4R)	+++	506.2	Free Base	A
119-133	OCH_3	H/CH_2CN	$C(CH_3)_2$	+++	507.2	Free Base	A

			(1S,4R)				
119-134	OCH_3	H/CH_2-3-pyridyl	$C(CH_3)_2$ (1S,4R)	+++	559.2	Free Base	A
119-135	CH_3	H/$(CH_2)_3$-(2-oxo-1-pyrrolidinyl)	$C(CH_3)_2$ (1S,4R)	+++, +++	577.3	Free Base, Formate Salt	A
119-136	CF_3	H/3-pyridyl	$C(CH_3)_2$ (1S,4R)	+++	583.2	Free Base	B
119-137	OCH_3	H/$(CH_2)_3$-(2-oxo-1-pyrrolidinyl)	$C(CH_3)_2$ (1S,4R)	+++	593.3	Free Base	A
119-138	CF_3	H/$(CH_2)_3$-(2-oxo-1-pyrrolidinyl)	$C(CH_3)_2$ (1S,4R)	+++	631.2	Free Base	A

* synthetic method A, B, or C

EXAMPLE 120

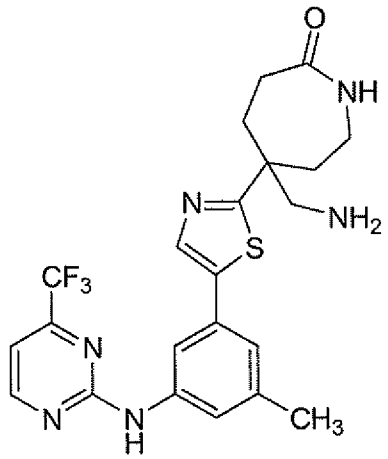
Ethyl (1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate



(1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (100 mg, 0.197 mmol) was dissolved in ethanol (3 ml) and concentrated sulfuric acid (10.52 µl, 0.197 mmol) added. The reaction mixture was stirred for 16 hours. The reaction mixture was extracted with ethyl acetate (3x) and washed with saturated aqueous sodium bicarbonate. Solvent evaporation gave the title compound (88 mg, 0.165 mmol, 83 % yield). ESI: [M + H]+ *m/z* 535.2. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.82 (d, *J* = 4.9, 1H), 7.93 (d, *J* = 9.6, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 4.07 (dt, *J* = 10.8, 17.9, 2H), 2.31 (s, 3H), 2.05 (s, 3H), 1.96 – 1.78 (m, 3H), 1.65 (m, 2H), 1.18 (m, 3H), 1.09 (s, 3H), 0.97 (s, 3H). rhSYK activity = +++

EXAMPLE 126

5-(aminomethyl)-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one

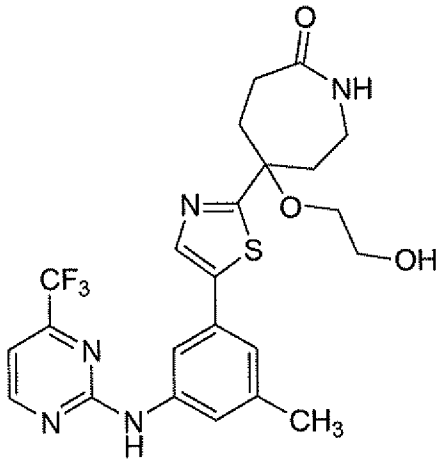


Step 1: Diisobutylaluminum hydride (1M in Hexanes, 0.239 ml, 0.239 mmol, 1.2 equiv) was addedto a solution of 8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]decane-8-carbonitrile (100 mg, 0.20 mmol) at -10 °C and the resulting cloudy mixture was stirred at -10°C for 1 h. A second addition of DIBAL (1M in Hexanes, 0.239 ml, 0.239 mmol, 1.2 equiv) was made at -10°C and the reaction was allowed to slowly warm to 23°C and then stir for 4 days. The reaction was quenched with 1:1:3 mixture of water:aqueous 6N NaOHand the particulate matter was removed via filtration. The remaining filtrate was partitioned between EtOAc (2x55 ml) and water (65 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford *N*-(3-{2-[8-(aminomethyl)-1,4-dioxaspiro[4.5]dec-8-yl]-1,3-thiazol-5-yl}-5-methylphenyl)-4-(trifluoromethyl)pyrimidin-2-amine (39 mg, 39%), as an off-white solid. MS ESI: $[M + H]^+$ *m/z* 506.1. ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.6 Hz, 1H), 7.93 (s, 1H), 7.45 (bs, 1H), 7.28 (s, 1H), 7.08-7.04 (m, 2H), 4.06-3.95 (m, 6H), 2.51-2.35 (m, 7H), 1.95-1.71 (m, 4H).

Step 2: Sodium azide (20.45 mg, 0.315 mmol, 3.0 equiv) was added to a stirring solution of the product of Step1 (53 mg, 0.11 mmol) in chloroform (5 ml). Methanesulfonic Acid (0.082 ml, 1.258 mmol, 12 equiv) was added and the reaction was capped and stirred at 65°C for 1 h. The yellow mixture was partitioned between EtOAc (2x85 ml) and saturated aqueous $NaHCO_3$ (90 ml), and the combined organic layers were dried over $MgSO_4$ and concentrated. The residual colorless oil was purified via reverse-phase HPLC (Acetonitrile/ Water gradient with 0.1% TFA present). The desired fractions were partitioned between EtOAc (2x55 ml) and saturated aqueous $NaHCO_3$ (65 ml). The combined organic layers were dried over Na_2SO_4 and concentrated, providing the desired title compound (1.3 mg, 2.5%) as a colorless solid-oil. MS ESI: $[M + H]^+$ *m/z* 477.21. ^1H NMR (500 MHz, CD_3OD) δ 8.72 (d, 1H, *J* = 4.6 Hz), 8.19 (bs, 1H), 7.98 (s, 1H), 7.44 (s, 1H), 7.16 (s, 1H), 7.13 (d, 1H, J = 4.6 Hz), 3.45 (s, 2H), 2.95 (m, 2H), 2.05 (s, 3H), 1.90-1.57 (m, 6H). rhSYK activity = +++

EXAMPLE 127

5-(2-hydroxyethoxy)-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one

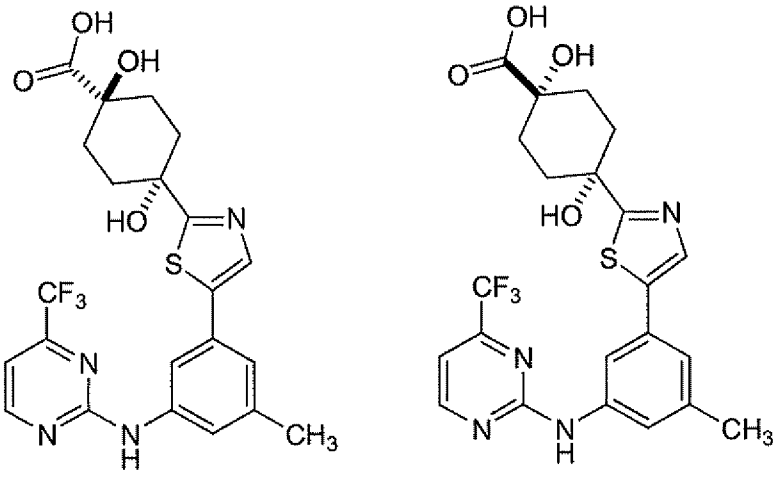


Step1: A flame dried microwave vessel was charged with a solution of sodium hydride (4.26 mg, 0.106 mmol, 2.0 equiv) in anhydrous DMF (1 ml). *tert*-butyl {3-[2-(4-hydroxy-7-oxoazepan-4-yl)-1,3-thiazol-5-yl]-5-methylphenyl}[4-(trifluoromethyl)pyrimidin-2-yl]carbamate (30 mg, 0.05 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (19.1 mg, 0.08 mmol, 1.5 equiv) were added, causing an exotherm and color change from tan to dark orange. This mixture was heated at 125 °C for 30 min. The resulting mixture of products was purified via reverse-phase HPLC (acetonitrile/ water gradient with 0.05% TFA present), to afford *tert*-butyl (3-{2-[4-(2-hydroxyethoxy)-7-oxoazepan-4-yl]-1,3-thiazol-5-yl}-5-methylphenyl)[4-(trifluoromethyl)pyrimidin-2-yl]carbamate (14 mg, 33%), as an orange oil. MS ESI: $[M + H]^+$ *m/z* 722.2

Step 2: A bi-phasic mixture of the product from Step 1 (15 mg, 0.02 mmol) in acetonitrile and water with 0.05% TFA (reverse-phase HPLC solvent system) was heated at 125 °C for 10 minutes. The reaction was concentrated *in vacuo*, and the residual oil was partitioned between EtOAc (2x40 ml) and saturated aqueous $NaHCO_3$ (55 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the desired title product (8.1 mg, 77%) as a yellow oil. MS ESI: $[M + H]^+$ *m/z* 508.2 ^1H NMR (500 MHz, DMSO) δ 10.3 (m, 1H), 8.82 (m, 1H), 8.04 (m, 1H), 7.98 (s, 1H), 7.54 (m, 1H), 7.45 (s, 1H), 7.17 (s, 1H), 4.68 (m, 1H), 3.98 (m, 2H), 3.55 (m, 2H), 3.00-2.79 (m, 2H), 2.38 (s, 3H), 2.37-1.82 (m, 3H), 1.37-1.01 (m, 3H). rhSYK activity = +++

EXAMPLES 140(1) AND 140(2)

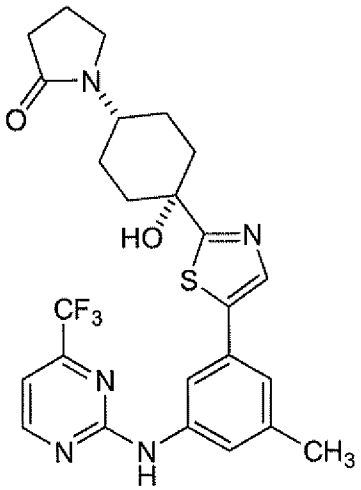
Trans-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid and *cis*-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid



To a suspension of 4-Hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanone (77 mg, 0.17 mmol) and zinc iodide (10 mg, 0.033 mmol) in CH_2Cl_2 (1 mL), was added trimethylsilyl cyanide (115 μL, 0.858 mL).The resultant suspension was stirred for 14 h at rt. Additional zinc iodide (10 mg, 0.033 mmol) and trimethylsilyl cyanide (115 μL, 0.858 mL) were added, and the resultant suspension was stirred for 5 d at room temperature. HCl (1 mL, 12 N) was then added and stirring continued for 14 h at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate, extracted wtih EtOAc (3x), dried over Na_2SO_4 and concentrated *in vacuo*. The cis- and trans-isomers were separated via HPLC (20-75% CH_3CN:H_2O with a 0.1% TFA modifier). The fractions containing the desired product were diluted with ethyl acetate, washed with aqueous saturated sodium hydrogen carbonate, dried over $MgSO_4$, filtered and concentrated to afford provide *trans*-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (6 mg, 7%) as a white solid and *cis*-1,4-dihydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (5 mg, 6%) as a white solid. Characterization data for the *trans* isomer: MS ESI: $[M + H]^+$ *m/z* 495. ^1H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.8, 1H), 7.93 (d, *J* = 14.9, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 2.31 (s, 3H), 2.07 – 1.91 (m, 4H), 1.85 (s, 2H), 1.72 (d, *J* = 9.9, 2H). rhSYK activity = +++. Characterization data for the cis isomer: MS ESI: $[M + H]^+$ *m/z* 495. ^1H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.8, 1H), 7.94 (s, 2H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.15 (s, 1H), 2.31 (s, 3H), 2.20 (d, *J* = 13.0, 2H), 2.09 (d, *J* = 10.4, 2H), 1.57 (m, 4H). rhSYK activity = +++

EXAMPLE 141

1-{C*is*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}pyrrolidin-2-one

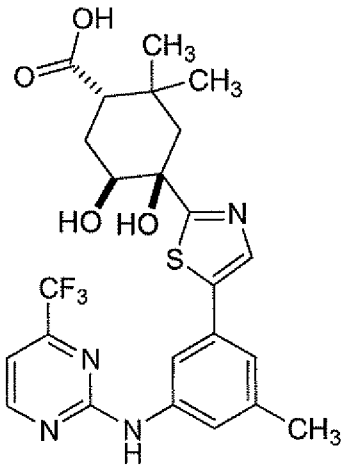


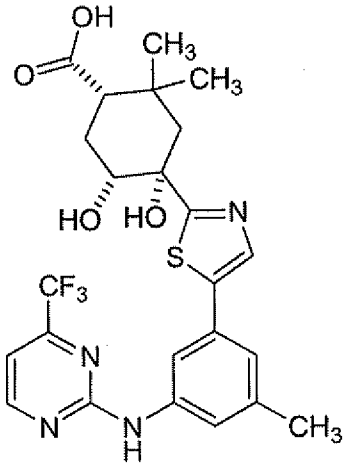
Step 1: To a solution of *cis*-4-amino-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanol (50 mg, 0.111 mmol) in dichloromethane (1 mL) was added triethylamine (0.047 ml, 0.334 mmol) and 4-chlorobutyryl chloride (0.015 ml, 0.133 mmol) sequentially. The resultant white suspension was stirred 1 h at room temperature, filtered, washed with THF, and concentrated *in vacuo* to afford 4-chloro-*N*-{*cis*-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexyl}butanamide as an off-white solid (61 mg) which was used in the subsequent reaction without further purification.

Step 2: To a solution of the product from Step 1 (61 mg, 0.110 mmol) in THF (2 mL) was added sodium hydride (14.5 mg, 0.363 mmol) at 0 °C.. The suspension was stirred 15 min at 0 °C, then allowed to warm to rt and stirred 14 h at rt. The reaction was quenched with saturated aqueous ammonium chloride, extracted with EtOAc (3x), dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel column chromatography (0%-10% MeOH:CH_2Cl_2) gave the title compound (33 mg, 58%) as a white solid. ESI: $[M + H]^+$ *m/z* 518. ^1H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.95 (d, *J* = 6.4, 2H), 7.46 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.15 (s, 1H), 6.03 (s, 1H), 3.83 (s, 1H), 2.31 (s, 3H), 2.21 (m, 3H), 1.91 (m, 9H), 1.45 (m, 2H). rhSYK activity = ++++

EXAMPLES 142(1) AND 142(2)

1,4-*Trans*, 1,5-*trans*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid and 1,4-*cis*, 1,5-*cis*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid





Step 1: Methyl *cis*-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (570 mg, 1.095 mmol) was suspended in Eaton's Reagent (4.14 mL, 21.9 mmol) and heated to 60 °C for 1.5 h. The reaction mixutre was allowed to cool to rt, and the reaction quenched via the slow addition of aqueous sodium bicarbonate. The reaction mixture was extracted with EtOAc (3x), dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel column chromatography (10%-35% EtOAc:hexanes) and separation of the diastereomers via HPLC gave 6,6-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohex-3-ene-1-carboxylic acid (127 mg, 23%) as a colorless foam. ESI: $[M + H]^+$ *m/z* 503.

Step 2: The product of Step 1 (41 mg, 0.082 mmol) was dissolved in acetone (800 µL) and water (100 µL). Osmium tetroxide (4% in water, 199 µL, 0.033 mmol) and 4-methylmorpholine *N*-oxide (38.2 mg, 0.326 mmol) were added, and the suspension was stirred 1 h at rt. The reaction was quenched with 5% aqueous $Na_2S_2O_5$ and stirred for 15 min at rt, extracted with EtOAc (3x),dried over Na_2SO_4 and concentrated *in vacuo*. Purification via silica gel column chromatography (20%-75% EtOAc:Hexanes) gave methyl 1,4-*trans*, 1,5-*trans*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate and methyl 1,4-c*is*, 1,5-*cis*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (28 mg, 64%) as a colorless oil as an apparent ~4:1 mixture of diastereomers. ESI: $[M + H]^+$ *m/z* 537.

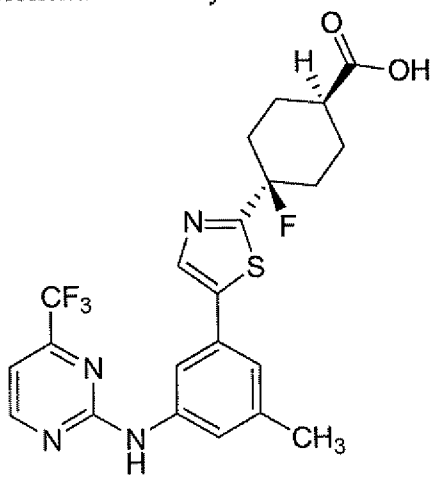
Step 3: 4,5-Dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (43 mg, 0.080 mmol) was dissolved in methanol (500 µL). Sodium hydroxide (1.0 M in water, 481 µL, 0.481 mmol) was added, and the suspension was heated in a microwave to 100 °C for 20 min. The mixture was acidified to a pH of 3-4 with HCl (1 M in water) and diluted with water and 10% IPA:$CHCl_3$. The layers were separated and the aqueous layer was re-extracted with 10% IPA:$CHCl_3$(2x). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via reversed phase HPLC (40-90% CH_3CN:H_2O) afforded 1,4-*trans*, 1,5-*trans*-4,5-

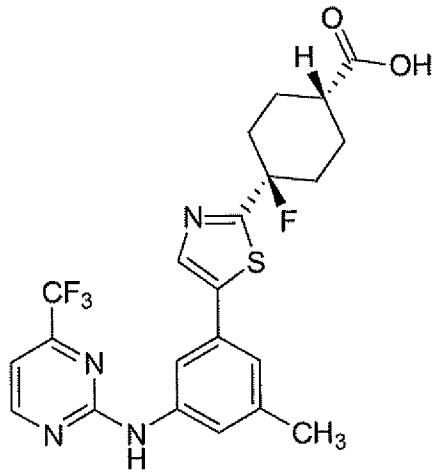
dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (13 mg, 31%) as a white solid and 1,4-*cis*, 1,5-*cis*-4,5-dihydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (17 mg, 41%) as a white solid. Characterization data for the *1,4-cis, 1,5-cis* compound: MS ESI: $[M + H]^+$ *m/z* 523. ^1H NMR (500 MHz, CD_3OD) δ 8.71 (d, *J* = 4.9, 1H), 8.01 (s, 1H), 7.97 (s, 2H), 7.45 (s, 1H), 7.13 (d, *J* = 4.8, 2H), 4.06 (dd, *J* = 4.5, 11.9, 1H), 2.50 (dd, *J* = 3.0, 13.1, 1H), 2.37 (s, 3H), 2.24 (q, *J* = 13.0, 1H), 2.01 (d, *J* = 14.7, 1H), 1.84 (d, *J* = 14.7, 2H), 1.22 (s, 3H), 1.10 (s, 3H). rhSYK activity = +++. Characterization data for the *1,4-trans, 1,5-trans* compound: MS ESI: $[M + H]^+$ *m/z* 523. ^1H NMR (500 MHz, CD_3OD) δ 8.71 (d, *J* = 4.9, 1H), 8.01 (s, 1H), 7.96 (s, 2H), 7.46 (s, 1H), 7.13 (d, *J* = 5.0, 2H), 4.61 (dd, *J* = 4.5, 10.9, 1H), 2.58 – 2.44 (m, 2H), 2.38 (s, 3H), 2.28 – 2.16 (m, 1H), 1.96 (d, *J* = 13.7, 1H), 1.75 (d, *J* = 14.0, 1H), 1.30 (s, 3H), 0.98 (s, 3H). rhSYK activity = +++

EXAMPLES 151(A) AND 151(B)

cis-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid

trans-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid





Step 1: To a flask containing *tert*-butyl 4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (400 mg, 0.75 mmol) was added dichloromethane (3.7 mL) and ethanol (2.2 mL). Deoxo-fluor (0.69 mL, 3.74 mmol) was added and the reaction was stirred for one hour. The reaction was then diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Flash chromatography was used for purification to yield *tert*-butyl *trans*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (175 mg, 0.33 mmol, 44% yield) and *tert*-butyl *cis*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (140

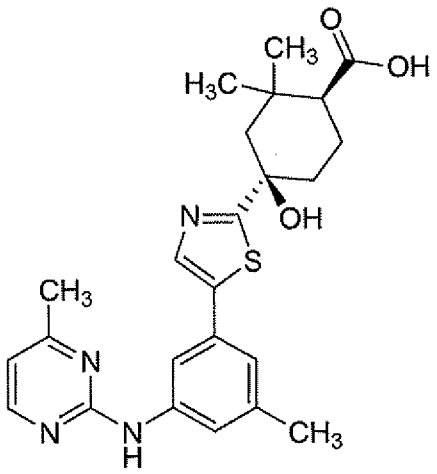
mg, 0.21 mmol, 28% yield). ESI of *trans* isomer: $[M + H]^+$ *m/z* 537. ESI of *cis* isomer: $[M + H]^+$ *m/z* 537.

Step 2 with cis isomer: To a solution of *tert*-butyl *cis*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (67 mg, 0.13 mmol) in dichloromethane (2.5 mL) was added 2,6-lutidine (0.15 mL, 1.25 mmol) and TBSOTf (0.86 mL, 3.75 mmol). The reaction was stirred for one hour. The mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Supercritical fluid chromatography (40%/60% methanol/CO_2) was used for purification to yield *cis*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (17 mg, 0.035 mmol, 28% yield). MS ESI: $[M + H]^+$ *m/z* 461. ^1H NMR (600 MHz, DMSO-d_6) δ 12.20 (s, 1H), 10.26 (s, 1H), 8.81 (d, *J* = 4.8, 1H), 8.05 (d, *J* = 2.7, 1H), 8.00 (s, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 4.9, 1H), 7.18 (s, 1H), 2.40 (t, *J* = 12.1, 1H), 2.16 (s, 3H), 2.12 – 1.97 (m, 4H), 1.94-1.87 (m, 2H), 1.67 (dt, *J* = 9.5, 12.9, 2H). rhSYK activity = +++

Step 2 with trans isomer: To a solution of *tert*-butyl *trans*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylate (175 mg, 0.33 mmol) in dichloromethane (6.5 mL) and 2,6-lutidine (0.38 mL, 3.26 mmol) was added TBSOTf (2.25 mL, 9.78 mmol). The reaction was stirred for one hour. The mixture was diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica and then reverse phase HPLC was used for purification to yield *trans*-4-fluoro-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid (70 mg, 0.15 mmol, 45% yield. MS ESI: $[M + H]^+$ *m/z* 461. ^1H NMR (600 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.81 (d, *J* = 4.8, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 4.7, 1H), 7.17 (s, 1H), 2.38 (s, 1H), 2.29 (s, 5H), 2.03 – 1.87 (m, 2H), 1.88 – 1.71 (m, 4H). rhSYK activity = +++

EXAMPLE 152

(1*S*,4*R*)-4-Hydroxy-2,2-dimethyl-4-{5-[3-methyl-5-(4-methyl-pyrimidin-2-ylamino)-phenyl]-thiazol-2-yl}-cyclohexanecarboxylic acid



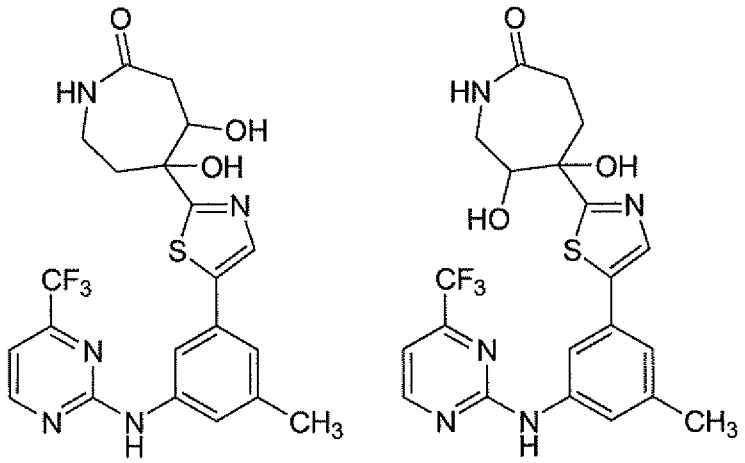
Step 1: To a mixture of (4-methyl-pyrimidin-2-yl)-[3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amine (20.0 g, 56.9 mmol), (1*S*,4*R*)-4-(5-Bromo-thiazol-2-yl)-4-hydroxy-2,2-dimethyl-cyclohexanecarboxylic acid methyl ester (19.8 g, 56.9 mmol), and $PdCl_2(dppf)_2$ (2.33 g, 2.85 mmol) in degassed 2-methyltetrahydrofuran (237 mL), was added sodium carbonate (2 M in H_2O, 56.9 mL, 114 mmol). The reaction flask was purged with nitrogen and then heated to 70 °C for 5 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered over celite. The solution was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (Isco CombiFlash 100:0 to 40:60, hexanes:ethyl acetate), then by Chromatography on silica gel (2:98, methanol:dichloromethane) provided 17.5 g (37.4 mmol 66 %) of (1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-{5-[3-methyl-5-(4-methyl-pyrimidin-2-ylamino)-phenyl]-thiazol-2-yl}-cyclohexanecarboxylic acid methyl ester as a light tan foam.

Step 2: To a solution of the product of Step 1 (16.5 g, 35.3 mmol) in methanol (115 mL) was added sodium hydroxide (1M, 123 mL, 123 mmol) and the mixture was heated to 70 °C for 2.5 hours. The reaction was cooled to 30 °C and hydrochloric acid (1 N, 123 mL, 123 mmol) was added. The reaction was aged for 1.5 hours and filtered to provide 15.3 g (33.7 mmol, 96%) of the title compound as a white solid. MS ESI: $[M + H]^+$ *m/z* 453.0. ^1H NMR (600 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.55 (s, 1H), 8.32 (d, *J* = 5.0, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.02 (s, 1H), 6.72 (d, *J* = 5.0, 1H), 5.86 (s, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.14 (dd, *J* = 12.7, 3.1, 1H), 2.00 (ddd, *J* = 18.6, 13.2, 6.0, 1H), 1.88 – 1.77 (m, 3H), 1.62 (d, *J* = 14.1, 1H), 1.55 (dq, *J* = 13.5, 3.3, 1H), 1.09 (s, 3H), 0.97 (s, 3H). rhSYK activity = +++

EXAMPLES 160(a) and 160(b)

4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one

5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one



Step 1: 5-Hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (**example 10**, 300 mg, 0.65 mmol) was suspended neat in phosphorus pentoxide (1.2 mL, 12.9 mmol) and stirred at 65 °C for 2 h., then cooled to room temperature, and carefully poured into saturated aqueous sodium bicarbonate. After the exotherm ceased, the mixture was extracted with ethyl acetate (2x). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by reverse phase HPLC (45:55 to 85:15 acetonitrile:water with a 0.1% trifluoroacetic acid modifier) to afford 5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,3,6,7-tetrahydro-2*H*-azepin-2-one and 5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,3,4,7-tetrahydro-2*H*-azepin-2-one (70:30 mixture, 119 mg, 0.26 mmol, 41% yield) as a yellow solid. MS ESI: $[M + H]^+$ *m/z* 446.1.

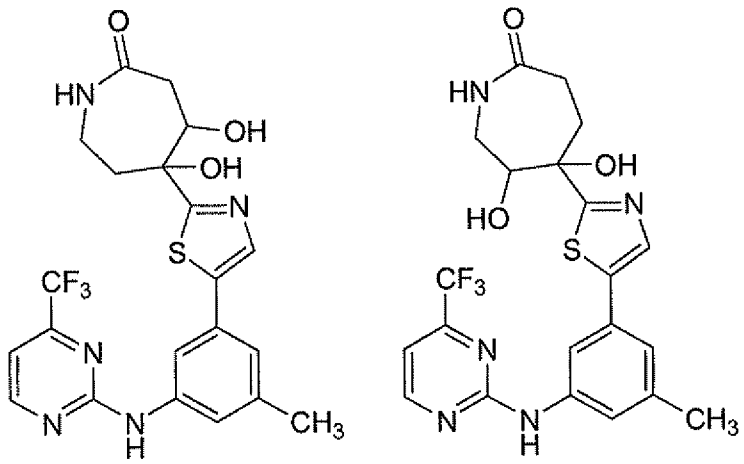
Step 2: The 70:30 mixture of products from Step 1 (100 mg, 0.22 mmol) was dissolved in acetone (1 mL) and water (125 µL). Osmium tetroxide (4% in H_2O, 548 µL, 0.09 mmol) and 4-methylmorpholine *N*-oxide (105 mg, 0.90 mmol) were added and the suspension was stirred for 1 h at room temperature. The reaction was quenched with 5% aqueous sodium thiosulfate and stirred for 15 minutes. The mixture was washed with ethyl acetate (3x), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a mixture of 4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one and 5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (70:30, 40 mg, 0.084 mmol 37% yield) as a brownish-yellow solid. MS ESI: $[M + H]^+$ *m/z* 480.1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.80 (d, $J = 4.9$, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 7.53 – 7.36 (m, 2H), 7.23 (d, $J = 4.9$, 1H), 7.11 (s, 1H), 5.92 (s, 1H), 5.86 (s, 1H), 5.12 – 5.01 (m, 1H), 4.04 – 3.99 (m, 1H), 3.58 – 3.36 (m, 1H), 3.19 – 3.09 (m, 1H), 2.96 – 2.75 (m, 1H), 2.30 (s, 3H), 2.04 – 1.82 (m, 2H)

rhSYK activity = +++

EXAMPLES 161(A), 161(B), 161(C) AND 161(D)

4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one

5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one



Two stereoisomers each

Step 1: The 70:30 mixture of 4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one and 5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (30 mg; Examples 160(a) and 160(b)) was subjected to purification by chiral supercritical fluid chromatography (4/6 2-propanol/ CO_2 with a flow rate of 50 mL/min and a 19 minute run time) to afford the stereoisomers of 4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]azepan-2-one and 5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)-pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one.

Enantiomer 1 [cis] 5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (3.2 mg, 6.25 μmol, 10% yield). MS ESI: $[M+H]^+$ *m/z* 480. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, J = 4.9, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.53 (s, 1H), 7.47 (s, 1H), 7.27 (d, J = 4.9, 1H), 7.13 (s, 1H), 6.01 (s, 1H), 5.17 (d, J = 5.9, 1H), 3.81 – 3.73 (m, 1H), 3.54 (m, 1H), 2.82 (m, 2H), 2.31 (s, 3H), 2.04 – 1.93 (m, 2H), 1.93 – 1.86 (m, 1H). rhSYK activity = +++

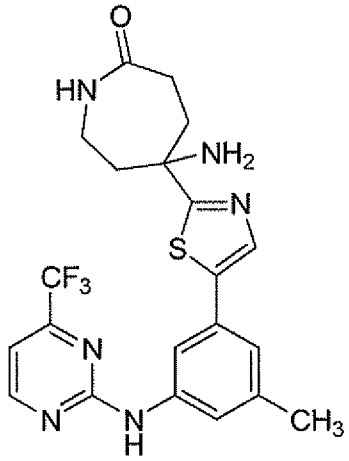
Enantiomer 2 [cis] 4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (9.0 mg, 0.019 mmol, 30% yield). MS ESI: $[M+H]^+$ *m/z* 480. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, J = 4.9, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.27 (d, J = 4.9, 1H), 7.13 (s, 1H), 6.06 (s, 1H), 5.18 (d, J = 5.7, 1H), 4.04-4.00 (m, 1H), 3.47-3.40 (m, 1H), 3.15 (d, J = 5.3, 1H), 2.90 (s, 1H), 2.31 (s, 3H), 2.18 (s, 1H), 1.97 – 1.82 (m, 2H). rhSYK activity = +++

Enantiomer 3 [cis] 5,6-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (3.3 mg, 6.88 μmol, 11% yield). MS ESI: $[M+H]^+$ *m/z* 480. ^1H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.53 (s, 1H), 7.47 (s, 1H), 7.28 (d, *J* = 4.9, 1H), 7.14 (s, 1H), 6.01 (s, 1H), 5.17 (d, *J* = 5.9, 1H), 3.82 – 3.71 (m, 1H), 3.53 (m, 1H), 2.91 – 2.75 (m, 2H), 2.31 (s, 3H), 2.04 – 1.93 (m, 2H), 1.93-1.86 (m, 1H). rhSYK activity = +++

Enantiomer 4 [cis] 4,5-dihydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one (5.1 mg, 0.011 mmol, 17% yield). MS ESI: $[M+H]^+$ *m/z* 480. ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.83 (d, *J* = 4.9, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.27 (d, *J* = 4.9, 1H), 7.13 (s, 1H), 6.06 (s, 1H), 5.18 (d, *J* = 5.7, 1H), 4.05-4.00 (m, 1H), 3.44 (s, 1H), 3.15 (d, *J* = 5.2, 1H), 2.90 (s, 1H), 2.31 (s, 3H), 2.18 (s, 1H), 1.97 – 1.84 (m, 2H). rhSYK activity = +++

EXAMPLE 162

5-amino-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one



Step 1: To a stirred solution of (S)-(-)-2-methyl-2-propanesulfinamide (854 mg, 7 mmol) and 1,4-dioxaspiro[4,5]decan-8-one (1 g, 6.40 mmol) in tetrahydrofuran (13 mL) was added titanium(IV) ethoxide (5.11 mL, 16 mmol). The mixture was stirred for 4 h at room temperature, poured over stirring saturated aqueous sodium bicarbonate (10 mL) and acetonitrile (10 mL), and stirred for 20 minutes. Magnesium sulfate was added and the mixture was stirred for 20 minutes, filtered over celite and concentrated. The residue was purified by column chromatography on silica gel (10:90 to 70:30 ethyl acetate:hexanes gradient) to afford *N*-(1,4-dioxaspiro[4.5]dec-8-ylidene)-2-methylpropane-2-sulfinamide (466 mg, 1.8 mmol, 28% yield) as a white solid. MS ESI: $[M+H]^+$ *m/z* 260.

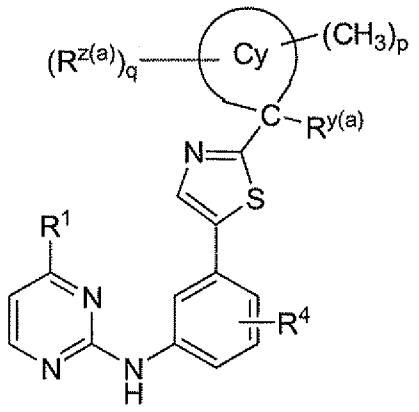
Step 2: To diisopropyl amine (318 μL, 2.23 mmol) in tetrahydrofuran (3.7 mL) at 0 °C was added *N*-butyllithium (2.5 M in hexanes, 892 μL, 2.23 mmol). The mixture was stirred for 15 minutes, then cooled to -78 °C. **INTERMEDIATE 4** (250 mg, 0.74 mmol) dissolved in

tetrahydrofuran (1 mL) was added dropwise over 5 minutes. The mixture was stirred for 30 minutes at -78 °C, then the product of Step 1 (212 mg, 0.82 mmol) dissolved in tetrahydrofuran (1 mL) was added dropwise. The reaction mixture was stirred for 2 h, and then quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate (3x), and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated. Purification by column chromatography on silica gel (0:100 to 80:20 ethyl acetate:hexanes gradient, then 0:100 to 15:85 methanol:dichloromethane gradient) afforded 2-methyl-*N*-{8-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-1,4-dioxaspiro[4.5]dec-8-yl}propane-2-sulfinamide (318 mg, 0.40 mmol, 75% yield) as a brown solid. MS ESI: $[M + H]^+$ *m/z* 596.

Step 3: To the product of Step 2 (100 mg, 0.13 mmol) was added chloroform (630 μL), sodium azide (24.5 mg, 0.38 mmol), and methanesulfonic acid (98 μL, 1.51 mmol). The mixture was heated to 65 °C for 1.5 h., cooled to room temperature, diluted with water, and extracted with ethyl acetate (2x). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by reverse phase HPLC (35:65 to 70:30 acetonitrile:water with a 0.1% trifluoroacetic acid modifier). The fractions containing the desired product were diluted with ethyl acetate and free based with saturated aqueous sodium bicarbonate. The separated organic layer was dried over magnesium sulfate, filtered and concentrated to afford the title compound (38 mg, 0.083 mmol, 66 % yield) as an orange oil. MS ESI: $[M+H]^+$ *m/z* 463. ^1H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.83 (s, 1H), 8.75 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.49 (s, 1H), 7.28 (d, J = 4.7, 1H), 7.16 (s, 1H), 2.39 – 2.08 (m, 9H), 1.30 – 0.99 (m, 4H). rhSYK activity = +++

WHAT IS CLAIMED IS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

p is 0 to 4;

q is 0, 1 or 2;

Cy is selected from C4-7cycloalkyl, oxetanyl, pyrrolidinyl, piperidinyl, and azepanyl;

R1 is selected from H, C1-4alkyl, C1-4haloalkyl, C3-6cycloalkyl, and OC1-4alkyl;

R4 is selected from H, C1-4alkyl, and C3-4cycloalkyl;

Ry(a) is aminomethyl, OH, OCH_3, OCH_2CH_2OH, F, CN, $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$, $NR^{a(a)}R^{a(a)}$, $NHC(O)C_{1-3}$alkyl (optionally substituted with OH), $NHC(O)NH_2$, $NHSO_2NH_2$, $NHSO_2C_{1-3}$alkyl, or $NHSO_2C_{1-3}$haloalkyl;

Rz(a) is selected from (A) C1-4 alkyl optionally substituted with one to three groups independently selected from OH, NH_2, CN, $CO_2R^{a(a)}$ and $CONH_2$, (B) C1-3fluoroalkyl, (C) halogen, (D) CN, (E) COC_{1-4}alkyl (optionally substituted with one or two groups independently selected from $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (F) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (G) $CO\text{-}C_{3-6}$cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (H) C_{0-3}alkyl-$CO_2R^{a(a)}$, (I) $-C(O)NR^{b(a)}R^{c(a)}$, (J) $-OR^{a(a)}$, (K) $-OC(O)R^{a(a)}$, (L) $-NR^{b(a)}R^{c(a)}$, (M) $-NHC(O)C_{1-4}$alkyl (optionally substituted with one to three OH or a $CONR^{a(a)}R^{a(a)}$), (N) $-NHSO_2C_{1-3}$alkyl, (O) $-NHSO_2NH_2$, (P) oxo, (Q) 1,3,4-oxadiazole-2(3H)-one, (R) 1,2,4-oxadiazole-5(4H)-one, (S) SO_2NH_2, (T) SO_2C_{1-3}alkyl, (U) SO_2C_{1-3}haloalkyl, and (V) SO_2Ph;

Ra(a) is H or C1-4alkyl;

Rb(a) and Rc(a) are independently selected from (A) H, (B) C3-6cycloalkyl optionally substituted with OH, (C) heteroaryl selected from imidazolyl, pyridyl and indolyl, (D) tetrahydrofuranyl, (E) benzyl, (F) phenyl optionally substituted with one or two groups independently selected from $(CH_2)_{0-2}OH$ and F, (G1) C1-4alkyl and (G2) C1-4haloalkyl, wherein (G1) and (G2) are each optionally substituted with one to three groups independently selected from (i) OH, (ii) C3-6cycloalkyl optionally substituted with one or two groups

independently selected from C_{1-4}alkyl, $CONH_2$, CO_2H and CH_2OH, (iii) $CONH_2$, (iv) SO_2NH_2, (v) SO_2C_{1-4}alkyl, (vi) 4- to 7-membered monocyclic heterocyclyl optionally substituted with one or two groups independently selected from oxo, $(CH_2)_{0-2}OH$, and C_{1-4}alkyl, (vii) a 5- or 6-membered heteroaryl optionally substituted with one or two groups independently selected from carboxy, $(CH_2)_{0-2}OH$, and C_{1-4}alkyl, (viii) CN, (x) OC_{1-4}alkyl, (ix) CO_2H, (xii) $NR^{a(a)}C(O)C_{1-4}$alkyl, (x) phenyl optionally substituted with one or two groups independently selected from $(CH_2)_{0-2}OH$, SO_2NH_2, CF_3, F and Cl, (xi) 1-pyrrolidinyl optionally substituted with oxo, (xii) 1-imidazolidinyl optionally substituted with oxo, (xiii) 1-piperidinyl optionally substituted with oxo, and (xiv) 4-morpholinyl; or

$R^{b(a)}$ and $R^{c(a)}$ together with the nitrogen atom to which they are attached form a 6- or 7-membered heterocycle having 0 to 1 additional heteroatom selected from N, O and S, wherein said heterocycle is optionally substituted with one or two groups independently selected from oxo, CN, $(CH_2)_{0-2}OH$, acetyl, benzyl, SO_2C_{1-4}alkyl, $CONH_2$, methoxymethyl, carboxymethyl, $CO_2R^{a(a)}$ and C_{1-4}alkyl.

2. A compound of Claim 1 wherein Cy is cyclohexyl.

3. A compound of Claim 2 wherein p is 0, 1 or 2; q is 1; and $R^{z(a)}$ is selected from $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH.

4. A compound of Claim 1 wherein Cy is piperidinyl.

5. A compound of Claim 4 wherein p is 0; q is 0; and $R^{z(a)}$ is selected from (i) COC_{1-4}alkyl (optionally substituted with $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (ii) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (iii) CO-C_{3-6}cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (iv) C_{0-3}alkyl-$CO_2R^{a(a)}$, (v) $CONR^{a(a)}R^{a(a)}$, (vi) CONH-phenyl (optionally substituted with one or two groups independently selected from C_{1-4}alkyl, CN, and Cl), (vii) CONH-C_{3-6}cycloalkyl, (viii) SO_2NH_2, (ix) SO_2C_{1-3}alkyl, (x) SO_2C_{1-3}haloalkyl, and (xi) SO_2Ph.

6. A compound of Claim 1 wherein Cy is azepanyl; p is 0; q is 1; and $R^{z(a)}$ is oxo.

7. A compound of Claim 1 wherein $R^{y(a)}$ is OH.

8. A compound of Claim 7 wherein Cy is cyclohexyl; p is 0, 1 or 2; q is 1; and $R^{z(a)}$ is selected from $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH.

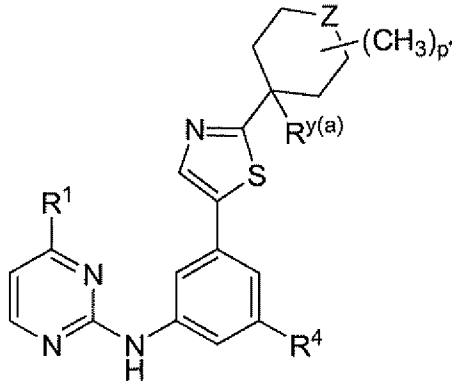
9. A compound of Claim 7 wherein Cy is piperidinyl; p is 0; q is 0; and $R^{z(a)}$ is selected from (i) COC_{1-4}alkyl (optionally substituted with $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (ii) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (iii) CO-C_{3-6}cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (iv) C_{0-3}alkyl-$CO_2R^{a(a)}$, (v) $CONR^{a(a)}R^{a(a)}$, (vi) CONH-phenyl (optionally substituted with one or two groups independently selected from C_{1-4}alkyl, CN, and Cl), (vii) CONH-C_{3-6}cycloalkyl, (viii) SO_2NH_2, (ix) SO_2C_{1-3}alkyl, (x) SO_2C_{1-3}haloalkyl, and (xi) SO_2Ph.

10. A compound of Claim 7 wherein Cy is azepanyl; p is 0; q is 1; and $R^{z(a)}$ is oxo.

11. A compound of Claim 1 wherein $R^{y(a)}$ is $CONH_2$.

12. A compound of Claim 11 wherein Cy is cyclohexyl; p is 0, 1 or 2; q is 1; and $R^{z(a)}$ is selected from $CO_2R^{a(a)}$, $CONR^{b(a)}R^{c(a)}$ and $NHC(O)C_{1-4}$alkyl optionally substituted with OH.In one aspect Cy is cyclohexyl.

13. A compound of Claim 1 having the formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein

Z is $-CR^{z(b)}R^{z(c)}-$, $-N(R^{z(d)})-$, $-CH_2-N(R^{z(d)})-$, or -NHC(O)-;

p' is 0 to 3, with the proviso that p is 0 when Z is –NHC(O)-;

$R^{z(b)}$ is selected from (A) H, (B) C_{1-4} alkyl optionally substituted with one to three groups independently selected from OH, NH_2, CN, $CO_2R^{a(a)}$ and $CONH_2$, (C) halogen, (D) CN, (E) $-C(O)R^{a(a)}$, (F) $-C(O)_2R^{a(a)}$, (G) $-C(O)NR^{b(a)}R^{c(a)}$, (H) $-OR^{a(a)}$, (I) $-OC(O)R^{a(a)}$, (J) $-NR^{b(a)}R^{c(a)}$, (K) $-NHC(O)C_{1-4}$alkyl (optionally substituted with OH), (L) $-NHSO_2C_{1-3}$alkyl, (M) $-NHSO_2NH_2$, (N) 1,3,4-oxadiazole-2(3H)-one, and (O) 1,2,4-oxadiazole-5(4H)-one;

$R^{z(c)}$ is H or methyl;
$R^{z(d)}$ is selected from (A) H, (B) C_{1-3} alkyl optionally substituted with a group selected from $CO_2R^{a(a)}$ and $CONH_2$, (C) C_{1-3}fluoroalkyl, (D) COC_{1-4}alkyl (optionally substituted with one or two groups independently selected from $OR^{a(a)}$, CN, $CO_2R^{a(a)}$, $CONR^{a(a)}R^{a(a)}$, and $NR^{a(a)}R^{a(a)}$), (E) CO-phenyl (optionally substituted with one or two groups independently selected from ethynyl, $CO_2R^{a(a)}$, CN, F and OH), (F) CO-C_{3-6}cycloalkyl (optionally substituted with OH or $CO_2R^{a(a)}$), (G) C_{0-3}alkyl-$CO_2R^{a(a)}$, (H) $CONR^{a(a)}R^{a(a)}$, (I) CONH-phenyl (optionally substituted with one or two groups independently selected from C_{1-4}alkyl, CN, and Cl), (J) CONH-C_{3-6}cycloalkyl, (K) SO_2NH_2, (L) SO_2C_{1-3}alkyl, (M) SO_2C_{1-3}haloalkyl, and (N) SO_2Ph; and
R^1, R^4, $R^{y(a)}$, $R^{a(a)}$, $R^{b(a)}$ and $R^{c(a)}$ are as defined in Claim 1.

14. A compound of Claim 13 wherein Z is –NHC(O)- and $R^{y(a)}$ is OH.

15. A compound of Claim 13 wherein Z is -$CHR^{z(b)}$– and p' is 0, 1 or 2; and $R^{z(b)}$ is CO_2H,$CONHR^{b(a)}$, $NHC(O)C_{1-4}$alkyl (optionally substituted with OH).

16. A compound of Claim 13 wherein Z is -$CHR^{z(b)}$–, p' is 0, 1 or 2, and $R^{y(a)}$ is OH or $CONH_2$.

17. A compound of Claim 16 wherein $R^{z(b)}$ is CO_2H, $CONH_2$, or $NHC(O)C_{1-4}$alkyl (optionally substituted with OH).

18. A compound of Claim 1 selected from the group consisting of:
(1R,4S)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1S,4R)-4-[5-(3-cyclopropyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-{5-[3-methyl-5-(4-methyl-pyrimidin-2-ylamino)-phenyl]-thiazol-2-yl}-cyclohexanecarboxylic acid;
(1S,4R)-4-[5-(3-{[4-(difluoromethyl)pyrimidin-2-yl]amino}-5-methylphenyl)-1,3-thiazol-2-yl]-4-hydroxy-2,2-dimethylcyclohexanecarboxylic acid;
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(propan-2-yloxy)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
trans-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
cis-4-hydroxy-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;

5-hydroxy-5-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]azepan-2-one;
cis-4-[(hydroxyacetyl)amino]-1-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide; and
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]cyclohexanecarboxamide;
(1*S*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*S*,4*S*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1*R*,4*R*)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxylic acid;
(1R,4S)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
(1S,4R)-4-hydroxy-2,2-dimethyl-4-[5-(3-methyl-5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}phenyl)-1,3-thiazol-2-yl]cyclohexanecarboxamide;
or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effect amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. A method for the treatment or prevention of a SYK-mediated disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1.